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The effect of background liked music on acute pain perception and its neural correlates

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Abstract

Music shows tremendous promise in pain relief, especially when considering its non-pharmacological nature. However, our understanding of the precise mechanisms behind music-induced analgesia (MIA) remains poor. The positive emotional state induced by music is one of the key components explaining MIA. To test this possibility and reveal its neural correlates, the present study applied nociceptive laser stimuli to 28 healthy participants when their liked or disliked songs were played as background music, or when they were resting in silence. Differences among conditions were quantified by self-reports of pain intensity and unpleasantness, as well as brain activations in response to acute laser stimuli. As expected, liked music significantly lowered pain ratings to acute painful stimuli compared to disliked music and no music. Consistent with this observation, brain activations in response to acute painful stimuli were decreased within brain areas encoding sensory components of pain, such as the right precentral and postcentral gyri (PreCG/PoCG), brain areas related to affective components of pain, such as the anterior cingulate cortex and bilateral putamen, and brain areas associated with motor control and avoidance reactions to pain, such as the left cerebellum, when liked music was played in the background in comparison to disliked music. Importantly, the relationship between music listening and differences in pain ratings of two music conditions was mediated by the magnitude of right PreCG/PoCG and left cerebellum activations. These findings deepened our understanding of the analgesic benefits of background liked music, a property relevant to clinical applications.

KEYWORDS

emotional modulation, fMRI, liked background music, music-induced analgesia

1 | INTRODUCTION

In the past decade, there has been a surge of interest in applying music as a nonpharmacological adjunct to conventional pain

management (Bernatzky et al., 2011; Chai et al., 2017; Lu et al., 2021). As a safe and nonaddictive approach, music has been used for healing in many cultures, which can be dated back to ancient Egyptian and Greece. Accumulating evidence from meta-analyses on music-induced

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analgesia (MIA) indicates that music listening is effective in clinical practice for the modulation of chronic pain (Garza-Villarreal et al., 2017) and acute postoperative pain (Hole et al., 2015). Despite numerous clinical reports of music benefits in the management of different pain conditions, the underlying neural mechanisms are widely unknown. This is partly because clinical practice involves the coexistence of multiple therapeutic factors and environmental conditions. Thus, several studies in which painful stimuli were applied to healthy individuals were conducted to reveal brain correlates of MIA without potential confounding factors (e.g., drugs, pain conditions, and durations). Although there is no consensus as to what kind of music is the best for pain alleviation and by what means music modulates pain perception, it is consistently reported that self-chosen preferred, pleasant music is more likely to reduce pain in comparison to both active and passive control conditions (Garcia & Hand, 2016; Guetin et al., 2012; Howlin & Rooney, 2021), and several possible underlying mechanisms have been proposed accordingly (Lu et al., 2021; Lunde et al., 2019).

In theory, MIA could occur mainly through two very different processes. One model proposes that MIA is achieved through emotionally induced effects of music. For instance, listening to preferred music reduces pain (Hekmat & Hertel, 1993; Lu et al., 2019), and the pain decreases as a function of self-reported music pleasantness (Roy et al., 2008), suggesting a positive emotional impact of music on pain processing. An alternative model proposes that music listening offers effective distraction, thereby pulling one's attention away from pain (Mitchell et al., 2006; Ruscheweyh et al., 2011). Using magnetoencephalography, Hauck et al. (2013) found the analgesic effect induced by preferred music on laser heat pain was associated with a significant power reduction of delta-band activity in the cingulate gyrus. Since the laser-evoked activity in the delta band contributes to the late laser-evoked potentials generated in the cingulate cortex, whose amplitude has been found to be modulated by distraction (Lorenz & Garcia-Larrea, 2003), this finding indicated attentional engagement away from painful stimulation when listening to preferred music.

In parallel, using functional magnetic resonance imaging (fMRI), two studies identified several key regions associated with MIA. Specifically, Dobek et al. (2014) compared individuals' brain responses to noxious thermal stimuli while listening to preferred music or resting in silence. They observed significant differences in BOLD responses in areas of the limbic system between the two conditions, including the ventral tegmental area, nucleus accumbens, insula, and anterior cingulate cortex (ACC). Similarly, Antioch et al. (2020) suggested that listening to preferred music, in contrast to resting in silence, mediated the brain responses to electrical stimuli in the ACC. It is not surprising that music listening involves neural circuits responsible for reward and pleasure processing (Koelsch, 2014; Mas-Herrero et al., 2021). Indeed, long-established lines of research have suggested that dopamine release occurs with highly pleasant music listening, and the magnitude of the response was related to the reported degree of pleasure felt (Salimpoor et al., 2011). These results provide strong evidence indicating music-induced emotional modulation of pain processing. On the other hand, these neuroimaging findings bring more questions than answers. First, the contrast

between the music and no music conditions cannot distinguish the music- and sound-induced effects, as the pain reduction observed from such contrast could be attributed to distraction of auditory stimuli rather than emotion induction of preferred music. Second, the two studies mainly focused on pain-related brain responses with no psychophysiological correlations, providing limited information about the mechanisms underlying MIA.

To overcome these limits, the present study employed one's disliked music as an active control, which allows for direct comparison between music with distinct preferences (i.e., liked vs. disliked). We hypothesized that the modulation of pain-related brain activations associated with liked music results possibly from interactions between pain and emotional brain networks. To test this hypothesis, the present investigation applied acute painful stimuli to healthy participants when their liked or disliked songs were played as background music. As music-induced emotion accumulates over time (Krumhansl, 1997), participants were first passively listening to music for 5 min prior to the pain rating task. We defined passive listening as attentive listening while remaining still (i.e., not tapping along to the music). Differences among the two music conditions were quantified through self-reports of pain intensity and unpleasantness (PU) and brain activity as measured by fMRI. In addition, a no music condition was included as a passive control condition. This manipulation allowed us to determine the influence of auditory stimuli per se in pain relief by comparing music conditions (regardless of the valence music conveyed) with no music condition (i.e., the disruptive effect induced by sounds) and to exclude the possibility that the different response to painful stimuli between the liked and disliked music conditions was due to a hyperalgesic effect of disliked music rather than an analgesic effect of liked music.

2 | MATERIALS AND METHODS

2.1 | Pretest screening

To include participants whose liked music were others' disliked music, and vice versa, a pre-test screening was administered online to collect lists of liked and disliked music. Seventy participants were recruited online and asked to provide three of their most liked songs and three of their most disliked songs. After excluding repetitive songs, 33 songs with a high frequency of occurrence in both liked and disliked music lists were selected. An additional group of participants ($n = 135$) was asked to rate each of these songs on a scale ranging from 1 (*dislike*) to 7 (*like*) in terms of how much they liked it. Finally, 14 pairs of right-handed participants were selected for the formal experiment, which would be powered enough to detect a medium-sized effect (see the Participants section). In each pair, one participant's most liked music was the other's most disliked music. In other words, each participant's liked music was used as another participant's disliked music, such that group-averaged data analysis involved the comparison of identical sets of stimuli. Similar manipulation was used in a previous study (Blood & Zatorre, 2001).

2.2 | Participants

The required sample size for exploring the music effect on pain was determined using G*Power software (available at <http://www.gpower.hhu.de/en.html>) by setting statistical power ($1-\beta$) at .80 with a medium effect size ($f = 0.25$) based on the result from a previous meta-analysis study on MIA (Lu et al., 2021), and a significance level (α) at .05 (Cunningham & McCrum-Gardner, 2007). A priori test for repeated-measures analysis of variance (rmANOVA) with within factors (three measurements) yielded the minimum required sample size of 28; therefore, 28 self-reported right-handed volunteers (17 females, mean $\pm$ SD age = 21 ± 2 years, age range = 19–26 years) with normal hearing and normal or corrected-to-normal vision participated in the study. None reported any auditory, neurological, or psychiatric disorder. Participants had neither chronic pain nor analgesics use 24 hours prior to the experiment. They were all musically naive individuals (i.e., none of them had more than 1 year of formal musical training; mean $\pm$ SD = 0.04 ± 0.19 years). All participants gave their written consent and filled out an fMRI safety form prior to testing. The study was approved by the local ethics committee of the Institute of Psychology, Chinese Academy of Sciences (Ref. No: H17026).

2.3 | Stimuli

2.3.1 | Auditory stimuli

After excluding repetitive songs from the 28 selections of 14 pairs of participants, 18 songs with different motifs were used in the present study (see Table S1). All selected music pieces contained lyrics and most were performed in Mandarin by Chinese singers. The music genre, duration, tempo, and other music structures varied from one piece to another, suggesting a diverse music taste in our sample. Prior to the formal experiment, participants rated their liked and disliked music on an 11-point Numerical Rating Scale (NRS); that is, *how often do you listen to this piece of music* (i.e., frequency); *how familiar are you with this piece of music* (i.e., familiarity); *how much do you like this piece of music* (i.e., liking); *how much do you want to listen to this piece of music* (i.e., wanting); and *how much do you expect that this piece of music could lead to pain reduction* (i.e., expectation). As expected, participants showed distinct attitudes toward their liked and disliked music. Specifically, the Wilcoxon signed-rank test showed that the ratings on frequency, familiarity, liking, wanting, and expectation for their liked music were significantly higher than those for their disliked music, all $p < .001$ (see Table S2). Unsurprisingly, these measures were intercorrelated to some extent. For instance, liking was positively correlated with wanting for both liked and disliked music (see Table S3).

2.3.2 | Nociceptive stimuli

Nociceptive-specific radiant-heat stimuli were generated by an infrared neodymium yttrium aluminum perovskite (Nd: YAP) laser with a

wavelength of 1.34 μm (Electronic Engineering, Italy). At this wavelength, laser pulses directly activate nociceptive terminals in the most superficial skin layers (Iannetti et al., 2006). Laser pulses were directed to a circular area (diameter = 4 cm) on the dorsum of the subject's left hand. A He-Ne laser pointed to the area to be stimulated. The laser beam was transmitted via an optic fiber, and its diameter was set at ~ 7 mm (~ 38 mm²) by focusing lenses. The duration of the laser pulse was 4 ms. After each stimulus, the target of the laser beam was shifted by at least 1 cm in a random direction to avoid nociceptor fatigue or sensitization. To determine the laser intensity used in the experiment and to familiarize themselves with the laser stimuli, participants were instructed to rate the pain intensity (PI) of an initial series of laser stimuli prior to the experiment on an NRS ranging from 0 (*no sensation*) to 10 (*the worst pain imaginable*), with 4 represents denoting pinprick pain threshold (Hu et al., 2014). The energy of laser stimuli to be used in the formal experiment was individually determined by increasing the stimulus energy in steps of 0.25 J until an average rating of 6 out of 10 was obtained, which represents a moderate level of pain. The energies used in the present study were 3.98 ± 0.47 J across all participants, ranging from 2.75 to 4.5 J.

2.4 | Experimental procedure

The MRI session consisted of three functional runs to identify brain regions preferentially responding to nociceptive laser stimuli under different experimental conditions, and two runs of acquisition of high-resolution anatomical images (T1-weighted and T2-weighted) between every two functional runs (see Figure 1a). During the task-fMRI scan, participants were instructed to keep their eyes open and look at a cross fixation, which was presented in the center of the MRI-compatible screen located at the rear of the scanner and viewed by participants through a mirror mounted on the head coil. Music was played throughout the whole run in the liked and disliked music conditions. For the first 5 min of each functional scan, participants were resting or listening to music presented via a pair of MRI-compatible headphones, if any, while remaining still. Sequentially, participants were requested to evaluate their arousal (*calm-excited*), the valence assigned to what they have just heard (*negative-positive*), self-felt pleasantness (*unpleasant-pleasant*), and the extent to which they were attracted by what they have just heard with an emphasis on the degree of attention they paid to external sounds (i.e., attractiveness, *low-high*) within 20 s (5 s for each). After that, participants were presented with a pain rating task, in which they were asked to ignore the auditory stimuli to limit the possible influence of attention, and rate PI and PU by the end of each trial (Figure 1b). In this way, the task requirement was comparable in the three experimental conditions (i.e., pain rating only). Twenty nociceptive stimuli were delivered during each task-fMRI run. Each trial started with a 6 s fixation of a white cross centered on the screen, followed by the delivery of a nociceptive laser stimulus. Participants were asked to rate the perceived PI and PU within 10 s (5 s for

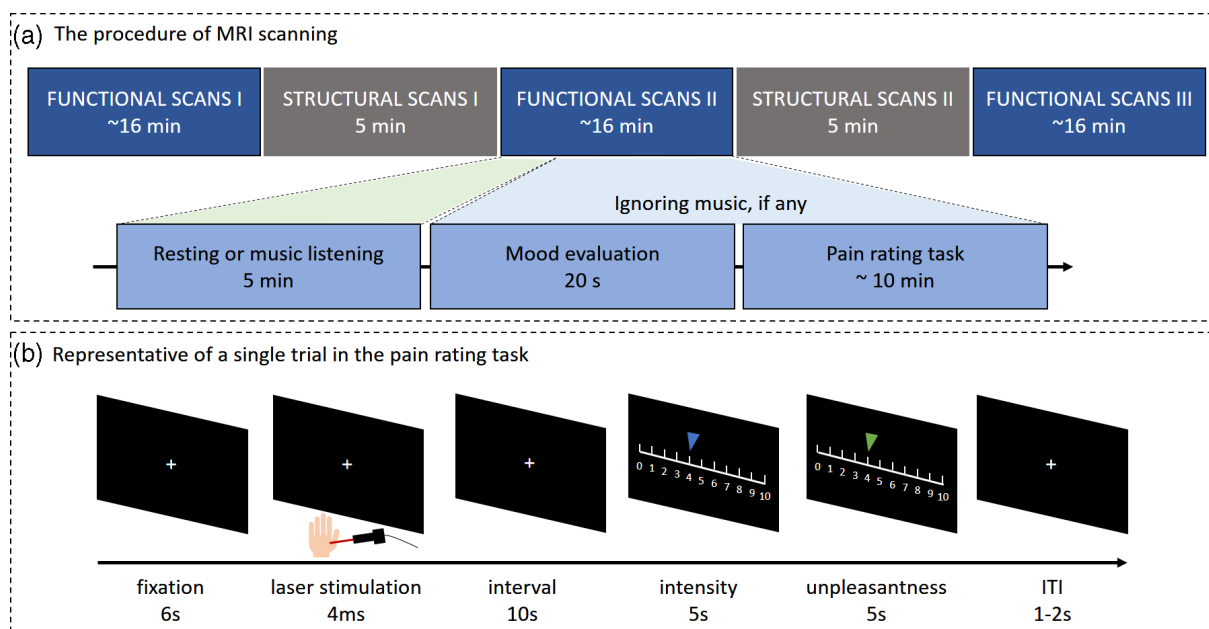


FIGURE 1 MRI scanning paradigm and experimental design. (a) The MRI session consisted of three functional runs and two runs of acquisition of high-resolution anatomical images between every two functional runs. For the first 5 min of each functional scan, participants were resting or listening to music, while remaining still. Sequentially, participants were requested to evaluate their arousal, the valence assigned to what they have just heard, self-felt pleasantness, and the extent to which they were attracted by what they have just heard within 20 s. After that, participants were presented with a pain rating task. (b) Representative of a single trial in the pain rating task, in which participants were asked to ignore the auditory stimuli and rate pain intensity (PI) and unpleasantness (PU) by the end of each trial. Twenty nociceptive stimuli were delivered during each task-fMRI run. Each trial started with a 6 s fixation of a white cross centered on the screen, followed by the delivery of a nociceptive laser stimulus. Participants were asked to rate the perceived PI and PU within 10 s after a 10-s interval. The intertrial interval (ITI) was 1 or 2 s randomly.

each) after a 10-s interval on an 11-point NRS by pressing buttons on a shank in their right hand. The intertrial interval (ITI) was 1 or 2 s randomly.

2.5 | MRI image acquisition

Both structural and functional MRI data were acquired on a 3.0 Tesla GE-MRI scanner. Participants were laid in a supine position in the scanner with cushions fit around their heads to reduce motion artifacts and the impact of scanner noise. For each participant, a T1-weighted structural image was acquired using 3D SPGR pulse sequence (TR/TE = 6.896 ms/2.992 ms, flip angle = 8°, FOV = 256 mm × 256 mm, matrix = 256 × 256, slices = 176, slice thickness = 1 mm). In addition, a T2-weighted structural image was acquired using 3D Cube T2 pulse sequence (TR/TE = 2500/71.482 ms, flip angle = 90°, FOV = 256 mm × 256 mm, matrix = 256 × 256, slices = 176, slice thickness = 1 mm) for clinical assessment, therefore it was not included in data analysis. Participants were asked to keep their eyes closed during the subsequent acquisition of high-resolution anatomical images. A whole-brain gradient-echo echoplanar imaging (GE-EPI) sequence was used for obtaining functional data (TR/TE = 2000/2.9 ms; flip angle: 90°; FOV = 192 mm × 192 mm; matrix = 64 × 64; slices = 43; slice thickness = 3 mm).

2.6 | Data analysis

2.6.1 | Behavioral data analysis

The evaluations and subjective ratings of PI and PU were compared using one-way rmANOVA with a within-subject factor of condition, as rmANOVA is not very sensitive to departures from the multivariate normal distribution (Cohen, 2013). Greenhouse–Geisser adjustments were used in light of violations of the sphericity assumption. When the main effect was significant ($p < .05$), post hoc paired-sample t -tests were performed. Bonferroni correction was applied for multiple comparisons. Partial eta-squared (η_p^2) was calculated to reflect the effect size. The link between subjective ratings, mood ratings (music-conveyed valence and self-felt pleasantness) after 5-min music listening, and brain activations was quantified by the Spearman's rank correlation, as it is not sensitive to extreme values (de Winter et al., 2016).

2.6.2 | Image preprocessing

fMRI data were preprocessed and analyzed using Statistical Parametric Mapping 12 (SPM12) (Wellcome Trust Center for Neuroimaging,

London). The first 162 volumes in each run (i.e., 5 min of listening to music or resting) were discarded to allow for signal stabilization. Images were slice-time corrected using the middle slice and realigned to the mean slice. The resulting images were normalized to the Montreal Neurological Institute (MNI) space (resampling voxel size = $3 \times 3 \times 3$ mm³) and then smoothed with a 5 mm full-width at half maximum Gaussian kernel. Moreover, we band-pass filtered images temporally (0.01–0.15 Hz). Six head motion estimates and two physiological time series (white matter and cerebrospinal fluid) were also regressed out.

2.6.3 | Task fMRI analysis

After preprocessing, first-level analyses were conducted using the general linear model. Regressors included three conditions (liked music, disliked music, and no music) convolved with the canonical hemodynamic response function with temporal derivatives. Moreover, we accounted for temporal autocorrelations using a first-order autoregressive model (AR[1]). To identify brain regions activated by laser stimuli, we submitted stimulation-related contrast images (liked music, disliked music, and no music) to group-level analyses using a random effect analysis with one-sample *t*-tests. One-way rmANOVA was then employed to test if there were any differential activations among the three conditions. We also conducted planned comparisons to specifically examine the effect of music listening on pain perception (i.e., $1/2 \times [\text{liked music} + \text{disliked music}] - \text{no music}$) as well as the effect of liked music relative to disliked music on pain perception (i.e., $\text{disliked music} - \text{liked music}$). In whole-brain analyses, the significance threshold was set at $p = .005$ at the voxel level and $p_{\text{FDR}} = .05$ at the cluster level.

2.6.4 | Mediation analysis

To examine the roles of pain-related areas in MIA, we extracted BOLD signals in clusters that showed significant differences between the two music conditions, and correlated the effect of listening to

liked music on these clusters (disliked music – liked music) with perceptual rating differences between the two conditions (disliked music – liked music) using the Spearman's rank correlation coefficient. We also conducted a within-subject mediation analysis (Montoya & Hayes, 2017) to further test whether the MIA is mediated by activity in pain-related brain areas. The two music conditions were treated as the independent variable, pain ratings (intensity or PU) as the dependent variable, and BOLD responses in brain regions whose activity differed between the two music conditions as the mediating variable. Confidence intervals were constructed using the percentile bootstrap method based on 1000 bootstrap samples to test the statistical significance of each path in the mediation model.

3 | RESULTS

3.1 | Emotional state evaluations after 5 min with or without music listening

As shown in Table 1, participants' emotional states after 5 min of music listening or resting were different among the three conditions, as reflected by the significant main effects of condition for all dimensions, that is, arousal ($F_{[2, 54]} = 10.03$, $p < .001$, $\eta_p^2 = .27$), valence ($F_{[2, 54]} = 37.40$, $p < .001$, $\eta_p^2 = .58$), pleasantness ($F_{[2, 54]} = 34.05$, $p < .001$, $\eta_p^2 = .56$), and attractiveness ($F_{[2, 54]} = 12.81$, $p < .001$, $\eta_p^2 = .32$). Post hoc pairwise comparisons further revealed that participants felt more positive and pleasant after listening to liked music (both $p < .001$), but less pleasant after listening to disliked music ($p < .05$), when compared with no music condition. In addition, two music conditions were also significantly different in terms of valence and pleasantness ratings (both $p < .001$). Moreover, the ratings of music-conveyed valence and self-felt pleasantness were highly correlated in both liked (Spearman's $\rho = .660$, $p < .001$) and disliked music conditions (Spearman's $\rho = .746$, $p < .001$). As expected, both music conditions were more attractive than no music condition (both $p < .05$). By contrast, the attractiveness and arousal ratings were not significantly different in liked and disliked conditions, suggesting that equal amount of attention was allocated to the music pieces with

TABLE 1 One-way repeated-measures ANOVA on mood evaluations after 5 min with or without music listening, and the effect of experimental conditions on subjective ratings of pain intensity (PI) and unpleasantness (PU).

	Subjective ratings (mean ± SD)			One-way repeated-measures ANOVA			Post hoc pairwise comparisons (corrected <i>p</i> value)		
	No music	Liked	Disliked	$F_{(2,54)}$	<i>p</i>	η_p^2	no music vs liked	Liked vs disliked	no music vs disliked
Arousal	4.07 ± 1.82	6.50 ± 2.20	5.07 ± 2.07	10.03	<.001	0.27	<.001	.11	.10
Valence	5.21 ± 1.60	7.57 ± 1.43	4.29 ± 1.49	37.40	<.001	0.58	<.001	<.001	.12
Pleasantness	5.68 ± 1.49	7.54 ± 1.29	4.36 ± 1.68	34.05	<.001	0.56	<.001	<.001	.005
Attractiveness	5.64 ± 1.99	7.96 ± 1.84	6.93 ± 2.07	12.81	<.001	0.32	<.001	.10	.048
PI	5.58 ± 1.47	4.81 ± 1.50	5.60 ± 1.52	11.95	<.001	0.31	<.001	.001	>.99
PU	5.06 ± 1.92	3.57 ± 1.76	5.49 ± 1.81	21.07	<.001	0.44	<.001	<.001	.74

distinct preference and the evoked arousal was comparable in the two music conditions.

3.2 | Music-induced analgesic effect during the pain rating task

As shown in Table 1 and Figure 2a, the main effect of condition was significant for both pain ratings on intensity ($F_{[2, 54]} = 11.95, p < .001, \eta_p^2 = .31$) and PU ($F_{[2, 54]} = 21.07, p < .001, \eta_p^2 = .44$). Specifically, participants reported lower pain ratings in the liked music condition than in the other two conditions (all $p \leq .001$). However, there was no significant difference in ratings between the disliked and no music conditions. In addition, there was a trend that the more positive emotional valence participants felt for the liked music, the lower the level of PU in their subsequent pain rating task, but the correlation coefficient was not statistically significant (Spearman's $\rho = -.360, p = .060$). Other correlation coefficients between emotional state ratings after 5-minute music listening and pain ratings were also not significant in either liked or disliked music condition (all $p > .10$).

At the neurophysiological level, painful stimuli elicited brain activations in all three conditions within a wide range of brain regions, including the bilateral insula, supplementary motor area (SMA), dorsal striatum (i.e., putamen and caudate), thalamus, precentral and postcentral gyri (PreCG/PoCG), and ACC ($p_{FDR} < .05$, Figure 2b). One-way rmANOVA showed significant differences of activations in several small clusters (i.e., bilateral putamen, PreCG/PoCG, ACC, right temporal gyrus, right superior temporal gyrus, and cerebellum; < 40 voxels in all clusters) among the three conditions.

Furthermore, we first examined the effect of music listening (i.e., music vs. no music) on pain perception and found no significant music activation (both liked and disliked music) relative to the no music condition. We then specifically tested whether receiving pain stimuli while liked music was played in the background differentially activated the brain compared to disliked music (i.e., liked music vs. disliked music). During the pain rating task, liked music decreased brain activations in the right PreCG/PoCG, ACC, middle cingulate cortex (MCC), bilateral putamen, left middle frontal gyrus, right precuneus, bilateral lingual gyri, and left cerebellum (Figure 3; Table 2).

3.3 | Music-induced analgesic effects mediated by brain activations

More importantly, the pain rating differences in both intensity and PU between the two music conditions (disliked music – liked music) were associated with the differences in brain activations (disliked music – liked music) in the right PreCG/PoCG (PI: Spearman's $\rho = .511$ and $p = .005$; PU: Spearman's $\rho = .419$ and $p = .027$), left putamen (PI: Spearman's $\rho = .383$ and $p = .044$; PU: Spearman's $\rho = .374$ and $p = .050$), and left cerebellum (PI: Spearman's $\rho = .384$ and $p = .044$; PU: Spearman's $\rho = .412$ and $p = .030$; see Figure 4). These results suggested that the right PreCG/PoCG, left putamen,

and left cerebellum may mediate the analgesic effect of liked music listening. To explicitly test these hypotheses, we ran mediation analyses with BOLD responses in these clusters as the mediators for PI and PU, respectively (Figure 5). Brain activity in the right PreCG/PoCG mediated the relationship between music listening and PI ratings ($a*b = 0.447$, 95% CI = [0.095, 0.841]), but not between music listening and pain PU ratings ($a*b = 0.533$, 95% CI = [−0.027, 1.128]). The left cerebellum also mediated the connection between music listening and pain ratings (PI: $a*b = 0.364$, 95% CI = [0.126, 0.689]; pain PU: $a*b = 0.466$, 95% CI = [0.110, 1.034]). However, brain responses in the left putamen did not significantly mediate the influence of music listening on pain ratings (PI: $a*b = 0.262$, 95% CI = [−0.052, 0.610]; pain PU: $a*b = 0.390$, 95% CI = [−0.092, 0.990]).

4 | DISCUSSION

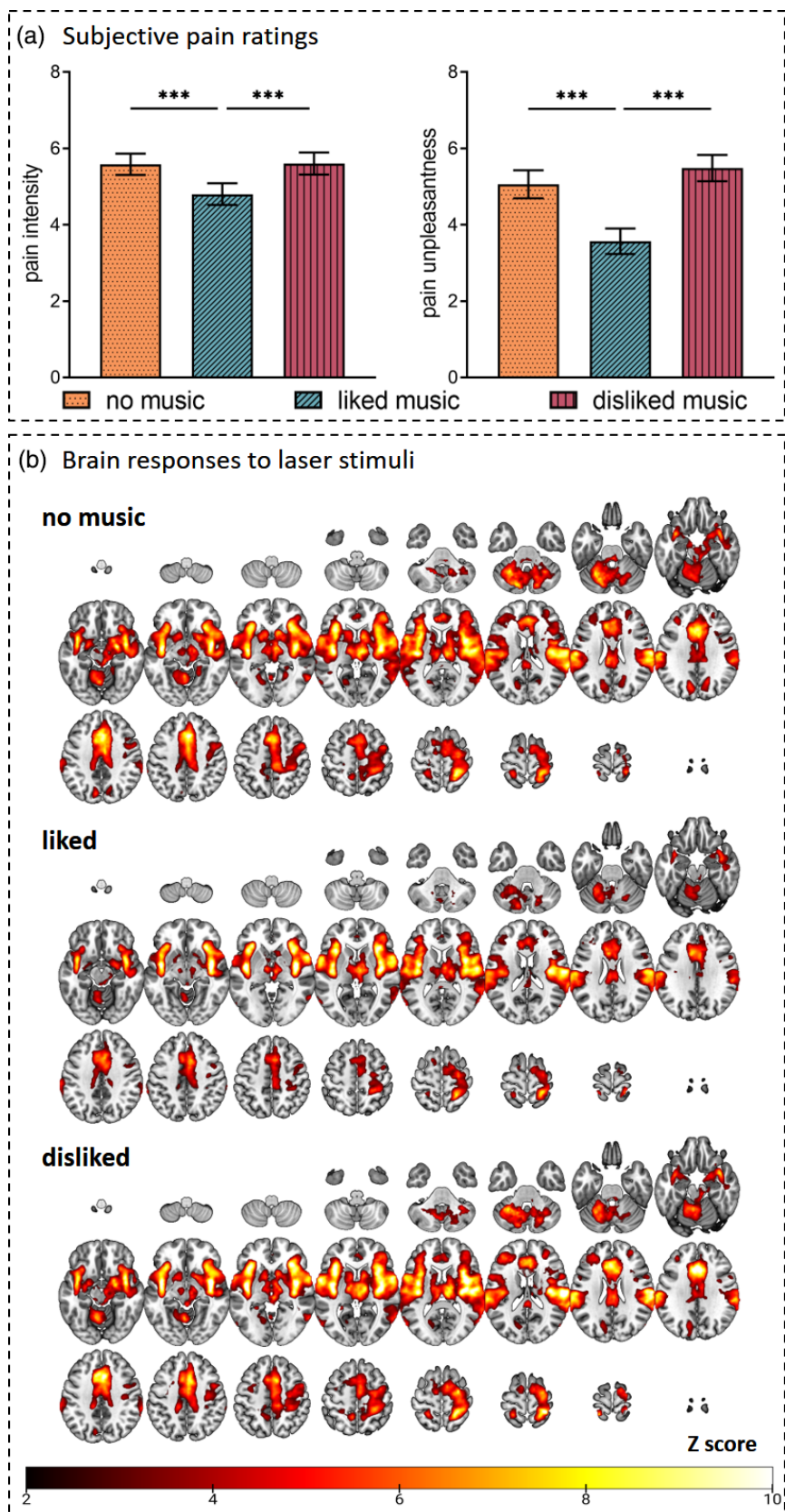
The present study examined the extent to which one's liked music reduces pain when it was played in the background. Both structural and functional fMRI data were recorded to identify possible neural correlates of liked music induced analgesic effects. As expected, liked music significantly lowered pain ratings to acute painful stimuli, when compared with disliked music and no music. Consistent with this observation, brain activations in response to acute painful stimuli were decreased within pain-related brain areas, such as the right PreCG/PoCG, ACC, MCC, bilateral putamen, left middle frontal gyrus, right precuneus, bilateral lingual gyri, and left cerebellum, when liked music was played in the background in comparison to disliked music. Importantly, the analgesic effect of liked music (i.e., the difference between the liked and disliked music conditions) on pain ratings was mediated by the magnitude difference of right PreCG/PoCG and left cerebellum activations under two music conditions. These findings deepened our understanding of the analgesic benefits of background liked music, a property relevant to clinical applications.

One of the main findings of the present study is that participants were likely to experience a pain reduction in both intensity and PU, even when liked music was played in the background. Music, especially preferred or pleasant music, can provide an immersive and absorbing experience even when it serves as background music, thus boosting mood (Koelsch, 2020; Schafer et al., 2013) and increasing the sense of control that would further interference with pain processing (Basinski et al., 2018; Bernatzky et al., 2011; Mitchell et al., 2006). This finding is in good agreement with previous studies, suggesting that background liked music is not only useful in stabilizing mood and decreasing state anxiety (Kipnis et al., 2016) but also a promising tool in pain management (Lu et al., 2021).

Another main finding is that the analgesic effect of liked music observed in this study came primarily from the emotional modulation of pain, rather than the attentional distraction from pain (Lu et al., 2019; Roy et al., 2008). First, the role of attention is considered to be minimal in this study, as participants were asked to ignore the accompanying sound during the pain rating task. Second, participants'

FIGURE 2 Subjective pain ratings and brain activations in response to painful stimuli.

(a) Subjective ratings of pain intensity (left) and unpleasantness (right) for each condition. Data from no music, liked music, and disliked music conditions are expressed as mean $\pm$ SEM in orange, cyan, and pink, respectively. (b) Brain regions in response to painful stimuli under three experimental conditions, including bilateral insula, supplementary motor area, dorsal striatum (i.e., putamen and caudate), thalamus, precentral gyrus, postcentral gyrus, and anterior cingulate cortex. *** Indicates $p \leq .001$.



ratings of arousal and attractiveness for liked and disliked music were comparable (Table 1). If the pain reduction was mainly attributed to attentional modulation, one would expect an analgesic effect induced

by disliked music as well. However, it is not the case in the present study. Disliked music caused neither decreases nor increases in pain ratings compared to the no music conditions. These findings suggest

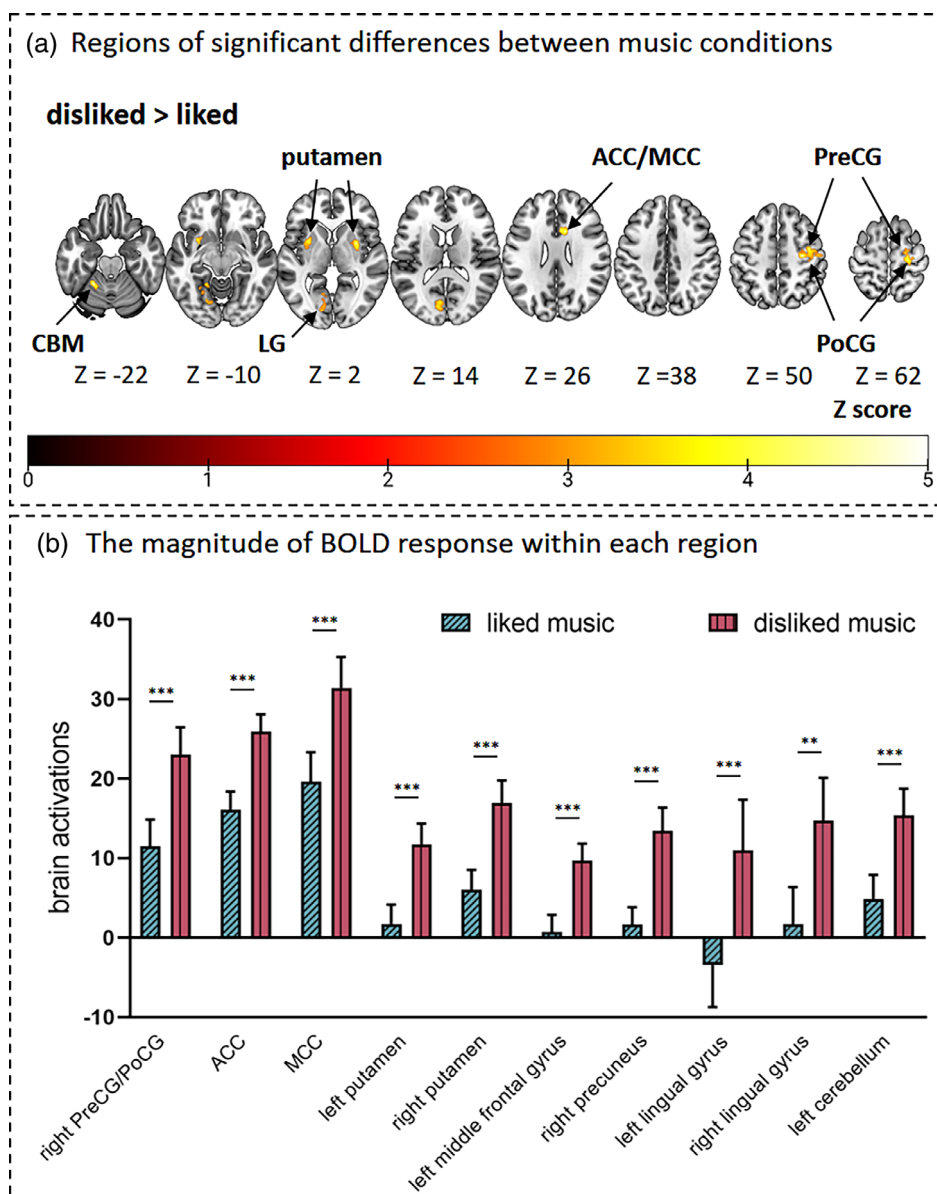


FIGURE 3 Differential brain activations between the liked and disliked music conditions. (a) Neuroanatomic regions demonstrating significant differences between the two music conditions. (b) The magnitude of BOLD responses within each significant brain region. All results were thresholded at $p < .005$ at the voxel level and $p_{FDR} < .05$ at the cluster level. ACC: anterior cingulate cortex; CBM: cerebellum; LG: lingual gyrus; MCC: middle cingulate cortex; PoCG: postcentral gyrus; PreCG: precentral gyrus. Data from the liked music and disliked music conditions are expressed as mean $\pm$ SEM in cyan and pink, respectively. *** Indicates $p \leq .001$; ** Indicates $p < .01$.

TABLE 2 Brain regions showed significant differences between liked and disliked music conditions.

Area	Area (AAL3)	Cluster size	P_{FDR}	Peak (x, y, z)
PreCG/PoCG	Precentral_R	219	<.001	30, -16, 50
ACC	ACC_sup_R, Cingulate_Mid_R	57	.001	12, 14, 26
MCC	Cingulate_Mid_L, Cingulate_Mid_R	77	<.001	12, -7, 41
Left putamen	Putamen_L, Insula_L, Amygdala_L	83	<.001	-30, 8, -7
Right putamen	Putamen_R	65	.001	33, -4, 5
Left middle frontal gyrus	Frontal_Mid_2_L, Frontal_Sup_2_L	29	.040	-27, 44, 8
Right precuneus	Precuneus_R, Parietal_Sup_R	67	.001	15, -49, 59
Left lingual gyrus	Lingual_L, Calcarine_L, Cuneus_L	127	<.001	-9, -58, -1
Right lingual gyrus	Lingual_R, Calcarine_R	33	.025	27, -61, 2
Left cerebellum	Cerebellum_4_5_L, Lingual_L	70	.001	-21, -49, -25

Note: Clusters were considered significant only if they reached a threshold of voxel-level $p < .005$ and cluster-level FDR-corrected $p < .05$.

Abbreviations: ACC: anterior cingulate cortex; ACC_sup: supracallosal anterior cingulate cortex; Cingulate_Mid: middle cingulate and paracingulate gyri; Frontal_Mid: middle frontal gyrus; Frontal_Sup: superior frontal gyrus; L: left; MCC: middle cingulate cortex; Parietal_Sup: superior parietal lobule; PreCG: precentral gyrus; PoCG: postcentral gyrus; R: right.

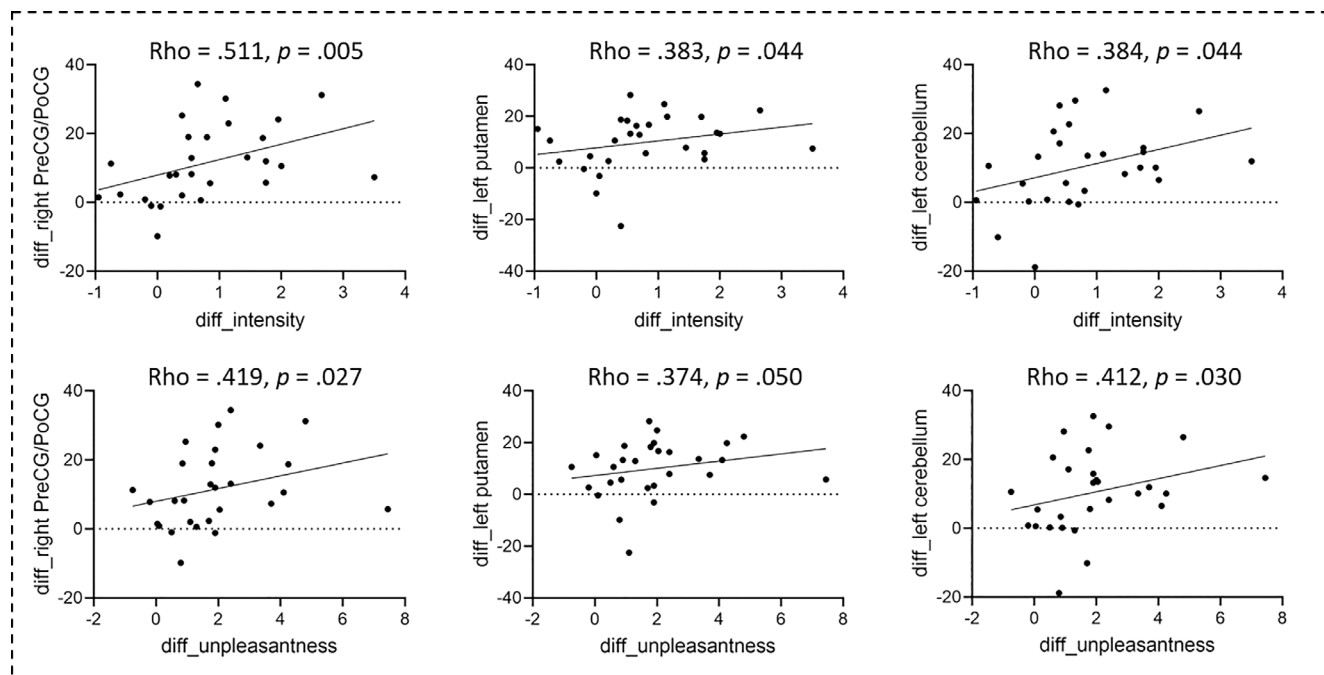


FIGURE 4 Correlations between subjective rating difference (disliked – liked) and brain activation difference (disliked – liked). Significant correlations of the magnitude difference of BOLD responses in the right PreCG/PoCG, left putamen, left cerebellum and the rating differences of subjective pain intensity (upper panel), unpleasantness (lower panel) between the liked and disliked music conditions. PoCG: postcentral gyrus; PreCG: precentral gyrus.

that pleasure induced by liked music can relieve pain, but PU induced by disliked music does not necessarily cause a hyperalgesic effect.

All music pieces used in the present study were pseudo-self-selected, therefore they varied at both psychoacoustics (i.e., timbre) and physical (i.e., harmonics) levels. Despite these differences, we observed a significant impact of background liked music on pain processing, suggesting that personal music preference plays an influential role in the efficacy of MIA (Mitchell & MacDonald, 2006). Indeed, liked music often evokes feelings of intense pleasure in listeners, sometimes experienced as “thrills” or “goose bumps” (Goldstein, 1980) and these feelings can be accumulated as music unfolded in time (Krumhansl, 1997). Therefore, participants still immersed themselves in a positive emotional state even when liked music was played in the background, which further led to pain reduction. Although we observed no significant correlations between mood ratings and pain ratings, there was a trend that the more positive emotional valence participants felt for the liked music, the lower the level of PU in their subsequent pain rating task. This finding is in line with previous study showing that the emotional valence of researcher-selected music contributed to MIA (Roy et al., 2008). It should be noted, however, that music-conveyed valence and self-felt pleasantness are sometimes not equivalent for researcher-selected music (Salimpoor et al., 2009). Therefore, self-selected music is assumed to induce a stronger analgesic effect in comparison to researcher-selected music (Garcia & Hand, 2016; Mitchell & MacDonald, 2006). Similar to the responses to music that were self-selected by participants themselves (Salimpoor et al., 2009), our pseudo-self-selected

music were comparable in terms of music-induced valence and self-felt pleasantness, and the two measures were extremely correlated, indicating that pseudo-self-selected music can serve as an alternative of self-selected music in music-related pain management programs.

The emotional modulation of music on pain perception was further supported by the fMRI results. First, brain areas recruited during the pain rating task (e.g., bilateral insula, SMA, putamen and caudate, thalamus, PreCG/PoCG, and ACC; Figure 2b) did not fully overlap with those activated by music listening per se, such as the auditory cortex and the reward circuitry (Blood & Zatorre, 2001; Koelsch, 2020; Mas-Herrero et al., 2021; Salimpoor et al., 2015), indicating that our fMRI results essentially highlighted the neural substrates of pain processing modulated by background music rather than neural responses to the music itself. Second, our finding that the music condition did not elicit significant brain activation relative to no music condition supports the hypothesis that MIA may be more related to personal preferences (emotional valence) than music delivery itself (Garza-Villarreal et al., 2017). More importantly, significant differences were found in the right PreCG/PoCG, ACC, MCC, bilateral putamen, left middle frontal gyrus, right precuneus, bilateral lingual gyri, and left cerebellum under the contrast between the liked and disliked music conditions (Figure 3a). These regions were consistently activated during the presentation of acute painful stimuli and correlated with subjective pain ratings (Apkarian et al., 2005; Jensen et al., 2016; Peyron et al., 2000). Specifically, liked music reduced the activations in the ACC and MCC, brain regions involved in processing pain-related affect (Rainville et al., 1997) and showed decreased

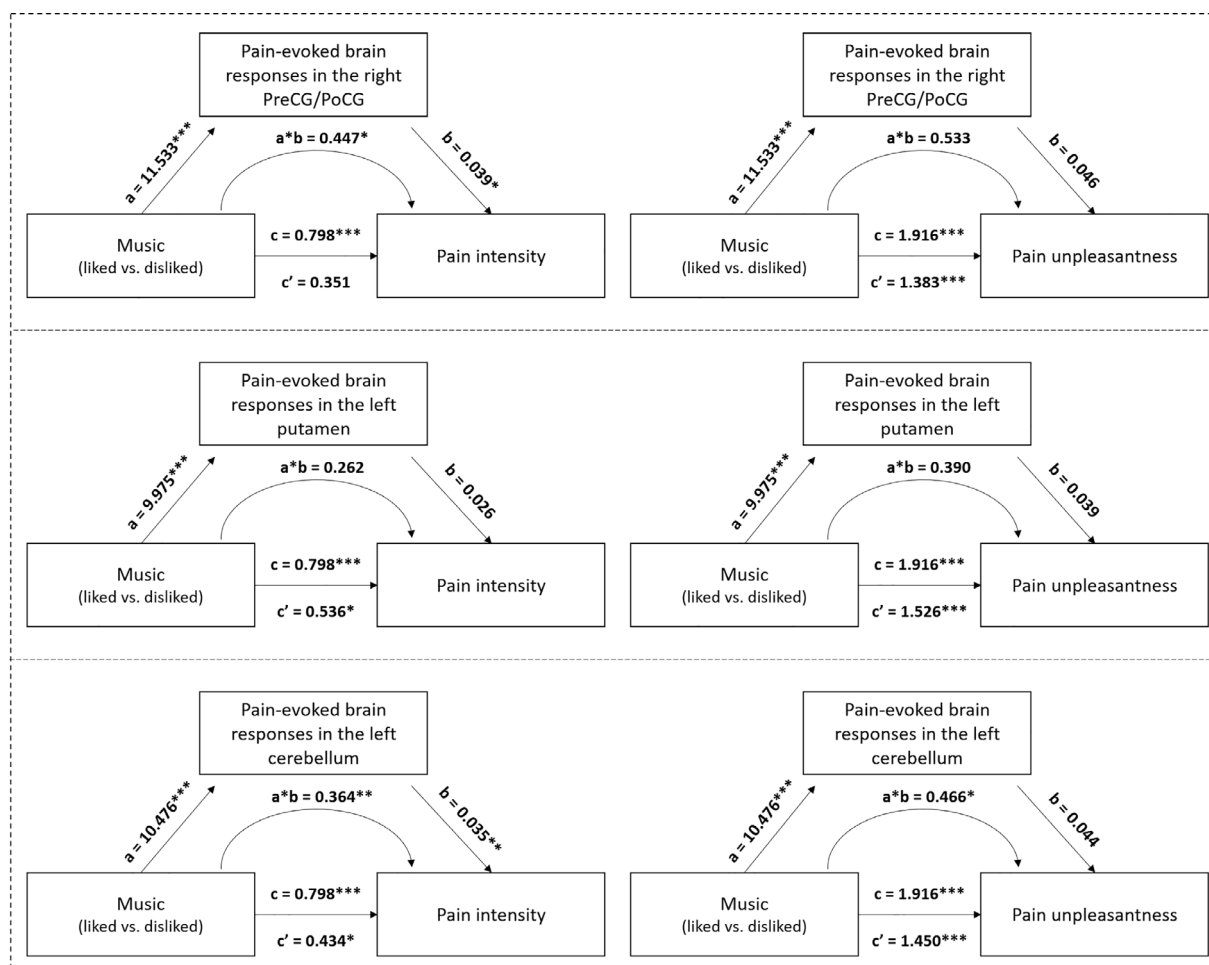


FIGURE 5 Mediation analyses of the analgesic effect of liked music on perceived pain intensity (PI) and unpleasantness (PU). Brain activity in the right PreCG/PoCG mediated the relationship between music listening and PI ratings but not between music listening and pain PU ratings (upper panel), and the left cerebellum mediated the connection between music listening and pain ratings in both intensity and PU (lower panel). Brain responses in the left putamen did not significantly mediate the influence of music listening on pain ratings (middle panel). *** Indicates $p < .001$; ** Indicates $p < .01$; * Indicates $p < .05$.

activity during pain relief (Tracey & Dickenson, 2012). Moreover, the precuneus and lingual gyrus are believed to be involved in processing emotions associated with pleasurable music listening (Putkinen et al., 2021). These brain regions are structurally connected to various cortical and subcortical areas involved in affective aspects of pain processing, and their suppressed activations indicate that liked music exerts top-down modulations of subsequent sensory stimuli, that is, via the inhibitory control of emotionally related brain regions on the pain processing pathways (Dobek et al., 2014).

Additionally, liked music also decreased activations of the right PreCG/PoCG, left putamen, and left cerebellum, brain regions associated with the sensory and motor aspects of pain processing (Starr et al., 2011). The activation differences between two music conditions of these brain regions were positively correlated with differences in pain ratings (Figure 4), and the activations of the right PreCG/PoCG and left cerebellum further mediated the music effect on pain ratings (Figure 5). These results may suggest a potential role of the sensorimotor system in MIA. Indeed, MIA may arise from alternations in brain

activities of these specific regions. Varying areas related to sensorimotor system were modulated during music listening (Gordon et al., 2018), resulting from processing music features and emotions (Koelsch et al., 2021). Since the sensorimotor cortex is thought to be involved in pain perception and analgesia (Gombaut & Holmes, 2022), while the cerebellum is involved in motor responses to pain as well as aversive processing (Baumann et al., 2015), the multidimensional roles of these specific brain regions might allow music-induced changes in brain activity to affect pain perception. Additionally, both sensorimotor cortex and cerebellum are interconnected with brain regions of the ascending and descending pain modulation pathways (Holmes et al., 2021; Moulton et al., 2010). That is, it is also possible that the liked-music-induced analgesic effect at least partially results from the interactions between sensorimotor and pain modulation networks. This speculation is in line with a previous study showing a decreased connectivity between PreCG and auditory cortex when listening to liked music, in which the change was correlated with PI (Garza-Villarreal et al., 2015).

We acknowledge several limitations in our current study, which should be considered in future studies. First, this study mainly focused on the MIA effect on experimental pain in a group of healthy participants, which might be problematic from a translational perspective, as people with chronic pain may have distinct strategies associated with music listening. Second, our findings only demonstrated that acute emotional states induced by liked music (in a timescale of minutes) could attenuate pain. It is necessary for future work to investigate the long-term effect of music on both acute and chronic pain, and determine whether the effect of long-term music listening and its neural correlates are the same as those observed in the present study. Third, although we observed a mediating effect of the right PreCG/PoCG and left cerebellum in MIA, this result may be derived from a general difference in sensorimotor functions between two music conditions, as no related data (e.g., the speed or force of response button presses) were collected in the present study to dismiss this possibility. Therefore, the role of the right PreCG/PoCG and left cerebellum in MIA needs to be explored directly in further investigations. Last, we cannot completely rule out the possible influence of attentional modulation, even though we explicitly asked the participants to ignore what they had heard during the pain rating task. The music-related attentional modulation in pain processing deserves further consideration, as various music activities that require attentional engagement (e.g., music making and tapping along with music) have shown their potential in pain reduction (Dunbar et al., 2012). For future studies, additional conditions requiring attention to music should be considered.

In conclusion, music is a low-cost, readily available activity that many people engage in regularly in different cultures and contexts, which can be easily implemented in pain management. Our results highlight a significant impact of liked music on pain perception when played in the background. Corroborating behavioral findings, the present study identified the key regions responsible for the liked-music-induced analgesic effect and emphasized a mediating role of the right PreCG/PoCG and left cerebellum in the MIA. Understanding the merits of MIA has practical as well as theoretical importance because each has direct implications for the design of interventions.

AUTHOR CONTRIBUTIONS

Xuejing Lu contributed to the experimental design, data analysis, results interpretation, and writing. Xin Hou assisted in data collection. Libo Zhang contributed to the data analysis and editing. Hong Li and Yiheng Tu assisted in data analysis. Huqing Shi and Li Hu contributed to the experimental design, results interpretation, and writing.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data will be made available from the corresponding author on request.

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