

Brain network functional connectivity changes induced by music-induced analgesia in fibromyalgia patients

Received: 1 August 2025

Accepted: 18 March 2026

Published online: 24 March 2026

Cite this article as: Pan M., Hou J., Yang Q. *et al.* Brain network functional connectivity changes induced by music-induced analgesia in fibromyalgia patients. *Sci Rep* (2026). <https://doi.org/10.1038/s41598-026-45376-6>

Mengting Pan, Jiancheng Hou, Qingqing Yang, Yukun Chen, Jue Deng, Maoping Zheng, Changan Sun & Ying Liu

We are providing an unedited version of this manuscript to give early access to its findings. Before final publication, the manuscript will undergo further editing. Please note there may be errors present which affect the content, and all legal disclaimers apply.

If this paper is publishing under a Transparent Peer Review model then Peer Review reports will publish with the final article.

ARTICLE IN PRESS

Running Head: Fibromyalgia and Music-Induced Analgesia

Brain network functional connectivity changes induced by music-induced analgesia in fibromyalgia patients

Mengting Pan M.A.^{1,2*}, Jiancheng Hou Ph.D.^{3,4*}, Qingqing Yang Ph.D.^{5*}, Yukun Chen Ph.D.^{1,2}, Jue Deng Ph.D.⁶, Maoping Zheng Ph.D.^{1,2}, Changan Sun M.A.⁷, Ying Liu Ph.D.^{1,2#}

¹ Academy of Music, Southwest University, Chongqing, China

² Mental Health Research Institute of Chinese Music, Southwest University, Chongqing, China

³ Research Center for Cross-Straits Cultural Development, Fujian Normal University, Fuzhou, Fujian, China

⁴ Department of Radiology, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin, United States

⁵ School of Basic Medicine, Kunming Medical University, Kunming, Yunnan, China

⁶ Cognitive Neuroscience and Abnormal Psychology Laboratory, Fujian Police College Fuzhou City, Fujian Province, China

⁷ School of Education and Public Administration, Suzhou University of Science and Technology, Suzhou, Jiangsu, China

* The authors are equal contribution.

Corresponding authors:

Dr. Ying Liu,

Academy of Music, Mental Health Research Institute of Chinese Music,
Southwest University,

No 2, Tiansheng Road,

Beibei District,

Chongqing 400715, China

liuying6167@swu.edu.cn

Abstract

Introduction: Music can liberate positive power of pain management in fibromyalgia (FM) patients through multiple neural modulation. However, traditional brain research preferred to investigate the neural characteristics of music-induced analgesia (MIA) based on the seed points of functional activation, which limits the understanding of the connection states of the whole-brain functional synchronization network involved in FM's music listening. The current study aimed to investigate the whole-brain network functional connectivity (FC) differences of resting-state functional magnetic resonance imaging (RS-fMRI) before and after music listening in FM patients using a data-driven analysis approach.

Methods: Using a publicly available dataset, the RS-fMRI data from 20 FM patients were analyzed. A network-based FC approach was applied to compare intra- and inter-network FC changes across the visual network (VN), somatosensory network (SMN), ventral attention network (VAN), default mode network (DMN), and subcortical network (SC).

Results: After music listening, FM patients exhibited significant reduction in evaluation of pain intensity (PI), and also exhibited changed intra-network FC within the VAN and VN; changed inter-network FC between the VAN and DMN, between the VN and SMN or DMN, between the SMN and DMN, and between the VN and SMN or DMN, respectively. What's more, correlations were found between post-pre changes in subjective pain ratings and post-pre changes in network FC. Positive correlations were found between PI's reduction and the increase of inter-network FC between the right fusiform (VN) and left middle insula (SMN), and also found between the reduction of pain unpleasantness (PU) and the increase of inter-network FC between the left middle insula (SMN) and left posterior occipital cortex (DMN).

Discussion: The network FC results here provided new evidence to the

inter/intra-networks in VN, SMN, VAN, DMN, and subcortical network, explaining that FM patients may generate cognitive processing from bottom to top and emotion regulation from top to down to realize their MIA.

Key words: fibromyalgia; music-induced analgesia; resting-state fMRI; network functional connectivity; data-driven

Introduction

Fibromyalgia (FM) is present in as much as 2% to 8% of the population, is characterized by widespread pain, and is often accompanied by fatigue, memory problems and sleep disturbances (Daniel J. Clauw, 2014). The treatment of FM involves multiple methods, including nonpharmacological therapies (education, exercise, cognitive behavioral therapy) and pharmacological therapies (tricyclics, serotonin norepinephrine reuptake inhibitors, and gabapentinoids). Recent years, music therapy has been an important nonpharmacological method with positive biological and psychological function in pain management clinically and non-clinically (Finn & Fancourt, 2018). With harmonious, emotional, and personal sound features, music can liberate therapeutic power for psychological regulation of pain (e.g., emotional regulation, motor coordination, cognitive enhancements, stress relief, etc.) and physiological intervention of pain by regulating circadian rhythm system (heart rate/blood/breathing pressure adjustment, pain control, sleep intervention, etc.), regulating hormones, such as dopamine, oxytocin and melatonin etc (Valenti et al., 2012) and brain neural activities (Hauck et al., 2012; Hirokawa & Ohira, 2003).

The effect of music pain reduction, also called as music-induced analgesia (MIA), has been widely used in clinical treatment of many diseases. MIA has been demonstrated in healthy participants exposed to experimental pain (Choi et al., 2018) and in patients experiencing acute (Cakmak et al., 2017; Simavli et al., 2014),

postoperative (Hole et al., 2015), and chronic pain (Garza-Villarreal et al., 2017). Based on the cerebral signature for pain perception (Tracey & Mantyh, 2007), cognition (e.g., attentional diversion and cognitive reappraisal), emotion (e.g., affective regulation), and neurobiology (e.g., neural plasticity and functional connectivity) were proposed as the main aspects of MIA (Lunde et al., 2019). The aspect of cognition is often discussed in regards to MIA is distraction and attention, which can situate the analgesic capacity of music on a cognitive level (Basinski et al., 2021; Chang et al., 2015). Other explanations suggest that music-induced emotion is a key mechanism, which function in pleasure enhancement and anxiety reduction (Roy et al., 2008; Valevicius et al., 2023). Among the functions of cognition, emotion, and neurobiology, the brain neural activity of music intervention to pain is a key link to explain its cognitive process and emotion regulation. The functional magnetic resonance imaging (fMRI) has demonstrated that when participants listen to their favorite music compared with no music during painful stimulation, different patterns of neural activation and functional connectivity were found in several areas of the brain, brainstem, and spinal cord, including regions within the limbic system and areas known to be involved in the descending pain-modulatory system (Dobek et al., 2014) and brain functional connectivity (FC) across these neural networks between regions such as the insula, thalamus, hypothalamus, amygdala and hippocampus (Powers et al., 2022).

Actually, with the increasingly prominent physical and mental effects of music, more and more attention has been paid to the brain functional mechanism of MIA, which can provide important neural evidence for explaining the processing patterns and key brain regions in which music participants in pain management. By playing music to participants with their liked or disliked songs, a study found that liked

music significantly rated with lowered pain ratings to acute painful stimuli compared to disliked music and no music; the lowered pain ratings were connected with 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 (Lu et al., 2023). Other studies have also found that listening to music can activate the reward circuitry (Zatorre, 2015) and multiple cortical, subcortical, and cerebellar regions encompassing multiple brain networks (Chan & Han, 2022), which are all important neural bases for participating in MIA (Powers et al., 2022). The evidence suggest that the role of music analgesia is a process involving the integration of multiple functional brain regions, so it is necessary to further explore the FC characteristics of brain (Werner et al., 2023).

Pando-Naude et al. (2019) examined the resting-state functional connectivity (RSFC) of MIA in FM patients. They performed RSFC seed-based correlation analyses using pain and analgesia-related regions-of-interest (ROIs) to determine the effects before and after the MIA intervention in FM and health controls (HC). The results showed that listening to music reduced pain in FM patients and this analgesic effect was related to a decrease of the RSFC on the left angular gyrus (AnG) seed with right PoCG and right precuneus, as well as a RSFC increase of the left amygdala seed with right middle frontal gyrus. The authors proposed that MIA may arise because of a top-down modulation, probably originated by distraction, relaxation, positive emotion, or a combination of these mechanisms (Pando-Naude et al., 2019).

As Lunde and colleagues proposed that in-depth analysis of MIA' mechanisms should not exist only in the knowledge but also in the use of existing analytical

techniques (Lunde et al., 2019). The seed-based RSFC approach only provides the functional interactions between specific regions, which generally requires a defined ROI, so the results are strongly limited by ROI chosen (Smith et al., 2011; Tian et al., 2012). Understanding brain activity patterns in a data-driven way can avoid limitations and flaws in assumptions, especially when the mechanism of MIA function is uncertain. Moreover, network science mainly examines the brain regions' interactions, and it has been employed to study the human brain as one kind of the relationships of complex system. The human brain is organized to be a global network but with regular functional laws; it integrates with the large long- and the local short-range connections, in order to keep and support the high-level cognition ability (Li et al., 2018; Park & Friston, 2013). As far as we known, relatively less studies have examined the effect of MIA on brain network. Therefore, the current study aimed to investigate the RS-fMRI whole-brain network FC differences by MIA in FM patients through a data-driven approach.

Methods

Data source

The participants' information, and their RS-fMRI and anatomical T1 dataset, were obtained from a public dataset via OpenNeuro with accession number ds001928 (<https://openneuro.org/datasets/ds001928/versions/1.1.0>). There were twenty female FM patients (mean age = 46.4 ± 12.4 years old, ranged from 22 to 70 years). Ethical approval was granted by the Bioethics Committee of the Instituto de Neurobiología, UNAM. The inclusion and exclusion criteria followed those outlined by Pando-Naude et al. (2019).

Stimulus materials

Prior to the study, participants provided a list of songs or artists that they would like to listen during the experiment. The Songs were familiar, very pleasant, and slow. The slow pace was defined as a tempo of <120 beats per minute (bpm), determined by the experimenters using a metronome. Participants reported how pleasant the song was on a 11-point verbal scale (0 = unpleasant, 10 = very pleasant), and to be selected, the song had to be rated at least 9-10. When provided with only the artist's name, the experimenter selected the songs based on two fixed acoustic criteria: harmony (pleasurable), participants' oral reporting, and slow tempo. Based on a previous study, music-induced analgesia for chronic pain was higher when participants chose familiar and happy music, making self-selection and familiarity an important mechanism for this effect (Pando-Naude et al. 2019).

Design and paradigm

Auditory stimuli were used the NordicNeuroLab AS (Bergen, Norway) MRI safety headphones, and their presenting orders were balanced among the participants in order to avoid sequential effects. Each participant underwent two RS-fMRI acquisitions that were performed before (pre-) and after (post-) music listening, each lasting five minutes. Inside the MRI scanner, participants listened to a 5-minute segment of familiar, slow paced, and highly pleasant music, and no imaging was recorded during music listening. Before the RS-fMRI acquisition, the anatomical T1-weighted data were acquired (Pando-Naude et al., 2019).

Meantime, two behavioral tasks, the pain intensity (PI) and the pain unpleasantness (PU), were tested while the FM patients were in the MRI scanner and using the verbal rating scale (0 = no pain, 10 = worst pain possible). PI measures the

pain sensory, and the PU measures the evaluative and emotional dimension of pain (Pando-Naude et al., 2019). The two tasks were performed before and after the music stimuli.

MRI data acquisition

The original neuroimaging dataset was acquired on a 3.0 Tesla GE Discovery MR750 scanner (HD, General Electric Healthcare, Waukesha, WI, USA) and a commercial 32-channel head coil array. The parameters for RS-fMRI data were: TR = 3000 ms, TE = 40 ms, flip angle = 90°, field of view = 256 × 256 mm², voxel size = 2 × 2 mm, number of slices = 43, matrix = 128 × 128, slice thickness = 3 mm, gap = 0 mm. The parameters for anatomical T1-weighted data were: TR = 7.7 ms, TE = 3.2 ms, flip angle = 12°, field of view = 256 × 256 mm², matrix = 256 × 256, slice thickness = 1 mm, number of slices = 168, gap = 0 mm.

Data preprocessing

Preprocessing for RS-fMRI data were performed using the Data Processing and Analysis of Brain Imaging (DPABI) toolbox version 6.0 (<http://rfmri.org/dpabi>). This toolbox involves one main function called Data Processing Assistant for Resting-state fMRI Advanced Edition toolbox (DPARSF V5.3) (Chang & Glover, 2010; Yan et al., 2016), which is a convenient plug-in software that works with Matlab and Statistical Parametric Mapping (SPM, version 12) (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). The original data was firstly arranged; the first five volumes were ignored so that participants could get used to scanner noise. The preprocessing steps, in order, includes slice timing, realignment, regressing out head motion parameters (scrubbing with Friston 24-parameter model

regression) and normalization (spatial normalization to the MNI template, resampling voxel size of $3 \times 3 \times 3$ mm) (Chao-Gan & Yu-Feng, 2010; Kuhn et al., 2012). The symmetric correlation matrix (considered as spontaneous neural connectivity) for a 142×141 network, which include 142 regions/nodes with the Dosenbach atlas across whole brain (Dosenbach et al., 2010), was generated in each participant. Therefore, each participant had 20,022 unique pairwise RSFC in total, but only half of the pairwise RSFC (10,011) within the network was used for next network construction, because the top right half and bottom left half were the same in matrix.

Network functional connectivity construction

Each participant's network functional connectivity (FC) was constructed with the DPABINet V1.1 that is included in DPABI V6.0. The 142 nodes in the Dosenbach atlas were classified into seven subnetworks: visual network (VN), somatosensory network (SMN), ventral attention network (VAN), dorsal attention network (DAN), default mode network (DMN), subcortical network (SC) and frontoparietal network (FPN) (Yeo et al., 2011). Based on the 142×141 matrix generated at the preprocessing step, the network FC for any pair of two nodes was calculated as Pearson's linear correlation coefficient, and the Fisher-z transformation was then used for the symmetric correlation matrix. It needs to be mentioned that the smoothing was not used to the brain network analysis because the core objective of brain network analysis is to accurately measure the functional connectivity relationships among discrete brain regions (Power et al., 2014); if smoothing is used in brain network analysis, it will have serious problems such as that the signals between brain regions are no longer pure and will artificially and falsely increase

the functional connection value between two brain nodes (Craddock et al., 2012; Power et al., 2014); or that smoothing can blur the spatial boundaries of the networks, reducing the specificity of internal connections within the network and the clarity of separation between networks; or that smoothing can make brain nodes no longer independent at the signal level (Power et al., 2014; Wig et al., 2011).

Statistical analysis

The statistical analysis was performed in DPABINet. The paired t -test (after vs. before music listening) was conducted to compare the network FC differences between the post- vs. pre-music listening in FM patients. The gender and age were considered as covariates. The multiple comparison correction was used the permutation false discovery rate (FDR) corrected $p < .05$ in DPABINet, and the results were visualized by DPABINet Viewer. Moreover, the correlation analysis based on Pearson's correlation between the PI (or the PU; the difference value between post-minus pre-music listening) and the network FC (the difference value between post-minus pre-music listening) was set to $p < .05$ with SPSS software version 23 without multiple-comparison corrections.

Results

Behavioral test

The paired t -test showed that after music listening, the FM patients' PI was significantly decreased, and the PU was marginally decreased (see **Table 1**), compared to before music listening.

Table 1. Behavioral tasks between post- vs. pre-music listening.

Tasks	Post-music listening	Pre-music listening	$t_{(19)}$	p
PI	3.350 (3.249)	4.300 (3.011)	-2.967	.008
PU	3.700 (3.481)	4.500 (3.137)	-1.775	.092

Note: The values in parentheses are the standard deviation.

Network functional connectivity changes

Table 2 and **Figures 1 and 2** show the significant intra- and inter-network FC differences between post- vs. pre-music listening in FM patients. Compared to pre-music listening, post-music listening induced enhanced intra-network FC between the right ventral frontal cortex and right ventromedial prefrontal cortex, or the left anterior insula within the VAN; between the left posterior occipital cortex and right temporal cortex within the VN; but induced decreased intra-network FC between the right parietal lobule and right middle insula within the VAN.

Compared to pre-music listening, post-music listening induced enhanced inter-network FC between the VAN and DMN; between the VN and SMN or DMN, respectively. Moreover, compared to pre-music listening, post-music listening induced decreased inter-network FC between the SMN and DMN; between the VN and SMN or DMN, respectively.

Table 2. Paired t -test differences of network FC between post- vs. pre-music listening in FM patients.

Nodes		Networks		t value	p value
R ventral frontal cortex	R ventromedial prefrontal cortex	VAN	VAN	3.2234	.0032
R ventral frontal cortex	L anterior insula	VAN	VAN	3.3303	.0044
L ventral frontal cortex	R precuneus	VAN	DMN	3.8209	.0016
R fusiform	L middle insula	VN	SMN	3.2523	.0042
L occipital cortex	L angular gyrus	VN	DMN	4.1321	.0010
L occipital cortex	L posterior cingulate cortex	VN	DMN	3.5877	.0024

R occipital cortex	L precuneus	VN	DMN	3.2515	.0020
L posterior occipital cortex	R temporal cortex	VN	VN	3.1380	.0018
R parietal lobule	R middle insula	VAN	VAN	-3.3123	.0030
L middle insula	L posterior cingulate cortex	SMN	DMN	-3.2179	.0054
R occipital cortex	R temporal cortex	VN	SMN	-3.5258	.0032
R posterior occipital cortex	R inferior temporal cortex	VN	DMN	-3.3244	.0040

Note: VN: visual network; SMN; somatosensory network; VAN: ventral attention network; DMN: default mode network; L: left; R: right. Positive t value means post- had increased network FC than pre-music listening, and negative t value means post- had decreased network FC than pre-music listening.

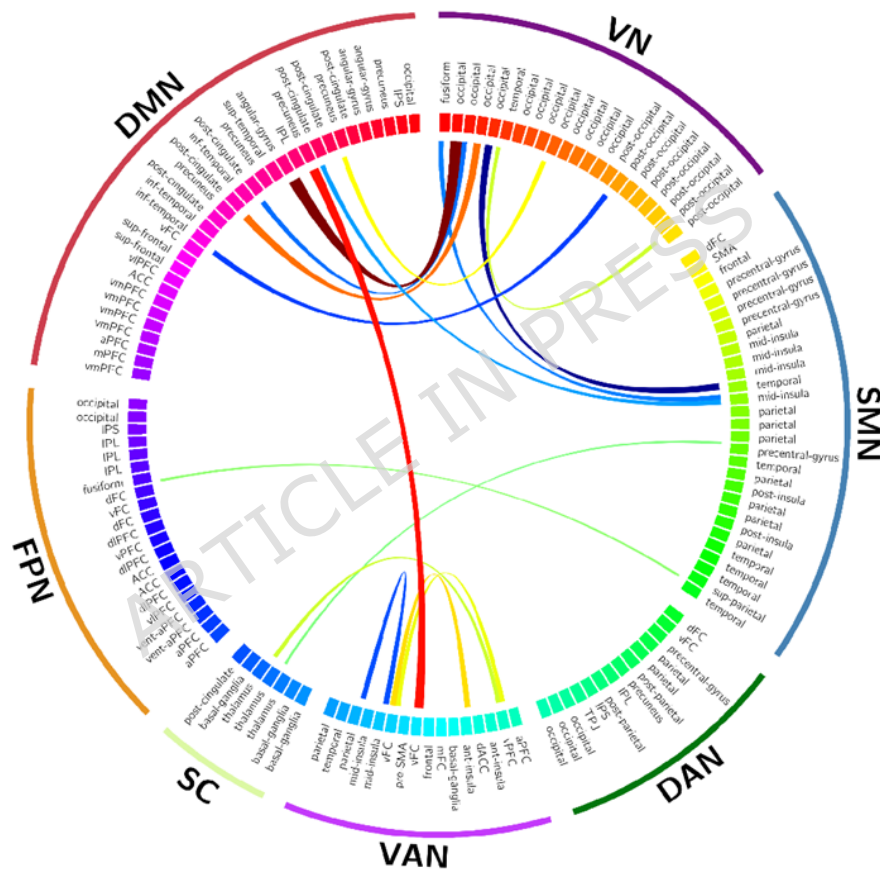


Figure 1. The circus representation of network functional connectivity (FC) differences between post- vs. pre-music listening.

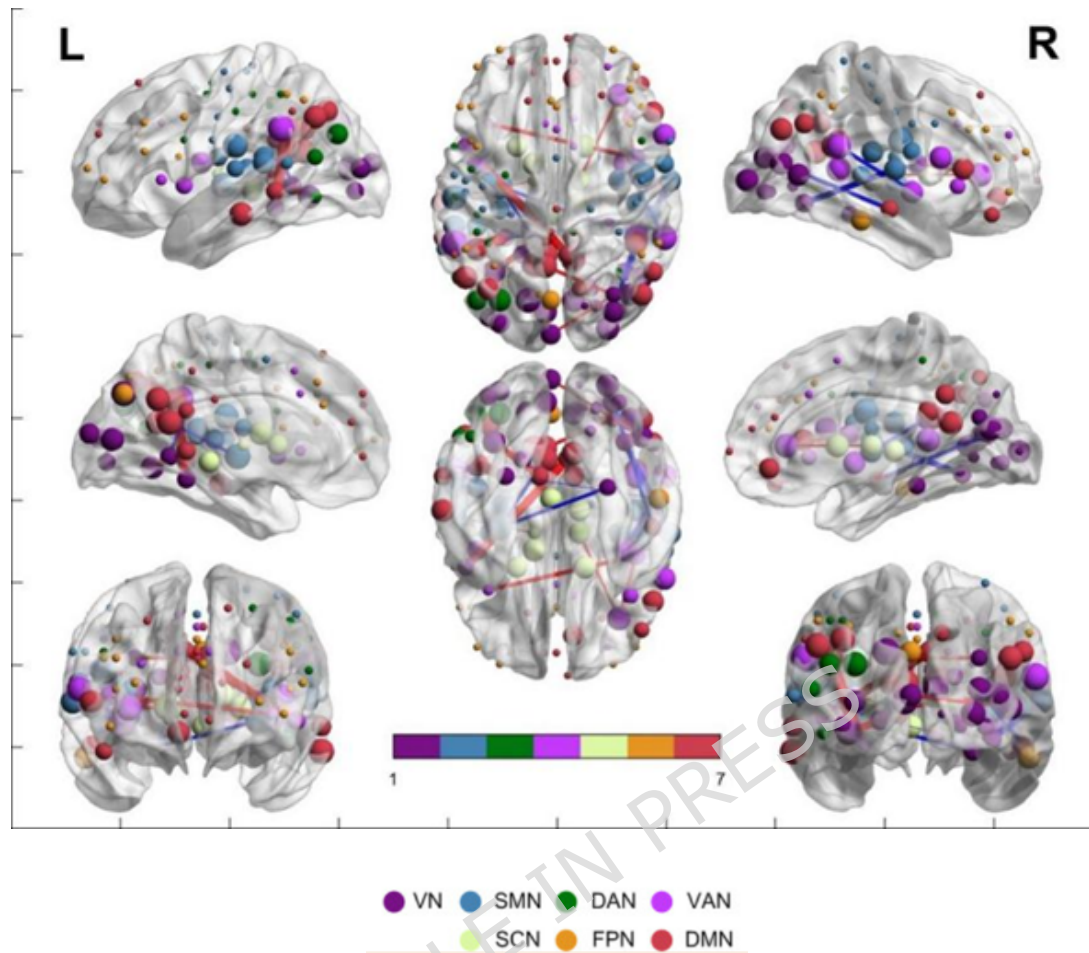


Figure 2. The brain network functional connectivity (FC) differences between post- vs. pre-music listening. Red line means post- had increased network FC than pre-music listening, blue line means post- had decreased network FC than pre-music listening.

Correlation analysis

There was a significant positive correlation between the change in PI (post- minus pre-music listening) and the change in inter-network FC between the right fusiform (VN) and left middle insula (SMN). Similarly, a significant positive correlation was found between the change in PU and the change in inter-network FC between the left middle insula (SMN) and left posterior cingulate cortex (DMN). (see **Table 3**).

Table 3. Correlations between behavioral tasks and network FC.

Tasks		Nodes	Networks		<i>r</i>	<i>p</i>
PI	Right fusiform	Left middle insula	VN	SMN	0.449	.047
PU	Left middle insula	Left posterior cingulate cortex	SMN	DMN	0.528	.017

Discussion

To our knowledge, this is the first study to analyze RS-fMRI whole-brain network FC differences between post- vs. pre-music listening in FM through data-driven analysis. After music listening, FM patients exhibited significant reduction in evaluation of PI and nonsignificant reduction in PU. Within VAN, increased FC was found between the right ventral frontal cortex and right ventromedial prefrontal cortex, and between the right ventral frontal cortex and left anterior insula; decreased FC was found between the right parietal lobule and right middle insula. Within VN, increased FC was observed between the left posterior occipital cortex and right temporal cortex. Among the networks, increased FC was found between the left ventral frontal cortex and right precuneus (VAN-DMN), as well as between the left occipital cortex and left angular gyrus, left occipital cortex and left posterior cingulate cortex, and right occipital cortex and left precuneus (VN-DMN). Decreased FC was found between the left middle insula and left posterior cingulate cortex (SMN-DMN), between the right occipital cortex and right temporal cortex (VN-SMN). What's more, when compared the post-pre behavioral data and brain data, significantly positive correlations were found between PI and the inter-network FC of the right fusiform (VN) and left middle insula (SMN), and also significantly positive correlation between post-pre PU and the inter-network FC of the left middle insula (SMN) and left posterior

cingulate cortex (DMN). These results provide an important evidence for understanding the neural mechanisms of MIA.

Behavioral results demonstrated the effective regulation of music on pain perception in FM patients. Specifically, the PI level in FM patients changed significantly after the music listening, and the PU also decreased but did not reach significant level. The results indicate that music may independently regulate pain perception and pain emotion; that is, the generation of MIA may both involve cognitive processing and emotion regulation, which can be explained by the general framework of three factors affecting pain perception as elaborated by Tracey and Mantyh (2007), who also primarily proposed three aspects of MIA: cognition, emotion, and neurobiology (Lunde et al., 2019). The cognitive-factor is often discussed in regards to MIA is distraction and attention, which can situate the analgesic capacity of music on a cognitive level (Basinski et al., 2021; Chang et al., 2015). The emotion-factor suggests that music-induced emotion is a key mechanism and functions in pleasure enhancement and anxiety reduction (Roy et al., 2008; Valevicius et al., 2023). When participants listen to their favorite music compared with no music during painful stimulation, fMRI studies have demonstrated different activation in several areas of the limbic system and areas known to be involved in the descending pain-modulatory system (Dobek et al., 2014) and brain functional connectivity across these neural networks between regions such as the insula, thalamus, hypothalamus, amygdala and hippocampus (Powers et al., 2022). Meanwhile, when exploring the cognitive mechanisms in music listening or music interventions for pain, the *Cognitive Vitality Model* illustrates that MIA happens with five themes: automated attention, cognitive agency, meaning-making and enjoyment, musical integration, and cognitive vitality (Howlin & Rooney, 2020). From these two theoretical models it can

be speculated that the difference between PI and PU was formed from the gradual emergence of cognitive processing at different levels and different themes.

By analyzing the neural activities, FM patients were found with significant RS-fMRI whole-brain network FC differences before and after music listening. From the Table 2 and Figures 1 to 2, it can be seen that VAN and VN show an increased intra-network FC after music listening in FM. The VAN, comprised of the temporoparietal junction and ventral frontal cortex, usually responds to relevant external environmental stimuli, and is generally activated when an unexpected event occurs and breaks one's attention from the current task (Corbetta et al., 2008; Farrant & Uddin, 2015). In current study, within the VAN, the right ventral frontal cortex shows enhanced connectivity with the right ventromedial prefrontal cortex and left anterior insula. Ventral frontal cortex has been found to be tightly connected with social emotion regulation (Chemerinski et al., 2002) and emotional visual-auditory integration processes (Baumgartner et al., 2006). The ventromedial prefrontal cortex is a host of interrelated functions, such as decision-making, emotion process, empathy, and memory process (Alexander et al., 2023; Schneider & Koenigs, 2017). Anterior insula is also a multifaceted brain structure in a wide range of emotional and cognitive functions (Wang et al., 2019). During a meta-analytic evidence from neuroimaging studies about chronic pain, the anterior insula has also been found as a robust functional biomarker for chronic pain (Ferraro et al., 2022). The increased connection between right ventral frontal cortex with right ventromedial prefrontal cortex and left anterior insula indicates that music listening may reduce FM patients' PI and PU by invoking multiple cognitive and emotional regulation processes.

Meanwhile, this activation of FC network not only involves the temporal regions, but also utilizes the functions of the visual cortex to participate in regulating pain.

Within the VN, the left posterior occipital cortex shows enhanced connectivity with the right temporal lobe. The VN, providing interactions of top-down and bottom-up mechanisms in human visual cortex (Dijkstra et al., 2017; McMains & Kastner, 2011), has also been found tightly correlated with music training (Alluri et al., 2017; Luo et al., 2012) and provides perceptual interaction with the environment for non-auditory imagery (Pando-Naude et al., 2019). Also, between the VN and DMN, enhanced connectivity was found between the visual areas (bilateral occipital cortex) and the limbic systems (right precuneus, left angular gyrus, left posterior cingulate cortex, left precuneus). What's more, VN shows enhanced connectivity with the SMN and DMN, especially with enhanced connectivity of the bilateral occipital cortex with the insula, cingulate cortex, precuneus. During music processing, the occipital cortex is activated mainly by mental imagery (Aleman et al., 2000) and music understanding (Bouhali et al., 2020). Limbic systems were found to be engaged in bottom-up attention appraisal and top-down emotional regulation (Comte et al., 2016). Combining these findings with the behavioral reduction in PI and PU, the FC here can provide a comprehensive explanation that music listening may regulate FM patients' pain either by awakening the bottom-up experience (e.g., regulating attention through auditory or visual imagination, or by regulating the top-down emotional regulation.

In current study, decreased intra-network FC was also found in the VAN (the right parietal lobule and right middle insula), and decreased inter-network FC was found among the SMN, DMN, and VN. The right middle insula shows decreased connectivity with the right parietal lobule, the left middle insula shows decreased connectivity with the left posterior cingulate cortex. The parietal lobe and insula are important brain regions involved in the attention-related alterations of pain (Bushnell et al., 2013),

and also proposed as top-down orienting of attention' system (Corbetta & Shulman, 2002). The insula is an important area verifying human's automatic music processing and emotion processing during music-evoked emotion in non-musicians (Koelsch et al., 2021; Pando-Naude et al., 2019). In older people with early music training experience, the anterior insula was also found positively functional connected with the frontal area when general musical experience appeared for an automatically potential protective mechanism across lifespan (Ai et al., 2022). As the crucial component of the limbic (emotional) part of the brain, the insula is also important for encoding the emotional and motivational aspects of pain (Ostrowsky et al., 2002) and both participates in pain sensation (PI) and pain affect (PU) (Craig, 2011). The decreased FC here may indicate that after music listening, FM patients may need to reduce the inter-activation among different emotional cortex (insula, cingulate cortex) in order to allocate resources to cognitive regulation or physical responses with outside environmental information (Bushnell et al., 2013; Powers et al., 2022). What's more, the decreased network FC here was also consistent with the correlations of behavioral tasks and network FC (Table 3). In correlation analysis between behavioral tasks and network FC, positive correlations were found between the PI and the inter-network FC between the right fusiform (VN) and left middle insula (SMN), and also between the PU and the inter-network FC between the left middle insula (SMN) and left posterior cingulate cortex (DMN). These correlated trends indicate right fusiform mainly participated in regulating PI and left posterior cingulate cortex mainly participated in regulating PU, while left middle insula participated both in regulating PI and PU that during MIA. The comprehensive pain regulation results of left middle insula may be explained by its emotional regulation function from top to down (Baumgartner et al., 2006; Koelsch, 2010). Although we classified the ACC and

anterior insula into the VAN following Yeo et al. (2011), these regions are also widely recognized as core nodes of the salience network (SN), which plays a key role in chronic pain. Thus, our findings can also be interpreted from the perspective of SN-DMN interactions. It is important to note that the anatomical delineation of the middle insula in the Yeo atlas places it at the intersection of the VAN and SMN in both hemispheres, rather than assigning it strictly to one network per hemisphere. Therefore, while our analysis utilized this predefined atlas, the observed functional connectivity changes involving the left and right middle insula should be interpreted with caution. These regions likely serve as critical hubs integrating both attentional (VAN) and sensorimotor (SMN) processes. Consequently, our findings may reflect the multifaceted role of the insula in both bottom-up attention capture and the somatosensory aspects of pain, rather than strict hemispheric functional asymmetry.

Overall, this research, through data-driven analysis of brain functional networks, provides evidence of the neural network activities related to emotion regulation and cognitive processing in the MIA process of FM patients. However, the current study is not without limitations. Although it is the first study to apply a data-driven analysis approach in FM's MIA, it relies on a publicly available and limited amount dataset rather than original experimental data. As such, we cannot ensure that all potential confounding variables that may influence the experimental results have been adequately controlled. What's, the study did not design steps for independently detecting PI and PU and has no purposeful steps to distinguish the cognitive processing from emotion regulation, which limited the investigation of MIA's neural mechanism. Future research could further optimize the experiment design to investigate the dynamic process and the corresponding brain networks in MIA to optimize the clinical application of music in chronic pain. In the end, we did

not investigate the average within or between network connectivity strength changed. Due to the limited amount of dataset, if we did an average calculation, the connections within different networks or between networks would eventually be overwhelmed in this exploratory study. Therefore, we reported the specific region-to-region (or node-to-node) changes that were significant rather than making claims at the level of whole networks.

It is also important to address a methodological nuance regarding the functional network assignment of the insular cortex in current study. The network labels presented in current results (e.g., left middle insula as SMN, right middle insula as VAN) were derived strictly from the Dosenbach 142-node atlas (Dosenbach et al., 2010), which is parcellated based on the Yeo 7-network template (Yeo et al., 2011). However, the middle insula is a functionally heterogeneous region that lies at the intersection of the VAN and the SMN in both hemispheres. In the Yeo atlas, significant portions of the left middle insula also overlap with the VAN, indicating that a binary, hemisphere-dependent classification does not fully capture its complex functional anatomy. Therefore, while we have retained the original atlas labels in current results section to maintain methodological transparency and reproducibility, we acknowledge that this parcellation approach has inherent limitations in border zones such as the insula. The observed functional connectivity changes involving the middle insula should not be interpreted as evidence of strict hemispheric specialization (i.e., left = SMN, right = VAN). Instead, we propose that these findings reflect the multifaceted role of the mid-insula as a cross-network integration hub. Its involvement in MIA likely encompasses both attentional reorienting (typically associated with the VAN) and the processing of somatosensory and affective components of pain (typically associated with the SMN and salience

networks). This interpretation aligns with our correlation results, where the left middle insula (labeled SMN) correlated with both PI and PU, suggesting a confluence of sensory and emotional processes. Future studies employing data-driven parcellation techniques or dynamic functional connectivity analyses may further elucidate the insula's precise role in mediating music-induced analgesia.

Conclusion

As the first data-driven study to analyze RS-fMRI whole-brain network FC differences in FM before and after music listening, the current study effectively investigated the neural correlates of MIA in FM patients. The significant whole-brain network FC differences indicates that FM's MIA may generated with cognitive processing from bottom to top and emotion regulation from top to down by data-driven evidence of inter/intra-networks in the VN, SMN, VAN, and DMN. In future, relying on more intelligent data-driven brain network approaches, more neurological evidence can be found to reveal the music-induced brain function and promote its clinical practice on physiological and mental health rehabilitation.

References

- Ai, M., Loui, P., Morris, T. P., Chaddock-Heyman, L., Hillman, C. H., McAuley, E., & Kramer, A. F. (2022). Musical Experience Relates to Insula-Based Functional Connectivity in Older Adults. *Brain Sci*, *12*(11). <https://doi.org/10.3390/brainsci12111577>
- Aleman, A., Nieuwenstein, M. R., Bocker, K. B., & de Haan, E. H. (2000). Music training and mental imagery ability. *Neuropsychologia*, *38*(12), 1664-1668. [https://doi.org/10.1016/s0028-3932\(00\)00079-8](https://doi.org/10.1016/s0028-3932(00)00079-8)
- Alexander, L., Wood, C. M., & Roberts, A. C. (2023). The ventromedial prefrontal cortex and emotion regulation: lost in translation? *J Physiol*, *601*(1), 37-50. <https://doi.org/10.1113/jp282627>
- Alluri, V., Toiviainen, P., Burunat, I., Kliuchko, M., Vuust, P., & Brattico, E. (2017). Connectivity patterns during music listening: Evidence for action-based processing in musicians. *Hum Brain Mapp*, *38*(6), 2955-2970. <https://doi.org/10.1002/hbm.23565>
- Basinski, K., Zdun-Ryzewska, A., Greenberg, D. M., & Majkowicz, M. (2021). Preferred

- musical attribute dimensions underlie individual differences in music-induced analgesia. *Sci Rep*, *11*(1), 8622. <https://doi.org/10.1038/s41598-021-87943-z>
- Baumgartner, T., Lutz, K., Schmidt, C. F., & Jancke, L. (2006). The emotional power of music: how music enhances the feeling of affective pictures. *Brain Res*, *1075*(1), 151-164. <https://doi.org/10.1016/j.brainres.2005.12.065>
- Bouhali, F., Mongelli, V., Thiebaut de Schotten, M., & Cohen, L. (2020). Reading music and words: The anatomical connectivity of musicians' visual cortex. *Neuroimage*, *212*, 116666. <https://doi.org/10.1016/j.neuroimage.2020.116666>
- Bushnell, M. C., Ceko, M., & Low, L. A. (2013). Cognitive and emotional control of pain and its disruption in chronic pain. *Nat Rev Neurosci*, *14*(7), 502-511. <https://doi.org/10.1038/nrn3516>
- Cakmak, O., Cimen, S., Tarhan, H., Ekin, R. G., Akarken, I., Ulker, V., Celik, O., Yucel, C., Kisa, E., Ergani, B., Cetin, T., & Kozacioglu, Z. (2017). Listening to music during shock wave lithotripsy decreases anxiety, pain, and dissatisfaction : A randomized controlled study. *Wien Klin Wochenschr*, *129*(19-20), 687-691. <https://doi.org/10.1007/s00508-017-1212-0>
- Chan, M. M. Y., & Han, Y. M. Y. (2022). The functional brain networks activated by music listening: A neuroimaging meta-analysis and implications for treatment. *Neuropsychology*, *36*(1), 4-22. <https://doi.org/10.1037/neu0000777>
- Chang, C., & Glover, G. H. (2010). Time-frequency dynamics of resting-state brain connectivity measured with fMRI. *Neuroimage*, *50*(1), 81-98. <https://doi.org/10.1016/j.neuroimage.2009.12.011>
- Chang, Y. H., Oh, T. H., Lee, J. W., Park, S. C., Seo, I. Y., Jeong, H. J., & Kwon, W. A. (2015). Listening to music during transrectal ultrasound-guided prostate biopsy decreases anxiety, pain and dissatisfaction in patients: a pilot randomized controlled trial. *Urol Int*, *94*(3), 337-341. <https://doi.org/10.1159/000368420>
- Chao-Gan, Y., & Yu-Feng, Z. (2010). DPARSF: A MATLAB Toolbox for "Pipeline" Data Analysis of Resting-State fMRI. *Front Syst Neurosci*, *4*, 13. <https://doi.org/10.3389/fnsys.2010.00013>
- Chemerinski, E., Nopoulos, P. C., Crespo-Facorro, B., Andreasen, N. C., & Magnotta, V. (2002). Morphology of the ventral frontal cortex in schizophrenia: relationship with social dysfunction. *Biol Psychiatry*, *52*(1), 1-8. [https://doi.org/10.1016/s0006-3223\(01\)01363-4](https://doi.org/10.1016/s0006-3223(01)01363-4)
- Choi, S., Park, S. G., & Lee, H. H. (2018). The analgesic effect of music on cold pressor pain responses: The influence of anxiety and attitude toward pain. *PLoS One*, *13*(8), e0201897. <https://doi.org/10.1371/journal.pone.0201897>
- Comte, M., Schon, D., Coull, J. T., Reynaud, E., Khalfa, S., Belzeaux, R., Ibrahim, E. C., Guedj, E., Blin, O., Weinberger, D. R., & Fakra, E. (2016). Dissociating Bottom-Up and Top-Down Mechanisms in the Cortico-Limbic System during Emotion Processing. *Cereb Cortex*, *26*(1), 144-155. <https://doi.org/10.1093/cercor/bhu185>
- Corbetta, M., Patel, G., & Shulman, G. L. (2008). The reorienting system of the human brain: from environment to theory of mind. *Neuron*, *58*(3), 306-324. <https://doi.org/10.1016/j.neuron.2008.04.017>
- Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci*, *3*(3), 201-215. <https://doi.org/10.1038/nrn755>
- Craddock, R. C., James, G. A., Holtzheimer, P. E., 3rd, Hu, X. P., & Mayberg, H. S. (2012). A whole brain fMRI atlas generated via spatially constrained spectral

- clustering. *Hum Brain Mapp*, 33(8), 1914-1928. <https://doi.org/10.1002/hbm.21333>
- Craig, A. D. (2011). Significance of the insula for the evolution of human awareness of feelings from the body. *Ann N Y Acad Sci*, 1225, 72-82. <https://doi.org/10.1111/j.1749-6632.2011.05990.x>
- Daniel J. Clauw, M. (2014). Fibromyalgia: a Clinical Review. *311*(15), 1547-1555. <https://doi.org/10.1001/jama.2014.3266>
- Dijkstra, N., Zeidman, P., Ondobaka, S., van Gerven, M. A. J., & Friston, K. (2017). Distinct Top-down and Bottom-up Brain Connectivity During Visual Perception and Imagery. *Sci Rep*, 7(1), 5677. <https://doi.org/10.1038/s41598-017-05888-8>
- 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. *J Pain*, 15(10), 1057-1068. <https://doi.org/10.1016/j.jpain.2014.07.006>
- Dosenbach, N. U., Nardos, B., Cohen, A. L., Fair, D. A., Power, J. D., Church, J. A., Nelson, S. M., Wig, G. S., Vogel, A. C., Lessov-Schlaggar, C. N., Barnes, K. A., Dubis, J. W., Feczko, E., Coalson, R. S., Pruett, J. R., Jr., Barch, D. M., Petersen, S. E., & Schlaggar, B. L. (2010). Prediction of individual brain maturity using fMRI. *Science*, 329(5997), 1358-1361. <https://doi.org/10.1126/science.1194144>
- Farrant, K., & Uddin, L. Q. (2015). Asymmetric development of dorsal and ventral attention networks in the human brain. *Dev Cogn Neurosci*, 12, 165-174. <https://doi.org/10.1016/j.dcn.2015.02.001>
- Ferraro, S., Klugah-Brown, B., Tench, C. R., Yao, S., Nigri, A., Demichelis, G., Pinaridi, C., Bruzzone, M. G., & Becker, B. (2022). Dysregulated anterior insula reactivity as robust functional biomarker for chronic pain-Meta-analytic evidence from neuroimaging studies. *Hum Brain Mapp*, 43(3), 998-1010. <https://doi.org/10.1002/hbm.25702>
- Finn, S., & Fancourt, D. (2018). The biological impact of listening to music in clinical and nonclinical settings: A systematic review. *Prog Brain Res*, 237, 173-200. <https://doi.org/10.1016/bs.pbr.2018.03.007>
- Garza-Villarreal, E. A., Pando, V., Vuust, P., & Parsons, C. (2017). Music-Induced Analgesia in Chronic Pain Conditions: A Systematic Review and Meta-Analysis. *Pain Physician*, 20(7), 597-610. <https://www.ncbi.nlm.nih.gov/pubmed/29149141>
- Hauck, M., Metzner, S., Rohlfs, F., Lorenz, J., & Pain, A. K. E. J. (2012). The Influence of Music and Music Therapy on Pain-Induced Neuronal Oscillations Measured by Magnetencephalography. *154*(4), 539-547. <https://doi.org/10.1016/j.pain.2012.12.016>
- Hirokawa, E., & Ohira, H. J. J. o. m. t. (2003). The effects of music listening after a stressful task on immune functions, neuroendocrine responses, and emotional states in college students. *40*(3), 189-211.
- Hole, J., Hirsch, M., Ball, E., & Meads, C. (2015). Music as an aid for postoperative recovery in adults: a systematic review and meta-analysis. *Lancet*, 386(10004), 1659-1671. [https://doi.org/10.1016/S0140-6736\(15\)60169-6](https://doi.org/10.1016/S0140-6736(15)60169-6)
- Howlin, C., & Rooney, B. (2020). The Cognitive Mechanisms in Music Listening Interventions for Pain: A Scoping Review. *J Music Ther*, 57(2), 127-167. <https://doi.org/10.1093/jmt/thaa003>
- Koelsch, S. (2010). Towards a neural basis of music-evoked emotions. *Trends Cogn*

- Sci*, 14(3), 131-137. <https://doi.org/10.1016/j.tics.2010.01.002>
- Koelsch, S., Cheung, V. K. M., Jentschke, S., & Haynes, J. D. (2021). Neocortical substrates of feelings evoked with music in the ACC, insula, and somatosensory cortex. *Sci Rep*, 11(1), 10119. <https://doi.org/10.1038/s41598-021-89405-y>
- Kuhn, S., Vanderhasselt, M. A., De Raedt, R., & Gallinat, J. (2012). Why ruminators won't stop: the structural and resting state correlates of rumination and its relation to depression. *J Affect Disord*, 141(2-3), 352-360. <https://doi.org/10.1016/j.jad.2012.03.024>
- Li, Q., Wang, X., Wang, S., Xie, Y., Li, X., Xie, Y., & Li, S. (2018). Musical training induces functional and structural auditory-motor network plasticity in young adults. *Hum Brain Mapp*, 39(5), 2098-2110. <https://doi.org/10.1002/hbm.23989>
- Lu, X., Hou, X., Zhang, L., Li, H., Tu, Y., Shi, H., & Hu, L. (2023). The effect of background liked music on acute pain perception and its neural correlates. *Hum Brain Mapp*, 44(9), 3493-3505. <https://doi.org/10.1002/hbm.26293>
- Lunde, S. J., Vuust, P., Garza-Villarreal, E. A., & Vase, L. (2019). Music-induced analgesia: how does music relieve pain? *Pain*, 160(5), 989-993. <https://doi.org/10.1097/j.pain.0000000000001452>
- Luo, C., Guo, Z. W., Lai, Y. X., Liao, W., Liu, Q., Kendrick, K. M., Yao, D. Z., & Li, H. (2012). Musical training induces functional plasticity in perceptual and motor networks: insights from resting-state fMRI. *PLoS One*, 7(5), e36568. <https://doi.org/10.1371/journal.pone.0036568>
- McMains, S., & Kastner, S. (2011). Interactions of top-down and bottom-up mechanisms in human visual cortex. *J Neurosci*, 31(2), 587-597. <https://doi.org/10.1523/JNEUROSCI.3766-10.2011>
- Ostrowsky, K., Magnin, M., Ryvlin, P., Isnard, J., Guenot, M., & Mauguiere, F. (2002). Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. *Cereb Cortex*, 12(4), 376-385. <https://doi.org/10.1093/cercor/12.4.376>
- Pando-Naude, V., Barrios, F. A., Alcauter, S., Pasaye, E. H., Vase, L., Brattico, E., Vuust, P., & Garza-Villarreal, E. A. (2019). Functional connectivity of music-induced analgesia in fibromyalgia. *Sci Rep*, 9(1), 15486. <https://doi.org/10.1038/s41598-019-51990-4>
- Park, H. J., & Friston, K. (2013). Structural and functional brain networks: from connections to cognition. *Science*, 342(6158), 1238411. <https://doi.org/10.1126/science.1238411>
- Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage*, 84, 320-341. <https://doi.org/10.1016/j.neuroimage.2013.08.048>
- Powers, J. M., Ioachim, G., & Stroman, P. W. (2022). Music to My Senses: Functional Magnetic Resonance Imaging Evidence of Music Analgesia Across Connectivity Networks Spanning the Brain and Brainstem. *Front Pain Res (Lausanne)*, 3, 878258. <https://doi.org/10.3389/fpain.2022.878258>
- Roy, M., Peretz, I., & Rainville, P. (2008). Emotional valence contributes to music-induced analgesia. *Pain*, 134(1-2), 140-147. <https://doi.org/10.1016/j.pain.2007.04.003>
- Schneider, B., & Koenigs, M. (2017). Human lesion studies of ventromedial prefrontal cortex. *Neuropsychologia*, 107, 84-93. <https://doi.org/10.1016/j.neuropsychologia.2017.09.035>

- Simavli, S., Gumus, I., Kaygusuz, I., Yildirim, M., Usluogullari, B., & Kafali, H. (2014). Effect of music on labor pain relief, anxiety level and postpartum analgesic requirement: a randomized controlled clinical trial. *Gynecol Obstet Invest*, *78*(4), 244-250. <https://doi.org/10.1159/000365085>
- Smith, S. M., Miller, K. L., Salimi-Khorshidi, G., Webster, M., Beckmann, C. F., Nichols, T. E., Ramsey, J. D., & Woolrich, M. W. (2011). Network modelling methods for fMRI. *Neuroimage*, *54*(2), 875-891. <https://doi.org/10.1016/j.neuroimage.2010.08.063>
- Tian, L., Ren, J., & Zang, Y. (2012). Regional homogeneity of resting state fMRI signals predicts Stop signal task performance. *Neuroimage*, *60*(1), 539-544. <https://doi.org/10.1016/j.neuroimage.2011.11.098>
- Tracey, I., & Mantyh, P. W. (2007). The cerebral signature for pain perception and its modulation. *Neuron*, *55*(3), 377-391. <https://doi.org/10.1016/j.neuron.2007.07.012>
- Valenti, V. E., Guida, H. L., Frizzo, A. C. F., Cardoso, A. C. V., Vanderlei, L. C. M., & Clinics, L. C. d. A. J. (2012). Auditory Stimulation and Cardiac Autonomic Regulation. *67*(8). [https://doi.org/10.6061/clinics/2012\(08\)16](https://doi.org/10.6061/clinics/2012(08)16)
- Valevicius, D., Lepine Lopez, A., Diushekeeva, A., Lee, A. C., & Roy, M. (2023). Emotional responses to favorite and relaxing music predict music-induced hypoalgesia. *Front Pain Res (Lausanne)*, *4*, 1210572. <https://doi.org/10.3389/fpain.2023.1210572>
- Wang, X., Wu, Q., Egan, L., Gu, X., Liu, P., Gu, H., Yang, Y., Luo, J., Wu, Y., Gao, Z., & Fan, J. (2019). Anterior insular cortex plays a critical role in interoceptive attention. *Elife*, *8*. <https://doi.org/10.7554/elife.42265>
- Werner, L. M., Skouras, S., Bechtold, L., Pallesen, S., & Koelsch, S. (2023). Sensorimotor synchronization to music reduces pain. *PLoS One*, *18*(7), e0289302. <https://doi.org/10.1371/journal.pone.0289302>
- Wig, G. S., Schlaggar, B. L., & Petersen, S. E. (2011). Concepts and principles in the analysis of brain networks. *Ann N Y Acad Sci*, *1224*, 126-146. <https://doi.org/10.1111/j.1749-6632.2010.05947.x>
- Yan, C. G., Wang, X. D., Zuo, X. N., & Zang, Y. F. (2016). DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. *Neuroinformatics*, *14*(3), 339-351. <https://doi.org/10.1007/s12021-016-9299-4>
- Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zollei, L., Polimeni, J. R., Fischl, B., Liu, H., & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*, *106*(3), 1125-1165. <https://doi.org/10.1152/jn.00338.2011>
- Zatorre, R. J. (2015). Musical pleasure and reward: mechanisms and dysfunction. *Ann N Y Acad Sci*, *1337*, 202-211. <https://doi.org/10.1111/nyas.12677>

Conflict of interest

All authors have no conflicting interests.

ARTICLE IN PRESS

Acknowledgments

Conceptualization and Investigation: Mengting Pan, Jiancheng Hou, Ying Liu. Data curation: Jiancheng Hou, Ying Liu. Formal analysis: Mengting Pan, Jiancheng Hou. Funding acquisition: Jiancheng Hou, Maoping Zheng, Ying Liu. Methodology: Jiancheng Hou, Qingqing Yang, Jue Deng, Ying Liu. Software: Qingqing Yang, Yukun Chen, Changan Sun. Visualization: Mengting Pan, Jiancheng Hou, Maoping Zheng, Ying Liu. Writing-original draft: Mengting Pan, Jiancheng Hou, Ying Liu. Writing-review & editing: Qingqing Yang, Yukun Chen, Maoping Zheng, Changan Sun, Ying Liu.

Funding

Sponsorship for this study and the Rapid Service Fee were funded by the National Natural Science Foundation of China (No. 32200823); the Chongqing Graduate Education Reform Fund (No. YJG233025); the Chongqing Educational Science Planning Project (No. K23ZG2020062); the Chongqing Undergraduate Education Reform, Development, and Practice of Music Students (No. 243045); the Basic Research Project of Central University of China (No. SWU2209508); and the Fujian Normal University Research Start-Up Funding (Y0720304K05).