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Perspectives on music and pain: From evidence to theory and application

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Perspectives on music and pain: From evidence to theory and application

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Editorial: Perspectives on music and pain: from evidence to theory and application

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Editorial on the Research Topic
Perspectives on music and pain: from evidence to theory and application

Research on music, as a non-pharmacological adjunct or alternative to traditional pain management, can take many perspectives (e.g., music therapy, psychology, neuroscience, medical specialties, nursing, rehabilitation). The studies and review articles are scattered across a myriad of journals. The present *Frontiers* Research Topic and ebook aimed to provide the first singular collection of peer-reviewed articles on music and pain, moreover, one that is open access, in the highly visible *Frontiers* catalog. The call for papers was launched in *Frontiers in Pain Research* and subsequently in *Frontiers in Psychology: Auditory Cognitive Neuroscience* and *Frontiers in Neuroscience: Auditory Cognitive Neuroscience* seeking contributions that would bridge disciplines, from clinical applications to laboratory-generated data to evidence-based theories. An enthusiastic response led to 10 accepted papers.

As a reward, stress reliever, mood regulator, distractor, and appraisal tool (see **Figure 1**), music interferes with pain processing through diverse neural pathways. Neuroimaging studies suggest that music and pain share pathways, including areas that encode sensory (e.g., somatosensory cortex) and affective (e.g., anterior cingulate cortex) components (1–4).

The present articles reflect the variety of influences of music on modulators, such as mood, cognitive state, and expectations, that can shape the experience of pain. Likewise, the types of music explored differ on a variety of dimensions such as whether

- Music functions as a distractor due to increased cognitive load, as associative prompts for reminiscence, or as engagement in motoric or creative processes (as in improvising);
- Music is selected by client, experimenter, or computer;
- Patients or study participants passively listen to background music or engage in active listening, performance, or composition;
- Patients make music alone, with a therapist, with one or more other individuals, or with technology.

Each article uniquely affirms the multidimensionality of the music interventions and human responses examined. Glomb et al. in a study of persons with chronic or somatoform pain explored pain scale and heart-rate variability as indices of effectiveness of Music-Imaginative Pain Treatment. Patients individually created expressive compositions–one for

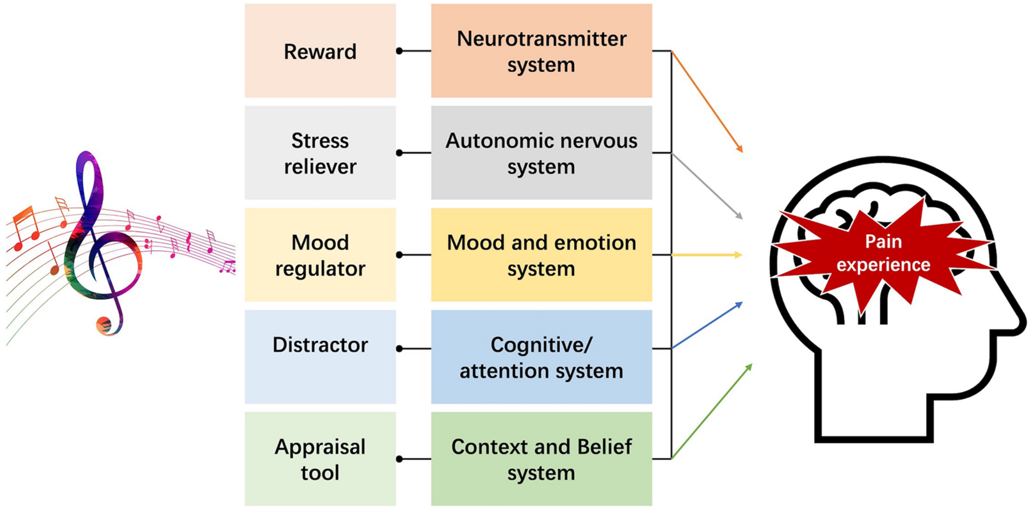

FIGURE 1
Illustration of the main influences of music that can affect the experience of pain [extended and adapted from the work and Figure 1 by Lunde et al. (5) and Figure 1 by Sihvonen et al. (6)].

chronic pain, the other for healing–with the help of the therapist and access to musical instruments. Reduced pain was observed for subjective pain scale measures, but individual differences obscured group patterns in heart rate variability. A related case study by Metzner et al., illustrates how the intervention allows clients, who lack knowledge of music performance, to create and control the performance of their pain-related compositions. Schneider et al. also compared the role of music making during a novel small-group music and exercise condition as compared to exercise alone. The music-making condition was associated with less anxiety and more motivation to exercise than was the exercise-only condition. The intervention highlights the potential importance of both active engagement in music and group interaction and synchronization [see also (7)]. Like Metzner et al., Lepping et al., working with patients with fibromyalgia, also recorded heart rate and showed a trend of vagal heart rate increase from baseline to music listening condition.

Several studies explore choices of music by individuals to reduce their pain. Howlin et al. conducted a survey to determine whether selected music provides an "immersive and absorbing experience" (musical integration) and an increased feeling of control (cognitive agency). In their own Cognitive Vitality Model these two mechanisms are nesting stages among other mechanisms. Valevicius et al. found that personally selected music that most effectively reduced pain was associated with more chills and more highly rated pleasantness. A qualitative component of their study revealed that this music belonged to a category of "moving/ bittersweet" as compared to three other semantic categories. Soyeux and Marchand demonstrated the effect of a web app-based personalized music intervention on pain, treating music as a possible digital medicine to prevent, manage, or treat pain conditions.

Researchers also continue to investigate underlying brain structures and networks of pain mechanisms. To this end, Powers et al. report an fMRI study, the "first of its kind to assess the effects of music analgesia using complex network analyses in the human brain and brainstem". They showed that music altered connectivity across neural networks between such regions as the insula, thalamus, hypothalamus, amygdala, and hippocampus, and its presence was correlated with decreased unpleasantness (but not intensity) of pain. Given the complexity of the pain experience and music interventions, Hunt writes directly to music therapists to encourage greater openness to mechanistic study of the role of music therapy on pain. She points to a variety of forward-thinking research contexts, for example, measuring the physiological synchronization between participant and therapist during improvised music expressive of pain or healing, and integrating these analyses with participant post-session pain reports. A final case study of Mercadillo and Garza-Villarreal reports benefits of music analgesia for a person who experienced 20 years of chronic pain, noting as well, reduced withdrawal symptoms associated with decreasing reliance on pharmacological analgesics.

This compendium reflects a broad range of current research on music and pain but is not exhaustive, missing research on animals, extensive clinical studies, childbirth, musicians' pain, and music therapy group processes. The recent IASP definition of pain now accommodates for the experience of nonverbal human beings, such as infants and persons with dementia (8). These populations were not part of any reported studies. We note that all studies in the collection address chronic pain or experimentally controlled pain stimulation. Acute pain, which is short lived and more difficult to study, nevertheless deserves more examination, as principles underlying it may differ from those underlying chronic pain.

In closing, this Research Topic can potentially have three types of impact: first, encourage health care practitioners who regularly deal with people in pain, to suggest to their patients the opportunity that music might provide, or to suggest or prescribe working with a music therapist; second, stimulate increased inclusion of the topic of music in reviews of interventions for the treatment of pain, and third, provide a foundation and inspiration for future research in this area of music and pain.

Author contributions

AC: Conceptualization, Project administration, Visualization, Writing – original draft, Writing – review & editing. AH: Conceptualization, Visualization, Writing – original draft, Writing – review & editing, Project administration. EG: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. XL: Conceptualization, Project administration, Visualization, Writing – original draft, Writing – review & editing. AJC initiated the present Research Topic, taking a leadership role and welcoming co-authorship of experts in music and pain, XL, EAG-V, and AMH. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Dobek CE, Beynon ME, Bosma RL, Stroman PW. Music modulation of pain perception and pain-related activity in the brain, brain stem, and spinal cord: a functional magnetic resonance imaging study. *J Pain*. (2014) 15:1057–68. doi: 10.1016/j.jpain.2014.07.006

2. Garza-Villarreal EA, Jiang Z, Vuust P, Alcauter S, Vase L, Pasaye EH, et al. Music reduces pain and increases resting state fMRI BOLD signal amplitude in the left angular gyrus in fibromyalgia patients. *Front Psychol*. (2015) 6:1051. doi: 10.3389/fpsyg.2015.01051

3. Pando-Naude V, Barrios FA, Alcauter S, Pasaye EH, Vase L, Brattico E, et al. Functional connectivity of music-induced analgesia in fibromyalgia. *Sci Rep*. (2019) 9:15486. doi: 10.1038/s41598-019-51990-4

4. Lu X, Hou X, Zhang L, Li H, Tu Y, Shi H, et al. The effect of background liked music on acute pain perception and its neural correlates. *Hum Brain Mapp*. (2023) 44:3493–505. doi: 10.1002/hbm.26293

5. Lunde SJ, Vuust P, Garza-Villarreal EA, Vase L. Music-induced analgesia: how does music relieve pain? *PAIN*. (2019) 160:989–93. doi: 10.1097/j.pain.0000000000001452

6. Sihvonen AJ, Pitkäniemi A, Särkämö T, Soinila S. Isn't there room for music in chronic pain management? *J Pain*. (2022) 23:1143–50. doi: 10.1016/j.jpain.2022.01.003

7. Werner LM, Skouras S, Bechtold L, Pallesen S, Koelsch S. Sensorimotor synchronization to music reduces pain. *PLoS ONE*. (2023) 18:e0289302. doi: 10.1371/journal.pone.0289302

8. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised international association for the study of pain definition of pain. *PAIN*. (2020) 161:1976–82. doi: 10.1097/j.pain.0000000000001939

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Music to My Senses: Functional Magnetic Resonance Imaging Evidence of Music Analgesia Across Connectivity Networks Spanning the Brain and Brainstem

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Pain is often viewed and studied as an isolated perception. However, cognition, emotion, salience effects, and autonomic and sensory input are all integrated to create a comprehensive experience. Music-induced analgesia has been used for thousands of years, with moderate behavioural effects on pain perception, yet the neural mechanisms remain ambiguous. The purpose of this study was to investigate the effects of music analgesia through individual ratings of pain, and changes in connectivity across a network of regions spanning the brain and brainstem that are involved in limbic, paralimbic, autonomic, cognitive, and sensory domains. This is the first study of its kind to assess the effects of music analgesia using complex network analyses in the human brain and brainstem. Functional MRI data were collected from 20 healthy men and women with concurrent presentation of noxious stimulation and music, in addition to control runs without music. Ratings of peak pain intensity and unpleasantness were collected for each run and were analysed in relation to the functional data. We found that music alters connectivity across these neural networks between regions such as the insula, thalamus, hypothalamus, amygdala and hippocampus (among others), and is impacted by individual pain sensitivity. While these differences are important for how we understand pain and analgesia, it is essential to note that these effects are variable across participants and provide moderate pain relief at best. Therefore, a therapeutic strategy involving music should use it as an adjunct to pain management in combination with healthy lifestyle changes and/or pharmaceutical intervention.

Keywords: functional MRI, human neuroimaging, music analgesia, pain, cognitive/affective pain modulation, network connectivity, structural equation modelling

INTRODUCTION

Music has been used to alter our perception of pain for thousands of years in cultural, experimental, and clinical environments (1–3). A number of prior studies have demonstrated behavioural effects of music on subjective ratings of pain, including significant decreases in both pain intensity (1, 4–9) and unpleasantness (4, 6, 8, 10, 11), with a 70% higher likelihood of reduced pain (1) and increased pain thresholds (12–14). Furthermore, there is also evidence that the capacity of music to modulate pain is reduced when individuals exhibit higher levels of pain catastrophizing (12). However, a recent meta-analysis found that these effects are highly variable across individuals and studies due to a number of factors including methodological variations across studies, and the underlying mechanisms remain unclear (15).

Hypotheses regarding the underlying mechanisms of music analgesia range from purely distraction (cognition) (16, 17) to purely emotional (valence, arousal, reward) (6, 10, 18). However, these effects may not be separable (19, 20) and an interaction between cognitive, emotional, and sensory domains is the most likely foundation for pain relief from music (3, 6, 10). Lunde et al. (3) described a set of integrated factors, adapted from Tracey and Mantyh (21), which contribute to music analgesia including context, cognition, emotion, neurotransmitters, and predictability of the music itself. A subsequent meta-analysis expanded on this theory by arguing that music can suppress pain by acting as a reward, stress reliever, mood regulator, and distractor (2). This idea is supported by the observation that pleasurable music reduces anxiety and stress through downregulation of the autonomic nervous system (22–24), increasing dopamine and serotonin release in the striatum (12, 25, 26), increasing μ-opioid receptor and endorphin production (27), and recruiting reward and limbic regions to modulate motivation, learning and valuation (18, 25, 28). Anxiety, stress, learning, and reward play prominent roles in how we evaluate the relative importance of painful stimuli and our ability to cognitively and emotionally regulate pain (29–33). Furthermore, increased opioid receptor, endorphin, dopamine, and serotonin production directly interact with the descending opioidergic analgesic pathway consisting of the periaqueductal grey (PAG)-rostral ventromedial medulla (RVM)-spinal cord (34–36). Along with other types of emotional stimuli, music has widely been thought to influence pain via this pathway (3, 13, 27, 37, 38).

While evidence for music analgesia has been described behaviorally, few functional investigations of neural effects in humans have been reported. These include only four previous fMRI studies (8, 13, 37, 39), a study employing EEG (10), and one EMG study (40). Previous fMRI studies have reported attenuation of the anterior cingulate cortex with music during pain stimulation (13), altered resting-state connectivity after music listening in participants with fibromyalgia (8), and differences between pain-plus-music and pain-only conditions across several cortical, limbic, brainstem and spinal cord regions (37).

The objective of this study was to use functional MRI to build on the foundation of existing behavioural evidence to further investigate the neural basis of music analgesia in human participants. We acquired data from healthy individuals during the application of acute noxious thermal stimulation with and without concurrent presentation of pleasurable music individually selected by each participant. Behavioural ratings of pain intensity and unpleasantness were recorded to assess the subjective effects of music analgesia, along with the temperatures required to produce moderate pain. We hypothesised that having a participant listen to pleasant music of their choice while they experience acute heat pain would result in altered descending pain regulation via the PAG-RVM pathway, compared to experiencing the pain stimulus without music. Moreover, we hypothesised that this regulation would be mediated by input from limbic, paralimbic, and reward regions.

MATERIALS AND METHODS

All procedures were approved by the institutional human research ethics review board and complied with the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans. Informed consent for all study procedures was obtained in writing prior to the onset of study training and participants were informed that they could cease participation at any time.

Participants

Twenty healthy participants (10 female, 10 male) ranging from 21 to 33 years of age (23 ± 3 years, mean ± standard deviation) were recruited from the local community through online advertisements and posted notices. Participants were free of any history of neurological disease or injury, major medical illness, psychiatric disorder or pre-existing pain condition and were not taking any centrally acting medications (i.e., antidepressants) or prescription medication for pain relief. Participants were also instructed to refrain from taking over the counter pain medication (e.g., ibuprofen) on the day of study participation to avoid interference with normal, healthy pain responses.They were also free of any contraindications for the MRI environment including pregnancy, claustrophobia, metal implants or injuries from metal fragments, or inability to lie still. All participants were screened for eligibility through a secure online form.

Eligible participants were asked to complete a battery of validated questionnaires to characterise individual traits of mental health, social behaviours, and pain catastrophizing, which all relate to the sensory and affective dimensions of pain. The questionnaires included the Beck Depression Inventory-II (BDI-II) (41), the State/Trait Anxiety Inventory (STAI) (42), the Social-Desirability Scale (SDS) (43), and the Pain Catastrophizing Scale (PCS) (44). The BDI-II assesses the affective, motivational, cognitive, and somatic symptoms of depression. The STAI measures the transient condition of state anxiety as well as the chronic condition of trait anxiety. The SDS provides an assessment of whether participants are concerned with social approval, such as providing pain ratings in a way that they believe the researchers would approve of. The PCS reflects how individuals respond to pain, such as tendencies to feel helpless and/or magnify the threat value of a stimulus. Participants were not excluded from participating given high or low scores on any of these questionnaires. The resulting scores were used in correlational analyses with functional MRI data to determine if behavioural and psychological traits relate to neurological activity during the experience of pain. Group means for each scale were computed and individual scores were compared with subsequent pain ratings from each participant.

All participants were instructed to bring six selections of familiar, pleasurable music of any genre on a USB-drive in .mp3 format, as music chosen by the participants has been shown to have greater effect than music chosen by the researchers (5, 45). These selections were required to be at least 210 s long to correspond with the length of each scan and yield a rating of 7.5 or higher on 10-point scales of happiness, familiarity, and alertness. During functional scans, participants experienced two experimental conditions: noxious thermal stimulation with simultaneous presentation of pleasurable music (i.e., "Music" runs), and noxious thermal stimulation alone (i.e., "No-Music" runs). Half of the scans were carried out in each condition, in a randomised order. The researchers randomly assigned music selections to the Music runs, and a different selection was played for each music run.

Experimental Procedures

Protocol Training Session

Immediately prior to imaging, participants underwent a 45-min training session in a "sham" MRI lab within the Queen's University MRI Facility. The purpose of training was to familiarise participants with the study paradigm, including scales with which they would rate their pain experience, the noxious thermal stimulus and timing of stimulation. Participants were trained to use validated 100-point numerical pain intensity and unpleasantness rating scales (NPS), with verbal descriptors at intervals of 10 (**Figure 1A**) (46–48). Participants were encouraged to rate in increments of 5, and the researcher checked each rating with the participant to ensure that they were becoming familiarised with the scales. They were informed that pain intensity describes more of the sensory/discriminative dimension of pain whereas unpleasantness describes the emotional/affective component of the perceived pain. The ratio of each participants' pain rating to the temperature used to elicit that pain rating was used as a "normalised pain score." A higher pain score may indicate that participants who experienced a particular pain rating at a lower temperature are more sensitive to pain than those that experienced the same pain rating but required a higher temperature to produce that pain. This method was used to standardise our pain measures given that participants were not all subjected to the same stimulus temperatures.

To elicit acute experimental pain, thermal stimulation was applied with an MRI-compatible robotic contact-heat thermal stimulator (RTS-1), which raised and lowered a 3 cm-square aluminium thermode to and from the participants' skin via pneumatic pistons (49–52). The stimulus was applied to the thenar eminence of the right hand, corresponding to the sixth cervical segment of the spinal cord. The timing and duration of heat-contacts, along with thermode temperature, were under precise control by custom-made software in MATLAB? (Mathworks Inc., Natick, MA). Each test consisted of ten 1.5-s heat contacts over the span of 30 s in order to elicit sustained behavioural and neural responses and to avoid habituation of nociceptors in the skin. Participants were trained with a standard set of temperatures, ranging from 45 to 52 °C presented in the same order, and were individually calibrated to a temperature corresponding to a tolerable average pain rating of 50 intensity units ("Moderate Pain", **Figure 1A**) (53). Participants were kept blinded to this objective, as well as to the temperatures used during the tests, to avoid any potential response bias, and the upper limit of 52°C was set to avoid causing damage to the skin. Additionally, participants were instructed to remove their hand from the stimulator if their pain ratings ever exceeded 70 NPS units to avoid causing distress or very strong pain. Once calibrated, participants moved on to the next stage of training.

A mock-up of the MRI scanner (sham-MRI) was used to train participants on the stimulation paradigm and timing that they would experience in the MRI, and to familiarise them with the confined environment. This process was also intended to reduce variations in the data that may be caused by anxiety and bulk motion across repeated fMRI acquisitions. Participants were positioned supine in the sham-MRI with a mirror over their eyes to view a rear projection screen displaying the pain intensity and unpleasantness scales, and the RTS-1 under their right hand. A simulated version of the fMRI protocol was carried out at the calibrated temperature, with recorded MRI sounds played for them on a speaker to simulate the scanner environment. The 210-s stimulation paradigm is shown in **Figure 1B**. Participants were instructed to silently rate the intensity and unpleasantness of each contact as they felt them, and to remember only the highest ratings on both scales. The peak ratings of pain intensity and unpleasantness were recorded, and the calibration temperature was confirmed or adjusted based on these ratings; this temperature and stimulation paradigm was then used during the subsequent imaging session.

Functional MRI Data Acquisition

Functional MRI was carried out on a Siemens 3 tesla MRI system (Siemens Magnetom Trio, Erlangen, Germany). Participants were positioned head-first and supine with foam supports under their knees and arms to minimise bulk motion during scanning. The RTS-1 was positioned at their side, under the palm of the right hand and foam earbuds were provided to ensure optimal sound quality for the music. A 32-channel head coil was used to obtain images of the brain and brainstem and a mirror positioned above the participants' eyes allowed them to view a rear projection screen which displayed prompts for timing of the stimulation paradigm and the pain rating scales during each run. The peripheral pulse was recorded from all participants with a sensor attached to their left index finger, and participants were provided with a squeeze-ball to signal the experimenter in the event of an emergency, or if they did not wish to continue the study. After setup, participants were instructed to remain as still as possible and wait for audio instructions provided to them through the earbuds. Sound quality was checked after the first music run to ensure that participants could hear the music at an appropriate volume over the sounds of the scanner.

Localizer images were acquired in three planes to provide a reference for subsequent slice positioning. A sagittal, T1-weighted anatomical scan was also acquired using a 3D MPRAGE sequence to aid in normalisation of functional data with $1 \times 1 \times 1$ mm^3 resolution, a repetition time (TR) of 1,760 ms, echo time (TE) of 2.2 ms, inversion time of 900 ms, and flip angle = 9°. In order to produce high quality images of the brain, and maintain this quality in the brainstem, simultaneous multi-slice imaging with an acceleration factor of 2 was used

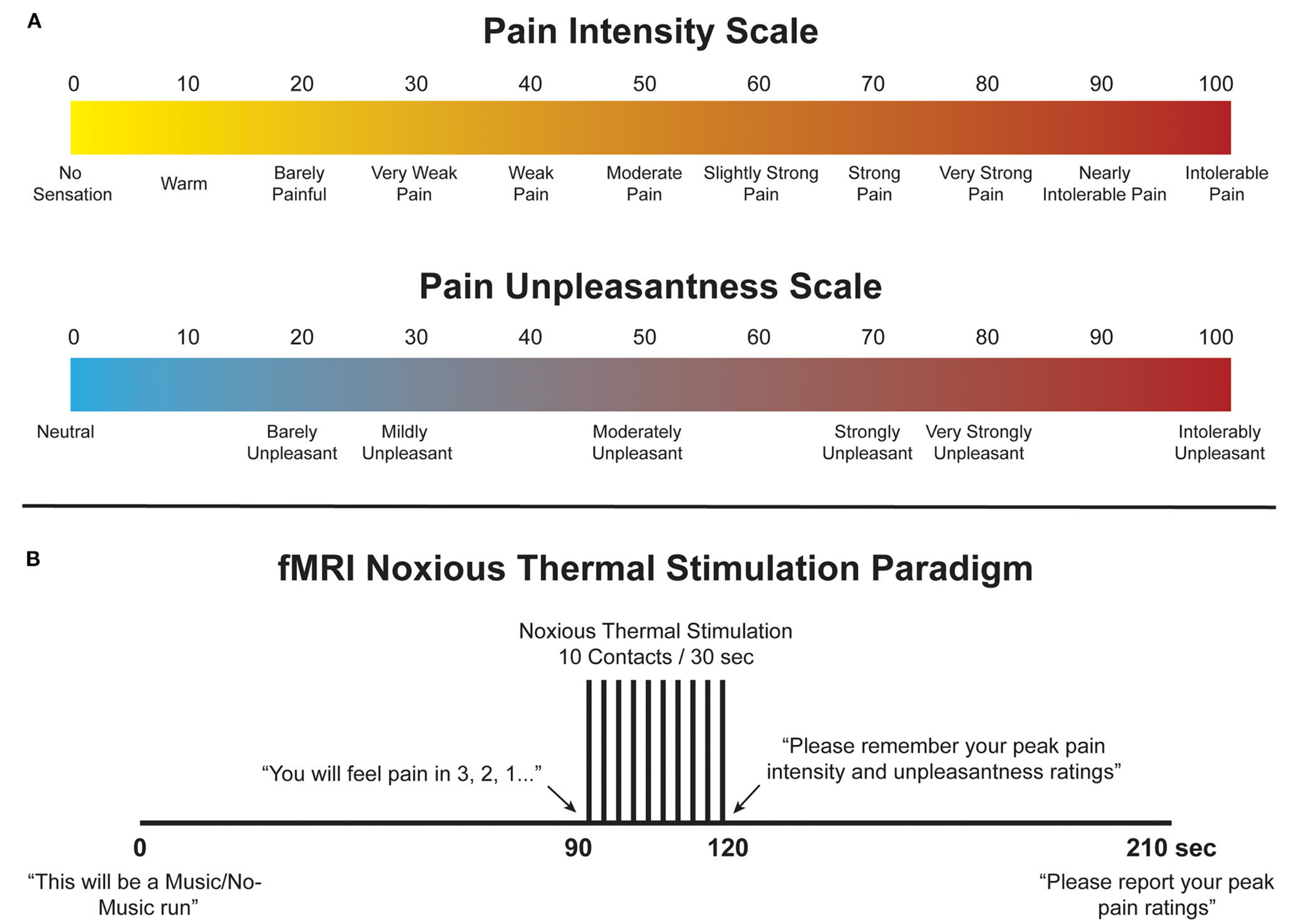

FIGURE 1 | (A) Numerical Pain Scales (NPS) used to train participants to rate their pain intensity and unpleasantness. These scales were also displayed during functional scans to aid participants in rating their pain during the experiment. **(B)** Stimulation paradigm used during the training and imaging sessions. For Music runs, the music was synchronised to begin with the onset of scanning and continued throughout until completion.

for BOLD functional scans. A gradient-echo imaging method, with echo-planar spatial encoding (GE-EPI), was used with a flip angle of 84°. The 3D volume spanned from the top of the first cervical vertebra to the corpus callosum, with a TE of 35 ms for optimal T_2^*-weighted BOLD sensitivity in the brain. The TR was set at 2,000 ms per volume, and 105 volumes were recorded to produce a time-series spanning 210 s (3.5 min). Data were acquired in 48 contiguous axial slices, 2.1 mm thick, with a 180 × 180 mm field of view, and an 84 × 84 matrix, resulting in 2.1 mm isotropic resolution, with an anterior/posterior phase-encoding direction.

Multiple runs of each condition (Music and No-Music) were acquired in a randomly interleaved order and participants were informed of which condition to expect at the beginning of each run. The stimulation paradigm followed the same timing as in the sham-MRI run (**Figure 1B**), with periods of expectation, stimulation, and relief. Participants provided their peak pain intensity and unpleasantness ratings at the end of each run, and these ratings were recorded. During the Music condition, the music was synchronised to begin at the exact same time as scanning, and it played throughout the scan. The initial baseline period therefore allowed the participant to become engrossed in the music before the onset of thermal stimulation. In between each run, the MRI operator confirmed that the participant was comfortable and alert before continuing. In total, 10 runs were acquired for each participant, half spent in each condition, in a randomised order.

Data Analysis

Behavioural Analyses

As they were not normally distributed, pain intensity and unpleasantness ratings were investigated across study conditions using 2-tailed, Wilcoxon signed-rank tests, with a significance threshold of $p < 0.05$. The relationships between questionnaire scores, pain intensity and unpleasantness ratings, and normalised pain scores in the No-Music (unmodulated) condition were also tested across all individuals using Spearman's rho correlations,

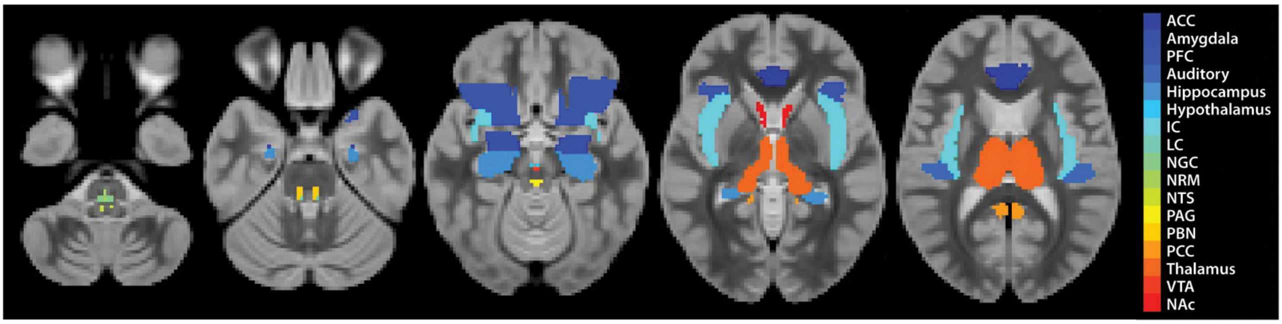

FIGURE 2 | Region definitions for each ROI. Each region is shown as a single colour, as described in the legend.

also with significance inferred at a threshold of $p < 0.05$. This was done to determine whether a relationship could be found between participants' individual characteristics and their subjective pain behaviours in an acute, experimental setting.

Data Pre-processing

Functional MRI data were pre-processed using Statistical Parametric Mapping software (SPM-12, The Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, UK) in MATLAB (MathWorks, Natick, MA, USA). Pre-processing steps included conversion to NIfTI format, co-alignment to correct for bulk motion, and spatial normalisation to pre-defined anatomical templates from the Montreal Neurological Institute (MNI). Images were re-sized to 2 mm cubic voxels prior to normalisation for compatibility with the MNI template, and data were cleaned to reduce noise by fitting and subtracting signal variations corresponding to the motion parameters determined during co-alignment.

Subsequent data analyses focused on characterising temporal BOLD responses and relationships between regions known or suspected to be involved in pain, music and emotion processing, and autonomic regulation (54–57) (**Figure 2**). We aimed to identify the relationships between study conditions (Music vs. No-Music), individual pain scores, the period of the stimulation paradigm (i.e., before, during, and after the noxious stimulus was applied), and personal characteristics (questionnaire scores). For the purposes of prior studies we had created a combined anatomical template and anatomical region map that spans the brain, brainstem and spinal cord (51, 58). For this study, the relevant reference images consisted of the MNI152 template, included in SPM-12, and anatomical regions maps from the CONN15e software (59). Brainstem regions not included in the CONN15e region map were supplemented based on examples and anatomical descriptions (54, 60–64), and freely shared atlases as described by Pauli et al. (65), Keren et al. (66), and Harvard atlases (https://www.med.harvard.edu/AANLIB/).

Structural Equation Modelling

Structural equation modelling (SEM) is a data-driven family of statistical techniques which are used to identify patterns of correlation/covariance among a set of BOLD responses within and across regions of interest (ROIs) (58, 67, 68).

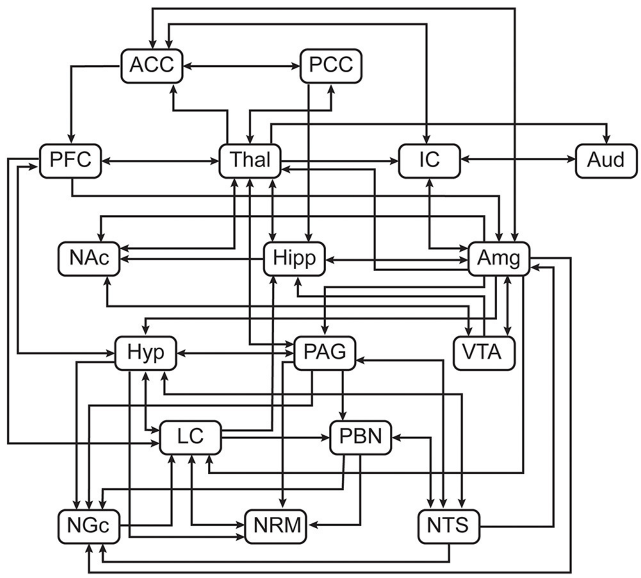

FIGURE 3 | Pre-defined anatomical model of connections between regions of interest.

Our SEM methods are focused on characterising temporal relationships by explaining as much variance as possible through use of a pre-defined anatomical model of connections across the brain and brainstem. This pre-defined model is based on known neuroanatomy, including directionality, between ROIs (**Figure 3**) and includes: ***brain regions***-pre-frontal cortex (PFC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), insular cortex (IC), auditory cortex (Aud), thalamus (Thal), amygdala (Amg), hippocampus (Hipp), nucleus accumbens (NAc), and hypothalamus (Hyp); ***midbrain regions***-periaqueductal grey matter (PAG), and ventral tegmental area (VTA); ***pontine regions***-locus coeruleus (LC), and parabrachial nucleus (PBN); ***rostral medulla regions***-nucleus raphe magnus (NRM), nucleus gigantocellularis (NGc) and nucleus tractus solitarius (NTS) (54). These areas were chosen to cover a comprehensive array of centres for somatosensation, audition, pain processing and perception, music and emotion processing, and autonomic homeostatic regulation (28, 29, 54, 56, 69–71). Some existing anatomical connections were pruned from the network model in order to limit the number of comparisons and to highlight important connections, keeping the focus on connections known to be involved in pain processing and modulation. Data were averaged across clusters of voxels to reduce the number of statistical comparisons to be made and to increase the signal-to-noise ratio over that of single-voxel analyses. Each ROI was functionally divided into 7 sub-regions based on time-series characteristics using k-means clustering. Once defined, identical sub-regions were used across the group for both study conditions. The VTA, however, was divided into 4 sub-regions as it contained fewer voxels than other regions. This process limits potential bias when dividing each ROI into sub-regions as it assumes that each ROI can have more than one function (72–76). Here, we used SEM as a means to investigate coordination across networks of regions. This method has successfully identified robust networks of connectivity across the brain, brainstem, and spinal cord in our previously published work (51, 58, 68, 73–75, 77, 78).

SEM was carried out by means of a general linear model to calculate linear weighting factors (β) which indicate the relative contribution of each connection to the overall network model, using the time-series data across participants, separately for each condition. The calculations are dependent on the following logic: if region A receives input from regions B and C, and the BOLD signal time-series responses in these regions are S_A, S_B, and S_C, respectively, then: $S_A = \beta_{AB} S_B + \beta_{AB} S_B + e_A$; where e_A is the residual signal variation that is not explained by the fit (67). The weighting factors were calculated separately for each network component, consisting of a sub-region receiving input (target) with multiple regions providing input (sources). Networks were investigated for every combination of anatomical sub-regions of each ROI to identify the sub-regions that resulted in the best fits to the data measured.

The significance of connectivity values (β) was determined based on their average values across the group, and the estimated standard errors. Significance was inferred at a family-wise-error corrected $p_{\text{fwe}} < 0.05$ which accounted for the total number of network combinations that were tested across combinations of anatomical sub-regions. With this process, connections with β-values which were significantly different than zero were identified and used for subsequent second-level analyses.

Analysis of Variance and Covariance

Analyses of variance (ANOVA) and covariance (ANCOVA) were employed as a means of comparing study conditions, time periods of the stimulation paradigm, and behavioural ratings of pain. Connectivity values (β) were used as the dependent variable, with study "Condition" used as one discreet independent variable (Music or No-Music), and the time period (before or during pain, to test an effect of "Stimulation") as the second discrete independent variables for the ANOVA (i.e. Condition X Stimulation). An ANCOVA was also applied to β-values as the dependent variable, with study "Condition" as a discrete independent variable and "Pain Score" as a continuous independent variable for all 3 time periods of the study paradigm (i.e., Condition X Pain Score, before, during and after pain). Significance of these analyses was inferred at a false discovery rate (FDR) controlled $p < 0.05$.

Bayesian Regression

To further investigate temporal details of BOLD responses across ROIs, a Bayesian regression technique was applied to characterise variations across participants in relation to pain unpleasantness ratings and the stimulation temperature. This analysis was used to identify consistent features of BOLD responses in specific regions which were dependent on individual pain behaviours.

Bayesian regression was applied to each point in the BOLD time-series responses in each sub-region, for each individual, using pain unpleasantness ratings and stimulation temperatures as independent variables. The pain ratings and temperatures were first centred so the average values across all participants were equal to zero and scaled so that the largest differences from the average were equal to one. The data were then fit to approximate the consistent BOLD responses (S) at the average pain and temperature ratings (S_0), plus linear estimates of the BOLD variations with pain ratings (S_p) and temperature (S_t) (79): $S = S_0 + \text{pain rating } S_p + \text{temperature } S_t$. The fitting process therefore enables us to estimate BOLD response patterns (S_0) independent of individual differences in pain sensitivity or the stimulation temperature used, as well as to identify how the BOLD responses varied systematically across participants with different pain responses. The expected BOLD response for a region can thus be identified at the average stimulation temperature, as being $S_0 + S_p$ at the highest pain rating, and S_0 - S_p at the lowest pain rating.

RESULTS

Behavioural Results

Participants experienced a significant reduction in pain unpleasantness during the Music condition as compared to the No-Music condition, when the same temperature was applied. Pain unpleasantness ratings decreased by 13.8% from an average of 26.8 ± 13.4 to 23.1 ± 12.5 [mean ± standard deviation, $Z_{(19)} = -2.4$, $p < 0.017$], between the No-Music and Music conditions, respectively. Pain intensity ratings only decreased by 3.5% from 37.6 ± 12.4 (No-Music) to 36.3 ± 12.2 (Music), however this trend was not found to be significant across conditions ($Z_{(19)} = -1.10$, $p < 0.27$). Some degree of inter-subject variability was noted across participants within each condition, however a consistent trend of lowered pain ratings was observed during the Music condition (**Figure 4**).

Results of the Questionnaires to Assess Participant Characteristics

Group averages indicated that participants scored within normal ranges for all questionnaires including the STAI, SDS, BDI, and PCS (**Table 1**). Relationships between pain intensity, unpleasantness, normalised pain scores (pain unpleasantness/stimulation temperature), and questionnaire scores were investigated across the group using Spearman's rho correlations. Only two significant correlations were found

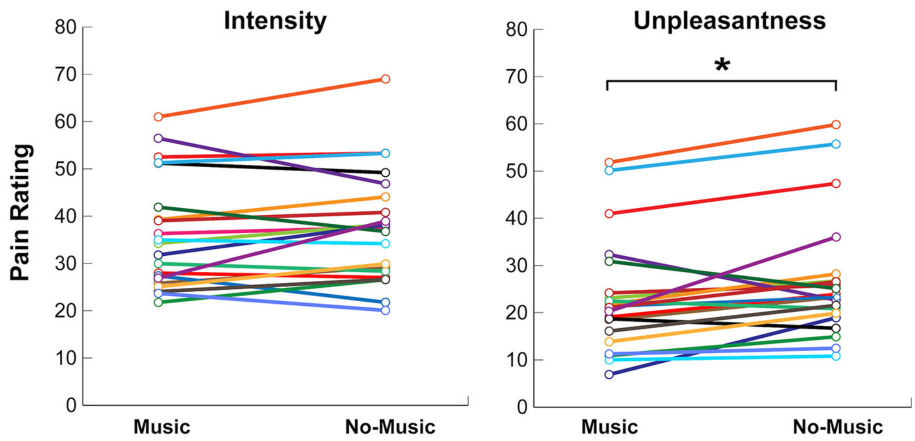

FIGURE 4 | Self-reported behavioural ratings for pain intensity and unpleasantness on numerical rating scales (NPS) during the Music and No-Music conditions. Each coloured line indicates a single participant. Significance at $p < 0.05$ is indicated (*).

between pain unpleasantness and BDI (*rho* (18) = −0.49, $p < 0.028$) and normalised pain score and BDI scores (*rho* (18) = −0.49, $p < 0.03$).

Functional MRI Results

Structural Equation Modelling

Significant connectivity was found within the network model during both study conditions, across all periods of the stimulation paradigm (i.e., before, during, and after noxious stimulation). Connections with weighting factors (β) significantly different than zero were observed across brain and brainstem regions and were mainly clustered at the level of the brain (PFC, ACC, PCC, insula, auditory cortex, thalamus, hippocampus, amygdala, NAc), with some projections to and from midbrain regions (PAG, VTA).

Analyses of Variance and Covariance

The results of the SEM analysis were used in secondary analyses to characterise the relationship between music, pain processing, timing of stimulation, and individual pain behaviours (normalised pain scores). An ANOVA (Condition X Stimulation) was implemented to observe the effect of music on pain processing in relation to the period of the stimulation paradigm. The results demonstrate significant main effects of Condition (Music vs. No-Music) and Stimulation (Before vs. During), in addition to one significant Interaction effect (**Table 2**). The main effect of stimulation was dominated by connections between the thalamus and insula, primarily from thalamus sub-region 4. Other connections impacted by the shift from before to during noxious stimulation (Time) include the following: amygdala → hippocampus, ACC → insula, insula → auditory cortex, and insula → amygdala. One connection was identified which was impacted by the study condition from the NAc → thalamus, and one connection from the hippocampus → thalamus revealed an interaction between study condition and stimulation effects.

An ANCOVA was used to investigate the relationship between the study condition and individual pain sensitivity using the normalised pain scores (Condition X Pain Score). A widespread set of connections across the brain and brainstem demonstrated significant main effects of Pain Scores and Condition, as well as one significant Interaction effect (**Table 3**). The ANCOVA identified significant effects of pain scores before and during noxious stimulation from the PCC → thalamus and the hippocampus → amygdala, respectively. An respectively. An example of this effect is shown in **Figure 5**, indicating a positive relationship between individual pain scores and connectivity strengths (β) for the hippocampus → amygdala connection during the experience of pain. The significant main effects of the study condition in this comparison were driven mainly by connections involving the hippocampus and thalamus. More specifically, we identified the following connections that differed across study conditions: **before stimulation**, hypothalamus → LC and NAc→ amygdala; **during stimulation**, hippocampus → thalamus and insula → amygdala; **after stimulation**, PCC → thalamus, hippocampus → amygdala, and auditory cortex → insula. Only one connection from the PAG → thalamus was identified to have significant interaction effects in the period after stimulation.

Bayesian Regression Results

The results of the Bayesian regression analysis provided average time-courses for all sub-regions at the median pain rating and temperature used. Here, we provide examples of average time-courses in the Music and No-Music conditions from specific sub-regions, as identified by the ANOVA and ANCOVA analyses (**Figure 6**). We chose to show these particular regions as they are involved in both affective and discriminatory aspects of pain, and they clearly indicate reactive and continuous neural activity in response to different periods of the stimulation paradigm. Details of BOLD responses for all ROIs and sub-regions in the Music and No-Music conditions can be found in **Supplementary Figures 1, 2**.

TABLE 1 | Results of questionnaires to characterise participants' individual characteristics and correlations with pain ratings and normalised pain scores in the No-Music condition.

	Questionnaire	Avg. Score ± SD	Percentile/Range	Intensity (*rho*)	Unpleasantness (*rho*)	Norm. Pain Score (*rho*)
STAI	State	31 ± 8	37%	−0.23	−0.36	−0.36
	Trait	34 ± 10	45%	0.04	0.03	0.33
SDS		16 ± 5	Average	−0.11	0.26	0.01
BDI		6 ± 7	Average	−0.20	−0.49*	−0.49*
PCS	Total	9 ± 7	22%	0.10	0.08	0.09
	Rumination	4 ± 3	23%	0.23	0.13	0.14
	Magnification	3 ± 2	47%	0.02	0.04	0.05
	Helplessness	2 ± 3	20%	0.01	0.03	0.03

STAI, State/Trait Anxiety Inventory; SDS, Social Desirability Scale; BDI, Beck Depression Inventory; and PCS, Pain Catastrophizing Scale with sub-domains of Rumination, Magnification and Helplessness. Average values and percentiles within normal distributions are indicated where available, or the assessment range is indicated. Correlation rho-values between questionnaire scores and each of pain intensity, unpleasantness and normalised pain scores are also listed, with significant values indicated with an asterisk (*) and df = 18 for all comparisons.

TABLE 2 | Results from the analysis of variance (ANOVA) comparing the effects of stimulation with the study condition (Condition X Stimulation).

ANOVA-Condition X Stimulation

	Source	Target	*p*-value	Source Sub-Region	Target Sub-Region
Stimulation					
	Thalamus	IC	3.09×10^{-8}	4	6
	Thalamus	IC	3.72×10^{-7}	4	1
	Thalamus	IC	6.01×10^{-7}	4	2
	Thalamus	IC	1.86×10^{-6}	4	3
	Thalamus	IC	2.95×10^{-6}	5	3
	Thalamus	IC	4.68×10^{-6}	4	4
	Amygdala	Hippocampus	4.90×10^{-6}	4	1
	Thalamus	IC	8.91×10^{-6}	4	5
	ACC	IC	9.77×10^{-6}	7	1
	Thalamus	IC	1.07×10^{-5}	5	6
	Thalamus	IC	1.48×10^{-5}	4	7
	IC	Auditory	1.55×10^{-5}	4	7
	Thalamus	IC	1.78×10^{-5}	5	2
	Thalamus	IC	1.82×10^{-5}	7	3
	IC	Amygdala	1.91×10^{-5}	6	4
	IC	Auditory	2.04×10^{-5}	1	7
Condition	NAc	Thalamus	1.45×10^{-5}	4	3
Interaction	Hippocampus	Thalamus	9.33×10^{-6}	7	3

Source indicates the modelled region providing input signalling to a modelled target region. The sub-region number indicates specific sub-regions out of seven for each region, which were identified by the ANOVA to have significant changes in connectivity based on Stimulation, Condition, or an Interaction.

DISCUSSION

This investigation provided evidence for behavioural and neural effects of music on the experience of pain in healthy individuals using functional MRI and showed that music affects pain regulation networks in specific ways. Compared with a No-Music condition, participants rated their pain unpleasantness significantly lower during the Music condition. This was reflected in significant network connectivity differences across conditions, in relation to normalised pain scores and the stimulus. Clear trends of cortico-limbic involvement in the effects of music reinforce the notion that music integrates cognitive, behavioural, emotional, and autonomic signalling to alter our perception of pain.

Although participants rated their pain unpleasantness 14% lower on average during the Music condition, their pain intensity scores, however, did not differ significantly across conditions. This is consistent with past behavioural studies of music analgesia which showed a decrease in unpleasantness but not intensity (10, 11), or a larger decrease in unpleasantness compared to intensity (4, 6), which could indicate that music analgesia involves more cognitive and affective modulation strategies than

TABLE 3 | Results from the analysis of covariance (ANCOVA) comparing individual pain scores to the study condition (Condition X Pain Score) at all time periods of the paradigm (before, during, and after stimulation). Source indicates the modelled region providing input signalling to a modelled target region.

ANCOVA-Condition X Pain Score

		Source	Target	*p*-value	Source Sub-Region	Target Sub-Region
Main effect of pain score	Before stim	PCC	Thalamus	1.82×10^{-5}	1	3
	During stim	Hippocampus	Amygdala	1.99×10^{-5}	5	4
	After stim	-	-	-	-	-
Main effect of Study condition	Before stim	Hypothalamus	LC	4.17×10^{-6}	4	5
		NAc	Thalamus	5.62×10^{-6}	4	3
	During stim	Hippocampus	Thalamus	4.37×10^{-6}	7	7
		Hippocampus	Thalamus	8.32×10^{-6}	7	3
		IC	Amygdala	2.04×10^{-5}	7	3
	After stim	PCC	Thalamus	3.98×10^{-6}	7	5
		Hippocampus	Amygdala	1.55×10^{-5}	3	6
		Auditory	IC	2.14×10^{-5}	6	1
Interaction effect	Before stim	-	-	-	-	-
	During stim	-	-	-	-	-
	After stim	PAG	Thalamus	7.76×10^{-6}	6	7

The sub-region number indicates specific sub-regions out of seven for each region, which were identified by the ANCOVA to have significant changes in connectivity based on Pain Scores, Condition, or Interaction effects.

sensory/discriminative effects. Music has also been shown to significantly decrease pain intensity alone (5, 7, 37), however these studies did not include measures of pain unpleasantness. A recent review rejects the focus on reduction of pain intensity as a one-dimensional assessment of the pain experience, as it fails to reflect emotional and cognitive dimensions included in the contemporary holistic clinical approach of pain management (55). Cognitive and emotional pain modulation strategies may arise from familiarity, reward, and positive emotional valences that each participant attributed to their selections of music (i.e., happy, stimulating, etc.), leading to passive distraction from the acute experimental pain, as previously suggested (6, 18).

Significant relationships were found between pain unpleasantness scores and depression, and normalised pain scores and depression, however these measures are related via the stimulation temperature. Although no other relationships were found, it has been previously shown that personal characteristics including emotional and cognitive state, pain catastrophizing, autonomic symptoms, and familiarity with music significantly impact the pain experience, however a larger sample size is required to elucidate these behavioural relationships (6, 12, 18, 80–83). Additionally, a range of scores were recorded for each questionnaire, but most responders fell in the "normal" or average range, therefore no meaningful correlations could be established.

Analyses of variance identified specific differences in connectivity, as calculated by SEM, which were dependent on changes across study conditions and time periods within the stimulation paradigm. Main effects of noxious stimulation dominate the comparison, specifically differences between periods before and during noxious stimulation, indicating that stimulation itself produces larger effects on connectivity than music. Multiple connections between the thalamus and insula differed in strength between these periods, which may indicate strong reactive responses to pain in these regions. The thalamus is an important integration centre for afferent sensory input,

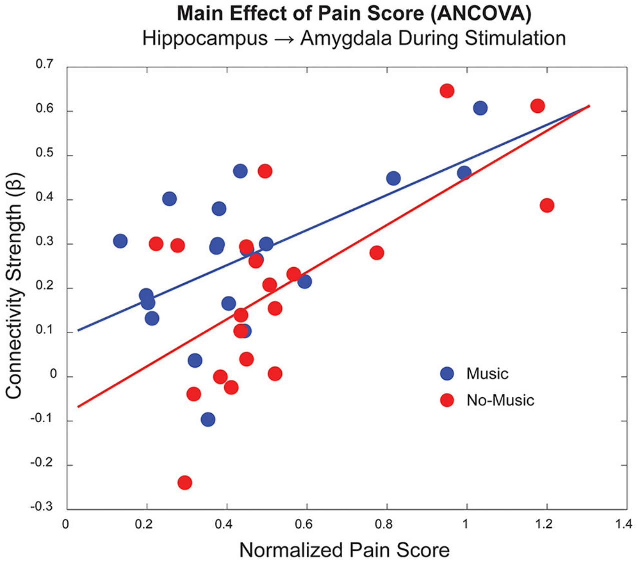

FIGURE 5 | Example of a main effect of pain score for a connection between the hippocampus and amygdala in the period during noxious stimulation, as shown in **Table 3** ($p < 1.99 \times 10^{-5}$). The horizontal axis indicates the average normalised pain score for each participant/condition, and the vertical axis indicates the connectivity strength (β) for this particular connection. The Music condition is displayed in blue, and the No-Music condition in red.

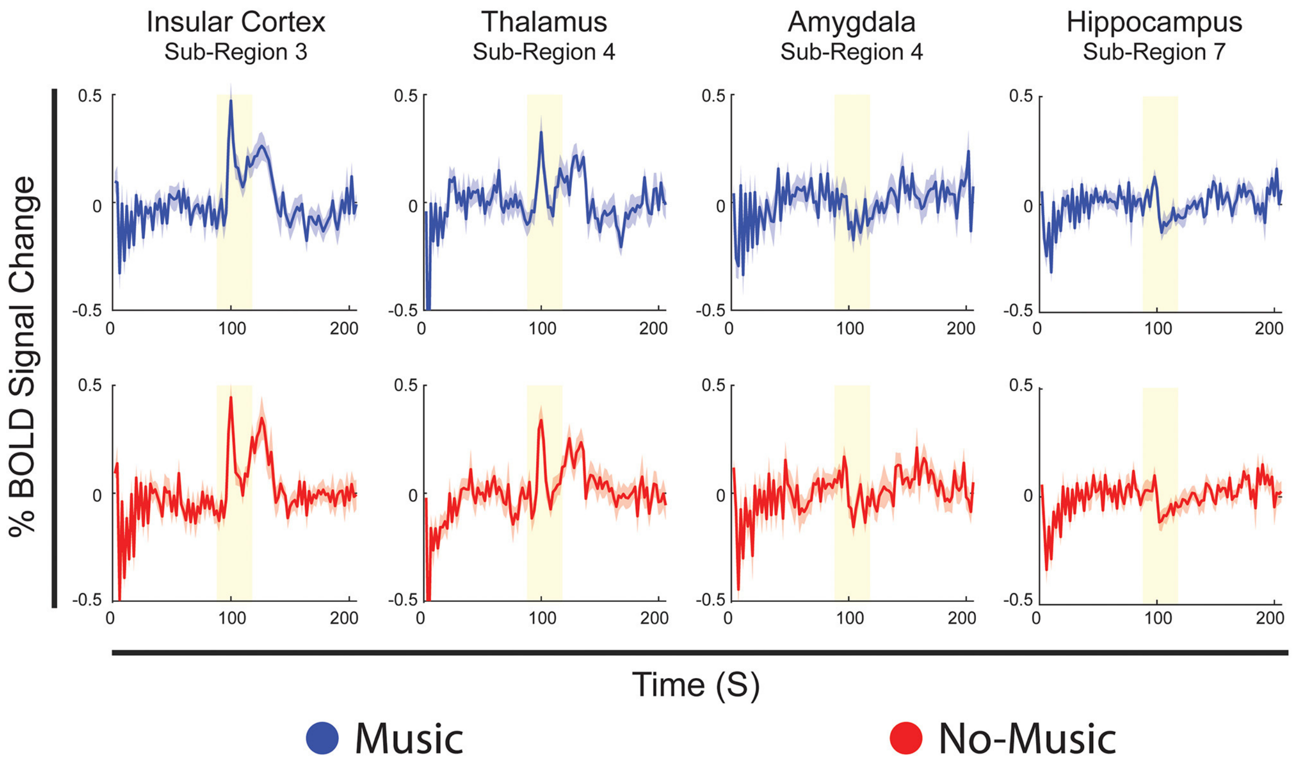

FIGURE 6 | Examples of Bayesian regression results showing average BOLD time-courses from specific sub-regions, identical for both conditions, selected from the analyses of variance and covariance. Time-courses are displayed in blue for the Music condition, and red for the No-Music condition. The vertical axis indicates percent BOLD signal change from the mean and the horizontal axis indicates time in seconds. The vertical yellow bar indicates the period of noxious stimulation.

and it relays noxious information to the posterior insular cortex which, in turn, acts as an integration point for nociception, emotion, salience, interoception, and autonomic homeostatic information (56, 57, 84, 85). This effect is also seen in results of the Bayesian regression (**Figure 6**), which demonstrate primarily reactive BOLD responses to noxious stimulation in both conditions in the insula and thalamus.

An effect of music was seen in all periods of the stimulation paradigm, compared with fewer effects of pain scores, and one interaction, calculated via analysis of covariance. Interestingly, insular connectivity that was affected by the study condition occurred only in the periods during and after stimulation, echoing the reactive, salient, effect of stimulation seen in ANOVA and Bayesian regression results in the insula. The involvement of the insula in the period after stimulation also supports evidence for integration of affective, cognitive, homeostatic, and interoceptive function, as participants experienced lingering after-sensations from noxious stimulation during this period and had opportunities to reflect on and appraise the pain that they had just felt (37, 56, 86). Affective processing surrounding the pain experience can also be inferred from this insular connection to the auditory cortex due to previous evidence for IC responses to emotional contents of auditory stimuli (87). Furthermore, music impacted connections between insula → amygdala and hippocampus → thalamus during the experience of pain, highlighting integration of limbic input in the effect of music analgesia of music analgesia (37, 88).

The ANCOVA also demonstrated a main effect of pain scores in two connections in the periods before and during noxious stimulation, indicating a potential priming effect of individuals' pain history and sensitivity on anticipation and sensation of pain. In the period before stimulation, participants experienced predictable anticipation of the impending pain, using this time for any natural behaviours including internally directed thought, daydreaming, expectation, etc. This effect may be inferred from a connection prior to stimulation between the PCC and thalamus, regions involved in the default mode network which is implicated in internally directed thought (89, 90). While the broad functions of the PCC are debated, it has been associated with emotional salience, discriminative avoidance learning, planning, attention, and episodic memory (90–92). The PCC and thalamus are both densely connected to limbic and paralimbic structures, including the amygdala and hippocampus, further implicating cognitive and emotional integration strategies in pain modulation (89, 93). The relationship with individual pain scores reinforces this suggestion as they relate to individual differences, memory, and cognitive/emotional appraisal of pain. Differences in cognitive strategies for pain modulation have been shown to be mediated by communication between regions involved in executive control and those involved with the "salience network" which includes many limbic regions (85, 94). Interestingly, connectivity between the amygdala and the hippocampus, largely involved with learning, memory, and emotion (95), varies based on pain scores during the period of noxious stimulation. This connection may further demonstrate the effects of personal pain history and sensitivity on the cognitive/emotional context during the subjective experience of pain. The strong relationship between pain behaviours and neural activity can be seen in the plot of this connection between these two regions during noxious stimulation (**Figure 5**).

Bayesian regression analyses demonstrate temporal properties of BOLD responses and show predictable, reactive responses to noxious stimulation in regions such as the insula and thalamus, indicating predominantly sensory/discriminative signalling effects. Regions such as the amygdala and hippocampus show more continuous signalling, suggesting potential cognitive/affective integration across the paradigm (**Figure 6**). While reactive responses to the stimulus are quite similar across conditions in the insula and thalamus, the amygdala and hippocampus show greater changes in signal amplitude across conditions during stimulation. This further reinforces the notion that limbic regions may work to modulate our perception of pain as we anticipate, experience, and recover from it, rather than simply reacting to a noxious sensation. Noticeable differences in BOLD signal fluctuations across Music and No-Music conditions are seen in the periods before and after stimulation in all regions, indicating altered anticipation and relief across conditions. Lastly, regions such as the insula, frontal cortex, and ACC reacted most strongly to a change in the period of the stimulation paradigm (i.e., onset of scanning, onset/offset of pain), suggesting that salience to a change in our environment plays a role in the holistic experience of pain (**Supplementary Figures 1, 2**) (96, 97).

Although this study demonstrated important broad effects of music analgesia across neural networks in the brain and brainstem, there are limitations to consider. While there is a wealth of behavioural knowledge regarding music analgesia, there is limited functional neurological data to build upon. Functional MRI is an inherently indirect method and, as such, provides information about neural activity via changes in blood oxygenation, which are related to the local metabolic demand. However, we do not have information regarding excitatory or inhibitory signalling. Additionally, the noise of the scanner may compete with the sound of the music, potentially confounding the analgesic effects. SEM is based on a pre-determined anatomical model and therefore contains limited information, for example some possible anatomical connections were omitted to decrease the number of multiple comparisons and necessary computing power. Even so, we were limited to describing the main findings related to the hypothesis, as these analyses produce too many detailed results to discuss in one text. Additionally, to maximise data quality in small brainstem regions, our field of view omitted superior regions of the cortex and therefore we could not capture the primary somatosensory cortex, which is directly involved in the sensory experience of pain. The fMRI methods were optimised for brain regions, and challenges with imaging in the lower brainstem regions may also have limited BOLD sensitivity in these regions. Our goal when calibrating the stimulation temperature is to produce the same approximate pain intensity (i.e., moderate pain) in all participants. As seen in **Figure 5**, the individual differences in normalised pain scores (pain unpleasantness rating / temperature °C) are closely related to the connectivity values seen across participants and conditions. Despite individual variability across participants we were still able to detect significant differences in network connectivity between Music and No-Music conditions, providing evidence for a neural basis of music analgesia. Additional investigations should be undertaken in the future to specifically address individual differences in functional data of this type and extend the age range beyond young adults. Finally, it is difficult to distinguish effects of cognition, emotion, salience, attention/distraction, and expectation of treatment (music), as these are closely linked. None the less, we believe that our results accurately reflect the complex network of interconnected regions with many functions that contribute to the pain experience (98).

Here, we have provided evidence for the behavioural and neural effects of music analgesia through individual ratings of pain, and changes in network connectivity by means of fMRI. The effect of music on pain perception appears to involve cognition, emotion, memory, salience, and multi-sensory integration, and serves to reduce primarily the unpleasantness of pain. Connecting with music on an emotional level may have the advantage of reducing pain in predictable scenarios such as medical procedures and positively impact the quality of life and daily function of those living with chronic pain.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PS and JP designed the study and carried out data analysis. PS, JP, and GI carried out data collection. All authors have read and approved of the paper. All authors contributed to interpretation of the results and writing of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpain.2022.878258/full#supplementary-material

REFERENCES

1. Cepeda MS, Carr DB, Lau J, Alvarez H. Music for pain relief. *Cochrane Database Syst Rev.* (2006) 2:CD004843. doi: 10.1002/14651858.CD004843.pub2
2. Lu X, Yi F, Hu L. Music-induced analgesia: an adjunct to pain management. *Psychol Music.* (2021) 49:1165–78. doi: 10.1177/0305735620928585
3. Lunde SJ, Vuust P, Garza-Villarreal EA, Vase L. Music-induced analgesia: how does music relieve pain? *Pain.* (2019) 160:989–93. doi: 10.1097/j.pain.0000000000001452
4. Hsieh C, Kong J, Kirsch I, Edwards RR, Jensen KB, Kaptchuk TJ, et al. Well-loved music robustly relieves pain: a randomized, controlled trial. *PLoS ONE.* (2014) 9:e107390. doi: 10.1371/journal.pone.0107390
5. Mitchell LA, MacDonald RA. An experimental investigation of the effects of preferred and relaxing music listening on pain perception. *J Music Ther.* (2006) 43:295–316. doi: 10.1093/jmt/43.4.295
6. Garza-Villarreal EA, Wilson AD, Vase L, Brattico E, Barrios FA, Jensen TS, et al. Music reduces pain and increases functional mobility in fibromyalgia. *Front Psychol.* (2014) 5:90. doi: 10.3389/fpsyg.2014.00090
7. Perlini AH, Viita KA. Audioanalgesia in the control of experimental pain. *Can J Behav Sci.* (1996) 28:292–301. doi: 10.1037/0008-400X.28.4.292
8. Pando-Naude V, Barrios FA, Alcauter S, Pasaye EH, Vase L, Brattico E, et al. Functional connectivity of music-induced analgesia in fibromyalgia. *Sci Rep.* (2019) 9:15486. doi: 10.1038/s41598-019-51990-4
9. Cabon MLF-B A, Genestet S, Quinio B, Misery L, Woda A, Bodéré C. Impact of music on first pain and temporal summation of second pain: a psychophysical pilot study. *Music Percept.* (2021) 38:267–81. doi: 10.1525/mp.2021.38.3.267
10. Lu X, Thompson WF, Zhang L, Hu L. Music reduces pain unpleasantness: evidence from an EEG study. *J Pain Res.* (2019) 12:3331–42. doi: 10.2147/JPR.S212080
11. Garcia RL, Hand CJ. Analgesic effects of self-chosen music type on cold pressor-induced pain: motivating vs. relaxing music. *Psychol Music.* (2016) 44:967–83. doi: 10.1177/0305735615602144
12. Chai PR, Gale JY, Patton ME, Schwartz E, Jambaulikar GD, Wade Taylor S, et al. The impact of music on nociceptive processing. *Pain Med.* (2020) 21:3047–54. doi: 10.1093/pm/pnaa070
13. Antioch I, Furuta T, Uchikawa R, Okumura M, Otogoto J, Kondo E, et al. Favorite music mediates pain-related responses in the anterior cingulate cortex and skin pain thresholds. *J Pain Res.* (2020) 13:2729–37. doi: 10.2147/JPR.S276274
14. Furuta T. The effects of auditory stimulation with pleasant and unpleasant sound on the pain threshold of gingiva and skin. *Oral Health Dent Sci.* (2019) 3:1–5. doi: 10.33425/2639-9490.1044
15. Lee JH. The effects of music on pain: a meta-analysis. *J Music Ther.* (2016) 53:430–77. doi: 10.1093/jmt/thw012
16. Hauck M, Metzner S, Rohlffs F, Lorenz J, Engel AK. The influence of music and music therapy on pain-induced neuronal oscillations measured by magnetencephalography. *Pain.* (2013) 154:539–47. doi: 10.1016/j.pain.2012.12.016
17. Mitchell LA, MacDonald RA, Brodie EE. A comparison of the effects of preferred music, arithmetic and humor on cold pressor pain. *Eur J Pain.* (2006) 10:343–51. doi: 10.1016/j.ejpain.2005.03.005
18. Pereira CS, Teixeira J, Figueiredo P, Xavier J, Castro SL, Brattico E. Music and emotions in the brain: familiarity matters. *PLoS ONE.* (2011) 6:e27241. doi: 10.1371/journal.pone.0027241
19. Villemure C, Bushnell MC. Cognitive modulation of pain: how do attention and emotion influence pain processing? *Pain.* (2002) 95:195–9. doi: 10.1016/S0304-3959(02)00007-6
20. Vuilleumier P. How brains beware: neural mechanisms of emotional attention. *Trends Cogn Sci.* (2005) 9:585–94. doi: 10.1016/j.tics.2005.10.011
21. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron.* (2007) 55:377–91. doi: 10.1016/j.neuron.2007.07.012
22. Li X, Hu L. The role of stress regulation on neural plasticity in pain chronification. *Neural Plast.* (2016) 2016:6402942. doi: 10.1155/2016/6402942
23. McKinney CH, Antoni MH, Kumar M, Tims FC, McCabe PM. Effects of guided imagery and music (GIM) therapy on mood and cortisol in healthy adults. *Health Psychol.* (1997) 16:390–400. doi: 10.1037/0278-6133.16.4.390
24. McKinney CH, Tims FC, Kumar AM, Kumar M. The effect of selected classical music and spontaneous imagery on plasma beta-endorphin. *J Behav Med.* (1997) 20:85–99. doi: 10.1023/A:1025543330939
25. Salimpoor VN, Benovoy M, Larcher K, Dagher A, Zatorre RJ. Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nat Neurosci.* (2011) 14:257–62. doi: 10.1038/nn.2726
26. Chai PR, Carreiro S, Ranney ML, Karanam K, Ahtisaari M, Edwards R, et al. Music as an adjunct to opioid-based analgesia. *J Med Toxicol.* (2017) 13:249–54. doi: 10.1007/s13181-017-0621-9
27. Stefano GB, Zhu W, Cadet P, Salamon E, Mantione KJ. Music alters constitutively expressed opiate and cytokine processes in listeners. *Med Sci Monit.* (2004) 10:MS18–27.
28. Blood AJ, Zatorre RJ. Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proc Natl Acad Sci U S A.* (2001) 98:11818–23. doi: 10.1073/pnas.191355898
29. Wise RA. Dopamine, learning and motivation. *Nat Rev Neurosci.* (2004) 5:483–94. doi: 10.1038/nrn1406
30. Salimpoor VN, Zald DH, Zatorre RJ, Dagher A, McIntosh AR. Predictions and the brain: how musical sounds become rewarding. *Trends Cogn Sci.* (2015) 19:86–91. doi: 10.1016/j.tics.2014.12.001
31. Zatorre RJ. Musical pleasure and reward: mechanisms and dysfunction. *Ann N Y Acad Sci.* (2015) 1337:202–11. doi: 10.1111/nyas.12677
32. Tu Y, Bi Y, Zhang L, Wei H, Hu L. Mesocorticolimbic pathways encode cue-based expectancy effects on pain. *J Neurosci.* (2020) 40:382–94. doi: 10.1523/JNEUROSCI.1082-19.2019
33. Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, et al. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *J Neurosci.* (2001) 21:9896–903. doi: 10.1523/JNEUROSCI.21-24-09896.2001
34. Reynolds DV. Surgery in the rat during electrical analgesia induced by focal brain stimulation. *Science.* (1969) 164:444–5. doi: 10.1126/science.164.3878.444
35. Fields HL, Basbaum AI. Central nervous system mechanisms of pain modulation. In: Wall PD, Melzack R, editors. Textbook of Pain. New York, NY: Churchill Livingstone (1994). p. 243–57.
36. Potvin S, Grignon S, Marchand S. Human evidence of a supra-spinal modulating role of dopamine on pain perception. *Synapse.* (2009) 63:390–402. doi: 10.1002/syn.20616
37. Dobek CE, Beynon ME, Bosma RL, Stroman PW. Music modulation of pain perception and pain-related activity in the brain, brain stem, and spinal cord: a functional magnetic resonance imaging study. *J Pain.* (2014) 15:1057–68. doi: 10.1016/j.jpain.2014.07.006
38. Dunbar RI, Kaskatis K, MacDonald I, Barra V. Performance of music elevates pain threshold and positive affect: implications for the evolutionary function of music. *Evol Psychol.* (2012) 10:688–702. doi: 10.1177/147470491201000403

39. Garza-Villarreal EA, Jiang Z, Vuust P, Alcauter S, Vase L, Pasaye EH, et al. Music reduces pain and increases resting state fMRI BOLD signal amplitude in the left angular gyrus in fibromyalgia patients. *Front Psychol.* (2015) 6:1051. doi: 10.3389/fpsyg.2015.01051
40. Roy M, Lebuis A, Hugueville L, Peretz I, Rainville P. Spinal modulation of nociception by music. *Eur J Pain.* (2012) 16:870–7. doi: 10.1002/j.1532-2149.2011.00030.x
41. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of beck depression inventories -IA and -II in psychiatric outpatients. *J Pers Assess.* (1996) 67:588–97. doi: 10.1207/s15327752jpa6703_13
42. Spielberger CD. State-Trait Anxiety Inventory for Adults (STAI-AD). *APA PsycTests*. (1983) doi: 10.1039/t06496-000
43. Crowne DP, Marlowe D. A new scale of social desirability independent of psychopathology. *J Consult Psychol.* (1960) 24:349–54. doi: 10.1037/h0047358
44. Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess.* (1995) 7:524. doi: 10.1037/1040-3590.7.4.524
45. Garza-Villarreal EA, Pando V, Vuust P, Parsons C. Music-induced analgesia in chronic pain conditions: a systematic review and meta-analysis. *Pain Physician.* (2017) 20:597–610. doi: 10.36076/ppj/2017.7.597
46. Vierck CJ. Jr., Cannon RL, Fry G, Maixner W, Whitsel BL. Characteristics of temporal summation of second pain sensations elicited by brief contact of glabrous skin by a preheated thermode. *J Neurophysiol.* (1997) 78:992–1002. doi: 10.1152/jn.1997.78.2.992
47. Price DD, Hu JW, Dubner R, Gracely RH. Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. *Pain.* (1977) 3:57–68. doi: 10.1016/0304-3959(77)90035-5
48. Staud R, Cannon RC, Mauderli AP, Robinson ME, Price DD, Vierck CJ. Jr. Temporal summation of pain from mechanical stimulation of muscle tissue in normal controls and subjects with fibromyalgia syndrome. *Pain.* (2003) 102:87–95. doi: 10.1016/s0304-3959(02)00344-5
49. Yessick LR, Pukall CF, Ioachim G, Chamberlain SM, Stroman PW. An investigation of descending pain modulation in women with Provoked Vestibulodynia (PVD): alterations of spinal cord and brainstem connectivity. *Front Pain Res*. (2021) 2:682483. doi: 10.3389/fpain.2021.682483
50. Bosma RL, Stroman PW. Spinal cord response to stepwise and block presentation of thermal stimuli: a functional MRI study. *J Magn Reson Imaging.* (2014) 41:1318–25. doi: 10.1002/jmri.24656
51. Stroman PW, Powers JM, Ioachim G, Warren HJM, McNeil K. Investigation of the neural basis of expectation-based analgesia in the human brainstem and spinal cord by means of functional magnetic resonance imaging. *Neurobiol Pain.* (2021) 10:100068. doi: 10.1016/j.ynpai.2021.100068
52. Staud R, Craggs JG, Robinson ME, Perlstein WM, Price DD. Brain activity related to temporal summation of C-fiber evoked pain. *Pain.* (2007) 129:130–42. doi: 10.1016/j.pain.2006.10.010
53. Staud R, Robinson ME, Price DD. Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. *J Pain.* (2007) 8:893–901. doi: 10.1016/j.jpain.2007.06.006
54. Millan MJ. Descending control of pain. *Prog Neurobiol.* (2002) 66:355–474. doi: 10.1016/S0301-0082(02)00009-6
55. Porreca F, Navratilova E. Reward, motivation, and emotion of pain and its relief. *Pain.* (2017) 158:S43–9. doi: 10.1097/j.pain.0000000000000798
56. Craig AD. Interoception: the sense of the physiological condition of the body. *Curr Opin Neurobiol.* (2003) 13:500–5. doi: 10.1016/S0959-4388(03)00090-4
57. Craig AD. A new view of pain as a homeostatic emotion. *Trends Neurosci.* (2003) 26:303–7. doi: 10.1016/S0166-2236(03)00123-1
58. Warren HJM, Ioachim G, Powers JM, Stroman PW. How fMRI -Fibromyalgia. *J Pain Res.* (2021) 14:381–98. doi: 10.2147/JPR.S290795
59. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect.* (2012) 2:125–41. doi: 10.1089/brain.2012.0073
60. Liebe T, Kaufmann J, Li M, Skalej M, Wagner G, Walter M. *In vivo* anatomical mapping of human locus coeruleus functional connectivity at 3 T MRI. *Hum Brain Mapp.* (2020) 41:2136–51. doi: 10.1002/hbm.24935
61. Chiang MC, Bowen A, Schier LA, Tupone D, Uddin O, Heinricher MM. Parabrachial complex: a hub for pain and aversion. *J Neurosci.* (2019) 39:8225–30. doi: 10.1523/JNEUROSCI.1162-19.2019
62. Naidich TP, Duvernoy HM, Delman BN, Sorensen AG, Kollias SS, Haacke EM. *Internal Architecture of the Brain Stem With Key Axial Sections. Duvernoy's Atlas of the Human Brain Stem and Cerebellum*. New York, NY: Springer-Verlag/Wien (2009). p. 79–82. doi: 10.1007/978-3-211-73971-6
63. Talairach J, Tournoux P. *Co-Planar Stereotaxic Atlas of the Human Brain*. New York NY: Thieme Medical Publishers, Inc. (1988).
64. Leijnse JN, D'Herde K. Revisiting the segmental organization of the human spinal cord. *J Anat.* (2016) 229:384–93. doi: 10.1111/joa.12493
65. Pauli WM, Nili AN, Tyszka JM. A high-resolution probabilistic *in vivo* atlas of human subcortical brain nuclei. *Sci Data.* (2018) 5:180063. doi: 10.1038/sdata.2018.63
66. Keren NI, Lozar CT, Harris KC, Morgan PS, Eckert MA. *In vivo* mapping of the human locus coeruleus. *Neuroimage.* (2009) 47:1261–7. doi: 10.1016/j.neuroimage.2009.06.012
67. Stroman PW. Validation of structural equation modeling methods for functional MRI data acquired in the human brainstem and spinal cord. *Crit Rev Biomed Eng.* (2016) 44:227–41. doi: 10.1615/CritRevBiomedEng.2017020438
68. Stroman PW, Warren HJM, Ioachim G, Powers JM, McNeil K. A comparison of the effectiveness of functional MRI analysis methods for pain research: the new normal. *PLoS ONE.* (2020) 15:e0243723. doi: 10.1371/journal.pone.0243723
69. Bosma RL, Ameli Mojarad E, Leung L, Pukall C, Staud R, Stroman PW. Neural correlates of temporal summation of second pain in the human brainstem and spinal cord. *Hum Brain Mapp.* (2015) 36:5038–50. doi: 10.1002/hbm.22993
70. Khan HS, Stroman PW. Inter-individual differences in pain processing investigated by functional magnetic resonance imaging of the brainstem and spinal cord. *Neuroscience.* (2015) 307:231–41. doi: 10.1016/j.neuroscience.2015.08.059
71. Bosma RL, Mojarad EA, Leung L, Pukall C, Staud R, Stroman PW, et al. FMRI of spinal and supra-spinal correlates of temporal pain summation in fibromyalgia patients. *Hum Brain Mapp.* (2016) 37:1349–60. doi: 10.1002/hbm.23106
72. Craig AD. How do you feel? interoception*:* the sense of the physiological condition of the body nature reviews. *Neuroscience.* (2002) 3:655–66. doi: 10.1038/nrn894
73. Harita S, Ioachim G, Powers J, Stroman PW. Investigation of resting-state BOLD networks in the human brainstem and spinal cord. *Neuroscience.* (2019) 404:71–81. doi: 10.1016/j.neuroscience.2019.02.009
74. Ioachim G, Powers JM, Stroman PW. Comparing coordinated networks across the brainstem and spinal cord in the resting state and altered cognitive state. *Brain Connect.* (2019) 9:415–24. doi: 10.1089/brain.2018.0659
75. Ioachim G, Powers JM, Warren HJM, Stroman PW. Coordinated human brainstem and spinal cord networks during the expectation of pain have elements unique from resting-state effects. *Brain Sci*. (2020) 10:568. doi: 10.3390/brainsci10090568
76. Stroman PW, Ioachim G, Powers JM, Staud R, Pukall C. Pain processing in the human brainstem and spinal cord before, during and after the application of noxious heat stimuli. *Pain.* (2018) 159:2012–20. doi: 10.1080/24740527.2019.1591821
77. Harita S, Stroman PW. Confirmation of resting-state BOLD fluctuations in the human brainstem and spinal cord after identification and removal of physiological noise. *Magn Reson Med.* (2017) 78:2149–56. doi: 10.1002/mrm.26606
78. Stroman PW, Ioachim G, Powers JM, Staud R, Pukall C. Pain processing in the human brainstem and spinal cord before, during, and after the application of noxious heat stimuli. *Pain.* (2018) 159:2012–20.
79. Stroman PW, Ioachim G, Powers JM, Staud R, Pukall C. Pain processing in the human brainstem and spinal cord before, during, and after the application of noxious heat stimuli. *Pain.* (2018) 159:2012–20. doi: 10.1097/j.pain.0000000000001302
80. Kornelsen J, McIver TA, Stroman PW. Unique brain regions involved in positive versus negative emotional modulation of pain. *Scand J Pain.* (2019) 19:583–96. doi: 10.1515/sjpain-2018-0341
81. McIver TA, Kornelsen J, Stroman PW. Diversity in the emotional modulation of pain perception: an account of individual variability. *Eur J Pain.* (2018) 22:319–32. doi: 10.1002/ejp.1122

82. Tracey I, Ploghaus A, Gati JS, Clare S, Smith S, Menon RS, et al. Imaging attentional modulation of pain in the periaqueductal gray in humans. *J Neurosci.* (2002) 22:2748–52. doi: 10.1523/JNEUROSCI.22-07-02748.2002
83. Villemure C, Bushnell MC. Mood influences supraspinal pain processing separately from attention. *J Neurosci.* (2009) 29:705–15. doi: 10.1523/JNEUROSCI.3822-08.2009
84. Lu C, Yang T, Zhao H, Zhang M, Meng F, Fu H, et al. Insular cortex is critical for the perception, modulation, and chronification of pain. *Neurosci Bull.* (2016) 32:191–201. doi: 10.1007/s12264-016-0016-y
85. Seeley WW. The salience network: a neural system for perceiving and responding to homeostatic demands. *J Neurosci.* (2019) 39:9878–82. doi: 10.1523/JNEUROSCI.1138-17.2019
86. Xue G, Lu Z, Levin IP, Bechara A. The impact of prior risk experiences on subsequent risky decision-making: the role of the insula. *Neuroimage.* (2010) 50:709–16. doi: 10.1016/j.neuroimage.2009.12.097
87. Zhang Y, Zhou W, Wang S, Zhou Q, Wang H, Zhang B, et al. The roles of subdivisions of human insula in emotion perception and auditory processing. *Cereb Cortex.* (2019) 29:517–28. doi: 10.1093/cercor/bhx334
88. Thompson JM, Neugebauer V. Cortico-limbic pain mechanisms. *Neurosci Lett.* (2019) 702:15–23. doi: 10.1016/j.neulet.2018.11.037
89. Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. *Brain.* (2014) 137:12–32. doi: 10.1093/brain/awt162
90. Brewer JA, Garrison KA, Whitfield-Gabrieli S. What about the "Self" is processed in the posterior cingulate cortex? *Front Hum Neurosci.* (2013) 7:647. doi: 10.3389/fnhum.2013.00647
91. Maddock RJ, Garrett AS, Buonocore MH. Posterior cingulate cortex activation by emotional words: fMRI evidence from a valence decision task. *Hum Brain Mapp.* (2003) 18:30–41. doi: 10.1002/hbm.10075
92. Maddock RJ, Garrett AS, Buonocore MH. Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval. *Neuroscience.* (2001) 104:667–76. doi: 10.1016/S0306-4522(01)00108-7
93. Robertson RT, Kaitz SS. Thalamic connections with limbic cortex. I thalamocortical projections *J Comp Neurol.* (1981) 195:501–25. doi: 10.1002/cne.901950308
94. Cheng JC, Bosma RL, Hemington KS, Kucyi A, Lindquist MA, Davis KD. Slow-5 dynamic functional connectivity reflects the capacity to sustain cognitive performance during pain. *Neuroimage.* (2017) 157:61–8. doi: 10.1016/j.neuroimage.2017.06.005
95. Anand KS, Dhikav V. Hippocampus in health and disease: an overview. *Ann Indian Acad Neurol.* (2012) 15:239–46. doi: 10.4103/0972-2327.104323
96. Taylor KS, Seminowicz DA, Davis KD. Two systems of resting state connectivity between the insula and cingulate cortex. *Hum Brain Mapp.* (2009) 30:2731–45. doi: 10.1002/hbm.20705
97. Legrain V, Iannetti GD, Plaghki L, Mouraux A. The pain matrix reloaded: a salience detection system for the body. *Prog Neurobiol.* (2011) 93:111–24. doi: 10.1016/j.pneurobio.2010.10.005
98. Moayedi M, Salomons TV, Atlas LY. Pain neuroimaging in humans: a primer for beginners and non-imagers. *J Pain.* (2018) 19:e1–21. doi: 10.1016/j.jpain.2018.03.011

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Improvement of pain experience and changes in heart rate variability through music-imaginative pain treatment

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Music-imaginative Pain Treatment (MIPT) is a form of music therapy addressing pain experience and affective attitudes toward pain. It includes two self-composed music pieces: one dedicated to the pain experience (pain music, PM) and the other to healing imagination (healing music, HM). Our non-experimental study addresses patients with chronic somatoform pain disorders participating in MIPT. The goal is to gain insight into the direct effect mechanisms of MIPT by combining outcome measures on both the objective physiological and subjective perception levels. The research questions are directed toward changes in pain experience and heart rate variability and their correlations. Thirty-seven hospitalized patients with chronic or somatoform pain disorders receiving MIPT participated in this study. Demographic data and psychometric measures (Symptom Check List SCL90, Childhood Trauma Questionnaire CTQ) were collected to characterize the sample. Subjective pain experience was measured by McGill Pain Questionnaire (SF-MPQ), and Heart Rate Variability by 24 h-ECG. Data analysis shows a reduction of reported pain from $M_{T1} = 19.1$ (SD = 7.3) to $M_{T2} = 10.6$ (SD = 8.0) in all dimensions of the SF-MPQ. HRV analyses shows a reduced absolute power during PM and HM, while a relative shift in the autonomic system toward higher vagal activity appears during HM. Significant correlations between HRV and MPQ could not be calculated. Findings are interpreted as a physiological correlate to the psychological processes of the patients. Future studies with more participants, a control-group design, and the integration of medium- and long-term effects are recommended.

KEYWORDS

psychosomatics, somatoform pain disorder, music-imaginative pain treatment, heart rate variability, pain perception

Introduction

Music-imaginative pain treatment for chronic pain

In the context of pain treatment common music interventions utilize the simple listening to recorded music with the aim to enhance relaxation or distraction in painful situations. In contrast to this, professional music therapy focusses on psychic or interactive processes set in motion by playing music or listening to it. This corresponds to a more active involvement through emotional engagement and cognitive reflection within a therapeutic relationship. This approach is particularly relevant for chronic pain disorders.

In Germany, music therapy has a long tradition as part of the multi-professional treatment of hospitalized patients in departments for psychosomatic medicine (1). According to the national S3-guideline on "non-specific, functional and somatoform physical complaints" (2), music therapy is mentioned as a viable accompanying therapy approach, particularly for severe courses of disease. In this context, Music-imaginative Pain Treatment (MIPT) is an intervention that proves to be increasingly successful. It was initially developed as "entrainment" within a single session (3, 4) and later established as a manualized treatment by Metzner (5).

MIPT makes use of live music. In a room equipped with various musical instruments, the patient develops two pieces of music with the assistance of a trained music therapist. The first composition corresponds to the patient's experience of pain ("pain music"), while the other explores the ideas, or imaginations, of relief ("healing music"). Thereafter the therapist performs the two pieces of music, one after the other, as the patient is listening (application phase). MIPT involves a trusting, supportive therapeutic relationship and thorough verbal processing of what has appeared during the therapy sessions.

By presenting the two compositions one after another in the application phase a shift of pain experience in terms of intensity can be observed but predominantly in terms of the pain's qualitative character. Hauck et al. (6) found different patterns of neuronal activations in healthy subjects depending on which of the two compositions were presented. This correlated with the likewise different pain ratings during listening to PM and HM. Therefore, MIPT flexibilises the pain experience and furthermore the affective attitudes toward the pain. It increases the feeling of self-efficacy and promotes communication skills (7). The modification of the pain experience can be appropriately explained as a 2-folded approach. On one side, a transmodal process links affective-sensory pain with auditive music experience; on the other side, an imaginative activity leads to an assignment of musical symbols to pain (5).

Empirical research of MIPT has focused either on the activation of neuronal processes by MEG resp. EEG-measures (6, 8) or on therapeutic processes by qualitative studies (9, 10). Up to now, outcome studies (3, 11, 12) show promising results, but they are not transferable to patients with somatoform pain disorders, and existing systematic reviews do not include studies on this clientele (13–16).

Chronic pain, music and heart rate variability

As music can influence heart rate variability (HRV) (17–19), not solely psychosocial but also (neuro-) physiological effects of MIPT can be assumed. HRV is considered an indicator of autonomic regulation/counter-regulation in patients with chronic pain disorders. Already in 1992, Gebhart and Rendich (20) assumed that the vagal afferents are an integral component of endogenous pain control systems. Koenig et al. (21) conducted a systematic review and meta-analysis on seven studies investigating group differences in vagally mediated HRV-Parameters in patients with headache disorders. The HRV-Parameters RMSSD and HF were reduced, but the authors emphasized the need for further research, as meta-regression analyses on covariates revealed significant differences by clinical etiology, age, gender, and length of HRV recording.

The spectral indices of cardiovascular autonomic control as measured by the spectral analysis of heart period and the mean systolic arterial pressure in women with Fibromyalgia syndrome seem to present good relative reliability. The FMS patients exhibited reduced activation of the sympathetic nervous system (in the LF power, heart rate, and mean arterial pressure) (22). However, a previous study (23) does not indicate dysregulation of spontaneous baroreflex sensitivity.

Goals and objectives of the present study

Our study addresses patients with chronic somatoform pain disorders participating in MIPT. The primary goal is to gain insight into the direct effect mechanisms of MIPT by combining outcome measures on both the objective physiological and subjective perception levels. Our non-experimental study is considered a first step toward collecting quantitative data under naturalistic conditions. Findings of interrelationships between physiological changes during MIPT and short-time positive effects in pain ratings would form the basis for an extensive RCT.

Hypotheses and research questions

Based on clinical observations, we expected to observe a reduction of sensory and affective pain experience after MIPT.

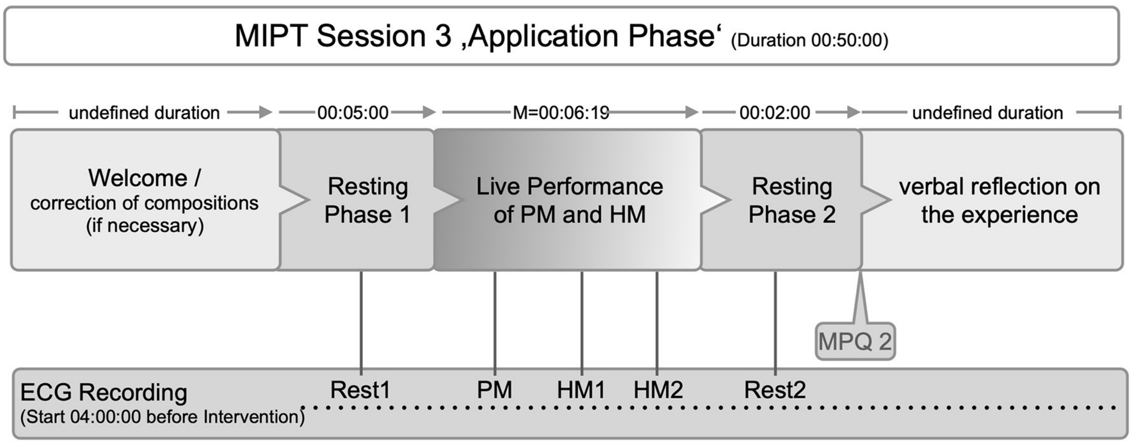

FIGURE 1
Course of the intervention (ECG, Electrocardiogramm; MPQ 2, McGill Pain Questionaire at T2; PM, pain music; HM, healing music; Rest1/PM/HM1/HM2/Rest2, time points for HRV analyses).

Further, we were concerned with whether this is reflected on a physiological level by an increase in parasympathetic activity. Specifically, the research questions of our study were as follows: 1. Does the experience of pain improve between the start (T1) and the end of MIPT (T2)? 2. Is it possible to measure different response reactions in the autonomic nervous system when the patient listens to his/her two music pieces? 3. Are pain ratings at T2 correlated with changes in HRV-Parameters during MIPT? Based on clinical experience and evidence-based data from HRV changes in healthy subjects, we hypothesized:

H1–Subjective pain experienced at the beginning of MIPT (T1) is significantly improved after listening to the two music pieces (T2).

H2–Parasympathetic activity significantly increases while listening to the second music piece ("healing music").

H3–Increased parasympathetic activity while listening to the second music piece ("healing music") correlates negatively to the reduction of pain experienced after MIPT (T2).

Methods and materials

Study design and participants

This study recruited participants consecutively between 09/2016 and 10/2020 from hospitalized pain patients at the Department of Psychosomatic Medicine and Psychotherapy, University Hospital, Otto-von-Guericke-University Magdeburg, and the Department of Psychosomatic Medicine and Psychotherapy, University Medical Centre Ulm, both in Germany. After the specialist assessment, all patients who met the inclusion criteria were referred to MIPT within the first week of hospitalization. Inclusion criteria were the following primary ICD-10 diagnoses: Chronic pain disorder (F45.40 and F45.41) or somatoform pain disorders (F45.0, F45.1, F45.2, F45.3, F45.8, F45.9). Since this study uses a naturalistic study design, patients who took special heart medication (beta-blockers, ACE inhibitors, antiarrhythmics) or psychotropic drugs and analgesics, including opiates, were not excluded. Medication was systematically documented and taken into account in the data analysis. Exclusion criteria were a diagnosis of acute cardiac arrhythmias and previous participation in MIPT.

The study was approved by the ethics committees of the University Hospital and Medical Faculty of Otto von-Guericke-University Magdeburg (File reference: 179/16) and the University Medical Center Ulm (File reference: 201/18). It was carried out following the recommendation of the ICH-GCP guidelines, Declaration of Helsinki. All participants gave written informed consent before participation.

MIPT-intervention

The participants received MIPT in the initial phase of the inpatient stay as the only music-therapeutic intervention. The intervention follows the manualized four treatment steps, which are usually divided into three sessions of 50 min each (5): 1. structured pain interview; 2. "composition phase": creating a music piece addressing the pain experience ("pain music" PM) and another music piece addressing imaginations of relief ("healing music" HM); 3. "application phase": live performance of the self-composed music pieces by the music therapist to the patient combined with 4. subsequent verbal reflection.

Figure 1 shows the course of intervention as follows: Patients were equipped with an ECG-Holter monitor (see below) at

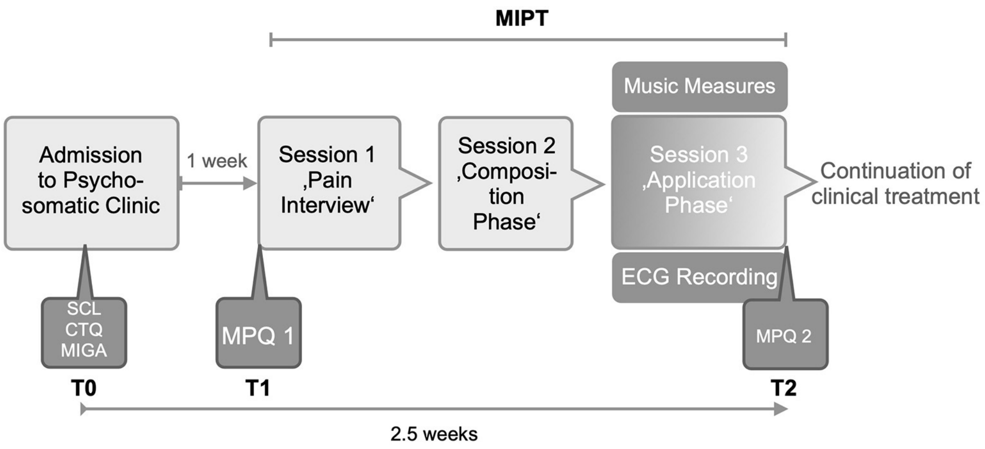

FIGURE 2
Study design (MIPT, Music-imaginative Pain Treatment; SCL, Symptom Check List; CTQ, Childhood Trauma Questionnaire; MIGA, MIGA Questionnaire; MPQ, McGill Pain Questionnaire; ECG, Electrocardiogramm).

a minimum of 4 h before the 3rd MIPT-session ("application phase") to accommodate the device. The intervention started with a greeting, a short reflection on the current state of health and on PM's and HM's veracity. Then, patients were seated in a comfortable position. Hand signals were agreed upon before the arrangement of the music. They serve as indicators for the beginning, end, tempo, and dynamics because there is no conversation during the music intervention itself. After a resting phase, participants listened to the music pieces performed by the music therapist.

Demographic data, psychometric measures, music measures

Basic demographic items and potential confounding variables (shift work, chronic medication with influence on the heart rhythm, diabetes mellitus, untreated thyroid diseases and treated thyroid diseases with thyroid blood parameters outside the normal range, cardiac diseases, use of nocturnal oxygen or nightly continuous positive airway pressure) were collected with the MIGA questionnaire (24).

To capture the burden of symptoms in the intervention group immediately after admission to the hospital (T0), we used the following questionnaires: Symptom Check List (SCL90) (25) with 90 items and the German version of the Childhood Trauma Questionnaire (CTQ) (26) with 25 items. The German short version of the McGill Pain Questionnaire (SF-MPQ) (27) measures the subjective pain experience before (T1) and after (T2) MIPT. It records the sensory component (sum of 11 items) and the affective pain qualities (sum of four items).

Live performances of PM and HM during the "application phase" were audiotaped. The duration of the music was calculated to the second. Figure 2 shows the timepoints for the psychometric and musical data collection.

Physiological measures

The basis for the HRV analysis were 24-h ECG recordings (model: MT-101 or Medilog® AR12 PLUS Schiller AG, Baar, Switzerland) from voluntary patients who had participated in pain therapy. For this purpose, a 2-channel ECG recording at a sampling rate of 1,000 Hz is stored on the SD card located in the Holter ECG. The raw data RR time series (NN-Interval resp. Normal beat-to-Normal beat) were transferred to the Medilog® DARWIN2 Enterprise analysis software package for the total recording time (artifact correction). The data were checked automatically and visually by a healthcare professional for clinical abnormalities and converted into text files comprising consecutive NN intervals. The subjects completed an activity protocol to note the activities in the following 24 h while wearing the ECG.

The HRV parameters were calculated with the Kubios HRV 3.4.3 software (University of Eastern Finland, Kuopio, Finland). The measuring NN intervals and the HRV analysis correspond to the quality criteria recommendations according to the national and international guidelines (28, 29).

Taking the ECG measurement into account, some experimental modifications had to be introduced, i.e., 5-min rest periods before and after the music. The composition representing the pain experience (PM) is played for at least 2 min, and the composition representing the idea of alleviation (HM) is played immediately afterward for at least 5 min. If the respective music pieces fall below the specified time periods, participants are to be regarded as dropouts due to a lack of evaluability on the HRV markers.

Artifact correction was done with an artifact identification threshold of 0.3 s and a smoothness prior method for detrending NN intervals (Lambda = 500, f_c = 0.035 Hz). Mean RR and HRV parameters from time and frequency domains were calculated. Calculated time domain parameters were the standard deviation of NN intervals (SDNN) and the root mean square of successive RR interval difference (RMSSD) in milliseconds. The following frequency domain parameters were calculated using the autoregressive methods (AR): Total power (TP), the low frequency (LF) from 0.04 to 0.15 Hz, and high frequency (HF) from 0.15 to 0.40 Hz. Additionally, the relative power of the HF band (%) was calculated for each experimental phase. Because the shortest experimental phase has a duration of 2 min, the Total Power consisted primarily of HF and LF.

The experimental phases are a resting period before program start (Rest 1), "pain music" period (PM), "healing music" period (HM 1) with first 2 min and last 2 min (HM 2), and resting period at the end (Rest 2) (see Figure 1).

Statistical analysis

All data were checked for normality using the Shapiro Wilk's test. The hypotheses were tested using *t*-tests for paired (within-subject) and independent (between-group) samples. Similarly, a non-parametric test was applied for paired (Wilcoxon sign rank) and independent (Wilcoxon rank-sum aka Mann-Whitney U test) samples to confirm parametric results. Statistical significance was set to $p < 0.05$ two-sided. All statistical analyses were calculated using Stata v15.1 SE (Stata Corp. College Station, Texas).

Results

Sample

Initially, 51 participants were recruited. This number was reduced by 14 dropouts (1 weak health condition, one refusal of study participation, three early treatment termination, nine insufficient ECG data). No causal connection to music therapy was reported. The final sample comprised 37 participants with chronic or somatoform pain disorders who engaged in MIPT for the duration of the study. A balanced distribution of participants between the two clinics could not be achieved due to the different resources. Therefore, 64.4 % of the sample comes from Magdeburg.

TABLE 1 Demographic Data, psychometric measures, and musical data: SCL90, Symptom Check List; GSI, Global Severity Index; CTQ, Childhood Trauma Questionnaire.

Number of participants	**N = 37 (Magdeburg n1 = 26; Ulm n2 = 11)**			
Demographic data				
Mean age (years)	49.6 (SD 10.7)			
Female	28	76%		
Occupation				
Full- or part-time employed	13	35%		
Registered unemployed	11	29%		
Unable to work for 6–24 weeks	25	66%		
Early retirement/disability pension	12	33%		
Unknown	1	2%		
Current smoking	21	56%		
Psychometric measures	**mean (SD)**	**median**	**min**	**max**
SCL90 GSI (*N* = 36)	1.4 (0.7)	1.4	0.35	3.3
GSI T-value>60 (*N*, %)	*N* = 28	80%		
CTQ total score (*N* = 36)	55.6 (11.5)	39	95	53 d
Music measures				
Mean music duration (*N* = 36)	06:19 (SD 01:44)			

Demographic data, psychometric measures, music measures

Table 1 provides an overview of the demographic data, psychometric and musical measures, that characterize our sample. The mean age of all participants was 50 years (SD = 10.9), 33% were diagnosed with Chronic pain disorder (ICD-10: F45.40 and F45.41). The symptom burden of our sample, measured with SCL 90, showed high values in Global Severity: 1.4 (SD = 0.7). The CTQ total mean (n = 36) was M = 55.6 (SD = 11.5). The prevalence in the subscales was highest for the emotional abuse M = 11.6 (6.6), emotional neglect M = 16.3 (6.1) and physical neglect M = 10.7 (2.7).

A total number of each 36 PM and 36 HM have been composed. The mean duration of combined PM and HM during the application phase was 06:19 min (SD 01:44). The musical characteristics varied according to the subjective pain experience and imagination of relief. Two examples of PM and HM are provided as Supplementary material.

Outcome variables

Pain ratings

All patients that were included in the study completed the full questionnaires. Cronbach's alpha on the sensory scale was 0.67 (T0) and 0.82 (T1). Cronbach's alpha on the affective scale

TABLE 2 Pain ratings at two timepoints measured by McGill Pain Questionnaire (German Short Form).

		Pain ratings at T1					Pain ratings at T2						
MPQ SF	*N*	Mean	SD	Min	Max	p50	Mean	SD	Min	Max	p50	T-test *p* 2-sided	Wilcoxon sign rank *p* 2-sided
Sensory (Ia)	32	12.6	5.9	4	26	13	7.6	5.9	0	28	7	<0.001	<0.001
Affective (Ib)	32	6.8	2.5	2	11	6.5	3.2	2.8	0	11	2.5	<0.001	<0.001
Total (Ia+Ib)	32	19.3	7.2	9	33	18.5	10.8	8.4	0	39	10	<0.001	<0.001
VAS	30	6.8	2	1	10	7	4	2.8	0	10	4	<0.001	<0.001
Pain perception now	31	2.4	1.4	0	5	3	1.7	1	0	3	2	<0.001	<0.001

TABLE 3 Cardiologic baseline measures.

HRV parameter baseline	Mean (SD)	Median	Min	Max
Mean RR (ms)	761 (120)	561	1,050	752
SDNN (ms)	21.8 (13.7)	6.06	68.6	18.5
RMSSD (ms)	16.3 (12.1)	3.08	53.5	14.7
PNN50 (%)	3.14 (7.6)	0	34.8	0
LF (ms^2)	397 (609)	18.1	2,821	113
HF (ms^2)	150 (299)	2.83	1,547	69.4
Relative LF (%)	59.8 (20.1)	10.9	86.9	63.4
Relative HF (%)	26.2 (22.2)	4.15	87.4	18.9
Total power (ms^2)	615 (919)	29.5	4,743	243

was 0.52 (T0) and 0.71 (T1). Table 2 shows that there is a reduction of reported pain from $M_{T1} = 19.1$ (SD = 7.3) to $M_{T2} = 10.6$ (SD = 8.0) and in all dimensions of the MPQ-SF. These data confirm our first hypothesis stating a significant reduction of sensory and affective pain experience shortly after the completion of MIPT.

Physiological measures

Since the HRV data may have high interindividual variability and different reactivity, the baseline data were determined beforehand as a starting point to perform the individual normalization. The HRV during resting measurements is subject to only a few influences. As mentioned in the sample section, there were dropouts due to insufficient ECG data. Experimental periods with an artifact rate of 5% or higher were excluded from the analysis (nine periods in three patients). Six patients had an ECG that could not be analyzed due to high age and diagnose-related ectopic beats. Table 3 shows the cardiologic baseline measures of the sample.

The short analysis phases were selected to investigate the mean differences of the Mean RR and HRV parameters during the test phases "pain music" (PM) and "healing music" (HM1). Table 4 documents physiological data during PM and HM1 2 min after each piece of music have started.

The HRV parameter Total Power (TP), which reflects the overall variability, is reduced ($p = 0.0288$) in the phase of the HM (644.0 ms; SD = 948.0 ms vs. 432.0 ms; SD = 608.0 ms^2). The parameter Total Power reflects the overall level of the autonomic-regulation status, which means that the regulation status is lower during HM. Even when using a correction factor, the comparability of the determined absolute frequency powers seems to be limited due to the strong spread. The standard deviations (SD) are larger than the mean values of these parameters.

The relative Power (%) in the HF band (HF-Power %) is completely different. The HF band reflects parasympathetic activity. It's relative power increases during HM1 [22.9% (SD = 15.8%) vs. 27.9% (SD = 16.3%); $p = 0.0288$]. Figure 3 shows boxplots of a 2-min study phase for four selected HRV parameters.

The modulation of the parasympathetic tone helps to maintain the dynamic vegetative regulation. The absolute power in this respiratory band does not differ in these two phases. So, while the absolute power is reduced in TP and HF, there appears to be a relative shift in the autonomic system toward higher vagal activity.

Correlation between painratings and HRV-data

Although negative correlations between the change of HRV parameters from PM-HM1 with the actual pain experience were observed in this sample, the parametric and non-parametric correlation coefficients were small and not significant.

Discussion

While in our study a significant reduction in pain experience before (T1) and after (T2) MIPT was found, the data on heart rate variability during the "application phase" of MIPT were much more complex than expected. Significant correlations between the two variables could not be calculated. These findings require more detailed analysis and interpretation in the following.

TABLE 4 Comparison of Mean RR and HRV parameters in the phase during Pain Music (PM) and Healing Music (HM1).

Variable	*N*	Pain music (PM)					Healing music (HM1)					*T*-test *p* 2-sided	Wilcoxon sign rank *p* 2-sided
		Mean	SD	Min	Max	p50	Mean	SD	Min	Max	p50		
Mean RR (ms)	36	772	109	599	1,088	763	772	122	606	1,100	760	>0.10	>0.10
SDNN (ms)	36	22.3	14.8	6.2	72.5	17.5	18.8	11.2	5.2	58.8	15.8	0.051	0.011
RMSSD (ms)	36	16.0	10.6	2.8	46.0	13.9	14.9	10.3	3.0	49.5	12.9	>0.10	>0.10
LF (ms^2)	36	471	808	13	4,161	173	282	462	5	2,629	118	>0.10	0.011
HF (ms^2)	36	106.0	146.0	1.9	724.0	57.6	108.0	154.0	2.6	724.0	62.3	>0.10	>0.10
Relative LF (%)	36	63.7	17.1	24.5	91.8	67.2	61.1	16.4	22.2	84.5	63.4	>0.10	>0.10
Relative HF (%)	36	22.9	15.8	3.4	62.3	19.2	27.9	16.3	5.5	63.5	26.4	0.021	0.029
Total power (ms^2)	36	644	948	33	4,789	281	432	608	23	3,294	209	>0.10	0.029

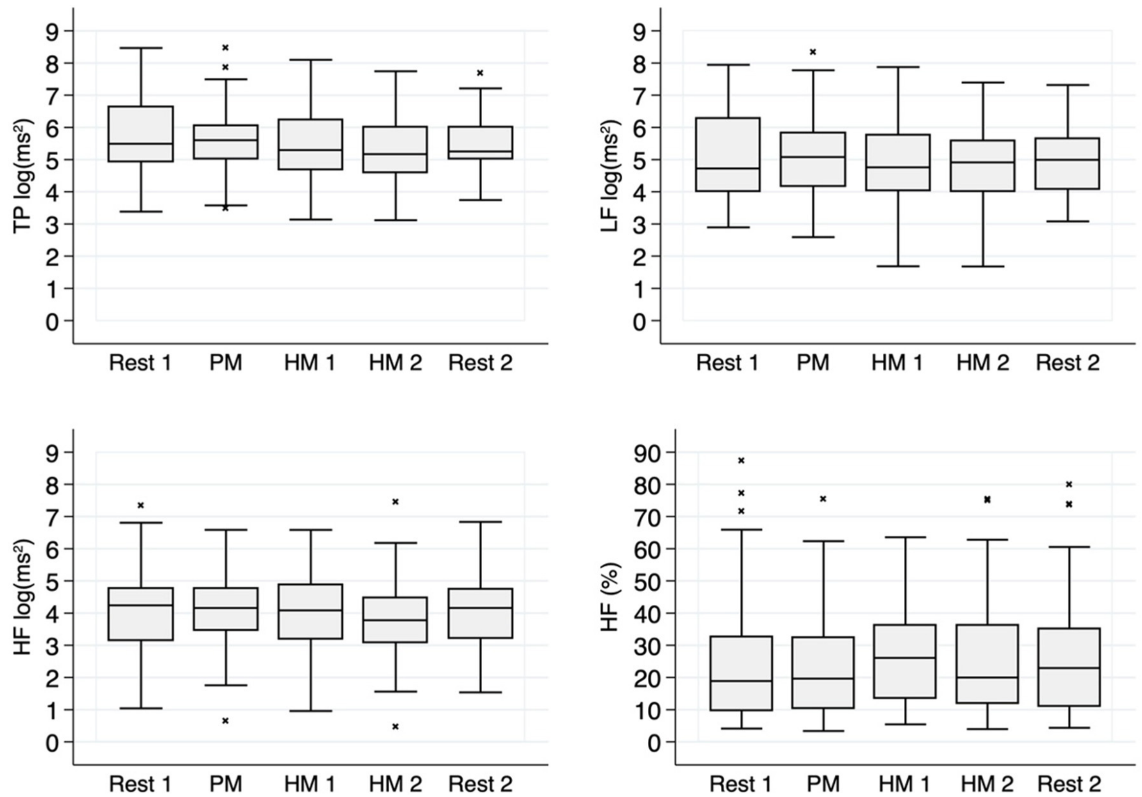

FIGURE 3
HRV-Parameter from frequency domain: Rest: Resting period before (1; $N = 37$) and after (2; $N = 37$) music, PM: Pain Music ($N = 37$), HM: Healing Music first 2 min (1; $N = 36$) and last 2 min (2; $N = 36$). The sample size differs due to a shorter duration of HM in one case.

Study relevance: Challenges in the treatment of chronic somatoform pain disorders

Chronic pain is a multidimensional phenomenon related to somatic illness, personal life history, psychological vulnerability, and interpersonal relationships. A particular therapeutic challenge is posed by the group of patients with chronic somatoform pain disorder included in our study. This clientele has a somatic understanding of illness predominantly. Demographic data of the study participants revealed a precarious professional situation, while the psychometric data showed a particularly increased symptom burden. Furthermore, our sample is characterized by childhood traumatization, notably emotional abuse and neglect. The psychologically harsh living conditions in childhood can lead to a lack of ability to differentiate between physical pain and affects (30), and can be accompanied by incoherent verbal and nonverbal communication (31). This gives reason to integrate music therapy as a partly nonverbal element of Germany's multimodal inpatient treatment of chronic pain.

Improvement of pain experience

Our measures show a significant reduction in the pain ratings in a period of < 2 weeks, and our first hypothesis, H1, can therefore be confirmed. However, the improvement cannot be attributed to our intervention alone, as MIPT is an element of a multimodal inpatient treatment concept and because of lack of a control condition. Other studies on MIPT with comparable clients are not yet available, not even when applying another music therapy intervention. Therefore, we cannot relate our results to available data sets.

Considering that long standstills often characterize the treatment of chronic somatoform pain disorders, our results are nevertheless remarkable. Even minor improvements can be interpreted as a positive sign that an intervention has started working. The contribution of MIPT we regard as a music-induced change in pain perception. Compared to music therapy approaches that use music for relaxation, mindfulness, or distraction, patients in MIPT are encouraged to engage with their pain experience actively and directly. By creating a musical product and communicating in this way, subjective pain experience becomes an object of perception, resulting in perceptual structures and habituated attitudes changing. Not only moments of altered pain perception in the initial phase of the inpatient stay but experiences of self-efficacy are decisive for the treatment progress, as they raise the patients' hope and increase motivation.

Physiological data

The role of vagal afferents in the modulation of pain is established. A systematic review by Koenig et al. (32) includes 20 studies on HRV in healthy adults with experimentally induced pain. It shows an increase in sympathetic-baroreflex activity indexed by an increase in low frequency (LF) spectrum and a decrease in vagal-parasympathetic activity indexed by a decrease in high frequency (HF) spectrum. Healthy individuals with self-reported pain symptoms may have lower parasympathetic activity, indexed by pNN05, RMSSD, and HF (33).

Our HRV data found a more complex situation than has been found in music intervention studies with healthy people. In our view, this might be due to fundamental differences between healthy and severely ill persons. The clinical picture of chronic pain patients is often associated with pronounced vegetative accompanying symptoms in addition to the pain symptoms. The pain perception includes the hypothalamic-pituitary-adrenal axis (HPA axis) with involvement of the autonomic nervous system (ANS) (23). This demonstrates a reduced ability to be activated and adapted to stressful situations in chronic pain patients. People with reduced sympathetic activity show a deficit of pain-inhibiting mechanisms with an increased pain perception (34). On this basis, it is remarkable that the measured HRV changes refer to very low durations of the music in our study. Despite a manifest baseline situation, the immediate effect of listening to the self-composed music can be observed well between the measuring time points during the application phase of MIPT.

We explain our findings psychologically because there is no physiological reference data so far. In the beginning, the HRV parameter Total Power (TP) remains approximately the same during the "pain music" compared to the resting phase, probably caused by tension when anticipating what is about to come. In the phase of "healing music," TP, mainly comprising of HF and LF, decreased. As exciting music decreases the HRV (17), HM can no longer be understood as relaxation music but as one that can be thrilling for the patient with chronic pain. Interestingly, when HM started and TP tendentially decreased, HF percentage increased. This indicates a shift toward lower mixed sympathetic and parasympathetic activity. We interpret our findings as a physiological correlate of the psychological work of the patients, which, generally speaking, consists in resolving the conflict between the desire for healing and the fear of change. Given the complexity of the physiological data and the lack of significance, our hypotheses H2 and H3 cannot be confirmed.

Limitations and outlook

The small sample size and the lack of a control group limit the validity of our results. The high dispersion of data does not allow a statement about general tendencies of physiological reactions to the intervention. We attribute this to the characteristics of our naturalistic study and the range of individual propensities within our sample. Different cardiologic and psychopathological starting points could have been the reason for different reactions to the music therapy treatment. This might explain why a significant correlation between HRV and MPQ could not be calculated.

Our present study is unique so far. Although our results are only indicative, they have raised research questions for future studies. They also provide insight into immediate physiological reactions to self-composed music pieces as well as into complex physiological and psychological interactions during MIPT. Therefore, our study has increased knowledge of individualized chronic pain treatment with an activating and partly confronting model of music therapy. In a follow-up study, we recommend including a control group and expanding to measurements of intermediate and longer-term impacts of MIPT.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by University Hospital and Medical Faculty of Otto-von-Guericke-University Magdeburg (File reference: 179/16) University Medical Center Ulm (File reference: 201/18). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SM, JF, IB, and SG: conception and design. SG and MD: study therapists. MJ: statistical analysis plan. SM, IB, MJ, JF, and HG: first draft. All authors reviewed and edited the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpain.2022.943360/full#supplementary-material

SUPPLEMENTARY AUDIOS 1 AND 2
Pain Music (PM).

SUPPLEMENTARY AUDIOS 3 AND 4
Healing Music (HM).

References

1. Schmidt HU, Kächele H, Oerter U, Scheytt-Hölzer N. Musiktherapie in der deutschen Psychosomatik: Krankenversorgung, Weiterbildung, Forschung. *Psychotherapeut.* (2003) 48:155–65. doi: 10.1007/s00278-003-0306-5

2. Schaefert R, Hausteiner-Wiehle C, Häuser W, Ronel J, Herrmann M, Henningsen P. Klinische Leitlinie. Nicht-spezifische, funktionelle und somatoforme Körperbeschwerden. *Deutsches Ärzteblatt.* (2012) 109:803–19. doi: 10.3238/arztebl.2012.0803

3. Rider M. Entrainment mechanisms are involved in pain reduction, muscle relaxation, and music-medicated imagery. *J Music Ther.* (1985) 22:183–92. doi: 10.1093/jmt/22.4.183

4. Dileo C, Bradt J. Entrainment, resonance, and pain-related suffering. In: Dileo C, editor. *Music Therapy and Medicine: Theoretical and Clinical Applications.* MD: AMTA, Silver Spring (1999). p. 181–8.

5. Metzner S. A polyphony of dimensions: music, pain and aesthetic perception. *Music Med.* (2012) 4:164–71. doi: 10.1177/1943862112449486

6. Hauck M, Metzner S, Rohlffs F, Lorenz J, Engel AK. The influence of music and music therapy on neuronal pain induced oscillations measured by MEG. *Pain.* (2013) 154:539–47. doi: 10.1016/j.pain.2012.12.016

7. Metzner S, Frommer J. Die performative und bedeutungsgenerierende Dimension von Musik in der musiktherapeutischen Schmerzbehandlung. *Psychodynamische Psychotherapie/Sonderheft Musiktherapie.* (2014) 224–33. Available online at: https://elibrary.klett-cotta.de/basket/cart

8. Hunt AM, Fachner J, Clark-Vetri R, Raffa RB, Rupnow-Kidd C, Maidhof C, et al. Neuronal effects of listening to entrainment music versus preferred music in patients with chronic cancer pain as measured *via* EEG and LORETA imaging. *Front Psychol.* (2021) 12:588788. doi: 10.3389/fpsyg.2021.588788

9. Schrauth T. Die Musik der musik-imaginativen Schmerzbehandlung. *Musiktherapeutische Umschau.* (2015) 36:224–35. doi: 10.13109/muum.2015.36.3.224

10. Metzner S. *Darstellung und Transformation von Schmerzerleben in der Musik-imaginativen Schmerzbehandlung.* Göttingen: Vandenhoeck and Ruprecht unipress (2018). doi: 10.14220/9783737008020

11. Bradt J. The effects of music entrainment on postoperative pain perception in pediatric patients. *Music Med.* (2010) 2:150–7. doi: 10.1177/1943862110369913

12. Kwan M, Soek A, Seah T. Music therapy as a non-pharmacological adjunct to pain management: Experiences at an acute hospital in Singapore.

Prog Palliat Care. (2012) 21:151–7. doi: 10.1179/1743291X12Y.0000000042

13. Koenig J, Warth M, Oelkers-Ax R, Wormit A, Bardenheuer HJ, Resch F, et al. I need to hear some sounds that recognize the pain in me: an integrative review of a decade of research in the development of active music therapy outpatient treatment in patients with recurrent or chronic pain. *Music Med.* (2013) 5:150–61. doi: 10.1177/1943862113490739

14. Lee JH. The effects of music on pain: a meta-analysis. *J Music Ther.* (2016) 53:430–77. doi: 10.1093/jmt/thw012

15. Garza-Villarreal EA, Pando V, Vuust P, Parsons D. Music-induced analgesia in chronic pain conditions: a systematic review and meta-analysis. *Pain Physician.* (2017) 20:597–610. doi: 10.36076/ppj/2017.7.597

16. Martin-Saavedra JS, Vergara-Mendez LD, Talero-Gutiérrez C. Music is an effective intervention for the management of pain: an umbrella review. *Complement Ther Clin Pract.* (2018) 32:103–14. doi: 10.1016/j.ctcp.2018.06.003

17. Koelsch S, Jancke L. Music and the heart. *Eur Heart J.* (2015) 36:3043–9. doi: 10.1093/eurheartj/ehv430

18. Fuchs D, Hillecke TK, Warth M. Relaxation effects of musially guided resonance breathing: a randomized controlled pilot study. *Music Med.* (2018) 10:104–12. doi: 10.47513/mmd.v10i2.576

19. Mojtabavi H, Saghazadeh A, Valenti VE, Rezaei N. Can music influence cardiac autonomic system? a systematic review and narrative synthesis to evaluate its impact on heart rate variability. *Complement Ther Clin Pract.* (2020) 39:101162. doi: 10.1016/j.ctcp.2020.101162

20. Gebhart GF, Randich A. Vagal modulation of nociception. *APS J.* (1992) 1:26–32. doi: 10.1016/S1058-9139(06)80007-0

21. Koenig J, DeWayne P, Williams P, Kemp AH, Thayer JF. Vagally mediated heart rate variability in headache patients—a systematic review and meta-analysis. *Cephalalgia.* (2016) 36:265–78. doi: 10.1177/0333102415583989

22. Andrade CP, Zamunér AR, Forti M, de França TF, da Silva E. Reliability of heart period and systolic arterial pressure variabilities in women with fibromyalgia syndrome. *Clin Rheumatol.* (2016) 35:2347–52. doi: 10.1007/s10067-016-3284-z

23. Friederich HC, Schellberg D, Mueller K, Bieber C, Zipfel S, Eich W. Stress und autonome Dysregulation bei Patienten mit einem Fibromyalgiesyndrom. *Schmerz.* (2005) 1:185–94. doi: 10.1007/s00482-004-0335-1

24. Sammito S. *Alters- und geschlechtsabhängige Referenzwerte für die Herzfrequenzvariabilität*. Habilitationsschrift. Magdeburg: Medizinische Fakultät der Otto-von-Guericke-Universität Magdeburg (2017).

25. Franke GH. *Die Symptom-Checkliste von Derogatis* Deutsche Version* Manual, 2nd ed, revised [Symptom Checklist of Derogatis* German version* Manual, 2nd ed., revised]*, Göttingen: Beltz (2002).

26. Wingenfeld K, Spitzer C, Mensebach D, Grabe JH, Hill A, Gast U, et al. Die deutsche Version des Childhood Trauma Questionnaire (CTQ): Erste Befunde zu den psychometrischen Kennwerten. *PPmP.* (2010) 60:442–50. doi: 10.1055/s-0030-1247564

27. Melzack R. The short-form McGill pain questionnaire. *Pain®*. (1987) 30:191–7. doi: 10.1016/0304-3959(87)91074-8

28. Sammito S, Thielmann B, Seibt R, Klussmann A, Weippert M, Böckelmann I. Guideline for the application of heart rate and heart rate variability in occupational medicine and occupational science. *ASU Int.* (2015) 6:1–29. doi: 10.17147/ASUI.2015-06-09-03

29. Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. *Circulation.* (1996) 93:1043–65.

30. Egle UT, Nickel R, Hoffmann SO. Psychodynamische Psychotherapie bei chronischem Schmerz. In: Kröner-Herweg B, Frettlöh J, Klinger R, Nilges P, editors. *Schmerzpsychotherapie*. Heidelberg: Springer (2007). p. 617–24. doi: 10.1007/978-3-540-72284-7_34

31. Merten J, Brunnhuber S. Facial expression and experience of emotions in psychodynamic interviews with patients suffering from a pain disorder. *Psychopathology.* (2004) 37:266–71. doi: 10.1159/000081982

32. Koenig J, Jarczok MN, Ellis RJ, Hillecke TK, Thayer JF. Heart rate variability and experimentally induced pain in healthy adults: a systematic review. *Eur J Pain.* (2014) 18:301–14. doi: 10.1002/j.1532-2149.2013.00379.x

33. Koenig J, Jarczok MN, Ellis RJ, Warth W, Hillecke TK, Thayer JF. Lowered parasympathetic activity in apparently healthy subjects with self-reported symptoms of pain: preliminary results from a pilot study. *Pain Practice.* (2015) 15:314–8. doi: 10.1111/papr.12177

34. Okifuji A, Turk DC. Stress and psychophysiological dysregulation in patients with fibromyalgia syndrome. *Appl Psychophysiol Biofeedback.* (2002) 27:129–41. doi: 10.1023/A:1016243710507

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Autonomic nervous system markers of music-elicited analgesia in people with fibromyalgia: A double-blind randomized pilot study

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Purpose: To investigate the feasibility of using music listening by adults with fibromyalgia (FM) as a potential tool for reducing pain sensitivity.

Patients and methods: We report results from a double-blind two-arm parallel randomized pilot study (NCT04059042) in nine participants with FM. Pain tolerance and threshold were measured objectively using quantitative sensory tests; autonomic nervous system (ANS) reactivity was measured with an electrocardiogram. Participants were randomized to listen to instrumental Western Classical music or a nature sound control to test whether music listening elicits greater analgesic effects over simple auditory distraction. Participants also completed separate control testing with no sound that was counterbalanced between participants.

Results: Participants were randomized 1:1 to music or nature sounds (four Music and five Nature). Although the groups were not different on FM scores, the Music group had marginally worse temporal pain summation ($p = 0.06$), and the Nature group had higher anxiety scores ($p < 0.05$). Outcome measures showed a significant difference between groups in the magnitude of change in temporal summation between sessions ($p < 0.05$), revealing that the Nature group had greater pain reduction during audio compared to silence mode, while the Music group had no difference between the sessions. No significant effects were observed for either mechanical pain tolerance or ANS testing. Within the Music group, there was a trend of vagal response increase from baseline to music listening, but it did not reach statistical significance; this pattern was not observed in the Nature group.

Conclusion: Auditory listening significantly altered pain responses. There may be a greater vagal response to music vs. nature sounds; however, results could be due to group differences in pain and anxiety. This line of study will help in determining whether music could be prophylactic for people with FM when acute pain is expected.

KEYWORDS

pain, auditory distraction, quantitative sensory testing, music, nature sounds

Introduction

The term "centralized pain" describes any central nervous system (CNS) dysfunction or pathology that may contribute to the development or maintenance of chronic pain (1–3). There is a growing appreciation of the role of CNS augmentation in pain processing in many chronic pain conditions (2, 4). A hallmark of the centralized pain phenotype is the presence of hyperalgesia and reduced or absence of endogenous analgesia (5–7). Data from quantitative sensory testing (QST) studies suggest a wide, bell-shaped distribution in pain sensitivity across the general population. Most individuals with centralized pain fall on the right side of this curve and have QST findings consistent with hypersensitivity (hyperalgesia and allodynia) (1, 8–13). QST evidence of widespread hypersensitivity is consistently observed in many chronic pain conditions, including FM, irritable bowel syndrome, tension headache, low back pain, temporomandibular joint disorder, interstitial cystitis, and vulvodynia (14–23). Widespread hypersensitivity is often measured through QST sensitivity testing of pain to pressure on the thumbnail bed. As evidence suggests, temporal summation, which is the phenomenon of amplifying pain perception after being subjected to repeated or continuous noxious stimulation, despite having the same intensity of the stimulus (24), is an essential role player in FM (25, 26). Therefore, in this study, we used QST to objectively measure pain sensitivity and temporal summation while listening to music compared to listening to nature sounds in patients with FM.

Music has been previously shown to influence parameters of the autonomic nervous system associated with anxiety (27), such as slowing heart rate (28) and respiration (29). Music listening can also reduce acute pain during surgery (30), post-operative recovery (31), orthodontic procedures (32), orthopedic rehabilitation (33), and during thermic pain induction in healthy participants (34, 35). The *subjective* analgesic, anxiolytic, and antidepressant effects of music for people with chronic pain were recently confirmed in a meta-analysis (36). However, the impact of music listening on objective measures of pain sensitivity in patients with chronic pain has not yet been described. The goal of this pilot study was to understand the possible analgesic effects of music listening on objective measures of pain sensitivity in patients with fibromyalgia (FM).

The analgesic effect of music is thought to occur through several mechanisms: Contextual, Cognitive, Emotional, and Physiological (37, 38). First, music provides a predictable *context* that can increase the listeners' sense of control. This is further enhanced if the music is familiar, as this can bring in other effects that are not related to aspects of music specifically, such as setting up expectations and heightening nostalgia. Studies have shown the greatest analgesic effects when music is selected by participants. Second, similar to other types of stimulation, such as reading or listening to nature sounds (39), music can serve as a *cognitive* distraction and take attention away from the painful stimulus. Third, music is a powerful inducer of *emotion* (40, 41). Music that is positive, liked by the listener, and low on arousal has the strongest analgesic effect (34). Finally, music listening interventions and music therapy have also been shown to reduce anxiety and depression (42, 43). The anxiolytic effect may be due to the *physiological* effect of music on the parasympathetic nervous system, increasing the vagal response and reducing heart rate and respiration rate (27). Music also has effects on the brain directly, causing the release of endogenous opioids and dopamine and activating the areas of the descending pain modulatory system (44, 45). The specific musical characteristics that yield the greatest analgesic effects are difficult to pinpoint, as there is no standard for reporting. Meta-analyses have revealed that music with 60–80 beats per minute, in a major key, and without lyrics or percussion has the largest effects (46).

Previous studies in patients with FM have shown that patients have reduced self-reported pain and increased mobility after even a short, 10-min music listening intervention. After listening to the music of their choice, participants were faster in a standard mobility assessment, that is, the timed-up-and-go task (47). A second study using resting-state functional magnetic resonance imaging confirmed the impact of 5-min music listening intervention on the centralized descending pain modulatory system (DPMS), identified as changes in functional connectivity between regions of the DPMS that positively correlated with

TABLE 1 Participant demographic variables by audio group assignment (Music, Nature).

	Music group ($n = 4$)	Nature group ($n = 5$)	U/X^2	p
Age (years) [M (SD)]	49.18 (13.86)	40.28 (9.93)	6.00	0.41
Dominant hand, right [n (%)]	4 (100%)	5 (100%)	–	–
Gender, female	4 (100%)	5 (100%)	–	–
Sex assigned at birth, female	4 (100%)	4 (80%)	0.90	0.34
Race, white	4 (100%)	5 (100%)	–	–
Ethnicity: not Hispanic or Latinx	2 (50%)	5 (100%)	3.21	0.20
Hispanic or Latinx	1 (25%)	0 (0%)		
Other/unknown/no response	1 (25%)	0 (0%)		
Relationship status: married	2 (50%)	4 (80%)	3.60	0.31
Never married	1 (25%)	0 (0%)		
Divorced or separated	1 (25%)	1 (20%)		
Education: high school/GED	0 (0%)	0 (0%)	3.94	0.27
Some college	1 (25%)	1 (20%)		
Technical/associate's degree	0 (0%)	1 (20%)		
Bachelor's degree	0 (0%)	2 (40%)		
Advanced/professional degree	3 (75%)	1 (20%)		

Continuous measures were assessed with independent samples Mann–Whitney U-tests; categorical variables were assessed with Chi-square tests.
CI, confidence interval; M, mean; SD, standard deviation; GED, general education development.

changes in pain scores (48). To our knowledge, this is the first study to investigate whether objectively measured pain sensitivity is reduced by music listening in patients with FM.

The goal of the current study was to identify whether music listening has a promising analgesic effect during pain threshold and tolerance testing for patients with FM that supersedes any effect of auditory distraction. We used standardized music, rather than music selected by the participants, so that we could determine whether the specific music characteristics described above (i.e., slow tempo, consonant harmonies, no lyrics, or percussion) would be sufficient to elicit an analgesic effect. While a personalized choice might elicit a greater effect, it would not be possible to determine whether the effect was due to the music characteristics or from the person's previous associations and memories with that music. We hypothesized that because the nature listening condition provides a distraction from pain sensations, and may also provide some of the same Contextual, Cognitive, Emotional, and Physiological impacts as music, both listening conditions (Music and Nature) would reduce pain sensitivity compared to testing during silence. However, as noted previously, the emotional and physiological impacts are anticipated to be stronger in music due, in part, to temporal structure and expectancy building. Therefore, we hypothesized that music listening would reduce pain sensitivity compared to nature sounds. We further hypothesized that music would increase vagal input to the autonomic nervous system, decreasing heart rate and increasing heart rate variability compared to both silence and nature sounds, and that analgesic responsiveness would be moderated by symptoms of FM, anxiety, and depression.

Materials and methods

Participants

Participants with a diagnosis of FM were recruited from pain clinics located at a large Midwestern US university medical center and by word of mouth. Eligible participants were 18 years or older, able to read and speak English, willing to refrain from alcohol, nicotine, and physical activity or exercise on the day of testing, and on a stable dose of adjunctive pain medications, including tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and gabapentinoids. Participants were excluded if they were not able to provide written consent, were pregnant, had peripheral neuropathy in the upper extremities, and had a severe physical impairment or co-morbid medical conditions, such as blindness, deafness, paraplegia, cancer, autoimmune disorder, liver failure or cirrhosis, hepatitis, cardiovascular disease, illicit drug or opioid abuse, or average daily opioid dosing of >15 mg oral morphine equivalents (e.g., > two 5 mg oxycodone tablets/day or >three 5 mg hydrocodone

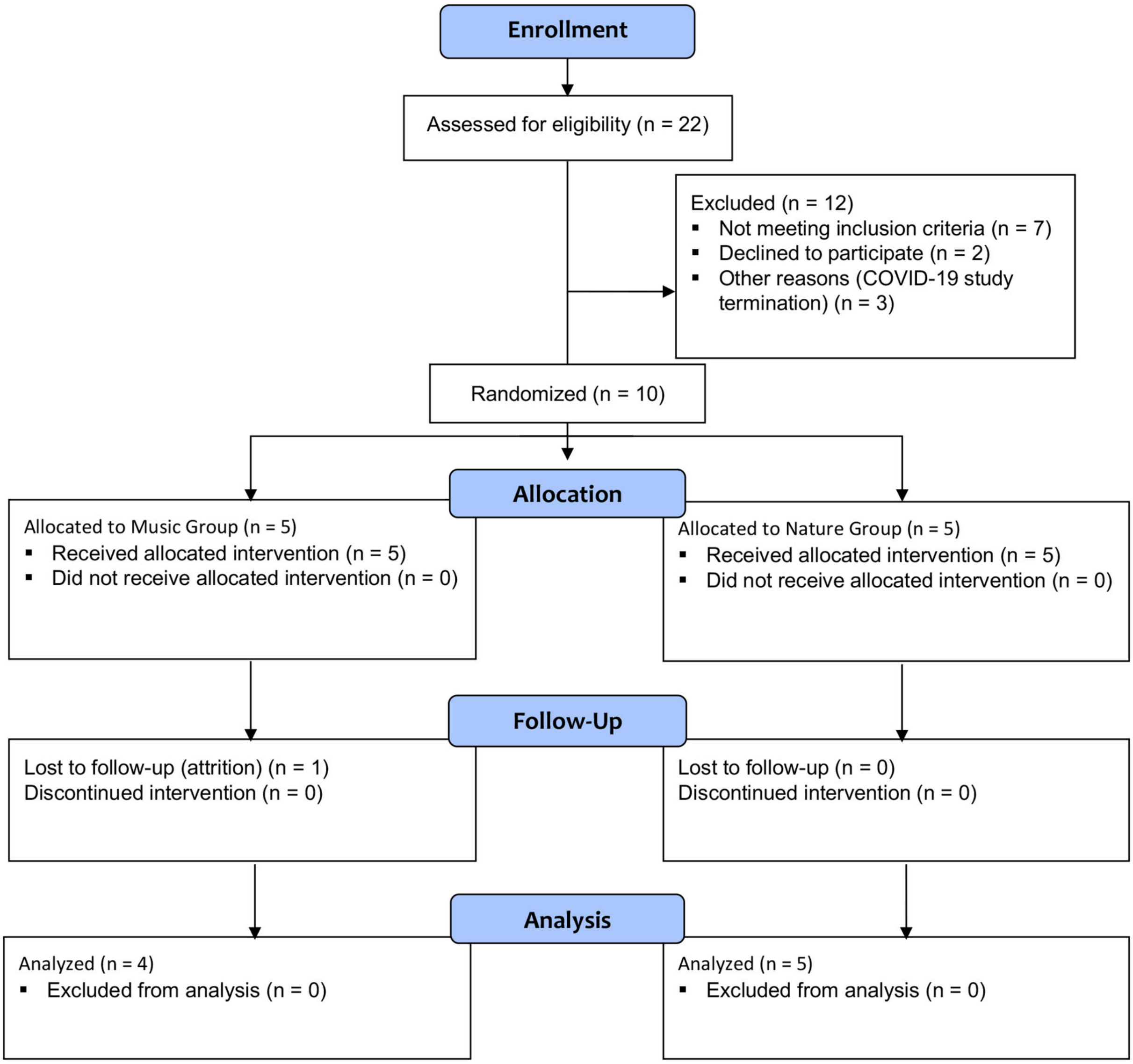

FIGURE 1
CONSORT 2010 flow diagram.

tablets/day). Conversions were made based on well-accepted conversion tools (49, 50).

Ten White female participants with FM were enrolled in the study (Table 1). Centralized pain and nearly any chronic pain condition are 1.5–2 times more common in women than in men (51). One person in the Music group did not return for the second visit and was lost to follow-up. That person only received the silence session and was not included in the analysis (Figure 1).

The intended sample size was 40 participants with FM based on power analysis; however, due to the COVID-19 pandemic, recruitment was stopped and only 10 participants took part in this study.

Measures

Participant self-report measures related to pain and music

Demographics

Participants completed a demographics questionnaire that included questions on participant sex, gender, age, race, ethnicity, marital status, education level, body mass index, and current medications.

Fibromyalgia-ness

Fibromyalgia-ness (FMness) is a measure of pain and co-morbid symptom extensiveness and severity, calculated by combining the scores of the Widespread Pain Index with the Symptom Severity Scale from the 2011 FM Survey (52) to derive a continuous metric purportedly indicative of the degree of CNS pain amplification present in a given individual (53).

Clinical pain severity

Pain severity and functional interference due to pain were assessed using the Brief Pain Inventory (BPI). The BPI is validated for chronic, non-malignant forms of pain, and asks patients to rate their current pain intensity, as well as their worst, least, and average pain in the 7 days (0–10 NRS), and has been recommended by IMMPACT as a measure of choice for the assessment of pain in clinical research (54–56).

Fibromyalgia functional status

Current health and functional status in FM patients were measured using the Revised Fibromyalgia Impact Questionnaire (FIQR) (57). The FIQR measures physical functioning, work status, and overall wellbeing.

Depression and anxiety

Mood symptoms were assessed with the static short forms for depression and anxiety, developed by the NIH roadmap initiative PROMIS (58). The PROMIS measures have a standardized mean of 50, a standard deviation of 10, and a range of 1–100.

Music experience

Participants rated their music listening habits (i.e., frequency, styles, reasons for listening, etc.) using the Brief Music Experience Questionnaire (MEQ) (59). The Brief MEQ is a 53-item self-report measure of music centrality in the respondent's life, their musical aptitude, and experience with and reaction to music. Questions are rated using a 5-point Likert scale (1: very untrue and 5: very true), from which six summary scores are derived for Commitment to Music, Innovative Musical Aptitude, Social Uplift, Affective Reactions to Music, Positive Psychotropic Effects from Music, and Reactive Musical Behavior.

Autonomic nervous system activity (ECG)

The study participants' ECG data were recorded using three standard snap-on ECG electrodes with Biopac MP150 and Acqknowledge 4.3 software (Goleta, CA). ECG electrodes were placed under the collar bone and below the rib cage on the opposite side, with a ground electrode placed on the abdomen near the navel. The time of each condition (baseline, listening only, and pain while listening) was recorded by the investigator with a mark in the Acqknowledge recording. The ECG data were uploaded to Kubios software (Kuopio, Finland) for analysis. Summary metrics of heart rate and variability during each condition were corrected for within-session baseline levels and compared between conditions (listening only vs. pain while listening) and between auditory groups (music vs. nature sounds).

Quantitative sensory testing (QST)

Pain testing was performed using the Multimodal Automated Sensory Testing (MAST) system, a computerized QST device developed at the University of Michigan and currently being employed in several clinical trials, including the NIH MAPP Network. Two measures of QST were used in this study: mechanical pain sensitivity (MPS) and temporal summation (TS). MPS was assessed by applying discrete pressure stimuli to the thumbnail bed. The MAST system delivered an ascending series of 5-s duration stimuli at 25-s intervals, beginning at 0.50 kg/cm^2 and increasing in 0.50 kg/cm^2 intervals up to tolerance or a maximum of 10 kg/cm^2. Participants rated pain intensity after each stimulus on a 0 (no pain) – 100 (extreme pain) numerical rating scale (NRS). Pain threshold, the point at which participants rated >0 pain, and tolerance, the point at which participants rated >80 pain, were determined from this procedure. To measure TS, a 256 mN pinprick stimulus (MRC Systems, Heidelberg, Germany) was applied once to the forearm or hand, followed by a train of 10 identical stimuli at a rate of 1 Hz. Following the single stimulus and the train of 10 stimuli, patients reported the pain intensity of the pinprick sensation using the 0–100 NRS. This procedure was repeated three times, and the mean pain rating of the three stimulus trains was divided by the mean pain rating of the single stimuli to calculate a wind-up ratio (WUR); a WUR >1 indicates temporal summation (60).

Stimuli and procedures

Music and sound delivery

Auditory stimuli were presented using a digital music player and noise-canceling headphones. Four audio tracks were identified by number only, and the researcher was blinded to the contents of each tract. One track was music, one was nature sounds, and two were silence modes. The randomization procedure indicated to the researcher which track (1–4) should be used for the testing session. Each track began with instructions to the participant, indicating what they would hear during testing, and that they should continue to wear the headphones even if the track is silent so that the researcher would not know what they were hearing.

Music characteristics

The musical selections consisted of professional recordings of instrumental Western classical music selected by the researcher (Supplementary Table 1). All participants heard the same pieces in the same order. Instrumentation ranged from

TABLE 2 Participant reported clinical and musical experience variables by audio group assignment (Music, Nature).

	Music group ($n = 4$)	Nature group ($n = 5$)	U	p
WOLFE FMness [M (SD)]	17.00 (4.76)	13.00 (3.74)	5.00	0.29
BPI worst 2 average	4.25 (2.63)	4.20 (1.64)	11.00	1.00
FIQR score	45.50 (22.19)	40.23 (15.78)	7.00	0.56
PROMIS: depression	45.98 (5.30)	50.40 (5.79)	12.00	0.73
PROMIS: anxiety	52.65 (4.71)	59.92 (3.33)	20.00	0.02*
MEQ: commitment to music	2.04 (0.92)	1.60 (0.71)	7.00	0.56
MEQ: innovative musical aptitude	2.11 (0.63)	2.17 (1.08)	9.50	0.91
MEQ: social uplift	2.62 (0.48)	2.70 (1.22)	9.00	0.91
MEQ: affective reactions to music	4.03 (0.84)	4.40 (0.33)	12.50	0.56
MEQ: positive psychotropic effects from music	3.53 (1.00)	3.45 (0.58)	11.00	1.00
MEQ: reactive musical behavior	3.58 (0.57)	4.00 (0.66)	14.00	0.41

Continuous measures were assessed with independent samples Mann–Whitney U-tests.
*Indicates significant group differences at $p < 0.05$.
CI, confidence interval; M, mean; SD, standard deviation; FM, fibromyalgia; BPI, Brief Pain Inventory; FIQR, Fibromyalgia Impact Questionnaire–Revised; PROMIS, Patient-Reported Outcomes Measurement Information System; MEQ, Music Experience Questionnaire.

piano solo to full orchestra, but all were without lyrics or heavy percussion. Pitch ranged across pieces but was standard across participants and not controlled by either the participant or the researcher. The tempo for all pieces was slow (∼60 beats per minute). The pieces were in either major keys or minor keys, but all consisted primarily of consonant harmonies and sustained melodic phrases. Participants were allowed to control the volume to their individual comfort level.

Active control

Professional recordings of nature sounds (including forest, river, and wind sounds and birdsong) selected by the researcher without added music were used as the active control condition (Supplementary Table 1). All participants heard the same recording. This active control condition allowed for non-musical analgesic effects, such as distraction, to be controlled in the experimental design. Participants were allowed to control the volume to their individual comfort level.

Trial design

This was a single-center, two-arm parallel double-blind randomized controlled pilot study conducted in the United States (ClinicalTrials.gov, NCT04059042). Participants with FM underwent two testing sessions conducted 1 week apart: testing as usual with no sound (Silence), and testing while listening to instrumental Western classical music or nature sound control (Audio). Participants were randomized 1:1 to the two arms (Music or Nature sounds), counterbalanced for session order. Study data were collected and managed, and randomization was implemented using REDCap electronic data capture tools (61, 62).

Procedures

The study was conducted at a research laboratory within the medical center campus. Data were collected with participants seated in a small, quiet room across a small table from the researcher. The study team was blinded throughout data collection and analysis.

Participants in both arms had QST and electrocardiogram (ECG) testing on two separate days, conducted 1 week apart: baseline (Testing as Usual, Silence) and auditory listening (Music or Nature sounds) counterbalanced across participants. After obtaining informed consent, participants were fitted with ECG electrodes and were given instructions about the procedures. Participants were asked to wear noise-canceling headphones during all testing procedures, regardless of what they were hearing (music, nature sounds, or silence). The researcher wore ear plugs to remain blinded to what the participant was hearing and communicated with the participant through written instructions and gestures for the remainder of the test. Informed consent, instructions, and electrode placement took ∼30 min. After the electrodes and headphones were in place, the researcher left the room, and baseline ECG was recorded for 5 min while participants sat quietly. The researcher returned to the room, started the specified audio track, and then left the room for 10 min while participants sat quietly listening to the track. The researcher then returned to the room for QST testing while the participant continued to listen to the audio track. QST procedures lasted for 15 min.

TABLE 3 Pain variables by session (Audio, Silence) and audio group assignment (Music, Nature).

	Music group ($n = 4$) [M (SD)]	Nature group ($n = 5$) [M (SD)]	Statistical test	Z (p)
Temporal summation: audio	20.25 (14.29)	4.13 (5.60)	–	–
Temporal summation: silence	20.17 (13.14)	9.40 (7.44)	–	–
Session difference: audio vs. silence	–	–	Related-samples Wilcoxon signed-rank	39.00 (0.051[†])
Group difference: silence	–	–	Independent samples Mann–Whitney *U*	2.00 (0.06[†])
Group difference: audio	–	–	Independent samples Mann–Whitney *U*	2.00 (0.06[†])
Group difference in between session change	–	–	Independent samples Mann–Whitney *U*	19.00 (0.03*)
Mechanical pain tolerance: audio	4.12 (1.02)	5.17 (0.85)	–	–
Mechanical pain tolerance: silence	4.18 (1.00)	5.05 (0.94)	–	–
Session difference: audio vs. silence	–	–	Related-samples Wilcoxon signed-rank	18.00 (0.59)
Group difference: silence	–	–	Independent samples Mann–Whitney *U*	14.00 (0.41)
Group difference: audio	–	–	Independent samples Mann–Whitney *U*	16.00 (0.19)
Group difference in between session change	–	–	Independent samples Mann–Whitney *U*	14.00 (0.41)

Temporal summation is the difference in pain rating out of 100 between a single stimulus and the series of 10 in the non-dominant forearm. Mechanical pain tolerance is the pressure intensity (kg/cm^2) at which participants rated pain in their non-dominant thumb at 70 out of 100. Between-session pain measures were assessed with related-samples Wilcoxon signed-rank tests. Between-group comparisons were assessed with independent samples Mann–Whitney U-tests. Between-session change scores were calculated per participant as Audio minus Silence and compared between groups with independent samples Mann–Whitney U-tests.
*Indicates significant effects at $p < 0.05$.
[†]Indicates non-significant effects at $p < 0.10$.
M, mean; SD, standard deviation.

Written instruction reminders were provided to participants before each task. At the end of the first day of testing, participants completed surveys electronically for 30 min on a laptop through REDCap (61, 62). All sessions were conducted in the same way and lasted approximately the same amount of time. The total testing time was 1.5 h on the first day of testing and 1 h on the second day of testing. After completing all procedures on the second day of testing, participants were given $100 for their time.

Randomization sequence generation

Participants were randomized 1:1 to Music or Active Control (Nature sounds), counterbalanced for session order with Silence. Randomization was implemented with the REDCap Randomization tool (61, 62) using an order defined by a computer-generated online random number generator for the four possible session orders (Music/Silence, Silence/Music, Nature/Silence, and Silence/Nature), coded by track number only, and was stratified by gender.

Randomization allocation/concealment method and implementation

Audio tracks for Music, Nature sounds, and two tracks for Silence were labeled with dummy codes (1–4) to blind the researcher collecting the data. The original audio tracks were given to a person outside the study team who renamed the files and placed the code into a sealed opaque envelope. The researcher selected the track by a number assigned during the randomization procedure. Randomization was concealed from the researchers until the final group analysis.

Statistical analysis

Data were assessed for normality with tests for skewness and kurtosis (63). These tests revealed that several outcome variables had a non-normal distribution with skewness > |1| and kurtosis > |3| (Supplementary Table 2, Supplementary Figure 1). Therefore, non-parametric tests were conducted to compare groups and sessions (64). Demographic characteristics and questionnaire measures were compared between the two Audio Groups using independent samples Mann–Whitney

U-tests for continuous variables and Chi-square (X^2) test for categorical variables.

Pain outcome measures of temporal summation and mechanical pain tolerance were assessed using independent samples Mann–Whitney U-tests for between-group comparisons (Audio Group: Music, Nature) and related-samples Wilcoxon signed-rank test for within-subject comparisons (Sessions: Silence, Audio). To compare group differences in change in outcome measures across sessions, a magnitude of change score was calculated for each participant to reflect the degree of analgesia experienced during the Audio condition. For pain measures of temporal summation, for which higher values indicate worse pain, the score was calculated as Silence minus Audio; for mechanical pain tolerance, for which lower values indicate worse pain, the magnitude of change score was calculated as Audio minus Silence. Independent samples Mann–Whitney U-tests were then conducted for the magnitude of change scores for pain measures of temporal summation and mechanical pain tolerance.

The ANS measures of heart rate and heart rate variability (root mean square of successive differences, HRV) during listening and pain, corrected for baseline values, were assessed with independent samples Mann–Whitney U-tests for between-group comparisons (Audio Group: Music, Nature) and related-samples Wilcoxon signed-rank test for within-subject comparisons (Sessions: Silence, Audio). The magnitude of change score was calculated as Pain minus Listen to determine the within-session change during painful stimulation, and a second score was calculated as Pain minus Listen and Audio minus Silence to determine the change in analgesic effect across the sessions for each participant. The Pain minus Listen within-session magnitude of change was compared for within-subject comparisons between sessions (Silence, Audio) using related-samples Wilcoxon signed-rank test. To determine whether the Audio Groups (Music, Nature) differed in analgesic effect during pain, the magnitude of change score for Pain minus Listen and Audio minus Silence was compared using independent samples Mann–Whitney U-test. Statistical significance was set at $p < 0.05$ for each test.

Results

Demographic and questionnaire measures

Group differences in demographic measures are presented in Table 1. The groups did not differ in age, gender, ethnicity, relationship status, or education level. Questionnaire measures are presented in Table 2. Participants in both groups were experiencing moderate FM, depression, and anxiety symptoms. They also reported low to moderate commitment to music and innovative musical aptitude, but reported moderate to high affective reactions to music, positive psychotropic effects from music, and reactive musical behavior. The groups did not differ in FM symptom severity or musical experience; however, they were significantly different in symptoms of anxiety, with participants in the Nature group experiencing higher anxiety than participants in the Music group.

Pain measures

In the non-parametric tests for temporal summation, the difference between a single stimulus and a series of stimuli, the independent samples Mann–Whitney U-test identified a significant group difference in the magnitude of temporal summation between session changes ($p = 0.03$), with the Nature group showing lower temporal summation while listening to the audio compared to silence, while the Music group was not different between the sessions. The related-samples Wilcoxon signed-rank test for session revealed a non-significant trend ($p = 0.051$), with lower temporal summation during audio compared to silence. The independent samples Mann–Whitney U-test showed that temporal summation was marginally higher but not significantly different in the Music group compared to the Nature group ($p = 0.06$), indicating that participants in the Music group may have had higher temporal summation. Mechanical pain tolerance, the amount of pressure on the thumb that was rated at >80, was not significantly different between groups or between sessions (Table 3).

ANS measures

The independent samples Mann–Whitney U-test for heart rate revealed a non-significant trend for a group difference while Listening during Silence ($p = 0.06$), with the Nature group having slightly more reduced heart rate from baseline compared to the Music group (Figure 2). No other effects were significant. The non-parametric tests for heart rate variability (HRV) revealed no significant effects (Figure 3, Supplementary Table 3).

Discussion

In this pilot study, we measured the analgesic effects associated with music and nature sounds on objective autonomic system responsiveness to painful stimuli. Our experimental design allowed for blinding during both data collection and analysis, reducing the potential for bias. By counterbalancing the order of audio presentation, we showed the feasibility of repeated measures testing in patients with FM while controlling for order effects. Even in our small sample, randomization successfully yielded relatively matched groups, with no group differences observed for FM symptoms, age,

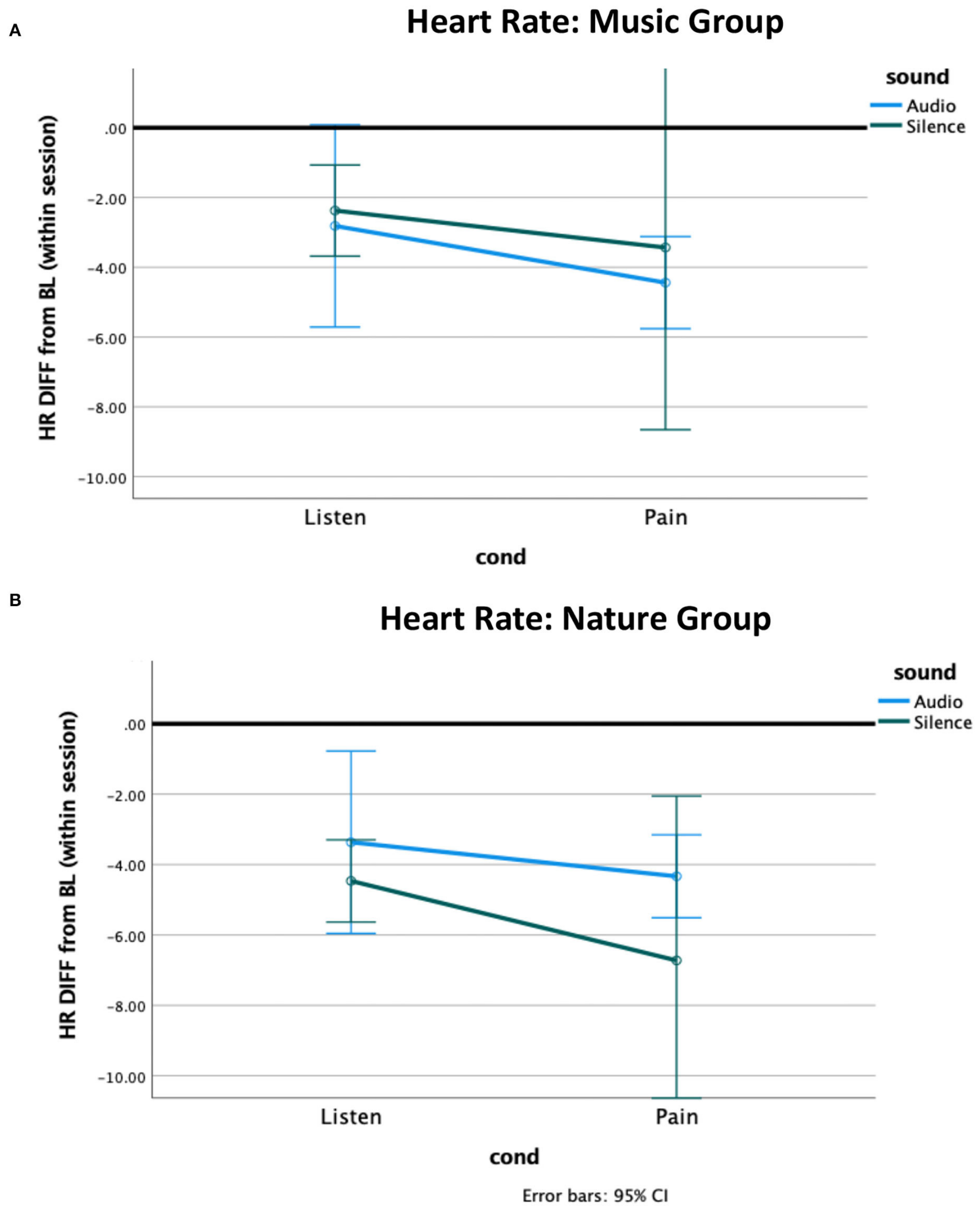

FIGURE 2
Heart rate difference from within-session baseline. The heart rate of both groups decreased from baseline to the listening condition and further decreased during pain. **(A)** The Music group had a greater pain-related decrease to music compared to silence, and **(B)** the Nature group had a greater pain-related decrease to silence compared to nature sounds.

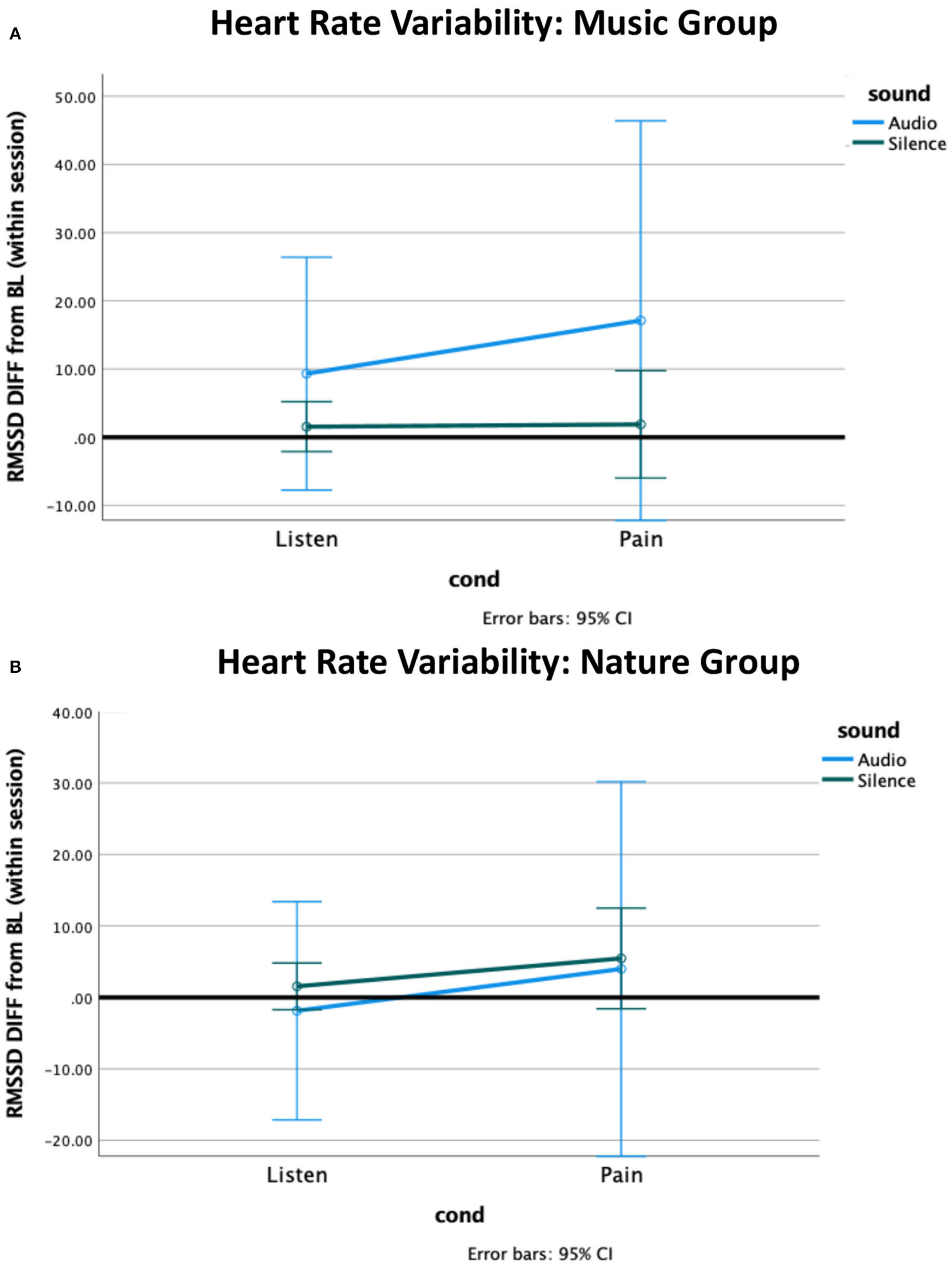

FIGURE 3
Heart rate variability (HRV) difference from within-session baseline. **(A)** The HRV in the Music group increased from baseline to the listening condition, and further increased during pain, with no effect observed for silence. **(B)** The Nature group had marginally greater HRV during pain. The HRV during pain was associated with a high standard deviation in both groups.

marital status, or education. By random chance, we did observe between-group differences in anxiety, although the Nature group was numerically only seven points higher than the Music group, and both groups were within one standard deviation of the standardized mean on the PROMIS scale.

Objective pain

This study aimed to manipulate two potential mechanisms for music-evoked analgesia: cognitive distraction and physiological or vagal response alteration. By using musical stimuli and active control (Nature sounds), and comparing to each participant's own Silence control, our experimental design allows for the examination of distraction due to general relaxing audio, as well as examining music-specific analgesia by comparing the Music to the Nature Sound condition directly. We hypothesized that both listening conditions (Music and Nature) would reduce pain sensitivity compared to testing during silence and that music listening would reduce pain sensitivity compared to nature sounds (32, 34, 36).

Temporal summation

We observed a strong effect of cognitive distraction, with reduced temporal summation during either audio condition compared to silence, indicating that the auditory stimulus was effective in reducing pain. The direction of the group difference was opposite to our hypothesis, with the Nature group showing an analgesic effect, while the Music group showed none. This could be due to the confound of anxiety symptoms between the groups, or it could be a potential confound of pre-existing differences in sensitization between the groups, as temporal summation overall was somewhat higher in the Music group compared to the Nature group (20).

Mechanical pain tolerance

Interestingly, we did not observe any effects of group or condition on tolerance to thumb pressure. This was surprising, as this test usually shows high sensitivity for variations in pain response (22). However, it is possible that the transient changes between sessions were too small to be observed in this small sample, and that a larger sample or longer intervention would be necessary to see differences in maximal pain tolerance.

ANS

Heart rate

We also hypothesized that music would increase vagal input to the autonomic nervous system, decreasing heart rate and increasing heart rate variability compared to both silence and nature sounds. Vagal response during pain is a coping mechanism (65). We did observe a small difference between the groups in heart rate pointing to the feasibility of the chosen stimuli, yet the direction was opposite to our hypothesis with the Nature group having greater reductions from baseline compared to the Music group. This could also be related to group differences in anxiety or other pre-existing physiological differences between the groups. The Nature group, having higher anxiety ($p = 0.02$), could have had elevated heart rate at baseline, thereby having more chance for the analgesic effect to be observed. In our analysis, we corrected for the within-session baseline to address this possibility.

Heart rate variability

Heart rate variability is a better measure for vagal response than raw heart rate (66). However, we observed no significant effects for HRV, suggesting that we were underpowered to observe a vagal response with this small sample. While not significant, the Music group did show a pattern of response that was consistent with vagal activation similar to other studies, with a reduction from baseline and then further reduction during pain, that was not observed in the Nature group (67, 68). Such anticipated response might be due to emotional expression toward the music stimulus, enjoyment, or simply just being entertained, an effect that might have been increased had the participants selected the music themselves. A larger sample would be needed to clarify whether there is a greater vagal response to music more generally.

Individual differences

Individual differences likely play a role in how a person will respond to auditory stimulation (69–71). While we measured many of these potential differences, including fibromyalgia symptoms, mood symptoms, and music experience, our small sample size did not allow for comparisons between them. However, these are likely important variables to consider in future trials.

Limitations

This study is limited by the small sample size, and the results should be interpreted with caution. Due to the small sample size, it was difficult to fully balance the groups. Our groups differed on anxiety potentially confounding our results, although all participants were in the mild to moderate anxiety range. Additionally, although it was not statistically significant, more participants in the Music group had attained education beyond a bachelor's degree. However, inherently when having a small sample size, it is somewhat easier to detect within-participant effects rather than between-participant effects. It is possible that a greater analgesic effect would be elicited from the music of an individual's choice, as that could potentially have greater associations with positive memories and previous experience, thus enhancing the physiological response. Our experimental design using nature sounds as an auditory control and carefully selected musical selections with characteristics hypothesized to facilitate relaxation and analgesia is a strength, and can be used in future studies to separate the effects of auditory distraction from music-specific effects.

Conclusion

In conclusion, our current results did not support our hypothesis of stronger analgesic effects of music vs. distracting nature sounds; however, we did observe strong effects of auditory distraction on pain temporal summation and tolerance. The confounding effect of anxiety symptoms in our study, as well as the individual differences observed on the MEQ, suggest that variability in mood and other factors may be important in understanding how individuals will respond to music or other auditory stimuli to gain therapeutic analgesic effects. While these results should be treated with caution, this study provides preliminary evidence that some individuals may benefit from music or audio stimulation as a treatment more than others. Further study is warranted.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://osf.io/84baz.

Ethics statement

The studies involving human participants were reviewed and approved by University of Kansas Medical Center Institutional Review Board Human Subjects Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

RL: conceptualization, methodology, formal analysis, investigation, data curation, writing of the original draft, project administration, and funding acquisition. MM: formal analysis, investigation, data curation, reviewing and editing, and project administration. AC: conceptualization, methodology, resources, writing of the original draft, reviewing and editing, and funding acquisition. ZM: reviewing and editing. LM: resources and reviewing and editing. KG: conceptualization, methodology, investigation, resources, and reviewing and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

AC serves as a consultant for Swing Therapeutics.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpain.2022.953118/full#supplementary-material

References

1. Williams DA, Clauw DJ. Understanding fibromyalgia: lessons from the broader pain research community. *J Pain.* (2009) 10:777–91. doi: 10.1016/j.jpain.2009.06.001

2. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain.* (2011) 152:S2–15. doi: 10.1016/j.pain.2010.09.030

3. Melemedjian OK, Tillu DV, Asiedu MN, Mandell EK, Moy JK, Blute VM, et al. BDNF regulates atypical PKC at spinal synapses to initiate and maintain a centralized chronic pain state. *Mol Pain.* (2013) 9:12. doi: 10.1186/1744-8069-9-12

4. Clauw DJ. Fibromyalgia: a clinical review. *JAMA.* (2014) 311:1547–55. doi: 10.1001/jama.2014.3266

5. Aasvang EK, Gmaehle E, Hansen JB, Gmaehle B, Forman JL, Schwarz J, et al. Predictive risk factors for persistent postherniotomy pain. *Anesthesiology.* (2010) 112:957–69. doi: 10.1097/ALN.0b013e3181d31ff8

6. Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *J Pain.* (2009) 10:556–72. doi: 10.1016/j.jpain.2009.02.002

7. Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, et al. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. *Pain.* (2008) 138:22–8. doi: 10.1016/j.pain.2007.10.033

8. Ablin K, Clauw DJ. From fibrositis to functional somatic syndromes to a bell-shaped curve of pain and sensory sensitivity: evolution of a clinical construct. *Rheum Dis Clin North Am.* (2009) 35:233–51. doi: 10.1016/j.rdc.2009.06.006

9. Diatchenko L, Nackley AG, Slade GD, Bhalang K, Belfer I, Max MB, et al. Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. *Pain.* (2006) 125:216–24. doi: 10.1016/j.pain.2006.05.024

10. Gwilym SE, Keltner JR, Warnaby CE, Carr AJ, Chizh B, Chessell I, et al. Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. *Arthritis Rheum.* (2009) 61:1226–34. doi: 10.1002/art.24837

11. Nielsen CS, Staud R, Price DD. Individual differences in pain sensitivity: measurement, causation, and consequences. *J Pain.* (2009) 10:231–7. doi: 10.1016/j.jpain.2008.09.010

12. Neddermeyer TJ, Fluhr K, Lotsch J. Principle components analysis of pain thresholds to thermal, electrical, and mechanical stimuli suggests a predominant common source of variance. *Pain.* (2008) 138:286–91. doi: 10.1016/j.pain.2007.12.015

13. Fillingim RB. Individual differences in pain responses. *Curr Rheumatol Rep.* (2005) 7:342–7. doi: 10.1007/s11926-005-0018-7

14. Wilder-Smith OHG, Tassonyi E, Arendt-Nielsen L. Preoperative back pain is associated with diverse manifestations of central neuroplasticity. *Pain.* (2002) 97:189–94. doi: 10.1016/S0304-3959(01)00430-4

15. Gibson SJ, Littlejohn GO, Gorman MM, Helme RD, Granges G. Altered heat pain thresholds and cerebral event-related potentials following painful CO_2 laser stimulation in subjects with fibromyalgia syndrome. *Pain.* (1994) 58:185–93. doi: 10.1016/0304-3959(94)90198-8

16. Giesecke J, Reed BD, Haefner HK, Giesecke T, Clauw DJ, Gracely RH. Quantitative sensory testing in vulvodynia patients and increased peripheral pressure pain sensitivity. *Obstet Gynecol.* (2004) 104:126–33. doi: 10.1097/01.AOG.0000129238.49397.4e

17. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum.* (2002) 46:1333–43. doi: 10.1002/art.10225

18. Greenspan JD, Slade GD, Bair E, Dubner R, Fillingim RB, Ohrbach R, et al. Pain sensitivity risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case control study. *J Pain.* (2011) 12:T61–74. doi: 10.1016/j.jpain.2011.08.006

19. Leffler AS, Hansson P, Kosek E. Somatosensory perception in a remote pain-free area and function of diffuse noxious inhibitory controls (DNIC) in patients suffering from long-term trapezius myalgia. *Eur J Pain.* (2002) 6:149–59. doi: 10.1053/eujp.2001.0312

20. Hsu MC, Harris RE, Sundgren PC, Welsh RC, Fernandes CR, Clauw DJ, et al. No consistent difference in gray matter volume between individuals with fibromyalgia and age-matched healthy subjects when controlling for affective disorder. *Pain.* (2009) 143:262–7. doi: 10.1016/j.pain.2009.03.017

21. As-Sanie S, Harris RE, Harte SE, Tu FF, Neshewat G, Clauw DJ. Increased pressure pain sensitivity in women with chronic pelvic pain. *Obstet Gynecol.* (2013) 122:1047–55. doi: 10.1097/AOG.0b013e3182a7e1f5

22. Petzke F, Harris RE, Williams DA, Clauw DJ, Gracely RH. Differences in unpleasantness induced by experimental pressure pain between patients with fibromyalgia and healthy controls. *Eur J Pain.* (2005) 9:325–35. doi: 10.1016/j.ejpain.2004.09.001

23. Berwick RJ, Siew S, Andersson DA, Marshall A, Goebel A. A systematic review into the influence of temperature on fibromyalgia pain: meteorological studies and quantitative sensory testing. *J Pain.* (2021) 22:473–86. doi: 10.1016/j.jpain.2020.12.005

24. Arendt-Nielsen L, Brennum J, Sindrup S, Bak P. Electrophysiological and psychophysical quantification of temporal summation in the human nociceptive system. *Eur J Appl Physiol Occup Physiol.* (1994) 68:266–73. doi: 10.1007/BF00376776

25. Staud R, Weyl EE, Riley JL 3rd, Fillingim RB. Slow temporal summation of pain for assessment of central pain sensitivity and clinical pain of fibromyalgia patients. *PloS ONE.* (2014) 9:e89086. doi: 10.1371/journal.pone.0089086

26. Pujol J, Lopez-Sola M, Ortiz H, Vilanova JC, Harrison BJ, Yucel M, et al. Mapping brain response to pain in fibromyalgia patients using temporal analysis of FMRI. *PLoS ONE.* (2009) 4:e5224. doi: 10.1371/journal.pone.0005224

27. Ribeiro MKA, Alcantara-Silva TRM, Oliveira JCM, Paula TC, Dutra JBR, Pedrino GR, et al. Music therapy intervention in cardiac autonomic modulation, anxiety, and depression in mothers of preterms: randomized controlled trial. *BMC Psychol.* (2018) 6:57. doi: 10.1186/s40359-018-0271-y

28. Hohneck A, Reyser C, Merx K, Weingartner S, Mavratzas A, Schumacher G, et al. Differential effects of sound intervention and rest on cardiovascular parameters in cancer patients: a randomized cross-over trial. *Integr Cancer Ther.* (2021) 20:1534735421995239. doi: 10.1177/1534735421995239

29. Witvliet CVO, Vrana SR. Play it again Sam: repeated exposure to emotionally evocative music polarises liking and smiling responses, and influences other affective reports, facial EMG, and heart rate. *Cogn Emot.* (2007) 21:3–25. doi: 10.1080/02699930601000672

30. Williams C, Hine T. An investigation into the use of recorded music as a surgical intervention: a systematic, critical review of methodologies used in recent adult controlled trials. *Complement Ther Med.* (2018) 37:110–26. doi: 10.1016/j.ctim.2018.02.002

31. Hole J, Hirsch M, Ball E, Meads C. Music as an aid for postoperative recovery in adults: a systematic review and meta-analysis. *Lancet.* (2015) 386:1659–71. doi: 10.1016/S0140-6736(15)60169-6

32. Fleming PS, Strydom H, Katsaros C, MacDonald L, Curatolo M, Fudalej P, et al. Non-pharmacological interventions for alleviating pain during orthodontic treatment. *Cochrane Database Syst Rev.* (2016) 12:CD010263. doi: 10.1002/14651858.CD010263.pub2

33. Hsu CC, Chen SR, Lee PH, Lin PC. The effect of music listening on pain, heart rate variability, and range of motion in older adults after total knee replacement. *Clin Nurs Res.* (2019) 28:529–47. doi: 10.1177/1054773817749108

34. Basinski K, Zdun-Ryzewska A, Majkowicz M. The role of musical attributes in music-induced analgesia: a preliminary brief report. *Front Psychol.* (2018) 9:1761. doi: 10.3389/fpsyg.2018.01761

35. Zhao H, Chen AC. Both happy and sad melodies modulate tonic human heat pain. *J Pain.* (2009) 10:953–60. doi: 10.1016/j.jpain.2009.03.006

36. Garza-Villarreal EA, Pando V, Vuust P, Parsons C. Music-induced analgesia in chronic pain conditions: a systematic review and meta-analysis. *Pain Physician.* (2017) 20:597–610. doi: 10.36076/ppj/2017.7.597

37. Lunde SJ, Vuust P, Garza-Villarreal EA, Vase L. Music-induced analgesia: how does music relieve pain? *Pain.* (2019) 160:989–93. doi: 10.1097/j.pain.0000000000001452

38. Sihvonen AJ, Pitkaniemi A, Sarkamo T, Soinila S. Isn't there room for music in chronic pain management? *J Pain.* (2022) 23:1143–50. doi: 10.1016/j.jpain.2022.01.003

39. Villarreal EA, Brattico E, Vase L, Ostergaard L, Vuust P. Superior analgesic effect of an active distraction versus pleasant unfamiliar sounds and music: the influence of emotion and cognitive style. *PLoS ONE.* (2012) 7:e29397. doi: 10.1371/journal.pone.0029397

40. Juslin PN, Sloboda JA. *Music and Emotion: Theory and Research.* Oxford, NY: Oxford University Press (2001), viii, p. 487.

41. Reybrouck M, Eerola T. Music and its inductive power: a psychobiological and evolutionary approach to musical emotions. *Front Psychol.* (2017) 8:494. doi: 10.3389/fpsyg.2017.00494

42. Aselton P. Sources of stress and coping in American college students who have been diagnosed with depression. *J Child Adolesc Psychiatr Nurs.* (2012) 25:119–23. doi: 10.1111/j.1744-6171.2012.00341.x

43. Brandes V, Terris DD, Fischer C, Loerbroks A, Jarczok MN, Ottowitz G, et al. Receptive music therapy for the treatment of depression: a proof-of-concept study and prospective controlled clinical trial of efficacy. *Psychother Psychosom.* (2010) 79:321–2. doi: 10.1159/000319529

44. Blood AJ, Zatorre RJ. Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proc Natl Acad Sci U S A.* (2001) 98:11818–23. doi: 10.1073/pnas.191355898

45. Salimpoor VN, Benovoy M, Larcher K, Dagher A, Zatorre RJ. Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nat Neurosci.* (2011) 14:257–62. doi: 10.1038/nn.2726

46. Martin-Saavedra JS, Vergara-Mendez LD, Pradilla I, Velez-van-Meerbeke A, Talero-Gutierrez C. Standardizing music characteristics for the management of pain: a systematic review and meta-analysis of clinical trials. *Complement Ther Med.* (2018) 41:81–9. doi: 10.1016/j.ctim.2018.07.008

47. Garza-Villarreal EA, Wilson AD, Vase L, Brattico E, Barrios FA, Jensen TS, et al. Music reduces pain and increases functional mobility in fibromyalgia. *Front Psychol.* (2014) 5:90. doi: 10.3389/fpsyg.2014.00090

48. Garza-Villarreal EA, Jiang Z, Vuust P, Alcauter S, Vase L, Pasaye EH, et al. Music reduces pain and increases resting state fMRI BOLD signal amplitude in the left angular gyrus in fibromyalgia patients. *Front Psychol.* (2015) 6:1051. doi: 10.3389/fpsyg.2015.01051

49. Brummett CM, Janda AM, Schueller CM, Tsodikov A, Morris M, Williams DA, et al. Survey criteria for fibromyalgia independently predict increased postoperative opioid consumption after lower-extremity joint arthroplasty: a prospective, observational cohort study. *Anesthesiology.* (2013) 119:1434–43. doi: 10.1097/ALN.0b013e3182a8eb1f

50. Janda AM, As-Sanie S, Rajala B, Tsodikov A, Moser SE, Clauw DJ, et al. Fibromyalgia survey criteria are associated with increased postoperative opioid consumption in women undergoing hysterectomy. *Anesthesiology.* (2015) 122:1103–11. doi: 10.1097/ALN.0000000000000637

51. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. *Arthritis Rheum.* (1990) 33:160–72. doi: 10.1002/art.1780330203

52. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RS, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR preliminary diagnostic criteria for fibromyalgia. *J Rheumatol.* (2011) 38:1113–22. doi: 10.3899/jrheum.100594

53. Wolfe F. Fibromyalgianess. *Arthritis Rheum.* (2009) 61:715–6. doi: 10.1002/art.24553

54. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the brief pain inventory for chronic nonmalignant pain. *J Pain.* (2004) 5:133–7. doi: 10.1016/j.jpain.2003.12.005

55. Jensen MP, Turner JA, Romano JM, Fisher LD. Comparative reliability and validity of chronic pain intensity measures. *Pain.* (1999) 83:157–62. doi: 10.1016/S0304-3959(99)00101-3

56. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain.* (2008) 9:105–21. doi: 10.1016/j.jpain.2007.09.005

57. Bennett RM, Friend R, Jones KD, Ward R, Han BK, Ross RL. The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. *Arthritis Res Ther.* (2009) 11:R120. doi: 10.1186/ar2783

58. Giesecke T, Williams DA, Harris RE, Cupps TR, Tian X, Tian TX, et al. Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors. *Arthritis Rheum.* (2003) 48:2916–22. doi: 10.1002/art.11272

59. Werner PD, Swope AJ, Heide FJ. The music experience questionnaire: development and correlates. *J Psychol.* (2006) 140:329–45. doi: 10.3200/JRLP.140.4.329-345

60. Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain.* (2006) 10:77–88. doi: 10.1016/j.ejpain.2005.02.003

61. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* (2009) 42:377–81. doi: 10.1016/j.jbi.2008.08.010

62. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform.* (2019) 95:103208. doi: 10.1016/j.jbi.2019.103208

63. Ghasemi A, Zahediasl S. Normality tests for statistical analysis: a guide for non-statisticians. *Int J Endocrinol Metab.* (2012) 10:486–9. doi: 10.5812/ijem.3505

64. Schober P, Vetter TR. Nonparametric statistical methods in medical research. *Anesth Analg.* (2020) 131:1862–3. doi: 10.1213/ANE.0000000000005101

65. Fabes RA, Eisenberg N. Regulatory control and adults' stress-related responses to daily life events. *J Pers Soc Psychol.* (1997) 73:1107–17. doi: 10.1037/0022-3514.73.5.1107

66. Nussinovitch U, Elishkevitz KP, Katz K, Nussinovitch M, Segev S, Volovitz B, et al. Reliability of ultra-short ECG indices for heart rate variability. *Ann Noninvasive Electrocardiol.* (2011) 16:117–22. doi: 10.1111/j.1542-474X.2011.00417.x

67. Forte G, Troisi G, Pazzaglia M, Pascalis V, Casagrande M. Heart rate variability and pain: a systematic review. *Brain Sci.* (2022) 12:153. doi: 10.3390/brainsci12020153

68. Koelsch S, Jancke L. Music and the heart. *Eur Heart J.* (2015) 36:3043–9. doi: 10.1093/eurheartj/ehv430

69. Martarelli CS, Mayer B, Mast FW. Daydreams and trait affect: the role of the listener's state of mind in the emotional response to music. *Conscious Cogn.* (2016) 46:27–35. doi: 10.1016/j.concog.2016.09.014

70. Carlson E, Burger B, London J, Thompson MR, Toiviainen P. Conscientiousness and extraversion relate to responsiveness to tempo in dance. *Hum Mov Sci.* (2016) 49:315–25. doi: 10.1016/j.humov.2016.08.006

71. Eerola T, Vuoskoski JK, Kautiainen H. Being moved by unfamiliar sad music is associated with high empathy. *Front Psychol.* (2016) 7:1176. doi: 10.3389/fpsyg.2016.01176

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The impact of music-imaginative pain treatment (MIPT) on psychophysical affect regulation – A single case study

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Music-imaginative Pain Treatment (MIPT) is part of the multi-professional treatment plan for hospitalised patients in departments for psychosomatic medicine. MIPT is an intervention that encourages the patient to create music representing pain and relief from pain and promotes active engagement and self-reflection. This single case study of a 46-year-old female patient diagnosed with chronic pain disorder with somatic and psychological factors includes narrative, demographic, psychometric, and cardiophysiological data. During the interventions, early childhood stress, which is a risk factor for developing chronic pain, turns out to be a crucial focal point in therapy and conspicuous in her handling of the music. Social trauma is considered an appropriate concept for a deeper understanding of the case.

KEYWORDS

somatoform pain disorder, music-imaginative paint treatment, affect regulation, trauma, heart rate variabiity

Introduction

How do pain perception and vegetative regulation of the cardiophysiological system (heart rate variability; HRV) change through music-imaginative pain treatment (MIPT) in a chronic pain patient? What is the development and sound of self-composed music for pain and relief? What influence do events from one's biography have on the course of treatment? How does the patient develop an awareness of the impact of biographical events on chronic pain during MIPT?

These questions are central in the single case study of Mrs S., who participated in a clinical study by Metzner et al. (2022) (1) with patients suffering from a chronic pain disorder and undergoing psychosomatic inpatient treatment. Rather than presenting outcomes this multi-perspective analysis aims to gain a differentiated insight into the complex impact levels, and their interconnections, that come into effect in MIPT. This case study presents the chronology of the treatment process. It successively integrates the surrounding quali-quantitative data, including psychometric data on (a) the baseline assessment at the beginning of the treatment, (b) the subjective pain intensity (pre-post), and (c) cardiophysiological data collected through Electrocardiogramm (ECG) and subsequent HRV analysis. Additionally, (d) narrative and musical data are collected through audio recordings.

Context, setting, intervention

In the Department of Psychosomatic Medicine and Psychotherapy at the University Hospital Magdeburg all kinds of psychosomatic disorders were treated. The multi-professional, complex treatment was based on a psychodynamic model. The treatment typically lasted 12 weeks. During this period, the patients received group and individual psychotherapy as well as music-, art-, social- and movement-therapy. Patients with a chronic pain disorder were offered MIPT during the first weeks of their inpatient stay, encompassing 4 sessions within 2 weeks.

Music-imaginative pain treatment (MIPT)

Music-imaginative pain treatment (MIPT) is an intervention that was initially developed as a form of "entrainment" within a single session (2, 3); later, it was established as a manualised treatment (4). Its professional implementation requires special further training.

MIPT takes place in an individual setting in a room equipped with a great variety of musical instruments. It comprises four treatment phases (I–IV), with three to four 50 min-sessions: firstly, the pain experience is explored in a detailed narrative interview and quantitatively recorded using a visual analogue scale (VAS) (see Section "Cardio-physiological data") (I). In the second step, the patient creates two sound compositions with the assistance of the therapist to express the pain experience (Pain Music; PM) and the idea of pain relief (Healing Music; HM) (II). No previous musical training is required for this. In the application phase (III), the music therapist plays the two compositions to the patient. The patient indicates the start and stop of PM and of HM, and controls the sequence of musical events as well as the music's tempo and dynamics. Finally (IV), the patient's experience is reflected on in a conversation, and new insights for the further course of therapy are discussed in the department. The role of the therapist is to provide a supportive framework for the exploration of the pain's characteristics, to assist the patient in the musical realisation of the pain experience and the ideas of relief, to empathise with the patient's experience both emotionally and musically, and to support the patient in this challenging, sometimes confrontational work. Clinical experience shows that MIPT gives the patient space to gain more flexibility when dealing with the pain experience and the affective attitudes toward pain more flexible. It increases the feeling of self-efficacy and promotes communication skills (5). In some cases, there is an insight into the underlying bio-psycho-social conditioning structure of chronic pain (6).

Case study: Mrs S.

Medical history, diagnoses and psychopathological findings at admission

Medical history

Mrs S. had been on sick leave for more than two years before admission. She had already been treated several times as an inpatient and day-care psychosomatic patient and once as a psychiatric patient due to a suicide attempt eight years ago. The focus so far had been a panic disorder, for which she was no longer able to leave the house. Mrs S. had been suffering from anxiety attacks for 20 years, for the last five years increasingly connected to problems in her marriage and at work. Due to the severe pain, especially in her legs, a rheumatological analysis was carried out, and fibromyalgia was diagnosed.

Diagnoses and psychopathological findings

- Chronic pain disorder, ICD 10: F 45.4 L through intervertebral disc protrusion L5/S1 on the right side
- Panic disorder, ICD-10 F41
- Combined personality disorder with dependent and histrionic components, ICD-l0 F61

The Symptom Checklist 90 (SCL 90) (7), which measures the current, perceived impairment due to physical and psychological symptoms, was used to assess the symptom burden on admission to the clinic (time: T0). Mrs S.'s basic psychological distress, according to the global characteristic value GSI (Global Severity Index), was in the range of "significantly increased" with 69 points. In comparison, the subscale "Obsessiveness" (72 points) was strongly increased, and the subscale "Phobic Anxiety" (77 points) was very strongly increased.

In addition, the short version of the Childhood Trauma Questionnaire (CTQ) (8) was used to assess emotional, physical and sexual abuse as well as emotional and physical neglect in childhood. In the case of Mrs S., the measured scores for three subscales resulted in the classification as "severe": "emotional abuse" (17 points), "emotional neglect" (17 points), and "physical neglect" (10 points).

Biography and current living situation

Mrs S. was born and grew up in a small town in East Germany during the time of the German Democratic

Republic (GDR) as the second child of state scientists and Socialist Unity Party (SED) members. Her older brother was favoured, while the patient only received recognition when she was in the newspaper for extraordinary achievements. If she got average grades at school, she was immediately grounded. If she was not on the podium in sports, she was criticised for not trying hard enough. Often she had to do additional training in the evening. Furthermore, she had to help a lot with household chores. If anything did not add up to the patent's standards, she was beaten by her mother with her "slipper" or by her father with his hand. As a teenager, her parents got her involved in politics, and she became a SED member herself.

Her first profession as a cook she did not choose herself. After two decades, she requalified to become an office clerk.

When Mrs S. got pregnant at the age of 20, she married the child's father against her parents' will. After the opening of the inner-German border, they moved to West Germany with their daughter. She felt oppressed in this marriage, that later turned violent and she decided to divorce her husband after 18 years of marriage. Then, she moved back to East Germany, where she married a second time. Mrs S. has been concerned about her husband's chronic illnesses.

At present Mrs S. is employed full-time in a zoo and pet shop but has been unable to work for 24 weeks. She states that she often worked there six days a week, for up to 12 h. This commitment at work was unnecessary and led to conflicts with her colleagues. She also went to the gym four times a week and worked out until completely exhausted.

Mrs S. in music therapy[1]

Mrs S.'s MIPT sessions were audio-recorded. The following account summarises her therapeutic process and integrates literal quotations from the patient.

Interview on pain (MIPT phase I)

Mrs S. describes her pain as starting from the hip and going through the legs into the feet and toes. Her arms were sensitive to pressure. The quality of the pain in the legs was tearing, tingling, like "stinging nettles". Mrs S. reported that she had been suffering from this pain continuously for two years. It is particularly severe in episodes where she suffers from feelings of weakness and gait disturbance. There is no apparent trigger. From her perspective, the pain comes from work overload, stress, and anger in her private life: "As if the soul says to the body: 'She does not listen to me; you have to tell her'." Tears come to her eyes.

Overall, Mrs S. feels exhausted and depressed. She observes an intense need for sleep and increasing forgetfulness. She is afraid of being considered a malingerer because all the treatment attempts with analgesics have had no effect. She had always had back pain in the past, but now she feels anger, despair, and helplessness. She sometimes seeks to hurt herself by trying to defy the pain actively, presses her toes firmly on the ground, walks barefoot on stones, and pinches her calves until they bruise: "There, I've shown you."

The composition of pain and healing music (MIPT phase II)

At the beginning of the session, the patient emphasises that her legs are always cramped and tense. When asked how she imagines music that describes her experience of pain, she answers: "Loud, bright, shrill. Like screaming." In the room equipped with numerous musical instruments, Mrs S. and her therapist search for suitable sound qualities. They try out various instruments until the patient decides on the marimba. A single bar, the D'', is struck with the wooden mallet quickly, loudly and in a constant penetrating pulse. This sound corresponds to the sharp, poignant quality of her pain. Then the next instrument is the cello. The strings are struck with the bow directly behind the bridge to express the loud, shrill scream that sounds "like a circular saw". The third instrument Mrs S. chooses is the bass slit drum. A specific note is struck quickly and consistently with a soft woollen mallet. The effect is a droning sound that the patient associates with her depressed state and her racing heart during a panic attack.

The patient is visibly tense as she selects and listens to the composition of sound qualities. "This really is it," she says. She wrings her hands and mentions immediate physical reactions (cramping in the legs, feeling hot, sweaty hands, racing heart). She says: "I am amazed that the sounds have such an effect on me. Without me having to do anything. It is automatic." The therapist and patient exchange ideas about how this music sounds rigid, mechanical and inhuman, like being in a factory with machines punching out metal. Mrs S. says: "If only I could sit down somewhere and let my feelings out. If only I could cry, but I can't."

The work on the pain music has required the whole session. Therefore, the healing music piece is being composed in another session. The patient is tense when she arrives at this session. She says that there had been an altercation on the ward. Nevertheless, she gets involved in the MIPT. She takes up a previously expressed idea about the composition of soothing sounds: they should be free, playful and reminiscent of a holiday at the Baltic Sea with her husband and dog. When the therapist asks her about childhood memories of the Baltic Sea, her mood changes. Even today, she feels disgust and

[1]For reasons of style, the course of therapy are written in the present tense.

shame when she thinks about having been forced by her parents to go to the nudist beach. Before those family holidays, she was often aggressive to other children or sick.

Musically, Mrs S. starts with the ocean drum[2]. She explores herself, sees herself in the water, in a playful fight with the waves, wants to be like the water, powerful, unstoppable, alive, "then nobody can harm me". Her family (parents, brother), on the other hand, would be intimidating "opponents". This fight has two sides: liberation from confinement and paternalism, but also pressure and physical exertion. However, she rejects the first way out of the situation: three soft sounds on the sansula[3]. Instead, she chooses the children's harp. The name alone seems to appeal to the patient. The lower 5–6 strings are to be arpeggiated irregularly, randomly, and with some louder notes in between. Nevertheless, the music seems a little mechanical.

Mrs S. determines that the the healing music shall begin with the children's harp, and then the ocean drum is added. The patient remarks that she has no cramped legs and feet and no sweaty hands at the moment.

Application of music (MIPT phase III)

During the MIPT session, the 24 h-ECG is running (see Section "Cardio-physiological data"). The device was put on beforehand so that the patient could get used to it before music therapy. The patient is excited and curious about what to expect. She has already felt anxiety on the way to the music therapy room. The therapist explains the course of the session. Due to the ECG-measurement there is a 5-minute resting phase before the start of the pain music. The pain music lasts two and a half minutes. The stroking on the cello does not work as arranged; the sound is not shrill enough but rather rough and uneven. The patient demanded the booming pulse on the bass slit drum twice more intensely. The healing music could not be realised as planned. The playing on the children's harp became too lively, and the ocean drum's sound seemed too halting. The music ends after a total of 7 min and 33 s.

In the following conversation, Mrs S. expresses her exhaustion. The silence of the 5-minute resting phase has been experienced as torturous by her. It reminded her of her mother ignoring her for days as punishment. (The therapist would have skipped the quiet phase if Mrs S. had mentioned these memories before.) The end of the pain music she experienced as a degrading "begging for mercy", also like in childhood. The pain intensity had risen to point 9 on the 10-point VAS. The therapist inquires about her reason for increasing the droning of the bass slit drum. "I wanted to push the pain to the extreme and prove how much I can take". When the therapist confronts the patient with the fact that this could be seen as auto-aggression, connections between the childhood traumas and the chronic pain become clear. The patient is frightened and sad: "Because what I do is never good enough. I have always had to endure the punishments in my life."

"The healing music had slowly brought relaxation, and the pain intensity decreased – in everyday life as well ..." says the patient. But she can only endure moments of well-being for a short time because this triggers feelings of guilt and worthlessness. To avoid this she escapes again into task fulfilment and performance.

The patient leaves the session emotionally agitated, but at the same time, she seems more relaxed. She expresses relief that she has put it all behind her and needs to let it sink in.

Reflection (MIPT phase IV)

Mrs S. says that the last MIPT session had a strong impact. She had talked about it in other therapies and also with her husband. For her, it is so frightening that not only did her childhood experiences have such a significant influence on her, but also she treated herself just as badly for a long time. The patient, who previously had problems identifying and verbalizing her emotions recognizes now a conglomerate of bewilderment, sadness, bitterness and disappointment, but at the same time also longing, especially for her parents, her daughter and her granddaughter, with whom she has had no contact at all for a year. "The fact that I talked about my parents like that and couldn't show any emotions kept me on edge. And my body then reacted in such a violent way – also to the music."

Although the process has not been easy, Mrs S. experiences MIPT as a constructive process. The therapists offers the audio recording of the music for her own use or as a keepsake. Mrs S. likes to receive it, even though she may not listen to it, saying: "After all, it belongs to me – despite everything".

Quantitative data

Pain intensity/10-step visual analogue scale (VAS) before and after

Pain intensity was measured at two points in time. In **Table 1**, both assessments (current and retrospective/forward-looking) are included.

[2]The ocean drum is a drum, invented by the French composer Olivier Messiaen) that makes sounds similar to those of the ocean.

[3]The sansula made by the HOKEMA company, is a further development of the kalimba, a sound reed instrument from the south of Africa

Cardio-physiological data

The HRV analysis of the application of self-composed music during MIPT as well as of entire day was included in analysis. The patient had a 24 h-ECG recording with the medilog R AR12 PLUS device (SCHILLER, Baar, Switzerland). That is a 3-channel ECG device with automatic detection of R waves, for which the sampling rate has been set to 1,000 Hz as recommended by the national guideline (9). Artefacts were manually removed from the raw ECG data using the medilog R DARWIN2 Enterprise processing software (SCHILLER, Baar, Switzerland) and prepared as Riva Rocci data (RR) interval series for HRV analysis. The program Kubios HRV Version 2.0, University of Eastern Finland, Kuopio, Finland (10, 11) was used to analyse the HRV parameters. The HRV parameters were determined in the time, frequency and phase domain.

Analysis of the 24-hour ECG recording

The assessment of the ECG recording over 24 h showed that the patient has a continuous still normal-frequency sinus rhythm with isolated ventricular extrasystoles with compensatory pauses (*n* = 30; 0.02%) and isolated supraventricular extrasystoles (*n* = 2). There are no higher grade volleys, and no prolonged pauses are seen. The mean heart rate (HR) was high, indicating higher sympathetic activation with 95 beats/min during the day and 73 beats/min during the night (reference values for females 45–46 years according to Lohninger, 2017, *p*. 232–33 (12): mean heart rate 24 h 69.7–78.1/Median 73.9 beats/min; mean heart rate day 75.57–84.4/Median 80 beats/min; mean heart rate night 61.1–69.3/Median 62.2 beats/min). Dynamic A (difference mean HR day/sleep) is strong for the 46-year-old, indicating, among other things, sustained activation during the day (reference values for females 45–46 years according to Lohninger, 2017, *p*. 234 (12): dynamic A 12.8–18.7/Median 15.7 beats/min). Over the entire recording period (23:59:59), this value was 87 beats/min and thus significantly above the average value for women of this age. The maximum HR was recorded at 09:59:52 at 144 beats/min (BMP) (see **Figure 1**) during the first minutes of the music therapy phase. The minimum HR was measured at 54 beats/min at 03:59:22 (during sleep).

Overall, the 24 h-ECG recording is to be considered within the normal range.

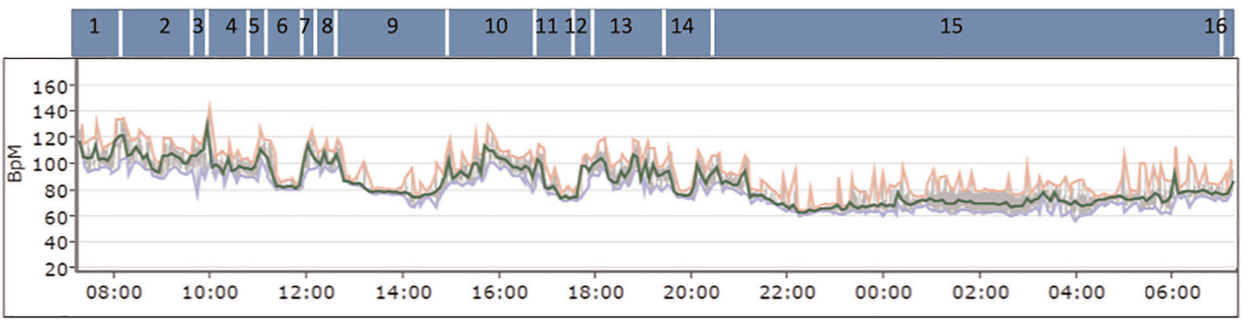
TABLE 1 Self-assessment of pain intensity at different points in time (10-step visual analogue scale VAS).

Time/time span	Pain intensity
Current: Start of MIPT	6
Retrospective average over the last four weeks	8
End of treatment	4
Retrospective application phase (pain music)	9
Retrospective application phase (healing music)	6
Current: Completion of MIPT	4

Evaluation of HR variability from the 24 h-ECG

When assessing the 24 h-ECG recording, a restricted HRV, especially in the range of RMSSD (12.4 ms) and SD1 (8.8 ms), as well as a clear shift in the frequency band (LF/HF) towards the sympathetic nervous system (value above 5) can be seen and should be considered overall as a sign of a disturbed sympathovagal balance (13) (**Figures 2**, **3**).

The spectrogram of the 24 h-ECG recording, especially during daytime hours, clearly shows an increased sympathetic activation with a decrease of the vagus as a



Colour legend: red=max; violet=min; green=average
Phases: 1= breakfast (7:17), 2 = rounds and individual consultation (08:15), 3 = walk (09:45), 4 = music therapy (10:00), 5 = walk (10:55), 6 = lying down (11:15), 7= lunch (12:00), 8 = run (12:15), 9 = sleep (12:40), 10 = walk (15:00), 11 = rest (16:50) , 12 = dinner (17:30), 13 = argument (18:00), 14 = relaxation therapy (19:30), 15 = sleep (20:00), 16 = get up (07:00)

FIGURE 1
Course of heart rate (HR) (note: the time on the *X*-axis is the recording time from the time the ECG device was applied).

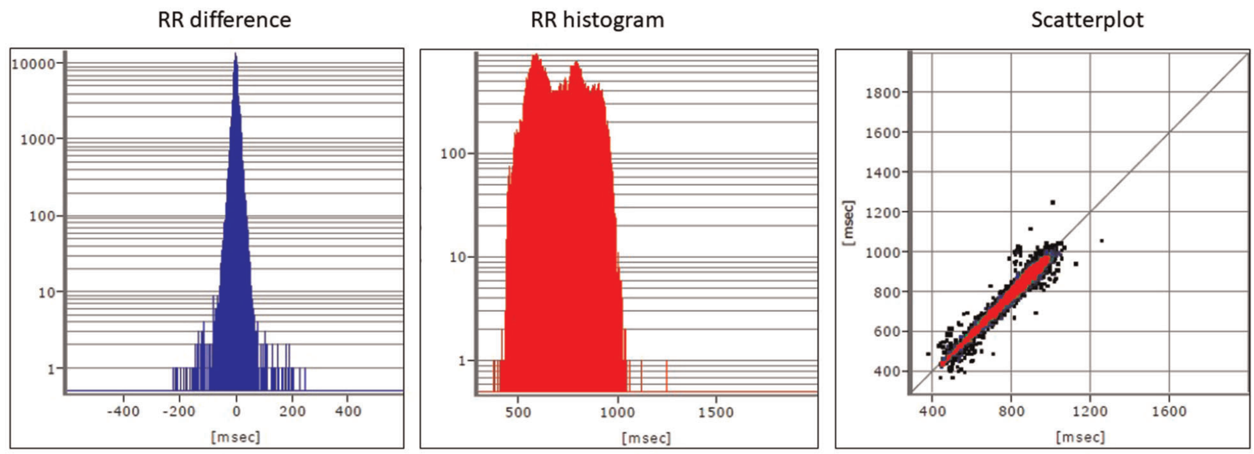


FIGURE 2
HRV parameters from the time domain as well as the representation of the scatterplot.

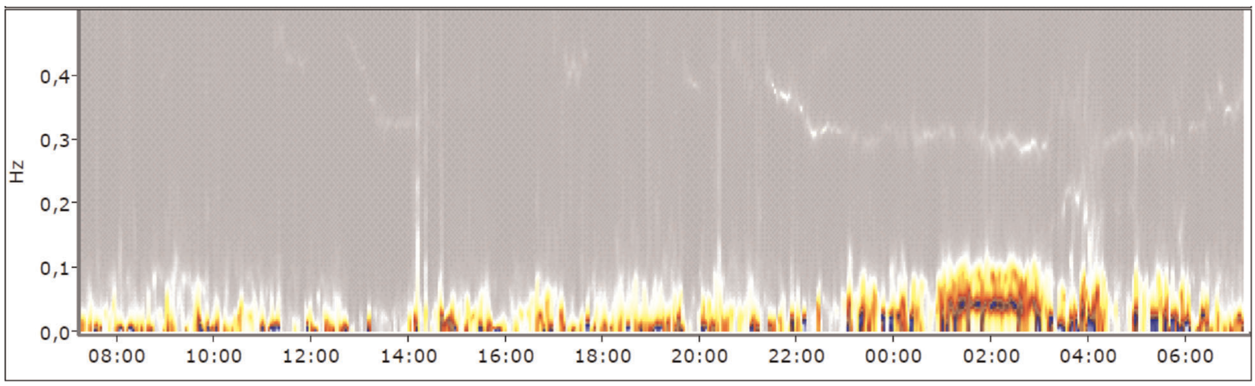


FIGURE 3
Spectrogram (note: the time on the *X*-axis is the recording time starting from the moment the ECG device was applied).

sign of tension (**Figure 3**). Especially in the time between 6:00 PM and 7:30 PM, when the patient kept her patient diary, the sympathetic activity was higher. This can be explained by psychological stress due to that cognitively and emotionally demanding task.

Evaluation of HRV during the application phase

For comparability of data, 5-minute intervals are used. **Figure 4** shows the course of the RR intervals during the 2.5-minute pain music and the first 2.5 min of the healing music. Strong deflections of the HR are observed in the first 20–30 s of the pain music. Afterwards, the values stabilise at a high level before decreasing about 40 s after the start of the healing music.

The frequency-related calculation shows a very pronounced parameter LF/HF of 8.1 during the first 5 min of music application. The vagal activity is clearly subject to sympathetic activity. The relative proportion of HF power is 0.9%, LF power 7.7% and VLF 91.4% (see **Figure 5**).

Discussion

The guiding questions for the discussion of the results were mentioned in the introduction.

Unlike a clinical trial, which generates generalisable results, an individual case study offers the possibility to qualitatively reconstruct the inner relationships between the different dimensions. Therefore in the following, the therapy process with its narrative and musical data and the results of the

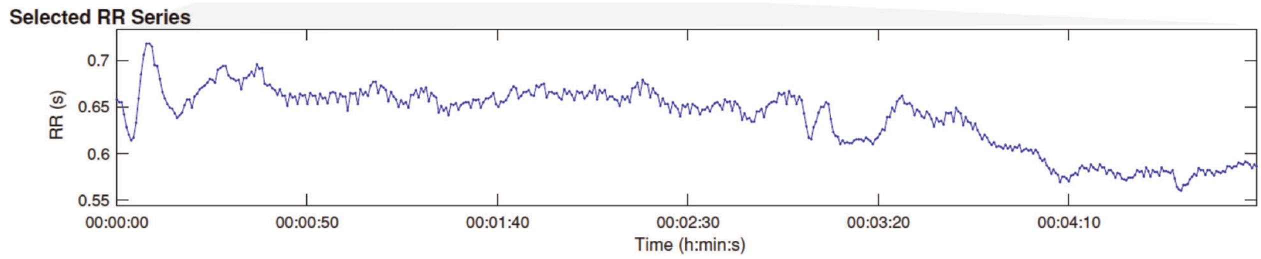
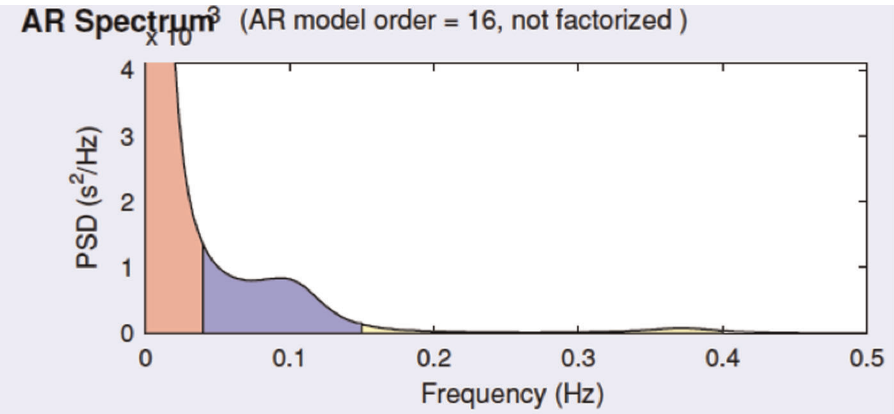


FIGURE 4
Course of RR intervals during the first 5 min of music application (2.5 min of pain music and 2.5 min of healing music).



Frequency Band	Peak (Hz)	Power (ms^2)	Power (%)	Power (n.u.)
VLF (0–0.04 Hz)	0.0000	909	91.4	
LF (0.04–0.15 Hz)	0.0400	76	7.7	89.0
HF (0.15–0.4 Hz)	0.1500	9	0.9	11.0
Total		994		
LF/HF		8.104		

FIGURE 5
Frequency for RR difference and for RR histogram during the first 5 min of music application.

psychometric and cardio-physiological measurements are interrelated and interpreted.

Psychometric, narrative and music data

Mrs S. was exhausted when she came to the hospital. She had a significantly increased symptom burden as determined by the SCL90 after several years of illness history and various failed treatment attempts. Her biography and verbal statements during the MIPT were in line with her one-sided performance orientation and harshness toward her body, its abilities, sensations, and needs, which manifested in a neglectful attitude towards her own emotional impulses and individual wishes. The data measured by the CTQ reflected her memories of having been mistreated, of beatings, humiliation, and emotional neglect during childhood. The attitudes of her parents who were loyal to the state were regarded by the therapist as formative. These attitudes were based on the social, societal and political norms that once applied in the GDR and were realized in everyday behaviors, including the style of upbringing. In the context of the social climate in a dictatorship with the primacy of the collective, the compulsion to conform to a socialist image of human beings, and the ever-present potential persecution of dissenters, an intertwining of individual and social traumatisation (14) is to be assumed. This interpretation cannot be substantiated on the basis of the material, but it would be an explanation for the expectation of punishment and for the patient's ruthlessness towards herself. A good inner object from whom she received empathy, benevolence, and support was not evident at any point in her narratives.

Interpreting the music composed by Mrs S. to represent her physical pain from a psychodynamic perspective it not only seems mechanical and cruel, but also the way the cello is treated, is reminiscent of abuse. Also the actually soft-sounding marimba was used for creating slamming and relentlessly penetrating noise. In addition, there was the autoaggressive demand during the application phase to increase the dynamics, which drove the therapist into a conflict. On the one hand, she had to follow the guidelines of the method and accurately implement the patient's wishes, and on the other hand, she realised that she was being led to do violence to the patient (musically). The line to re-traumatisation is very thin here. In this case, the therapist relies on the fact that the previous exchange with the patient was stable and that clear stop signs were agreed upon. Nevertheless, the risk remains and represents a considerable demand on therapeutic skills Nevertheless, the patient may have experienced some relief by externalising inner experience, which in turn is the prerequisite for recognising that she herself had also contributed to the tension and fixation of her chronic pain.

It can be seen as success that Mrs S. was able to develop an idea of what pain relief might feel like for her. However, the healing music was associated not only with positive but also with unpleasant memories and was composed in such a way that an exact implementation was fraught with risks due to the intended indeterminacy and irregularity of the sounds. Thus, the potential for failure could be interpreted as the lack of ability to take care of one's own well-being.

From a clinical perspective the patient's fear of physical and psychological relaxation is understandable, because in view of the diagnosed personality disorder it was uncertain whether the existing ego structures would be sufficient to withstand disappointment, anger and grief over the psychological injuries she had suffered. Therefore, the score on the VAS at the end of treatment representing the desired goal has to be discussed carefully. On the one hand, expressing the pain and thus experiencing self-efficacy might have led to feelings of relief. On the other hand, it was impossible to say if her statements corresponded to what Mrs S. actually felt, or if she (unconsciously) wanted to fulfil the expectations of others. For patients with chronic somatoform pain disorder, affect perception, affect differentiation and affect expression can be difficult; this extends to verbal and psychometric verification of what is felt.

For this reason, cardiophysiological measures were included in this case study to obtain primary data. HRV as an indicator of stress and as an vegetative equivalent of affects is not distorted by translation into language, nor by socially desirable behaviors.

Cardiophysiological data

The 24 h-ECG measurement although still to be considered within the normal range indicated that the patient suffered from permanent tension. The increased HR and sympathetic activity can be observed day and night and peaked when the patient wrote in her diary in the evening after the music therapy. In those moments, she was alone with her thoughts and realisations of how much she had gotten into a vicious cycle due to her autoaggressive behavior exacerbating both pain and panic.

The evaluation of the HRV showed a generally disrupted sympathovagal balance. However, there were also immediate physiological reactions during the application phase of MIPT. There are strong deflections of the HR and the RR distances in the first 20–30 s of the pain music connected to the reported feelings of being punished and remembering her mother's behavior. The RR distances stabilised afterwards but remained at a high level. The strong tension corresponded to the increased pain intensity measured with VAS. This might be related to feeling confronted with her pain and traumatic experiences, with which the patient tried to cope auto-aggressively. From a cardiophysiological point of view, after the beginning of the healing music at 2′30″, no immediate relaxation occurs, but only after about one and a half minutes. This indicates that the patient had difficulty relaxing. She succeeded at least partially, but from a psycho-traumatological point of view, caution was required because, to her, relaxation meant the decline of psychological defence.

The reactualisation of the traumatic experience that occurred during the rest phase and the pain music required stabilisation and self-assurance. The self-composed healing music, the subsequent short conversation, and the surrounding inpatient treatment could also be factors contributing to this. However, it can only be concluded indirectly from subsequent sessions within the framework of MIPT.

Limitations

This study shows only short-term effects. The long-term impact of MIPT on psychological and physiological well-being cannot be derived from this case report. Also the clinical study in which this patient was participating only gives initial indications of short-term effects (1). However our findings will later help to better explain treatment successes or failures in the context of a larger clinical study (RCT). We recommend an expansion to measurements of intermediate and longer-term impacts of MIPT.

Future perspective

In the psychotherapeutic treatment of somatoform pain disorders, the perception and verbalisation of feelings are essential to learning to differentiate between body symptoms and affect (15). Therefore, it makes sense to offer arts therapies in multimodal pain treatment, especially music therapy like MIPT. In our concept it was scheduled right at the beginning of the inpatient stay to initiate a creative process that can distract from habitual attitudes and ingrained behaviors and thus promote the achievement of the therapy objective. Physical, sensual-aesthetic, inner- and intrapsychic, and emotional processes are triggered through collaborative music-making (exploring, composing), listening to music and reflecting – aspects which are interrelated on many levels. MIPT can be a suitable starting point and after completion other music therapy methods can also be integrated into the longer-term inpatient and/or outpatient treatments of chronic pain disorders. As shown by the case presented here, a complex set of conditions of a chronic pain disorder becomes visible during few MIPT-sessions, and one should also reckon with a traumatic history. Because MIPT belongs to the confrontational therapy methods, the authors regard the professional experience of the therapist on the one hand and the embedding in a multimodal concept on the other hand as obligatory for its application.

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author/s.

Ethics statement

This study involving human participants was reviewed and approved by the ethics committee of the University Hospital and Medical Faculty of Otto von-Guericke-University Magdeburg (File reference: 179/16). The patients/participants provided their written informed consent to participate in this study and for the publication of this case report.

Author contributions

Conception and design (SM, JF, IB, SG); Study therapist (SG); Statistical HRV-analysis (IB); First draft (SM, IB, SG, JF). All authors reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Metzner S, Jarczok MN, Böckelmann I, Glomb S, Delhey M, Guendel H, et al. Improvement of pain experience and changes in HRV through music-imaginative pain treatment. *Front Pain Res.* (2022) 3:943360. doi: 10.3389/fpain.2022.943360

2. Rider M. Entrainment mechanisms are involved in pain reduction, muscle relaxation, and music-medicated imagery. *J Music Ther.* (1985) 22(4):183–92. doi: 10.1093/jmt/22.4.183

3. Dileo C, Bradt J. Entrainment, resonance, and pain-related suffering. In: C Dileo, editors. *Music therapy and medicine: theoretical and clinical applications.* MD: AMTA, Silver Spring (1999). p. 181–8.

4. Metzner S. A polyphony of dimensions: music, pain and aesthetic perception. *Music Med.* (2012) 4(3):164–71. doi: 10.1177/1943862112449486

5. Metzner S, Frommer J. Die performative und bedeutungsgenerierende dimension von Musik in der musiktherapeutischen Schmerzbehandlung [the performative and meaning-generating dimension of music in music therapy pain treatment]. *Psychodyn Psychother/Sonderheft Musiktherapie.* (2014) 13(4):224–33.

6. Metzner S. *Darstellung und Transformation von Schmerzerleben in der Musik-imaginativen Schmerzbehandlung.* Göttingen: Vandenhoeck & Ruprecht Unipress (2018).

7. Franke GH. *Die symptom-checkliste von derogatis* deutsche version*manual, 2nd ed, revised [symptom checklist of derogatis*German version*manual, 2nd ed., revised].* Göttingen: Beltz (2002).

8. Wingenfeld K, Spitzer C, Mensebach D, Grabe JH, Hill A, Gast U, et al. Die deutsche version des childhood trauma questionnaire (CTQ): erste befunde zu den psychometrischen kennwerten. *PPmP Psychother Psychosom Medizinische Psychol.* (2010) 60:442–50. doi: 10.1055/s-0030-1247564

9. Sammito S, Thielmann B, Seibt R, Klussmann A, Weippert M, Böckelmann I. S2k-Leitlinie: Nutzung der Herzschlagfrequenz und der Herzfrequenzvariabilität in der Arbeitsmedizin und Arbeitswissenschaft [Guideline for the application of heart rate and heart rate variability in occupational medicine and occupational science.]: Reg-Nr. 002-042. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF) (2021). Available online at: https://www.awmf.org/uploads/tx_szleitlinien/002-042l_S2k_Nutzung-Herzschlagfrequenz-Herzfrequenzvariabilitaet-Arbeitsmedizin-Arbeitswissenschaft_2022-03_1.pdf

10. Niskanen JP, Tarvainen MP, Ranta-aho PO, Karjalainen PA. Software for advanced HRV analysis. *Comput Methods Programs Biomed*. (2004) 76 (1):73–81. doi: 10.1016/j.cmpb.2004.03.004

11. Tarvainen MP, Niskanen JP, Lipponen JA, Ranta-aho PO, Karjalainen PA. Kubios HRV – heart rate variability analysis software. *Comput Methods Programs Biomed*. (2014) 113(1):210–20. doi: 10.1016/j.cmpb.2013.07.024

12. Lohninger A. Herzratenvariabilität. In: Garza-Villarreal EA, editor *Das HRV-praxis-lehrbuch [heart rate variability. The HRV practice textbook]*. Wien: Facultas Universitätsverlag (2017).

13. Sammito S, Böckelmann I. New reference values of heart rate variability during ordinary daily activity. *Heart Rhythm*. (2017) 14(2):304–7. doi: 10.1016/j.hrthm.2016.12.016

14. Hamburger A. Social trauma. A bridging concept. In: A Hamburger, C Hancheva, VD Volkan, editors. *Social trauma – an interdisciplinary textbook*. Cham: Springer Nature Switzerland (2021). p. 3–16.

15. Egle UT, Nickel R, Schwab R, Hoffmann SO. Die somatoforme schmerzstörung [somatoform pain disorder]. *Deutsches Ärzteblatt*. (2000) 97: Heft 21.

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Mechanistic research approaches in music therapy for pain: Humanizing and contextualized options for clinician-researchers

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Introduction

Mechanistic research refers to investigating and measuring a health-related change resulting from an intervention (1). Such research typically requires a large dataset and highly controlled protocols, which has been challenging for music therapy researchers (2), especially for those who prioritize complex, individualized needs contextualized in systems that affect access to healthcare and impose traumas that compound patients' pain experiences. I will discuss these tensions and propose ways that mechanistic research into music and pain interventions can be clinically relevant for music therapists. This discussion grows in urgency as more patients seek treatment for pain associated with long COVID (3) and as researchers gain more understanding of the role of neuroplasticity in chronic pain (4), increasing demand for biopsychosocial pain interventions such as music therapy. Only recently have researchers focused on identifying and validating cognitive mechanisms of pain relief using music (5). The body of research investigating neurological mechanisms on music interventions for pain focus on music listening rather than music therapy interventions; two studies investigating neurological responses to music therapy for pain involve case studies (6) or address lab-induced pain (7). Though these support at least two different ways music therapy can support analgesia (music as distraction vs. music as active coping), more evidence is needed.

Music therapists should collaborate with researchers on undertaking mechanistic studies on music interventions that will lead to more effective, accessible, and relevant supports for pain management. I will highlight several research methodologies and how each approach is particularly relevant to this cause. Humanizing, intersubjective research approaches have the potential to capture the most effective elements of music as an experiential intervention. Outcomes of such research will help practitioners refine interventions and increase access to effective, music-based pain relief.

Guiding values for research about music therapy for pain

The following core values are among those particularly important to music therapists conducting research with chronic pain populations.

Inclusive evidence-based practice

For centuries, Western medical hierarchies have valued reductionistic, mechanistic studies to demonstrate the effectiveness of interventions. In the context of music therapy for pain, we need more clarity regarding whether and what kind of music is a mediating (causal) or moderating (affecting strength and direction) variable in pain relief, and what other factors may lead to beneficial outcomes. Though many medical practitioners and scientists advocate for more rigorous and urgent investigation into music therapy and music interventions (8), such research is ethically and clinically difficult for music therapists (2). Systematic reviews are at the top of the Evidence Based Practice (EBP) hierarchy, whereas qualitative studies are lower [e.g., as cited in Melnyk, (9)]. Groups such as the Cochrane Collaboration (https://www.cochranelibrary.com) aim to synthesize evidence of interventions to inform practitioners' choice of intervention; due to its strong influence, in 2016 90% of the WHO guidelines contained Cochrane evidence (https://www.cochrane.org/news/use-cochrane-reviews-inform-who-guidelines). Though there is no current Cochrane review on music for pain, several Cochrane reviews address music therapy and music medicine interventions in pain and medical contexts, each advocating for more robust clinical evidence (10–13). Magee and Stewart discuss how inclusion criteria for Cochrane reviews are narrowly defined, often excluding studies containing relevant qualitative data (2). Though considered less informative in the evidence hierarchy, these qualitative datasets have valid implications for treatment efficacy. Music therapists regularly witness patients' subjective responses within the music-based therapeutic relationship (14). Therefore, music therapists often advocate for a broader conceptualization of EBP, including rigorous qualitative and mixed methods research (15).

Ecological validity

Given the limitations of standardized intervention delivery in a relational modality such as music therapy, researchers increasingly strive for ecological validity–designing research in naturalistic settings, and using individualized treatment approaches in the context of a therapeutic relationship. Holleman et al. argue that researchers should explain their rationale for such designs, defining the design's "naturality" and "complexity", and recognizing the design's limitations (16). Data collection, the music experience, and the relationship with the therapist are all affected by the environment, personal experience and situatedness, and therapeutic intention (14). These factors are particularly important to address when investigating the fluid and subjective phenomenon of pain: clinicians want the freedom to exercise clinical decision-making as much as possible to replicate real-world experiences. Accordingly, research participants would experience individualized treatment in the context of a clinical relationship, rather than in a standardized delivery designed for a lab setting. Ecological validity must be a major consideration for research in this area, given the complexity of patients' pain experiences.

Social justice

Westernized healthcare has often disenfranchised pain patients, particularly women and minorities (17, 18). Many such patients seek alternative means of pain support because of practitioners' lack of understanding of their pain experiences or lack of access to effective care. Where available and accessible, music therapy has been an option for such patients. Future researchers should assess whether new and refined interventions are feasible and can be made accessible for patients who have historically been marginalized from effective pain treatment, and they must intentionally study the impacts of systemic marginalization on the pain experience–including neurobiological effects. Researchers should integrate such findings with research on the effects of event-related and repeated trauma on the CNS, including to what degree symptoms of "catastrophizing" and "anxiety" (4, 8) are related to trauma and pain response, and understanding how different music interventions could address limbic system overactivation. Such work could link neurological biomarkers to cognitive mechanisms of music interventions for pain (5).

Research approaches

Music therapist researchers may choose several approaches to accommodate these core values of inclusive EBP, ecological validity, and social justice.

Flexible RCT protocols

Approaches permitting treatment individualization within a standard protocol are perhaps highest in the medical EBP hierarchy. Few such studies involve music therapy targeting pain in individuals, though these do not report outcomes on pain measures (19, 20) or the results are not yet published (21). Examples in other contexts include clinical improvisation for depression (22, 23) and autism (24) and customized songs for preterm infants and their caregivers (25). A neuroimaging study (26) resulting from Erkkilä et al., (22) found that twelve weeks of individualized music improvisation led to resting-state brain changes in depressed participants, perhaps related to affective expression. This result could relate to chronic pain patients whose symptoms correspond with dysregulated mood and trauma history, a potential avenue for future investigation.

A flexible RCT design utilizing neuroimaging could explicate the unique role of music therapy vs. other relational interventions, clarifying music therapy's clinical significance. If music therapy interventions lead to identifiable activation/physiological responses, these could inform effective treatments. For example, should the different neural responses to contrasting music interventions observed in Hauck et al. (7) and Hunt et al. (6) prove to be robust in a flexible RCT, then clinicians would be better informed in selecting a music listening vs. an entrainment intervention for a given patient experiencing pain. Biomarkers may predict treatment responses to pain, and determine criteria for indications/contraindications for specific interventions, perhaps identifying the role of neuroplasticity in chronic pain and the degree to which music interventions can affect pain perception and neural organization, or how to best support patients with persistent neuropathic pain resulting from viral infections such as COVID-19. Furthermore, such biomarkers can be validating to patients who have had no explanation for their pain—affirming their experiences while supporting the benefits of nonpharmacological interventions focusing on biopsychosocialspiritual domains.

Mixed methods

Many music therapists are familiar with the potential of mixed methods designs to help explain the nuances of music interventions; Bradt et al. (27) give an overview of such designs particularly useful for music therapy research. Despite their great potential, there are still few mixed methods studies, perhaps due to their complexity and challenges in publishing outcomes (28). Examples in music and pain research include the mixed method intervention design (29) employed by Bradt et al. (30) and Low et al. (31). In both studies, researchers embedded semistructured interviews within an RCT. The qualitative responses highlighted the limitations of standardized instruments for the target population and also helped refine understanding of the mechanisms of change. For example, in Bradt et al. (30), focus group participants shared how the quality of life scale lacked relevance to their lived experience due to its assumptions about participants' socioeconomic and social status. Participants in both Bradt et al. (30) and Low et al. (31) also explained how they were unable to report all their perceived benefits of the intervention *via* the standardized measures, and how unexpected outcomes related to beneficial behaviors that improved participants' quality of life. Mixed methods approaches continue to evolve according to researchers' questions and needs. Neurophenomenology and social neuroscience approaches also integrate quantitative and qualitative data to address questions that are highly relevant for investigating music interventions for pain.

Neurophenomenology

Neurophenomenology, initially developed by Varela (32), seeks to undertake neurobiological investigations of subjectivity and consciousness. The approach has evolved from the very focused investigation of brief mental and sensory tasks (e.g., 33) to include an integrated investigation of the biological and subjective experience of a guided music and imagery session (34). Given the wide range of foci and data, there is a continuum of sequencing and integrating phenomenological data with neuroimaging, summarized in Berkovich-Ohana et al. (35). Generally, practitioner-researchers would identify the phenomenological focus of the clinical intervention and determine whether to examine neuroimaging data and phenomenological investigation simultaneously or in different sequences. These approaches would yield rich information regarding both the pain experience and different kinds of music experiences–whether receptive or active, provided by a music therapist or music medicine practitioner, and at any level of practice, perhaps using levels described by Dileo (36) including Distraction/Refocusing, Supportive, Cathartic/Expressive, Existential, and/or Transformational. Thus neurophenomenology offers flexible approaches to integrating biomechanistic information with patients' subjective pain experiences in the context of music interventions.

Social neuroscience

Like neurophenomenology, social neuroscience approaches seek to preserve the ecological validity of the target phenomena, while focusing on experiences where the therapeutic relationship is the primary mechanism of change (37). This approach is best suited for interventions where the musical relationship is primary ("music *as* therapy" rather than "music *in* therapy"; 38), and where researchers seek to investigate ongoing music experiences *in vivo* rather than discrete, decontextualized stimuli. Previous studies of this kind have investigated the relationship between multiple participants' physiological signals using EEG and/or ECG (hyperscanning) to determine patterns of physiological synchronization aligned with moments of interest (MOI; as mutually identified by research participants) during a therapy session. This approach aligns musical interaction with physiological changes as they occur over time, providing a structure to investigate mechanisms of change (37). Several examples include analysis of EEG and ECG and clinical improvisation between client-therapist dyads in stroke rehabilitation (15), EEG and music-evoked imagery between a participant-therapist dyad in a psychotherapy session (39), EEG and active music therapy between children and their observing parents (40), and EEG and active music therapy between a participant and clinician and the participant's observing parent (41). Understanding how individual brains relate to interactive, relational therapies can help shape the therapeutic approach. Thus, Tucek et al. (15) and Kang et al. (41) propose that research in this area could seek to optimize intervention strategies for individual patients, perhaps by automating MOI detection in neural signals based on neural and subjective data, indicating when the dyad experiences the most effective moments of "engagement, insight, emotional intensity, and regulation" (15, p. 19). This approach can work with nuances of patients' pain experiences, which fluctuate in response to many factors. It is well suited for pain interventions such as Entrainment (42)/ Music Imaginative Pain Treatment (43) which harnesses the musical relationship between client and therapist to support pain relief. For example, an investigator would examine the physiological synchronization between participant and therapist during therapist- and participant-identified MOIs during the improvised pain and healing music, and integrate these analyses with the participant's subjective post-session pain reports.

Discussion

Given the complexity of researching music interventions for pain, no wonder music therapists may resist a narrow focus on biomechanistic RCT research. As well as investigating physiological responses to an intervention, mechanisms may also be realized across biopsychosocialspiritual domains. For example, research showing self-efficacy as a benefit of music therapy for pain (31) and as a consequence of a sequence of cognitive, affective, sensory, and phenomenological experiencing of music listening for pain relief (5) demonstrate the interrelatedness of these domains. This calls for an increased understanding of the nested situatedness of individuals, groups, communities, and systems in which clinicians and their participants live and receive care. To accomplish such wide-ranging investigations, the field needs more collaboration among diverse research groups, each with expertise in particular approaches, driven by their mission to investigate, develop, and refine feasible and acceptable music-based pain relief. One example of such a collaboration is the International Association for Music and Medicine (IAMM) Special Interest Group on Music Therapy and Chronic Pain (44) which keeps abreast of current research, explores methodological and theoretical concerns to address in future studies, and identifies research priorities–all while centering patients' and stakeholders' voices.

Whereas research approaches striving for ecological validity can help with such questions, we still must consider the larger social context and health infrastructures in which these interventions are embedded. Public health experts, ethnographers, and social scientists could help investigate these systemic mechanisms *via* participatory action research (PAR) projects involving minoritized groups and general medicine practitioners to develop effective implementation/adaptation of music interventions for pain (e.g., PAR design in Ref. 45). Such approaches can explicate the medical systems and sociocultural barriers to music-based pain care in a given context. In a PAR project, community advocates and other stakeholders would guide and give feedback to researchers, helping them to refine the intervention to best meet that community's needs.

Accordingly, ethical, practical, and relevant research into the mechanisms of music therapy interventions for pain is possible. Such research requires transdisciplinary clinical and research collaboration with careful attention to contextual layers, where experienced music therapists can guide teams to effectively identify and navigate participants' unique clinical situations. Research teams should also situate their work in the larger body of research and their communities to enhance our collective understanding.

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References

1. National Institute of Allergy and Infectious Diseases. *What is a mechanistic study?* U.S. Department of Health and Human Services, Bethesda, MD: National Institutes of Health (2020). Available at: https://www.niaid.nih.gov/grants-contracts/what-mechanistic-study

2. Magee WL, Stewart L. The challenges and benefits of a genuine partnership between music therapy and neuroscience: a dialog between scientist and therapist. *Front Hum Neurosci.* (2015) 9:223. doi: 10.3389/fnhum.2015.00223

3. Ojeda A, Calvo A, Cuñat T, Mellado-Artigas R, Comino-Trinidad O, Aliaga J, et al. Characteristics and influence on quality of life of new- onset pain in critical COVID-19 survivors. *Eur J Pain.* (2022) 26:680–94. doi: 10.1002/ejp.1897

4. Chen T, Wang J, Wang Y-Q, Chu Y-X. Current understanding of the neural circuitry in the comorbidity of chronic pain and anxiety. *Neural Plast.* (2022) 2022:4217593. doi: 10.1155/2022/4217593

5. Howlin C, Rooney B. The cognitive mechanisms in music listening interventions for pain. *J Music Ther.* (2020) 57(2):127–67. doi: 10.1093/jmt/thaa003

6. Hunt AM, Fachner J, Clark-Vetri R, Raffa RB, Rupnow-Kidd C, Maidhof C, et al. Neuronal effects of listening to entrainment music versus preferred music in patients with chronic cancer pain as measured via EEG and LORETA imaging. *Front Psychol.* (2021) 12:588788. doi: 10.3389/fpsyg.2021.588788

7. Hauck M, Metzner S, Rohlffs F, Lorenz J, Engel AK. The influence of music and music therapy on pain-induced neuronal oscillations measured by magnetencephalography. *Pain.* (2013) 154:539–47. doi: 10.1016/j.pain.2012.12.016

8. Sihvonen A, Pitkäniemi A, Särkämö T, Soinila S. Isn't there room for music in chronic pain management? *J Pain.* (2022) 23(7):1143–50. doi: 10.1016/j.jpain.2022.01.003

9. Melnyk BM. *Implementing the evidence-based practice (EBP) competencies in healthcare: A practical guide to improving quality, safety, and outcomes.* Indianapolis, IN: Sigma Theta Tau (2016).

10. Bradt J, Dileo C, Shim M. Music interventions for preoperative anxiety. *Cochrane Database Syst Rev.* (2013) (6):CD006908. doi: 10.1002/14651858.CD006908.pub2

11. Bradt J, Dileo C. Music interventions for mechanically ventilated patients. *Cochrane Database Syst Rev.* (2014) (12):CD006902. doi: 10.1002/14651858.CD006902.pub3

12. Bradt J, Dileo C, Myers-Coffman K, Biondo J. Music interventions for improving psychological and physical outcomes in people with cancer. *Cochrane Database Syst Rev.* (2021) (10):CD006911. doi: 10.1002/14651858.CD006911.pub4

13. Magee WL, Clark I, Tamplin J, Bradt J. Music interventions for acquired brain injury. *Cochrane Database Syst Rev.* (2017) (1):CD006787. doi: 10.1002/14651858.CD006787.pub3

14. Tucek G, Maidhof C, Vogl J, Heine A, Zeppelzauer M, Steinhoff N, et al. EEG Hyperscanning and qualitative analysis of moments of interest in music therapy for stroke rehabilitation–A feasibility study. *Brain Sci.* (2022) 12:565. doi: 10.3390/brainsci12050565

15. Abrams B. Evidence-based music therapy practice: an integral understanding. *J Music Ther.* (2010) 47(4):351–79. doi: 10.1093/jmt/47.4.351

16. Holleman GA, Hooge ITC, Kemner C, Hessels RS. The "real-world approach" and its problems: a critique of the term ecological validity. *Front Psychol.* (2020) 11:721. doi: 10.3389/fpsyg.2020.00721

17. Vaughn IA, Terry EL, Bartley EJ, Schaefer N, Fillingim RB. Racial-ethnic differences in osteoarthritis pain and disability: a meta-analysis. *J Pain.* (2019) 20(6):629–44. doi: 10.1016/j.jpain.2018.11.012

18. Bazargan M, Cobb S, Assari S, Bazargan-Hejazi S. Physical and mental health quality of life among underserved African American and Latino older adults. *Ethn Health.* (2022) 30:1–17. doi: 10.1080/13557858.2022.2027886

19. Hanser S, Bauer-Wu S, Kubicek L, Healy M, Manola J, Hernandez M, et al. Effects of a music therapy intervention on quality of life and distress in women with metastatic breast cancer. *J Soc Integr Oncol.* (2006) 4(3):62–6. doi: 10.2310/7200.2006.003

20. Palmer JB, Lane D, Mayo D, Schluchter M, Leeming R. Effects of music therapy on anesthesia requirements and anxiety in women undergoing ambulatory breast surgery for cancer diagnosis and treatment: a randomized controlled trial. *J Clin Oncol.* (2015) 33(28):3162–8. doi: 10.1200/JCO.2014.59.6049

21. Ettenberger M, Maya R, Salgado-Vasco A, Monsalve-Duarte S, Betancourt-Zapata W, Suarez-Cañon N, et al. The effect of music therapy on perceived pain, mental health, vital signs, and medication usage of burn patients hospitalized in the intensive care unit: a randomized controlled feasibility study protocol. *Front Psychiatry.* (2021) 12:714209. doi: 10.3389/fpsyt.2021.714209

22. Erkkilä J, Gold C, Fachner J, Ala-Ruona E, Punkanen M, Vanhala M. The effect of improvisational music therapy on the treatment of depression: protocol for a randomised controlled trial. *BMC Psychiatry.* (2008) 8:50. doi: 10.1186/1471-244X-8-50

23. Fachner J, Erkkilä J. The Finnish research model of a music therapy practice treating depression. *Musiktherapeutische Umschau.* (2013) 34(1):35–45. doi: 10.13109/muum.2013.34.1.37

24. Geretsegger M, Holck U, Gold C. Randomised controlled trial of improvisational music therapy's effectiveness for children with autism spectrum disorders (TIME-A): study protocol. *BMC Pediatr.* (2012) 12:2. doi: 10.1186/1471-2431-12-2

25. Loewy J, Stewart K, Dassler AM, Telsey A, Homel P. The effects of music therapy on vital signs, feeding, and sleep in premature infants. *Pediatrics.* (2013) 131:902–18. doi: 10.1542/peds.2012-1367

26. Fachner J, Gold C, Erkkilä J. Music therapy modulates fronto-temporal activity in the rest-EEG in depressed clients. *Brain Topogr.* (2013) 26(2):338–54. doi: 10.1007/s10548-012-0254-x

27. Bradt J, Burns DS, Creswell JW. Mixed methods research in music therapy research. *J Music Ther.* (2013) 50(2):123–48. doi: 10.1093/jmt/50.2.123

28. Bradt J. Where are the mixed methods research studies? *Nord J Music Ther.* (2021) 30(4):311–3. doi: 10.1080/08098131.2021.1936771

29. Creswell JW. *A concise introduction to mixed methods research.* Thousand Oaks, CA: Sage (2015).

30. Bradt J, Norris M, Shim M, Gracely EJ, Gerrity P. Vocal music therapy for chronic pain management in inner-city african Americans: a mixed methods feasibility study. *J Music Ther.* (2016) 53(2):178–206. doi: 10.1093/jmt/thw004

31. Low MY, Lacson C, Zhang F, Kesslick A, Bradt J. Vocal music therapy for chronic pain: a mixed methods feasibility study. *J Altern Complement Med.* (2020) 26(2):113–22. doi: 10.1089/acm.2019.0249

32. Varela FJ. Neurophenomenology: a methodological remedy for the hard problem. *J Conscious Stud.* (1996) 3(4):330–49.

33. Lutz A, Lachaux J-P, Martinerie J, Varela FJ. Guiding the study of brain dynamics by using first-person data: synchrony patterns correlate with ongoing conscious states during a simple visual task. *Proc Natl Acad Sci USA.* (2002) 99:1586–91. doi: 10.1073/pnas.032658199

34. Hunt AM. Protocol for a neurophenomenological investigation of the guided imagery and music experience (part II). *Music Med.* (2017) 9(2):116–27. doi: 10.47513/mmd.v9i2.572

35. Berkovich-Ohana A, Dor-Ziderman Y, Trautwein F-M, Schweitzer Y, Nave O, Fulder S, et al. The hitchhiker's guide to neurophenomenology – the case of studying self boundaries with meditators. *Front Psychol.* (2020) 11:1680. doi: 10.3389/fpsyg.2020.01680

36. Dileo C. The future of medical music therapy for adults. In: C Dileo, editors. *Envisioning the future of music therapy.* Philadelphia, PA: Temple University (2016). p. 71–80. Available at: https://scholarshare.temple.edu/bitstream/handle/20.500.12613/6287/Dileo-Monograph-2016.pdf?sequence=1&isAllowed=y

37. Fachner J. Communicating change–meaningful moments, situated cognition and music therapy–A reply to north. *Psychol Music.* (2014) 42:791–9. doi: 10.1177/0305735614547665

38. Bruscia KE. *Improvisational models of music therapy.* Springfield, IL: Charles C. Thomas (1987).

39. Fachner JC, Maidhof C, Grocke D, Nygaard Pedersen I, Trondalen G, Tucek G, et al. "Telling me not to worry…" Hyperscanning and neural dynamics of emotion processing during guided imagery and music. *Front. Psychol.* (2019) 10:1561. doi: 10.3389/fpsyg.2019.01561

40. Samadani A, Kim S, Moon J, Kang K, Chau T. Neurophysiological synchrony between children with severe physical disabilities and their parents during music therapy. *Front Neurosci.* (2012) 15:531915. doi: 10.3389/fnins.2021.531915

41. Kang K, Orlandi S, Lorenzen N, Chau T, Thaut M. Does music induce interbrain synchronization between a non-speaking youth with cerebral palsy (CP), a parent, and a neurologic music therapist? A brief report. *Dev Neurorehabil.* (2022) 25(6):426–32. doi: 10.1080/17518423.2022.2051628

42. Dileo C, Bradt J. Entrainment, resonance, and pain-related suffering. In: C Dileo, editors. *Music therapy and medicine: theoretical and clinical applications.* Silver Spring, MD: American Music Therapy Association (1999). p. 181–8.

43. Metzner S. A polyphony of dimensions: music, pain and aesthetic perception. *Music Med.* (2012) 4(3):164–71. doi: 10.1177/1943862112449486

44. International Association for Music & Medicine. *Music therapy and chronic pain* (2022). Available at: https://iammonline.com/iamm2022library/mt-chronicpain/

45. Devan H, Perry M, Yaghoubi M, Hale L. "A coalition of the willing": experiences of co-designing an online pain management programme (iSelf-help) for people with persistent pain. *Res Involv Engagem.* (2021) 7(28). doi: 10.1186/s40900-021-00275-0

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Effects of active musical engagement during physical exercise on anxiety, pain and motivation in patients with chronic pain

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The experience of anxiety is central to the development of chronic pain. Music listening has been previously shown to exert analgesic effects. Here we tested if an active engagement in music making is more beneficial than music listening in terms of anxiety and pain levels during physical activity that is often avoided in patients with chronic pain. We applied a music feedback paradigm that combines music making and sports exercise, and which has been previously shown to enhance mood. We explored this method as an intervention to potentially reduce anxiety in a group of patients with chronic pain ($N = 24$, 20 female and 4 men; age range 34–64, $M = 51.67$, $SD = 6.84$) and with various anxiety levels. All participants performed two conditions: one condition, *Jymmin*, where exercise equipment was modified with music feedback so that it could be played like musical instruments by groups of three. Second, a *conventional workout condition* where groups of three performed exercise on the same devices but where they listened to the same type of music passively. Participants' levels of anxiety, mood, pain and self-efficacy were assessed with standardized psychological questionnaires before the experiment and after each condition. Results demonstrate that exercise with musical feedback reduced anxiety values in patients with chronic pain significantly as compared to conventional workout with passive music listening. There were no significant overall changes in pain, but patients with greater anxiety levels compared to those with moderate anxiety levels were observed to potentially benefit more from the music feedback intervention in terms of alleviation of pain. Furthermore, it was observed that patients during *Jymmin* more strongly perceived motivation through others. The observed diminishing effects of *Jymmin* on anxiety have a high clinical relevance, and in a longer term the therapeutic application could help to break the Anxiety Loop of Pain, reducing chronic pain. The intervention method, however, also has immediate benefits to chronic pain rehabilitation, increasing the motivation to work out, and facilitating social bonding.

KEYWORDS

chronic pain, physical activity, musical feedback, musical agency, anxiety, motivation

Introduction

Pain is a highly subjective experience that is universally perceived by human beings and informs us about potential health problems. However, pain is sometimes persistent and in duration exceeds the normal healing process (1), occasionally leading to chronic pain. This has become a major health issue throughout the world. Around 20% of the adult population of developed countries at some point in their life suffer from chronic pain and its profound effects on their quality of life (2). Furthermore, chronic pain is associated with high emotional distress, fatigue, physical disability (e.g., limited in their general activity), cognitive and psychological impairments (e.g., depression, anxiety) and social isolation (3). These factors lead to a cumulative allostatic load (a composite index of indicators of strain on organs and tissues) in chronic pain patients (4), which has an accelerating effect on the aging process with respect to cognitive and physiological functionality (5).

Chronic pain may have different mechanism of etiopathogenesis, which makes a thoroughly diagnostic process important, if necessary in an interdisciplinary context of medicine. It is for example necessary to differentiate between nociceptive–neuropathic pain and stress-induced pain, because different treatments are considered differently effective depending on the type of pain. Stress-induced pain seems to be initiated without nociceptive lesions (6, 7).

Avoidance behavior and anxiety hinder recovery

The interplay of pain, physical disability and psychological impairment (especially depression and anxiety) creates a vicious cycle of avoidance behavior in chronic pain patients. In its most simple form, the perception of pain symptoms (such as muscle tension, stiffness, etc.) leads to less physical activity (avoidance behavior) that over time leads to a reduction of physical fitness and capabilities, which in turn leads to the perception of more/greater pain symptoms (8). Therefore anxiety and fear of pain play a central role in the development of chronic pain, probably even more than the intensity of the pain sensation itself (9).

Furthermore, recent evidence shows that anxiety mediates the vicious cycle between an anticipation of pain and pain [**Figure 1** (10)]. This study demonstrated that heightened anxiety in patients with chronic wounds is associated with the quantity of newly developed wounds, heavy exudation, and wound necrosis. This finding has been discussed in terms of a mechanism the authors called "nocebo hyperalgesia", whereby anticipation of pain causes an emotional anxiety response that leads to a nocebo-like generation of pain.

Benefits of physical activity in the treatment of chronic pain

A number of clinical studies have demonstrated the positive effects of regular physical activity in the treatment of nearly all types of chronic pain (3) and exercise therapy is recommended as a first-line treatment in the management of chronic non-specific low back pain by the European Guidelines (11). Additionally, recommencement of physical activity is important for patients with chronic pain in terms of promoting general health, well-being and quality of life (12). Evidence furthermore indicates that physical exercise activates central pathways associated with an opioid-mediated analgesia (13).

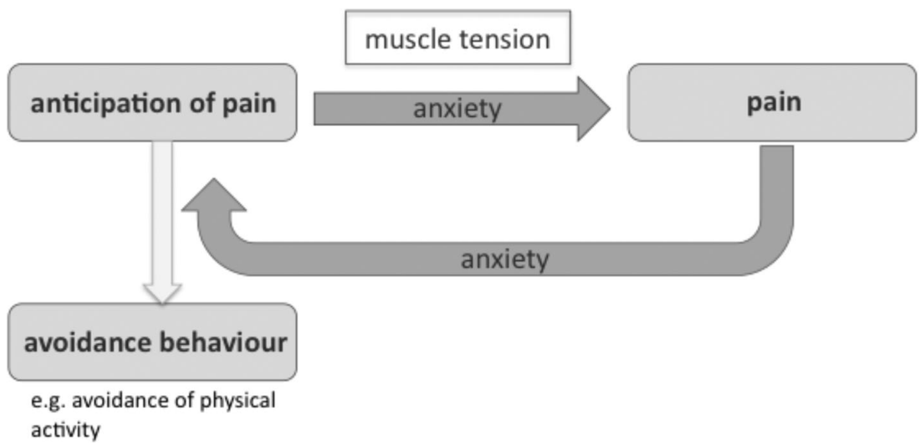

FIGURE 1
Anxiety loop of pain.

Perceived barriers to physical activity

Chronic pain is associated with a psychomotor slowing and an overall "stiffening effect", which adds to the patients' sensation that physical activity is highly exhausting and fatiguing (14). Furthermore, depression and anxiety, both highly prevalent in chronic pain patients, foster physical disability and limit general level of patient activity (15). Depression has been shown to be associated with a decreased level of physical exercise (16). Anxiety has been suggested to be instrumental for a number of negative effects on perceived pain: Lowering the pain threshold (17), increasing attention to the pain sensation (18), and creating the percept of tightness and constriction in the patient (19). This renders it rather unlikely for the patient to engage in exercise and enjoy physical activity. Moreover, the limiting effect of movement disability on general activity in chronic pain patients leads to a deterioration of mood and social functioning, which increases the risk to develop psychological comorbidities such as depression (3).

Efficacy of musical interventions in the management of chronic pain

Recently, the use of music as a component of chronic pain intervention has gained greater importance. A number of clinical studies on chronic pain have shown that music listening can lead to reduced stress and pain levels (20–22). For example, pain-reducing effects associated with music listening have been shown in patients with fibromyalgia syndrome, where pain is perceived in the fibrous tissues of the body, such as muscles, tendons, and ligaments (20). The authors have argued that the observed analgesic effects of music in this study may partly be due to emotional effects related to the perception of pleasure and relaxation (20).

Another recent study showed a reduction in pain, anxiety and depression in chronic pain patients who underwent daily music listening sessions during hospitalization and at home (this intervention however also included describing their experiences at the end of each listening session to care staff (22);. Pain-reducing effects were reported by the participants to sustain for up to one month after the last music intervention session.

The precise mechanisms underlying the observed music effects on chronic pain are still unclear. Research of musical effects on pain (not chronic pain) suggest that music may decrease pain sensation *via* a release of endorphins and changes in the catecholamine levels; it may also be beneficial in this respect by diverting attention from the experience of pain (23, 24). This endorphin theory of musical analgesia has been further elaborated in a study where musical agency due to singing, clapping, instrument playing etc. was associated with a increase in pain tolerance, probably also in relation to enhanced endorphin release by high-energy musical activities (25). However, it is unclear how such musical effects may be called upon when addressing effects on chronic pain.

Benefits of the interaction of music and sports in pain

Only a few studies have addressed the investigation of pain perception combining physical activity with music (26). In a repeated measure single-case series of patients with fibromyalgia an influence of music and walking speed on pain level was examined. While an average gait speed was observed to be higher with fast music and lower with slow music, an increase in walking speed was not associated with pain increase (26). In a recent study a significant increase in pain threshold as measured with the cold pressor task was demonstrated as an effect of musical agency during fitness machine workout (27). In this paradigm fitness equipment was modified so that participants could use the fitness equipment as musical instruments, jointly creating a musical performance as part of the fitness workout.

Research questions and hypotheses—possible benefits of workout with musical agency in chronic pain management

In the present study we investigated the effects of a novel music-sports intervention, which allows participants to be musically expressive by operating on fitness machines. This intervention has been called *Jymmin*. In previous studies it has been shown that perceived exertion is decreased and motor efficiency and muscle relaxation increased when combining workout with musical agency in such a way compared to a control condition where music was listened to passively during workout (*conventional workout*). These observed physiological effects were discussed in terms of increased emotional motor control during the musical agency condition (28).

In a further study with a similar *Jymmin* paradigm, participants reported an enhanced mood after *Jymmin* compared to conventional workout with music listening (29). This may be especially relevant to an intervention with chronic pain patients, given that 63% of patients suffering from severe pain have previously reported the need to enhance their mood [results of the European survey of chronic pain patients (2)]. In addition, the observed mood enhancing effects due to fitness training with musical feedback also suggests that musical agency makes the training on workout machines more desirable (29). In this previous study also an investigation of anxiety was addressed, that in the investigated student population did not show an effect.

Authors argued that this might be due to a ceiling effect given the relatively low anxiety of participants to begin with and that it would be interesting to repeat the experiment with a high anxiety cohort (29).

Based on the above-mentioned positive effects of a combination of exercise machine workout and musical agency, the present study aimed at investigating its possible benefits on chronic pain management. Pain management has been described as the "intention to modulate patients' pain or their response to pain using multimodal approaches in a collaborative relationship with the patient" with a focus on self-efficacy and patients' participation (1).

Given the complexity of chronic pain and its underlying psychological mechanisms, recent research suggests to more strongly consider co-occurrences/co-morbidities in pain patients and especially to more systematically address a role of depression and anxiety in the treatment of chronic pain (30, 31). Accordingly, in the current study we addressed both an investigation of chronic pain levels and psychological parameters that have been directly implicated in the development of chronic pain. These parameters were investigated according to the following hypotheses - note that the *experimental* condition is named *Jymmin* condition and includes a workout on fitness machines with musical feedback, while the *control* condition is named *conventional workout* condition as it includes workout on fitness machines with passive music listening:

1. The difference of baseline anxiety score and anxiety score after *Jymmin* significantly differs from the difference of baseline anxiety score and anxiety score after *conventional workout*; anxiety decreases more strongly after *Jymmin*.
2. The difference of baseline mood score and mood score after *Jymmin* significantly differs from the difference of baseline mood score and mood score after *conventional workout;* mood increases more strongly after *Jymmin*.
3. The difference of baseline pain level and pain level after *Jymmin* significantly differs from the difference of baseline pain level and pain level after *conventional workout*; pain level decreases more strongly after *Jymmin*.
4. The difference of baseline locus of control score and locus of control score after *Jymmin* significantly differs from the difference of baseline locus of control score and locus of control score after *conventional workout*; the external locus of control decreases and the internal locus of control increases more strongly after *Jymmin*.
5. The difference of baseline generalized self-efficacy score and generalized self-efficacy score after *Jymmin* significantly differs from the difference of baseline generalized self-efficacy score and generalized self-efficacy score after *conventional workout*; the generalized self-efficacy increases more strongly after *Jymmin*.

In addition to these hypotheses, exploratory analyses were used to gain further insights into how different parameters of the intervention may relate to each other and how training-related effects were perceived by participants, immediately and one day after the intervention (self-constructed items and follow-up questions).

Methods

Participants

Twenty-four participants (20 female and 4 men; age range 34–64, $M = 51.67$, $SD = 6.84$) took part in the experiment. None of the participants were professional body builders, musicians, or athletes. Clinical data showed that all participants were suffering from chronic pain, which has been defined as pain that persists or recurs for more than three months, with no clear physical causes (e.g., stress-induced pain conditions). Co-morbid conditions were present in the majority of patients as assessed with the *Brief Patient Health Questionnaire* (32); see section of experimental procedure): 34.8% of participants showed a depressive or major depressive syndrome, 4.4% of participants classified for a panic syndrome, and 21.7% showed both a depressive/ major depressive and panic syndrome. Patients' scheduled discharge date of the clinic varied between one to four weeks ($M = 2.7$, $SD = 1.3$). On the day of the experiment, patients' pain levels ranged from 0.3 to 9.4 ($M = 5.14$, $SD = 3.04$) as indicated on a Visual Analog Scale of 0–100 mm. 30.4% ($n = 7$) of participants suffered from mild pain, 26.1% ($n = 6$) from moderate pain, and 43.5% ($n = 10$) from severe pain (**Figure 2**). Inclusion criteria were any type of chronic pain and the ability to perform a physical exercise intervention. An exclusion criterium was accordingly a disability to perform physical exercise. Participants were referred by their treating therapist/doctor at the rehabilitation centre.

The study adhered to the guidelines of the Declaration of Helsinki and was approved by the ethics committee of the University of Leipzig, Germany. In addition, informed consent was obtained from all participants from the clinic.

Experimental design

The experiment included two conditions: In one condition the participants worked out on fitness machines while passively listening to music (*conventional workout condition*); in a second condition they worked out on fitness machines while listening to a musical feedback of their own movements (*Jymmin condition*). All participants performed both conditions of the experiment, the *Jymmin condition* and the *conventional workout condition*. The physical workout was

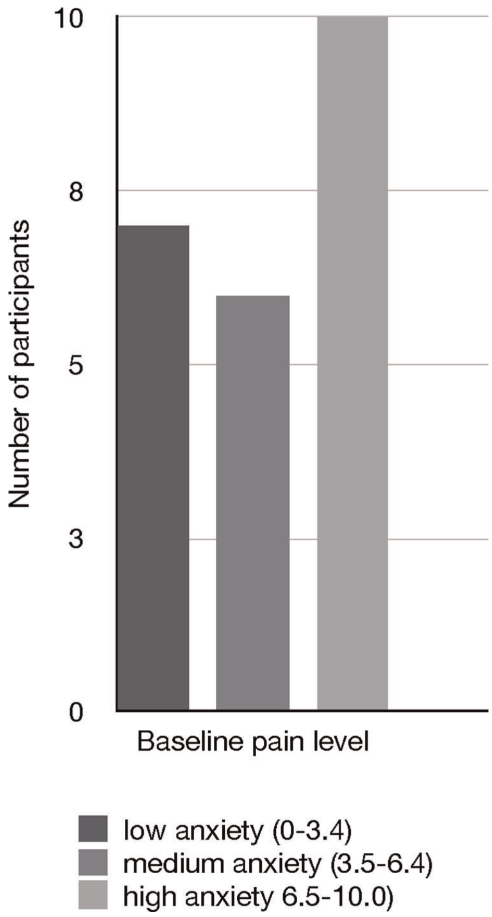

FIGURE 2
The figure depicts patients' pain levels as measured on a visual analog scale (1–100 mm) before the intervention.

conducted with three different fitness machines, a tower (lat pulldown), a stomach trainer, and a stepper. All three machines are standard fitness machines that are commercially available and they allow for guided movements.

In the *Jymmin* condition the movements of participants on the fitness machines were mapped to a music composition software (Ableton Live 8) so that the deflection of the fitness machines was translated into musical parameters of an acoustic feedback signal [for a detailed description see (29, 28)]. Each fitness machine produced a different musical soundscape, and the combined musical feedback of all three fitness machines created sounds at a constant tempo of 130 bpm (beats per minute) and could interactively be combined into a holistic musical piece, which allowed for group performances of three participants in one group. The musical interaction was predefined in terms of sounds to be modulated, the musical parameters to be modulated, and the metric of the music. The music style used in the experiment was rather minimalistic electronic music. In the experiment one interactive musical composition was used, chosen by the experimenters. This consisted of musical elements that could be varied in a contained fashion determined by the composer so that participants had the experience that the more they exerted themselves with a certain movement on their respective fitness equipment, the greater the arousal of the musical element they controlled with sound, creating for each participant the experience that they could control their part of the interactive music composition expressively. The musical performances of all patient groups in the *Jymmin* condition were recorded and played back during the *conventional workout* condition (with exception of the first group who listened to a recording of their own *Jymmin* condition) to ensure a comparable exposure to the same musical piece during both experimental conditions. Furthermore, we controlled for the sequence in which both conditions were performed, so that half of the patients first performed *Jymmin*, and the other half first performed *conventional workout* (cross-over design).

Experimental procedure

Patients suffering from chronic pain were recruited from a psychosomatic clinic and centre for stress-related diseases and pain disorders in Germany. Participants were randomly assigned to different time slots, such that eight groups (each consisted of three participants) were formed and tested on two consecutive days. Before participants started with the workout conditions, they were asked to fill out general information items on gender, age, and standardized questionnaires to assess a baseline of their physical and mental state before the experiment. The following questionnaires were given to the participants in the same order as presented here: Multidimensional Mood Questionnaire (MDMQ) (33), State-Trait Anxiety Inventory [STAI; the current study assessed only the state anxiety (34)], Pain Visual Analogue Scale (100 mm VAS), Rotter Internal-External Locus of Control Scale (I-E) (35), and the Generalized Self-Efficacy Scale (GSE) (36).

After the baseline assessment of the patients' physical and mental state, patients entered the training room and were asked to choose their preferred fitness machine (participants performed both conditions on the same fitness machine). A short explanation on how to use the fitness machines correctly in terms of physiologically healthy movements was given by the experimenter, followed by the task instruction: "Use the fitness machines now in a way in which you are physically comfortable." Each of the conditions was performed for 10 min; during which all participants could hear the sound through a speaker system. After each condition patients took a rest and were then asked to fill-out the *MDMQ, STAI, VAS, I-E* and *GSE* questionnaires a second and third time. In addition the following self-constructed items relating to the training context were assessed after each condition.

Training related self-constructed items

Self-constructed items assessing subjective ratings of both training contexts were used to allow for additional explorative analyses. Training related self-constructed items assessed the perceived pain, impairment by pain and anxiety of pain during workout with the following nine questions: "How much did you perceive pain during workout?", "how much did you suffer from pain during workout?", "how much were you afraid that your pain would get stronger during workout?", "how much did you feel impaired by pain during workout?". Furthermore, it was assessed how well patients felt during workout in regard to their workout group and the music: "How comfortable did you feel in the group during workout?" and "how much did you like the music during workout?". In addition, patients were asked about their motivation to workout: "How motivated did you feel?", "how much did you feel motivated by your fellow training partners?" and "how much do you think this type of training could help you to exercise despite the experience of pain?". Answers were given on a Visual Analogue Scale ranging from 1 ("not at all") to 100 mm ("very strongly"). At the end of the experiment patients filled out the *Brief Patient Health Questionnaire (Brief-PHQ* (32); to assess possible co-morbidities that are known to be common in chronic pain.

Follow-up questionnaire

For further insights about how the intervention was perceived by patients with chronic pain, we used a follow-up questionnaire, which allowed for additional explorative analyses. In this follow-up questionnaire one day after the experiment participants were asked to answer intervention-specific questions on physical and psychological experiences during the remainder of the previous day: "To which extent did you experience positive physical effects during the remainder of the day after the workout intervention?", "to which extent did you experience positive mood effects during the remainder of the day after the workout intervention?", "to which extent did you experience an improvement in bodily relaxation during the remainder of the day after the workout intervention?", "to which extent did you experience an improvement in mental relaxation during the remainder of the day after the workout intervention?" and "how much were you impressed by yourself actually performing a 20 min workout?". In addition, anticipation and motivation to perform workout with musical agency were assessed: "How would you describe your anticipation of *Jymmin*?", "how much do you think it could help you to perform *Jymmin* regularly?" and "how much would you like to use *Jymmin* at home?". Answers were given on a Visual Analogue Scale ranging from 1 ("not at all") to 100 mm ("very strongly").

Data analysis

The behavioral data were analyzed with non-parametric tests using SPSS 22 (IBM). Guidelines for missing responses on standardized questionnaires were applied as indicated in the corresponding questionnaire manuals. If participants had too many missing responses in the questionnaires, more than the corresponding guidelines allowed for, they were indicated in SPSS and excluded from the corresponding analysis. In order to obtain mean scores for the subscales of the *MDMQ* and locus of control questionnaire, responses for each subscale were averaged. In total, data from the *pain VAS* were analyzed for 22 participants, data from the *STAI* for 17 participants, data from the *MDMQ* for 16 participants, data from the *I-E scale* for 23 participants, and data from the *GSE* for 21 participants. For hypotheses testing in the current study, Wilcoxon Signed Rank Tests were applied. A Bonferroni-correction was applied to account for multiple comparisons, resulting in a significance level of $p = 0.01$ (.05 divided by the 5 hypotheses tested in this study).

Results

Results of standardized psychological questionnaires

A Wilcoxon Signed Ranks Test for dependent samples was applied to test hypothesis 1 that anxiety decreases more strongly after *Jymmin*. Results showed that the *difference of baseline* anxiety score and anxiety score after *Jymmin* (*Mdn* = 7.00) differed significantly from the *difference of baseline* anxiety score and anxiety score after *conventional workout* (*Mdn* = 2.00). Anxiety decreased significantly stronger after the *Jymmin* condition, $Z = -2.520$, $p = 0.006$ (one-tailed), $r = 0.43$ (see **Figure 3**). Note that no sequence effect was found for differences in anxiety scores using the Mann–Whitney *U* Test.

An additional exploratory analysis was performed to gain further insight about how anxiety may have influenced other relevant aspects of physical engagement. Spearman's correlations were carried out to investigate if anticipation of pain is related to perceived pain as discussed in previous studies (10). Spearman's correlation matrices showed that being anxious about experiencing pain during workout correlated positively with the patients' pain level during both exercising in the *Jymmin* condition ($N = 22$, $r_s = 0.706$, $p <$ 0.001) and *conventional workout* condition ($N = 23$, $r_s = 0.500$, $p = 0.015$). Being anxious about experiencing pain during workout also correlated both with the degree to which patients felt impaired by their pain during the workout on fitness machines during the *Jymmin* condition ($N = 23$, $r_s =$

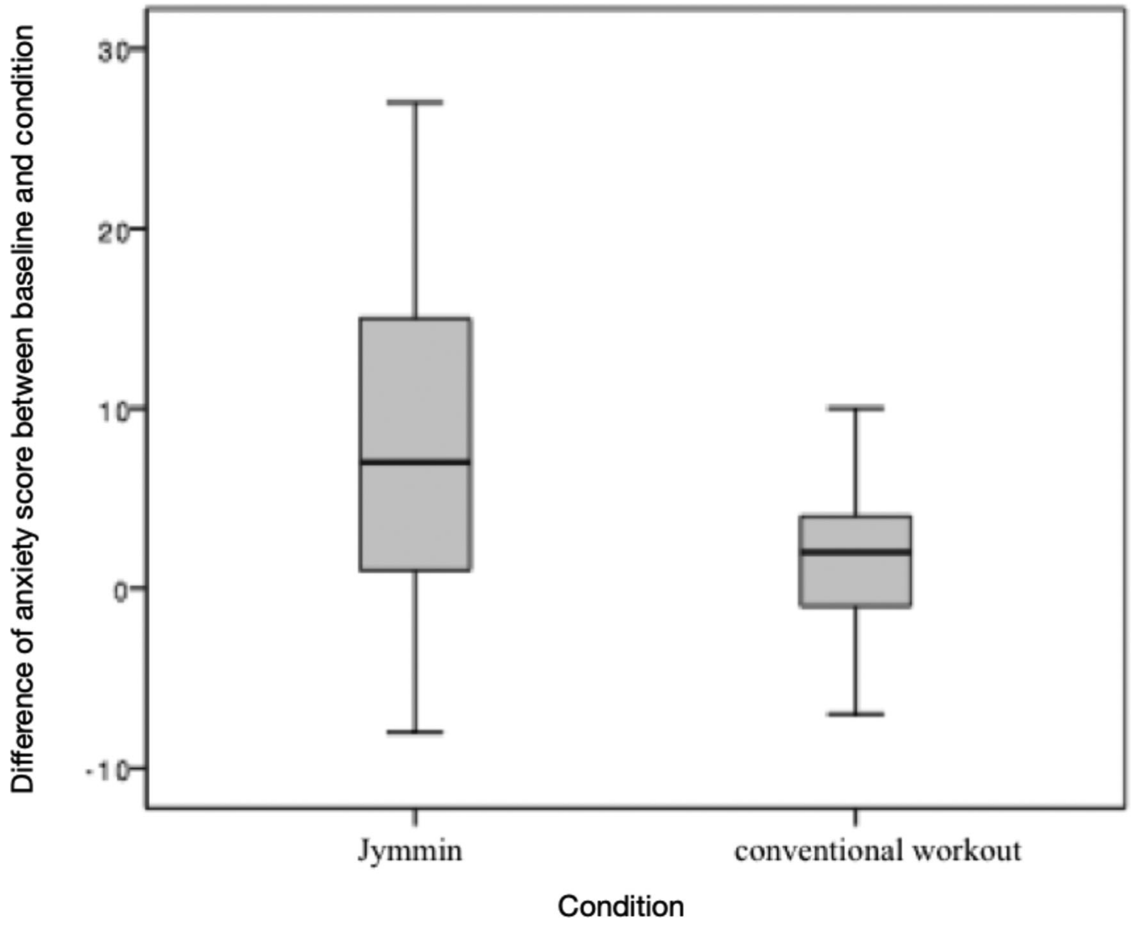

FIGURE 3
The figure depicts differences of baseline anxiety scores and the anxiety scores after *Jymmin* or *conventional workout* condition as measured with the *STAI*. A Wilcoxon Signed Rank Test revealed a significant difference between medians of the difference between baseline and the *Jymmin* condition, and the difference between baseline and the *conventional workout* condition. Anxiety total scores declined stronger after the *Jymmin* condition as compared to the *conventional workout* condition.

0.840, $p < 0.001$) and the *conventional workout* condition ($N = 23$, $r_s = 0.847$, $p < 0.001$). Interestingly, being anxious about experiencing pain during workout correlated negatively with feeling comfortable in the group during the *conventional workout* condition ($N = 23$, $r_s = -0.481$, $p = 0.020$), but not during the *Jymmin* condition ($N = 23$, $r_s = 0.061$, $p = 0.781$).

A Wilcoxon Signed Ranks Test for dependent samples was applied to test hypothesis 2 that mood increased more strongly after *Jymmin*. Results revealed that the difference of baseline mood score and mood score after *Jymmin* ($Mdn = -3.00$) did not differ significantly (after Bonferroni-correction) from the difference of baseline mood score and mood score after *conventional workout* ($Mdn = 1.00$), $Z = -2.171$, $p = 0.015$ (one-tailed), $r = 0.38$, as measured with the *MDMQ*. Again, no sequence effect was found.

Furthermore, to test the hypothesis 3 that pain levels decrease more strongly after *Jymmin* a Wilcoxon Signed Ranks Test for dependent samples was applied. Results revealed that the difference of baseline pain level and pain level after *Jymmin* ($Mdn = 0.30$) did not significantly differ from the difference of baseline pain level and pain level after *conventional workout* ($Mdn = 0.10$), $Z = -1.429$, $p = 0.074$ (one-tailed) as measured with the *pain VAS*. No sequence effect was found for differences in pain level using the Mann–Whitney *U* Test.

Interestingly, the level of anxiety before the patients started the intervention could play a role on the interventional effects on pain perception. We performed a subsequent analysis where we analyzed two subgroups of patients separately: patients with medium anxiety (STAI ≤ 45; $n = 8$) and patients with high anxiety levels (STAI > 45, $n = 14$; **Figure 4**). Descriptive statistics seem to suggest that those patients who had high anxiety levels benefitted from both conditions in terms of pain reduction, and to a stronger degree from the *Jymmin* condition. However, those patients who reported medium levels of anxiety seem to display a trend of increases

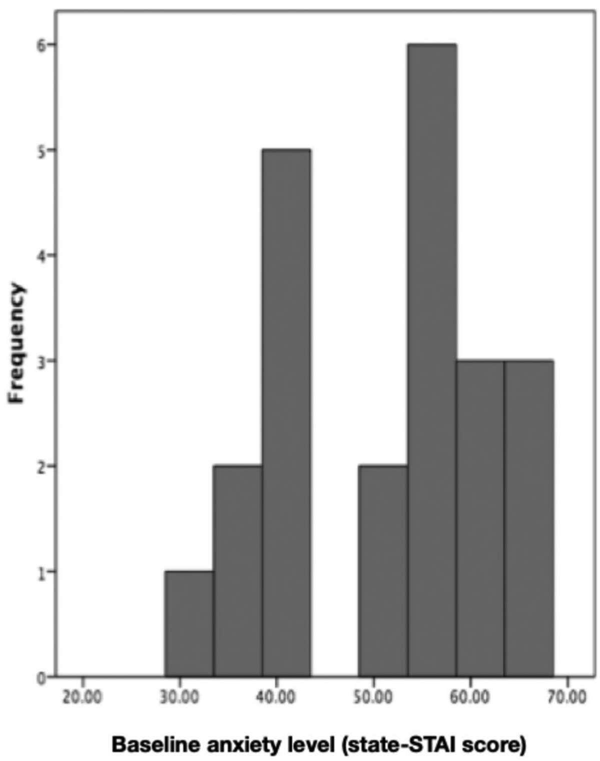

FIGURE 4
The figure depicts baseline anxiety levels of participants.

in pain perception after both conditions (Table 1). Note however, that differences are not significant.

In addition, a Wilcoxon Signed Ranks Test was applied to test hypothesis 4: External locus of control decreases and the internal locus of control increases more strongly after *Jymmin*. Results showed that the difference of baseline external locus of control score and external locus of control score after *Jymmin* ($Mdn = 0.00$) did not differ significantly from the difference of baseline external locus of control score and external locus of control score after *conventional workout* ($Mdn = 0.00$), $Z = -0.182$, $p = 0.428$ (one-tailed), nor did sequence have an effect on the outcome. The difference of baseline internal locus of control score and internal locus of control score after *Jymmin* ($Mdn = 0.00$) did not significantly differ from the difference of baseline internal locus of control score and internal locus of control score after *conventional workout* ($Mdn = 0.00$), $Z = 0.000$, $p = 0.500$ (one-tailed). Again, sequence did not affect the results.

Similar results were found for the *generalized self-efficacy scale*. A Wilcoxon Signed Ranks test was applied to test hypothesis 5 that self-efficacy increases more strongly after *Jymmin*. The difference of baseline self-efficacy score and self-efficacy score after *Jymmin* ($Mdn = -1.00$) did not differ significantly from the difference of baseline self-efficacy score and self-efficacy score after *conventional workout* ($Mdn = -2.00$), $Z = -0.856$, $p = 0.196$ (one-tailed), nor did sequence has an effect on the results.

TABLE 1 Descriptive statistics on levels of anxiety and changes in pain perception.

Anxiety level	n	Pain level at baseline	Pain level after Jymmin	Pain level after conventional workout
Medium anxiety	8	Mdn = 4.25 Var = 9.37	Mdn = 4.80 Var = 7.43	Mdn = 5.85 Var = 4.73
High anxiety	14	Mdn = 6.85 Var = 7.59	Mdn = 4.55 Var = 7.98	Mdn = 5.70 Var = 5.01

Medians and variances of pain level for both experimental conditions are displayed for patients with medium anxiety levels at baseline and for patients with high anxiety at baseline.

Additional explorative analyses-results of training related self-constructed items and follow-up questionnaire

Explorative analyses on training related items and follow-up questionnaires were performed using Wilcoxon Signed Ranks Tests. Note that in explorative analyses two-tailed *p*-values were calculated and no Bonferroni correction was applied. Results showed significant effects of musical agency on motivation mediated through the group experience. In the *Jymmin* condition ($Mdn = 5.10$) patients ($N = 21$) were significantly more motivated through other group members than during the *conventional workout* condition ($Mdn = 4.80$), $Z = -2.660$, $p = 0.008$ (two-tailed), $r = 0.41$ (see Figure 5). Self-motivation did not differ significantly between *Jymmin* ($Mdn = 6.50$) and *conventional workout* ($Mdn = 6.70$). Furthermore, the patients ($N = 23$) liked the music during the *Jymmin* condition ($Mdn = 4.50$) significantly more than during the *conventional workout* condition ($Mdn = 2.90$), $Z = -2.766$, $p = 0.006$ (two-tailed), $r = 0.41$.

In addition, liking the music in the *Jymmin* condition correlates significantly positive with feeling comfortable in the group ($N = 23$, $r_s = 0.594$, $p = 0.003$) and how *Jymmin* was perceived as an incentive to do sports despite the feeling of pain ($N = 23$, $r_s = 0.629$, $p = 0.001$). Moreover, liking the music during *Jymmin* correlates positively with generalized self-efficacy scores after the *Jymmin* condition ($N = 21$, $r_s = 0.630$, $p = 0.002$; Figure 6), but liking the music during *conventional workout* does not show such a correlation ($N = 23$, $r_s = 0.218$, $p = 0.317$).

Results of the follow-up questionnaire were assessed with visual analog scales (1–100 mm). Note that because participants performed both conditions as part of the experimental cross-over design, no differentiation of the following assessments was made between conditions. Furthermore, responses of 50 or higher were defined as

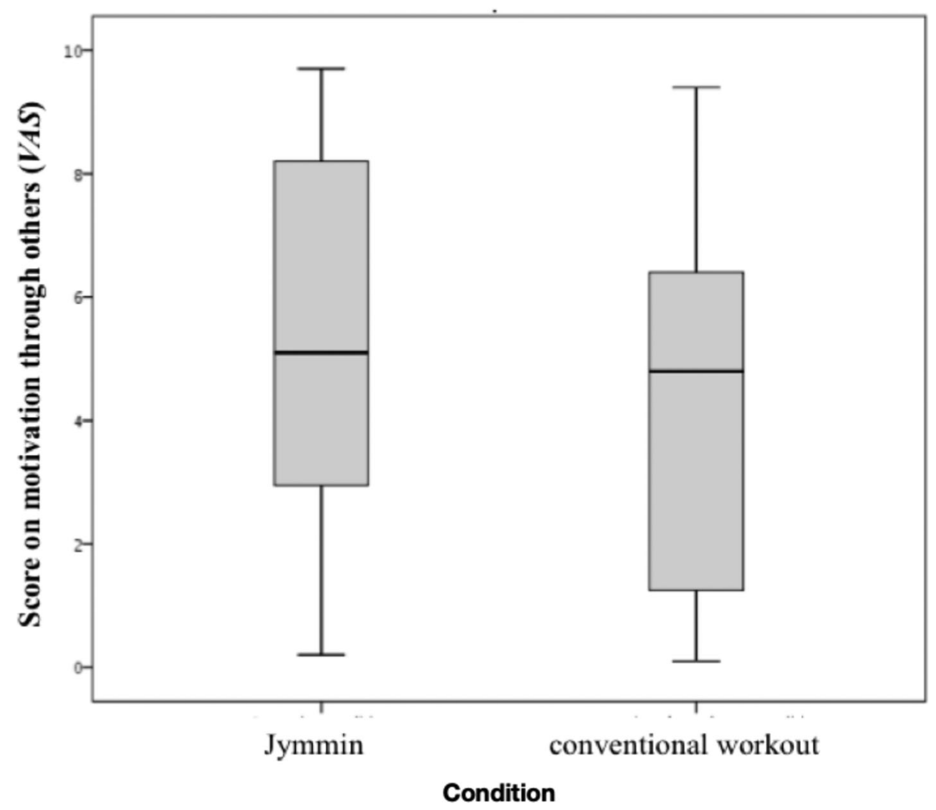

FIGURE 5
The figure depicts scores on the motivation through others during the *Jymmin* or *conventional workout* condition as measured on a *VAS*. A Wilcoxon Signed Rank Test revealed significant difference between medians of the *Jymmin* and *conventional workout* condition. The motivation through other training partners was significantly higher during *Jymmin* as compared to *conventional workout*.

medium to high effects. For each item of the questionnaire the percentage of participants was calculated who responded in the range above 50. 100% of the participants was defined as the total number of patients who took part in the experiment ($N = 24$). Patients who did not fill out the items in the questionnaire were considered in the analysis as if they had responded lower than 50. Results of the follow-up questionnaire showed that more than one third of the patients (37.5%) were experiencing medium to high positive physical effects during the remainder of the day after the workout intervention. Furthermore, 41.6% of all patients reported a medium to high positive effect on their mood during the rest of the day. The experience of an enhanced mood lasted for 0.5–7 h after the workout ($N = 14$, $M = 3.39$, $SD = 2.19$). In addition, bodily and mental relaxation was reported by about one third of the patients (33.4%).

Results on questions regarding the *Jymmin* intervention revealed that 66.7% of the patients had a positive attitude towards the *Jymmin* intervention (scale of 50 or higher). Furthermore, 45.6% of the patients believed that *Jymmin* could help them (scale of 50 or higher) to exercise regularly. In addition, 37.5% of the patients would like (scale of 50 or higher) to do *Jymmin* at home. Overall, over half of the patients (54.2%) were positively surprised by themselves to have sustained a fitness training for a total duration of 20 min.

Discussion

Results show that patients who worked out with musical feedback during the *Jymmin* condition had significantly reduced anxiety levels compared to when they exercised in the *conventional workout* condition, in which they passively listened to music while working out (status quo in fitness training). Physical activity is known to be highly beneficial in the treatment of chronic pain, for example increasing the patients' overall quality of life (12). However, patients' anticipation of pain tends to lead directly to avoidance behavior so that they do not engage in physical activity. Alternatively, when they do engage in physical activity, their anticipation of pain tends to lead to a state of anxiety and tension, which renders exercise less effective, more exhausting and more painful. As illustrated by the Anxiety Loop of Pain (**Figure 1**), (state) anxiety plays a crucial role in the avoidance

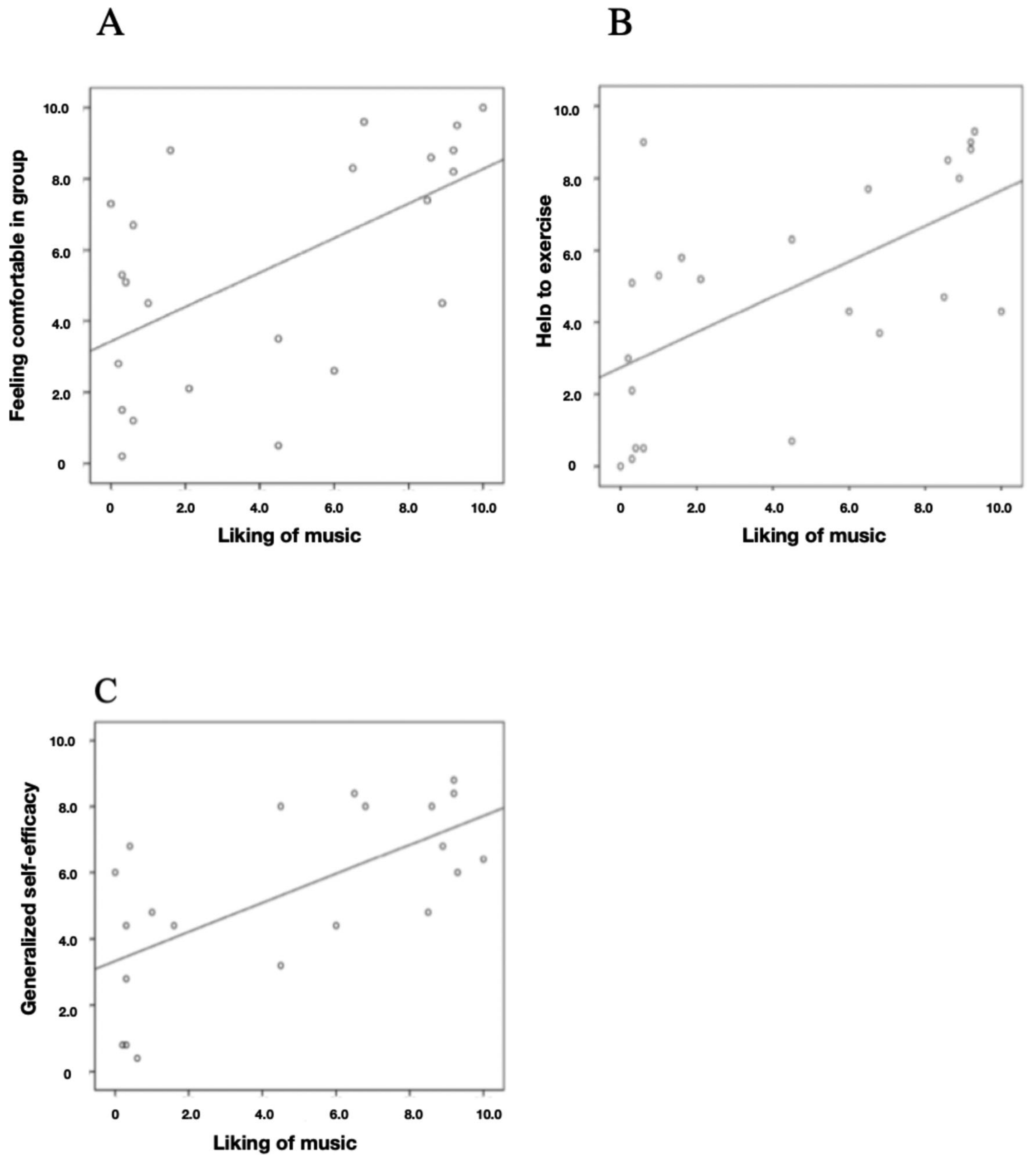

FIGURE 6
The figure depicts Spearman's correlations of (A) how liking the music during the *Jymmin* condition correlated with how comfortable they felt within the training group, (B) how much liking the music during *Jymmin* correlated withy how much they thought *Jymmin* would be an incentive to exercise despite having pain, and (C) how liking the music during *Jymmin* correlated with generalized self-efficacy scores after performing *Jymmin* as measured with the GSE.

of physical activity in chronic pain patients, amplifying the feedback between pain and the anticipation of pain. The current results therefore are highly relevant to our understanding of how this vicious cycle (Anxiety Loop of Pain) may be broken (Figure 7).

Two mechanisms may account for the observed effect of musical agency during exercise on anxiety. First, previous evidence suggested that workout with musical feedback/agency led to a higher metabolic muscle efficiency, which is associated with greater muscle relaxation [less activation of the antagonist muscle (28);]. Muscle relaxation corresponds to a decrease in muscle tension, which has been described to be one of the most prominent physiological signals directly related to the subjective percept of anxiety [other less salient

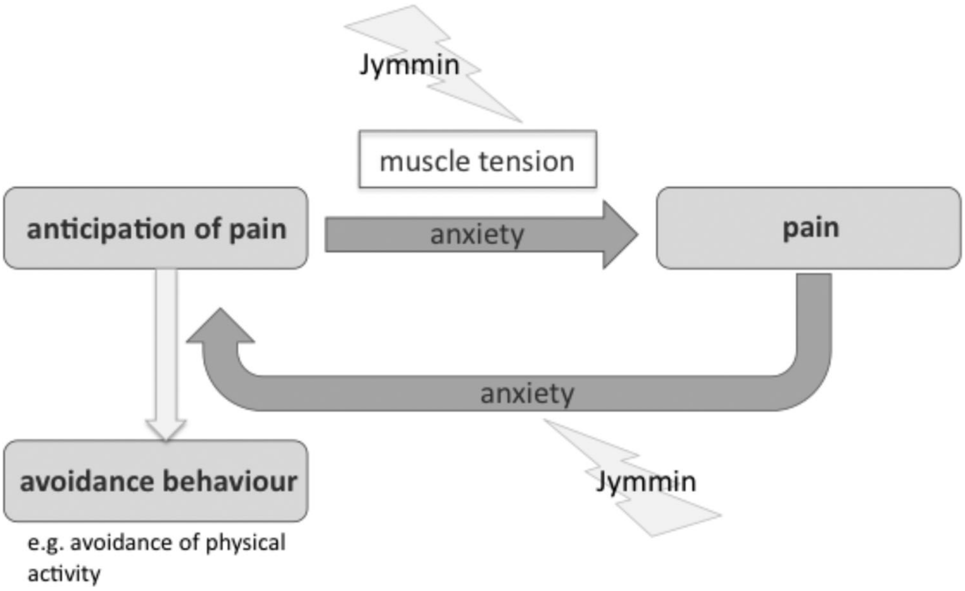

FIGURE 7
Influence of *Jymmin* on the Anxiety Loop of Pain. Disruptive effect of *Jymmin* on the depicted loop are indicated by the lightning symbol.

cues comprise parameters of the stress reaction such as blood pressure (37);]. Given that muscular tension in chronic pain patients can be seen as a psycho-physiological correlate of learned fear (38) such a decreasing effect on muscle tension by doing *Jymmin* is likely to also have had an influence on their subjective percept of anxiety. In the current study we investigated a one-time intervention, we expect that the observed positive effects on anxiety would help to positively condition the movement experience with multiple use and could therefore be a useful approach to help chronic pain patients deal with avoidance behavior. However, this still remains to be tested in further studies.

Second, an alternative explanation for the observation that anxiety is reduced after *Jymmin* may be that an increased cognitive demand due to musical agency and a guided attention to the whole movement and involved body parts *via* the immediate music-feedback may have positively altered the attentional state such that they have less capacity/attentional resources to monitor pain symptoms and focus on possible pain experiences.

The above finding demonstrates that in the management of chronic pain it should be helpful to consider the influence of anxiety. This is especially the case when trying to engage patients to join and enjoy physical activities. Given its emotionally engaging and largely positive effects in listeners music is thus a powerful tool to facilitate this process.

Results of the present study showed that pain levels of patients did not change from baseline in either condition. This is surprising, given that music listening has previously been observed to ameliorate perceived pain in chronic pain patients (20, 22), and we had hypothesized that musical agency would decrease pain levels during the sports intervention. This may relate to two aspects, first the music presented in previous studies was either calming music aimed at inducing relaxation, or music that participants favored. These participants thus probably perceived this music as relatively pleasant, whereas in the present study the perceived valence of the utilized music (which was pre-selected and aimed at energizing participants for the sports workout) varied strongly between participants.

Second, in previous studies reporting positive effects of music listening the chronic pain patients only listened to the music and they were not required to exercise on fitness machines as it was the case in the present study. In each of the two sports interventions applied (and generally in every sports intervention), patients both anticipate and perceive discomfort and physical pain. Therefore it is plausible that with respect to pain the effects of making sports counteract those of musical analgesia. Indeed it seems somewhat surprising that in the present study pain levels did not increase in either of the sports conditions (that were both associated with music-actively making music or passively listening to music). Given that the vicious cycle between anticipation of pain and pain is mediated by anxiety (illustrated in **Figure 7**) the observed decrease in anxiety in both experimental conditions (but stronger during *Jymmin*) may have contributed to such a lack of effect of exercise on pain levels. Note that this is in accord with descriptive values that showed a non-significant trending in the predicted direction rather indicating a stronger decrease in pain after *Jymmin*. In addition, a subsequent analysis showed that patients with high anxiety levels at baseline seem to experience a greater benefit from the Jymmin condition in terms of pain reduction as compared to the conventional workout condition. Furthermore, greater variances in pain levels after Jymmin were observed. It may be interesting to investigate in further studies with a greater number of participants, which characteristics of patients with chronic pain need to be considered in order to differentiate for which patients the described music intervention is effective.

Furthermore, the present study aimed at investigating possible effects of musical agency during exercise on locus of control and generalized self-efficacy in chronic pain patients. No such effects on locus of control and self-efficacy were observed. However, a significant correlation was observed that relates to generalized self-efficacy: Liking the music during *Jymmin* correlates positively with generalized self-efficacy scores after the *Jymmin* condition, whereas liking the music during *conventional workout* does not show such a correlation. In other words, patients who enjoyed the outcome of their musical agency perceived a transfer to generalized self-efficacy. Alternatively, it could be the other way around, such that those participants who had greater self-efficacy scores were also prone to more strongly engage in musical agency and as a result could enjoy the outcome of their effort (literally). It is plausible that in the *conventional workout* condition therefore the perceived aesthetic quality of the music had no relation to self-efficacy.

The current data show that when patients were musically expressive together in a group, this enhanced their motivation to exercise more strongly than working out within the same group while listening to music passively. The higher motivation through others is probably at least partly due to contagious processes on the motor and emotional level. These contagious processes are probably amplified by the circumstance that participants are committing themselves through their exertion to a common aesthetic goal. Given that humans are social animals, such a goal will be best achieved as a joint endeavor where participants encourage each other with the means available, and also where participants more strongly feel a social obligation to participate than during the conventional workout condition. Musical expression is known to be a strong motivator to engage groups of people in activities and is present in most if not all important social rituals and occasions. Accordingly participants probably used the musical expression available to them as a communicational tool to motivate other training partners for example by performing with more enthusiasm when others seemed to wear out.

Limitations of the current study

A limitation of the current study is the relatively small number of patients that could be included in the data analyses due to a substantial number of missing responses in the standardized questionnaires. Chronic pain patients are known to suffer from cognitive impairments such as concentration and attention deficits. Therefore, computer-based questionnaires in which missing responses are immediately indicated to the participant might be a good option to address this issue in future research.

The current investigation did not include a condition where patients only performed exercise in the absence of music presentation. It would be interesting to compare pain levels after either of the two current exercise-and-music conditions (where music is either made actively or passively listened to) with such a control condition, where patients would probably perceive increased pain levels due to exercise (which they regularly report during sports exercise). However, note that including a control condition aimed at inducing pain in chronic pain patients would ethically have to be carefully considered.

Locus of control and generalized self-efficacy that have been investigated in the current study are rather stable over time and probably hardly changed by a one-time intervention. In future research it might be preferable to ask intervention specific questions on self-control and self-efficacy such as control over pain during and after the experimental intervention.

Implications and future research

The present study shows how being musically expressive during exercise machine workout reduces anxiety levels in chronic pain patients. This finding is highly relevant to the management of chronic pain, because anxiety is a key factor in hindering chronic pain patients to engage in physical activities, mediating the vicious Anxiety Loop of Pain (**Figure 7**).

Two things are often perceived to cause anxiety in a chronic pain patient, (1) Engaging in physical activity, (2) Engaging in social interaction. While physical activity is usually perceived to amplify pain, social interaction is rather perceived as a challenge and additional burden as soon as pain arises. That both aspects may be combined to create a positive experience, getting less anxious while engaging both in a workout and a social activity, can serve as an example to the chronic pain patient that intense physical activity can be enjoyed socially. It is important to note that this activity can even be enjoyed without full pain relief, which in many chronic pain patients unfortunately is beyond reach. Thus the combination of workout and musical agency seems promising for chronic pain management, reducing anxiety and promoting physical activity.

The social aspect of the intervention presented here is highly important as it provides experiences of being motivated by others as well as feeling comfortable within a social group.

Chronic pain patients often suffer from social isolation as a result of their decreased general activity level. In addition, they are afraid of being somewhere else than at home when strong pain arises. In a rehabilitation context, where group therapeutic interventions are regularly applied, a positive experience with such an "anticipation-of-pain" evoking activity could result in positive transfer effects to other group interventions.

Future research should address long-term effects of the music-sports intervention investigated here. It would be of great interest to examine how repeatedly breaking the vicious Anxiety Loop of Pain with *Jymmin* could with regular training over time systematically decrease chronic pain. This would then further increase the motivation of patients to perform physical workout, facilitating physical rehabilitation. In addition, long-term effects on mood should be assessed, as well as more general concepts of patients' well-being and quality of life. This could be complemented assessing physiological data such as heart rate, blood pressure, heart rate variability, hormone levels etc., which would help to better understand mechanisms of how the musical feedback intervention relates to pain perception during physical exercise. It would also be relevant for future studies to analyze the impact of the current intervention for a prolonged time to evaluate its effect with respect to different stages of the development of chronic pain.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics committee of the University of Leipzig. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LS, UTE, DK, TF: designed the experiment. LS, DK, WS, TF: wrote the manuscript. LS: did the data analysis. UTE, AV: supervision and infrastructure. All authors contributed to the article and approved the submitted version.

Conflict of interest

TF is a founding member of the start-up Jymmin GmbH that tries to make music feedback technology available in rehabilitation. TF has no formal role in the GmbH but owns shares. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Takai Y, Yamamoto-Mitani N, Abe Y, Suzuki M. Literature review of pain management for people with chronic pain. *Jpn J Nurs Sci*. (2015) 12(3):167–83. doi: 10.1111/jjns.12065

2. Müller-Schwefe GHH. European Survey of chronic pain patients: results for Germany. *Curr Med Res Opin*. (2011) 27(11):2099–106. doi: 10.1185/03007995.2011.621935

3. Pickering G, Gibson S. *Pain, emotion and cognition: A Complex nexus*. Switzerland: Springer International Publishing (2015).

4. van der Windt D. The role of co-morbidity in accumulating risk of chronic pain. *Pain*. (2012) 153(2):259–60. doi: 10.1016/j.pain.2011.10.040

5. Simmonds M, Turner B. (502) long term, high dose opioids in veterans with chronic pain: are there benefits or just burdens? *J Pain*. (2014) 15(4):S101. doi: 10.1016/j.jpain.2014.01.414

6. Roth G, Egle UT. Neurobiologie von Schmerz und stress. *Ärztl Psychother*. (2016) 11(3):120–9. Available at: https://elibrary.klett-cotta.de/article/99.120110/aep-11-3-120

7. Egle UT, Klinger D. Grundprinzipien der Behandlung stressbedingter Schmerzsyndrome. *Ärztl Psychother*. (2016) 11(3):155–61. Available at: https://elibrary.klett-cotta.de/article/99.120110/aep-11-3-155

8. Martin A, Rief W. Somatoforme Störungen. In: HU Wittchen, J Hoyer, editors. *Klinische psychologie & psychotherapie*. Berlin, Heidelberg: Springer (2011). p. 1021–38.

9. Crombez G, Eccleston C, Van Damme S, Vlaeyen JWS, Karoly P. Fear-avoidance model of chronic pain: the next generation. *Clin J Pain*. (2012) 28(6):475–83. doi: 10.1097/AJP.0b013e3182385392

10. Woo KY. Unravelling nocebo effect: the mediating effect of anxiety between anticipation and pain at wound dressing change. *J Clin Nurs*. (2015) 24(13–14):1975–84. doi: 10.1111/jocn.12858

11. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, et al. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J*. (2006) 15(Suppl 2):S192–S300. doi: 10.1007/s00586-006-1072-1

12. Koes BW, van Tulder MW, Thomas S. Diagnosis and treatment of low back pain. *Br Med J*. (2006) 332(7555):1430–4. doi: 10.1136/bmj.332.7555.1430

13. Bement M, Sluka K. Exercise-induced hypoalgesia: an evidence-based review. In: Sluka KA, editor. *Mechanisms and management of pain for the physical therapist, 2nd edn, Ch. 10.* Seattle: Wolters Kuwer, IASP Press (2016). p. 177–201.

14. Simmonds MJ, Novy D, Sandoval R. The differential influence of pain and fatigue on physical performance and health status in ambulatory patients with human immunodeficiency virus. *Clin J Pain*. (2005) 21(3):200–6. doi: 10.1097/00002508-200505000-00002

15. Castro M, Kraychete D, Daltro C, Lopes J, Menezes R, Oliveira I. Comorbid anxiety and depression disorders in patients with chronic pain. *Arq Neuropsiquiatr*. (2009) 67(4):982–5. doi: 10.1590/S0004-282X2009000600004

16. Roshanaei-Moghaddam B, Katon WJ, Russo J. The longitudinal effects of depression on physical activity. *Gen Hosp Psychiatry*. (2009) 31(4):306–15. doi: 10.1016/j.genhosppsych.2009.04.002

17. Rhudy JL, Meagher MW. Fear and anxiety: divergent effects on human pain thresholds. *Pain*. (2000) 84(1):65–75. doi: 10.1016/S0304-3959(99)00183-9

18. Carter LE, McNeil DW, Vowles KE, Sorrell JT, Turk CL, Ries BJ, et al. Effects of emotion on pain reports, tolerance and physiology. *Pain Res Manag*. (2002) 7(1):21–30. doi: 10.1155/2002/426193

19. Huffman JC, Pollack MH. Predicting panic disorder among patients with chest pain: an analysis of the literature. *Psychosomatics*. (2003) 44(3):222–36. doi: 10.1176/appi.psy.44.3.222

20. Garza-Villarreal EA, Wilson AD, Vase L, Brattico E, Barrios FA, Jensen TS, et al. Music reduces pain and increases functional mobility in fibromyalgia. *Front Psychol*. (2014) 5:90. doi: 10.3389/fpsyg.2014.00090

21. Onieva-Zafra MD, Castro-Sánchez AM, Matarán-Peñarrocha GA, Moreno-Lorenzo C. Effect of music as nursing intervention for people diagnosed with fibromyalgia. *Pain Manag Nurs*. (2013) 14(2):e39–e46. doi: 10.1016/j.pmn.2010.09.004

22. Guétin S, Giniès P, Siou DKA, Picot MC, Pommié C, Guldner E, et al. The effects of music intervention in the management of chronic pain: a single-blind, randomized, controlled trial. *Clin J Pain*. (2012) 28(4):329–37. doi: 10.1097/AJP.0b013e31822be973

23. Mitchell LA, MacDonald RAR, Knussen C. An investigation of the effects of music and art on pain perception. *Psychol Aesthet Creat Arts*. (2008) 2:162–70. doi: 10.1037/1931-3896.2.3.162

24. Brown CJ, Chen ACN, Dworkin SF. Music in the control of human pain. *Music Ther*. (1989) 8:47–60. doi: 10.1093/mt/8.1.47

25. Dunbar RIM, Kaskatis K, MacDonald I, Barra V. Performance of music elevates pain threshold and positive affect: implications for the evolutionary function of music. *Evol Psychol Int J Evol Approaches Psychol Behav*. (2012) 10(4):688–702. doi: 10.1177/147470491201000403

26. Prasanna SS, Mayo S, Simmonds M. Influence of music on gait speed in fibromyalgia. In: Canadian Physiotherapy Association. (2013).

27. Fritz TH, Bowling DL, Contier O, Grant J, Schneider L, Lederer A, et al. Musical agency during physical exercise decreases pain. *Front Psychol*. (2018) 8:2312. doi: 10.3389/fpsyg.2017.02312

28. Fritz TH, Hardikar S, Demoucron M, Niessen M, Demey M, Giot O, et al. Musical agency reduces perceived exertion during strenuous physical performance. *Proc Natl Acad Sci USA*. (2013) 110(44):17784–9. doi: 10.1073/pnas.1217252110

29. Fritz TH, Halfpaap J, Grahl S, Kirkland A, Villringer A. Musical feedback during exercise machine workout enhances mood. *Front Cogn Sci*. (2013) 4:921. doi: 10.3389/fpsyg.2013.00921

30. Asmundson GJG, Katz J. Understanding the co-occurrence of anxiety disorders and chronic pain: state-of-the-art. *Depress Anxiety*. (2009) 26(10):888–901. doi: 10.1002/da.20600

31. Kroenke K, Outcalt S, Krebs E, Bair MJ, Wu J, Chumbler N, et al. Association between anxiety, health-related quality of life and functional impairment in primary care patients with chronic pain. *Gen Hosp Psychiatry*. (2013) 35(4):359–65. doi: 10.1016/j.genhosppsych.2013.03.020

32. Manual Komplettversion und Kurzform. [cited 2022 Nov 1]. Available from: https://docplayer.org/20849309-Manual-komplettversion-und-kurzform.html.

33. Steyer R, Schwenkmezger P, Notz P, Eid M. Der Mehrdimensionale Befindlichkeitsfragebogen (MDBF; The Multidimensional Mood State Questionnaire, MDMQ). Handanweisung Gött Hogrefe. (1997).

34. Spielberger CD. Assessment of state and trait anxiety: conceptual and methodological issues. *South Psychol*. (1985) 2:6–16. Corpus ID: 149542499

35. Social Learning and Clinical Psychology by ROTTER, Julian B. Fine Hardcover | Between the Covers-Rare Books, Inc. ABAA (1954). [cited 2022 Nov 1]. Available from: https://www.abebooks.com/first-edition/Social-Learning-Clinical-Psychology-ROTTER-Julian/30927410991/bd

36. Schwarzer R, Jerusalem M. General Self-Efficacy Scale - PsycNET. [cited 2022 Nov 1]. Available from: https://psycnet.apa.org/doiLanding?doi=10.1037%2Ft00393-000

37. Progressive Muskelentspannung | Hogrefe. [cited 2022 Nov 1]. Available from: https://www.hogrefe.com/de/shop/progressive-muskelentspannung-92629.html#1+1

38. Klinger R, Matter N, Kothe R, Dahme B, Hofmann UG, Krug F. Unconditioned and conditioned muscular responses in patients with chronic back pain and chronic tension-type headaches and in healthy controls. *Pain*. (2010) 150(1):66–74. doi: 10.1016/j.pain.2010.03.036

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A web app-based music intervention reduces experimental thermal pain: A randomized trial on preferred versus least-liked music style

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Digital technologies are increasingly being used to strengthen national health systems. Music is used as a management technique for pain. The objective of this study is to demonstrate the effects of a web app-based music intervention on pain. The participants were healthy adults and underwent three conditions: Conditioned Pain Modulation (CPM), Most-Liked Music (MLM) and Least-Liked Music (LLM). The music used is MUSIC CARE©, a web app-based personalized musical intervention ("U" Sequence based on a musical composition algorithm). Thermal pain was measured before starting the 20-min music intervention and after three time points for each music condition: 2.20, 11.30, and 20 min. Mean pain perceptions were significantly reduced under both LLM and MLM conditions. Pain decrease was more important under MLM condition than LLM condition at 2.20 min with a mean difference between both conditions of 9.7 (±3.9) ($p = 0.0195$) and at 11.30 min [9.2 (±3.3), $p = 0.0099$]. LLM is correlated with CPM but not MLM, suggesting different mechanisms between LLM and MLM. Musical intervention, a simple method of application, fits perfectly into a multidisciplinary global approach and helps to treat the pain and anxiety disorders of participants.
Clinical trial registration: [https://clinicaltrials.gov/ct2/show/NCT04862832], ClinicalTrials.gov [NCT04862832].

KEYWORDS
music, pain, digital therapeutics, experimental pain in humans, adult, endogenous pain modulation, conditioned pain modulation

Introduction

Music has been reported as a management technique of acute and chronic pain since 1960 (1) and is nowadays widely used as an alternative or complementary treatment to reduce patient pain (2). Music is easy to implement in clinical contexts as it is safe, non-invasive, and inexpensive (3, 4). Multiple clinical environments can be found using music today (5, 6) for conditions such as childbirth (7–10), resuscitation (11), cardiac surgery (12, 13), cancer (14, 15), in cardiology, during a catheter installation (16), or cataract surgery (17).

Converging evidence suggests that music is indeed beneficial for different types of pain (13, 14, 18, 19), in addition to psychological distress, ranging from smaller-scale mood improvements to anxiety disorders (20). Music can also improve the management of chronic pain conditions, such as cancer by reducing pain and its associated components of anxiety, depression, and quality of life (21).

There are different music procedures used to reduce pain (22), especially one based on music in a medical context (23). In the treatment of pain, the most widely used music is relaxing (5), even if no consensus was reached to indicate a difference between relaxing and stimulating music's ability to reduce pain.

A multitude of endogenous mechanisms can modulate pain perception. Music involves different inputs such as sensory, cognitive, or emotional (24), which, according to the Neuromatrix theory of pain (25) can modulate the final pain perception. Music-induced analgesia could be explained by a change of perception such as distraction (26). Another potential mechanism is the recruitment of Conditioned Pain Modulation (CPM). CPM is based on the recruitment of diffuse noxious inhibitory control (DNIC) from different structures in the brainstem (e.g., periaqueductal gray, nucleus raphe Magnus) following a localized nociceptive stimulation (27). However, CPM is also influenced by descending higher center activities (28). Music is suggested to increase the efficacy of descending mechanisms like conditioned pain modulation (CPM) (29). Brain imaging studies reported that listening to music activate spinal and supraspinal regions known to be involved in endogenous descending pain modulation (30).

Perceived pleasantness has also been suggested to play a role in the analgesic potential of music. Pleasant music according to the participant is superior to unpleasant music or silence in decreasing experimental pain (31). Allowing the patient to choose the style of music adds to pain relief and adds a sense of control over pain (5, 6, 32–34). Paying attention to personal musical preferences and cultural background are among the main characteristics of a successful musical intervention (35, 36). However, in many studies evaluating the effect of music on pain, there is a lack of details of the musical choice (33). It was also reported that pain was even more reduced when participants were selecting preferred music from a list given by the researcher (5). Recent technological developments now enable patients or caregivers to control the use of music-based interventions using hand-held devices. Silence condition is frequently used as a control condition for music, as sensory, cognitive or emotional inputs are limited during this condition.

Studying the effect of music-based interventions in medical contexts is complex and requests strong methodology. Discussion with researchers in this field suggested that the main methodological research challenges relate to treatment, outcomes, research designs, and implementation (37). According to a systemic review, music sessions should last between 20 and 60 min and consist principally of harmonic variations (38). There is a growing interest to design and implement new and cost-effective online treatments using technological advances. The Ministries of Health of the WHO European Region are increasingly investing in Digital Therapeutics (DTx). They are helping overcome barriers to the adoption of DTx to strengthen health systems and to explore ways to accelerate DTx for public health. Digital health technologies can improve access to health services, lower costs, improve the quality of care and increase the efficiency of health systems. They offer ways to manage personal health, with a focus on disease prevention rather than just treatment (39).

Based on these recent scientific recommendations, MUSIC CARE©, a web app-based personalized music intervention, has developed a "U" Sequence based on a musical composition algorithm. The music sequence can last from 20 to 60 min and is divided into several phases that gradually enable the patient to lower their pain and anxiety levels in line with the "U" Sequence technique (11, 40, 41). Previous studies had confirmed the effectiveness of this web app-based music intervention in reducing pain and/or anxiety in patients with a variety of conditions (2, 42, 43).

The principal objective of this study was therefore to describe the effects of a web app-based music intervention on the modulation of pain and the difference between the most-liked music (MLM) and least-liked music (LLM) conditions. A secondary objective was to compare the effect of CPM with MLM and LLM on pain perception. Our hypothesis was that most-liked music will be superior to least-liked music in reducing pain perception. Our second hypothesis was that the pain relief during the music interventions would be correlated with CPM, suggesting comparable mechanisms.

Materials and methods

Study design

A randomized, multi-center, open-label, controlled, crossover clinical trial was conducted in four centers: Sherbrooke University Hospital Centre, Sherbrooke University, the campus of Bishop's University and Cégep Champlain. Participants were recruited in these 4 centers, but the procedures were conducted at Sherbrooke University Hospital Centre by two research assistants. This study was composed of 3 experimental sessions on 3 consecutive days: on day 1 CPM was tested in all participants for a baseline endogenous pain inhibition measurement. All subjects then entered a randomized crossover part of the study with MLM or LLM on day 2 and day 3.

Participants

Thirty-three healthy adults [20 women and 13 men mean age of 23.5 years (±4,9)] participated in this study. Participants were excluded if they were musicians with knowledge of music theory, diagnosed and taking medication for chronic pain, skin problems, psychological or neurological pathologies. The protocol was approved by the ethics committee of *Centre Hospitalier Universitaire de Sherbrooke* and informed consent was obtained from all participants. The verbal and written instructions including the questionnaires were presented in French or English at the choice of the participant. The patient flow chart is presented in Figure 1.

Web app-based music intervention

The web app-based music intervention was administered using headphones *via* a tablet-based application called *MUSIC CARE©*. The *MUSIC CARE©* app is a receptive music intervention and utilizes the "U" sequence (Figure 2) designed to gradually relax the listener (41–43).

It is implemented using a musical sequence of 20 min that was divided into 6 different musical pieces at 3–4 min each. The first five sections are in minor mode where the first one starts with stimulating musical rhythm 80–95 beats per minute (bpm). Then, the remaining four sub-pieces are presented in a blended fashion in an attempt for the patient to gradually fall into a relaxed state *via* a gradual reduction in musical tempo (40–80 bpm), orchestral size, frequencies, and volume (descending arms of the "U") followed by a phase of maximum relaxation (downward phase of the "U"). The last section is in major mode which corresponds to a phase that gradually returns to baseline dynamics (ascending arms of the "U"). This is thought to induce a catharsis. This construction is hypothesized to

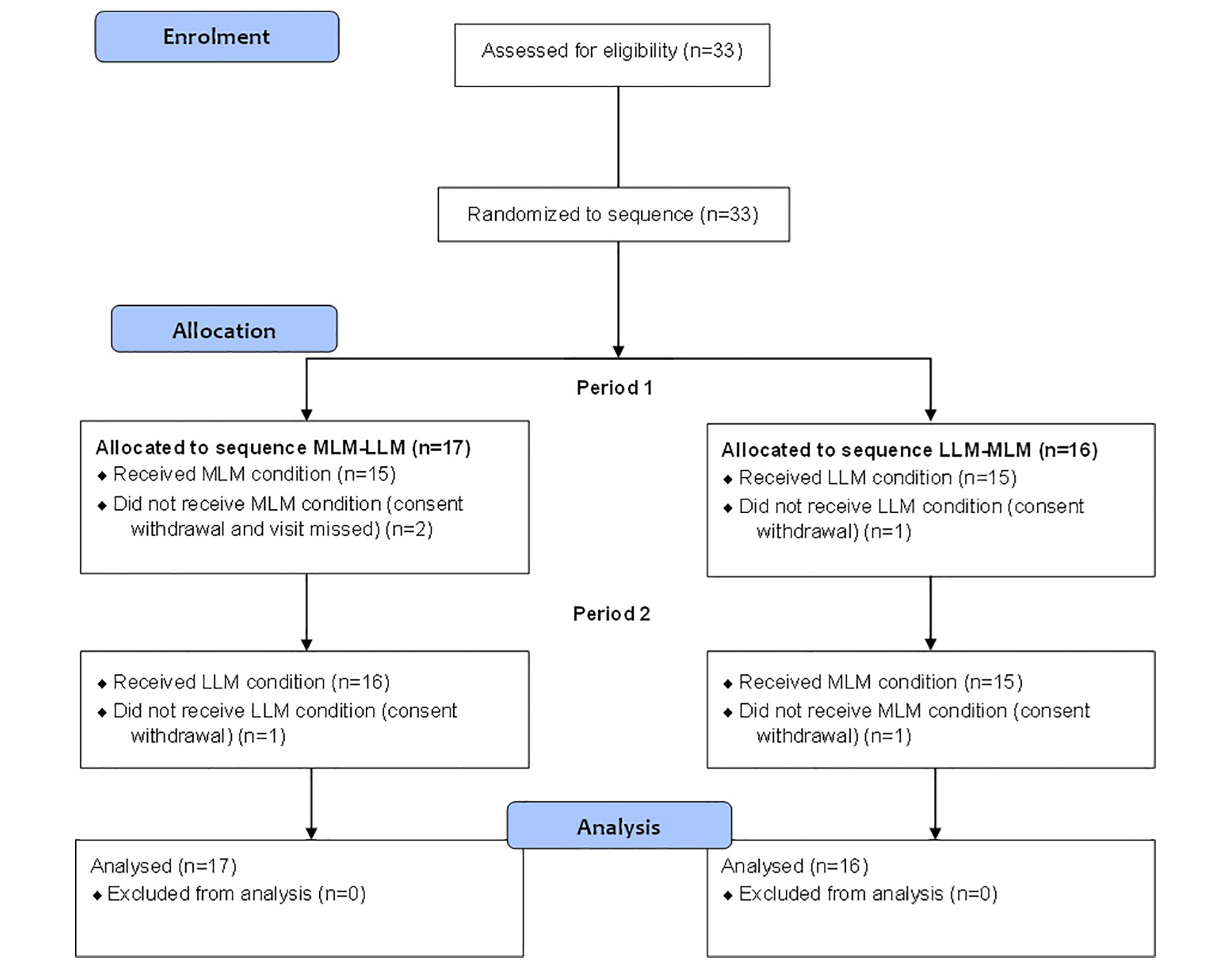

FIGURE 1
Participant flow chart following consolidated standards of reporting trials guidelines for MLM-LLM and LLM-MLM randomized arms.

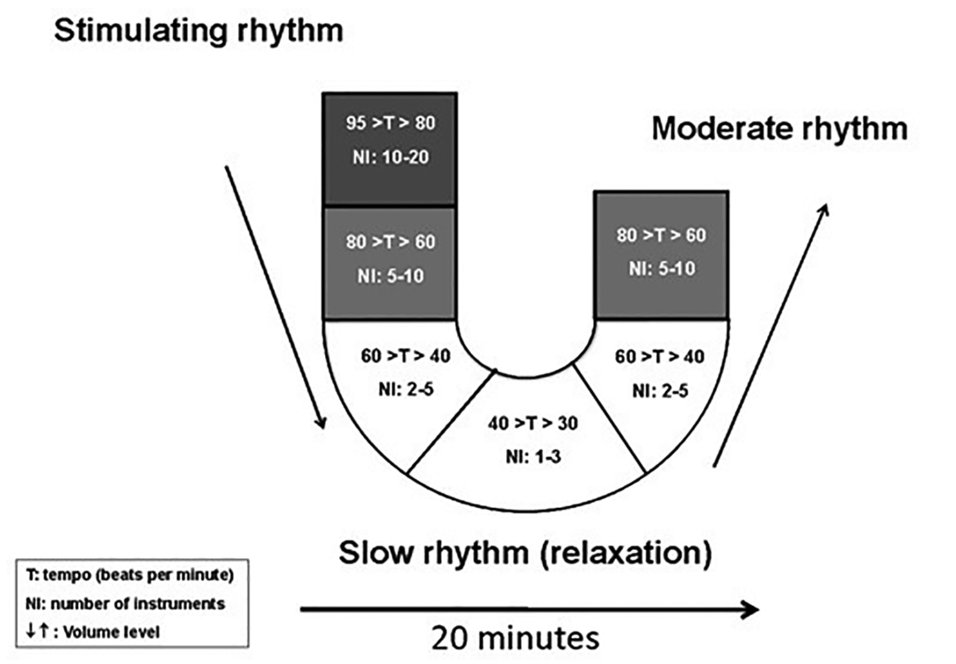

FIGURE 2
The "U" sequence. The musical sequence of 20 min is divided into 6 different musical pieces at 3–4 min each.

allow a mirror effect with the patient's emotions throughout the sequence. This is similar to the iso principle of music therapy (44) that describes the process of alteration of the patient's state by music. The minor mode validates the patient's suffering (negative emotions) and then the relaxation phase calms the patients, and finally the major mode incites positive emotions. In 1936 it was shown that the minor mode is known to be related to negative emotions while the major mode is related to positive emotions (45).

Thirty musical sequences were available (classical, folk, jazz, reggae and traditional music from South America, Caledonia, Asia, India or the Middle East) (**Table 1**), allowing for a personalized choice for the subjects. The music sequences are all 20 min, instrumental, professionally recorded in the studio and composed specifically for the MUSIC CARE© application and are thus unfamiliar to participants. The participants of this group listened, with headphones (QuietComfort® 25 Acoustic Noise Cancelling® headphones, Framingham, Massachusetts, Bose Corporation) plugged to a tablet (Samsung Galaxy Tab, 2013, 3 Lite 7.0, Suwon, South Korea, Samsung Electronics Co., Ltd.) to 30 s samples of the available sequences and rated them on a 0–10 scale in which 0 is "I do not want to listen to this one" and 10: "I really want to listen to this one." The order of the 30 samples was randomized for each participant. The highest rating was selected for the MLM condition and the lowest was for the LLM condition.

Thermal stimulation and conditioned pain modulation (CPM)

CPM was measured the first day in all subjects to have a baseline of the efficacy of endogenous pain modulation as previously describe (46). Since CPM is variable amongst healthy subjects and patients (47, 48), this baseline permitted to test for a correlation in pain changes between CPM and music sessions that could suggest comparable mechanisms.

The CPM paradigm to study the efficacy of inhibitory mechanisms is obtained by calculating the difference in pain levels elicited by the test stimulus (TS) before and after the conditioning stimulus (CS) (46, 48). The TS was generated by a 3 cm^2 thermode (TSA II, NeuroSensory Analyzer, Medoc Instruments, North Carolina, USA) applied on the non-dominant forearm of each participant at a predetermined, individually tailored temperature (pain levels of 50/100 based on pretests). The temperature remains constant over the next 120 s. Participants were asked to continuously record their pain level using a 10 cm Computerized Visual Analog Scale (CoVAS). Participants were asked to move the slider to reflect their pain from the left boundary (identified as "no pain"—score = 0) to the right boundary (identified as "worst pain imaginable"—score = 100). The CoVAS sampling rate was set at 10 Hz (10 pain measurements per second). The CS consists of a cold pressor test (CPT), wherein subjects immerse the opposite forearm in a cold-water bath (10°) for 120 s. The

TABLE 1 Number of participants by musical style choices for most-liked music (MLM) and least-liked music (MLM).

Style	Cuban	Flamenco	Celtic	Asian	African	Oriental	Indian	Reggae 1	Reggae 2	South American	Afro beat	Guitar ballad	Blues
Chosen as MLM	0	3	2	0	2	1	0	2	0	1	0	0	2
LLM	1	0	0	3	1	3	1	0	1	1	0	1	0
	Electro jazz	Jazz ballad	Folk guitar		Rock guitar	Piano	Accordion	Classical music 1 (Classical)	Classical music 2 (Classical)	Classical music 3 (Romantic)	Classical music 4 (Romantic)	Classical music 5 (baroque)	Film music
Chosen as MLM	0	0	2		2	0	2	2	2	3	4	1	2
LLM	13	1	2		1	0	1	1	0	0	0	0	0

thermal stimulation intensities used before and after the music conditions are the same as the one used for the CPM paradigm.

Measures

Sociodemographic data collected were sex, age and years of schooling.

For anxiety, the State Trait Anxiety Inventory (STAI) was used. There are two subscales: one for trait anxiety (STAI-Trait Y2) and one for state anxiety (STAI-State Y1). Each subscale contains 20 items and each statement is rated on a 4-point scale from: 1 "not at all" to 4 "very much so." The overall score for each subscale ranges from 20 to 80. Participants with a score of 20–45 have low anxiety, 46–55 moderate anxiety and 56–80 severe anxiety.

For depression, the Beck Depression Inventory (BDI) was used. There are 21 items on a 4-point scale, so the overall score is from 0 to 63. Participants with a score from 0 to 10 do not have depression, between 11 and 16, they have mild mood disturbance, 17–20 borderline clinical depression, 21–30 moderate depression, 31–40 severe depression and more than 40 extreme depression.

For pain catastrophizing, the Pain Catastrophizing Scale (PCS) was used. There are 13 items from 0: "not at all" to 4: "all the time". The overall score ranges from 0 to 52 in which participants with a score between 0 and 16 are non-catastrophizers, 17–29 are low catastrophizers and 30–52 severe catastrophizers.

At the end of the music intervention (i.e., after 20 min of listening), the perception of time was evaluated. The duration of the session was not communicated to the participants and they were asked how long they thought the session had lasted.

Procedure

There was three testing days for each participant. The participant was seated in a comfortable chair in a quiet room. The first day, before the pain tests started, consent form was read and signed by the participants. Then, the MLM and LLM were determined according to the process described above. Sociodemographic data, STAI, BDI and PCS questionnaires were administered. Then, a first 2-min thermal pain test was performed followed by the CPT and a second thermal pain test. The second and third days consisted of a first two-minute thermal pain test followed by one of the music conditions (MLM or LLM). The order of music condition was randomized per a generated randomized sequence of integers based on a pseudo-random number algorithm. Under the music conditions, three thermal pain tests were performed: the first one at 2.20 min after the music started; the second one was after the relaxation phase at

11.30 min and the third one after the whole 20-min cycle. STAI questionnaire was also completed during these testing days.

Statistical analyses

Based on data from previous studies managed in the Pain Research Laboratory (MUSEC: music, emotion and cognition), an effect size (d of Cohen) of 0.69 was used for sample size calculation (49). With a power of 80% and a type I risk of 5% (50), thirty-three participants needed to be included.

Evolution of overall pain perception was performed using a mixed effect model for repeated measures with an unstructured covariance matrix. Comparisons of continuous endpoints between pre-and post-condition, and between conditions were performed using paired student *t*-tests or Wilcoxon Sign Rank tests (non-parametric form of paired student *t*-tests, if distributions for variables were not normal). Bonferroni method was used for the correction of multiple comparisons.

All statistical tests were conducted using SAS® Studio (version 3.8, Edition enterprise, SAS Institute Inc, Cary, NC, USA). Comparisons of continuous endpoints between pre-and post-condition, and between conditions were performed using Wilcoxon Sign Rank tests (non-parametric form of paired student *t*-tests, as distributions for all dependent variables were not normal) (51). Normality of the distributions was tested using Shapiro-Wilk test. Comparisons between both music conditions were performed using Grizzle's model for crossover design with condition, period and sequence as fixed effects and participants within sequence as a random effect. Carryover effect was tested using Student *t*-tests. Statistics reported include means ± standard deviation and associated two-tailed *p* values as significance levels (cut-off of 0.05 for statistical significance). The research was submitted and approved by the Human Health Research Ethics Board from the CHUS. The analysis was conducted under the Intent-to-Treat (ITT) principle maintaining balance generated from the original random treatment allocation and avoiding statistical bias. As suggested for ITT, we ignored noncompliance, protocol deviations, withdrawal, and anything that happens after randomization (52). All subjects were then included in the analysis.

Results

Thirty-three participants were included in the study. Three participants failed to complete the protocol (3 conditions), two completed only the CPT condition and one did not complete MLM condition. Among these 33 participants, all were randomized in the crossover part (17 to sequence 1 and 16 to sequence 2, **Figure 1**). The results of this controlled, randomized study are presented in compliance with the guidelines from the Consortium on the Assessment of Non-pharmacological Treatments (53).

The sociodemographic and baseline characteristics of the participants are described in **Table 2**. The mean age of the participants was 23.5 ± 4.9 years. There were 20 females (60.6%). In our sample, 28 participants had low trait anxiety, four moderate and one severe. For depression, 28 had no depression, four had mild mood disturbance and one had borderline clinical depression non-diagnosed. As for pain catastrophizing, we had 17 non-catastrophists, 14 mild catastrophizers and two severe ones.

Primary endpoint

Before the music intervention, mean pain perceptions were similar in both conditions: 55.2 (SD ± 12.0) in MLM and 55.6 (SD ± 9.5) in LLM. Overall, mean pain perceptions were significantly reduced under LLM and MLM conditions (p = 0.0090 and $p < 0.0001$, respectively), earlier under MLM condition (2.20 min) compared to LLM (20 min) (**Table 3** and **Figure 3**).

Under LLM condition, the reduction in pain levels was 4.4 (SD ± 14.2) after 2.20 min ($p = 0.2862$), 5.7 (SD ± 15.3) after 11.30 min ($p = 0.1467$) and 12.4 (SD ± 18.4) after 20 min (p = 0.0024). Under MLM condition, the reduction in pain levels was 14.2 (SD ± 17.3) after 2.20 min ($p = 0.0003$), 15.1 (SD ± 17.5) after 11.30 min ($p < 0.0001$) and 13.6 (SD ± 18.0) after 20 min ($p = 0.0009$).

Secondary endpoints

Reduction in pain observed at 2.20 min under MLM condition is comparable to the one observed under the CPM condition. Under CPM condition, the reduction in pain levels was 14.7 (SD ± 29.9) after the immersion of the participants' arm in 10 degrees circulating water for 2 min.

Mean pain perceptions were significantly more reduced under MLM condition than under LLM condition at 2.20 min

TABLE 2 Demographic and baseline characteristics.

Characteristics	Total (N = 33)
Age (years), mean (SD)	23.5 (4.9)
Gender, *n* (%)	
Female	20 (60.6)
Male	13 (39.4)
STAI Y2 Trait Anxiety Score (20–80), mean (SD)	36.9 (10.7)
BDI score (0–63), mean (SD)	5.1 (4.6)
PCS score (0–52, mean (SD)	16.7 (10.2)

SD, standard deviation.

TABLE 3 Pain perception under MLM and LLM.

Music	Timepoint	*n*	Value mean (SD)	Change mean (SD)	Reduction (%)	*p* value (pairwise)	*p* value (overall)
LLM	Before	31	55.6 (9.5)				
	2.20 min	31	51.2 (17.7)	−4.4 (14.2)	8	0.2862*	
	11.30 min	30	49.5 (15.8)	−5.7 (15.3)	10	0.1467*	
	20 min	31	43.2 (18.1)	−12.4 (18.4)	22	0.0024*	0.0090
MLM	Before	31	55.2 (12.0)				
	2.20 min	30	41.2 (17.2)	−14.2 (17.3)	26	0.0003*	
	11.30 min	30	40.4 (20.3)	−15.1 (17.5)	27	<0.0001*	
	20 min	30	41.8 (18.5)	−13.6 (18.0)	25	0.0009*	<0.0001
CPM	Before	33	59.2 (10.0)				
	After	33	44.5 (19.7)	−14.7 (29.9)	25	0.0003	

*Adjusted with Bonferroni correction.

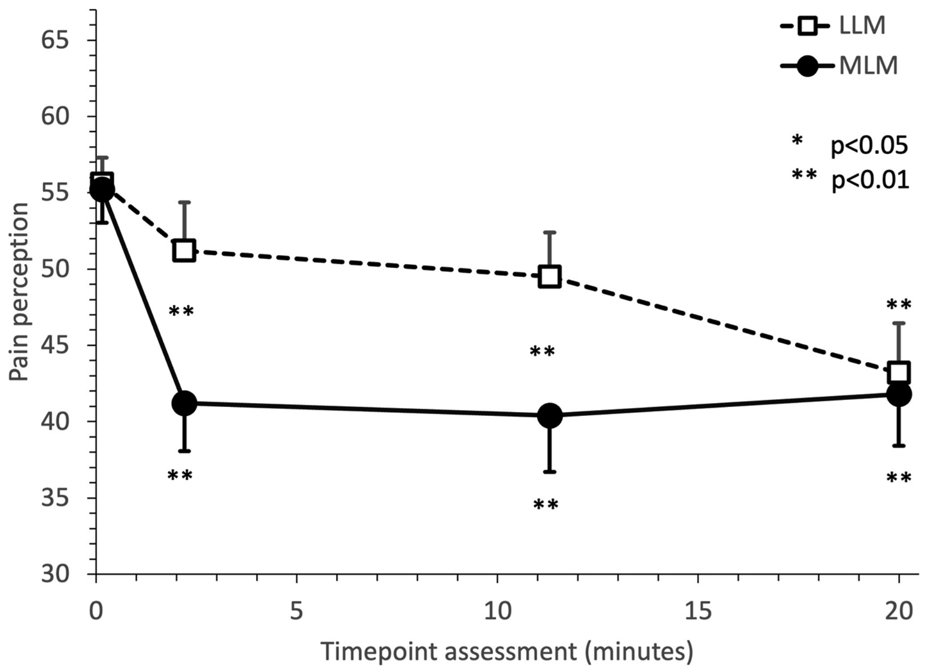

FIGURE 3
Evolution of mean pain perception under music intervention. Pain perception was collected using a Computerized Visual Analog Scale (CoVAS), which consists of a slider running along a 100 mm horizontal slider connected to the computer. Participants were asked to move the slider to reflect their pain from the left boundary (identified as "no pain"—score = 0) to the right boundary (identified as "worst pain imaginable"—score = 100). Timepoints of assessments were before music intervention, 2.20 min after the music started, 11.30 min after the music started (after the relaxation phase) at and after the whole 20-min cycle. Both conditions (LLM and MLM) are represented. Whiskers indicate SEMs.

with an adjusted mean difference between both conditions of 9.7 (±3.7) ($p = 0.0459$) and at 11.30 min with an adjusted mean difference between both conditions of 8.9 (±3.4) ($p = 0.0420$) (Table 4). The differences between MLM and LLM are no longer significantly different after 20 min ($p = 1.0000$).

Regarding the perception of time, the musical intervention session appeared to be significantly shorter under MLM condition with a mean duration of 14.8 min (SD ± 5.5) than under the LLM condition with a mean perceived duration of 18.9 min (SD ± 7.1) ($p = 0.0239$).

No significant differences have been found between the conditions and the mood scores (BDI) or the pain catastrophizing scores (PCS). There was a small but significant level of anxiety difference between the 3 conditions

TABLE 4 Comparison of pain perception decrease between MLM and LLM.

Timepoint	Condition	LSMeans (SD)	95% CI	*p* value
2.20 min	MLM	−14.2 (2.8)	−20.0; −8.4	
	LLM	−4.5 (2.8)	−10.3; 1.2	
	LLM-MLM	9.7 (3.7)	2.0; 17.3	0.0459*
11.30 min	MLM	−15.1 (2.9)	−21.0; −9.2	
	LLM	−6.2 (2.9)	−12.1; −0.4	
	LLM-MLM	8.9 (3.4)	2.0; 15.8	0.0420*
20 min	MLM	−13.8 (3.1)	−20.2; −7.3	
	LLM	−12.4 (3.1)	−18.8; −6.1	
	LLM-MLM	1.3 (3.7)	−6.3; 8.9	1.0000*

Pain perception evolution is analysed using a generalized linear model with period, sequence and treatment as fixed effects, participants within sequence as random effect, and value before music intervention as a covariate.
*Adjusted with Bonferroni correction.

TABLE 5 Influence of factors on pain perception decrease.

Factor	Timepoint	Condition	*p* value/*p* value (*r*)
Age		CPM	0.6896 (0.07)
	2.20 min	MLM	0.0140 (0.44)
	2.20 min	LLM	0.8306 (0.04)
	11.30 min	MLM	0.2943 (0.20)
	11.30 min	LLM	0.2332 (0.22)
	20 min	MLM	0.1327 (0.28)
	20 min	LLM	0.4922 (0.13)
Sex		CPM	0.5432
	2.20 min	MLM	0.4911
	2.20 min	LLM	0.8235
	11.30 min	MLM	1.0000
	11.30 min	LLM	0.6669
	20 min	MLM	0.3223
	20 min	LLM	0.6122
CPM	2.20 min	MLM	0.0546 (0.35)
	2.20 min	LLM	0.0471 (0.36)
	11.30 min	MLM	0.2409 (0.22)
	11.30 min	LLM	0.3285 (0.18)
	20 min	MLM	0.5043 (0.13)
	20 min	LLM	0.7403 (−0.06)

For factors age and CPM, r Pearson coefficient and *p* value are provided; for sex *p* value coming from Wilcoxon signed rank test is provided.

($p = 0.0335$), with an average value of 31.5 (±7.7) under the CPT condition, 30.7 (±9.4) under the LLM condition and 27.7 (±6.9) under the MLM condition.

Finally, to verify for similarities in the amplitude of the pain reduction between CPM and music sessions, correlation analysis were done between pain changes for CPM, MLM and LLM and different parameters like age and sex. A correlation on pain perception evolution at 2.20 min between CPM and LLM conditions was shown (Pearson coefficient of 0.36, $p = 0.0471$) as well as a correlation on pain perception evolution at 2.20 min between age and MLM condition (Pearson coefficient of 0.44, $p = 0.0140$) (**Table 5**).

Discussion

For the past few years, digital therapeutics (DTx), a subset of digital health, is changing the healthcare delivery system with evidence-based technologies driven by high quality software to prevent, manage, or treat a medical disorder or disease and that improve patient outcomes (54). The consensus among researchers in the field of DTx is that it requires more clinical data and investigation to be fully evaluated. Music is one of these approaches that was demonstrated to have significant pain reduction effects for different clinical conditions (3–6).

Several mechanisms have been suggested to understand music-induced pain reduction. A significant correlation between music pleasantness and pain reduction in healthy subjects was reported, suggesting the importance of the emotional valence for music-induced pain reduction (31). However, in another study also using experimental pain, the authors found that emotional responses were not correlated to the analgesic effects, but that perception of control in the selected music during the experiment and the engagement with music in the subject's everyday life were the most important parameters (55). Interestingly, antagonists drugs of endogenous dopamine and opioids did not reduce the effect of music analgesia (56). The authors found that the main source of the effect was related to the expectation of analgesia from music, suggesting mechanisms comparable to placebo analgesia. Based on these results, we could conclude that distraction and expectation are probably the main effect, but other mechanisms including endogenous pain modulation such as CPM was suggested (29). In support of this hypothesis, a study measured pain-related activity in the brain, brainstem, and spinal cord using magnetic resonance imaging (MRI) during sessions of favorite music versus no music (30). They found significant activation during the music session in regions related to descending pain inhibition mechanisms implicated in CPM such as the periaqueductal gray, rostral ventromedial medulla, and the spinal cord.

The goal of the present study was to compare the effect of most-liked music to least-liked music on pain perception at different times during the 20-min music sessions. We also compared the effects of CPM with the two music sessions on pain perception in the same subjects. A positive correlation between CPM and the music conditions will not determine if the mechanisms are the same but will give a hint in that direction and confirm the interest of future tests on music-induced analgesia mechanisms.

For the effect of music on pain, we found that the pain level decreased is significantly higher under MLM condition than under LLM condition from 2.20 min of listening to 11.30 min. At the end of the 20-min session, the decrease in pain level is comparable under LLM and MLM. Pain alleviation is thus faster and stable for MLM from the beginning up to 20 min, while the LLM's pain alleviation is by increments needing more than half of the session to perceive a decrease in pain with end results statistically comparable for both conditions.

The cold pressor pain significantly reduced pain perception, supporting a CPM effect. The only significant correlation between music and CPM is for pain perception at 2.20 min for LLM. We can theorize that the "unpleasant" effect of the least preferred music might have activated inhibitory mechanisms such as the unpleasant aspect of the cold pressor pain during the immersion of the arm in cold water. We did not systematically ask for feedback regarding the music at the end of the session, but several subjects spontaneously reported that they finally learned to enjoy the music that they rated as their LLM at the beginning later during the listening. As the music ends up being enjoyed, this "counter-irritation-like" effect of "unpleasant music" seems to disappear with time. This could be due to the mere-exposure effect (57). This cognitive principle states that the more you are exposed to something, the more you like it. This could also suggest that the mechanism of action of music could be comparable to CPM over the first 2 min, but that beyond that, music would allow pain control according to other neurophysiological mechanisms.

It was reported that pleasant music decreased pain more than unpleasant music and silence (31). This is congruent in part with our results as after 2.20 min of LLM, pain perception was higher than after MLM. Participants reported enjoying the MLM more than the LLM when choosing the music at the beginning. Some subjects also spontaneously reported learning to enjoy fairly more the LLM over time. All the conditions may act from different endogenous descending modulatory systems, according to the time frames. More direct evaluation of the implicated mechanisms would be of interest in future studies.

Another interesting aspect is the perception of time during the music conditions. The musical intervention session appeared to be perceived as significantly shorter under MLM condition than the LLM condition. This effect could be related to the "immersive" effect of most-liked music compared to least-liked music. Using subjects' selected music in video games is enhancing time underestimation (58). Other important psychological factors are anxiety, depression and pain catastrophizing that can affect pain perception (59–61). In this study the only significant effect was a lower anxiety score during MLM compared to CPT, suggesting a relaxation effect of MLM. Altogether these results suggest that MLM is rapidly active in reducing pain, reduce anxiety and give the impression that the time was shorter than it was. All positive characteristics for intervention pain control during painful procedures.

MUSIC CARE©, the web app-based music intervention evaluated has good ecological validity, which is hard to find in experimental music studies. It is already used in clinical contexts to alleviate pain and allows for reduced consumption of analgesics. The analgesia provided by medication usually starts 20–30 min after intake. However, the MLM chosen shows here a music-induced analgesia already present after 2.20 min and maintained for 20 min. As a result, using the participants' favorite MUSIC CARE©'s style could be a convenient and valuable adjuvant to acute pain treatments. Moreover, with its selection of 30 different styles of music, it has more potential of personalized care. Patients in clinics could also bring their own music and increase even more the valence of the music and its associated analgesia. Nevertheless, in an experimental setting, MUSIC CARE© allowed for a higher comparability between the music sequences compared to many music interventions studies as they are all constructed in the same way.

This study has some limitations. We compared music-induced analgesia to the cold bath to induce CPM to look for similarities or differences in responses. Other control conditions could have been used. The silence gives a setting with no distraction of attention or emotions (62). White noise, pink noise (white noise using the same frequency range as music) or audio books could be used. These approaches distract attention and have very limited emotional potential (63). They are painless auditory inputs and already used in some research as control conditions to music (11). Future studies comparing different distraction modalities could be of interest.

These results are comparable to previous studies (64–66). Future studies with patients experiencing chronic pain to see the effect on clinical pain and related endogenous pain modulation mechanisms would be important. Brain activation could be assessed as well when listening to MUSIC CARE© to better understand the related brain regions implicated. To further explore musical appreciation, it would also have been interesting to include any measures that extend beyond participants' mentions of their own experiences with the conditions. The literature supports enormous diversity in antecedents and causes of music appreciation across contexts, individuals, cultures, and historical periods. But the processes implicated in that are still unexplored (67).

In conclusion, MLM significantly reduce pain perception and more rapidly than LLM, but both types are analgesics after 20 min. Interestingly, the LLM pain reduction was correlated with CPM after 2.20 min. We hypothesized that the unpleasantness of the LLM music is triggering a "counterirritation effect" possibly comparable to CPM that fades over time when the unpleasantness seems to fade over time. LLM is correlated with CPM but not MML, suggesting different mechanisms between LLM and MLM.

In France, general practitioners can now prescribe music as part of the overall pain management of patients suffering from chronic diseases. This means that apps like MUSIC CARE© can be prescribed by general practitioners and used outside the hospital environment. The MUSIC CARE© application is currently used in 500 hospital departments around the world. The music intervention is administered *via* a smartphone- (or tablet- and computer-) based application called MUSIC CARE© which is low-cost, highly available to the public, and usable in a home environment. The MUSIC CARE© app is a receptive music intervention, allowing the patient to freely adjust the length of and choose the preferred style between varying sequences of instrumental music.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Human Health Research Ethics Board from the CHUS. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Both OS and SM have substantially contributed to data collection, analysis and the manuscript preparation. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Gardner WJ, Licklider JC, Weisz AZ. Suppression of pain by sound. *Science*. (1960) 132(3418):32–3. doi: 10.1126/science.132.3418.32

2. Hoareau SG, De Diego E, Guetin S. Pain management and music therapy. *Rev Infirm*. (2016) 217:31–3. doi: 10.1016/j.revinf.2015.10.025

3. Lunde SJ, Vuust P, Garza-Villarreal EA, Vase L. Music-induced analgesia: how does music relieve pain? *Pain*. (2019) 160(5):989–93. doi: 10.1097/j.pain.0000000000001452

4. Li CH, Liu CK, Yang YH, Chou MC, Chen CH, Lai CL. Adjunct effect of music therapy on cognition in Alzheimer's disease in Taiwan: a pilot study. *Neuropsychiatr Dis Treat*. (2015) 11:291–6. doi: 10.2147/NDT.S73928

5. Kuhlmann AYR, de Rooij A, Kroese LF, van Dijk M, Hunink MGM, Jeekel J. Meta-analysis evaluating music interventions for anxiety and pain in surgery. *Br J Surg*. (2018) 105(7):773–83. doi: 10.1002/bjs.10853

6. Bradt J, Dileo C, Potvin N. Music for stress and anxiety reduction in coronary heart disease patients. *Cochrane Database Syst Rev*. (2013) 2013(12):CD006577. doi: 10.1002/14651858.CD006577.pub3

7. Robinson A. Music therapy and the effects on laboring women. *Ky Nurse*. (2002) 50(2):7.

8. Phumdoung S, Good M. Music reduces sensation and distress of labor pain. *Pain Manag Nurs*. (2003) 4(2):54–61. doi: 10.1016/S1524-9042(02)54202-8

9. Ebneshahidi A, Mohseni M. The effect of patient-selected music on early postoperative pain, anxiety, and hemodynamic profile in cesarean section surgery. *J Altern Complement Med*. (2008) 14(7):827–31. doi: 10.1089/acm.2007.0752

10. Hole J, Hirsch M, Ball E, Meads C. Music as an aid for postoperative recovery in adults: a systematic review and meta-analysis. *Lancet*. (2015) 386(10004):1659–71. doi: 10.1016/S0140-6736(15)60169-6

11. Jaber S, Bahloul H, Guetin S, Chanques G, Sebbane M, Eledjam JJ. Effects of music therapy in intensive care unit without sedation in weaning patients versus non-ventilated patients. *Ann Fr Anesth Reanim*. (2007) 26(1):30–8. doi: 10.1016/j.annfar.2006.09.002

12. Jafari H, Emami Zeydi A, Khani S, Esmaeili R, Soleimani A. The effects of listening to preferred music on pain intensity after open heart surgery. *Iran J Nurs Midwifery Res*. (2012) 17(1):1–6.

13. Hamid MR A, Mansor MB, Zainal Abidin MF. Music therapy for reducing anxiety in patients undergoing total knee replacement surgery under subarachnoid

anesthesia. *J Orthop Surg*. (2022) 30(2):10225536221122347. doi: 10.1177/10225536221122347

14. Rennie C, Irvine DS, Huang E, Huang J. Music therapy as a form of nonpharmacologic pain modulation in patients with cancer: a systematic review of the current literature. *Cancers*. (2022) 14(18):4416. doi: 10.3390/cancers14184416

15. Duzgun G, Karadakovan A. Effect of music on pain in cancer patients in palliative care service: a randomized controlled study. *Omega*. (2021) 10:302228211059891. doi: 10.1177/00302228211059891

16. Karakul A, Akgul EA, Yaliniz R, Mese T. Effectiveness of music during cardiac catheterization on children's pain, fear, anxiety and vital signs: a randomized, blind controlled trial. *J Pediatr Nurs*. (2022) 65:e56–62. doi: 10.1016/j.pedn.2022.02.009

17. Guerrier G, Abdoul H, Jilet L, Rothschild PR, Baillard C. Efficacy of a web app-based music intervention during cataract surgery: a randomized clinical trial. *JAMA Ophthalmol*. (2021) 139(9):1007–13. doi: 10.1001/jamaophthalmol.2021.2767

18. Evans D. The effectiveness of music as an intervention for hospital patients: a systematic review. *J Adv Nurs*. (2002) 37(1):8–18. doi: 10.1046/j.1365-2648.2002.02052.x

19. Monteiro J, da Silva Barbirato D, Moraes SLD, Pellizzer EP, do Egito Vasconcelos BC. Does listening to music reduce anxiety and pain in third molar surgery?-a systematic review. *Clin Oral Investig*. (2022) 26(10):6079–86. doi: 10.1007/s00784-022-04640-5

20. McFerran KS, Hense C, Koike A, Rickwood D. Intentional music use to reduce psychological distress in adolescents accessing primary mental health care. *Clin Child Psychol Psychiatry*. (2018) 23(4):567–81. doi: 10.1177/1359104518767231

21. Fernando G, Wanigabadu LU, Vidanagama B, Samaranayaka TSP, Jeewandara J. "Adjunctive effects of a short session of music on pain, low-mood and anxiety modulation among cancer patients" - a randomized crossover clinical trial. *Indian J Palliat Care*. (2019) 25(3):367–73. doi: 10.4103/IJPC.IJPC_22_19

22. Raglio A, Oasi O. Music and health: what interventions for what results? *Front Psychol*. (2015) 6:230. doi: 10.3389/fpsyg.2015.00230

23. Gochenour KS, Ellis RS, Meredith SL, Vesely KC, Kang P, Haefner S. Music and medicine come together over pain in the air medical transport environment. *Air Med J*. (2020) 39(6):484–8. doi: 10.1016/j.amj.2020.08.003

24. Sarkamo T, Tervaniemi M, Laitinen S, Forsblom A, Soinila S, Mikkonen M, et al. Music listening enhances cognitive recovery and mood after middle cerebral artery stroke. *Brain*. (2008) 131(Pt 3):866–76. doi: 10.1093/brain/awn013

25. Melzack R. Pain and the neuromatrix in the brain. *J Dent Educ*. (2001) 65(12):1378–82. doi: 10.1002/j.0022-0337.2001.65.12.tb03497.x

26. Fields HL, Basbaum A, Heinrich RL. Central nervous system mechanisms of pain modulation. In: SB McMahon, M Koltzenburg, editors. *Wall and melzack's texbook of pain. 5*. Philadelphia: Elsevier Limited (2006). p. 125–42.

27. Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). II.lack of effect on non-convergent neurones, supraspinal involvement and theoretical implications. *Pain*. (1979) 6(3):305–27. doi: 10.1016/0304-3959(79)90050-2

28. Goffaux P, Redmond WJ, Rainville P, Marchand S. Descending analgesia–when the spine echoes what the brain expects. *Pain*. (2007) 130(1-2):137–43. doi: 10.1016/j.pain.2006.11.011

29. Chai PR, Gale JY, Patton ME, Schwartz E, Jambaulikar GD, Wade Taylor S, et al. The impact of music on nociceptive processing. *Pain Med*. (2020) 21(11):3047–54. doi: 10.1093/pm/pnaa070

30. Dobek CE, Beynon ME, Bosma RL, Stroman PW. Music modulation of pain perception and pain-related activity in the brain, brain stem, and spinal cord: a functional magnetic resonance imaging study. *J Pain*. (2014) 15(10):1057–68. doi: 10.1016/j.jpain.2014.07.006

31. Roy M, Peretz I, Rainville P. Emotional valence contributes to music-induced analgesia. *Pain*. (2008) 134(1-2):140–7. doi: 10.1016/j.pain.2007.04.003

32. Bradt J, Norris M, Shim M, Gracely EJ, Gerrity P. Vocal music therapy for chronic pain management in inner-city African Americans: a mixed methods feasibility study. *J Music Ther*. (2016) 53:178–206. doi: 10.1093/jmt/thw004

33. Bradt J, Teague A. Music interventions for dental anxiety. *Oral Dis*. (2018) 24(3):300–6. doi: 10.1111/odi.12615

34. Mitchell LA, MacDonald RA. An experimental investigation of the effects of preferred and relaxing music listening on pain perception. *J Music Ther*. (2006) 43(4):295–316. doi: 10.1093/jmt/43.4.295

35. Good M, Picot BL, Salem SG, Chin CC, Picot SF, Lane D. Cultural differences in music chosen for pain relief. *J Holist Nurs*. (2000) 18(3):245–60. doi: 10.1177/089801010001800306

36. Hamburg MA, Collins FS. The path to personalized medicine. *N Engl J Med*. (2010) 363(4):301–4. doi: 10.1056/NEJMp1006304

37. Grau-Sanchez J, Jamey K, Paraskevopoulos E, Dalla Bella S, Gold C, Schlaug G, et al. Putting music to trial: consensus on key methodological challenges investigating music-based rehabilitation. *Ann N Y Acad Sci*. (2022) 1518:12–24. doi: 10.1111/nyas.14892

38. Martin-Saavedra JS, Vergara-Mendez LD, Pradilla I, Velez-van-Meerbeke A, Talero-Gutierrez C. Standardizing music characteristics for the management of pain: a systematic review and meta-analysis of clinical trials. *Complement Ther Med*. (2018) 41:81–9. doi: 10.1016/j.ctim.2018.07.008

39. World Health Organization. Towards a digital health roadmap for the WHO European Region. World Health Organization (2019). Available at: https://www.euro.who.int.

40. Guetin S, Soua B, Voiriot G, Picot MC, Herisson C. The effect of music therapy on mood and anxiety-depression: an observational study in institutionalised patients with traumatic brain injury. *Ann Phys Rehabil Med*. (2009) 52(1):30–40. doi: 10.1016/j.annrmp.2008.08.009

41. Guetin S, Coudeyre E, Picot MC, Ginies P, Graber-Duvernay B, Ratsimba D, et al. Effect of music therapy among hospitalized patients with chronic low back pain: a controlled, randomized trial. *Ann Readapt Med Phys*. (2005) 48(5):217–24. doi: 10.1016/j.annrmp.2005.02.003

42. Guetin S, Ginies P, Siou DK, Picot MC, Pommie C, Guldner E, et al. The effects of music intervention in the management of chronic pain: a single-blind, randomized, controlled trial. *Clin J Pain*. (2012) 28(4):329–37. doi: 10.1097/AJP.0b013e31822be973

43. Mercadie L, Mick G, Guetin S, Bigand E. Effects of listening to music versus environmental sounds in passive and active situations on levels of pain and fatigue in fibromyalgia. *Pain Manag Nurs*. (2015) 16(5):664–71. doi: 10.1016/j.pmn.2015.01.005

44. Heiderscheit A, Nielsen C. Making music: a medicinal dose. *Caring*. (2010) 29(8):14–7.

45. Hevner K. Experimental studies of the elements of expression in music. *Am J Psychol*. (1936) 48(2):246. doi: 10.2307/1415746

46. Tousignant-Laflamme Y, Page S, Goffaux P, Marchand S. An experimental model to measure excitatory and inhibitory pain mechanisms in humans. *Brain Res*. (2008) 1230:73–9. doi: 10.1016/j.brainres.2008.06.120

47. Ocay DD, Ye DL, Larche CL, Potvin S, Marchand S, Ferland CE. Clusters of facilitatory and inhibitory conditioned pain modulation responses in a large sample of children, adolescents, and young adults with chronic pain. *Pain Rep*. (2022) 7(6):e1032. doi: 10.1097/PR9.0000000000001032

48. Potvin S, Marchand S. Pain facilitation and pain inhibition during conditioned pain modulation in fibromyalgia and in healthy controls. *Pain*. (2016) 157(8):1704–10. doi: 10.1097/j.pain.0000000000000573

49. Sutton KS, Pukall CF, Chamberlain S. Diffuse noxious inhibitory control function in women with provoked vestibulodynia. *Clin J Pain*. (2012) 28(8):667–74. doi: 10.1097/AJP.0b013e318243ede4

50. Cohen J. A power primer. *Psychol Bull*. (1992) 112(1):155–9. doi: 10.1037/0033-2909.112.1.155

51. Curran PJ, West SG, Finch JF. The robustness of test statistics to nonnormality and specification error in confirmatory factor analysis. *Psychol Methods*. (1996) 1:16–29. doi: 10.1037/1082-989X.1.1.16

52. Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res*. (2011) 2(3):109–12. doi: 10.4103/2229-3485.83221

53. Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P, Group CN. CONSORT statement for randomized trials of nonpharmacologic treatments: a 2017 update and a CONSORT extension for nonpharmacologic trial abstracts. *Ann Intern Med*. (2017) 167(1):40–7. doi: 10.7326/M17-0046

54. Khirasaria R, Singh V, Batta A. Exploring digital therapeutics: The next paradigm of modern health-care industry. *Perspect Clin Res*. (2020) 11(2):54–8. doi: 10.4103/picr.PICR_89_19

55. Howlin C, Stapleton A, Rooney B. Tune out pain: agency and active engagement predict decreases in pain intensity after music listening. *PLoS One*. (2022) 17(8):e0271329. doi: 10.1371/journal.pone.0271329

56. Lunde SJ, Vuust P, Garza-Villarreal EA, Kirsch I, Moller A, Vase L. Music-induced analgesia in healthy participants is associated with expected pain levels but not opioid or dopamine-dependent mechanisms. *Front Pain Res*. (2022) 3:734999. doi: 10.3389/fpain.2022.734999

57. Zajonc RB. Attitudinal effects of mere exposure. *J Pers Soc Psychol*. (1968) 9:1–27. doi: 10.1037/h0025848

58. Cassidy GG, Macdonald RA. The effects of music on time perception and performance of a driving game. *Scand J Psychol*. (2010) 51(6):455–64. doi: 10.1111/j.1467-9450.2010.00830.x

59. Sullivan MJ, Rodgers WM, Kirsch I. Catastrophizing, depression and expectancies for pain and emotional distress. *Pain*. (2001) 91(1-2):147–54. doi: 10.1016/S0304-3959(00)00430-9

60. Bair MJ, Robinson RL, Eckert GJ, Stang PE, Croghan TW, Kroenke K. Impact of pain on depression treatment response in primary care. *Psychosom Med*. (2004) 66(1):17–22. doi: 10.1097/01.PSY.0000106883.94059.C5

61. Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, et al. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *J Neurosci*. (2001) 21(24):9896–903. doi: 10.1523/JNEUROSCI.21-24-09896.2001

62. McCaul KD, Malott JM. Distraction and coping with pain. *Psychol Bull*. (1984) 95(3):516–33. doi: 10.1037/0033-2909.95.3.516

63. Leventhal H. I know distraction works even though it doesn't!. *Health Psychol*. (1992) 11(4):208–9. doi: 10.1037/h0090350

64. Guetin S, De Diego E, Mohy F, Adolphe C, Hoareau SG, Touchon J, et al. A patient-controlled, smartphone-based music intervention to reduce pain—a multi-center observational study of patients with chronic pain. *Eur J Integr Med*. (2016) 8:182–7. doi: 10.1016/j.eujim.2016.01.002

65. Nilsson U. The anxiety- and pain-reducing effects of music interventions: a systematic review. *AORN J*. (2008) 87(4):780–807. doi: 10.1016/j.aorn.2007.09.013

66. Siedliecki SL, Good M. Effect of music on power, pain, depression and disability. *J Adv Nurs*. (2006) 54(5):553–62. doi: 10.1111/j.1365-2648.2006.03860.x

67. Thompson WF, Bullot NJ, Margulis EH. The psychological basis of music appreciation: structure, self, source. *Psychol Rev*. (2022). doi: 10.1037/rev0000364. [Epub ahead of print]

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How do people with chronic pain choose their music for pain management? Examining the external validity of the cognitive vitality model

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Music interventions for pain are more successful when patients choose the music themselves. But little is known about the attentional strategies used by chronic pain patients when choosing or using music for pain management, and the degree to which these attentional strategies align with the cognitive mechanisms outlines in the cognitive vitality model (CVM, a recently developed theoretical framework that outlines five cognitive mechanisms that mediate the analgesic effects of music for pain management). To investigate this question, we used a sequential explanatory mixed method approach, which included a survey, online music listening experiment, and qualitative data collection, with chronic pain patients (n=70). First, we asked chronic pain patients to name a piece of music that they would use to manage their chronic pain, and answer 19 questions about why they chose that particular piece of music using a questionnaire based on the CVM. Next, we asked chronic pain patients to listen to high energy and low energy pieces of music, to understand aesthetic music preferences and emotional responses at the group level. Finally, participants were asked to qualitatively tell us how they used music to manage their pain. Factor Analysis was completed on the survey data, and identified a five-factor structure in participant responses that was consistent with five mechanisms identified in the CVM. Regression analysis indicated that chronic pain patients choose music for pain management if they think it will facilitate *Musical Integration and Cognitive Agency*. *Musical Integration* refers to the degree to which the music can provide an immersive and absorbing experience. *Cognitive Agency* refers to having an increased feeling of control. At the group level, participants reported a preference for low energy music, and reported that they found high energy music more irritating. However, is it important to note that individual people had different music preferences. Thematic synthesis of patient responses highlighted how these processes mediate the analgesic benefits of music listening from the perspective of chronic pain patients, and highlighted the wide range of music used by participants for chronic pain management including electronic dance music, heavy metal and Beethoven. These findings demonstrate that chronic pain patients use specific attentional strategies when using music for pain management, and these strategies align with the cognitive vitality model.

KEYWORDS

pain, music, music listening, psychology, chronic painpsychology, cognitive mechanisms

Introduction

The World Health Organization recommends arts-based interventions including music interventions as part of routine clinical care (Fancourt et al., 2019). This is particularly welcome for conditions that are not adequately managed by pharmacological treatments, such as chronic pain (Mainka et al., 2016). The international association for the study of pain defines pain as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020). This definition highlights that pain is a multi-dimensional experience, with cognitive, affective, and sensory components (Melzack, 1999), which means that pain management also needs to incorporate multi-dimensional and multi-disciplinary approaches alongside traditional pharmacological treatment, such as psychological therapies, tailored physiotherapy, and occupational therapy. The multi-disciplinary team can help patients to build physical strength, self-confidence and develop cognitive strategies to cope with extreme pain 'flare-ups'. Music-based interventions provide new avenues to a wider range of supports for chronic pain patients; however, there is still much debate in terms of the way to optimize the introduction of music. For example, music interventions can be self-directed music listening (Gold and Clare, 2013) structured music therapy (Fitzpatrick et al., 2019), or as a cue to movement (Murrock and Higgins, 2009) which can indirectly improve pain management outcomes.

This use of music in interventions in routine pain management settings is supported by the results of several meta-analyses which indicate that music interventions reduce self-rated chronic pain (Garza-Villarreal et al., 2017), and can subsequently reduce the need for analgesic medication (Lee, 2016). The popularity of music interventions is also propelled by patients themselves who reportedly enjoy music listening and often use it as a way to relax (Fitzpatrick et al., 2019). One of the most appealing aspects of music interventions is that they are completely flexible and can quickly be adapted to meet the immediate needs of the patient. Additionally, music listening can be done at a time and place that is convenient for the patient (Robb et al., 2018; Fitzpatrick et al., 2019) and does not require additional hospital appointments or specialized equipment.

What are the cognitive mechanisms that mediate the analgesic benefits of music listening?

Self-chosen music is the greatest predictor of effective music-listening interventions for pain (Lee, 2016), and people with pain tend to choose music for pain management with different characteristics to what researchers and practitioners might think is optimal (Howlin and Rooney, 2021a). For example, although many experimenters and practitioners will select low-energy, instrumental music with gentle rhythms on behalf of a person with pain, the person with pain is more likely to choose more energetic, rhythmic music with lyrics. But little is known about the cognitive processes associated with such choice. In order to further refine music interventions and increase their overall therapeutic quality, there is a growing need to understand the cognitive mechanisms that mediate the beneficial effects of music-listening interventions (Keenan and Keithley, 2015; Lee, 2016). To this end, the Cognitive Vitality Model (CVM; Howlin and Rooney, 2020) provides a theoretical framework to understand the cognitive mechanisms involved in music interventions for pain management. The original Cognitive Vitality model is depicted in a previous publication (Howlin and Rooney, 2020), and a revised version based on the findings of the current study is presented in Figure 1. The CVM outlines five cognitive mechanisms that account for the different stages of cognitive engagement that involve that lead to the wellbeing effects observed in response to music (1) *Automated Attention* orientates the individual's attention to the music and provides a lower-level distraction from pain. (2) *Cognitive Agency* is the way in which the person actively feels in control of the music, and uses self-directed music-listening strategies to actively engage with the music (3) *Meaning-Making and Enjoyment* is required to elicit personal reflection or aesthetic appreciation to deepen the level of engagement with the music, which motivates the person to keep listening and reduces the perceived effort involved in active listening. Meaning-making is key to emotional regulation processes as people can use the perceived meaning of music to reappraise their own thoughts and feelings, or because the person may have strong personal associations or memories with the music (e.g., going to concerts with friends, dancing at a wedding) that lead to a range of emotional responses. Eventually, after continued, uninterrupted engagement with the music (4) *Musical Integration*

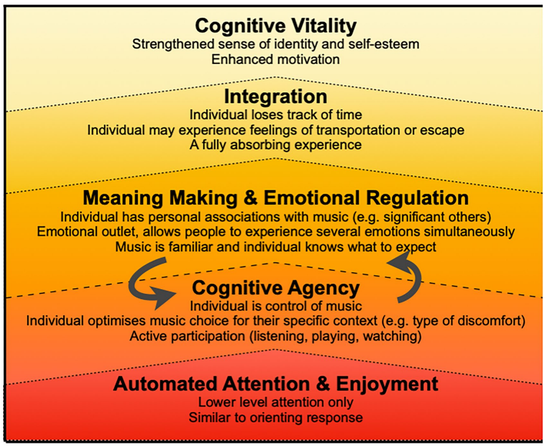

FIGURE 1
Cognitive mechanisms in cognitive vitality model. This depiction of the Cognitive Vitality Model includes details provided by chronic pain patients in the current study. The original version of the cognitive vitality model can be found in Howlin and Rooney (2020). Adapted with permission.

can occur, which means that the music is absorbed fully into the individual's conscious experience on a cognitive, and emotional level. When musical integration occurs, the individual tends to lose track of time or feel like they have escaped, zoned out, or been transported to another place. Full absorption into the musical experience prevents the formation of competing constructions of reality that include the pain experience. Finally the person feels an enhanced sense of (5) *Cognitive Vitality* and cognitive energy which facilitates adaptive coping, an enhanced locus of control and a strengthened sense of self. Together these five mechanisms describe different states of cognitive engagement with music where people transition from lower level attention through to full absorption, and posits that higher levels of absorption in musical experiences elicit stronger wellbeing benefits. As indicated in Figure 1 automated attention forms the basis of deeper levels of engagement, and agentic, meaningful music experiences will be more likely to elicit the most benefits.

Empirical support for the CVM has been partly established in experimental studies (Howlin and Rooney, 2021b). Participants were presented with excerpts from music tracks to listen to while completing the cold pressor task, which involved submerging their hands into ice water until they felt a sense of discomfort. A unique experiment was devised to give participants perceived control of the music, when in fact it was pre-determined by the experimental design. When participants had the illusion that they were choosing the music, they demonstrated a higher pain tolerance compared to when they had no choice in the music. Additionally, self-rated enjoyment was a strong predictor of increased pain tolerance. Together these results provide evidence for the role of Cognitive Agency and Enjoyment in mediating the analgesic effects of music listening in the context of synthetic or experimental pain.

Although the CVM provides a framework for understanding the cognitive mechanisms that mediate the wellness benefits of music engagement, it is important to examine the external validity of the model. In the current study, we specifically focus on the perspective of chronic pain patients. This is particularly important because the psychological experience of chronic pain is different from the psychological experience of acute pain, because there is no sense of certainty that it will dissipate completely (Mitchell et al., 2007; Gold and Clare, 2013; Finlay, 2014). In order to understand the relevance of the CVM to chronic pain management, it is necessary to evaluate the model specifically with chronic pain patients.

How does the CVM relate to the analgesic potential of self-chosen music?

One of the first things to explore is the degree to which the mechanisms outlined in the CVM relate to the *analgesic potential* of music selected by the patient. The analgesic potential of the music is the degree to which patients estimate that their music selection will be helpful with their pain management. Understanding the factors that contribute to the analgesic potential of music is important because self-selected music is the best predictor of a successful music intervention (Bradt et al., 2016; Garza-Villarreal et al., 2017, p.; Lee, 2016). The specific motivations patients have for choosing music is considered to be an important component in mediating the analgesic potential of music listening (Linnemann et al., 2015), because they increase patient motivation to maintain active cognitive engagement (Mitchell and MacDonald, 2006; Pothoulaki et al., 2008; Roy et al., 2008; Siedliecki, 2009; Good et al., 2010; Nguyen et al., 2010; Vaajoki et al., 2012; Finlay, 2014; Hsieh et al., 2014; Nagata et al., 2014; Linnemann et al., 2015). Previous research has identified that different pieces of music can be used to achieve the same analgesic benefits, a circumstance known as *functional equivalence* (Swaminathan and Schellenberg, 2015). What is not known is whether patients use the same cognitive strategies with different pieces of music to achieve these benefits. It is now time to explore how specific cognitive strategies relate to the analgesic potential of music. This will help to understand which mechanisms are more important in designing music-listening interventions for pain management.

Chronic pain patients' preferences for specific intramusical features (e.g., music energy, tempo, key, or rhythmicity) is also an important factor to consider in music interventions. In line with current theories of emotional engagement with music (Juslin et al., 2008, 2014; Koelsch, 2010) the authors do not propose any specific music feature will be superior for pain management in a universal way, but instead, the analgesic benefits of music will be driven by patient preferences. This means that different types of music with different features can achieve the same analgesic benefits (Bradt et al., 2016; Lee, 2016; Garza-Villarreal et al., 2017), and is known as functional equivalence (Thaut, 2016), because different pieces of music can serve the same 'function'. However, the key issue now is to identify and understand what the function of music listening is, in pain management contexts. Although many studies highlight the importance of using music to help people with pain to relax, a recent systematic compilation of music preferences for pain management, identified that people tend to choose music with a higher level of energy representing a range of valences (e.g., heavy metal music, electronic dance music, and upbeat pop music) compared music chosen by experimenters (e.g., typically classical, acoustic, and non-lyrical; Howlin and Rooney, 2021a). This undermines the idea that specific pieces of music will be more effective for pain management, and suggests that greater focus needs to be placed on the specific attentional and cognitive strategies used in music interventions. This study will help to disentangle the relative contributions between the cognitive strategies used in music interventions for pain management, and characterize chronic pain patients' preferences for high-energy or low-energy music.

Present study

The present study examined the nature of patient choice in music-listening interventions using an online survey and experimental design. The main aim of this study was to examine the external validity of the CVM. A questionnaire based on the mechanisms identified in the CVM was used to identify the degree to which patients' motivations for choosing music for pain management aligned with the CVM. Additionally, a qualitative thematic analysis was used to gain a deeper understanding of patients' experience of music listening for pain management. A secondary aim of this study was to assess chronic pain patients' preference for different musical features, which was assessed using by asking chronic pain patients to provide aesthetic and emotional ratings for different music samples.

These aims were addressed with the following research questions:

> RQ1a: Can the analgesic potential of patients' self-chosen music be predicted by components of the CVM?
>
> RQ1b: Do patient descriptions of music listening for pain correspond with the CVM?
>
> RQ2: Do patients with chronic pain report any preferences in terms of the type of music that they find most beneficial for pain management?

Materials and methods

Study design

This study used an online survey and experimental design accessible by smart phone, tablet or home personal computer. A sequential explanatory mixed method approach was used to address the main research question (Ivankova et al., 2006) which involves two phases. The first phase involved a quantitative exploratory factor analysis of questionnaire responses and a subsequent regression analysis. The second phase involved a qualitative thematic analysis of patients' responses to an open question. Mixed-methods sequential explanatory designs are particularly useful to capture the multi-dimensional aspects of pain experience and pain management (Melzack, 1999; Carr, 2009). The study design was approved by St. Vincent's Hospital Research Ethics Board, and all chronic pain patients provided anonymous electronic consent in line with hospital ethics policy and General Data Protection Regulations.

Patient recruitment

Patients with chronic pain were invited to participate in the study through pain management clinics in St. Vincent's University Hospital, Dublin, and online through social media, using twitter and Facebook. The primary researcher attended weekly clinics and provided information leaflets for the study to 400 patients over 6 weeks. Patients named their diagnosis, which was then classified by the primary researcher according to the International Classification of Diseases 11 (ICD-11) definitions for chronic pain (Treede et al., 2015).

Measures

Subjective pain

Participants rated their pain intensity and pain unpleasantness on mixed Numeric Rating Scales (NRS) using a pointer, before listening to the music. The 100-point intensity scale had three anchor points 'no pain' (0), 'moderate pain' (50), and 'worst pain imaginable' (100). The 100-point unpleasantness scale ranged from 'not unpleasant' (0) to 'extremely unpleasant' (100). Numeric rating scales (NRS) are considered the gold standard for measuring patient's subjective feeling of pain intensity and pain unpleasantness, because they are more sensitive than other self-report measures that treat pain as a unidimensional construct (Breivik et al., 2008).

Analgesic potential of self-chosen music

Patients were asked to estimate how much their chosen music piece would help to reduce their pain on a continuous Likert scale ranging from 0 'it would not help at all' to 100 'It would help a lot'.

Wellbeing

The CASP-19 Quality of Life Scale was used to measure wellbeing based on four domains; Control, Autonomy, Self-realization, and Pleasure (CASP; Hyde, et al., 2003). The CASP-19 includes 19 items which are scored on a 4-point Likert scale

TABLE 1 Initial 19 items included in cognitive vitality questionnaire.

Factor 5 Musical Integration	This song produces a whole-body experience
	I lost track of time as I am listening to music
	Listening to this song gives me an opportunity to be myself
	This song gives me mental strength
Factor 4 Personal Meaning	The lyrics in this song are meaningful to me
	This is a beautiful piece of music to me
	Most people would agree with my opinion of this song
	This song does not remind me of any specific memories*
	Listening to this song reminds me of good times*
Factor 3 Motivation	Overall how much does this song make you want to move
	Overall how much are you energized by this song
Factor 2 Cognitive Agency	I have a specific reason that I would listen to this song
	I do not think this was a good choice of song
Factor 1 Attention and Enjoyment	Overall how much were you bored by this song? A
	Overall how much did you enjoy this song?
	This is mainly just Background music
	This song does not capture my attention
	Overall, how much were you distracted by this song?
	This song would take over my thoughts effortlessly*

ranging from 0 'never' to 3 'often'. Scores range from 0 to 57 with higher scores indicating a higher quality of life.

Cognitive vitality questionnaire

Twenty-one items were created for the Cognitive Vitality Questionnaire based on the CVM (Howlin and Rooney, 2020). The initial items were constructed based on 75 journal articles, which included patient qualitative reports, neuroscientific research, clinical trials, and psychology experiments. Each item provided a statement that described a reason for choosing a piece of music, and participants were asked to rate the degree to which they agreed or disagreed with each statement. Participants responded on a Likert scale ranging from 0 'strongly disagree' to 100 'completely agree'. Nineteen items were included in the initial questionnaire and factor analysis, and the 16 items that contributed to the final factor structure were kept for the final analysis. The items included in final questionnaire can be seen in Table 1.

Nineteen items were included in the original cognitive vitality questionnaire. *items did not load onto the factor structure of the questionnaire so data from these questions were not included in the final analysis, and should not be used.

Musical emotional response

Participants completed the short version of the Geneva Emotional Musical Scale (GEMS-9; Zentner et al., 2008) to evaluate emotional response to each piece of music. The GEMS presents a nine-dimensional emotional structure to account for emotional responses to music. Each factor is independent of the other factors which has been established with exploratory and confirmatory factor analyses and the model provides a better account of emotional responses to music than non-domain-specific emotional models (Zentner et al., 2008).

Music stimuli

A pilot study was used to select 6 pieces of music which were used in a previous lab-based experiment (Howlin and Rooney, 2021b), and the same pieces of music were used in the current study. For the pilot study six people provided familiarity ratings on a continuous rating scale from 0 'not familiar at all' to 10 'extremely familiar' (See Table 2). Familiarity was controlled for to reduce the likelihood that people would provide aesthetic ratings and emotional responses based on their personal familiarity with the music rather than the audio features, because familiarity presents enhanced opportunities for emotional engagement and enjoyment for the listener (Good et al., 2010; Brattico and Pearce, 2013), independently of the music features. The Spotify Audio features of danceability, energy, and tempo were used to control for different audio features, based on the results of a previous study that identified that people tend to choose music with significantly higher levels of danceability, energy and lower levels of instrumentalness compared to music chosen by experimenters (Howlin and Rooney, 2021a). These Spotify audio features were used based on the results of a previous study that demonstrated that people tended to choose music that was significantly higher in energy. Music with high levels of energy, danceability, and tempo

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TABLE 2 Music Stimuli and Familiarity Ratings from Pilot Study.

Title	Artist	Energy	Danceability	Familiarity Rating
				M (SD)
Low Energy Music				
Sleeping Music	Deep Sleep Music Collective	0.00	0.13	3.0 (3.2)
This Isn't You	Kyle Dixon	0.02	0.13	2.6 (3.2)
Danger of Hell	Thomas Newman	0.01	0.19	2.2 (2.7)
High-Energy Music				
Solero	Sons of Maria	0.94	0.80	2.6 (2.6)
Lighthearted	Deep Chills	0.43	0.77	1.8 (1.3)
The Balance	Moses Boyd	0.84	0.61	1.0 (1.2)

These six pieces of music were selected from a wider pool of 20 songs which were selected based on the Spotify audio features of Energy, and Danceability. All of these pieces of music were instrumental without lyrics. M = Mean, SD = Standard Deviation. Energy and Danceability are absolute values taken from the Spotify Developer website that run from a minimum of 0 to a maximum of 1. Familiarity was rated by 6 human participants in a separate pilot study and is scored from a minimum of 0 to a maximum of 10.

was labeled as *High Energy*, and music with low levels of energy, danceability, energy, and tempo was labeled as *Low Energy*. All songs that were commercially available without lyrics had a mean familiarity rating of 3 or lower. This resulted in three Low-Energy music pieces: *Sleeping Music* by Deep Sleep Music Collective, *This Isn't You* by Kyle Dixon, and *Danger of Hell* by Thomas Newman; and three High-Energy music pieces: *Solero* by Sons of Maria, *Lighthearted* by Deep Chills, and *The Balance* by Moses Boyd.

Procedure

Participants completed the online survey at a time and location that was convenient for them. Each participant listened to six pieces of music which were presented in counterbalanced order. For each piece, participants completed the GEMS-9; (Zentner et al., 2008) and rated the music in terms of enjoyment, boredom, and irritation. Once the music-listening trials were complete participants were then asked to name any song that they thought would be good to help manage their pain, and rate the analgesic potential of their chosen song. Next, participants completed the Cognitive Vitality Questionnaire in response to the song that they had chosen. Finally, in an open question, participants were asked if they had "anything else to add about listening to music when you have chronic pain." The experiment took approximately 45 min to complete.

Data analysis

Exploratory factor analysis was conducted on participants responses to the cognitive vitality questionnaire to examine the factor structure of the responses. Regression analysis was then used to examine if scores for each factor could predict ratings for how effective the participants thought the self-chosen song would be for pain management. This allowed us to examine which factors were most important in mediating the analgesic benefits of music listening from chronic pain patients perspective. The qualitative analysis was used to explore the quantitative results in more detail.

Results

Patient characteristics

Seventy patients with chronic pain completed the study. Nine participants were recruited from pain management clinics in St. Vincent's University Hospital, Dublin. Additionally, 61 participants were recruited to participate *via* social media. The entire sample of 70 patients had an age range of 18–70 ($M = 43.12$, SD = 12.09), and was comprised of 56 females, 13 males, and 1 transgender person. The sample consisted of 26 (37.1%) patients with primary chronic pain, 17 (24.3%) patients with chronic musculoskeletal pain, 7 (10.0%) patients with neuropathic pain, 6 (8.6%) patients with multiple independent diagnoses, 6 (8.6%) patients with chronic visceral pain, 4 (5.7%) patients with chronic postsurgical and posttraumatic pain, 3 (4.3%) patients with chronic headache and orofacial pain, and 1 (1.4%) patient with chronic cancer pain. Pain intensity scores ranged from 0 to 10 with a mean of 5.43 (SD = 1.98). Pain unpleasantness scores ranged from 0 to 9 with a mean of 5.20 (SD = 1.99). Wellbeing scores measured using the CASP-19 ranged from 7 to 54 and patients reported a mean wellbeing score of 28.31 (SD = 9.48).

(RQ1a) To what extent can the analgesic potential of patients' self-chosen music be predicted by components of the CVM?

The main research question was examined using a sequential explanatory mixed methods approach. This approach allows us to conduct a quantitative analysis followed by a qualitative analysis in order to gain a greater understanding of the quantitative findings (Ivankova et al., 2006).

The goal of the quantitative phase was to identify the degree to which the mechanisms outlined in the CVM relate to the *analgesic potential* of music selected by the patient. In order to achieve this the quantitative analysis was conducted in two parts. First, an exploratory factor analysis was conducted to examine the factor structure of the questionnaire and quantify how patient responses corresponded with the cognitive mechanisms identified in the CVM. Second, a regression analysis was conducted to examine how patient scores for each factor of the cognitive vitality questionnaire predicted the analgesic potential of the patients chosen song.

Factor structure of cognitive vitality questionnaire

An exploratory factor analysis was conducted to examine the factor structure of the cognitive vitality questionnaire, to examine the factor structure of the questionnaire, and to identify the patterns that emerge in patient's agreement with the cognitive mechanisms identified in the CVM. Initially, a principal components analysis was completed on all 21 items in the Cognitive Vitality Questionnaire (CVQ). The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.75, which indicated that we achieved sampling adequacy (Kaiser, 1974). Bartlett's test of sphericity (Bartlett, 1954) indicated that there were sufficient intercorrelations between the items to justify the application of Exploratory Factor Analysis [$\chi^2(171) = 561.69$ $p < 0.001$]. On examination of the scree plot, and the eigenvalues, a five-factor solution was determined as the most appropriate to fit the model. This decision eliminated one factor that had an eigenvalue greater than one; however, this factor only included two negatively worded items, that were not otherwise related, and it appeared to the research team that it was more likely that it was the wording of the item that was causing people to rate them similarly rather than an underlying construct. Instead, the remaining five factors were considered to represent the latent constructs outlined in the CVM, and a common factor analysis was completed. Principal axis factoring, with a Promax rotation with Kaiser Normalization was used to account for the fact that the data was negatively skewed (as patients were positive overall) and the small sample size (Fabrigar et al., 1999). This method was determined as appropriate because it does not require a large sample size and makes no assumptions about the underlying distributions of the data (Watkins, 2018). Items with a loading of less than 0.4 were removed. Each factor was named based on the content of the final items included in each factor, in line with the proposed factors of the CVM.

The five-factor solution was examined for adequacy. Each factor was loaded by a minimum of two items (see Table 3 for eigenvalues and communalities for each factor), and each item was cleanly loaded onto only one factor. Following Factor rotation factor 1 accounted for 10.57% of the common variance, factor 2 accounted for 6.86% of the common variance, factor 3 accounted for 9.06% of the common variance, factor 4 accounted for 7.65% of the common variance, and factor 5 accounted for 29.91% of the common variance. In total the five factors accounted for 64.12% of the variance in agreement scores. The factor correlation matrix indicated that the factors were correlated at less than 0.3 except for factor 1 and factor 2 which were correlated at 0.54, and factor 1 and factor 4 which were correlated at 0.39. Given these results, the five-factor solution was accepted as an adequate structural representation of the Cognitive Vitality Questionnaire (CVQ).

TABLE 3 Factor analysis table for cognitive vitality questionnaire.

	F5	F4	F3	F2	F1	Communality
CVQ18 This song produces a whole-body experience	0.879					0.657
CVQ17 I lost track of time as I am listening to music	0.780					0.747
CVQ20 Listening to this song gives me an opportunity to be myself	0.640					0.462
CVQ13 This song gives me mental strength	0.619					0.582
CVQ2 Overall how much were you bored by this song?					0.861	0.790
CVQ1 Overall how much did you enjoy this song?					0.690	0.787
CVQ10 This is mainly just Background music					0.642	0.557
CVQ16 This song does not capture my attention					612	0.501
CVQ3 Overall, how much were you distracted by this song?					0.561	0.417
CVQ5 Overall how much does this song make you want to move			0.949			0.635
CVQ4 Overall how much are you energized by this song			0.721			0.613
CVQ9 The lyrics in this song are meaningful to me		0.825				0.440
CVQ15 This is a beautiful piece of music to me		0.565				0.615
CVQ14 most people would agree with my opinion of this song		0.435				0.440
CVQ11 I have a specific reason that I would listen to this song				0.631		0.429
CVQ12 I do not think this was a good choice of song				0.574		0.517
Eigenvalue	5.70	1.45	1.72	1.30	2.01	
%of Total Variance	29.30	7.65	9.06	6.87	10.57	
Total Variance					64.12%	

F1 Attention and Enjoyment, F2 Cognitive Agency, F3 Motivation, F4 Personal Meaning, F5 Musical Integration and Vitality.

However, it was noted that factor 2 and factor 3 would benefit from additional items.

Factor 1 was labeled *Attention and Enjoyment* and refers to the way in which any music will automatically grab people's attention and that enjoyment or reward responses are implicit in the automatic engagement.

Factor 2 was labeled *Cognitive Agency* and refers to the specific reasons people have when choosing a piece of music to listen to which can increase the patient's locus of control.

Factor 3 was labeled *Motivation* and is a subcomponent of the mechanism called cognitive vitality and refers to the *motivation* that people can feel as a result of personal music listening.

Factor 4 was labeled *Personal Meaning* and refers to the personal connection people have with and may remind them of a significant person or event in their life or be an important part of their identity.

Finally, factor 5 was labeled *Musical Integration and Vitality* which refers to how music is integrated into the person's conscious awareness on a cognitive and emotional level. Musical Integration relies on absorption in the music and is characterized by losing track of time.

These factors corresponded with the factors outlined in the CVM, with some minor adjustments; enjoyment overlapped more with automated attention processes rather than with meaning-making as proposed in the original CVM. This suggests that attention and enjoyment are more tightly interlinked from a chronic pain patient's perspective, and meaning and enjoyment may be separate processes. Additionally, some aspects of vitality were grouped more closely to integration, whereas aspects of vitality related to motivation loaded onto an independent factor. The high level of agreement from participants across the items suggests that these factors are a strong representation of the patients' intentions for analgesic music listening, and corresponds with the CVM. The implications of these variations in the boundaries between the factors are considered further in the discussion section.

Relationship between CVQ factors and analgesic potential of patient chosen music

Next, we examined how patient scores for each factor of the cognitive vitality questionnaire were related to the analgesic potential of the patients' chosen song. Once each factor was identified, mean scores were calculated for each factor. Each factor was then correlated with the *analgesic potential* of the music. To account for the marginal skewness in the data non-parametric Spearman's correlations were used. Overall higher levels of agreement with each factor were positively related to how much the music would help to reduce their pain experience. Moderate positive correlations were found between the analgesic potential rating and the factors *Musical Integration* $r_s(69) = 0.682$, $p < 0.001$, *Automated Attention* and *Enjoyment* $r_s(69) = 0.530$, $p < 0.001$, and *Cognitive Agency* $r_s(69) = 0.492$, $p < 0.001$. Weak positive correlations were found between the Benefit for Pain rating and Motivation $r_s(68) = 0.317$, $p < 0.01$ and *Meaning-Making* $r_s(68) = 0.318$, $p < 0.01$. The strength of the correlations was used to select which factors to include in a regression analysis. The three factors (*Musical Integration*, *Automated Attention* and *Enjoyment*, *and Cognitive Agency*) that were moderately correlated with the *analgesic potential* rating were then entered into a linear regression analysis to predict the outcome variable of analgesic potential. The regression model was significant, $F(1, 64) = 39.85$, $p < 0.001$, $R^2 = 0.559$. The analgesic potential was significantly predicted by *Musical Integration*, $ß = 0.67$, $t(63) = 6.69$, $p < 0.001$; SE = 0.10, 95% CI [0.47, 87], and *Cognitive Agency*, $ß = 0.24$, $t(63) = 2.96$, $p < 0.01$; SE = 0.08, 95% CI [0.08, 41]. This indicates that *Musical Integration* was the best predictor as it had the highest beta co-efficient of 0.67, followed by *Cognitive Agency,* with a beta co-efficient of 0.24. This means that for every 1-unit increase in Musical Integration scores for a chosen song, the analgesic potential of that song increased by 0.67. For every 1-unit increase in Cognitive Agency scores for a chosen song, the analgesic potential increased by 0.24. This suggests that Chronic pain patients think that the degree to which a song will elicit Musical Integration is the most important factor leading to subsequent analgesic benefits, but they also think that their specific music choices are an important component in achieving music analgesia (Figure 2).

(RQ1b) In what way do patient descriptions of music listening for pain correspond with the CVM?

The goal of the qualitative phase was to help understand why *Musical Integration* and *Cognitive Agency* were the mechanisms most closely linked to whether patients thought their chosen song would be beneficial for pain management. Qualitative analysis of patient responses to an open-ended question was completed using thematic synthesis and the results are displayed in Table 4. Forty-four patients responded to the open question. The thematic synthesis strategy was developed by the research team and involved three stages (Thomas and Harden, 2008). The first reviewer coded the text line by line according to its meaning or content. Next, codes were grouped together based on their similarity, so as to develop descriptive themes. Finally, descriptive themes were then grouped together to form analytical themes. When developing the analytical themes the researchers focused on descriptions related to *Musical Integration* and *Cognitive Agency* highlighted by patients as important in the quantitative phase. Additionally, two other analytical themes were developed based on patient responses. A second reviewer performed a credibility check on all of the descriptive themes and analytical themes and agreed with 90% of the coding decisions made by the first reviewer. After discussion between the reviewers, some codes were amended and both reviewers were in 100% agreement. Four themes were developed, Musical Integration, Cognitive Agency, Emotion Regulation, and Optimal Arousal.

Musical integration

The theme of *Musical Integration* included the descriptive themes of *absorption*, *transportation*, *escape from reality*, and *forget*

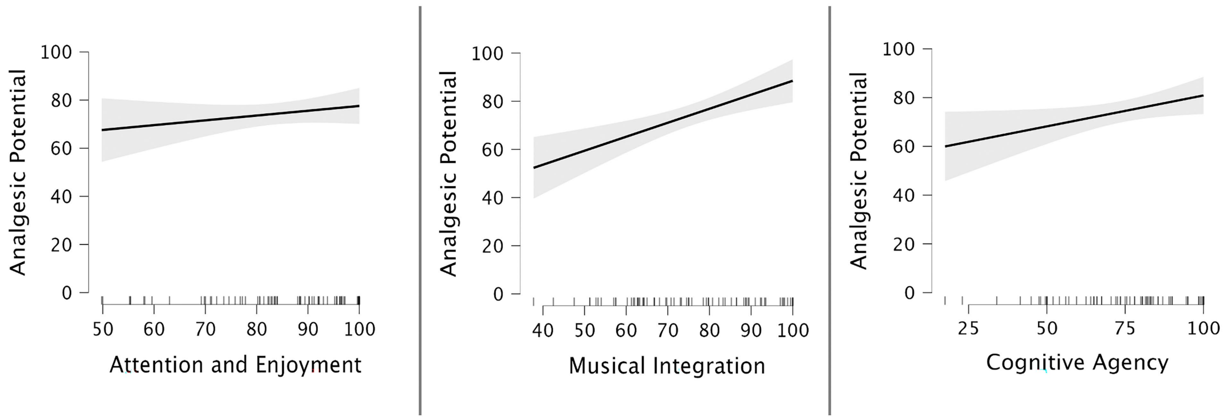

FIGURE 2
Regression plots of marginal effects. This diagram shows the individual marginal effects of each factor included in the linear regression model Attention and Enjoyment, Musical Integration, and Cognitive Agency. The *y*-axis indicates the analgesic potential scale from 0 to 100. The steeper slope for Musical Integration and Cognitive Agency illustrates that participants consider it to be more important when they are choosing their music than Attention and Enjoyment.

about pain. Participants described how music could be used as a mental escape from pain to transport them out of their current and subsequent experiences. As described by patient 30 "*I use music to transport myself out of this world*." The benefits of being transported away were attributed to emptying the mind of pain-related thoughts even though the physical sensation may be present as described by patient 34 "*So, it's more about Not Thinking. Pain may still be there but subdued*." Musical Integration was described as having long-lasting effects after music-listening due to an enhanced mood. This was highlighted by several patients including patient 3 "*It's an escape, not just into the music but beyond afterward with the effects on my mood directly lessening my pain*." Participants provided several descriptions of musical engagement that were consistent with absorption, e.g., "*zoned out*" and linked these to feeling disconnected from their current environment including physical pain sensations and thoughts about pain.

Cognitive agency

The theme of *Cognitive Agency* was comprised several descriptive themes including *independence, self-strengthening*, and *active engagement*. Participants described the importance of engaging in an activity that was personally important to them and emphasized the importance of music in their life more generally. Some participants expressed an independence in their music-listening preferences habits and emphasized that they thought the way that they used music to manage pain was quite specific to them and would be unlikely to benefit other people. For example, participant 10 reports "*This works for me and probably would not work for others*." Similarly, participants described that having an opportunity to express themselves in a way that was independent of their pain was an important factor in identifying the different parts of themselves that co-exist alongside their pain identity. This was highlighted by participant 6 "*It provides an anchor and reminds me that I am more than my illness.*" Additionally, several participants reported ways in which they actively engage with music, either by taking music lessons or by selecting specific soundtracks.

Emotion regulation

The theme of *Emotion Regulation* encompassed the descriptive themes of *Personal Meaning*, *Emotion Regulation*, and *Familiarity*. Participants reported that music can be used either to elevate mood or as an emotional release which may involve crying or laughing. Familiar music with meaningful lyrics was considered beneficial for emotion regulation by several participants. Two participants identified that they use music which reminds them of a significant loved one which brings them great comfort. Participant 17 summarized how music with a sentimental meaning made them feel happier: "*And sometimes it's nice just to listen to songs with sentimental meaning to bring me back to a happier time or place in my mind*." However, participants were divided on the degree to which emotional regulation can actually lessen the physical sensation of pain. While some participants reported that music can directly help their pain, other participants reported that music had no impact on their physical sensation of pain and was only useful for emotional regulation.

Optimal arousal

The theme of *Optimal Arousal* included the descriptive themes of *Attention and Enjoyment*, *Motivation*, *Relaxation*, and *Negative Effects*. The overwhelming commentary that came from participants reflected the importance of matching music energy to the desired outcome for the patient. Across the board patients highlighted the importance of matching the music to the participants' pain level, and the type of task they wished to engage in. Participant 36 summarizes how different types of music can be used for different activities: "*Sometimes I need energetic music I can sing along to while I try do some housework. Then to relax something more complex with various layers to it that I can close my*

TABLE 4 Results of qualitative analysis.

Analytical theme	Descriptive theme	Codes
Musical Integration	Escape From Reality	Escape beyond the music
		Getting lost
		Transportation
	Absorption	Particularly involving
		Zone out
	Forget about pain	Forget about troubles
		Take away thoughts of pain
Cognitive Agency	Individuality	Self-chosen music
		Unique music preference
		Specific genre or artist preferences
	Self-strengthening	Feeling more than the illness
		Lost without music
		Feel for a while you are just like everyone else
	Active Participation	Playing music
		Music Lessons
		Watching music videos
Emotion Regulation	Personal Meaning	Lyrics
		Sentimental Meaning
		Reminder of specific people
	Familiarity	Expecting the beat
		Familiar
	Emotional Regulation	Uplifting
		Emotional outlet
		Wallow too much
		Coping strategy
		Amplify emotion
		Experience different emotions simultaneously
Optimal Arousal	Relaxation	Calm music
		Peaceful atmosphere
		Meditation
		Complex music with layers
	Physical Motivation	Energetic music
		Music with a beat
		Music for Movement
	Match Music to outcome	Different music for different levels of pain
		Upbeat music for movement
		Dreamy instrumental music for relaxation
		Relaxing music can be boring

eyes and concentrate on and follow an instrument." An apparent paradox was identified by several participants that they liked music that could simultaneously energize them and help them to feel relaxed by relieving their tension. For example, participants 31 describes how they like '*soothing music*' that gets the '*circulation going*' Participants had very unique perspectives in terms of which features they thought would be most effective, and no features were considered universally effective by the patient group. For example, some chronic pain patients preferred strong beats, while others preferred meditative or string music. It is important to note that

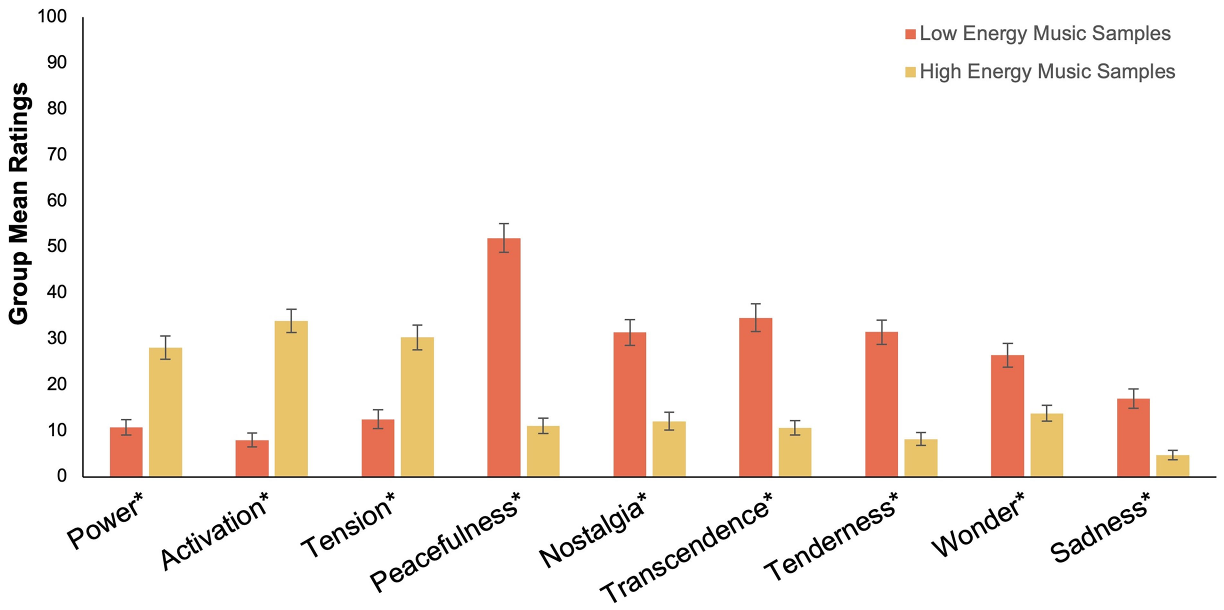

FIGURE 3
Group Mean Ratings for Emotional Responses For High Energy and Low Energy Music. This graph illustrates that chronic pain patients had significantly different emotional responses to high energy music compared to low energy music. Emotional ratings were provided on an amended version of the Short version of the Geneva Emotional Musical Scale (GEMS-9), using a scale of 1–100. The *y*-axis indicates the possible range of scores from 1 to 100. Error bars denote one standard error around the mean. Comparisons between the group mean scores of emotional responses were made using paired t-tests. *Significant at the 0.001 alpha level.

several patients reported that they would find any music irritating during times of severe pain, as highlighted by participants 61 "*in an episode of severe pain I would feel irritated listening to even my favorite music so was unable to choose a song to use as a therapy.*"

(RQ 2) Do patients with chronic pain report any preferences in terms of the type of music that they find most beneficial for pain management?

Finally, patient preferences in music for chronic pain management were explored. Paired t-tests were used to demonstrate that patients rated music that was classified as low energy (e.g., 'relaxing music') as significantly more enjoyable; $t(69) = 3.57$, $p < 0.001$ 95% CI [6.32, 22.39] with a significantly higher analgesic potential; $t(69) = 5.16$, $p < 0.001$ 95% CI [11.25, 25.42] and significantly less irritating $t(69) = 4.86$, $p < 0.001$ 95% CI [9.22, 22.10] compared to music with high levels of energy (e.g., 'motivating music'). However, while these results demonstrate that patients rated low-energy music as more enjoyable, more helpful for reducing pain, and less irritating compared to high-energy music, overall it is important to note that the wide confidence intervals here indicate a high degree of variation between individual patients. No difference was found in ratings of boredom between high-energy music and low-energy music. Additionally, we compared patients' emotional responses between the two types of music. Low-energy music was rated as inducing significantly higher levels of *Wonder*, *Transcendence*, *Tenderness*, *Peacefulness*, *Sadness*, and *Nostalgia* responses compared to high-energy music (See Figure 3). High-energy music was rated as inducing significantly higher levels of *Power*, *Activation*, and *Tension* responses compared to low-energy music (See Figure 3). These results indicate that chronic pain patients had different patterns of emotional responses to high-energy music compared to low-energy music.

Although different levels of enjoyment were identified between the two different types of music, we also wanted to investigate the role of enjoyment overall and examine how it relates to the analgesic potential in patients' chosen music. To account for the marginal skewness in the data a non-parametric Spearman's rho correlation was calculated. A moderate positive correlation was found between patient ratings of enjoyment and patient ratings for the analgesic potential of their chosen song, $r_s(69) = 0.497$, $p < 0.001$. Subsequently, a linear regression was calculated and identified that self-rated enjoyment was a significant predictor of how helpful people thought their chosen song was for pain management, $F(1, 67) = 11.57$, $p < 0.001$, $R^2 = 0.147$. This indicates that while enjoyment is a significant predictor of the likelihood of pain reduction, on its own it only accounts for 14.7% of the variance.

Discussion

Until now, the degree to which the CVM corresponds with chronic pain patients' experience of music listening as a pain management strategy, was untested. The main aim of this study was to explore the degree to which the analgesic potential of patients' self-chosen music can be predicted by components of the CVM. Overall, the findings demonstrate that patients rated the factors of *Musical Integration* and *Cognitive Agency* as the most strongly linked to the analgesic potential of their chosen song. This means that different pieces of music are being used by people with chronic pain to facilitate cognitive strategies that correspond with cognitive agency and musical absorption. This result was based on a quantitative analysis that was conducted in two parts. First, an exploratory factor analysis was conducted to examine the factor structure of the questionnaire and quantify how patient responses corresponded with the cognitive mechanisms identified in the CVM. The factor analysis demonstrated that the pattern of patient responses corresponded with five factors that represented the five cognitive mechanisms outlined by the CVM. This suggests that chronic pain patients are largely in agreement with the cognitive mechanisms outlined in the CVM. While patients may differ in the specific music that they choose for pain management, it seems that there is relatively strong agreement in terms of why patients are choosing the music. Second, a regression analysis was conducted to examine how patient scores for each factor of the cognitive vitality questionnaire predicted the analgesic potential of the patient's chosen song. The regression analysis demonstrated that the analgesic potential of the music was most strongly predicted by the factors of Musical Integration and Cognitive Agency. This result is in line with the CVM which emphasizes the importance of Musical Integration and Cognitive Agency in facilitating an enhanced sense of self and subsequent vitality as a result of music listening for pain management. Patients' tendency to acknowledge the relationship between the cognitive mechanisms of Cognitive Agency and Musical Integration and the music's analgesic potential suggests that patients have a conscious awareness of these two mechanisms. In this instance, patients recognized that their music choice was motivated by specific reasons, which gives participants a chance to exert their individual autonomy and subsequently enhance their internal locus of control. Additionally, patients' interpretation of Musical Integration on the questionnaire was tightly related to a strengthened sense of self and mental energy. This suggests that the mechanism of musical integration is not readily separable from the mechanism of cognitive vitality from the chronic pain patient's perspective and may be more tightly interwoven than initially outlined by the model. Similarly, chronic pain patients were more likely to consider enjoyment as a component of attention rather than meaning-making as proposed by the initial model.

These discrepancies between the initial proposed model, and chronic pain patients' ratings, need to be considered in further detail, both methodologically and theoretically. Factor 4, Personal Meaning, is intended to reflect meaning--making processes related to emotion regulation (Meyer, 2008). Given that chronic pain patients specified the importance of emotion regulation in their own words, it may be beneficial to try and create items that have more accessible everyday language to reflect meaning-making processes. Factor 1 automated attention and enjoyment reflects a lower-order cognitive process, and would not be expected to elicit analgesic effects in isolation (Howlin and Rooney, 2020) so it is not surprising that chronic pain patients did not consider this as one of the most important factors when choosing their music. Surprisingly, a new factor of Motivation emerged in the factor analysis and needs to be explored further. The items in Motivation were initially intended to group with Cognitive Agency, but the fact that they grouped as an independent factor and that participants identified in their own words that they like to choose music with optimal arousal suggests that chronic pain patients are aware of specific strategies that they use to choose music. Further clarification of the exact boundaries between each factor, and the order in which they occur could be determined using a confirmatory factor analysis, with additional items included in more accessible language. Nonetheless, the high-level agreement from participants across the items suggests that these items and factors are a strong representation of the patients' intention for analgesic music listening, which demonstrates that the CVM has reasonable external validity from chronic pain patients' perspective.

Patient descriptions of music listening for pain that correspond with the CVM

Patient descriptions of the benefits of music listening were used to explore the questionnaire responses in more detail using qualitative analysis. This helped to gain a greater understanding of the quantitative results, and to provide more insight into the specific reasons patients have for using music for pain management. The specific reasons for music listening are an important component of music-listening interventions (Linnemann et al., 2015), since they increased patients' motivation to maintain active engagement and sustain the musical experience (Mitchell and MacDonald, 2006; Mitchell et al., 2008; Pothoulaki et al., 2008; Roy et al., 2008; Nilsson, 2009; Siedliecki, 2009; Good et al., 2010; Nguyen et al., 2010; Vaajoki et al., 2012; Finlay, 2014; Hsieh et al., 2014; Nagata et al., 2014; Linnemann et al., 2015). Four themes were developed using thematic synthesis, which were Musical Integration, Cognitive Agency, Emotion Regulation, and Optimal Arousal. Since the two mechanisms of Musical Integration and Cognitive Agency were related to the analgesic potential of patient's self-chosen music, this will now be discussed in more detail.

Patient descriptions consistent with *Musical Integration* outlined that music absorption can help to provide an escape from the reality of pain. Specifically, patients reported that music could be used to transport them out of their current experience and helped them to stop thinking about their or problems and to focus on something else. These descriptions from patients correspond with the idea that music helps to reduce pain because it is absorbing on a cognitive and emotional level (Bradshaw et al., 2012; Gold and Clare, 2013; Guetin et al., 2013; Finlay, 2014). Patients' rich descriptions of musical integration suggest that full musical absorption as opposed to music listening is required to mediate the analgesic benefits of musical engagement. This highlights the importance of facilitating immersive music-listening experiences to support patient engagement with the music (Bradshaw et al., 2012). In order to maximize the likelihood that patients will become fully absorbed, it is important to consider the wider musical experience to reduce the presence of other major distractors (Brattico and Pearce, 2013; Lee, 2016). Also, additional strategies to enhance the music-listening experience, such as additional visual support (Chanda and Levitin, 2013) and an optimal listening environment should also be considered.

Patient descriptions related to the theme of *Cognitive Agency* encompassed active engagement and the importance of individuality which were related to a strengthened sense of self-identity and social connectedness. This is particularly important in chronic pain management contexts where people often experience low self-esteem and low self-efficacy due to diminished capacity as a result of having chronic pain (Jensen et al., 1991). This finding is in line with previous suggestions that personally significant music can be used to enhance an individual's sense of cognitive agency, and that this in turn can assist with identity formation (Saarikallio et al., 2020). Many patients with chronic pain become disconnected from their social network and experience a reduction in their capacity to complete daily activities. At the same time people with chronic pain report that they sometimes feel trapped and as if their personal world is getting smaller. Music listening can be used to help patients maintain a sense of their personal identity (Saarikallio et al., 2020) and a sense of agency, when people are encouraged to choose their own music (Howlin and Rooney, 2021b; Howlin et al., 2022). Additionally, music listening is a relatively easy activity, and perceived as less effortful compared to other types of cognitive tasks, which could be beneficial when patients may have diminished cognitive resources available due to the experience of chronic pain.

Patients' music preferences

A secondary aim of this study was to assess patient preference for music based on the levels of energy in the music. The results demonstrate that patients rated unfamiliar low-energy music as significantly more enjoyable, with a significantly higher analgesic potential and significantly less irritating compared to unfamiliar high-energy music. Additionally, patients demonstrated different patterns of emotional responses to music with low values of energy compared to music with high values of energy. Low-energy music was rated as inducing significantly higher *Wonder*, *Transcendence*, *Tenderness*, *Peacefulness*, *Sadness*, and *Nostalgia* emotional responses compared to *High-Energy* music. These results contrast with the results found in some experimental settings, where participants did not demonstrate a clear preference for a particular music energy (Zhao and Chen, 2009). This may be due to the fact that patients with chronic pain are already in a state of relatively high arousal due to the presence of pain, which means they are more likely to become overloaded by unfamiliar high-energy music compared to healthy participants. In line with Berlyne's (Berlyne, 1971) inverted-U theory in order to facilitate an enjoyable music-listening experience, music should not be too low in arousal or else it may be perceived as boring, and also should not be too high in arousal or it may be perceived as irritating. When we consider that patients have a tendency to choose music that is higher energy compared to experimenter music (Howlin and Rooney, 2021a), it is possible that the unfamiliar nature of this music may have made it particularly irritating due to a lack of context and meaning. We should consider the importance of optimizing arousal within the music-listening experience to ensure it is neither over stimulating or boring, based on each specific pain management context. It may be useful to introduce music that induces moderate levels of arousal to account for the possibility that chronic pain patients are already in an elevated state of arousal (Finlay and Rogers, 2015). In light of previous research and other findings from the present study, where possible participants will benefit from being given the option to choose their own music. This will allow them to select something that is optimal for their circumstances and serve to enhance their feelings of autonomy (Howlin and Rooney, 2021b).

Strengths and limitations

An important aspect of this study is that it is the first study to investigate the cognitive mechanisms that mediate the analgesic benefits of music interventions with a specific clinical population, using a pre-defined theoretical model. This is important because as we can see from these results, patient responses to music can be quite different to responses to music from healthy controls. Further work with different patient groups is required to develop our understanding of the cognitive mechanisms underlying successful music interventions. Precise clarification of the boundaries between each factor, and the order in which they occur could be determined using a confirmatory factor analysis, with additional items included in more accessible language. Nonetheless, the high-level agreement from participants across the items suggests that these items and factors are a strong representation of the patients' intention for analgesic music listening, which demonstrates that the CVM has reasonable external validity from chronic pain patients' perspective. It is also important to note the benefits of using research methods that facilitate enhanced patient access to the study. In this study, we used online data collection methods to include patients from a range of geographical locations who may be unable to attend multiple hospital appointments and invited patients to complete the survey at a time and location that was convenient for them. A limitation of this study is that it does not evaluate the direct effects of music listening for chronic pain management. Instead, this study focuses on the factors that patients think are most important in mediating the analgesic effects of music listening. An additional consideration of this study is that it was completed in an individual context, whereas most pain management programs tend to be completed in a group setting. Given that the social context of music listening can influence music preferences (Hargreaves and North, 1999), future studies may wish to consider examining the influence of social context or group dynamics on music-listening choices, to identify if people with chronic pain would have different music preferences in a group setting.

Implications

Until now the degree to which the CVM corresponds with chronic pain patients' experience of music listening as a pain management strategy, was untested. Overall, this study suggests that chronic pain patients' reasons for choosing music for pain management are broadly in line with the mechanisms outlined in the CVM (Automated Attention, Cognitive Agency, Meaning-Making, Musical Integration, and Cognitive Vitality). Chronic pain patients reported that the degree to which a song will elicit Musical Integration is the most important factor leading to subsequent analgesic benefits, but they also think that their specific music choices are an important component in achieving music analgesia. The role of motivation, and optimal arousal, was identified by participants as additional factors that need to be explored further. Qualitative responses from patients highlighted that Cognitive Agency was important because active engagement and individuality can help patients to strengthen their sense of self. This is particularly important for chronic pain management where people often experience low self-esteem and low self-efficacy due to diminished capacity, and pain management strategies that enhance the patient's internal locus of control have been shown to be the most effective (Crisson and Keefe, 1988; Mitchell and MacDonald, 2006; Mitchell et al., 2007; Finlay, 2014). Additionally, patient descriptions highlighted that Musical Integration is important because a truly immersive music-listening experience can provide an escape from painful experiences. Pain management programs aim to support patients in developing self-management skills, which requires ongoing motivation on behalf of the patient. Music-listening interventions provide an opportunity to support patients on a daily basis, by encouraging them to engage in a personally meaningful and absorbing activity. Additional focus should also be placed on the best way to incorporate music interventions in a multi-disciplinary approach to psychology-based pain management programs. For example, the role of music interventions as a support to physiotherapy has yet to be explored. The introduction of music to pain management programs may facilitate ongoing motivation and participation by enhancing patient's cognitive vitality. This may provide the basis for using music as a compliment to or therapeutic alternative to usual Cognitive Behavioral Therapy (CBT) based rehabilitation and maintenance for people with chronic pain.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by St. Vincent's Hospital Research Ethics Board. Anonymous electronic informed consent for participation was provided by all of the participants who took part in the study in accordance with the national legislation and the institutional requirements.

Author contributions

All authors CH, RW, PD, and BR contributed to the initial research design and write-up of the final manuscript. CH and RW were responsible for data collection. CH and BR were responsible for data analysis and interpretation. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Bartlett, M. S. (1954). A further note on the multiplying factors for various chi-square approximations in factor analysis. *J. R. Stat. Soc. Ser. B* 16, 296–298.

Berlyne, D. E. (1971). *Aesthetics and Psychobiology*. New York, NY: Appleton Century Crofts.

Bradshaw, D. H., Chapman, C. R., Jacobson, R. C., and Donaldson, G. W. (2012). Effects of music engagement on responses to painful stimulation. *Clin. J. Pain* 28, 418–427. doi: 10.1097/AJP.0b013e318236c8ca

Bradt, J., Dileo, C., Magill, L., and Teague, A. (2016). Music interventions for improving psychological and physical outcomes in cancer patients. *Cochrane Database Syst. Rev.* 8:CD006911. doi: 10.1002/14651858.CD006911.pub3

Brattico, E., and Pearce, M. (2013). The neuroaesthetics of music. *Psychol. Aesthet. Creat. Arts* 7, 48–61. doi: 10.1037/a0031624

Breivik, H., Borchgrevink, P. C., Allen, S. M., Rosseland, L. A., Breivik Hals, E. K., et al. (2008). Assessment of pain. Br. J. Anaesth 101, 17–24. doi: 10.1093/bja/aen103

Carr, E. C. (2009). Understanding inadequate pain management in the clinical setting: the value of the sequential explanatory mixed method study. *J. Clin. Nurs.* 18, 124–131. doi: 10.1111/j.1365-2702.2008.02428.x

Chanda, M. L., and Levitin, D. J. (2013). The neurochemistry of music. *Trends Cogn. Sci.* 17, 179–193. doi: 10.1016/j.tics.2013.02.007

Crisson, J. E., and Keefe, F. J. (1988). The relationship of locus of control to pain coping strategies and psychological distress in chronic pain patients. *Pain* 35, 147–154. doi: 10.1016/0304-3959(88)90222-9

Fabrigar, L. R., Wegener, D. T., Mac Callum, R. C., and Strahan, E. J. (1999). Evaluating the use of exploratory factor analysis in psychological research. *Psychol. Methods* 4, 272–299. doi: 10.1037/1082-989X.4.3.272

Fancourt, D., and Finn, S.World Health Organization, Regional Office for Europe, & Health Evidence Network. (2019). What is the evidence on the role of the arts in improving health and well-being?: a scoping review. Available at: https://www.euro.who.int/en/publications/abstracts/what-is-the-evidence-on-the-role-of-the-arts-in-improving-health-and-well-being-a-scoping-review-2019

Finlay, K. A. (2014). Music-induced analgesia in chronic pain: efficacy and assessment through a primary-task paradigm. *Psychol. Music* 42, 325–346. doi: 10.1177/0305735612471236

Finlay, K. A., and Rogers, J. (2015). Maximizing self-care through familiarity: the role of practice effects in enhancing music listening and progressive muscle relaxation for pain management. *Psychol. Music* 43, 511–529. doi: 10.1177/0305735613513311

Fitzpatrick, K., Moss, H., and Harmon, D. C. (2019). The use of music in the chronic pain experience: an investigation into the use of music and music therapy by patients and staff at a hospital outpatient pain clinic. *Music Med.* 11:6. doi: 10.47513/mmd.v11i1.639

Garza-Villarreal, E. A., Pando, V., Vuust, P., and Parsons, . (2017). Music-induced analgesia in chronic pain conditions: a systematic review and meta- analysis. bioRxiv [preprint]. doi: 10.1101/105148

Gold, A., and Clare, A. (2013). An exploration of music listening in chronic pain. *Psychol. Music* 41, 545–564. doi: 10.1177/0305735612440613

Good, M., Albert, J. M., Anderson, G. C., Wotman, S., Cong, X., Lane, D., et al. (2010). Supplementing relaxation and music for pain after surgery. *Nurs. Res.* 59, 259–269. doi: 10.1097/NNR.0b013e3181dbb2b3

Guetin, S., Charras, K., Berard, A., Arbus, C., Berthelon, P., Blanc, F., et al. (2013). An overview of the use of music therapy in the context of Alzheimer's disease: a report of a French expert group. *Dementia* 12, 619–634. doi: 10.1177/1471301212438290

Hargreaves, D. J., and North, A. C. (1999). The functions of music in everyday life: redefining the social in music psychology. *Psychol. Music* 27, 71–83. doi: 10.1177/0305735699271007

Howlin, C., and Rooney, B. (2020). The cognitive mechanisms in music listening interventions for pain: a scoping review. *J. Music. Ther.* 57, 127–167. doi: 10.1093/jmt/thaa003

Howlin, C., and Rooney, B. (2021a). Patients choose music with high energy, danceability, and lyrics in analgesic music listening interventions. *Psychol. Music* 49, 931–944. doi: 10.1177/0305735620907155

Howlin, C., and Rooney, B. (2021b). Cognitive agency in music interventions: increased perceived control of music predicts increased pain tolerance. *Eur. J. Pain* 25, 1712–1722. doi: 10.1002/ejp.1780

Howlin, C., Stapleton, A., and Rooney, B. (2022). Tune out pain: agency and active engagement predict decreases in pain intensity after music listening. *PLoS One* 17:e0271329. doi: 10.1371/journal.pone.0271329

Hsieh, C., Kong, J., Kirsch, I., Edwards, R. R., Jensen, K. B., Kaptchuk, T. J., et al. (2014). Well-loved music robustly relieves pain: a randomized, controlled trial. *PLoS One* 9:e107390. doi: 10.1371/journal.pone.0107390

Ivankova, N. V., Creswell, J. W., and Stick, S. L. (2006). Using mixed-methods sequential explanatory design: from theory to practice. *Field Methods* 18, 3–20. doi: 10.1177/1525822X05282260

Jensen, M. P., Turner, J. A., and Romano, J. M. (1991). Self-efficacy and outcome expectancies: relationship to chronic pain coping strategies and adjustment. *Pain* 44, 263–269. doi: 10.1016/0304-3959(91)90095-F

Juslin, P. N., Harmat, L., and Eerola, T. (2014). What makes music emotionally significant? Exploring the underlying mechanisms. *Psychol. Music* 42, 599–623. doi: 10.1177/0305735613484548

Juslin, P. N., Västfjäll, D., Juslin, N., and Västfjäll, D. (2008). Emotional responses to music: the need to consider underlying mechanisms. *Behav. Brain Sci.* 31, 559–575. doi: 10.1017/S0140525X08005293

Kaiser, H. F. (1974). An index of factorial simplicity. *Psychometrika* 39, 31–36. doi: 10.1007/BF02291575

Keenan, A., and Keithley, J. (2015). Integrative review: effects of music on cancer pain in adults. Oncol. Nurs. Forum, 42, E368–E375. doi: 10.1188/15.ONF.E368-E375

Koelsch, S. (2010). Towards a neural basis of music-evoked emotions. *Trends Cogn. Sci.* 14, 131–137. doi: 10.1016/j.tics.2010.01.002

Lee, J. H. (2016). The effects of music on pain: a meta-analysis. *J. Music. Ther.* 53, 430–477. doi: 10.1093/jmt/thw012

Linnemann, A., Kappert, M. B., Fischer, S., Doerr, J. M., Strahler, J., and Nater, U. M. (2015). The effects of music listening on pain and stress in the daily life of patients with fibromyalgia syndrome. *Front. Hum. Neurosci.* 9:10. doi: 10.3389/fnhum.2015.00434

Mainka, S., Spingte, R., and Thaut, M. (2016). "Music therapy in medical and neurological rehabilitation settings" in *Oxford handbook of music psychology*. eds. S. Hallam, I. Cross and M. Thaut. *2nd* ed (Oxford: Oxford University Press), 857–873.

Melzack, R. (1999). From the gate to the neuromatrix. *Pain* 82, S121–S126. doi: 10.1016/S0304-3959(99)00145-1

Meyer, L. B. (2008). *Emotion and Meaning in Music*. Chicago, IL: Univ. of Chicago Press.

Mitchell, L. A., and MacDonald, R. A. R. (2006). An experimental investigation of the effects of preferred and relaxing music listening on pain perception. *J. Music. Ther.* 43, 295–316. doi: 10.1093/jmt/43.4.295

Mitchell, L. A., MacDonald, R. A. R., and Knussen, C. (2008). An investigation of the effects of music and art on pain perception. *Psychol. Aesthet. Creat. Arts* 2, 162–170. doi: 10.1037/1931-3896.2.3.162

Mitchell, L. A., MacDonald, R. A. R., Knussen, C., and Serpell, M. G. (2007). A survey investigation of the effects of music listening on chronic pain. *Psychol. Music* 35, 37–57. doi: 10.1177/0305735607068887

Murrock, C. J., and Higgins, P. A. (2009). The theory of music, mood and movement to improve health outcomes. *J. Adv. Nurs.* 65, 2249–2257. doi: 10.1111/j.1365-2648.2009.05108.x

Nagata, K., Iida, N., Kanazawa, H., Fujiwara, M., Mogi, T., Mitsushima, T., et al. (2014). Effect of listening to music and essential oil inhalation on patients undergoing screening CT colonography: a randomized controlled trial. *Eur. J. Radiol.* 83, 2172–2176. doi: 10.1016/j.ejrad.2014.09.016

Nguyen, T. N., Nilsson, S., Hellstrom, A. L., and Bengtson, A. (2010). Music therapy to reduce pain and anxiety in children with cancer undergoing lumbar puncture: a randomized clinical trial. *J. Pediatr. Oncol. Nurs.* 27, 146–155. doi: 10.1177/1043454209355983

Nilsson, U. (2009). The effect of music intervention in stress response to cardiac surgery in a randomized clinical trial. *Heart Lung* 38, 201–207. rih. doi: 10.1016/j.hrtlng.2008.07.008

Pothoulaki, M., Macdonald, R. A. R., Flowers, P., Stamataki, E., Filiopoulos, V., Stamatiadis, D., et al. (2008). An investigation of the effects of music on anxiety and pain perception in patients undergoing haemodialysis treatment. *J. Health Psychol.* 13, 912–920. doi: 10.1177/1359105308095065

Raja, S. N., Carr, D. B., Cohen, M., Finnerup, N. B., Flor, H., Gibson, S., et al. (2020). The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain* 161, 1976–1982. doi: 10.1097/j.pain.0000000000001939

Robb, S. L., Hanson-Abromeit, D., May, L., Hernandez-Ruiz, E., Allison, M., Beloat, A., et al. (2018). Reporting quality of music intervention research in healthcare: a systematic review. *Complement. Ther. Med.* 38, 24–41. doi: 10.1016/j.ctim.2018.02.008

Roy, M., Peretz, I., and Rainville, P. (2008). Emotional valence contributes to music-induced analgesia. *Pain* 134, 140–147. PsycINFO. doi: 10.1016/j.pain.2007.04.003

Saarikallio, S. H., Randall, W. M., and Baltazar, M. (2020). Music listening for supporting adolescents' sense of Agency in Daily Life. *Front. Psychol.* 10:2911. doi: 10.3389/fpsyg.2019.02911

Siedliecki, S. L. (2009). Racial variation in response to music in a sample of African-American and Caucasian chronic pain patients. *Pain Manag. Nurs.* 10, 14–21. doi: 10.1016/j.pmn.2008.08.003

Swaminathan, S., and Schellenberg, E. G. (2015). Current emotion research in music psychology. *Emot. Rev.* 7, 189–197. doi: 10.1177/1754073914558282

Thaut, M. H., (2016). "History and research," in The Oxford Handbook of Music Psychology. 2nd edn. eds. S. Hallam, I. Cross, M. Thaut (OUP: Oxford), 893–904.

Thomas, J., and Harden, A. (2008). Methods for the thematic synthesis of qualitative research in systematic reviews. *BMC Med. Res. Methodol.* 8:45. doi: 10.1186/1471-2288-8-45

Treede, R.-D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., et al. (2015). A classification of chronic pain for ICD-11. *Pain* 156, 1003–1007. doi: 10.1097/j.pain.0000000000000160

Vaajoki, A., Pietilä, A.-M., Kankkunen, P., and Vehviläinen-Julkunen, K. (2012). Effects of listening to music on pain intensity and pain distress after surgery: an intervention. *J. Clin. Nurs.* 21, 708–717. doi: 10.1111/j.1365-2702.2011.03829.x

Watkins, M. W. (2018). Exploratory factor analysis: a guide to best practice. *J. Black Psychol.* 44, 219–246. doi: 10.1177/0095798418771807

Zentner, M., Grandjean, D., and Scherer, K. R. (2008). Emotions evoked by the sound of music: characterization, classification, and measurement. *Emotion* 8, 494–521. doi: 10.1037/1528-3542.8.4.494

Zhao, H., and Chen, A. C. N. (2009). Both happy and sad melodies modulate tonic human heat pain. J. Pain. 10, 953–960. doi: 10.1016/j.jpain.2009.03.006

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Case Report: "*I got my brain back*" A patient's experience with music-induced analgesia for chronic pain

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Listening to music has progressively been proposed as a complementary alternative for chronic pain; understanding its properties and its neurobiological bases is urgent. We show a phenomenological investigation of a woman who has lived 20 years with chronic pain. The inquiry involved her experience of the context in which she listens to music, the intensity and quality of pain, body mapping, memories, emotions, and cognition. The participant listens to music for different reasons, such as pain and anxiety relief, motivation to exercise, and quality of sleep, but all seem to revolve around different strategies for pain management. Experiences in physiological and cognitive aspects included perceived restorative sleep that may have improved the participant's general wellbeing and improved cognitive and motor performance as well as communication skills. The music enabled the participant not only to relieve pain but also withdrawal effects after discontinuing her opioid-based treatment. These effects may encompass endogenous opioid and dopamine mechanisms involving natural analgesia associated with pleasurable experiences. Future studies could consider phenomenological case studies and therapeutic accompaniment to reorient subjective properties of pain and expand quantitative and qualitative knowledge for more comprehensive reports on music and analgesia.

KEYWORDS

music, pain, opioids, clinical, music-induced analgesia, phenomenology, therapeutic accompaniment

1. Introduction

Even with proper therapy, a high number of patients with chronic pain experience negative consequences that affect their health, self-perception, interpersonal relationships, and life in general (Veehof et al., 1999). In this context, music listening has been progressively proposed as an add-on alternative due to its positive effects on pain, anxiety and depression symptoms, and its easy access. Understanding the analgesic effects and its neurobiological basis is urgent, but it still faces difficulties concerning experimental designs, especially to model placebo effects (Rosenkjær et al., 2022). Nevertheless, several studies have confirmed that listening to music reduces acute and chronic pain (see Garza-Villarreal et al., 2017; Lunde et al., 2019 for a review), hence the name "music-induced analgesia." For example, patients with low back pain showed improvement using music therapy (Guétin et al., 2005), and there is evidence of post-operatory analgesia using music (Kavak Akelma et al., 2020). A more recent study in mice showed that sound can induce analgesia via an auditory cortex–thalamus circuit (Zhou et al., 2022); however, there seem to be other mechanisms at play. The music chosen by the patients themselves (Li et al., 2011), valued as pleasant (Roy et al., 2008), and familiar (Shih-Tzu et al., 2010; van den Bosch et al., 2013), seems to be the most suitable for producing analgesic effects. However, the musical choice depends on multiple factors involving the individual history and culture. Its effects comprise imagination and metaphors that can only be understood subjectively. In addition, there are a few spaces where people living with pain or who have tried alternative therapies can share their experiences without stigma (Miglio and Stanier, 2022).

We show a phenomenological inquiry of a woman who has lived 20 years with chronic pain. After suspending her opioid-based treatment, she found music as an alternative for relief. Her experience is discussed considering neurobiological knowledge about pain and music. Therapeutic accompaniment is proposed as an alternative to understand similar experiences and to incorporate them into clinical and scientific fields.

2. Case description

The participant was a 58-year-old woman, a single mother of two adult children, and a grandmother of five grandchildren. She has a degree in accounting and a degree in environmental sciences. She was educated in music; she began to play the piano and the flute as a child and learned the guitar and saxophone in a self-taught way. She now works as a tax field auditor in the United States. She has been a chronic pain patient and has spent about 20 years on high doses of narcotic pain relievers after a car accident that caused her lower spine problems and created chronic pain.

In September 2021, she stopped taking medication "cold turkey." She found that music not only helped with the pain, but she also believes it repaired her "brain chemistry," which she felt to be affected due to long-term use of high doses of opioids, as well as the withdrawal symptoms.

Sharing her experience at the pain clinic, she was told initially that music was just a distraction and subsequently that she was very creative in using music to relieve pain, but she did not agree with that statement at all and was convinced that music works differently than only distraction. After observing the insistence of the participant on the effects of music to relieve pain, her physician from the Comprehensive Pain Program provided her with a research article reporting that music reduces pain and increases functional mobility in fibromyalgia (Garza-Villarreal et al., 2014). She was very intrigued about it, so she contacted the authors to share her experience and understand how music helps her manage chronic pain and gives her energy and motivation.

The study presented here was designed following the guidelines of the American Psychological Association (2002) and the Declaration of Helsinki and was approved by the Bioethics Committee of the Institute of Neurobiology of the Universidad Nacional Autónoma de México.

3. Diagnostic assessment

After having contacted the participant and knowing her case, a first open and free interview was carried out. In it, she shared her experience about her accident, the chronic pain she suffered, her diagnosis, treatment, and cessation of it, as well as the way she accessed music to deal with pain and her doubts about scientific research in this regard. A first analysis of this interview made it possible to identify the most relevant points for the participant and to develop two guides to investigate her experience of pain over 20 years in two conditions: without medication/with medication or with music. The aspects evaluated in both guides were as follows: intensity and quality of pain; body mapping; memories associated with pain; emotions; and cognition (perception, attention, learning, memory, and language). Each of the guides was answered in writing by the participant with the support and advice of the researcher. Subsequently, each of the points addressed in the guides were expanded verbally and developed in two interviews.

Then, the participant was instructed to make a list of the musical pieces that she considers most representative to relieve her pain and a list of the representative musical pieces that caused her pain. For each of the musical pieces, the participant indicated: the context in which she listens to that music; memories (if any) evoked; appeared images (visual, tactile, or auditory); emotions or feelings; parts of the body—in addition to the relief of the lower back and hips—that show sensations or experiences when listening (the way that piece of music makes her body feel). The participant indicated these elements in writing. In subsequent interviews, each piece of music was jointly listened by the participant and by the researcher, and each of the indicated aspects was expanded verbally and developed through questions directed by the researcher.

The complete investigation was carried out for 3 months. All interviews were conducted via Zoom and were recorded for later analysis covering a total of 6 h. Each experience guide and each list of music that relieves and causes pain was answered in 3 weeks.

Next, a third-person narrative and some testimonials respecting the explanatory style of the participant herself are present to understand, from her perspective, what she considers the most relevant from her experience. The narrative follows the neurophenomenological proposal that makes use of the experience communicated in first-person testimonials and emphasizes embodiment as a substrate of individuality (Varela et al., 1991; Díaz, 2022). We encourage the reader to review the more extensive narrative with verbatim illustrative testimonials shown in the Supplementary material.

3.1. Accident, treatment, and "cold turkey"

In 2001, a large car coming down a hill lost control and crashed into her, and pushed her car onto a busy street. At first, it did not hurt, but 6 h later she had excruciating pain in her spine and could not walk and then she began to feel sharp like shards of blast sticking. She received two sets of facet joint injections. When she stated that the second set of facet joint injections increased the pain in her lower spine and hips she was told, "*it was a steroidal flare but no doctor can currently tell me what it was.*" The pain increased almost permanently, and that is when she got her first prescription for oxycodone.

Her pain was mostly in the lower spine, and it felt like a type of crushed glass or like there was an ice pick in the middle between L3 and L4. She has a herniated bulging disk, nerve compression stenosis, and arthritis. Her second and third toes on her left foot have been tingling for 20 years since the accident and about 5 or 6 years after she developed sciatica.

She participated in a Comprehensive Chronic Pain program for the first time in 2019, when she was taking high doses of OxyContin. There they offered multidisciplinary rehabilitation, reiki, massages, and acupuncture, but she found no relief and she was angry about not finding alternatives to medication. As of September 2021, she was taking nearly 300 mg of extended-release OxyContin and 300 mg of immediate-release oxycodone so, she went cold turkey and that was the last time she took oxycodone. Intuitively, she thought she needed music with headphones and as the music played she felt like it was repairing or feeding her brain. She is currently using music, reiki, acupuncture, and Buddhist meditation for pain.

3.2. Pain experience, emotions, and cognition

Pain intensity and body location have fluctuated throughout these 20 years of treatment (see Figures 1, 2).

She has experienced a variety of emotions throughout these 20 years, mostly negative: exhaustion, stress, sadness, anger, frustration, and impatience.

She has also felt happiness and relaxation with pain relief, either from medication or music, but even when happiness was present, other emotions persisted when using medication: stress, isolation, anger, and frustration with the pain. Sleep was a prominent issue since she had insomnia for a long time, but now with music sleep has improved.

Before the music, her sense of touch was dulled, whether she felt pain or relief. With the music "*not only* [her] *sense of touch came back but the gray could went away.*"

She had difficulties concentrating while using narcotic medication. Using music "*has given* [her] *much more energy to pay attention to the things that matters*…."

In terms of learning and memory, she used to have a hard time remembering things and focusing on new material at work. With music, she has increased her learning ability and is alert with an overdose of joy and interested in everything again.

3.3. Music that relieves and causes pain

Now, she probably uses music almost every waking hour, except when she is in a meeting. She has approximately 80 playlists, and each playlist can have 15–100 tracks. From there, she can make lists of music to relieve pain but also to know what music causes her pain. She uses the tidal streaming service because they have a large library of music. However, the 3D music most streaming services have sounds like the band is playing in a gym with bad acoustics. High-fidelity headphones are crucial for good sound quality and the noise cancelation enhances the sound quality, so she can only hear the music. Although she has a stereo and albums, the stereo or the CD player is not effective.

Every day she tries to find music that relieves the pain, so she is always exploring what kind of rhythms, tones, and pitches are helping. In addition to sound properties, her exploration involves memories and physical sensations, and moods evoked by the songs, as well as certain body positions. With this, she can decide the most appropriate times to listen to each song. The experiences associated with each of the five songs that alleviate her pain the most are shown in Table 1 (more extensive testimonials in the Supplementary material).

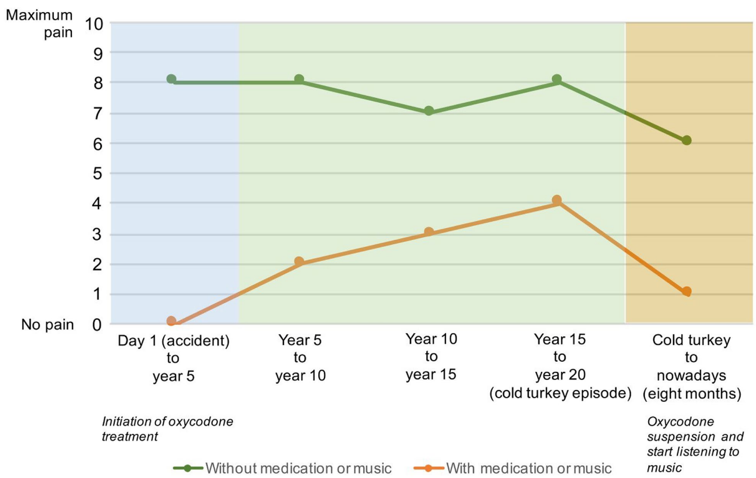

FIGURE 1
Pain intensity over 20 years from the accident to 8 months after the cold turkey episode: green line—intensity when the participant used medication (oxycodone from the 8th month after the accident to year 20 just before the cold turkey episode) or listened to music (at the end of year 20 to 8th month after at the moment of the assessment). Orange line—intensity when the participant did not use medication (before the oxycodone treatment and some rarely days when she suspended the treatment for a long 20years) or did not listen to music to relieve the pain. At first, 8months before the first dose of oxycodone, she felt an intensity of 8 and then fluctuated to 7 when she began to be more active, riding a bike, and having a natural path by eating anti-inflammatory foods and avoiding sugar and salt. When she started using the medication, she felt no pain at first, but it increased right before the cold turkey episode. Since she listens to music, she has had periods completely free of pain, sometimes 1 or 2days without pain, but with an intensity 6 if she does not listen to music: "*if you ask me where my pain average was in the last 2months I would say maybe a 3 in the worst period… Once in a while, if I go hiking up high elevations may be 6 or 7. But every day at my desk call week is 4 maybe.*"

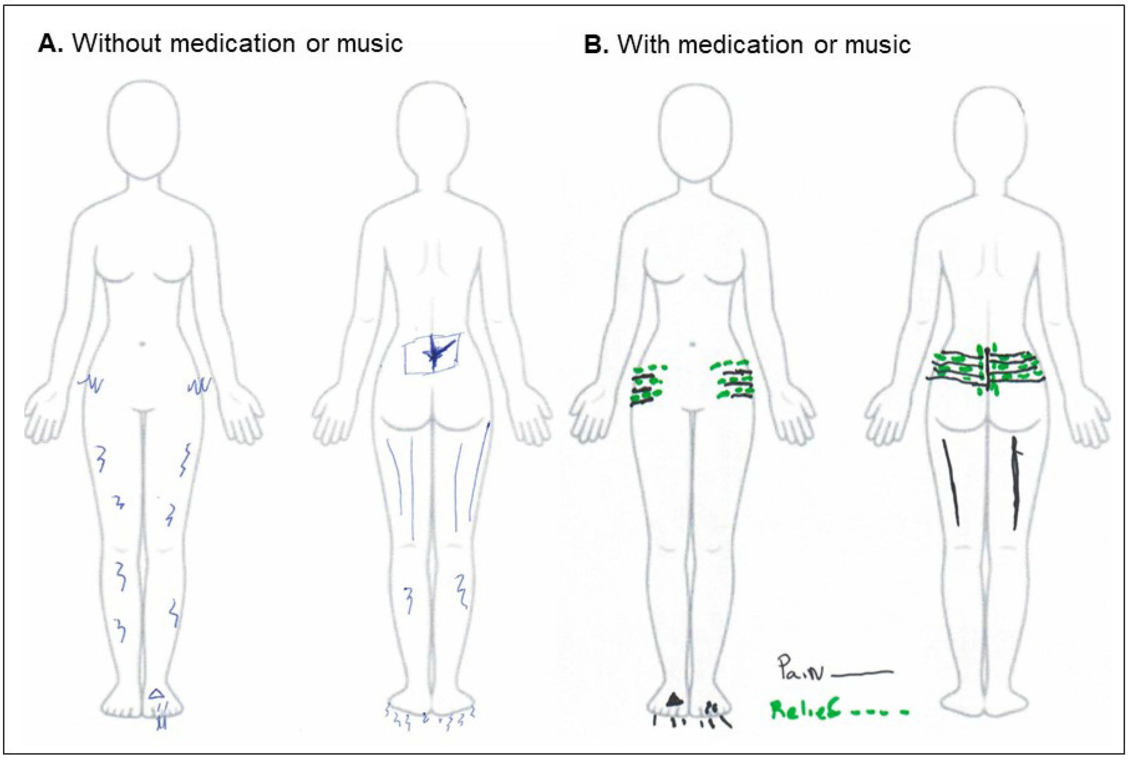

FIGURE 2
Location of pain when she has not used medication **(A)** and when she took medication or listened to music **(B)**. When there were no periods of medication, the pain was felt in the back of the legs, which was sciatica, and nerve pain in the legs and under the feet. When she took medication or listened to music, she felt pain in her lower spine and feet, where she also felt relief.

Her exploration has also allowed her to identify music that exacerbates her pain and that reminds her of social situations evoking anger or stress. So, she has built a list of music she avoids, as shown in Table 2 (more extensive testimonials in the Supplementary material).

4. Discussion

This case shows the experience of a person who found in music an alternative to alleviate her chronic pain. However, her first experience was not with pain but withdrawal effects after stopping opioid-based medication used for 20 years. Though medication provided her with pain relief, it also altered her perception of her body and emotions, making it difficult to experience wellbeing and perform daily activities. Although there is some evidence that music helps reduce substance abuse and craving, studies are not conclusive and its effects are not explained by the neurochemical mechanisms involved in the substances, but rather by positive feelings elicited by music that may decrease fear and guilt, and facilitate acceptance (Mays et al., 2008; Ghetti et al., 2022). A possible mechanism could involve endogenous opioids and dopamine released when listening to music and whose effects involve natural analgesia processes associated with pleasurable experiences (Lunde et al., 2019). However, a recent study showed that in acute pain, the expectation of analgesia predicted pain relief with music, even when blocking dopamine and endogenous opioids (Lunde et al., 2022). As for chronic pain, the mechanisms of music-induced analgesia are still unknown. Placebo effects could account for the music effect and have been previously suggested to be involved as part of the cognitive mechanisms of analgesia (Lunde et al., 2019). For example, we have shown that expectation of analgesia predicts levels of music-induced analgesia (Lunde et al., 2022), and expectation of analgesia is a known and complex mechanism involved in placebo effects (Rosenkjær et al., 2022).

Music-induced analgesia has been suggested to involve autonomic modulation through the descending pain modulatory system, elicited by top-down regulatory processes (Salimpoor et al., 2011; Garza-Villarreal et al., 2014, 2017). Such processes may contribute to positive emotional experiences associated with bodily sensations, as shown in phenomenological reports (Eschrich et al., 2008), as well as in the participant's testimonials referring to a variety of relief sensations in her spine, legs, and feet according to each type of music listened at different times and contexts. Imagination on the body may constitute a top-down element so that pain or relief experiences become figurative providing awareness and control over them (Miglio and Stanier, 2022).

An interesting note is a frequency with which the participant uses music (almost every waking hour), which contrasts with sessions proposed every so often (e.g., 20–30 min. daily; Garza-Villarreal et al., 2017). Additionally, she indicates certain instrumental properties, such as the acoustic quality and the use of high-fidelity headphones to elicit analgesia. Such testimonials may advise about the required frequency and instruments to produce and maintain analgesic effects. The complexity of analgesia includes the neurobiology linked to listening to music. This involves not only the auditory system and cortex but also

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TABLE 1 List of musical pieces that relieve the participant of pain the most, the context in which she listens to them, and associated experiences.

Music that relieves pain						
"Piece" Musician or band	Context in which the piece is listened	Memories (if any) this piece brings to mind	Visuals this piece brings to mind	Feelings this piece causes	Part of the body in which this piece is perceived (in addition to relieving pain in the lower spine and hips)	How this piece makes the body feel
"Golden" Alexis French	"When pain is the worst and I have to lay in a fetal position. I am usually lying in a fetal position on the bed"	"No memories. This is new music"	"I visualize gliding/flying among the clouds above an ocean shoreline"	Joy, peace, freedom, beauty.	"I feel this song throughout my entire body"	"It makes my body feel like it is floating and gently rolling on waves of clouds. My body feels light and in my mind it feels like the keys are tickling my entire body"
"Confines" (official live studio session with string quartet) Black Pumas	"At my desk, out running errands or laying in fetal position when pain is the worst"	"No memories. This is new music. My mind is absorbed in the notes and layers of notes"	"I visualize the instruments being played and the notes on sheets of music and just grooving to the beat"	"The string quartet and Eric Burton's singing voice is soothing and relaxing. The beat is also soothing and relaxing"	"The beat, the string quartet and Eric Burton's singing release pressure from my lower spine and relaxes my entire body. My body feels like it absorbs the music and is being uplifted and gently rocked to the beat"	Relaxed and soothed
"Know you better" (official audio version) Black Pumas	"At my desk or laying in fetal position when pain is the worst"	"No memories. This is new music. My mind is focused on the ticking of the percussion. However, it does remind me of when I would go to the underground dance scene in Chicago where Frankie Knuckles created Chicago house music. His live sets could put an entire crowd of 500 people into a trance. These were similar to raves, but before raves and better music (no electronic or techno crappy music)"	"I visualize the ticking of the percussion…a drum stick ticking against the rim of a snare drum and the other instruments being played"	"The ticking of the percussion focuses my mind while the singing and beat of the other instruments relieves stress as well as the pressure in my lower spine"	"I feel this song mostly in my mind in addition to relieving pain in my spine. It is very useful for increased pain that is caused by stress"	Relaxed
"The Panther" Manu Dibango	"I listen to this song when I am running either at the gym or outside and I start to feel increased pain"	No memories	"I visualize myself running faster and farther down a road"	Energetic	"I feel this song throughout my entire body"	"This song makes me feel stronger and more energetic and helps me to run through the pain"

(Continued)

TABLE 1 (Continued)

Music that relieves pain						
"Piece" Musician or band	Context in which the piece is listened	Memories (if any) this piece brings to mind	Visuals this piece brings to mind	Feelings this piece causes	Part of the body in which this piece is perceived (in addition to relieving pain in the lower spine and hips)	How this piece makes the body feel
"Ave Maria" Schubert Ave Maria with Renee Fleming	"This song is particularly helpful for increased pain from stress such as when stressed out in crowded stores, waiting in long lines or stress at work. I also use this song when I have to lie in a fetal position when pain is the worst for any reason -either increased pain from mechanical issues or stress"	"Visiting the Sistine Chapel and the Colosseum in the Vatican City and Rome"	"The Sistine Chapel, high, vaulted cathedral ceilings, the interior of the church I attended as a child; it was a beautiful church but the memories are not so great so I do not think of those"	"The sensation of being connected to the universe and the energy of all things, past, present and future"	"I can feel the singing along my vertebrae and hip bones gently pulling the pain out"	"Soothed, and releases pressure in my lower spine. It also makes my body feel like it is floating"
"The flower duet" Charlotte Church	"This song is also particularly helpful for increased pain from stress such as when stressed out in crowded stores, waiting in long lines or stress at work. I also use this song when I have to lie in a fetal position when pain is the worst for any reason -either increased pain from mechanical issues or stress"	No memories	"No visuals really, my mind is absorbed in the music"	Peace, calmness, optimism, and hope	"I feel it rolling throughout my inner body"	Weightless, gliding, and soothed
"Maybe tomorrow" Stereophonics	"This song works best for pain due to stress"	"Hitchhiking across the United States, being on the open road, traveling"	"Driving down an open road along the ocean coastline in a convertible, or being on the open road"	Freedom, happiness, serenity, optimism	Chest/Heart	"Releases stress and tension in my entire body. The vocals and the beat are soothing to me"

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TABLE 2 List of musical pieces that most cause pain to the participant and associated experiences.

Music that relieves pain						
Piece musician or band	Context in which the piece is listened	Memories (if any) this piece brings to mind	Visuals this piece brings to mind	Feelings this piece causes	Part of the body in which this piece is causes pain (in addition to lower spine and hips)	How this piece makes the body feel
"The Bigger Picture" Lil Baby	"Do not listen to this song as it causes me pain"	"This song reminds me of when my daughter was brutalized by a South Burlington, Vermont police officer for what is called in the Black community—"The crime of driving while Black" or more commonly known as "DWB". It also reminds me of how every time my son is out driving whether he will make it home safely. Having to give your children talks on how to remain safe around police because they are Black runs deep in how you see certain aspects of this society and is stressful. It also reminds me of how the University of Vermont police would pull us over if my son was in my car just to run our IDs"	"The day my daughter was brutalized by a South Burlington cop and how I had to be pulled out of the hospital trying to stop them from doing more harm at the request of the officer" "Getting pulled over by the Jersey police every time we took the Jersey Turnpike to visit my friend's mother in New York City. It got so bad that if he was driving I would lay down in the seat so I could not be seen while on the Turnpike or he would if I was driving" "Seeing a Chicago cop beat a small child in the back of a police car"	Anger, Outrage, Profound sadness	"Primarily in my chest as well as lower spine"	"Tense and heavy pressure on my chest"

(Continued)

TABLE 2 (Continued)

Music that relieves pain						
Piece musician or band	Context in which the piece is listened	Memories (if any) this piece brings to mind	Visuals this piece brings to mind	Feelings this piece causes	Part of the body in which this piece is causes pain (in addition to lower spine and hips)	How this piece makes the body feel
"Shelter" Vic Mensa, Wyclef Jean, Chance the Rapper	"Do not listen to this as it causes me pain"	Living in the projects in Chicago with my children where there were shootings every day and gang fights. Children had been shot and died right in front of my building. The police only came to our neighborhood to hunt and for target practice and no ambulance would come either" "Remembering how my daughter's school bus went right through the Cabrini Green high rises where there were snipers on the rooftops and how when my neighbor stood up against the Latin Kings they came and shot him and his son"	"My old neighborhood in Chicago"	"Profound sadness and anger about the way things are"	"Throughout my body in addition to my lower spine"	Heaviness, Physical exhaustion, Pain
"Unaccompanied Cello Suite No 1 in G Major" Yo-Yo Ma	"Do not listen to this as it causes me pain"	No memories	"Nails down a chalkboard"	"The scratchiness of the strings makes my skin crawl"	"The back of my neck, jaw and all the way down my spine"	"Tightness, clenching of jaw, uncomfortable to my ears"

(Continued)

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TABLE 2 (Continued)

Music that relieves pain						
Piece musician or band	Context in which the piece is listened	Memories (if any) this piece brings to mind	Visuals this piece brings to mind	Feelings this piece causes	Part of the body in which this piece is causes pain (in addition to lower spine and hips)	How this piece makes the body feel
"Overture from the marriage of Figaro" Mozart	"Do not listen to this as it causes me pain"	No memories	No visuals	"The quick build ups, then crashing loudly and at other times the build up and left hanging of the instruments along with the overall aggressiveness of the piece is stressful, too aggressive and too busy. It also has too many short musical phrases that go nowhere other than to connect to another, but different, phrase, the discontinuity is disorienting and stressful"	"In addition to my lower spine, it gives me a headache. It also bothers my eyes a great deal. When I am listening to music while relaxing I usually close my eyes to focus solely on the music, this piece makes me feel like my eyes are rolling around in their sockets"	Nauseated
"Houses of the Holy" Led Zeppelin	"No longer listen to this particular song by Led Zeppelin as it causes pain"	"Keg parties in high school"	No visuals	"The slightly discordant repeated guitar riffs hurt my ears and cause tension to the point it makes me tighten up my shoulders. The high pitched somewhat screeching vocals later in the song do the same"	"It hurts my ears in addition to my lower spine"	Tension

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its projections toward cortical and subcortical regions, such as the orbitofrontal cortex or the amygdala, which allow acoustic analyses of pitches, tones, rhythms, intensity, and roughness, as well as feelings and contexts (Boso et al., 2006). Thus, analgesia may involve expectations, attention, contexts, and moods that define the relief experience (Bingel and Tracey, 2008). That is why knowing the history of the person is crucial to know musical effects. Our participant's musical training feasibly influenced her ability to transfer auditory emotional experiences to other sensory modalities experiences (e.g., visual or tactile), as it is observed in trained musicians (Logeswaran and Bhattacharya, 2009). Moreover, it may have influenced her intuition to use music to relieve opioid withdrawal, to identify pieces with certain harmonies, pitches, tones, and rhythms that relieve pain, to appreciate music in a more emotionally and cognitively sophisticated way, and to avoid discordant pieces provoking her pain and evoking stressful situations (e.g., on social injustice).

In addition to positive feelings, improvements in physiological and cognitive aspects were mentioned. At this moment, the participant's sleep is perceived as continuous and restorative. It has been suggested that certain music favors the synchronization of biological rhythms with the beat structures in music and this produces relaxation and allows attention to be focused on synchrony but not on the stressful situation (Dickson and Schubert, 2019). Sleep is essential for proper endocrine and immune function, cognitive restoration, and memory consolidation (Zarcone, 2000; Stepanski and Wyatt, 2003). Therefore, better sleep may have provided the participant with general wellbeing and improved cognitive and motor performance during the day. The music chosen by the participant may also influence this improvement since listening to music perceived as pleasant perhaps modulates long-term episodic memory and enables memory formation and retrieval (Eschrich et al., 2008). Perhaps, associative learning on non-painful experiences in everyday life is present.

An interesting effect was the improvement of communication skills. Socialization implies a rewarding dynamic in itself (Berridge and Kringelbach, 2008). Meanwhile, music is suggested to be closely related to social perception and reward (Savage et al., 2020). Social rewarding may contribute to building spaces in which the participant expresses her pain with less stigma (Miglio and Stanier, 2022) and reinforces her learning of new experiences. In addition, some alternative practices performed by the participant may contribute to increasing the effects of music. Though there are a few studies on Reiki and its mechanisms are unknown, it has been increasingly used for pain and anxiety relief (Billot et al., 2019). Some acupuncture techniques have been reported to induce analgesia and to reduce the use of opioids for pain relief (Akça and Sessler, 2002). Meditation induces alleviation in chronic pain patients and helps reduce cravings. It elicits neural activation associated with maintaining attention and controlling bottom–up processes (Lee et al., 2012), so that it may contribute to reducing pain-related psychological effects and sympathetic reactivity related to anxiety and depression. In addition, meditation improves sleep quality, increases positive effect, and increases parasympathetic activation through relaxation and the cultivation of metacognitive resources, such as acceptance, resulting in perceptual distance from painful and distressing sensory and psychological stimuli (Britton et al., 2010; Amutio et al., 2018).

Across the interviews, the patient stated the use of music for different aspects of their ailment: for pain and anxiety relief, for exercise motivation, and for sleep quality, yet they all seem to revolve around different strategies for pain management and overall wellbeing. The fact that she mentioned that meditation was not possible before the therapeutic use of music suggests that music could also be used as a first approach to other aspects of the pain treatment like exercise or meditation.

Our participant's experience illustrates the complexity of pain that encompasses physiological, cognitive, and social spheres shaping the history and subjectivity of the person experiencing pain. The understanding of the effects of music to relieve pain and its neurobiological mechanisms must consider that history and subjectivity. For this, therapeutic accompaniment may be useful.

The accompanier constitutes a mediating figure between the patient and the institution. Originally proposed for psychiatric institutions with outpatient treatment, the accompanier performances as a health and psychosocial daily life monitor that allows the patient to reorient her/his subjectivity and to follow her/his experiences during the treatment. Moreover, it helps to communicate the experiences and systematize them for the better understanding of both, the patient, and the medical institution to design more sensitive treatments and research (Watkins, 2015; Rodríguez et al., 2019). In psychiatric patients, the accompaniment has revealed that music favors the reconstruction of identities, social integration, self-esteem, anxiety reduction, and motor performances (Andrade and Pedrão, 2005), as shown by our participant when expressing her experience in current physical activities. When reviewing her experience at the end of the interviews, the participant told the researchers her concern about what would happen if she stopped listening to music: *Would the effects on pain be lost? Would I feel pain all the time again?* There was no information in this regard to give the patient an accurate answer, but therapeutic accompaniment would help to reduce her anxiety in this regard and, perhaps, to gradually interrupt listening to music all the time to assess the durability of its effects. Therapeutic accompaniment is particularly relevant to the phenomenological method used in this study. The clinical instruments to assess pain expressions are limited and mostly made through scales and measures based on retrospective information. Subjective retrospective scales frequently coincide with other clinical or physiological measures, but as widely discussed by Miglio and Stanier (2022) on pain, and Copoeru (2014) on addiction, they displace the patient's story. Thus, the qualitative dimension that phenomenology provides about the entire patient experience complements retrospective limitations by providing imagination and metaphors used by the patient to conceptualize, represent, and express pain. The phenomenological information can be supplemented by the patient's clinical history to provide greater precision about their treatment experience over time.

In our opinion, the patient's analgesia seems to stem from multiple causes and mechanisms. For her, music appears to be the first and the strongest form of analgesia in addition to medication. Without the side effects of opioid medication and maintained analgesia with the music, this seemed to have opened possibilities for the patient to engage in other activities that are known to reduce pain such as exercise (Lesnak and Sluka, 2020) and meditation. The feeling of self-control over her body and pain may have further increased her pain threshold (Tracey, 2010), and the reduction of depression and anxiety symptoms together increased her quality of life.

Abruptly stopping opioid medication is not advised due to the potentially unbearable opioid withdrawal symptoms ranging from 7 to 14 days, depending on the medication. Although research shows symptoms are not life-threatening, there is a risk of relapse and binging, which can be life-threatening (Pergolizzi et al., 2020). We suggest that patients wanting to try listening to music as an add-on treatment and reduce opioid medication ask their physician to down-titrate (slowly lower) medication to avoid or reduce withdrawal effects. We also suggest to remember that not everyone may benefit from music and more research is needed.

In conclusion, here we showed the case of a patient with chronic pain who reported to stop the use of opioid medication and changed to music listening as her main analgesic intervention, which allowed her to further engage in exercise, meditation, and other activities. Her case suggests there may be individuals with chronic pain who may greatly benefit from music-induced analgesia and that it may be possible to use music to reduce any type of pain medication. Cognitive and emotional mechanisms of analgesia seem to be present in our patients, with the implication of the descending pain modulatory pathway. Scientific studies of music-induced analgesia focus on average or group results; however, we believe that single case studies and interviews could help fill in gaps of knowledge that may not otherwise be possible with group studies. Ideally, future studies should consider both strategies as complementary and perhaps describe quantitative and qualitative results for a more integral report. Physicians should also study how music may reduce pain medication, with the future goal of a more integral treatment. There are still more questions than answers; however, with the help of patients like her, we may further understand chronic pain and music-induced analgesia.

5. Patient perspective

The participant provided her signed informed consent after the nature of the study was explained. She reviewed the draft of the manuscript to verify the proper comprehension of her communicated experience and to remove personal or institutional information she did not agree to present. The manuscript was submitted to be published just after her approval. In her own words: "*I have completed reviewing the article, it is wonderful! I wish there was a definitive mechanism for how music is working for me but I will remain overjoyed that it does in fact work for me and leave those mysteries of the mechanism to future research. Your analysis is very informative and I greatly appreciate this opportunity as it is not only an opportunity to assist others possibly but also to help further describe and inform my experiences using music.*"

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Bioethics Committee of the Institute of Neurobiology of the Universidad Nacional Autónoma de México. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

EG-V developed the study concept and was contacted by the patient. RM performed the interviews. EG-V and RM analyzed and interpreted the interviews, drafted the manuscript, and approved the final version for submission.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2023.1141829/full#supplementary-material

References

Akça, O., and Sessler, D. I. (2002). Acupuncture. A useful complement of anesthesia? *Minerva Anestesiol.* 68, 147–151.

American Psychological Association (2002). Ethical principles of psychologist and code of conduct. *Am. Psychol.* 57, 1060–1073. doi: 10.1037/0003-066X.57.12.1060

Amutio, A., Franco, C., Sánchez-Sánchez, L. C., Pérez-Fuentes, M., Gázquez-Linares, J. J., van Gordon, W., et al. (2018). Effects of mindfulness training on sleep problems in patients with fibromyalgia. *Front. Psychol.* 9:1365. doi: 10.3389/fpsyg.2018.01365

Andrade, R. L., and Pedrão, L. J. (2005). Algumas considerações sobre a utilização de modalidades terapêuticas não tradicionais pelo enfermeiro na assistência de enfermagem. *Rev. Lat. Am. Enfermagem* 13, 737–742. doi: 10.1590/s0104-11692005000500019

Berridge, K. C., and Kringelbach, M. L. (2008). Affective neuroscience of pleasure: reward in humans and animals. *Psychopharmacology* 199, 457–480. doi: 10.1007/s00213-008-1099-6

Billot, M., Daycard, M., Wood, C., and Tchalla, A. (2019). Reiki therapy for pain, anxiety and quality of life. *BMJ Support. Palliat. Care* 9, bmjspcare-2019-001775–bmjspcare-2019-001438. doi: 10.1136/bmjspcare-2019-001775

Bingel, U., and Tracey, I. (2008). Imaging CNS modulation of pain in humans. *Physiology (Bethesda)* 23, 371–380. doi: 10.1152/physiol.00024.2008

Boso, M., Politi, P., Barale, F., and Enzo, E. (2006). Neurophysiology and neurobiology of the musical experience. *Funct. Neurol.* 21, 187–191.

Britton, W. B., Bootzin, R. R., Cousins, J. C., Hasler, B. P., Peck, T., and Shapiro, S. L. (2010). The contribution of mindfulness practice to a multicomponent behavioral sleep intervention following substance abuse treatment in adolescents: a treatment-development study. *Subst. Abus.* 31, 86–97. doi: 10.1080/08897071003641297

Cochrane Drugs and Alcohol GroupGhetti, C., Chen, X. J., Brenner, A. K., Hakvoort, L. G., Lien, L., et al. (2022). Music therapy for people with substance use disorders. *Cochrane Database Syst. Rev.* 2022:CD012576. doi: 10.1002/14651858.CD012576.pub3

Copoeru, I. (2014). Understanding addiction: a threefold phenomenological approach. *Hum. Stud.* 37, 335–349. doi: 10.1007/s10746-013-9307-8

Díaz, J.L. (2022). *El Enredo Mente-Cuerpo*. Ciudad de México: Herder

Dickson, G. T., and Schubert, E. (2019). How does music aid sleep? Literature review. *Sleep Med.* 63, 142–150. doi: 10.1016/j.sleep.2019.05.016

Eschrich, S., Münte, T. F., and Altenmüller, E. O. (2008). Unforgettable film music: the role of emotion in episodic long-term memory for music. *BMC Neurosci.* 9:48. doi: 10.1186/1471-2202-9-48

Garza-Villarreal, E. A., Pando, V., Vuust, P., and Parsons, C. (2017). Music-induced analgesia in chronic pain conditions: a systematic review and meta-analysis. *Pain Physician* 20, 597–610. doi: 10.36076/ppj/2017.7.597

Garza-Villarreal, E. A., Wilson, A. D., Vase, L., Brattico, E., Barrios, F. A., Jensen, T. S., et al. (2014). Music reduces pain and increases functional mobility in fibromyalgia. *Front. Psychol.* 5:90. doi: 10.3389/fpsyg.2014.00090

Guétin, S., Coudeyre, E., Picot, M. C., Ginies, P., Graber-Duvernay, B., Ratsimba, D., et al. (2005). Intérêt de la musicothérapie dans la prise en charge de la lombalgie chronique en milieu hospitalier (Étude contrôlée, randomisée sur 65 patients). *Ann. Med. Phys.* 48, 217–224. doi: 10.1016/j.annrmp.2005.02.003

Kavak Akelma, F., Altınsoy, S., Arslan, M. T., and Ergil, J. (2020). Effect of favorite music on postoperative anxiety and pain. *Anaesthesist* 69, 198–204. doi: 10.1007/s00101-020-00731-8

Lee, T. M. C., Leung, M. K., Hou, W. K., Tang, J. C. Y., Yin, J., So, K. F., et al. (2012). Distinct neural activity associated with focused-attention meditation and loving-kindness meditation. *PLoS One* 7:e40054. doi: 10.1371/journal.pone.0040054

Lesnak, J. B., and Sluka, K. A. (2020). Mechanism of exercise-induced analgesia: what we can learn from physically active animals. *Pain Rep.* 5:e850. doi: 10.1097/PR9.0000000000000850

Li, X. M., Yan, H., Zhou, K. N., Dang, S. N., Wang, D. L., and Zhang, Y. P. (2011). Effects of music therapy on pain among female breast cancer patients after radical mastectomy: results from a randomized controlled trial. *Breast Cancer Res. Treat.* 128, 411–419. doi: 10.1007/s10549-011-1533-z

Logeswaran, N., and Bhattacharya, J. (2009). Crossmodal transfer of emotion by music. *Neurosci. Lett.* 455, 129–133. doi: 10.1016/j.neulet.2009.03.044

Lunde, S. J., Vuust, P., Garza-Villarreal, E. A., Kirsch, I., Møller, A., and Vase, L. (2022). Music-induced analgesia in healthy participants is associated with expected pain levels but not opioid or dopamine-dependent mechanisms. *Front. Pain Res.* 3:734999. doi: 10.3389/fpain.2022.734999

Lunde, S. J., Vuust, P., Garza-Villarreal, E. A., and Vase, L. (2019). Music-induced analgesia: how does music relieve pain? *Pain* 160, 989–993. doi: 10.1097/j.pain.0000000000001452

Mays, K. L., Clark, D. L., and Gordon, A. J. (2008). Treating addiction with tunes: a systematic review of music therapy for the treatment of patients with addictions. *Subst. Abus.* 29, 51–59. doi: 10.1080/08897070802418485

Miglio, N., and Stanier, J. (2022). Beyond pain scales: a critical phenomenology of the expression of pain. *Front. Pain Res.* 3:895443. doi: 10.3389/fpain.2022.895443

Pergolizzi, J. V. Jr., Raffa, R. B., and Rosenblatt, M. H. (2020). Opioid withdrawal symptoms, a consequence of chronic opioid use and opioid use disorder: current understanding and approaches to management. *J. Clin. Pharm. Ther.* 45, 892–903. doi: 10.1111/jcpt.13114

Rodríguez, J. M., Rossi, G., and Díaz-Quiroz, A. (2019). Une invention propre à l'Amérique latine: l'accompagnant thérapeutique. *Inf. Psychiatr.* 95, 731–736. doi: 10.1684/ipe.2019.2023

Rosenkjær, S., Lunde, S. J., Kirsch, I., and Vase, L. (2022). Expectations: how and when do they contribute to placebo analgesia? *Front. Res. Found.* 13:817179. doi: 10.3389/fpsyt.2022.817179

Roy, M., Peretz, I., and Rainville, P. (2008). Emotional valence contributes to music-induced analgesia. *Pain* 134, 140–147. doi: 10.1016/j.pain.2007.04.003

Salimpoor, V. N., Benovoy, M., Larcher, K., Dagher, A., and Zatorre, R. J. (2011). Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nat. Neurosci.* 14, 257–262. doi: 10.1038/nn.2726

Savage, P. E., Loui, P., Tarr, B., Schachner, A., and Glowacki, L. (2020). Music as a coevolved system for social bonding. *Behav. Brain Sci.* 44:e59. doi: 10.1017/S0140525X20000333

Shih-Tzu, H., Good, M., and Zauszniewski, J. A. (2010). The effectiveness of music in relieving pain in cancer patients: a randomized controlled trial. *Int. J. Nurs. Stud.* 47, 1354–1362. doi: 10.1016/j.ijnurstu.2010.03.008

Stepanski, E. J., and Wyatt, J. K. (2003). Use of sleep hygiene in the treatment of insomnia. *Sleep Med. Rev.* 7, 215–225. doi: 10.1053/smrv.2001.0246

Tracey, I. (2010). Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. *Nat. Med.* 16, 1277–1283. doi: 10.1038/nm.2229

van den Bosch, I., Salimpoor, V. N., and Zatorre, R. J. (2013). Familiarity mediates the relationship between emotional arousal and pleasure during music listening. *Front. Hum. Neurosci.* 7:534. doi: 10.3389/fnhum.2013.00534

Varela, F., Thompson, E., and Rosch, E. (1991). *The Embodied Mind: Cognitive Science and Human Experience*. Cambridge: MIT Press

Veehof, L. J., Stewart, R. E., Meyboom-de Jong, B., and Haaijer-Ruskamp, F. M. (1999). Adverse drug reactions and polypharmacy in the elderly in general practice. *Eur. J. Clin. Pharmacol.* 55, 533–536. doi: 10.1007/s002280050669

Watkins, M. (2015). *J. Soc. Politic. Psychol.* 3, 324–341. doi: 10.5964/jspp.v3i1.103

Zarcone, V. P. (2000). "Sleep hygiene" in *Principles and Practice of Sleep Medicine*. eds. M. H. Kryger, T. Roth and W. C. Dement. *3rd* ed (Philadelphia: Saunders), 657–661.

Zhou, W., Ye, C., Wang, H., Mao, Y., Zhang, W., Liu, A., et al. (2022). Sound induces analgesia through corticothalamic circuits. *Science* 377, 198–204. doi: 10.1126/science.abn4663

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Emotional responses to favorite and relaxing music predict music-induced hypoalgesia

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Introduction: The hypoalgesic effect of music has long been established. However, the characteristics of music which are important for reducing pain have not been well-studied. Some research has compared subject-selected preferred music to unfamiliar music selected by researchers, and has typically found a superior effect from preferred music. In this study, we sought to discover what aspects of listeners' relationship with their preferred music was important in producing a hypoalgesic effect.
Methods: We conducted a thermal pain and music listening experiment with 63 participants (14 male, 49 female, mean age = 21.3), in which music excerpts were paired with thermal stimulations. Pain ratings of intensity and unpleasantness, as well as emotional response variables, were rated on visual analog scales. We also conducted brief structured interviews about participants' favorite music, on which we conducted thematic content analysis. Themes and emotion variables were analyzed for their effects on pain ratings.
Results: We first replicated the finding that favorite music outperforms experimenter-selected relaxing music in reducing pain unpleasantness (MD = −7.25, $p < 0.001$) and that the difference in hypoalgesia was partially mediated by an increase in musical chills (ab = −2.83, $p < 0.01$). We then conducted a theme analysis on the interview transcripts and produced four themes relating to emotional experience: *moving/bittersweet, calming/relaxing, happy/cheerful,* and *energizing/activating*. We found suggestive evidence that moving/bittersweet favorite music reduces pain unpleasantness through increased music pleasantness (ab = −5.48, $p < 0.001$) and more musical chills (ab = −0.57, $p = 0.004$).
Discussion: We find that music pleasantness and musical chills are salient predictors of music-induced hypoalgesia, and that different categories of favorite music derived from qualitative analysis may engage these emotional pathways to different degrees.

KEYWORDS
music, pain, emotion, theme analysis, hypoalgesia

1. Introduction

Music has been used to relieve pain for centuries, and in modern times, it has been found to reduce pain and anxiety in patients, as well as the need for medication (1–4). However, the mechanisms by which music reduces pain are not well understood (5). Some studies have indicated that subject-selected preferred music is more effective in reducing pain than experimenter-selected music (6, 7), but the structure of music preference and its contribution to pain relief have not been thoroughly examined.

Pain is a significant societal and individual burden, and there is a need for alternative ways to relieve it without over-reliance on pharmacological analgesics, which may produce side effects and dependencies (8–10). Music may be a viable non-pharmacological intervention for those undergoing surgery, surgical recovery, or with chronic pain conditions (11). To optimize music selection strategies for pain relief, research needs to identify the specific music attributes or emotional responses responsible for music-induced hypoalgesia.

One variety of music that is intuitively chosen in many experimental and clinical settings is relaxing music (6, 12, 13), but the effect of the level of relaxation in music on pain has not been systematically tested. Preliminary evidence suggests that relaxing music is better than stimulating music at relieving pain (7), but the low power in that study demands further investigation. One example of relaxing music that is already in use in clinical contexts is specially-composed relaxing music with a U- or L-shape of arousal, such as music produced by the MUSIC CARE app (12, 13). These instrumental tracks are composed in a variety of styles and genres, but possess a characteristic shape of arousal and tempo, where the tracks begin with a higher speed and energy before attempting to induce a state of deeper relaxation by transitioning to a slow, low-energy stage.

Some evidence suggests that subject-selected preferred music has a superior effect on pain relief regardless of the level of arousal in the music. Roy et al. (14) showed that for an equivalent level of arousal, pleasant consonant music reduced pain, while unpleasant dissonant music did not. In another experiment, Mitchell and McDonald (6) compared the effects of experimenter-selected relaxing music and subjects' preferred music on a cold pressor task. They found that only preferred music was able to reduce the intensity of pain, suggesting that relaxation in music might not be sufficient for hypoalgesia. Thus, in this study, we wanted to more deeply investigate the contribution of preference and emotion to music-induced hypoalgesia.

However, there are several ways of approaching music preference when selecting music for a pain relief study. One approach would be to present participants with several options of songs, of which they can choose the most pleasant (15). Another method is to allow participants to bring their all-time favorite music to the study, which incorporates additional aspects of preference such as familiarity, episodic memory associations, and individualized semantic meaning (16). More recent brain imaging studies (17) have opted to do this to ensure the most robust activation of brain structures related to processing music-related reward. However, the richness of different emotions, associations, and meanings that are involved in the experience of listening to one's favorite music has not been well-studied, particularly in the context of pain relief.

In this study, we sought to discover which aspects of the subjective experience of listening to favorite and relaxing music were particularly important for producing a hypoalgesic effect. We used a hybrid approach to this question, using a combination of qualitative and quantitative analyses. We invited 63 participants to come to the Roy pain laboratory on McGill campus to listen to relaxing and favorite music, as well as scrambled and silent controls, while receiving thermal stimulations. On the qualitative side, we conducted brief structured interviews with participants about their favorite songs and conducted a theme analysis (18) to categorize the content of these interviews. Four themes related to categories of emotional experience: *happy/cheerful, calming/relaxing, energizing/activating, and moving/bittersweet*. On the quantitative side, we examined the effects of several emotion variables on reducing pain, including music pleasantness, emotional arousal, and the incidence of "chills, thrills, or frissons", and whether these could explain differences in pain ratings between favorite and relaxing music, and differences in hypoalgesia associated with emotional themes.

2. Materials and methods

2.1. Participants

63 healthy participants were recruited for this study (14 male, 49 female; mean age = 21.3, SD = 2.1) (see **Table 1**). Participants were recruited through advertisements posted on Facebook and through an extra credit system in the McGill department of Psychology. Criteria for exclusion from the studies included a history or current diagnosis of neurological or psychiatric disorder, diagnosis of chronic pain syndrome or neuropathy, history of alcohol or substance abuse, and regular (>2 weekly) use of analgesics, anticonvulsants, narcotics, antidepressants, and anxiolytics. Participants received either monetary compensation or course credits for their time. Informed consent was obtained from all participants and the study was approved by the McGill University Research Ethics Board.

2.2. Stimuli

2.2.1. Thermal stimuli

Painful thermal stimuli were induced by applying a 9 cm^2 thermal contact probe (TSA-II Neurosensory Analyzer, Medoc LTD. Advanced Medical Systems, Israel) to the surface of the left inner forearm. This device has a 3 × 3 cm head which can output and maintain temperatures accurate to one decimal place. The sensation induced by the probe may be compared to a hot cup of coffee held against the skin. At the temperatures (<49.5°C) and time durations (10 s at plateau) at which this was done, there was no risk of physical harm to participants. The stimulations alternated between four different locations on the inner arm, where the ordering of locations was pseudo-random, with no stimulation of the same spot twice in a row.

2.2.2. Music

Music tracks for the active conditions were obtained in the following ways: (1) The participant's favorite music was selected

TABLE 1 Age and gender properties of the study sample.

	N	Mean	Median	SD
Male	14	22.3	22	1.84
Female	49	21.0	21	2.04
Total	63	21.3	21	2.07

by the participants themselves, and could come from any source, with the only requirement being that they were at least 3 min and 20 s in length. Participants were asked to select two tracks that represented "their favorite music of all time", and "the songs that they would bring with them to a desert island"; (2) The relaxing tracks were provided by the MUSIC CARE company (12) and cut to a length of 6 m 40 s, which contained a transition from a medium level of arousal to a low level of arousal ("L-shape" of arousal). Before the main procedure, participants could select between 7 tracks and could listen to 20-s samples to help them make their decision. The tracks included were "Cotton Blues", "Jamaicare", "Légende Celtique", "Musique de Film", "Nuit Cubaine", "Reggae Calédonien", and "Sega Mizik Kèr".

2.2.3. Controls

Scrambled controls for preferred music and relaxing tracks were produced by applying a scrambling algorithm to the tracks in the active conditions. The algorithm consisted of cutting the tracks into 500 ms fragments which were then randomly shuffled, with a 100 ms crossfade applied between them. This condition was intended to control for general acoustic properties of music (e.g., loudness, frequency spectrum) while lacking the musical structure of the original tracks. Silent trials were also used as a control condition for music. They were held for the same length of time as the music trials, and participants were asked to maintain their focus on the computer monitor during silent trials.

2.3. Procedure

The experiment consisted of pairing painful thermal simulations with music excerpts. Before beginning the main procedure, a sensory calibration procedure was conducted to estimate an appropriate stimulation temperature for each participant, corresponding to a rating of 50 on a 100-point scale (0 = "Not painful at all", 100 = "Extremely painful"). The calibration consisted of seven temperatures between 40°C and 49°C applied to each of four locations along the left inner forearm. For each stimulation, heat was applied for 15 s, with a 2.5-s rise and fall from a 32°C baseline and a 10-s plateau. After each stimulation, participants rated whether the stimulus was felt as (1) painful, or (2) warm, but not painful. If the stimulation was reported as painful, participants rated the intensity and unpleasantness of the pain on a 100-point visual analog scale. A generalized linear regression model was fitted to the calibration data in order to estimate a temperature corresponding to a pain rating of 50 out of 100, which was used for every stimulation of the main procedure.

The main music listening task consisted of a series of approximately 7-min blocks (Figure 1). Each block represented a different condition. These were (1) Participant-selected favorite music, (2) Relaxing instrumental tracks, (3, 4) Scrambled versions of the favorite and relaxing music, and (5) silence[1]. The favorite music condition consisted of two songs played sequentially, each cut to a duration of 3 m20 s; the relaxing tracks, being longer, consisted of one track of 6 m 40 s. The order of conditions was randomized. For the task, participants wore a pair of high-quality, over-ear headphones (Audio Technica ATH-M50) and fixed their gaze on a point in the center of the monitor. Within each block, there were eight 50-s cycles of music and stimulation. The music, scrambled music, or silence was played alone for 35 s before the thermal stimulation was added for the final 15 s (2.5 s ramp-up and ramp-down with a 10-s plateau). After each stimulation, participants had 15 s to rate the intensity and unpleasantness of the pain they experienced, during which time the music continued uninterrupted. At the end of each track, participants rated the music's pleasantness, their emotional arousal, and the number of chills they experienced.

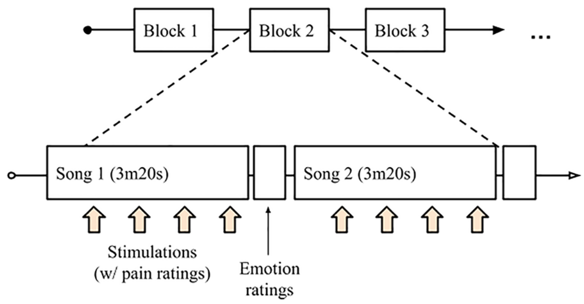

FIGURE 1
Structure of a block/condition. For favorite music and scrambled favorite music, two tracks of 3 m20 s were played; for MusicCare and scrambled MusicCare tracks, one longer track of 6 m40 s was played.

2.4. Measures

Quantitative variables were collected using visual analog scales (VAS) presented on a computer monitor, with anchors varying according to the variable measured. For pain, we collected two measures: (1) Pain intensity, representing the sensory dimension of pain, and (2) Pain unpleasantness, representing the affective dimension. A 0–100-point scale was used, with zero representing, e.g., "Not intense/unpleasant at all" and 100 representing "Extremely intense/unpleasant".

Similarly, we collected measures of music pleasantness, emotional arousal, and the incidence of "chills, thrills, or frissons". Music pleasantness was rated along a bipolar VAS, with −5 = "Extremely unpleasant", zero = "Neither pleasant nor unpleasant", and 5 = "Extremely pleasant". Emotional arousal was rated along a unipolar scale with zero = "Not emotional arousing at all" and 10 = "Extremely emotionally arousing". Finally, chills were measured using a four-point scale, with zero = "No chills at all", 1 = "One or two chills", 2 = "Three or four chills", and 4 = "Five or more chills".

[1]Two additional conditions, consisting of unfamiliar popular music, were included to test a hypothesis relating to a separate study (Valevicius et al., in preparation), but are discarded from this analysis.

2.5. Interviews

Participants were asked a series of open-ended questions about the favorite songs that they selected for the study. These consisted of three questions, asked separately for each of the two songs they selected. To assist participants in forming their answers, the songs were played in the background of the interview at a low volume. The interview took place at the end of the session. The questions are as follows:

(1) Why is this your favorite song, or why did you choose to bring this song? What do you like most about it?
(2) What thoughts, feelings, or images do you experience when you listen to this song?
(3) When do you listen to this song, or when do you find yourself wanting to listen to it?

The first question aimed to tap into what made the song salient to the participant. The second question focused on the content of the participant's experience when listening to the song. Finally, the third question was meant to tap into the function of the song, by asking participants what situations prompted them to listen to it.

2.6. Quantitative analysis

Linear regression analyses were performed using multilevel regression models using the R statistical programming language (19) and the lme4 package (20). Significance values were computed using the lmerTest package (21). Subject was used as a grouping factor for the intercept and all random effects. For specifying the random effects structures, we used a "keep it maximal" approach (22), including in the models any random effect term that did not interfere with model convergence. Figures were constructed using the R packages ggplot2 (23), sjPlot (24), and ggpubr (25).

For each analysis where pain was a dependent variable, several sources of nuisance variance were identified *a priori* and modeled using simple variables: (1) The trial number and (2) the log transform of the trial number were used to model sensitization and habituation, and (3) the location of the stimulation on the arm was included to model differences in mean pain between locations. Trial and log (trial) were *z*-scored and included as fixed and random effects as far as possible, and armspot was included as a grouping factor within subject. The noise models accounted for 8%–10% of the variance in both pain intensity and unpleasantness, in addition to the 46% accounted for by subject intercepts.

For testing the effects of categorical variables such as music conditions or favorite music themes, we used a dummy coding scheme (26), with the category of interest coded as one and the reference variable(s) coded as zero, and variables not of interest coded as NaN and thus excluded from the model. For a two-condition comparison (e.g., favorite music compared to scrambled favorite music), this resulted in a sample size of $n = 980$ and an effective sample size of approximately $n = 128$ after accounting for within-subject clustering of observations. This effective sample size was calculated using the intraclass correlation (ICC) observed for pain unpleasantness, which was 0.46.

Mediation analyses were conducted using the mediate package (27) with a simulation number of 500. Due to constraints on using the mediation package with multilevel regression models, the noise models (trial, log of trial, and armspot) were excluded from the mediation modeling.

Finally, in instances in this article where regression coefficients were converted into a standardized mean difference (SMD) or standardized effect size (d), we divided the coefficient by the average within-subject standard deviation (SD) for either pain unpleasantness or intensity (28). This value was 14.2 for both pain intensity and unpleasantness. Since all predictors were either dummy-coded or normalized, their standard deviations do not have to be accounted for.

2.7. Qualitative analysis

The qualitative interviews on subject-selected preferred music were analyzed using the theme analysis framework (18). Theme analysis requires researchers to consider their assumptions about the nature of the phenomenon they are categorizing. For this analysis, especially pertaining to themes describing emotional and psychological processes, we assumed a shared contribution of neuro-psychological realism and social construction, i.e., We assumed that emotional categories are based on evolved brain structures and functions and represent natural kinds to a certain degree (29, 30). However, the conceptual boundaries, nomenclature, and even the experience of these emotions are also dependent on cognitive, cultural, and linguistic factors (31). Therefore, we took a categorical approach to defining emotion themes, but allowed the interviewees' language to influence our categorization scheme rather than relying on a pre-defined theory or set of basic emotions.

Four researchers conducted the theme analysis. The process of determining the themes and sub-themes was conducted in an iterative and collaborative manner. Before constructing a list of codes, the researchers explored and familiarized themselves with the data and discussed the assumptions and goals of the analysis. Each researcher was assigned one half of the data to create a list of codes and themes, which were then integrated into a final list of codes through a series of discussions and revisions. The transcripts were then annotated using the final code list.

2.7.1. Quantitative analysis of themes

Each theme was numerically coded into the data as either zero or one, representing its presence or absence in the interview response for that song. We examined whether the presence of absence of certain themes moderated the effect of preferred music on pain ratings. To do this, we added the dummy coded variables as covariates in a linear mixed model using only observations for the favorite music condition.

To attempt to give external validity to the emotion themes, we used a computational method for extracting musical features established by Fricke and colleagues (32, 33). This method uses

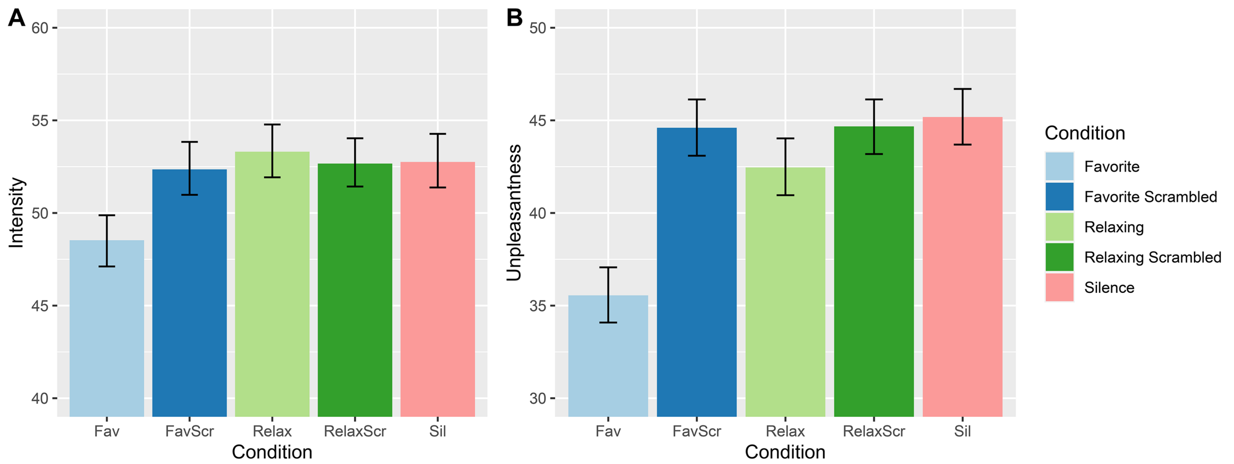

FIGURE 2
Means ratings of (A) pain intensity and (B) pain unpleasantness by condition, after controlling for between-subject mean pain ratings. Error bars = 95% CI.

the acoustic features of music and machine learning models to produce scores for different music dimensions, namely "arousal", a dimension of intensity or excitement, "valence", a dimension of happy to sad mood, and "depth", a dimension of cognitive and emotional complexity in music (33). The dimensions were extracted for all favorite music tracks and correlated with the presence or absence of emotion themes using a simple linear regression model, to see if the themes extracted by reading structured interviews could be correlated with features derived from the audio waveform of the songs.

Finally, we correlated the incidence of emotion themes with personality variables collected per participant using simple Pearson correlation. We administered a short form of the Big Five Inventory (34), the Five Factor Mindfulness scales (35), the Musical Engagement Test (36), and the Pain Catastrophizing Scale (37). The results of this analysis are given in **Supplementary Figure S1**.

3. Results

3.1. Comparisons of active conditions with their respective controls

We first examined whether the music condition could reduce pain intensity (INT) or pain unpleasantness (UNP) compared to their scrambled controls and silence (**Figure 2**). When compared to its scrambled control, favorite music reduced pain intensity (Mean Difference (MD) = −3.76, t (55.2) = −2.23, $p = 0.030$) and pain unpleasantness [MD = −9.05, t (57.9) = −4.62, $p < 0.001$], and also reduced pain when compared to silence (INT: MD = −5.14, t (155) = −3.71, $p < 0.001$; UNP: MD = −10.2, t (55.7) = −5.97, $p < 0.001$). Relaxing tracks did not significantly reduce pain intensity compared to their controls, however the effect on pain unpleasantness was trending towards significance when compared to scrambled music [MD = −2.51, t (55.4) = −1.34, $p = 0.19$] and silence [MD = −3.17, t (55.6) = −1.84, $p = 0.071$].

We also compared favorite and relaxing music to each other, and compared pain ratings between scrambled music and silence (**Figure 2**). We found that favorite music significantly reduced pain compared to relaxing tracks (INT: MD = −4.83, t (347) = −4.22, $p < 0.001$; UNP: MD = −7.25, t (53.8) = −4.81, $p < 0.001$). Meanwhile, none of the scrambled control conditions differed significantly from silence, with MDs under 0.7 and p-values above 0.6. The full results of the comparisons are given in **Supplementary Table S1**.

3.2. Effects of music pleasantness, emotional arousal, and chills

Figure 3 compares the mean values for music pleasantness, emotional arousal, and chills across the different conditions. As expected, music was perceived as being more pleasant and produced more chills compared to scrambled controls. Additionally, subject-selected favorite music had higher average ratings on all three measures compared to relaxing tracks.

In assessing the effects of music-related emotion variables on pain ratings (**Table 2**), we found that the amount of chills reported influenced both pain intensity [$B = -2.43$, t (485) = −2.88, $p < 0.01$] and pain unpleasantness [$B = -2.63$, t (618) = −3.05, $p < 0.01$]. Meanwhile, music pleasantness (a proxy for emotional valence) did not significantly influence pain intensity [$B = -2.40$, t (45.5) = −0.80, $p = 0.43$], but had a large effect on pain unpleasantness [$B = -8.74$, t (57.7.) = −2.39, $p = 0.02$]. Ratings of emotional arousal did not influence either pain intensity nor unpleasantness ($B < 0.4$, $p > 0.8$).

We therefore conducted three mediation models (**Figure 4A**) to determine whether the difference between favorite music and relaxing music could be explained by emotion variables. Model 1 and Model 2 tested whether chills could explain the difference in pain intensity and pain unpleasantness respectively. Model 3 tested whether music pleasantness could explain the difference in pain unpleasantness. For Model 1, we found a significant indirect effect

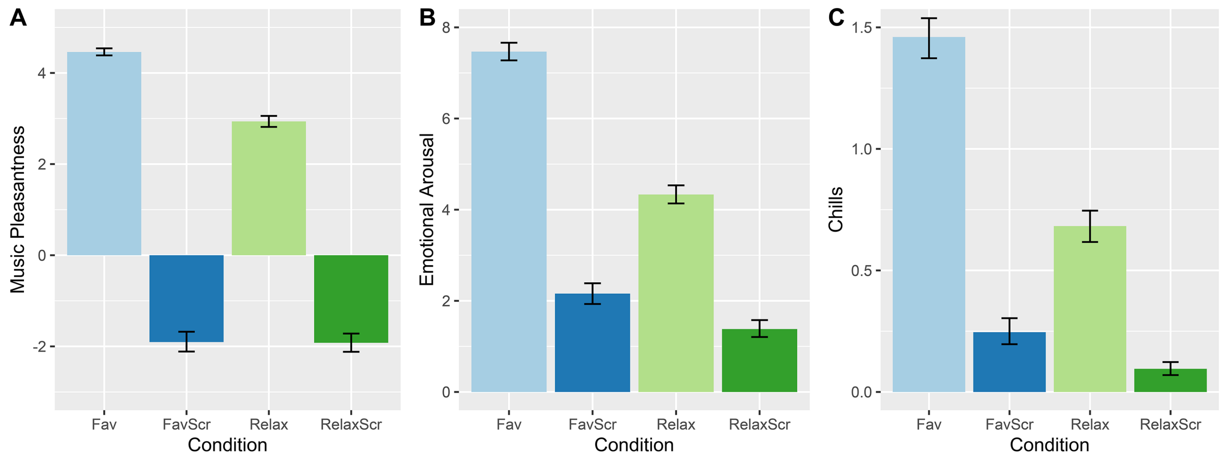

FIGURE 3
Mean ratings for (A) music pleasantness, (B) emotional arousal, and (C) chills across music and scrambled music conditions. See Methods (Section 2.4) for interpretation of y-axis values. Error bars = 95% CI.

TABLE 2 Effects of self-reported emotion variables on pain ratings.

Pain variable	Emotion variable	*B*	SE	df	*t*	*p*
Intensity	Music pleasantness	−2.40	3.00	45.5	−0.80	0.43
	Emotion arousal	−0.23	1.50	189.7	−0.16	0.88
	Chills	−2.43	0.84	485.5	−2.88	**0.0041**
Unpleasantness	Music pleasantness	−8.74	3.66	57.7	−2.39	**0.020**
	Emotion arousal	0.037	1.55	348.0	0.024	0.98
	Chills	−2.63	0.86	617.7	−3.051	**0.0024**

B, unstandardized beta, or points of pain on a 100-point scale per standard deviation change in the independent variable.
Bold indicates the significant p-value at $p < 0.05$.

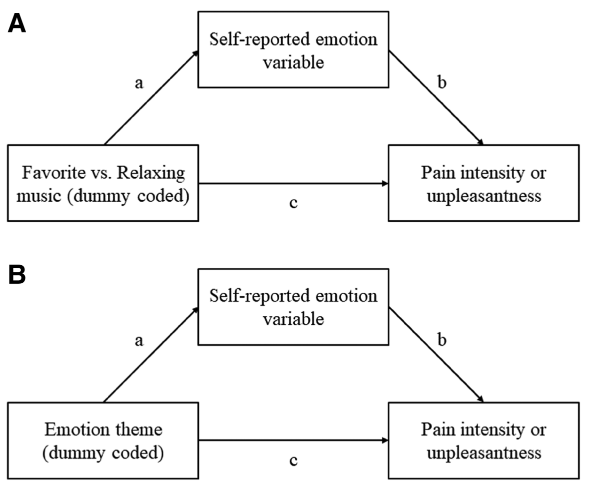

FIGURE 4
Mediation diagrams for analyzing (A) the difference between favorite and relaxing music, and (B) and the effects of emotion themes, using the three self-reported emotions variables as mediators: music pleasantness, emotional arousal, and chills.

on pain intensity through chills [ab = −2.63, 95% CI = (−5.23, −0.39), $p < 0.01$] with a proportion mediated of 0.59. For Model 2, we also found a significant indirect effect on pain unpleasantness via chills [ab = −2.83, 95% CI = (−5.14, −1.01), $p < 0.01$] with a proportion mediated of 0.48. Finally, in Model 3, we failed to find a significant indirect effect on pain unpleasantness via music pleasantness [ab = −1.74, 95% CI = (−6.07, 2.88), $p = 0.46$, prop. mediated = 0.36]. One caveat in this analysis is that chills and music pleasantness are collinear, and thus the individual effects may be smaller than if one variable is included as a lone covariate. However, even after removing chills as a covariate from Model 3, we did not observe a significant mediation effect, though the effect was closer to the threshold of significance ($p = 0.17$).

3.3. Qualitative analysis of favorite music interviews

Participants were asked three open-ended questions for each of the two favorite songs they selected for the experiment (see Methods). A thematic content analysis was carried out which revealed 17 themes: two were centered on musical aspects, four on associations (to memories, persons, or imagery), four represented emotional categories, three were related to activities (e.g., commutes, tasks, or leisure), and four described listening times (e.g., morning, evening). The full list is summarized in Supplementary Table S2.

The four emotion themes—energizing/activating, happy/cheerful, calming/relaxing, and moving/bittersweet—are the

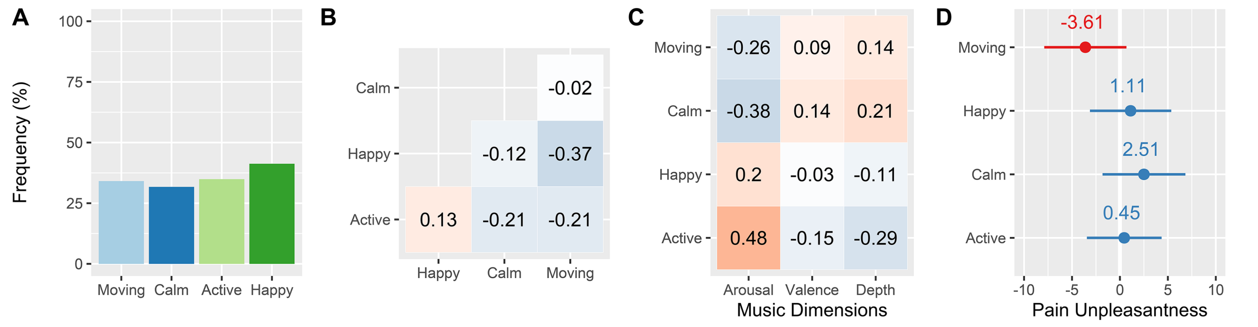

FIGURE 5
(A) Frequencies with which the emotion themes were reported in the study sample. (B) Intercorrelations between emotion themes. (C) Correlations between emotion themes and computer-extracted music dimensions. (D) Mean difference estimates of the pain-moderating effects of emotion themes. Error bars = 95% CI.

focus of this analysis, as they formed a conceptually unified set of emotional categories and displayed greater correlations with external variables (e.g., computer-rated music dimensions) than the other themes (Quantitative results for the full set of themes are available in **Supplementary Table S3**). They appeared in roughly equal proportion in the interview data (32%–41% of responses for each theme; see **Figure 4A**) and show relatively low collinearity (**Figure 5B**), which facilitated their interpretation. The emotion themes are as follows:

3.3.1. Energizing/activating

This theme encompasses descriptions of music such as "upbeat" (P02) and "pump-up" (P35). Participants mentioned that these songs gave them energy or raised their level of activation. For example, P05 mentioned wanting to listen to their song when they "want to be more 'up, up, up', when I need that energy…". P10 said they would listen to their song "every time I need energy. […] Some people take coffee […] and I will listen to that song every time I need to get in the mood to do something that I don't really want to do". "Power" was another common term. P57 described a song as, "Powerful. The beats are relatively quick. It's more of an aggressive song. […] It helps just empower you, I guess".

3.3.2. Happy/cheerful

The most frequent emotion theme was happiness. Very frequently, participants reported that their song made them happy (e.g., P24, "It really makes me happy"; P26, "I like this song because it makes me happy"). P27 reported that when they listened to their song, they experienced "just, like, happiness. I just want to bounce up and down. It just makes me smile". Other common terms were "uplifting" (P27), "joy" (P29), and "fun" (P30). Some participants mentioned using their song to get them out of a negative mood, as P32 describes: "When I'm feeling distracted, and when I'm feeling sad about life, I just pull this out with the video, […] I have it saved permanently on the tab, and I feel better after." Many participants simply said that "it makes me feel good" (P40) or that "it puts me in a really good mood" (P41).

3.3.3. Calming/relaxing

This theme referred to songs that were described as calm or peaceful, or that participants used to calm themselves down or relax. For example, P05 said about their song, "This is the best song for me to be relieved […] I thought maybe this song would really help me to calm down." P07 said of their song, "I like it because it's very mellow and chill". P21 described experiencing "a feeling of 'steady', like everything is smooth." Occasionally, participants paired the emotion with relaxing imagery, such as P34: "I just think about calmness and being on the beach"; or P05: "it's me walking along the riverside". Other times, participants reported listening to their song when stressed or anxious, using it to lower their level of arousal, such as P51, "I [usually listen to this song] when I'm really stressed," or P62, who listened to their song "mostly before competitions […] it relaxes my nerves. But I also listen to it before exams. I would say before going into something somewhat stressful."

3.3.4. Moving/bittersweet

This theme encompassed several sub-themes that were often difficult to categorize or describe. These songs did not seem to serve a concrete purpose, such as elevating mood, enhancing energy, or decreasing anxiety. Instead, the experience of varied and deep emotions seemed to be the end-in-itself. Many subjects described their songs as moving or emotional, and frequently referred to sad, bittersweet, or ambivalent feelings, such as P17: "This song in particular is super moving […] I just like it because it has so much emotion, but it's kind of negative emotion. Like passion, I guess." P18 said of their song, "it's kind of sad, kind of emotional but it's also a really great song." P19 said, "When I first listened to it, I got really emotional for some reason […] I started crying, and I think it has a really big emotional impact on that moment." A common sub-theme was romance or love. P08 described that "the melody is something that makes me feel beautiful and loving." P10 explained that "it's a love song, and it brings some feelings in me that I can't really describe." Another sub-theme was one of resonance with a deep sense of self or significant personal meaning. P12 said, "I find a lot of connection with the meaning of the song. Just in my life in relation to other people, so it just feels like a very constant idea in my life." P13: "I resonated with the message of it, so it's been important to me since it came out". This theme seems to refer to music listening experiences that feature mixed or negative emotions, a strong sense of meaning, and sub-themes of love or romance.

3.4. Quantitative analysis of emotion themes

Computer-extracted arousal, valence, depth values were computed for all the favorite songs (Fricke et al. 2018), and Pearson correlations were computed between these dimensions and the presence of emotion themes (**Figure 5C**). Energizing/Activating correlated highly with high arousal ($r = 0.47$, $p < 0.001$) and low depth ($r = -0.29$, $p < 0.001$); calming/relaxing correlated with low arousal ($r = -0.38$, $p < 0.001$) and high depth ($r = 0.21$, $p = 0.018$); and moving/bittersweet correlated with low arousal ($r = -0.26$, $p = 0.0039$). Happy/cheerful displayed no significant correlations.

We next examined whether the emotion themes could modulate the hypoalgesic effect of favorite music (**Figure 5D**). Because of the relatively small number of observations per subject in this analysis (eight), and the low variation in emotion themes within subjects, the dummy variables representing emotion themes were not modeled as random effects. Of the four emotion themes, we found a near-significant effect of moving/bittersweet on pain unpleasantness ratings [MD = −3.61, t (482) = −1.65, $p = 0.099$]. The effect of calming/relaxing was not significant [MD = 2.51, t (482) = 1.14, $p = 0.25$], but possibly indicated a small increase in pain unpleasantness ratings. Happy/cheerful and energizing/activating showed no apparent effect (MD < 1.2, $p > 0.6$).

To see if the suggestive effects of emotion themes could be explained by subjective emotion variables (music pleasantness, emotional arousal, and chills), we conducted a second mediation analysis (**Figure 4B**). In examining whether emotion themes predicted the emotion variables, we found that moving/bittersweet significantly predicted music pleasantness [$B = 0.44$, t (483) = 5.69, $p < 0.001$], emotional arousal [$B = 0.65$, t (457) = 5.44, $p < 0.001$], and musical chills [$B = 0.22$, t (466) = 3.72, $p < 0.001$]. Meanwhile, a negative association with chills was observed for happy/cheerful [$B = 0.22$, t (469) = −3.76, $p < 0.001$], calming/relaxing [$B = -0.28$, t (467) = −4.87, $p < 0.001$], and energizing/activating music [$B = -0.16$, t (461) = −2.94, $p = 0.0035$]. No association with music pleasantness or emotional arousal was found for the latter three themes.

Importantly, our study design was not sufficiently powered to disentangle the question of whether the differences in emotion variables were specifically due to the category of favorite music, or due to individual differences in proneness to chills or emotional engagement in music that is associated with the choice of favorite music. It is likely that the effects are a combination of these two factors. To test this hypothesis, we performed a cursory analysis using the Musical Engagement Test (MET). We found that, though total MET scores significantly predicted chills [$B = 0.30$, t (60.4) = 3.07, $p = 0.0033$], including them as covariates in a multivariate model did not change the relationship between moving/bittersweet music and chills or music pleasantness.

We computed mediation models on the emotion themes using chills and music pleasantness as mediators, in order to see if indirect effects existed which could explain the observable differences in pain ratings between emotion themes. We found that the suggestive effect of moving/bittersweet on pain unpleasantness could be significantly explained by ratings of music pleasantness [ab = −5.48, 95% CI = (−8.96, −2.56), $p < 0.001$, Prop. mediated = 0.84] and by chills [ab = −0.57, 95% CI = (−1.14, −0.14), $p = 0.004$, Prop. mediated = 0.16]. For calming/relaxing music, we found a significant indirect effect through chills [ab = 0.87, 95% CI = (0.25, 1.80), $p < 0.001$, Prop. mediated = 0.21], in which the lower number of reported chills resulted in increased pain ratings. The same indirect effect through chills was observed for happy/cheerful [$B = 0.61$, 95% CI = (0.12, 1.19), $p = 0.008$, Prop. mediated = 0.06] and energizing/activating music [$B = 0.43$, 95% CI = (0.081, 0.91), $p = 0.04$], though these did not translate into any apparent total effect.

Finally, we correlated the reporting of emotion themes with personality variables: The Big Five Inventory, Five Factor Mindfulness Scales, Musical Engagement Test, and the Pain Catastrophizing scale. After applying a conservative alpha value ($a = 0.02$, or a p-value threshold of 0.01) to adjust for multiple comparisons, an association between moving/bittersweet and affective, narrative, and social musical engagement existed ($p < 0.01$) and between energizing/activating and overall mindfulness ($p < 0.01$). At a more liberal alpha value of $a = 0.1$, we found that moving/bittersweet was associated with greater BFI openness and lower FFMQ non-judging and non-reacting scores ($p < 0.05$), and energizing/activating was associated with lower pain catastrophizing and affective musical engagement ($p < 0.05$) The full results are given in **Supplementary Figure S1**.

4. Discussion

Few studies have compared the effects of different categories of music on pain, or gone into depth on the components of music that are effective in reducing pain. In this study, we compared participant-selected favorite music to experimenter-selected relaxing music created by the MUSIC CARE company (12, 13). We also conducted a hybrid analysis on the favorite music, using brief structured interviews and thematic analysis (18) to construct theme categories, and then investigated the relationships between emotion themes, self-reported emotional variables, and pain.

We first found that participant-selected favorite music strongly reduced pain intensity and unpleasantness compared to silent and scrambled controls, with an effect size of about 10 points on a 100-

point scale for pain unpleasantness, or 0.7 standard deviations, and a smaller effect for intensity. Meanwhile, relaxing music was less effective in reducing pain, with an effect size of around 0.2 standard deviations on pain unpleasantness that did not reach statistical significance. One reason for this lack of a statistically significant effect of relaxing music may be a lack of power in our study design, which was estimated *post-hoc* at 0.63 for an effect of this size. However, our pattern of results does replicate previous research comparing preferred to relaxing music in an experimental pain paradigm (6), which also failed to show a significant effect of relaxing music on acute pain in a cold pressor task, which may indicate a general difficulty of achieving hypoalgesia from unfamiliar music in an experimental context.

In contrast, however, previous studies in clinical contexts have noted a significant effect of MUSIC CARE tracks on pain variables. A reason for this discrepancy may be that, due to experimental constraints, we were not able to present the tracks in the way they are intended to be used in a clinical setting (12). First, due to time constraints, we had to cut the 20-min tracks to about a 7-min window. In this window, we tried to include the transition from a higher-arousal starting tempo to the low-arousal middle part of the U-shaped arousal trajectory. In this way, we had some opportunity to induce the relaxed, low-arousal state that the tracks are intended to create. However, shortening both the induction part of the track and the low-arousal part may not have entrained participants to the same extent as the full track may have. A recent meta-analysis on music interventions in intensive care units has also shown that the length of the intervention is a critical component in pain relief, with interventions longer than 20 min showing a much larger effect than shorter interventions (38). In addition, our subjects were required to sit upright and attend to a computer monitor, which may not have allowed for the full induction of a relaxed state. Thus, the context and length of treatment may be an important component of leveraging relaxing music for pain relief.

After assessing the mean differences between relaxing music, favorite music, and controls, we examined the contribution of self-reported emotion variables. In conducting mediation analyses, we found that the incidence of musical chills significantly mediated the difference in pain ratings between relaxing and favorite music for both pain intensity and unpleasantness. Music pleasantness ratings, despite having a large direct effect on pain unpleasantness ratings, did not significantly explain the difference in pain scores between the two conditions. Self-reported ratings of emotional arousal did not affect either pain intensity nor unpleasantness. Thus, it seems that while both favorite and relaxing music judged as pleasant may be effective at reducing pain unpleasantness, there may be a neurophysiological process underlying chills which is preferentially recruited during favorite music that is more effective at reducing pain.

Neurological studies into music appreciation suggest that the mesolimbic dopamine pathway, including the nucleus accumbens (NAc), may be fundamental to both music enjoyment and music-induced chills (15, 17, 39, 40), and other studies have shown an association between NAc activation and pain perception (41, 42). One way in which activation of this pathway may alleviate pain is through the Motivation-Decision model (43, 44), where emotionally salient stimuli such as pain and music compete for conscious attention, possibly rooted in brain areas such as the insula and the anterior cingulate cortex (ACC), which are involved in interoceptive and emotional awareness. Another potential mechanism of music-induced hypoalgesia may be descending inhibitory pathways (41). The unique ability of chills to predict a reduction in pain intensity may point to this latter pathway being recruited during peak music listening experiences. Meanwhile, effects on pain unpleasantness may be primarily mediated by the former pathway, with the positive value of music competing with the negative value of pain when representing emotional states in conscious awareness. A recent fMRI study has provided suggestive evidence by finding a reduction in pain-related ACC activity during music listening (45). However, these hypothetical neurological mechanisms require substantial further study.

We next used a combination of qualitative and quantitative methods to analyze the effects of different aspects of listening to favorite music on pain perception. Using thematic content analysis, we extracted 17 themes from 126 brief structured interviews (two per participant). Four themes represented categories of emotional experience, which were the focus of our subsequent quantitative analyses. These were *happy/cheerful*, *energizing/activating*, *calming/relaxing*, and *moving/bittersweet*. Computer-extracted ratings of arousal, valence, and depth dimensions (32, 33, 46) provided some external validation of these categories, which had a variety of associations with arousal and depth (**Figure 5C**). The "moving/bittersweet" category is also comparable to the concept of "sweet sorrow" studied by contemporary researchers (47, 48), which involves the paradoxical appreciation many individuals have for sad music (49, 50).

We found suggestive evidence that the emotion themes differed in their ability to reduce pain, although with the relatively low power of this analysis, further research would be needed to confirm the existence of effects. We observed that moving/bittersweet was the strongest predictor of pain ratings, and showed indirect effects on pain unpleasantness via higher ratings of music pleasantness and musical chills. By comparison, calming/relaxing, happy/cheerful, and energizing/activating all showed lower levels of musical chills and significant indirect effects on pain unpleasantness, though significant total effects were not apparent.

Interestingly, calming/relaxing showed an opposite association with pain in comparison to moving/bittersweet, despite having a nearly identical computer-extracted feature profile, with lowered arousal and increased depth. Thus, it appears that a dimensional, music-centered approach such as the computer-extracted "Arousal, Valence, Depth" model (32, 33) may fail to account for certain experiences of music listening associated with mixed emotions or deeply meaningful experiences. This may highlight the need for more comprehensive subjective measures when studying music-induced hypoalgesia in future studies.

One issue with this analysis is that we were unable, due to limitations in our study design, to effectively disentangle the effects of emotion themes from individual differences in the average level of music appreciation and musical chills in participants who selected each type of favorite music. Thus, individuals who chose to bring moving/bittersweet songs may habitually experience more musical chills and musical enjoyment, resulting in lower pain ratings. However, a cursory analysis using scores from the Musical Engagement Test (36) failed to show evidence of this mediation dynamic. Future research could ask participants to bring songs from each category in order to tease apart these effects.

Finally, in assessing personality differences in participants who reported each theme, we found a significant association between moving/bittersweet and several aspects of musical engagement (affective, social, and narrative). We also found suggestive associations between moving/bittersweet and lower scores on the non-judging and non-reacting scales of the Five Factor Mindfulness scales (35), as well as higher scores on Big Five openness (34), indicating that participants who favor this theme may have a general tendency to engage more closely with their emotional experience, especially during music listening. Meanwhile, participants who reported the energizing/activating theme showed higher overall mindfulness scores, as well as suggestive associations with lower pain catastrophizing (37) and lower affective musical engagement. Further research could examine the links between personality and category of favorite music more closely.

Some limitations of our study include, as previously mentioned, that we did not use the relaxing tracks in their intended context. As such, the capacity of these tracks for reducing pain may be greater than what was suggested by our results, and may recruit additional mechanisms of hypoalgesia such as a hypnosis-like trance state (12). The results of our study are also limited to acute thermal pain in an experimental context, and further research is required to generalize it to clinical and chronic pain.

In terms of our qualitative analysis of themes in favorite music, our categorization scheme may be influenced by researcher biases and preconceptions. However, the varied associations with emotion variables, pain ratings, and computer-rated arousal, valence, and depth dimensions lend validity to these categories. The construct of moving/bittersweet also aligns with categorization schemes produced by other qualitative studies (47).

Finally, one potential limitation of the clinical use of favorite music for pain relief, particularly in an induced-pain or surgical context, may be that the negative aspects of the clinical experience may create aversive associations with the favorite music, reducing the pleasure individuals may take from it in the future. If this is the case, interventions would have to be selective or cautious about the use of favorite music for pain relief.

In conclusion, we find that favorite music is superior to experimenter-selected relaxing music in reducing acute thermal pain, and this difference is mediated by the strength of emotional responses to music, particularly the incidence of musical chills. In addition, the type of favorite music selected by the participant may modulate the effect on pain perception. Specifically, moving/bittersweet favorite music may be more effective in reducing pain due to increased music pleasantness ratings and musical chills. However, further research is needed to support these suggestive findings. Future research could also explore the neurobiological underpinnings of these effects, investigating in particular the roles of dopamine and the nucleus accumbens, as well as the insular and anterior cingulate cortex, in mediating the emotion-driven effects of music on pain.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://osf.io/m9xqd/.

Ethics statement

The studies involving humans were approved by McGill University Research Ethics Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

DV, ALL, and MR jointly designed the study. ALL and AD collected the data, and AD performed the interview transcription. DV, ALL, AD, and ACL all participated in the theme analysis, and DV conducted the quantitative analyses. The manuscript was written by DV, MR, and ALL. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpain.2023.1210572/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Correlations between personality variables and emotion themes reported in participant interviews (*n* = 126). An X indicates a non-significant correlation at an alpha value of 0.10, or a *p*-value of 0.05. The correlations between Active and FFMQ Total, and between Moving and the MET scales, survived after applying a *p*-value cutoff of 0.01 to adjust for multiple comparisons. BFI, big five inventory; FFMQ, five factor mindfulness questionnaire; MET, music engagement test.

SUPPLEMENTARY TABLE S1
Mean comparisons of favorite music, relaxing music, silence, and scrambled conditions. MD, mean difference in pain points on a 100-point scale.

SUPPLEMENTARY TABLE S2
Full list of themes arrived at by thematic content analysis. Frequency refers to the proportion of the 126 interviews in the study that contained a reference to this theme.

SUPPLEMENTARY TABLE S3
Full regression results of emotion themes predicting pain unpleasantness ratings. One model was computed per theme category. MD, Mean difference in pain points on a 100-point scale when the theme is present vs. absent.

References

1. Conrad C. Music for healing: from magic to medicine. *Lancet*. (2010) 376:1980–1. doi: 10.1016/S0140-6736(10)62251-9

2. Garza-Villarreal EA, Pando V, Vuust P, Parsons C. Music-induced analgesia in chronic pain conditions: a systematic review and meta-analysis. *Pain Physician*. (2017) 20:597–610. doi: 10.36076/ppj/2017.7.597

3. Kühlmann AYR, de Rooij A, Kroese LF, van Dijk M, Hunink MGM, Jeekel J. Meta-analysis evaluating music interventions for anxiety and pain in surgery. *BJS Br J Surg*. (2018) 105:773–83. doi: 10.1002/bjs.10853

4. Martin-Saavedra JS, Vergara-Mendez LD, Talero-Gutiérrez C. Music is an effective intervention for the management of pain: an umbrella review. *Complement Ther Clin Pract*. (2018) 32:103–14. doi: 10.1016/j.ctcp.2018.06.003

5. Lee JH. The effects of music on pain: a meta-analysis. *J Music Ther*. (2016) 53:430–77. doi: 10.1093/jmt/thw012

6. Mitchell LA, MacDonald RAR. An experimental investigation of the effects of preferred and relaxing music listening on pain perception. *J Music Ther*. (2006) 43:295–316. doi: 10.1093/jmt/43.4.295

7. Roy M, Lebuis A, Hugueville L, Peretz I, Rainville P. Spinal modulation of nociception by music: spinal modulation of nociception by music. *Eur J Pain*. (2012) 16:870–7. doi: 10.1002/j.1532-2149.2011.00030.x

8. Dodrill CL, Helmer DA, Kosten TR. Prescription pain medication dependence. *Am J Psychiatry*. (2011) 168:466–71. doi: 10.1176/appi.ajp.2010.10020260

9. Goldberg DS, McGee SJ. Pain as a global public health priority. *BMC Public Health*. (2011) 11:770. doi: 10.1186/1471-2458-11-770

10. Rice ASC, Smith BH, Blyth FM. Pain and the global burden of disease. *Pain*. (2016) 157:791–6. doi: 10.1097/j.pain.0000000000000454

11. Chai PR, Carreiro S, Ranney ML, Karanam K, Ahtisaari M, Edwards R, et al. Music as an adjunct to opioid-based analgesia. *J Med Toxicol*. (2017) 13:249–54. doi: 10.1007/s13181-017-0621-9

12. Guétin S, Falvay D, Chanques G, Jaber S, de Lattre S, Souche B, et al. Evaluation of the standardized MUSIC CARE© app in the treatment of pain: the u-shape composing technique. *Music Med*. (2014) 6:46–50. doi: 10.47513/mmd.v6i2.179

13. Guétin S, Brun L, Deniaud M, Clerc J-M, Thayer JF, Koenig J. Smartphone-based music listening to reduce pain and anxiety before coronarography: a focus on sex differences. *Altern Ther Health Med*. (2016) 22:60–3.

14. Roy M, Peretz I, Rainville P. Emotional valence contributes to music-induced analgesia. *Pain*. (2008) 134:140–7. doi: 10.1016/j.pain.2007.04.003

15. Blood AJ, Zatorre RJ. Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proc Natl Acad Sci*. (2001) 98:11818–23. doi: 10.1073/pnas.191355898

16. Juslin PN. From everyday emotions to aesthetic emotions: towards a unified theory of musical emotions. *Phys Life Rev*. (2013) 10:235–66. doi: 10.1016/j.plrev.2013.05.008

17. Salimpoor VN, Benovoy M, Larcher K, Dagher A, Zatorre RJ. Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nat Neurosci*. (2011) 14:257–62. doi: 10.1038/nn.2726

18. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol*. (2006) 3:77–101. doi: 10.1191/1478088706qp063oa

19. R Core Team. *R: A language and environment for statistical computing*. (2021). Available at: https://www.R-project.org/

20. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw*. (2015) 67(1):1–48. doi: 10.18637/jss.v067.i01

21. Kuznetsova A, Brockhoff PB, Christensen RHB. Lmertest package: tests in linear mixed effects models. *J Stat Softw*. (2017) 82(13):1–26. doi: 10.18637/jss.v082.i13

22. Barr DJ, Levy R, Scheepers C, Tily HJ. Random effects structure for confirmatory hypothesis testing: keep it maximal. *J Mem Lang*. (2013) 68:10.1016/j.jml.2012.11.001. doi: 10.1016/j.jml.2012.11.001

23. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. (2016). Available at: https://ggplot2.tidyverse.org

24. Lüdecke D. *sjPlot: Data Visualization for Statistics in Social Science*. (2021). Available at: https://CRAN.R-project.org/package=sjPlot

25. Kassambara A. *"ggplot2" Based Publication Ready Plots*. (2020). Available at: https://rpkgs.datanovia.com/ggpubr/

26. R Library Contrast Coding Systems for categorical variables. *UCLA Stat Consult Group*. (2021). Available at: https://stats.idre.ucla.edu/r/library/r-library-contrast-coding-systems-for-categorical-variables/ (Accessed July 15, 2021).

27. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. Mediation: R package for causal mediation analysis. *J Stat Softw*. (2014) 59:1–38. doi: 10.18637/jss.v059.i05

28. Cohen J. *Statistical power analysis for the behavioral sciences*. 2nd ed Hillsdale, NJ: L. Erlbaum Associates (1988). 567.

29. Izard CE. Basic emotions, natural kinds, emotion schemas, and a new paradigm. *Perspect Psychol Sci*. (2007) 2:260–80. doi: 10.1111/j.1745-6916.2007.00044.x

30. Panksepp J. *Affective neuroscience: The foundations of human and animal emotions*. Oxford: University Press (2004). 481.

31. Barrett LF, Mesquita B, Ochsner KN, Gross JJ. The experience of emotion. *Annu Rev Psychol*. (2007) 58:373–403. doi: 10.1146/annurev.psych.58.110405.085709

32. Fricke KR, Greenberg DM, Rentfrow PJ, Herzberg PY. Computer-based music feature analysis mirrors human perception and can be used to measure individual music preference. *J Res Personal*. (2018) 75:94–102. doi: 10.1016/j.jrp.2018.06.004

33. Greenberg DM, Kosinski M, Stillwell DJ, Monteiro BL, Levitin DJ, Rentfrow PJ. The song is you: preferences for musical attribute dimensions reflect personality. *Soc Psychol Personal Sci*. (2016) 7:597–605. doi: 10.1177/1948550616641473

34. Lang FR, John D, Lüdtke O, Schupp J, Wagner GG. Short assessment of the big five: robust across survey methods except telephone interviewing. *Behav Res Methods*. (2011) 43:548–67. doi: 10.3758/s13428-011-0066-z

35. Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. *Assessment*. (2006) 13:27–45. doi: 10.1177/1073191105283504

36. Greenberg DM, Rentfrow PJ. Rules of engagement: the structure of musical engagement and its personality underpinnings. In: Ginsborg J, Lamont A, Phillips M,

Bramley S, editors. Proceedings of the Ninth Triennial Conference of the European Society for the Cognitive Sciences of Music; 2015 Aug 17–22; Manchester, UK. (2015) 3.

37. Sullivan MJL, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess*. (1995) 7:524–32. doi: 10.1037/1040-3590.7.4.524

38. Richard-Lalonde M, Gélinas C, Boitor M, Gosselin E, Feeley N, Cossette S, et al. The effect of music on pain in the adult intensive care unit: a systematic review of randomized controlled trials. *J Pain Symptom Manage*. (2020) 59:1304–1319.e6. doi: 10.1016/j.jpainsymman.2019.12.359

39. Blood AJ, Zatorre RJ, Bermudez P, Evans AC. Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. *Nat Neurosci*. (1999) 2:382–7. doi: 10.1038/7299

40. Ferreri L, Mas-Herrero E, Zatorre RJ, Ripollés P, Gomez-Andres A, Alicart H, et al. Dopamine modulates the reward experiences elicited by music. *Proc Natl Acad Sci*. (2019) 116:3793–8. doi: 10.1073/pnas.1811878116

41. Wood PB. Role of central dopamine in pain and analgesia. *Expert Rev Neurother*. (2008) 8:781–97. doi: 10.1586/14737175.8.5.781

42. Woo C-W, Roy M, Buhle JT, Wager TD. Distinct brain systems mediate the effects of nociceptive input and self-regulation on pain. *PLOS Biol*. (2015) 13: e1002036. doi: 10.1371/journal.pbio.1002036

43. Fields H. A motivation-decision model of pain: the role of opioids. In: Flor H, Kalso E, Dostrovsky JO, editors. *Proceedings of the 11th World Congress on Pain*. Seattle: IASP Press (2006) pp. 449–59.

44. Porreca F, Navratilova E. Reward, motivation and emotion of pain and its relief. *Pain*. (2017) 158:S43–9. doi: 10.1097/j.pain.0000000000000798

45. Antioch I, Furuta T, Uchikawa R, Okumura M, Otogoto J, Kondo E, et al. Favorite music mediates pain-related responses in the anterior cingulate cortex and skin pain thresholds. *J Pain Res*. (2020) 13:2729–37. doi: 10.2147/JPR.S276274

46. Fricke KR, Greenberg DM, Rentfrow PJ, Herzberg PY. Measuring musical preferences from listening behavior: data from one million people and 200,000 songs. *Psychol Music*. (2021) 49:371–81. doi: 10.1177/0305735619868280

47. Peltola H-R, Eerola T. Fifty shades of blue: classification of music-evoked sadness. *Music Sci*. (2016) 20(1):84–102. doi: 10.1177/1029864915611206

48. Vuoskoski JK, Eerola T. The pleasure evoked by sad music is mediated by feelings of being moved. *Front Psychol*. (2017) 8. doi: 10.3389/fpsyg.2017.00439

49. Huron D, Vuoskoski JK. On the enjoyment of sad music: pleasurable compassion theory and the role of trait empathy. *Front Psychol* (2020) 11:1060. doi: 10.3389/fpsyg.2020.01060

50. Eerola T, Vuoskoski JK, Peltola H-R, Putkinen V, Schäfer K. An integrative review of the enjoyment of sadness associated with music. *Phys Life Rev*. (2018) 25:100–21. doi: 10.1016/j.plrev.2017.11.016