Impact of Music on First Pain and Temporal Summation of Second Pain: A Psychophysical Pilot Study

Mathilde Cabon & Anais Le Fur-Bonnabesse
Univ Brest, LIEN, Brest, France

Steeve Genestet & Bertrand Quinio
Brest University Hospital Centre, Brest, France

Laurent Misery
Univ Brest, LIEN, Brest, France

Alain Woda
Clermont Auvergne University, Clermont-Ferrand, France

Céline Bodéré
Univ Brest, LIEN, Brest, France

Passive music listening has shown its capacity to soothe pain in several clinical and experimental studies. This phenomenon—known as music-induced analgesia—could partly be explained by the modulation of pain signals in response to the stimulation of brain and brainstem centers. We hypothesized that music-induced analgesia may involve inhibitory descending pain systems. We assessed pain-related responses to endogenous pain control mechanisms known to depend on descending pain modulation: peak of first pain (PP), temporal summation (TS), and diffuse noxious inhibitory control (DNIC). Twenty-seven healthy participants (14 men, 13 women) were exposed to a conditioned pain modulation paradigm during a 20-minute relaxing music session and a silence condition. Pain was continually measured with a visual analogue scale. Pain ratings were significantly lower with music listening ($p < .02$). Repeated measures ANOVA indicated significant differences between conditions within PP and TS ($p < .05$) but not in DNIC. Those findings suggested that music listening could strengthen components of the inhibitory descending pain pathways operating at the dorsal spinal cord level.

Received: August 16, 2019, accepted October 4, 2020.

Key words: music, neuromodulation, first pain, temporal summation, diffuse noxious inhibitory control

To meet public health needs, contemporary medicine has reintegrated the use of complementary methods. Music-induced analgesia is a well-known phenomenon described as a reduction in pain perception while listening to music. Several clinical studies have reported a diminished sensitivity to acute and chronic pain through passive music listening (Gardner, Licklider, & Weisz, 1960; Good, 1996; Good & Ahn, 2008; Guétin et al., 2012). Music-induced analgesia also occurs in experimental pain procedures, using various pain models like the tonic heat pain test (Dobek, Beynon, Bosma, & Stroman, 2014; Roy, Peretz, & Rainville, 2007) and cold pressor test (Garcia & Hand, 2016; Mitchell & MacDonald, 2006). Relaxing and self-selected music pieces are known to be especially effective to reduce pain perception (Good & Ahn, 2008; Mitchell & MacDonald, 2006; Roy et al., 2007).

Acute pain is a complex and dynamic phenomenon under the influence of facilitatory and inhibitory mechanisms. Pain perception depends on the integration of nociceptive signals incoming from spinal cord to the brain, which in turn is modulated by descending pain pathways from the cortex and the brainstem to the spinal cord. As a result, pain experience is highly influenced by several endogenous nociceptive and antinociceptive mechanisms relying in part upon cognitive and emotional processes. The effects of engagement, distraction, and emotional reaction to music are frequently advanced to explain the underlying mechanisms of music-induced analgesia (Bernatzky, Presch, Anderson, & Panksepp, 2011; Bradshaw, Donaldson, Jacobson, Nakamura, & Chapman, 2011; Hauck, Metzner, Rohlffs, Lorenz, & Engel, 2013; Huang, Good, & Albert, 2007; Mitchell & MacDonald, 2006; Roy et al., 2007; Zhao & Chen, 2009). However, the role of descending modulatory mechanisms of pain is also probable. Modulation of pain perception by emotions and cognition implicates "top-down" processes found in the placebo effect (Goffaux, Redmond, Rainville, & Marchand, 2007; Price, Finniss, & Benedetti, 2008). This well-documented analgesia phenomenon is depending on the activation of descending pain-modulatory pathways originating from supraspinal regions and blocking nociceptive signals at a dorsal horn level (Basbaum & Field,

Music Perception, volume 38, issue 3, pp. 267–281, issn 0730-7829, electronic issn 1533-8312. DOI: https://doi.org/10.1525/mp.2021.38.3.267

1978; Millan, 2002; Bingel, Schoell, & Büchel, 2007; Eippert, Finsterbusch, Bingel, & Büchel, 2009; Ossipov, Dussor, & Porreca, 2010; for review, see Bingel & Tracey, 2008), as music-induced analgesia could be. Inhibitory descending pain systems could be triggered in response to the stimulation of brain and brainstem areas by music. When listening to music, the neural activity pattern observed with fMRI during an experimental pain procedure is consistent with the engagement of descending pain pathways (Dobek et al., 2014).

In order to assess the activation of those descending pain-modulatory systems in humans, psychophysical, and physiological methods have been used. Since early central facilitatory mechanisms initiated at a dorsal horn level are modulated by descending controls, their magnitudes provide information about supraspinal pain-modulation systems (Bingel et al., 2007; Fields, Basbaum, Clanton, & Anderson, 1977; Millan, 2002; Rustamov, Northon, Tessier, LeBlond, & Piché, 2019; Staud, Vierck, Cannon, Mauderli, & Price, 2001). The recruitment of descending pain inhibition systems can be tested through the quantification of first pain (peak of first pain; PP) and temporal summation of second pain (TS) (Bingel et al., 2007; Cheng, Erpelding, Kucyi, DeSouza, & Davis, 2015; Price et al., 2002; Staud et al., 2001). PP and TS are psychophysical pain responses of spinally mediated facilitatory mechanisms. They rely on two different types of afferent fibers that converge on dorsal horn cells of the spinal cord (Price, Hu, Dubner, & Gracely, 1977; Treede, Meyer, Raja, & Campbell, 1995). If descending inhibitory mechanisms play a role in music-induced analgesia, both PP and TS should be inhibited, as demonstrated with the spinal nociceptive withdrawal reflex (Roy et al., 2012). Another way to access the descending pain-modulatory systems is through diffuse noxious inhibitory control (DNIC)-testing. DNIC is an inhibitory descending control first described in animals (Le Bars, Dickenson, & Besson, 1979a, 1979b), also known as "pain inhibits pain." It is one of the main descending inhibitory pain pathways and this activation is thought to be dependent on distinct descending pain-modulatory systems (Patel & Dickenson, 2019; Villanueva & Le Bars, 1995). DNIC system relies upon a spinal-supraspinal-spinal feedback loop triggered by strong peripheral noxious stimuli (Bouhassira, Villanueva, Bing, & Le Bars, 1992). It implies that localized nociceptive stimulation can induce diffuse pain inhibition towards the rest of the body (Le Bars, 2002). Conditioned pain modulation (CPM) is the standard method used to assess DNIC (Granot et al., 2008; Kennedy, Kemp, Ridout, Yarnitsky, & Rice, 2016; Mackey, Dixon, Johnson, & Kong, 2017; Staud et al., 2001; Tousignant-Laflamme, Page, Goffaux, & Marchand, 2008).

We hypothesized that music-induced analgesia may be partly mediated by descending inhibitory pain pathways in association with emotion and relaxation processes. Thus, facilitatory pain mechanisms responses should be inhibited (e.g., PP and TS) and DNIC effect enhanced when individuals listened to a soothing pleasant music in comparison to a silence condition. We conducted a randomized crossover "within subjects" trial. Musical sequences were designed on a 20-minutes "U-model" developed by Music Care. The structure of this therapeutic tool yields relaxing and pleasant effects (Jaber et al., 2006) and it gives participants the possibility to select an instrumental sequence depending on the genre preference. We measured pain-related responses to pain control mechanisms using a sequential CPM paradigm. This pilot study aimed to determine whether this paradigm was effective to evaluate the effect of music on endogenous pain mechanisms. The main criterions were (1) the peak of first pain (2) TS amplitude and (3) DNIC amplitude, assuming that pain would be reduced in music condition.

Method

PARTICIPANTS

Twenty-eight healthy volunteers participated in this study. To archive a power of 90% and a level of significance of 5%, 28 participants were required to detect an expected difference of 13 points (Guétin et al., 2012) between pairs, for an expected standard deviation equal to 20. One participant failed to complete the test session due to software failure. Hence, 27 participants (14 men, 13 women), aged between 18 and 30 (23.11 ± 3.03 years), were included in the analysis. Participants were recruited using ads posted throughout the campus of the Université de Bretagne Occidentale and on social media. None of them had previously participated to other pain experiments. Exclusion criteria were as follows: any chronic or acute disease, any psychiatric disorder, hearing impairments, current acute pain, and the consumption of any analgesic drugs or central nervous system agents for 24 hours before the experiment. All participants filled out a series of questionnaires to ensure the absence of symptoms of depression or anxiety and pain catastrophizing because those factors are frequently associated with dysfunctional descending pain inhibition. Questionnaires included the French versions of the Beck Depression Inventory (BDI) (Pichot & Lempérière, 1964) and the Pain Catastrophizing Scale (PCS-CF) (French et al., 2005). Participants above the scores of

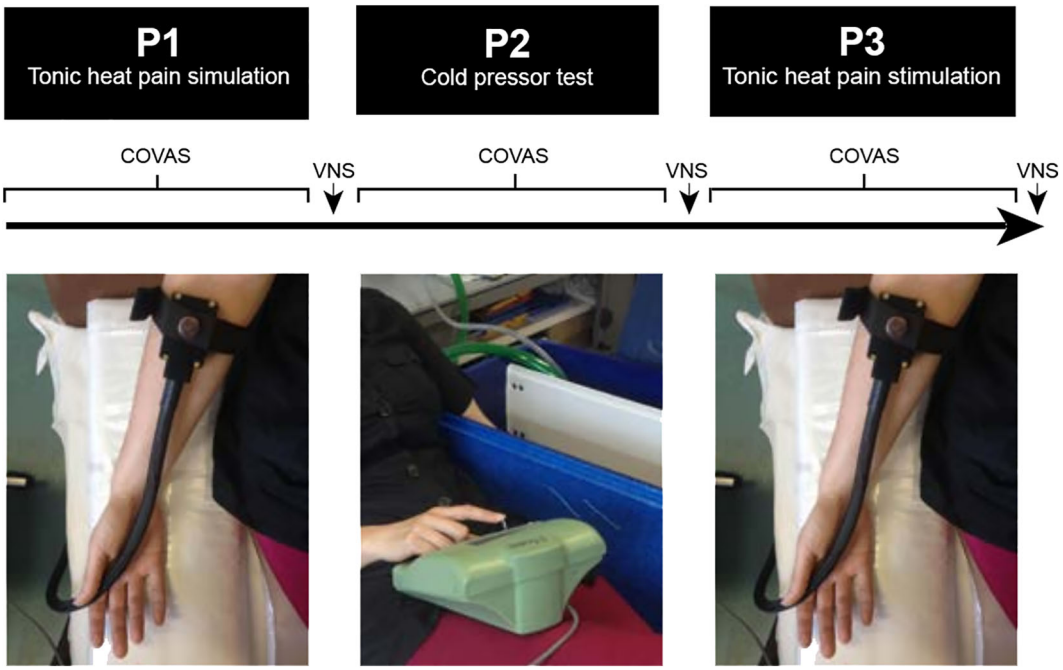

FIGURE 1. Experimental design of the thermal stimulation paradigm. Participants continually rated the pain with a computerized visual analog scale (CoVAS in picture B), induced by two tonic heat pain stimulations (P1 and P3, see A and C respectively) separated by a cold pressor test (P2, see B). All periods last two minutes. The average pain intensity was evaluated on a verbal numeric scale (VNS) at the end of each period. (From Tousignant-Laflamme et al., 2008).

respectively 7 and 23 or greater were not considered for inclusion. State anxiety during the visit was also screened using the Spielberger's State-Trait Anxiety Inventory (STAI) (Gauthier & Bouchard, 1993). All participants obtained a higher state score than the trait score, indicating that their anxiety level during this quiet test was inferior to their daily anxiety. All subjects were blinded to the hypothesis of the study. The study conformed to the ethical standards established in the Declaration of Helsinki, except for registration in a database. The experimental protocols were approved by the local ethics committee. All participants gave written informed consent prior to inclusion in the study.

MUSICAL STIMULI

Twenty-minute "U" sequences musical pieces were selected from Music Care (music-care.com) database. The "U-based" system corresponds to a therapeutic solution standardized for the management of chronic pain and developed by the company Music Care (Guétin et al., 2012). The "U" sequences are divided into three successive phases with gradual variations in tempo, instrumentation, frequencies, and volume. During the first ten minutes, there is a progressive reduction of the number of instruments (from 10–20 to 2–5), the beats per minute (from 90 to 50 bpm), the volume, and the frequencies. The changes in those musical parameters are assumed to induce a relaxation state. After this phase, the parameters stay constant during another ten minutes with a low tempo of 30 to 40 beats per minute and a maximum of three instruments. Finally, the music gradually increases during 10 minutes to a moderate tempo of 60 to 80 bpm associated with 5 to 10 instruments, to regain an ordinary state of consciousness. All sequences are instrumentally played by professional musicians and can be considered as soothing. Participants had to choose among a set of twenty-one musical genres (rock, classical, jazz, electro, etc.) the one that best suited them. This method ensures some homogeneity in the musical stimuli in terms of dynamic changes, tempo, and arousal while allowing each participant to choose his or her favorite musical genre. The pain threshold was fixed to a medium intensity on the allocate ruler. The self-selected music sequence was delivered through headphones with active noise reduction (Wireless headphone Model AH-NCW5OO, Denon Electronics, USA).

NOCICEPTIVE THERMAL STIMULATIONS

The thermal stimulation paradigm (see Figure 1) is based on an experimental pain model that allows

measuring PP, TS, and DNIC in a single session divided into three successive bunches of 120 seconds (Tousignant-Laflamme et al., 2008). This model associates conditioned pain modulation (CPM) with contact-heat induced pain. CPM is a reliable psychophysical experimental measure of the diffuse noxious inhibitory control (DNIC) (Kennedy et al., 2016). CPM paradigms typically imply the combination of two types of noxious stimuli. A test-stimulus is applied before and after a conditioning stimulus. Difference between both test-stimulus is interpreted as CPM-effect that reflects DNIC activation. In this study, dynamic quantitative sensory testing (QST) with noxious heat pain tests was used as test-stimulus and to evoke first and second pain. A 12°C cold pressor test (CPT) was employed as the conditioning stimulus. Figure 1 summarizes the sequential paradigm including two tonic heat pain stimulations (P1 and P3) separated by a 120-second CPT (P2).

Test-stimulus: Tonic Heat Pain Tests. Two contact heat pain tests were performed for 120 seconds each on the thumb side of the forearm, corresponding to the C6 dermatome, by means of a 3-cm^2 thermode (NeuroSensory Analyser Model TSA II, Medoc Instruments, Israel). The stimulation was administered at a constant temperature during the entire tests. Regarding precision, thermode's temperature remained constant throughout the 120 seconds after a constant rise (0.3°C/s) from the baseline (32°C) to the individually predetermined temperatures. The temperature was generated continuously by the thermode. Participants were blinded to the temperature used. This procedure allows studying two facilitatory pain-related phenomena arising at specific times (Granot et al., 2006; Nielsen & Arendt-Nielsen, 1998; Price & Dubner, 1977). First pain perception is characterized by a peak effect at about 30 seconds after reaching fixed temperature and is reflected by a sharp and brief pain enhancement (referred to as peak of first pain –PP). PP is followed by TS of second pain reflected in progressive pain amplification after about 60 seconds of constant or repetitive noxious heat stimulation. The difference between pain ratings at 120 and 60 seconds is defined as TS amplitude. The contact heat pain tests ensure an intra-subject high reliably of the TS-effect within 1 hour (Kong et al., 2013). Moreover, tonic heat stimulations provide a better reliability for CPM-effect than phasic nociceptive stimuli (Lie et al., 2017).

Conditioning Stimulus: Cold Pressor Test. A cold pressor test (CPT) was used as a conditioning stimulus to elicit a strong and prolonged pain sensation and to trigger DNIC. The conditioning stimulus consisted in the immersion of the left arm (up to the elbow) in circulating cold water maintained at 12°C for 120 seconds. All participants manage to keep the arm in the cooler during the entire 120 seconds of the CPT.

MEASURES

Pain perception was assessed with a computerized visual analog score (CoVAS), which provides real-time continuous measurement of pain intensity. This device allowed extracting a VAS value, ranged from 0 (absolutely no pain) to 100 (worst pain imaginable), for each of the 120 seconds of the test. In addition, participants reported the average pain intensity felt during the former period using a verbal numeric scale (VNS) from 0 to 100.

At the end of the music condition, and to provide further insight about their emotional experience, participants rated their self-selected music piece based on four dimensions with a VAS ranging from 0 to 10: relaxed–tense, very sad–very happy, unpleasant–pleasant, and angry–calm. Participants also used VAS to assess the level of satisfaction and the consistency between the expectation arisen in relation to the music titles and the listening of the music track.

STUDY DESIGN

The pilot study used a counterbalanced crossover design with two conditions, one with a self-selected music session (music condition) and one without (no-music condition), while undergoing the thermal stimulation paradigm (see Figure 2). The clusters were defined by presentation order: music condition followed by no-music condition (MN group, $n = 13$) versus no-music condition followed by music condition (NM group, $n = 14$). The randomization was pseudo-stratified by sex using a table of random numbers. Each condition lasted for 16 minutes with a 10-minutes rest period between, to allow the recovering of skin receptors. The music sequence was introduced 10 minutes before starting the thermal stimulation paradigm during music condition. In the no-music condition, participants rested in silence for 10 minutes. After the music condition, participants rated their musical sequence.

Before the experiment, participants practiced a pre-test phase in order to get familiarized with the CoVAS and the sensations produced by heat stimulation. A calibration of the thermode temperature was performed to individually adjust pain intensity to 50/100 VAS score. During this pre-test, the thermode was applied on the right forearm. Four phasic heat stimuli (36°C-50°C) were successively delivered to obtained pain threshold, pain tolerance and medium pain scores (50/100). However, the maximum temperature was

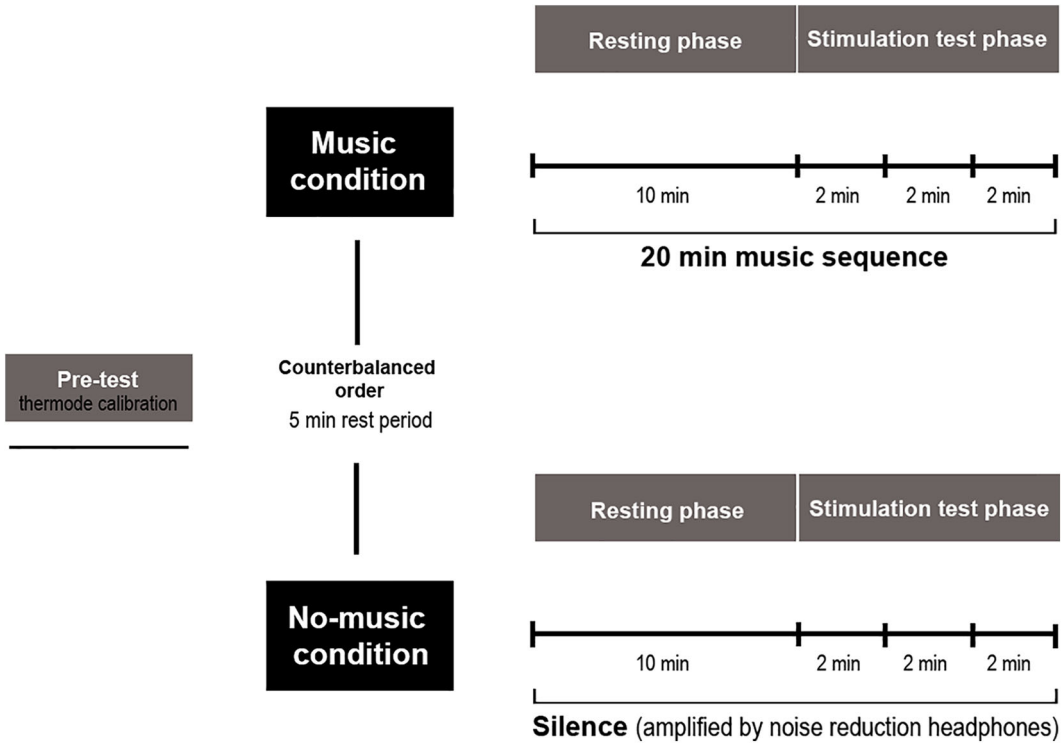

FIGURE 2. Study design. During the pre-test phase, the thermode temperature was individually calibrated to induce a 50/100 pain intensity with the CoVAS. The presentation order between the music vs. no-music conditions was randomly assigned between participants. After a resting phase in both conditions, the thermal stimulation paradigm was conducted with P1: first tonic heat pain test, P2: cold pressor test, P2: second heat pain test.

fixed at 46°C during the tonic heat pain tests to prevent tissue damage. This was not enough to provoke a 50/100 VAS score in 14 participants, with a lowest value of 20.

After this practice block, participants were comfortably lying down. Headphones were positioned with the noise reduction function on. They were given computerized VAS and advised to move the cursor toward the right when they would start to feel pain. The extreme left was defined as "no pain" and the extreme right as "worst pain imaginable." Before running the thermal stimulation paradigm, participants were told that the thermode temperature will remain stable even thought they could experience some subjective temperature variations.

STATISTICAL ANALYSES

Statistical analyses were calculated using Statistica version 13.3 for Windows (TIBCO Software, Inc., 2017). Significant level was set at a p value of less than .05. No significant deviation from normal distribution was detected using Q-Q plots inspection and Kolmogorov-Smirnov test, except for pain ratings at 60 second (VAS_{60}) during P3.

Prior to the study analyses, we determined PP, TS, and CPM scores (Figure 3). PP was individually estimated as the maximum pain rating that occurred during the first 30 seconds of the contact heat pain tests, under each condition and in each period. We calculated TS magnitude with within-period difference scores. TS magnitude was defined as the difference between VAS rating at 120 seconds (VAS_{120}) and VAS rating at 60 seconds (VAS_{60}) of the contact heat pain tests, under each condition (with and without music) and in each period (P1 and P3). Paired Student's t-test were used to ascertain TS in P1 by comparing VAS scores at T_{60} and T_{120} for each condition. The comparison between VAS_{60} and VAS_{120} ratings in P3 was tested using Wilcoxon matched-pairs signed rank test. Regarding DNIC activation, CPM was calculated across conditions as the mean VAS score during P1 (VAS P1) minus the mean VAS score during P3 (VAS P3). A three-way mixed ANOVA was conducted to confirm CPM inhibition with order groups (MN or NM) as between-subjects factor and conditions (music and no-music) and periods (P1 and P3) as within-subjects factors.

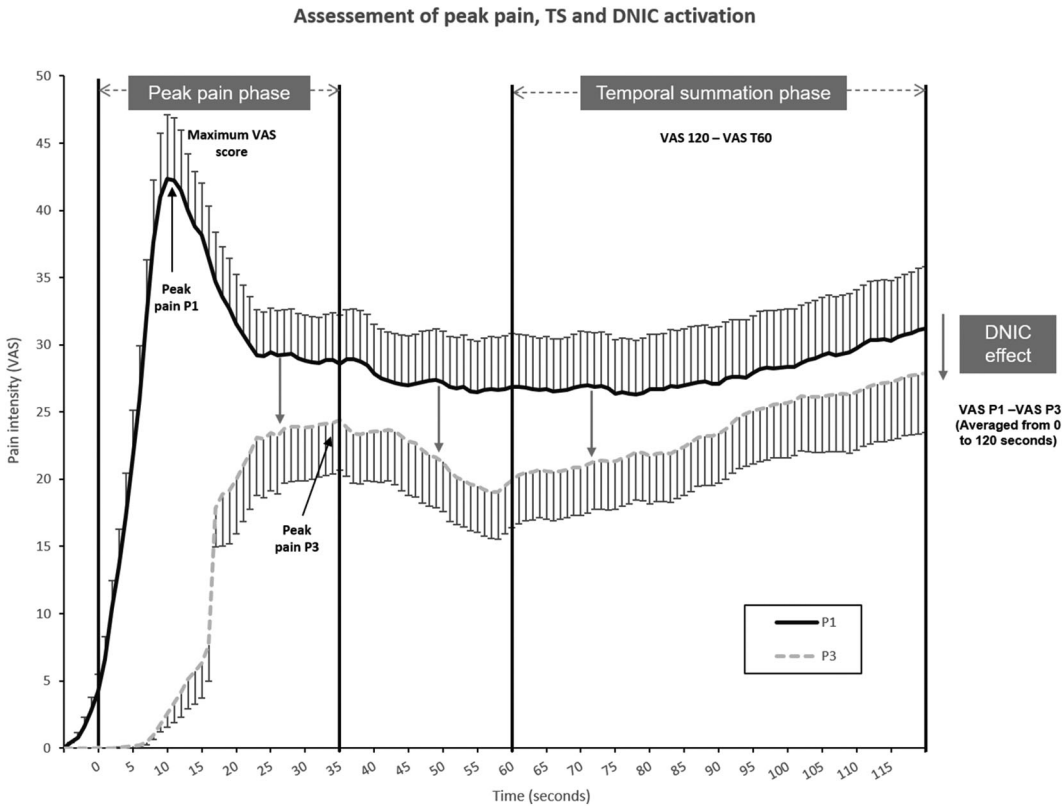

FIGURE 3. Average pain ratings before and after the cold pressor test during the first and the second heat pain tests (P1 and P2 respectively). Conditions are pooled together. The graph shows peak of first pain and TS during P1 and P3. DNIC-effect corresponds to the mean difference in average pain ratings during P3 and P1. Each dot represents the mean average VAS scores for all participants per second (mean ± SE).

Demographic and clinical characteristics differences between order groups (MN vs. NM) were detected by independent Student *t*-test for age, depression, anxiety, and catastrophism. For global perceived pain, a mixed repeated measures ANOVA was conducted with conditions and periods (P1, P2, and P3) as within-subjects factors and order groups as between-subjects factor. Same model was applied for PP and TS variables with two levels of periods (P1 and P3). CPM-effect (VAS P1 - VAS P3) was compared between conditions with a paired Student's *t*-test. For all ANOVAs, Greenhouse-Geisser correction was used when Mauchley's test of sphericity was violate. Post hoc tests were performed with Bonferroni corrections. Partial eta square (η^2) was used as the effect size for ANOVA analysis, while Cohen's d (*d*) was used for *t*-tests and Cliff's *Delta* (*D*) for Wilcoxon matched-pairs signed rank test (calculated with the Cliff's Delta Calculator from Macbeth, Razumiejczyk, & Ledesma, 2011). Partial eta square was interpreted as small effect = 0.01, medium effect = 0.06, large effect = 0.14 and Cohen's *d* was interpreted as small effect = 0.2, medium effect = 0.5, large effect = 0.8 in accordance with Cohen's guidelines (Cohen, 1977). Cliff's *Delta* was interpreted as follow: small = 0.11, medium = 0.28, large = 0.43 (Vargha & Delaney, 2000). The results of this randomized study are in compliance with the guidelines of the consortium on the assessment of non-pharmacological treatments.

Results

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Demographic and clinical characteristics of participants are summarized in Table 1. The average temperature to evoke a 50/100 score did not differ between order groups nor between sexes. STAI, BDI, and PCS-CF scales did not show any significant differences between the MN and NM groups.

On average, participants rated self-selected musical sequences very relaxing (1.62 ± 1.17), emotionally neutral (5.48 ± 1.66), very pleasant (8.15 ± 1.31), very

TABLE 1. *Demographic and Clinical Characteristics by Order Groups*

	Group MN ($N = 14$)[a]	Group NM ($N = 13$)[b]	p
Gender			
Male	7	7	
Female	7	6	
Age	23.57 ± 3.71	22.61 ± 2.10	.25
Thermode temperature	45.92 ± 0.27	45.85 ± 0.37	.51
Depression (BDI)	3.21 ± 2.42	2.77 ± 2.65	.51
Anxiety (STAI)			
State	26.64 ± 4.75	26.00 ± 4.76	.61
Trait	36.86 ± 7.42	37.92 ± 5.50	.55
Catastrophism (PCS-CF)	13.71 ± 5.45	14.54 ± 6.96	.62

Note: BDI: Beck Depression Inventory; STAI: Spielberger's State-Trait Anxiety Inventory; PCS-CF: Pain Catastrophizing Scale (mean ± SD); Group MN: group order music-no music; Group NM: group order no music-music.

calm (9.07 ± 0.86), satisfying (6.96 ± 1.94), and congruent with the statement (6.33 ± 2.45).

Assessment of TS and CPM. Figure 4 is a plot showing the averaged pain ratings per second for all participants during the total pain experimental procedure in both conditions. The curves display a pattern consistent with the typical responses to contact heat pain tests and CPM. In each experimental condition, Student's *t*-tests confirmed the presence of TS during P1. The last pain ratings (VAS_{120}) were significantly increased compared to VAS_{60} ratings for the no-music condition, ($t = 5.13$, $p < .001$, $d = 0.99$) and the music condition ($t = 5.61$, $p < .001$, $d = 1.08$). VAS_{120} ratings were also significantly higher than VAS_{60} ratings during P3 in the no-music condition ($z = 4.47$, $p < .001$, $D = 0.42$) and the music condition ($z = 4.43$, $p < .001$, $D = 0.34$). Furthermore, ANOVA revealed a significant reduction in heat pain intensity following the CPT, reflecting CPM inhibition. The average pain ratings between P1 and P3 were significantly different, $F(1, 25) = 8.75$, $p < .007$, $\eta^2 = 0.81$. Post hoc tests confirmed a significant higher VAS scores during the first tonic heat phase in both no-music ($p < .02$) and music conditions ($p < .03$).

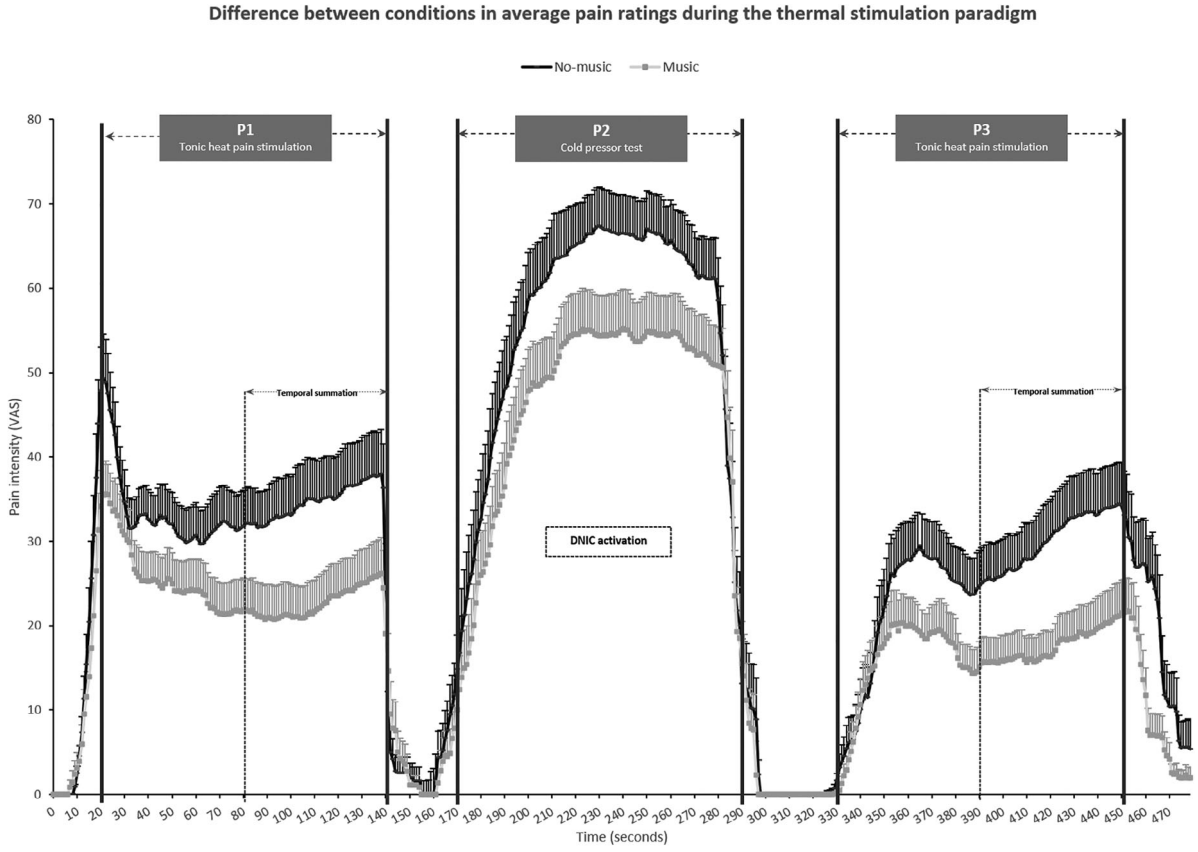

FIGURE 4. Differences between conditions in average pain ratings for all participants during the experimental pain procedure. Each dot represents the mean average VAS scores for all participants per second (mean ± *SE*).

TABLE 2. *Mean Pain Ratings Given by the Computerized Visual Analogue Scale (VAS) and the Verbal Numeric Scale (VNS) for Each Period of the Thermal Stimulation Paradigm*

	Averaged VAS Scores			VNS Scores		
Condition	P1	P2	P3	P1	P2	P3
No-music (mean ± SE)	34.33 ± 3.61	57.01 ± 4.18	29.31 ± 3.88	42.04 ± 3.30	62.96 ± 3.97	34.44 ± 3.20
Music (mean ± SE)	23.82 ± 3.26	46.34 ± 4.04	18.44 ± 2.53	30.74 ± 3.08	53.51 ± 3.89	25.18 ± 2.84

Note: values are expressed in VAS and VNS units (from 0 to 100)

EFFECT OF MUSIC ON GLOBAL PERCEIVED PAIN

Table 2 depicts mean VAS and VNS scores during P1, P2, and P3 by conditions. Pain ratings differed significantly across conditions; VAS: $F(1, 25) = 53.48$, $p < .001$, $\eta^2 = 0.68$; VNS: $F(1, 25) = 54.01$, $p < .001$, $\eta^2 = 0.68$, and across periods; VAS: $F(1, 25) = 32.95$, $p < .001$, $\eta^2 = 0.57$; VNS: $F(1, 25) = 39.63$, $p < .001$, $\eta^2 = 0.61$. Bonferroni corrections confirmed that the averaged pain perception was significantly higher during no-music condition than during music condition (VAS: $p < .002$, VNS: $p < .001$). Pain ratings were significantly higher during the CPT than during the first and the second tonic heat pain tests (VAS: $p < .001$, VNS: $p < .001$). There was no order effect. No significant interaction effect was found between condition and period, $F(1, 25) < 0.44$, $p > .75$). Post hoc tests showed that pain values in music condition were significantly lower than those in the no-music condition at P1, P2, and P3 (VAS: $p < .001$; VNS: $p < .001$), (see Figure 5a and 5b). In addition, average pain scores were significantly lower in P3 than in P1 for the two conditions (Figure 5b). However, this difference reached significance only for VNS (Music: $p < .001$; No-music: $p < .02$). Differences in mean VAS values between P1 and P3 were only significant when P2 was removed from the analysis.

EFFECT OF MUSIC ON TONIC HEAT PAIN TESTS

Peak of First Pain. PP ratings differed significantly across conditions, $F(1, 25) = 16.75$, $p < .001$, $\eta^2 = 0.40$, and across periods, $F(1, 25) = 19.44$, $p < .001$, $\eta^2 = 0.44$. No order effect was found, $F(1, 25) = 0.21$, $p > .65$. During the PP phase, the maximum pain intensity score was different between conditions ($p < .001$). The effect of condition was significant during P1 and P3 (P1: $p < .001$; P3: $p < .001$), where on average no-music condition was associated with rates higher (P1: 52.03 ± 5.10; P3: 37.63 ± 4.52) than during the music condition (P1: 40.88 ± 4.21; P3: 26.85 ± 4.28) (mean ± *SE*). In addition, a significant effect of period was found for both no-music and music conditions (*ps* < .001), suggesting the analgesic effect of CPM-inhibition on PP.

Temporal Summation of Second Pain. TS amplitude (mean ± *SE*) was found at 17.22 ± 3.36 VAS units for P1 and 17.89 ± 3.00 for P3 in the no-music condition. In the music condition, the magnitude of TS at P1 and P3 was 10.56 ± 1.88 and 10.11 ± 1.77 VAS units, respectively. The three-way ANOVA revealed a main effect of condition, $F(1, 25) = 15.82$, $p < .001$, $\eta^2 = 0.34$, with higher TS amplitude for the no-music condition than the music condition ($p < .001$). Post hoc tests demonstrated that TS magnitudes values were significantly decreased in the music condition for P1 ($p < .04$) and P3 ($p < .03$) (see Figure 5c). No significant order effect, $F(1, 25) = 0.08$, $p = .78$), neither period effect, $F(1, 25) = 0.018$, $p = .89$, were found. Interaction between condition and period was not significant, $F(1, 25) = 0.10$, $p = .75$.

EFFECT OF MUSIC ON CPM

No difference in CPM inhibition (VAS P1 – VAS P3) was found between the two conditions ($p = .88$).

Discussion

In this pilot study, we aimed to determine if music-induced analgesia may involve inhibitory descending pain pathways and whether the CPM paradigm associated with tonic heat pain stimuli was well suited to evaluate such involvement. The global activation pattern of the pain-related responses to endogenous pain mechanisms observed in this study is consistent with the initial results, accounting for the peak of first pain (PP), temporal summation of second pain (TS), and diffuse noxious endogenous control (DNIC)-effect (Tousignant-Laflamme et al., 2008). Psychophysically, our results show an inhibitory effect of music listening on the behavioral correlates of first and second pain, regardless of CPM-effect. The CPM paradigm used in this study appears to be a reliable and convenient tool to study central pain modulation, since the lack of music modulation on DNIC activation can be interpret as an interesting result. The outcomes suggest the

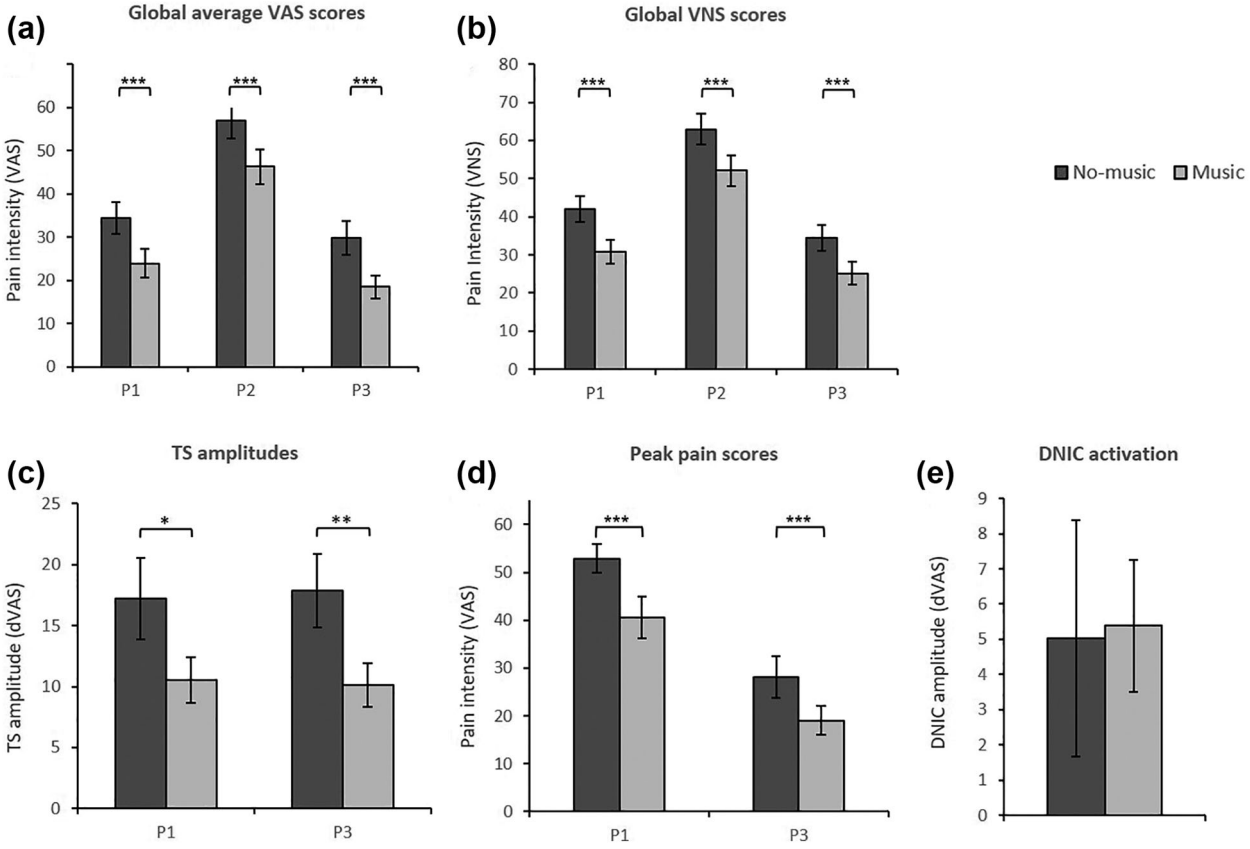

FIGURE 5. (a) Average electronic VAS scores during the three periods of the thermal stimulation paradigm. (b) Scores on the VNS during the three periods of the thermal stimulation paradigm. Pain intensity was significantly lower in the music condition for all period both VAS and VNS scores. (c) Differences between conditions in TS amplitude during each tonic heat pain tests. TS activation was significantly stronger when participants were not listening to music. (d) Differences between conditions in PP during each tonic heat pain tests. PP was significantly lower when participants were listening to music. (e) No difference between conditions was found in DNIC-effect. The *, **, *** denote the $p < .05$, $p < .01$, $p < .001$, respectively.

contribution of descending pain-modulatory systems in the analgesic effect of music and support the independency of DNIC feedback loop to the "top-down" descending inhibitory pain pathways.

EFFECTS OF MUSIC ON GLOBAL PERCEIVED PAIN

The participants chose musical pieces they rated as relaxed, emotionally neutral (neither happy nor sad), pleasant, and calm, confirming that the music choice ensured optimal conditions for music-induced analgesia (Good & Ahn, 2008; Roy et al., 2007). Participants reported significantly less pain with music compared to no music, confirming previous studies (Gardner et al., 1960; Good, 1996; Good & Ahn, 2008; Guétin et al., 2012). Pain ratings were approximately reduced by 10 units on the VAS and the VNS by music. It corresponded to about a 30% reduction of pain. It occurred during heat pain stimulations in this and other studies (Dobek et al., 2014; Roy et al., 2007). The present data indicates a music-induced analgesia triggered by cold nociceptive stimulation similar to what was observed for heat stimulations with a 18% reduction for all participants and without gender difference. However, other authors found analgesia to be effective on pain induced by cold pressure only in reducing pain unpleasantness (Garcia & Hand, 2016) or only in women (Mitchell & MacDonald, 2006). Differences in cold-water temperature may explain this discrepancy since those two studies used a 4 or 5°C temperature to elicit pain, in place of 12°C in the present work. Although 12°C was found sufficient to trigger a DNIC effect, pain perception is known to increase while the CPT temperature decreases (Mitchell, MacDonald, & Brodie, 2004; Tousignant-Laflamme et al., 2008). Music analgesia could be ineffective to reduce most severe pain. The same emotional brain circuits, including the amygdala, are known to be

activated by both music and pain stimulations (Blood & Zatorre, 2001; Koelsch, Fritz, Cramon, Muler, & Friederici, 2006; Neugebauer, 2015). Sharp pain could allocate some cerebral regions involved in affective process exclusively to nociceptive inputs, rendering music analgesia inefficient.

EFFECTS OF MUSIC ON PSYCHOPHYSICAL MEASUREMENTS

Psychophysical paradigms, such as TS of second pain and CPM, have been widely used to study endogenous pain facilitation and inhibition in healthy and clinical populations (Granot, Granovsky, Sprecher, Nir, & Yarnitsky, 2006; Granot et al., 2008; Horn-Hoffman, Kunza, Maddena, Schanbela, & Lautenbachera, 2018; Julien, Goffaux, Arsenault, & Marchand, 2005; Mackey et al., 2017; Nielsen & Arendt-Nielsen, 1998; Potvin et al., 2007; Price et al., 1977; Price et al., 2002; Tousignant-Laflamme et al., 2008). Along with functional imaging (Dobek et al., 2014) and the RIII reflex (Roy et al., 2011; Ruscheweyh, Kreusch, Albers, Sommer, & Marziniak, 2011), this study promotes psychophysical testing to evaluate the effect of music on inhibitory descending pain systems.

On one hand, we elicited peripheral and spinal pain facilitation with noxious heat stimulations in order to evaluate the effect of music listening on first and second pain responses. Acute pain perception is divided into two phases characterized by distinct temporal responses (Nielsen & Arendt-Nielsen, 1998; Ploner, Gross, Timmermann, & Schnitzler, 2002; Price & Dubner, 1977). First pain, which is also called fast-pain, is described as a sharp, pricking, and well-localized sensation. As we expected, this study demonstrated that music-induced analgesia induces an inhibitory effect on the peak of first pain (PP). During the first 30th seconds of the heat tests, maximum pain ratings were reduced by approximately 25% during the music session. PP is a first pain-related phenomenon that correlates to A-delta fibers activity (Tousignant-Laflamme et al., 2008; Treede et al., 1995), along with the spinal nociceptive withdrawal reflex (the RIII reflex; Dowman, 1991; Willer, Boureau, & Be-Fessard, 1978). A-delta fibers transmitted nociceptive information to central transmission neurons with a fast conduction velocity. Roy, Lebuis, Hugueville, Peretz, and Rainville (2012) investigated the modulatory effects of the emotional and arousal dimensions of music on the RIII reflex. RIII amplitude was found to decrease during the presentation of musical excerpts. Larger physiological effects were associated with pleasant-relaxing musical stimuli (Roy et al., 2012). Our results support, in accordance with this previous study, an inhibitory effect of music on pain signals conducted by A-delta fibers through descending modulation. Because music was judged as very pleasant and relaxing in the current study, both emotions and arousal induced by music could initiate the activation of the inhibitory pain pathways (Roy et al., 2012).

In addition, music listening was also found to affect second pain transmission. Second pain sensation is described as longer-lasting, burning, and more diffuse than first pain (Ploner et al., 2002). The amplitude of the temporal summation of second pain was reduced by about 40% when participants were listening to music. TS is the behavioral correlate of wind-up of spinal cord neurons (Chen, Shomojo, Svensson, & Arendt-Neilsen, 2000; Granot et al., 2006; Nielsen & Arendt-Nielsen, 1998; Potvin et al., 2007). It corresponds to an increase of pain perception associated with repetitive or persistent stimulations of nociceptive C-fibers (Nielsen & Arendt-Nielsen, 1998). Extended activation of those primary fibers enhances excitability of dorsal horn neurons (Li, Simone, & Larson, 1999), resulting in pain progressive amplification in association with changes in cerebral dynamics (Chen et al., 2000).

The concomitant impact of music listening on spinal pain transmission mediated by afferent A- and C-fibers strongly suggests the activation of supraspinal descending systems, involved in local spinal inhibition (Bingel et al., 2007; Calvino & Grilo, 2006; Cheng et al., 2015; Fields et al., 1977; Fields, Bry, Hentall, & Zorman, 1983). This is consistent with the implementation of descending inhibition pain pathways that blocked the transmission of nerve impulses from nociceptive non-specific dorsal horn neurons (Bingel et al., 2007; Fields et al., 1977). We propose that music listening could strengthen descending pain modulation by cerebral mechanisms that integrated psychological and physiological factors that are discussed below.

Our finding regarding spinal facilitatory pain mechanisms are at variance with those of Ruscheweyl et al. (2011) reporting no inhibition of PP and TS by music. This apparent discrepancy may be due to differences in goals and designs between the two studies. The purpose of this latter study was to assess whether PP and TS were modulated by several distraction tasks including music listening. In this context, participants were exclusively under music stimulation during the electrical pain procedure. In the current study, music was listened to for 10 minutes before the thermal stimulation paradigm, rendering the stimulus not only distracting but mainly as an inducer of emotions and relaxation. Furthermore, participants were asked to continually assess pain during the thermal stimulation paradigm so that their attention was intentionally

maintained toward painful stimulus, supporting the primacy of pain processing over any concurrent tasks (Miron, Duncan, & Bushnell, 1989). Thus, the effect of music distraction cannot be considered as a major factor in the interpretation of our results. The comparison between these two studies suggests that central modulation of pain by music depends on the activation of cerebral areas involved in emotional and/or relaxation processes.

On the other hand, inhibitory CPM-effect was well activated by CPM paradigm as expected, but not reinforced by music listening. This result is in evident opposition with the hypothesis that music could strengthen inhibitory descending pathways including DNIC. However, studies in rats demonstrated that this lower brainstem mediated inhibitory mechanism was relying on a spinal-supraspinal-spinal circuitry regardless of cortical brain activity (Bouhassira, Villanueva, Bing, & Le Bars, 1992; Patel & Dickenson, 2019; Villanueva & Le Bars, 1995). This result suggests that efferent inhibitory fibers involved in DNIC and music analgesia rely on distinct descending funiculars. We propose that CPM may be independent from emotion and/or relaxation as it is for distraction (Moont, Pud, Sprecher, Sharvit, & Yarnitsky, 2010). Therefore, cerebral process elicited by music stimulation could specifically target brainstem structures involved in general descending inhibitory pain pathways, irrespective of DNIC feedback loop.

The activation of descending inhibitory pathways in response to pleasurable music is consistent with imaging studies in humans that showed that pleasant music activates brain and brainstem areas such as the prefrontal cortex, the amygdala, and the periaqueductal gray, which are assumed to play a role in descending pain modulation (Blood & Zatorre, 2001; Dobek et al., 2014; Koelsch et al., 2006; Millan, 2002; Roy et al., 2009). Neuroendocrinological activities related to music or pain processes overlap suggesting, once more, the implication of central modulation in the antinociceptive effect of music (Blood & Zatorre, 2001; Dobek et al., 2014; Evers & Suhr, 2000; Goldstein, 1980; Koelsch et al., 2006; Neugebauer, 2015; Salimpoor, Benovoy, Larcher, Dagher, & Zatorre, 2011). Pleasurable experiences of music induce release of some of the neurotransmitters such as opioid, dopamine, and serotonin (Evers & Suhr, 2000; Goldstein, 1980; Salimpoor et al., 2011), which are associated with descending inhibitory pain modulation. The descending pain-modulation pathways originate from the periaqueductal gray, which contains populations of opioidergic and dopaminergic receptors (Fields, 2000; Wood, 2008). The opioid and dopamine neurons of the periaqueductal gray interact, contributing together to the activation of the descending serotonin track that project to the spinal dorsal horn, and inhibits A and C-fibers-mediated transmission (Doly, Fischer, Brisorgueil, Vergé, & Conrath, 2005; Pierce, Xie, Levine, & Peroutka, 1996). Recent functional magnetic resonance imaging responses in the amygdala and the periaqueductal gray were associated with a greater reduction of the dorsal horn responses in participants who received local heat pain stimulation when listening to music (Dobek et al., 2014). In conclusion, those results taken together are consistent with the hypothesis that emotions and relaxation induced by music could enhance the central neuromodulation of pain signaling from limbic and paralimbic regions to spinal dorsal horn.

LIMITS OF THE STUDY

Some limitations of our pilot study should be emphasized. The maximal temperature generated by the thermode was targeted at 46°C. This value was not enough to provoke in 14 participants a 50/100 VAS score. This may have limited the amplitude of the endogenous pain mechanisms. In particular, the absence of music modulation induced by CPM could be partly explained by an insufficient TS activation that would have hidden the role of DNIC in music analgesia.

The question of sexual difference in music-induced analgesia was not placed at the start of the study. For example, the possible role of female hormonal status (Iacovides, Avidon, & Baker, 2015) was not questioned. Therefore, our results, obtained with a small group, cannot be considered at variance with the higher sensitivity to experimental pain reported in healthy woman compared with men (Fillingim & Ness, 2000).

Finally, we recommend that this preliminary study be replicated with a larger sample size to include older healthy participants. The inclusion of additional variables is also recommended, such as music training, sound level, and stress assessment. Those potential factors could contribute to music-induced analgesia through distraction or engagement processes. Moreover, it would have been valuable to have some indicators of stress level before and after the thermal stimulation paradigm in each condition. The State-Trait Anxiety Inventory was the only criterion considered. In the future, the inclusion of at least a perceived stress scale before, between and after sessions would be valuable. In addition, the musical sequences used were soothing, instrumental, and new to the participants. These particular pieces of music question the impact of the arousal and the significance attached by the individual to the music type. Future studies should examine the reproducibility of the results with self-selected

preferred music, which should involve a high self-commitment and emotional engagement.

Conclusion

The current study shows the inhibitory effect of music on pain-related responses to spinal facilitatory pain mechanisms, consistent with the activation of descending inhibitory pain pathways. Given its universal and financial accessibility, we widely recommend music listening as a complementary approach to manage acute pain, in order to reinforce the descending pain modulation system.

Author Note

MC conceived the study design and conducted the recruitment and the outcomes assessments under the supervision of CB. ALFB provides her help and expertise in the experimental evaluations. MC analyzed the data. MC and CB wrote the paper. MC prepared figures and/or tables. CB, AW, ALFB, SG, BQ and LM reviewed drafts of the paper. All authors approved the final version of this paper.

We thank Music Care for the access to Music Care database. This study was funded by the APICIL foundation (reference 1084.17). The APICIL was not involved with the data collection or analysis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

Correspondence concerning this article should be addressed to Céline Bodéré, Laboratoire des Interactions Epithélium-Neurones, Faculté de médecine, Université de Bretagne Occidentale, 22 rue Camille Desmoulins, 29238 Brest, France. E-mail: celine.bodere@univ-brest.fr

References

Basbaum, A. I., & Fields, H. L. (1978). Endogenous pain control mechanisms: Review and hypothesis. *Annals of Neurology*, *4*(5), 451–462.

Bernatzky, G., Presch, M., Anderson, M., & Panksepp, J. (2011). Emotional foundations of music as a non-pharmacological pain management tool in modern medicine. *Neuroscience and Biobehavioral Reviews*, *35*(9), 1989–1999.

Bingel, U., Schoell, E., & Büchel, C. (2007). Imaging pain modulation in health and disease. *Current Opinion in Neurology*, *20*(4), 424–431.

Bingel, U., Schoell, E., Herken, W., Büchel, C., & May, A. (2007). Habituation to painful stimulation involves the antinociceptive system. *Pain*, *131*, 21–30.

Bingel, U., & Tracey, I. (2008). Imaging CNS modulation of pain in humans. *Physiology (Bethesda)*, *23*(3), 371–380.

Blood, A. J., & Zatorre, R. J. (2001). Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proceedings of the National Academy of Sciences*, *98*, 11818–11823.

Bouhassira, D., Villanueva, L., Bing, Z., & Le Bars, D. (1992). Involvement of the subnucleus reticularis dorsalis in diffuse noxious inhibitory controls in the rat. *Brain Research*, *595*, 353–357.

Bradshaw, D. H., Donaldson, G. W., Jacobson, R. C., Nakamura, Y., & Chapman, C. R. (2011). Individual differences in the effects of music engagement on responses to painful stimulation. *The Journal of Pain*, *12*(12), 1262–1273.

Calvino, B., & Grilo, R. M. (2006). Le contrôle central de la douleur. *Revue du Rhumatisme*, *73*(1), 10–18.

Chen, C., Shomojo, P., Svensson, L., & Arendt-nielsen, L. (2000). Brain dynamics of scalp evoked potentials and current source densities to repetitive (5-pulse train) painful stimulation of skin and muscle: Central correlate of temporal summation. *Brain Topography*, *13*(1), 59–72.

Cheng, J. C., Erpelding, N., Kucyi, A., Desouza, D. D., & Davis, K. D. (2015). Individual differences in temporal summation of pain reflect pronociceptive and antinociceptive brain structure and function. *The Journal of Neuroscience*, *35*, 9689–9700.

Cohen, J. (1977). *Statistical power analysis for the behavioral sciences.* Hillsdale, NJ: Lawrence Erlbaum Associates.

Dobek, C. E., Beynon, M. E., Bosma, R. L., & Stroman, P. W. (2014). Music modulation of pain perception and pain-related activity in the brain, brain stem, and spinal cord: A functional magnetic resonance imaging study. *The Journal of Pain*, *15*(20), 1057–1068.

Doly, S., Fischer, J., Brisorgueil, M-J., Vergé, D., & Conrath, M. (2005). Pre- and postsynaptic localization of the 5-HT7 receptor in rat dorsal spinal cord: Immunocytochemical evidence. *Journal of Comparative Neurology*, *490*(3), 256–269.

Dowman, R. (1991). Spinal and supraspinal correlates of nociception in man. *Pain*, *45*(3), 269–281.

Eippert, F., Finsterbusch, J., Bingel, U., & Büchel, C. (2009). Direct evidence for spinal cord involvement in placebo analgesia. *Science*, *326*(5951), 404.

Evers, S., & Suhr, B. (2000). Changes of the neurotransmitter serotonin but not of hormones during short time music perception. *European Archives of Psychiatry and Clinical Neuroscience*, *250*(3), 144–147.

Fields, H. L. (2000). Pain modulation: Expectation, opioid analgesia and virtual pain. *Progress in Brain Research*, *122*, 245–253.

Fields, H. L., Basbaum, A. I., Clanton, C. H., & Anderson, S. D. (1977). Nucleus raphe magnus inhibition of spinal cord dorsal horn neurons. *Brain Research*, *126*, 441–453.

Fields, H. L., Bry, J., Hentall, I., & Zorman, G. (1983). The activity of neurons in the rostral medulla of the rat during withdrawal from noxious heat. *The Journal of Neuroscience*, *3*(12), 2545–2552.

Fillingim, R. B., & Ness, T. J. (2000). Sex-related hormonal influences on pain and analgesic responses. *Neuroscience and Biobehavioral Reviews*, *24*, 485–501.

French, D. J., Noël, M., Vigneau, F., French, J. A., Cyr, C. P., & Thomas, R. (2005). L'Échelle de dramatisation face à la douleur PCS-CF: Adaptation canadienne en langue française de l'échelle Pain Catastrophizing Scale. [PCS-CF: A French-language, French-Canadian adaptation of the Pain Catastrophizing Scale.]. *Canadian Journal of Behavioural Science*, *37*(3), 181–192

Garcia, R., & Hand, C. (2016). Analgesic effects of self-chosen music type on cold pressor-induced pain: Motivating vs. relaxing music. *Psychology of Music*, *44*(5), 545–564.

Gardner, W. J., Licklider, J. C., & Weisz, A. Z. (1960). Suppression of pain by sound. *Science*, *132*, 32–33.

Gauthier, J., & Bouchard, S. (1993). Adaptation canadienne-française de la forme révisée du State Trait Anxiety Inventory de Spielberger. *Canadian Journal of Behavioural Science*, *25*(4), 559–578.

Good, M. (1996). Effects of relaxation and music on postoperative pain: A review. *Journal of Advanced Nursing*, *24*, 905–914.

Good, M., & Ahn, S. (2008). Korean and American music reduces pain in Korean women after gynecologic surgery. *Pain Management Nursing*, *9*(3), 96–103.

Goldstein, A. (1980). Thrills in response to music and other stimuli. *Physiological Psychology*, *8*, 126–129.

Granot, M., Granovsky, Y., Sprecher, E., Nir, R. R., & Yarnitsky, D. (2006). Contact heat-evoked temporal summation: Tonic versus repetitive-phasic stimulation. *Pain*, *122*, 295–305.

Granot, M., Weissman-fogel, I., Crispel, Y., Pud, D., Granovsky, Y., Sprecher, E., & Yarnitsky, D. (2008). Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: Do conditioning stimulus painfulness, gender and personality variables matter? *Pain*, *136*, 142–149.

Guétin, S., Giniès, P., Siou, D. K., Picot, M. C., Pommié, C., Guldner, E., Gosp, A. M., et al. (2012). The effects of music intervention in the management of chronic pain: A single-blind, randomized, controlled trial. *The Clinical Journal of Pain*, *28*, 329–337.

Hauck, M., Metzner, S., Rohlffs, F., Lorenz, J., & Engel, A. K. (2013). The influence of music and music therapy on pain-induced neuronal oscillations measured by magnetencephalography. *Pain*, *154*(4), 539–547.

Horn-Hofmanna, C., Kunza, M., Maddena, M., Schnabela, E. L., & Lautenbachera, S. (2018). Interactive effects of conditioned pain modulation and temporal summation of pain—The role of stimulus modality. *Pain*, *159*(12), 2641–2648.

Huang, S., Good, M., & Albert, J. (2007). Music reduced cancer pain via relaxation and distraction. [Abstract]. *The Journal of Pain*, *8*(4), S58.

Iacovides, S., Avidon, I., & Baker, F. C. (2015). Does pain vary across the menstrual cycle? A review. *European Journal of Pain*, *19*, 1389–1405.

Jaber, S., Bahloul, H., Guetin, S., Chanques, G., Sebbane, M., & Eledjam, J.-J. (2007). Effets de la musicothérapie en réanimation hors sédation chez des patients en cours de sevrage ventilatoire versus des patients non ventilés. *Annales Françaises d'Anesthésie et de Réanimation, 26*(1), 30–38.

Julien, N., Goffaux, P., Arsenault P., & Marchand, S. (2005). Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain*, *114*, 295–302.

Kennedy, D. L., Kemp, H. I., Ridout, D., Yarnitsky, D., & Rice, A. S. (2016). Reliability of conditioned pain modulation: a systematic review. *Pain*, *157*, 2410–2419.

Koelsch, S., Fritz, T., Cramon, D. Y., Muller, K., & Friederici, A. D. (2006). Investigating emotion with music: An fMRI study. *Human Brain Mapping*, *27*, 239–250.

Kong, J. T., Johnson, K. A., Balise, R. R., & Mackey, S. (2013). Test-Retest Reliability of Thermal Temporal Summation Using an Individualized Protocol. *The Journal of Pain, 14*(1), 79–88.

Le Bars, D. (2002). The whole body receptive field of dorsal horn multireceptive neurones. *Brain Research Review*, *40*(1-3), 29–44.

Le Bars, D., Dickenson, A. H., Besson, J. M. (1979a). Diffuse noxious inhibitory controls (DNIC) I. Effects on dorsal horn convergent neurones in the rat. *Pain*, *6*, 283–304.

Le Bars, D., Dickenson, A. H., & Besson, J. M. (1979b). Diffuse noxious inhibitory controls (DNIC) II. Lack of effect on non-convergent neurones, supraspinal involvement and theoretical implications. *Pain*, *6*, 305–327.

Li, J., Simone, D. A., & Larson, A. A. (1999). Wind-up leads to characteristics of central sensitization. *Pain*, *79*, 75–82.

Lie, M. U., Matre, D., Hansson, P., Stubhaug, A., Zwart, J. A., & Nilsen, K. B. (2017). A tonic heat test stimulus yields a larger and more reliable conditioned pain modulation effect compared to a phasic heat test stimulus. *Pain Reports*, *2*, e626.

Macbeth, G., Razumiejczyk, E., & Ledesma, R.D. (2011). Cliff's delta calculator: A non-parametric effect size program for two groups of observations. *Universitas Psychologica*, *10*, 545–555.

Mackey, I. G., Dixon, E. A., Johnson, K., & Kong, J. T. (2017). Dynamic quantitative sensory testing to characterize central pain processing. *Journal of Visualized Experiments*, *120*, e54452.

Millan, M. J. (2002). Descending control of pain. *Progress in Neurobiology, 66*(6), 355–474.

Miron, D., Duncan, G. H., & Bushnell, C. M. (1989). Effects of attention on the intensity and unpleasantness of thermal pain. *Pain*, *39*(3), 345–352.

Mitchell, L. A., Macdonald, R. A., & Brodie, E. E. (2004). Temperature and the cold pressor test. *The Journal of Pain*, *5*(4), 233–237.

Mitchell, L. A., & Macdonald, R. A. (2006). An experimental investigation of the effects of preferred and relaxing music listening on pain perception. *Journal of Music Therapy, 43*(4), 295–316.

Moont, R., Pud, D., Sprecher, E., Sharvit, G., & Yarnitsky, D. (2010). 'Pain inhibits pain' mechanisms: Is pain modulation simply due to distraction? *Pain*, *150*, 113–120.

Neugebauer, V. (2015). Amygdala pain mechanisms. *Handbook of Experimental Pharmacology*, *227*, 261–284.

Nielsen, J., & Arendt-nielsen, L. (1998). The importance of stimulus configuration for temporal summation of first and second pain to repeated heat stimuli. *European Journal of Pain*, *2*(4), 329–341.

Ossipov, M. H., Dussor, G. O., & Porreca, F. (2010). Central modulation of pain. *Journal of Clinical Investigation*, *120*(11), 3779–3787.

Patel, R., & Dickenson, A. (2019). A study of cortical and brainstem mechanisms of diffuse noxious inhibitory controls in anaesthetised normal and neuropathic rats. *European Journal of Neuroscience*, *51*(4), 952–962.

Pichot, P., & Lempériére, T. (1964). Analyse factorielle d'un questionnaire d'auto-évaluation des symptômes dépressifs. *Revue de Psychologie Appliquée*, *14*, 15–29.

Pierce, P. A., Xie, G. X., Levine, J. D., & Peroutka, S. J. (1996). 5-hydroxytryptamine receptor subtype messenger RNAs in rat peripheral sensory and sympathetic ganglia: A polymerase chain reaction study. *Neuroscience*, *70*(2), 553–559.

Ploner, M., Gross, J., Timmermann, L., & Schnitzler, A. (2002). Cortical representation of first and second pain sensation in humans. *Proceedings of the National Academy of Sciences*, *99*(19), 12444–12448.

Potvin, S., Stip, E., Tempier, A., Pampoulova, T., Bentaleb, L. A., Lalonde, P., et al. (2007). Pain perception in schizophrenia: No changes in diffuse noxious inhibitory controls (DNIC) but a lack of pain sensitization. *Journal of Psychiatric Research*, *42*(12), 1010–1016.

Price, D. D., & Dubner, R. (1977). Mechanisms of first and second pain in the peripheral and central nervous systems. *Journal of Investigative Dermatology*, *69*(1), 167–171.

Price, D. D., Hu, J. W., Dubner, R., & Gracely, R. H. (1977). Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. *Pain*, *3*, 57–68.

Price, D. D., Finniss, D. G., & Benedetti, F. (2008). A comprehensive review of the placebo effect: Recent advances and current thought. *Annual Review of Psychology*, *59*, 565–590.

Price, D. D., Staud, R., Robinson, M. E., Mauderli, A. P., Cannon, R. L., & Vierck, C. J. (2002). Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. *Pain*, *99*, 49–59.

Roy, M., Lebuis, A., Hugueville, L., Peretz, I., Rainville, P. (2012). Spinal modulation of nociception by music. *European Journal of Pain*, *16*(6), 870–877.

Roy, M., Peretz, I., & Rainville, P. (2007). Emotional valence contributes to music-induced analgesia. *Pain*, *134*(1-2), 140–147.

Roy, M., Piché, M., Chen, J. I., Peretz, I., & Rainville, P. (2009). Cerebral and spinal modulation of pain by emotions. *Proceedings of the National Academy of Sciences*, *106*, 20900–20905.

Ruscheweyh, R., Kreusch, A., Albers, C., Sommer, J., & Marziniak, M. (2011). The effect of distraction strategies on pain perception and the nociceptive flexor reflex (RIII reflex). *Pain*, *152*(11), 2662–2671.

Rustamov, N., Northon, S., Tessier, J., Leblond, H., & Piché, M. (2019) Integration of bilateral nociceptive inputs tunes spinal and cerebral responses. *Scientific Reports*, *9*, e7143.

Salimpoor, V. N., Benovoy, M., Larcher, K., Dagher, A., & Zatorre, R. J. (2011). Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nature Neuroscience*, *14*, 257–262.

Staud, R., Vierck, C. J., Cannon, R. L., Mauderli, A. P., & Price, D. D. (2001). Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain*, *91*, 165–175.

Tousignant-Laflamme, Y., Page, S., Goffaux, P., & Marchand, S. (2008). An experimental model to measure excitatory and inhibitory pain mechanisms in humans. *Brain Research*, *1230*, 73–79.

Treede, R. D., Meyer, R. A., Raja, S. N., & Campbell, J. N. (1995). Evidence for two different heat transduction mechanisms in nociceptive primary afferents innervating monkey skin. *Journal of Physiology*, *483*(3), 747–758.

Vargha, A., & Delaney, H. D. (2000). A critique and improvement of the CL common language effect size statistics of McGraw and Wong. *Journal of Educational and Behavioral Statistics*, *25*(2), 101–132.

Villanueva, L., & Le Bars, D. (1995). The activation of bulbo-spinal controls by peripheral nociceptive inputs: Diffuse noxious inhibitory controls. *Biological Research*, *28*(1), 113–125.

Willer, J. C., Boureau, F., & Be-fessard, D. (1978). Role of large diameter cutaneous afferents in transmission of nociceptive messages: Electrophysiological study in man. *Brain Research*, *152*, 358–364.

Wood, P. B. (2008). Role of central dopamine in pain and analgesia. *Expert Review of Neurotherapeutics*, *8*(5), 781–797.

Zhao, H., & Chen, A. C. N. (2009). Both happy and sad melodies modulate tonic human heat pain. *The Journal of Pain*, *10*(9), 953–960.