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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

"Brain areas responsible for music-induced analgesia"

"Περιοχές του εγκεφάλου που είναι υπεύθυνες για την αναλγησία που προκαλείται από τη μουσική"

ΜΑΡΙΑΝΝΑ ΕΥΑΓΓΕΛΙΑ ΚΑΨΕΤΑΚΗ

ΑΘΗΝΑ

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Abstract

In English

Introduction. Pain, a subjective feeling experienced by approximately a quarter of the world's population, can be relieved in many different ways. One inexpensive and non-pharmacological way is by listening to music, which is known as music-induced analgesia.

Aim. To identify all brain regions that are associated with music-induced analgesia.

Methods. A systematic literature review, a bibliometric analysis, as well as a meta-analysis using Neurosynth were conducted.

Results. In the systematic literature review, 2,148 results were found on Scopus and 2,241 on Pubmed, of which 16 were judged to be eligible after screening. These 16 studies were published between 2014 and 2023 across 12 journals. The number of citations ranged from 2 to 118 (mean = 23.8, SD = 29.4), and was associated with the year of publication ($r_s = -0.900$, $p < 0.001$), the impact factor of the journal ($r_s = 0.584$, $p = 0.018$), and the Altmetric score ($r_s = 0.576$, $p = 0.020$). The brain regions reported in the 16 studies to be associated with music-induced analgesia were similar to those identified through the Neurosynth meta-analysis. Specifically, the latter showed an overlap of pain and music activations in the following regions: left and right cerebellum, hippocampi, amygdalae, insula, superior temporal gyri, superior and inferior frontal gyri, supplementary motor area, left thalamus, right cingulate cortex, right nucleus accumbens, and inferior parietal lobules.

Conclusions. To a large extent, there was concordance in the brain regions that were found through the systematic literature review and those found when overlapping "pain" and "music" activations using Neurosynth. Future studies need to use a lesion approach to identify the brain regions involved in music-induced analgesia, as all the studies identified through the systematic literature review and the Neurosynth meta-analysis were correlational.

In Greek

Εισαγωγή. Ο πόνος, ένα υποκειμενικό αίσθημα που βιώνει περίπου το ένα τέταρτο του παγκόσμιου πληθυσμού, μπορεί να ανακουφιστεί με πολλούς τρόπους. Ένας οικονομικός και μη φαρμακολογικός τρόπος είναι η ακρόαση μουσικής, γνωστή ως μουσικά επαγόμενη αναλγησία.

Σκοπός. Να εντοπιστούν όλες οι περιοχές του εγκεφάλου που σχετίζονται με τη μουσικά επαγόμενη αναλγησία.

Μέθοδοι. Πραγματοποιήθηκε συστηματική ανασκόπηση της βιβλιογραφίας, βιβλιομετρική ανάλυση, και μετα-ανάλυση στο Neurosynth.

Αποτελέσματα. Στη συστηματική ανασκόπηση της βιβλιογραφίας, εντοπίστηκαν 2.148 αποτελέσματα στη βάση δεδομένων Scopus και 2.241 στο PubMed, εκ των οποίων 16 κρίθηκαν κατάλληλα μετά τον έλεγχο. Οι 16 αυτές μελέτες δημοσιεύτηκαν την περίοδο 2014–2023 σε 12 επιστημονικά περιοδικά. Ο αριθμός των αναφορών κυμαινόταν από 2 έως 118 (μέσος όρος = 23,8, τυπική απόκλιση = 29,4) και σχετιζόταν με το έτος δημοσίευσης (r_s = -0.900, p < 0.001), τον συντελεστή απήχησης του περιοδικού (r_s = 0,584, p = 0,018) και τη βαθμολογία Altmetric (r_s = 0,576, p = 0,020). Οι περιοχές του εγκεφάλου που αναφέρθηκαν στις 16 μελέτες ως σχετιζόμενες με τη μουσικά επαγόμενη αναλγησία ήταν παρόμοιες με αυτές που εντοπίστηκαν μέσω της μετα-ανάλυσης στο Neurosynth. Συγκεκριμένα, η τελευταία έδειξε επικάλυψη ενεργοποιήσεων πόνου και μουσικής στις ακόλουθες περιοχές: αριστερή και δεξιά παρεγκεφαλίδα, ιππόκαμποι, αμυγδαλές, νήσος, άνω κροταφικές έλικες, άνω και κάτω μετωπιαίες έλικες, συμπληρωματική κινητική

περιοχή, αριστερός θάλαμος, δεξιός φλοιός του προσαγωγίου, δεξιός επικλινής πυρήνας, και κάτω βρεγματικά λόβια.

Συμπεράσματα. Σε μεγάλο βαθμό υπήρξε συμφωνία ανάμεσα στις περιοχές του εγκεφάλου που εντοπίστηκαν μέσω της συστηματικής ανασκόπησης της βιβλιογραφίας και σε εκείνες που προέκυψαν από την επικάλυψη των ενεργοποιήσεων «πόνου» και «μουσικής» στο Neurosynth. Μελλοντικές μελέτες θα πρέπει να χρησιμοποιήσουν τη μεθοδολογία των βλαβών (lesion approach) για να προσδιορίσουν τις εγκεφαλικές περιοχές που εμπλέκονται στη μουσικά επαγόμενη αναλγησία, καθώς όλες οι μελέτες που εντοπίστηκαν μέσω της συστηματικής ανασκόπησης και της μετα-ανάλυσης Neurosynth ήταν συσχετιστικές.

Keywords

analgesia, music, pain, brain, neural correlates

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Abbreviations

ADHD: attention deficit hyperactivity disorder

Altmetric: alternative metrics

BA: Brodmann area

BOLD: blood-oxygenation-level–dependent

CT: computed tomography

DTI: diffusion tensor imaging

EEG: electroencephalogram

fMRI: functional magnetic resonance imaging

fNIRS: functional near-infrared spectroscopy

JASP: Jeffreys's amazing statistics program

LORETA: low resolution electromagnetic tomography

MIA: music-induced analgesia

MRI: magnetic resonance imaging

MRIcroGL: magnetic resonance imaging cross-platform graphics library

Nd: YAP: neodymium yttrium aluminum perovskite

PET: positron emission tomography

PRISMA: preferred reporting items for systematic reviews and meta-analyses

PTSD: post-traumatic stress disorder

rTMS: repetitive transcranial magnetic stimulation

SD: standard deviation

SPECT: single-photon emission computed tomography

tDCS: transcranial direct current stimulation

TMS: transcranial magnetic stimulation

VBM: voxel-based morphometry

VOS: visualization of similarities

Introduction

Pain: epidemiology

Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Bonica, 1979). Pain affects approximately 1 in 4 people worldwide (Zimmer et al., 2022). However, the percentage of people experiencing pain differs according to the country, occupation, type of pain, and age group. For example, the prevalence of lower back pain has been reported to be 32.3% in Indonesian people aged 60 years and above (Susanto et al., 2025), 38.5% in people in China aged 45 years and above (Jiang et al., 2025), and 61% in nurses in Palestine (Zaitoon et al., 2024). The prevalence of chronic pain has been reported to be between 12% and 48% in the European adult population (Rometsch et al., 2025), 20.5% among adults in America (Yong, Mullins and Bhattacharyya, 2022), and 20.8% among children and adolescents worldwide (Chambers et al., 2024). Regarding chronic non-cancer pain, its prevalence among military veterans from the general population is 30% (Qureshi et al., 2025). Among cancer survivors worldwide, the prevalence of cancer pain is 65.22% before, and 39.77% after cancer treatment (Getie, Ayalneh and Bimerew, 2025). Every day, headache is experienced by approximately 15.8% of the world's population (Stovner et al., 2022).

Considering its global burden, pain imposes a substantial cost on society. This is particularly significant given that in approximately 36% of patients experiencing pain this is chronic, according to a study examining US adults (Nahin et al., 2023). It is costly because it can lead to days missed off work, to reduced productivity on the days that someone is working, as well as the cost of carers and treatments. It was estimated that the cost of pain in the United States in 2010 ranged from 560 to 635 billion dollars (Gaskin and Richard, 2012).

The quality of life is often affected in people experiencing pain. It can affect one's ability to sleep, their ability to participate in recreational and social activities, their physical functioning, and can lead to the development of depressive symptoms and anxiety (Jensen, Chodroff and Dworkin, 2007).

Pain: Types and factors affecting it

Based on the pathophysiological mechanism, pain can be nociceptive, inflammatory, neuropathic, or functional (Woolf, 2004). The first is usually of short duration and due to a noxious stimulus. The second is due to inflammation, e.g. in conditions such as rheumatoid arthritis or inflammatory bowel disease (Wang et al., 2025). The third is due to a lesion in the nervous system (specifically in the somatosensory system). The fourth is due an abnormality in the way the nervous system processes normal stimuli (Woolf, 2004); in this type of pain, there is typically no defined structural abnormality (e.g. no mass lesion causing pressure to the surrounding organs of the body) or abnormal findings in, for example, blood tests or MRI (magnetic resonance imaging) scans. Finally, the pain can also be a combination of any of the above types of pain.

Its severity can be increased by many factors. First, if the underlying condition causing the pain becomes worse. For example, if a malignant tumour continues to enlarge, causing more pressure to the surrounding structures. Second, when the patient is feeling sad, anxious, stressed, fearful, or interprets pain as harmful (Michaelides and Zis, 2019). These mood changes may be because of feelings related to the pain-inducing condition or due to any other unrelated factor.

There are many ways in which pain is eliminated or reduced. First, by removing the underlying factor causing the pain. For example, if someone has pain in the lumbar region radiating towards one of their lower legs, this can often be due to a prolapsed disc in the lumbar region of the spine. Therefore, undergoing lumbar discectomy to release the pressure of the disc on the nerves of that region, can reduce or eliminate the pain. Although undergoing an operation will remove (hopefully permanently) the pain-inducing condition, this is an invasive approach and is associated with all the risks of an operation including those of receiving general anaesthesia. Second, by implementing techniques that improve the condition that is causing the pain. For example, weight loss management for obese people with pain due to osteoarthritis (Messier et al., 2000).

Third, by taking medications that aim to reduce pain. The way in which these can be administered varies. For example, it can be inhalatory, oral, intravenous, intramuscular, intra-articular, sublingual, rectal, subcutaneous, intrathecal (i.e. in the subarachnoid space) or epidural; the most invasive ones are usually the most effective and have the fastest onset. Apart from well-known medications such as paracetamol, opioids, and corticosteroids, there are also some emerging treatments. For example, platelet-rich fibrin (Estrin et al., 2025) and platelet-rich plasma injections seem to be effective particularly for musculoskeletal pain (Thu, 2022), acting by releasing bioactive proteins that are able to restore anatomical function (Grossen et al., 2022). Some major issues of using pain medications (particularly opioids) to relieve pain are tolerance, addiction, and side effects (Højsted and Sjøgren, 2007).

Fourth, by stimulating certain parts of the nervous system with the use of invasive or non-invasive methods. Examples of invasive methods are spinal cord stimulation (Lamer et al., 2019), deep brain stimulation, peripheral nerve (field) stimulation (Verrills et al., 2011; Xu et al., 2021), dorsal root ganglion stimulation (Harrison et al., 2018), radiofrequency ablation of nerves (neurotomy), and pulsed radiofrequency (Chua, Vissers and Sluijter, 2011). In spinal cord stimulation, the electrodes are placed in the epidural space adjacent to the spinal cord. This causes bidirectional propagation of action potentials of myelinated Aβ-fibres that are in the dorsal column of the spinal cord, thus activating the spinal dorsal horn pain network (Smits et al., 2013). In deep brain stimulation, the electrodes are placed in the brain; specifically, the tip of the electrode aims to stimulate the periventricular/periaqueductal grey matter, internal capsule, or sensory thalamus (Bittar et al., 2005). Radiofrequency ablation of nerves to treat pain targets the specific nerve that neuroanatomically is thought to be responsible for the pain. For amputation-related pain, targeted muscle reinnervation (ElAbd et al., 2024) and regenerative peripheral nerve interface surgery (Woo et al., 2016) seem to help alleviate the pain.

Examples of non-invasive methods are repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), low-intensity transcranial ultrasound stimulation (Xu et al., 2025), and transcutaneous electrical nerve stimulation (Jones and Johnson, 2009). The target of the first two (tDCS and rTMS) for treating pain is usually the primary motor cortex or prefrontal cortex (Pacheco-Barrios et al., 2020; Bai et al., 2024). Emerging regions that may also be used in the future for pain relief using tDCS and TMS (transcranial magnetic stimulation) are the cerebellum (Manda et al., 2025) and the primary somatosensory cortex (Antal et al., 2008).

Fifth, there are other management options that may be helpful in some people such as physiotherapy, physical exercise, massage, acupuncture, counseling sessions with a psychologist, meditation, and immersive virtual reality (Teh et al., 2024; Wang et al., 2025). The mechanism by which many of these work may be through distraction and induction of positive feelings.

Music therapy

Music therapy is a field in which music is used as a means of helping people with various health conditions. In Parkinson's patients, music therapy seems to improve their motor and non-motor symptoms, as well as their quality of life (García-Casares, Martín-Colom and García-Arnés, 2018). In patients with traumatic brain injury, stride length and executive function seem to improve after receiving music therapy (Mishra et al., 2021). In stroke patients, music therapy has been shown to improve their quality of life (Poćwierz-Marciniak and Bidzan, 2017) and depression (Dayuan et al., 2022), and among those with aphasia to improve their functional communication (i.e. the ability to produce sounds, symbols, or signs that are understood by other people in order to communicate in daily life), repetition, and naming skills (Liu et al., 2022). Music therapy can lead to improvement in depression and anxiety in patients with Alzheimer's disease (Guétin et al., 2009), multiple sclerosis (Ostermann and Schmid, 2006) or attention-deficit hyperactivity disorder (Park et al., 2023).

In this thesis, the focus was on music being used to reduce or alleviate pain.

Characteristics of music-induced analgesia

Because pain is such a complex phenomenon, particularly in terms of its pathophysiology and the many factors that can influence it, effective pain management likely requires a biopsychosocial approach. This means addressing pain from multiple angles: a biological one (e.g. medications that act on pain receptors), a psychological one (e.g. interventions that promote a positive mood or reduce distress), and a social one (e.g. fostering social support and reducing feelings of loneliness and uncertainty through connections with friends, family, and the broader community) (Sofaer-Bennett et al., 2007).

Music-induced analgesia is the change in pain perception induced by listening to music (Basinski, Zdun-Ryżewska and Majkowicz, 2018). This is an inexpensive and non-pharmacological way of helping reduce various types of pain. It has been shown to reduce pain not only in humans, but also in other animals. For example, Georgiou and colleagues (2024) found that among dogs undergoing skin surgery, less isoflurane and fentanyl was required in those exposed to music.

It has been suggested that possible mechanisms by which music can relieve pain are by causing distraction, regulating mood (e.g. positive emotions), relieving stress, or acting as a rewarding stimulus (Zaatar et al., 2024).

Music has been shown to relieve pain of different durations (acute or chronic), caused by various conditions (e.g. malignant, labor, procedural, or experimental) and many different age groups (Standley, 2002; Zhang et al., 2012; Tsai et al., 2014; Hole et al., 2015; Lee, 2016).

The types of music that have been shown to have the analgesic effects are hopeful and futuristic lyrics, happy melodies (Roy, Peretz and Rainville, 2008; Chopra, 2023), sad music (Guo et al., 2020), music that has been chosen by the participant (Garza-Villarreal et al., 2017) and is familiar to them (Mitchell and MacDonald, 2006).

Very few studies have examined the duration of the analgesic effect caused by music (Garza-Villarreal et al., 2017). Of the few studies that examine this, the duration of analgesia has been shown to not only be during the music listening period, but may last for a few days after the person has stopped listening to the music. For example, among the nine participants that Merrill and Amin (2021) examined, five reported that their pain recurred after three days of not listening to the designated listening period (which involved listening to music for 30 minutes twice per day for a month), whereas four volunteers reported that their pain had not recurred after three days of not listening to the music.

Brain regions

Brain areas responsible for a specific function can be identified via various methods. These can be broadly categorised into methods assessing healthy subjects and in those assessing patients. The first can include fMRI (functional magnetic resonance imaging) studies. The latter can include lesion-symptom mapping studies, in which a group of patients with focal lesions in various locations (e.g. due to a stroke) is usually included. This method (in contrast to fMRI) enables the identification of a causative relationship between a brain region and a function rather than just a simple correlation (which is found using fMRI), thus enabling the identification of which brain regions are important for (rather than just related to) a specific behaviour.

Neuroanatomical basis of pain

The way in which pain is processed is thought to be as follows (mentioned in detail in Bai et al., 2024). Primary afferent neurons deliver the nociceptive information to the spinal dorsal horn. Then, the information travels to higher-order brain centres (from the ventral posterior lateral/medial nucleus of the thalamus to primary and secondary somatosensory cortices). For the sensory-discriminative aspect of pain, information is thought to travel from the posterior thalamic nucleus to the secondary somatosensory cortex and posterior insula. For affective-motivational aspects of pain, information travels via the spinoreticulothalamic tract to the centromedian-parafascicular nuclei. For pain affect, information travels from the subnucleus reticularis dorsalis, to the parabrachial nucleus, to the mediodorsal thalamic nucleus, and then to the anterior cingulate cortex. The nociceptive information can be modulated by the periaqueductal grey matter, locally at the spinal dorsal horn by excitatory and inhibitory interneurons, or by supraspinal descending serotonergic, noradrenergic, and dopaminergic fibres.

Previous studies have identified brain regions that seem to be associated with pain (the so-called pain network) (Bastuji et al., 2016; De Ridder et al., 2022). The regions that seem to process pain in the healthy human brain include the thalamus, insula, somatosensory, prefrontal, anterior temporal, limbic, and anterior cingulate cortices (Peyron, Laurent and García-Larrea, 2000; Duerden and Albanese, 2013).

Brain regions involved in music perception

Previous studies have identified brain regions that seem to be associated with listening to music (Stewart et al., 2006; Alluri et al., 2017; Chan and Han, 2022). Different brain regions seem to be activated depending on the type of music, its tempo, dynamics, and the listener’s personal preference (Sun et al., 2013; Tian et al., 2013; Wilkins et al., 2014; Yang et al., 2025; Zhang et al., 2025).

As can be seen in Figures 1, 2, and 3, fMRI studies have shown that many regions are involved in processing rhythm, pitch, and tone, respectively, with the superior temporal gyrus showing particularly consistent activation. These activation maps are based on all fMRI studies to date that mention these terms and were generated using Neurosynth.

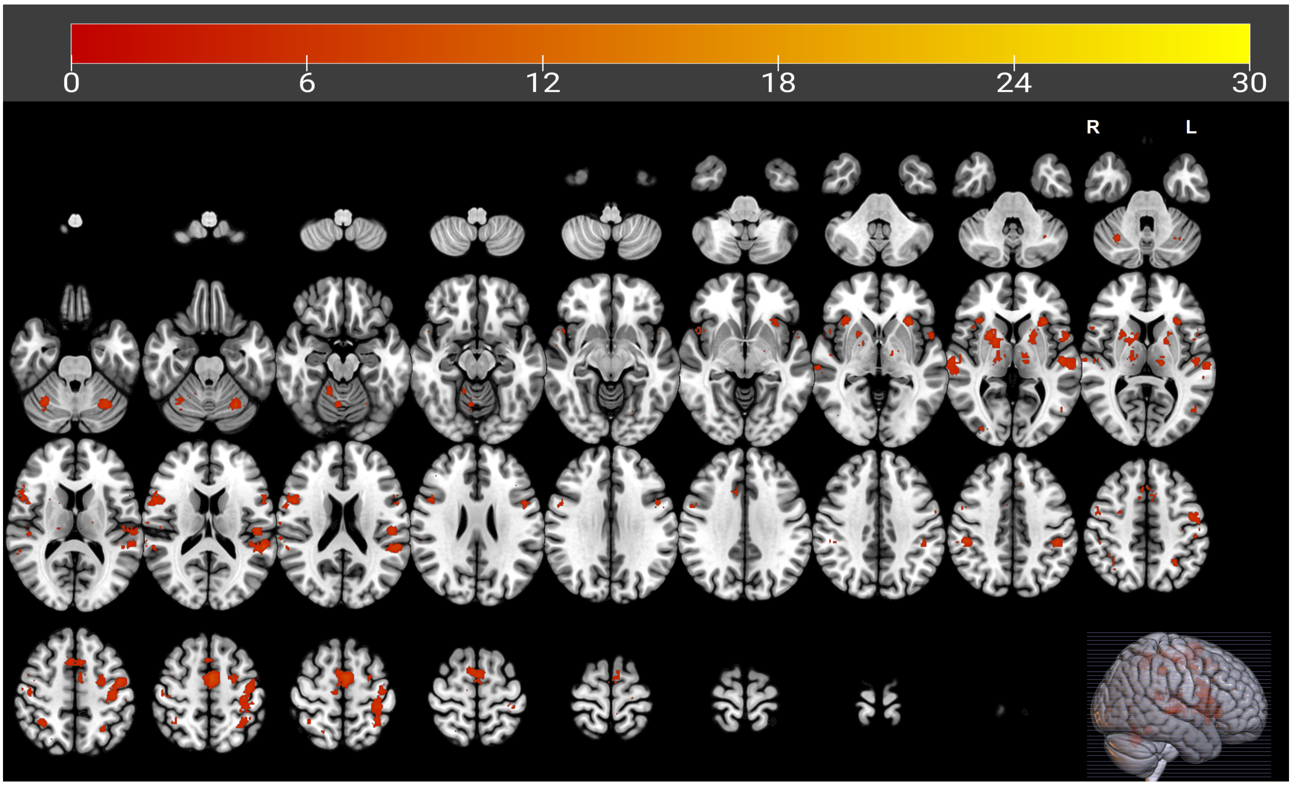

Figure 1. Brain activations related to the term “rhythm”, derived from a uniformity test map generated in Neurosynth.

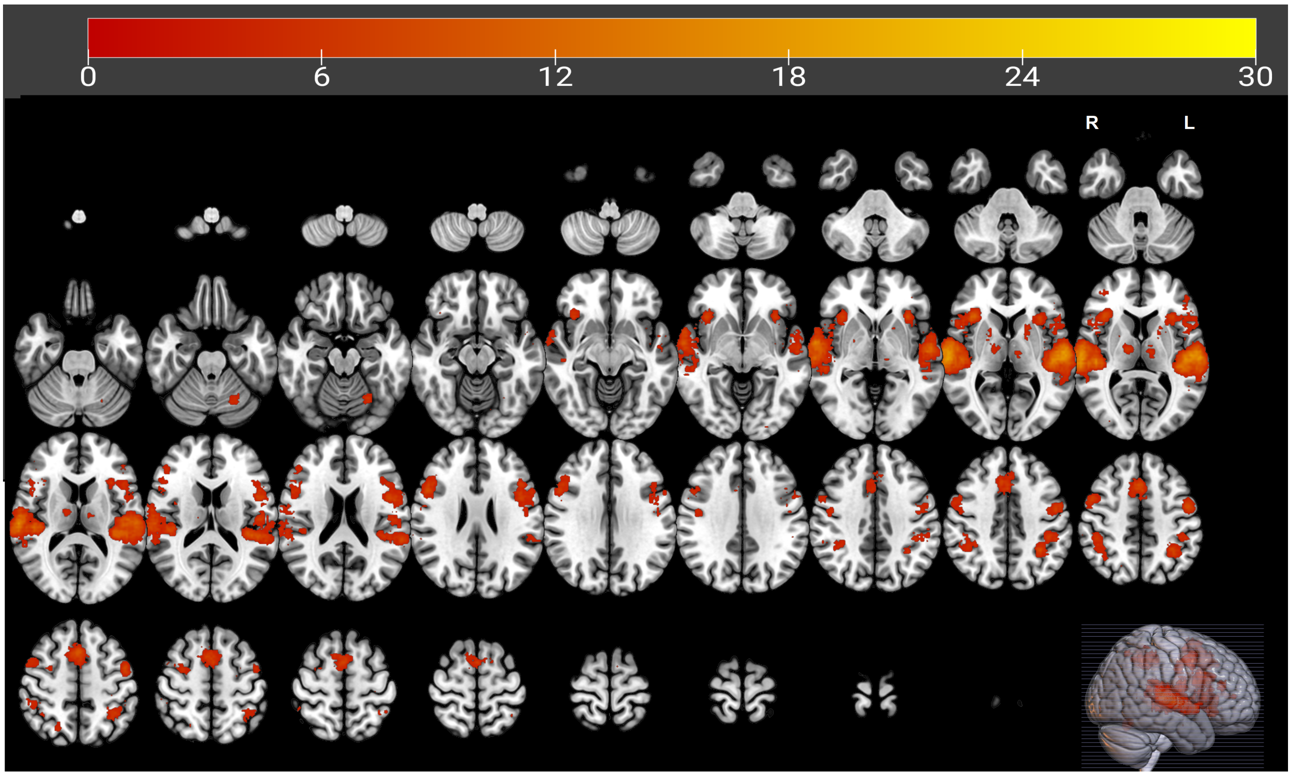

Figure 2. Brain activations related to the term "pitch", derived from a uniformity test map generated in Neurosynth.

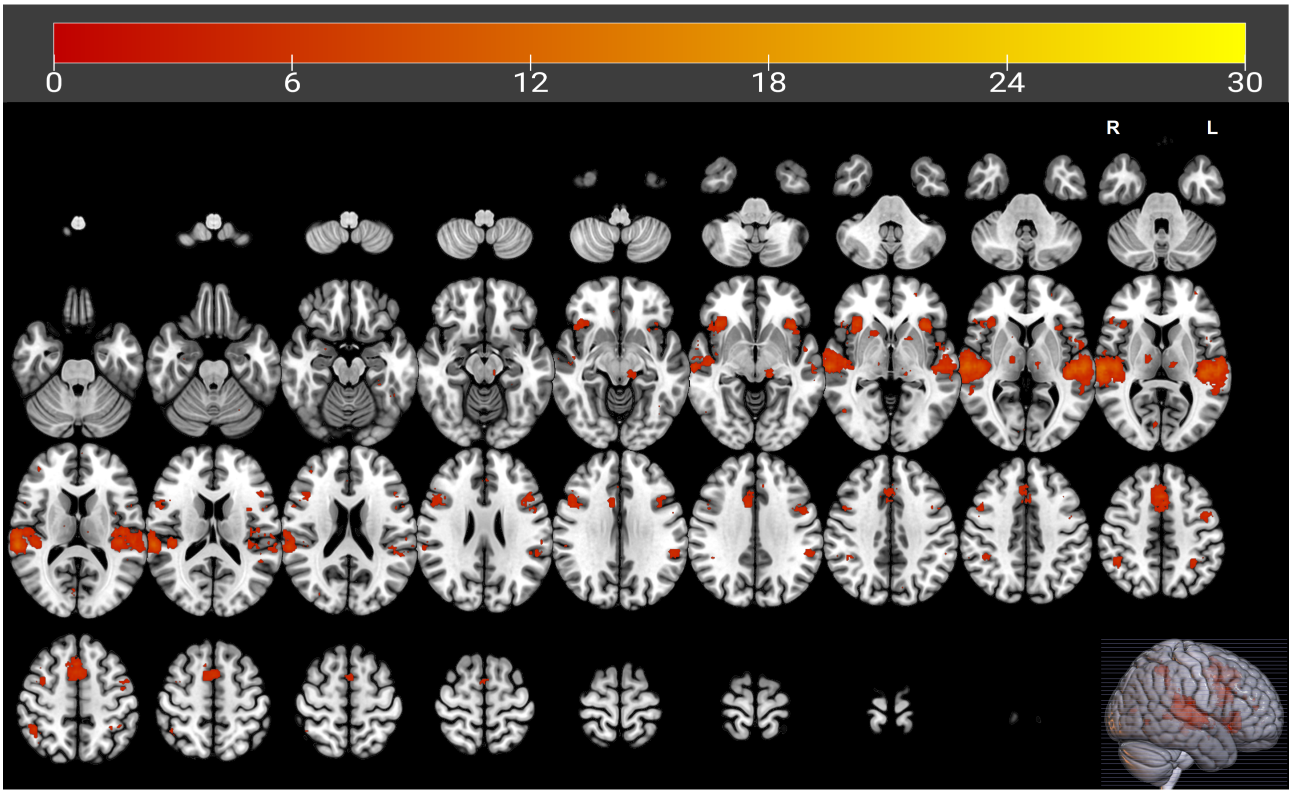

Figure 3. Brain activations related to the term “tone”, derived from a uniformity test map generated in Neurosynth.

Brain regions involved in both music and pain

Although there have been reviews examining music-induced analgesia (e.g. Lunde et al., 2019; Puri, 2024), there has not been a review that thoroughly examines the brain regions that are involved in this phenomenon.

<u>*Aim*</u>

The aim of this thesis was to find all brain regions that are associated with music-induced analgesia. To achieve this, the following approaches were employed.

First, a systematic literature review was conducted to find all brain regions that have been reported to be associated with music-induced analgesia. The hypothesis is that most of the brain regions responsible for music-induced analgesia will be the regions that are found when overlapping the “pain” with the “music” network (Neurosynth meta-analysis mentioned below). The aim was to identify the types of pain and types of music that have been examined, and whether these parameters influence the brain regions that have found to be responsible for music-induced analgesia. That is, a) whether it is a pain-general network (that is activated whatever the type of pain) or whether there are separate subnetworks of a pain-general network that are defined based on the type of pain, and b) whether it is a music-general network (that is activated whatever the type of music and independent of if we like that type of music or not) or whether there are separate subnetworks of a music-general network that are defined based on certain music parameters (e.g. type and likeability).

Second, a bibliometric analysis was conducted on the studies that were selected in the above systematic literature review.

Third, a meta-analysis using Neurosynth was conducted to identify brain activations related to pain and those related to music, with the hypothesis being that if there is an overlap of these activations, it may reveal which brain regions are involved in music-induced analgesia.

Methods and Materials

1) Systematic literature review

An extensive search of the literature was conducted to identify the brain regions responsible for music-induced analgesia, looking at studies that examine music-induced analgesia in healthy subjects and patients. A Boolean search was conducted on Scopus, to identify the presence of certain terms in the title or in the abstract. Specifically, the following Boolean search was used.

TITLE-ABS ((music* OR "music therap*" OR sing* OR song* OR rhythm* OR lullab* OR melod* OR "play* an instrument" OR "play* a music* instrument" OR "play* instrument*" OR "play* music* instrument*") AND (pain* OR analgesi* OR analgeti* OR nocicept* OR hyperalgesi* OR hyperalgeti* OR hypoalgesi* OR hypoalgeti* OR headache* OR ache* OR neuralgi* OR dysmenorrh* OR myalgi* OR fibromyalgi* OR arthralgi* OR otalgi* OR odontalgi* OR gastralgi* OR gastrodyni* OR cystalgi* OR proctalgi* OR thoracalgi* OR lumbalgi* OR pharyngalgi* OR mastalgi* OR cardialgi* OR heartburn* OR cephalodyni* OR mastodyni* OR oculodyni* OR colic* OR cramp* OR nephralgi* OR hepatalgi* OR splenalgi* OR enteralgi* OR spondylalgi* OR coxalgi* OR dactylalgi* OR podalgi* OR metatarsalgi* OR ischialgi* OR ureteralgi* OR urethralgi* OR sciatica OR causalgi* OR dyspareuni* OR algopareuni* OR vulvodyni* OR penodyni* OR scrotodyni* OR trigeminalgi* OR oesophagodyni* OR esophagodyni* OR glossodyni* OR stomatodyni* OR epigastralgi* OR clitorodyni* OR orchialgi* OR hernialgi* OR prostatodyni* OR dysuri*) AND (brain OR cortex OR cortic* OR lobe* OR gyr* OR hippocamp* OR amygdala OR neuroanatom* OR thalam* OR "basal ganglia" OR striat* OR insula*) AND (neuroimag* OR "brain imaging" OR EEG OR electroencephalogra* OR "PET scan" OR "diffusion tensor imaging" OR DTI OR "voxel-based morphometry" OR VBM OR "magnetic resonance" OR tDCS OR TMS OR MRI OR fMRI OR fNIRS OR "functional near-infrared spectroscopy" OR "white matter" OR "gray matter" OR connectivity OR "lesion symptom mapping" OR "positron emission tomography" OR "neural correlate*" OR SPECT OR "computed tomography" OR "CT scan*" OR "CT imag*" OR "arterial spin labeling" OR "blood oxygen level dependent" OR "bold activity" OR "functional imaging" OR "structural imaging" OR "transcranial direct current stimulation" OR "transcranial magnetic stimulation")) AND NOT TITLE-ABS ((animal* OR mouse OR mice OR rat OR rats OR murine OR rodent* OR macaque* OR monkey* OR nonhuman* OR "non human" OR "zebra finch" OR drosophila OR zebrafish*)) AND (LIMIT-TO (LANGUAGE, "English") OR LIMIT-TO (LANGUAGE, "Greek")) AND (LIMIT-TO (SRCTYPE, "j")) AND (LIMIT-TO (PUBSTAGE,"final")).

A search was also conducted on Pubmed. The following Boolean search was used: (((((music* [Title / Abstract] OR "music therap*" [Title / Abstract] OR sing* [Title / Abstract] OR song* [Title / Abstract] OR rhythm* [Title / Abstract] OR lullab* [Title / Abstract] OR melod* [Title / Abstract] OR "play* an instrument" [Title / Abstract] OR "play* a music* instrument" [Title / Abstract] OR "play* instrument*" [Title / Abstract] OR "play* music* instrument*" [Title / Abstract])) AND ((pain* [Title / Abstract] OR analgesi* [Title / Abstract] OR analgeti* [Title / Abstract] OR nocicept* [Title / Abstract] OR hyperalgesi* [Title / Abstract] OR hyperalgeti* [Title / Abstract] OR hypoalgesi* [Title / Abstract] OR hypoalgeti* [Title / Abstract] OR headache* [Title / Abstract] OR ache* [Title / Abstract] OR neuralgi* [Title / Abstract] OR dysmenorrh* [Title / Abstract] OR myalgi* [Title / Abstract] OR fibromyalgi* [Title / Abstract] OR arthralgi* [Title / Abstract] OR otalgi* [Title / Abstract] OR odontalgi* [Title / Abstract] OR gastralgi* [Title / Abstract] OR gastrodyni* [Title / Abstract] OR cystalgi* [Title / Abstract] OR proctalgi* [Title / Abstract] OR thoracalgi* [Title / Abstract] OR lumbalgi* [Title / Abstract] OR pharyngalgi* [Title / Abstract] OR mastalgi* [Title / Abstract] OR cardialgi* [Title / Abstract] OR heartburn* [Title / Abstract] OR cephalodyni* [Title / Abstract] OR mastodyni* [Title / Abstract] OR oculodyni* [Title / Abstract] OR colic* [Title / Abstract] OR cramp* [Title / Abstract] OR nephralgi* [Title / Abstract] OR hepatalgi* [Title / Abstract] OR splenalgi* [Title / Abstract] OR enteralgi* [Title / Abstract] OR spondylalgi* [Title / Abstract] OR coxalgi* [Title / Abstract] OR dactylalgi* [Title / Abstract] OR podalgi* [Title / Abstract] OR metatarsalgi* [Title / Abstract] OR ischialgi* [Title / Abstract] OR ureteralgi* [Title / Abstract] OR urethralgi* [Title / Abstract] OR sciatica [Title /

Abstract] OR causalgi* [Title / Abstract] OR dyspareuni* [Title / Abstract] OR algopareuni* [Title / Abstract] OR vulvodyni* [Title / Abstract] OR penodyni* [Title / Abstract] OR scrotodyni* [Title / Abstract] OR trigeminalgi* [Title / Abstract] OR oesophagodyni* [Title / Abstract] OR esophagodyni* [Title / Abstract] OR glossodyni* [Title / Abstract] OR stomatodyni* [Title / Abstract] OR epigastralgi* [Title / Abstract] OR clitorodyni* [Title / Abstract] OR orchialgi* [Title / Abstract] OR hernialgi* [Title / Abstract] OR prostatodyni* [Title / Abstract] OR dysuri* [Title / Abstract]))) AND ((brain [Title / Abstract] OR cortex [Title / Abstract] OR cortic* [Title / Abstract] OR lobe* [Title / Abstract] OR gyrus [Title / Abstract] OR gyri [Title / Abstract] OR hippocamp* [Title / Abstract] OR amygdala [Title / Abstract] OR neuroanatom* [Title / Abstract] OR thalam* [Title / Abstract] OR "basal ganglia" [Title / Abstract] OR striat* [Title / Abstract] OR insula* [Title / Abstract]))) AND ((neuroimag* [Title / Abstract] OR "brain imaging" [Title / Abstract] OR EEG [Title / Abstract] OR electroencephalogra* [Title / Abstract] OR "PET scan" [Title / Abstract] OR "diffusion tensor imaging" [Title / Abstract] OR DTI [Title / Abstract] OR "voxel-based morphometry" [Title / Abstract] OR VBM [Title / Abstract] OR "magnetic resonance" [Title / Abstract] OR tDCS [Title / Abstract] OR TMS [Title / Abstract] OR MRI [Title / Abstract] OR fMRI [Title / Abstract] OR fNIRS [Title / Abstract] OR "functional near-infrared spectroscopy" [Title / Abstract] OR "white matter" [Title / Abstract] OR "gray matter" [Title / Abstract] OR connectivity [Title / Abstract] OR "lesion symptom mapping" [Title / Abstract] OR "positron emission tomography" [Title / Abstract] OR "neural correlate*" [Title / Abstract] OR SPECT [Title / Abstract] OR "computed tomography" [Title / Abstract] OR "CT scan*" [Title / Abstract] OR "CT imag*" [Title / Abstract] OR "arterial spin labeling" [Title / Abstract] OR "blood oxygen level dependent" [Title / Abstract] OR "bold activity" [Title / Abstract] OR "functional imaging" [Title / Abstract] OR "structural imaging" [Title / Abstract] OR "transcranial direct current stimulation" [Title / Abstract] OR "transcranial magnetic stimulation" [Title / Abstract])))) NOT ((animal* [Title / Abstract] OR mouse [Title / Abstract] OR mice [Title / Abstract] OR rat [Title / Abstract] OR rats [Title / Abstract] OR murine [Title / Abstract] OR rodent* [Title / Abstract] OR macaque* [Title / Abstract] OR monkey* [Title / Abstract] OR nonhuman* [Title / Abstract] OR "non human" [Title / Abstract] OR "zebra finch" [Title / Abstract] OR drosophila [Title / Abstract] OR zebrafish* [Title / Abstract])).

Then, by reading the titles, abstracts, and full-texts of the publications, it was decided which publications were and which were not eligible for inclusion in the review. The publications that were included were articles written in English or Greek that had been published (i.e. not in press or preprints) in a journal anytime before the date that the searches were conducted (i.e. 20/08/2025 for Scopus, 26/8/2025 for Pubmed) referring to human brain regions that are involved in music-induced analgesia. No restriction was made as regards to the year in which the manuscript was published, the race, gender, ethnicity, nationality or cultural group of the study's participants, the number of participants, or the location and duration of the study.

A PRISMA (i.e. preferred reporting items for systematic reviews and meta-analyses) flow diagram (Figure 4) was used to document in detail the total number of search items identified through the search engines, the number of items that were excluded (and the reasons for which they were excluded) and the number of items that were included.

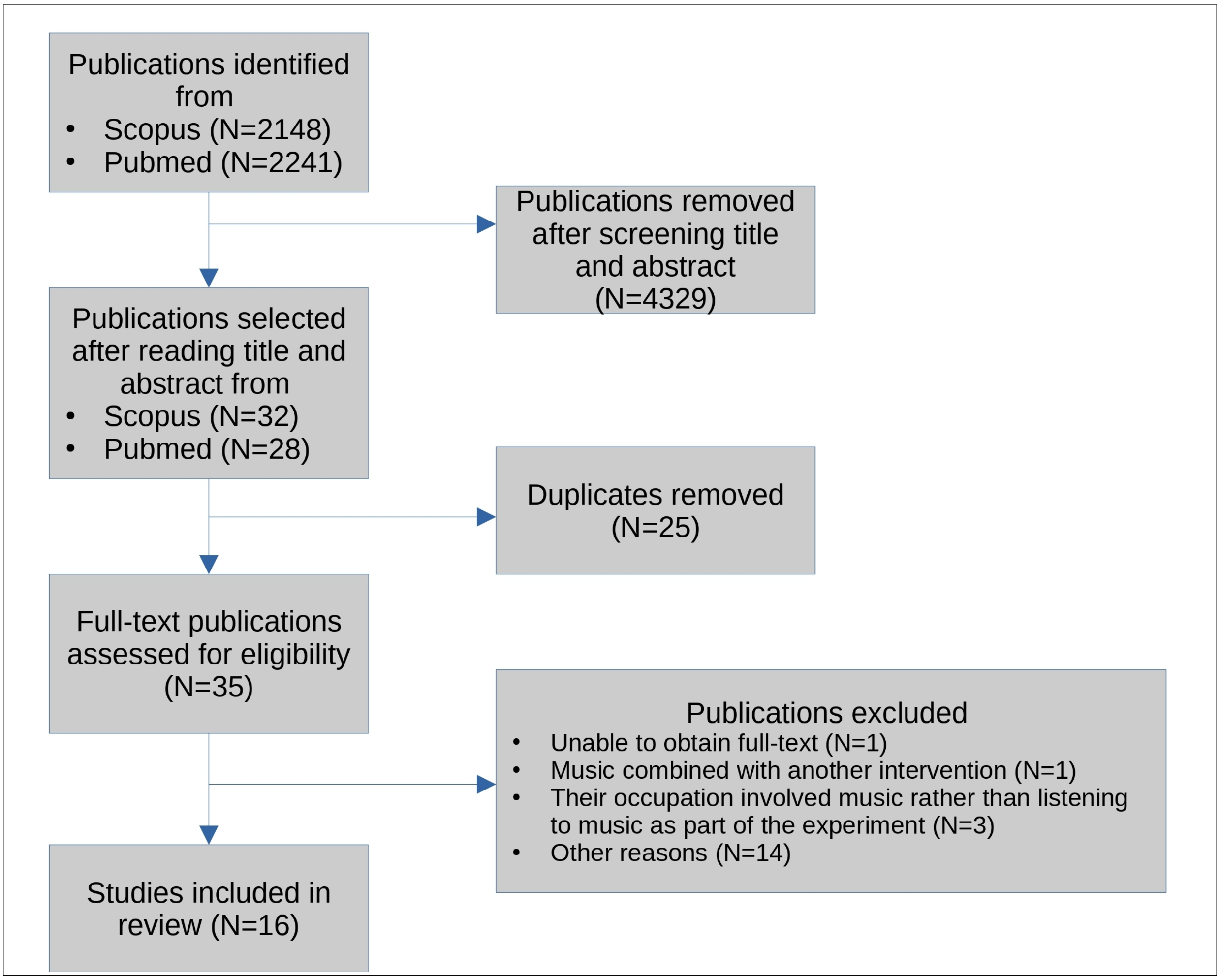

Figure 4. PRISMA flow diagram

2) Bibliometric analysis

Scopus was used to extract the following data for each publication: the total number of citations it has received (including self-citations), its length (number of pages), and the affiliations of all authors. The Altmetric (i.e. alternative metrics) score of each publication and the impact factor of each journal were obtained within one hour on 26/10/2025. For one journal, the impact factor was obtained from SCImago Journal Rank (Scimago Journal & Country Rank, no date), because it was not available on the journal's website.

The JASP (Jeffreys's amazing statistics program; version 0.95.3 / 2025) computer software was used to perform statistical analyses. The distribution of the data as well as the presence of outliers were examined using histograms, Q-Q plots, box and whisker plots, and the Shapiro–Wilk test for normality. Spearman's rank correlation coefficient (r_s), a non-parametric test, was used when parametric assumptions were not met. Excel functions were used to create a world map of the number of authors per country. VOSviewer (i.e. visualization of similarities viewer; version 1.6.20) was used to create a network of co-occurring words in the abstracts.

3) Neurosynth meta-analysis

Given the thousands of fMRI studies that have examined multiple cognitive functions, a tool is necessary to effectively combine all these data. This has been developed and is free and online. Neurosynth is able to gather all activations that have been reported for a given topic based on data from many fMRI studies. When a term is selected, Neurosynth provides two types of statistical inference maps through the meta-analysis: the association test map and the uniformity test map. Only the latter was chosen in this thesis. The reason was that although the association test map shows whether activation in a voxel is found more consistently in studies mentioning that term (compared to studies not mentioning that term), the uniformity test map shows how much each voxel is consistently activated in studies mentioning that term.

Neurosynth was used to identify first the activations in the brain related to pain and then activations related to music. Then, an overlap of the pain and music activation networks was made using MRIcroGL (magnetic resonance imaging cross-platform graphics library; version v1.2.20220720; MRIcroGL, no date).

Results

1) Systematic literature review

The Scopus search gave 2,148 results; after screening these results, 32 were identified as appropriate. The Pubmed search gave 2,241 results; after screening these results, 28 were identified as appropriate. Duplicates were then removed. This led to 35 publications whose full-text was read to determine whether they met the inclusion criteria. Of these 35 publications, N = 16 were included in this review (Table 1) and the rest were excluded (Table 2).

Table 1. Included studies.

Authors	Title	Year	Number of participants in the neuroimaging analysis	Age of participants	Control condition
Used fNIRS (functional near-infrared spectroscopy)					
Zhang et al.	A study based on functional near-infrared spectroscopy: Cortical responses to music interventions in patients with myofascial pain syndrome	2023	15	22-67 years old	No music
Du et al.	Effect of music intervention on subjective scores, heart rate variability, and prefrontal hemodynamics in patients with chronic pain	2022	37	65 years or older	No control condition
Sorkpor et al.	Assessing the impact of preferred web app-based music-listening on pain processing at the central nervous level in older black adults with low back pain:	2023	12	18-65 years old	Usual care (appropriate exercise directed by a clinician)

	An fNIRS study				without receiving 30-min music per day for a week
Used fMRI					
Antioch et al.	Favorite Music Mediates Pain-related Responses in the Anterior Cingulate Cortex and Skin Pain Thresholds.	2020	8	13-85 years old	No music
Pando-Naude et al.	Functional connectivity of music-induced analgesia in fibromyalgia	2019	20 healthy controls, 20 patients	21-70 years old	Pink noise
Usui et al.	Music intervention reduces persistent fibromyalgia pain and alters functional connectivity between the insula and default mode network	2020	23	20-59 years old	No music
Dobek et al.	Music modulation of pain perception and pain-related activity in the brain, brain stem, and spinal cord: A functional magnetic resonance imaging study	2014	12	18-40 years old	No music
Garza-Villarreal et al.	Music reduces pain and increases resting state fMRI BOLD signal amplitude in the left angular gyrus in fibromyalgia patients	2015	20	22-70 years old	Pink noise
Powers et al.	Music to My Senses: Functional Magnetic Resonance Imaging Evidence of Music Analgesia Across Connectivity Networks Spanning the Brain and Brainstem	2022	20	21-33 years old	No music
Lu et al.	The effect of background liked music on acute pain perception and its neural correlates	2023	28	19-26 years old	a) silence, b) disliked songs
Used EEG (electroencephalogram)					
Huang et al.	The effects of customised brainwave music on orofacial pain induced by orthodontic tooth movement	2016	36	Young (age range not mentioned)	a) cognitive behavioural therapy b) sitting

					without being instructed to do or listen to something specific
Thanyawinichkul et al.	The Efficacy of Binaural Beat Stimulation Mixed with Acoustic Music in Chronic Low Back Pain Management: A Randomized Controlled Trial	2022	22	27-70 years old	Acoustic music without 6 Hz-theta binaural beats
Gkolias et al.	Reduced pain and analgesic use after acoustic binaural beats therapy in chronic pain - A double-blind randomized control cross-over trial	2020	19	58.76 ± 14.64 (Mean and standard deviation)	Soft relaxing music without 5 Hz binaural beats
Guo et al.	Sad Music Modulates Pain Perception: An EEG Study	2020	40	Young (age range not mentioned)	No sound
Hunt et al.	Neuronal Effects of Listening to Entrainment Music Versus Preferred Music in Patients With Chronic Cancer Pain as Measured via EEG and LORETA Imaging	2021	3	55-75 years old	Entrainment music of a different participant
Lu et al.	Music reduces pain unpleasantness: Evidence from an EEG study	2019	30	18-28 years old	Silence or white noise

These are the studies that were included in the systematic literature review, categorised according to the neuroimaging method used.

Table 2. Excluded studies

Authors	Title	Year	Reasons for exclusion
Boller & Bogousslavsky	Paul Wittgenstein's right arm and his phantom: the saga of a famous concert pianist and his amputation	2015	They did not examine music-induced analgesia
Deng et al.	Brain Response of Major Depressive Disorder Patients to	2022	They did not examine pain

	Emotionally Positive and Negative Music		
Ettenberger et al.	Effect of music therapy on short-term psychological and physiological outcomes in mechanically ventilated patients: A randomized clinical pilot study	2024	Music was combined with another intervention
Halpin et al.	Pre-sleep alpha brain entrainment by audio or visual stimulation for chronic widespread pain and sleep disturbance: A randomised crossover feasibility trial	2025	Not all participants received auditory stimuli (some received visual stimuli)
Howland	Hey Mister Tambourine Man, play a drug for me: Music as medication	2016	I was not able to obtain the full-text of this publication
Huang & Charyton	A comprehensive review of the psychological effects of brainwave entrainment.	2008	This was a review, not an original study
Koelsch et al.	Tormenting thoughts: The posterior cingulate sulcus of the default mode network regulates valence of thoughts and activity in the brain's pain network during music listening	2022	They did not examine music-induced analgesia
Minen et al.	Treatment Options for Posttraumatic Headache: A Current Review of the Literature	2024	This was a review, not an original study
Pastor et al.	Pilot Study: The Differential Response to Classical and Heavy Metal Music in Intensive Care Unit Patients under Sedo-Analgesia	2023	They examined critically ill patients who were under sedo-analgesia and had traumatic brain injury, intraparenchymal or subarachnoid haemorrhage or status epilepticus. It is not clear whether pain was induced during the music intervention and it is not clear whether music led to pain reduction.
Pauwels et al.	Mozart, music and medicine	2014	This was a review, not an original study
Pinegger et al.	Composing only by thought: Novel application of the P300 brain-computer interface	2017	They did not examine music-induced analgesia
Särkämö et al.	Music perception and cognition: Development, neural basis, and	2013	This was a review, not an original study

	rehabilitative use of music		
Sternkopf et al.	The heating rate matters! contact heat evoked potentials in musicians and non-musicians	2025	Participants were musicians; they were not listening to music during the experiment
Strigo et al.	Enhancing chronic low back pain management: an initial neuroimaging study of a mobile interoceptive attention training	2024	They did not examine music-induced analgesia
Wagner et al.	Reduced heat pain thresholds after sad-mood induction are associated with changes in thalamic activity	2009	Music was combined with another intervention
Wang et al.	Five-week music therapy improves overall symptoms in schizophrenia by modulating theta and gamma oscillations	2024	They did not examine pain
Wu et al.	Analgesic effect of dance movement therapy: An fNIRS study	2024	Music was combined with another intervention
Zamorano et al.	Experience-dependent neuroplasticity in trained musicians modulates the effects of chronic pain on insula-based networks – A resting-state fMRI study	2019	Participants were musicians; they were not listening to music during the experiment
Zamorano et al.	Impact of Chronic Pain on Use-Dependent Plasticity: Corticomotor Excitability and Motor Representation in Musicians With and Without Pain	2024	Participants were musicians; they were not listening to music during the experiment

These are the studies that were excluded during the last screening stage of the systematic literature review.

The 16 studies identified in the systematic literature review included a total of 365 participants (minimum = 3 participants, maximum = 40 participants; mean = 22.8, with SD i.e. standard deviation being 11.4). All these studies used non-invasive brain imaging techniques. Specifically, 3 used fNIRS (functional near-infrared spectroscopy), 7 used fMRI, and 6 used EEG (electroencephalogram). Both fNIRS and fMRI rely on neurovascular coupling, but fNIRS is limited in that it has poorer spatial resolution (approximately 2-3 cm vs 0.3 mm voxels) and can only measure cortical activity up to 2 cm deep (Pinti et al., 2020). In contrast, EEG has poorer spatial resolution (5-9 cm) (Pinti et al., 2020), but better temporal resolution (milliseconds vs seconds) (Burle et al., 2015). This temporal and spatial resolution variety of the neuroimaging techniques investigating music-induced analgesia allows us to have a comprehensive understanding of which brain regions have been found to be associated with music-induced analgesia.

Among the 16 studies identified in the systematic literature review, there was variability in the types of pain experienced by the participants, how pain was induced, how it was measured, and the populations that were assessed (e.g. healthy people or fibromyalgia patients). The duration for which the participants listened to the music differed quite a lot across studies; in some studies the music intervention was just a few minutes and in others it was daily for a whole week (e.g. Du et al., 2022). In many studies, music was the only intervention given to induce pain relief, but in others, music was used as an add-on to the treatment they were already receiving, e.g. appropriate exercise (Du et al., 2022) or medications for pain-relief.

Studies using fNIRS

The first fNIRS study (Zhang et al., 2023) included patients with myofascial pain syndrome. Regional pain was triggered by applying pressure on the painful area. It was found that Brodmann areas (BA) 6, 9, 10, and 46 were less active when listening to soothing synthetic music (with frequencies of 8–150 Hz and 50–70 dB) compared to when they were not listening to music.

The second fNIRS study (Du et al., 2022) assessed people with chronic pain. Referred pain was induced by the thumb and maintaining 3–4 kg/cm2 pressure for 30 seconds. The music intervention was a 30 min daily session of listening to specific music (8–150 Hz, 50–70 dB) for 7 days. It was found that BA 6, 9, 10, and 46 were less active in the music (compared to the no-music) intervention group.

The third fNIRS study (Sorkpor et al., 2023) assessed people with low back pain. A handheld digital pressure algometer which had a 1 cm diameter flat robber probe was used to trigger pain, by pressing at approximately 0.3 kgf/cm2 per second at the lower back (specifically, on the intercristal line, 5cm left of the median line). The music intervention was participant-selected music from the MUSIC CARE app (MUSIC CARE App, no date). Post music intervention, a reduced activation was found in the primary motor and somatosensory cortices.

Studies using fMRI

In the first fMRI study (Antioch et al., 2020), pain was induced by delivering electrical stimulation to the patients' left ankle with a skin electrode. Each participant listened to their own favourite music. A specific location in the anterior cingulate cortex (Talairach coordinates x = −10, y = 12, z = 26) was less active when listening (compared to when not listening) to music.

In the second fMRI study (Pando-Naude et al., 2019), females with fibromyalgia and healthy controls were assessed. In fibromyalgia patients, listening to participant-selected slow-paced familiar pleasant music (compared to noise) led to a decrease in resting state-functional connectivity a) of the pain matrix, b) between left anterior cingulate cortex and right superior temporal gyrus, c) between left angular gyrus and right precuneus, d) between the pain matrix and right precuneus, right posterior cingulate gyrus and right orbitofrontal cortex, e) between the left anterior cingulate cortex and right posterior superior temporal gyrus and right superior parietal lobe, f) between the left angular gyrus and right precuneus, left superior frontal gyrus, right superior frontal gyrus, right posterior cingulate gyrus, and right posterior middle temporal gyrus, and g) between the left insula and left primary motor cortex. Increased connectivity was found between the left amygdala and right middle frontal gyrus. Also, the greater the experienced music-induced-analgesia, the larger the a) decrease in the resting state-functional connectivity between the angular gyrus, posterior cingulate cortex and precuneus, and b) increase in the resting state-functional connectivity between the amygdala and middle frontal gyrus.

In the third fMRI study (Usui et al., 2020), females with fibromyalgia were assessed. The music intervention was listening to one specific piece: Mozart's Duo for Violin and Viola No. 1, K. 423. The resting state-functional connectivity between the right insular cortex and the posterior cingulate cortex/precuneus was significantly different before (compared to after) the music intervention.

In the fourth fMRI study (Dobek et al., 2014), healthy non-musicians were assessed. Pain was administered by thermal stimulation on the thenar eminence of the right hand. The music intervention was participant-selected music. When comparing the music to the no-music condition, differences in activity (Blood-oxygenation-level–dependent, i.e. BOLD, response) were found in the ventral tegmental area, right nucleus accumbens, left insula, bilateral dorsal anterior cingulate cortex, right ventral anterior cingulate cortex, right parahippocampal gyrus, right orbitofrontal cortex, left primary somatosensory cortex, bilateral dorsolateral prefrontal cortex, right supplementary motor area, bilateral middle temporal gyrus, bilateral fusiform gyrus, left superior temporal gyrus, left primary auditory cortex, right hypothalamus, cerebellum, pulvinar, ventral posterolateral thalamus, bilateral precuneus, left secondary visual association cortex, rostral ventromedial medulla, dorsolateral pontine tegmentum and periaqueductal grey area.

The fifth fMRI study (Garza-Villarreal et al., 2015) assessed females with fibromyalgia. The music intervention was participant-selected relaxing music. After the music intervention, the left angular gyrus showed increased connectivity with the left caudate nucleus and right dorsolateral prefrontal cortex, and decreased connectivity with the right anterior cingulate cortex, right supplementary motor cortex, precuneus and right precentral gyrus. The lower the pain intensity following the music intervention, the higher the BOLD amplitude in the left angular gyrus.

The sixth fMRI study (Powers, Ioachim and Stroman, 2022) assessed healthy subjects. Pain was elicited by thermal stimulation of the thenar eminence of the right hand. The music intervention was participant-selected familiar and pleasurable music. While receiving the painful stimulus, differences in the connectivity between the following regions were found when comparing the music to the no-music condition: between the hippocampus and thalamus, and between the insula and amygdala.

The seventh fMRI study (Lu et al., 2023) assessed healthy participants. The music intervention was participant-selected liked and disliked music. Pain was elicited by applying radiant-heat stimuli using an infrared neodymium yttrium aluminum perovskite (Nd: YAP) laser on the dorsum of the left hand. Right pre- and post-central gyri and left cerebellum activity mediated the relationship between music listening and pain ratings.

Studies using EEG

The first EEG study (Huang et al., 2016) assessed healthy subjects with mild-to moderate malocclusion. Pain was elicited by a fixed orthodontic procedure, i.e. placing straight wire brackets for one month. The music intervention was brainwave music. Specifically, EEG data were acquired from each person in the brainwave music condition and then based on that data, music was composed by digitally filtering the brainwaves. During the brainwave music condition, EEG activity in the prefrontal, inferior frontal and posterior temporal lobes was associated with pain perception changes. The participants listening to brainwave music (compared to those receiving cognitive behavioural therapy or receiving no instructions) had increased frontal, parietal and occipital theta activity and increased parietal and occipital alpha activity.

The second EEG study (Thanyawinichkul et al., 2022) assessed patients with low back pain. They were asked to listen to acoustic piano music combined with or without 6 Hz binaural beats. When comparing the condition “before” to “after” acoustic piano music listening (without 6 Hz binaural beats), changes in brain activity were found in the left pre-frontal EEG channel (using z-score comparison).

The third EEG study (Gkolias et al., 2020) assessed people with chronic pain. They were asked to listen to soft relaxing music with or without 5 Hz binaural beats. There was an increase in the mean theta power at 5 Hz in the EEG after (compared to before) listening to soft relaxing music with 5 Hz binaural beats. Also, the larger the change in mean EEG theta power, the smaller the change in the reported pain scores.

The fourth EEG study (Guo et al., 2020) assessed healthy subjects. The music intervention was happy, neutral and sad music selected from the Chinese Affective Music Mood System. Pain was induced by placing participants’ hands in cold water for as long as possible. The following was noticed among people in which music increased the time for which they could tolerate pain. First, the EEG frequency spectrum was significantly different in the beta-2 and gamma bands of the O2 electrode and the gamma band of the P4 electrode when listening to sad music compared to no sound, indicating increased occipital and parietal activity when listening to sad music. Second, the longer they were able to tolerate the pain during sad music listening, the higher the spectrum amplitude in the gamma band at the P4 electrode. Third, when listening to happy or neutral music (compared to no sound) there was a greater reduction in the connections of the coherence network in the beta-2 and gamma bands. Fourth, when listening to sad music, there was a partial increase in prefrontal, parietal and occipital connections in the coherence network.

The fifth EEG study (Hunt et al., 2021) examined patients with chronic cancer pain. The music intervention involved entrainment music (i.e. a music therapist in collaboration with each participant created music that matched each participant's individual feeing of pain and then to match their individual healing experience) or participant-selected instrumental commercial music. In one of the participants, when comparing the music condition which he felt that had the best healing effect for his pain (for him, this was his own entrainment healing condition) to a different person's entrainment healing condition, there was an increase in the frequency bin of 8-10 Hz in the regions: right supramarginal gyrus, right precuneus and an increase in the frequency bin of 13-15 Hz in the regions: anterior cingulate, cingulate gyrus, right inferior temporal gyrus, and left superior frontal gyrus.

The sixth EEG study (Lu et al., 2019) examined healthy subjects. Pain was induced by delivering nociceptive-specific radiant-heat stimuli, using a Nd: YAP laser on the dorsal part of their left hand. The music intervention was participants' preferred music. In the music (compared to the silence) condition, the amplitude of P2 (a wave that seems to be mainly generated from the anterior and middle cingulate cortices) was smaller.

2) Bibliometric analysis

The 16 studies were published between 2014 and 2023 (Figure 5). They were published across 12 journals; most frequently in the *Journal of Pain Research* (3 publications). The impact factor of the journal in which they were published ranged from 0.1 to 4 (mean = 2.7, SD = 0.85). The number of authors in these publications ranged from 3 to 10 (mean = 6.8, SD = 2.45). Among the total of 109 authors in this field, most (N = 37 authors) were affiliated with China (Figure 6). The only inter-country collaborations that occurred in more than one publication were between researchers in Mexico and Denmark (specifically, a collaboration between these two countries occurred in two publications). The page count ranged from 6 to 19 (mean = 11, SD = 3.47). The number of citations ranged from 2 to 118 (mean = 23.8, SD = 29.4). The Altmetric score ranged from 0 to 125 (mean = 24.1, SD = 43). The most frequently co-occurring words in the abstracts of these publications can be found in Figure 7 with the most frequently occurring words being mia (an abbreviation of music-induced analgesia), subject, day, minute, week, pain intensity, pain perception, functional connectivity, and control group.

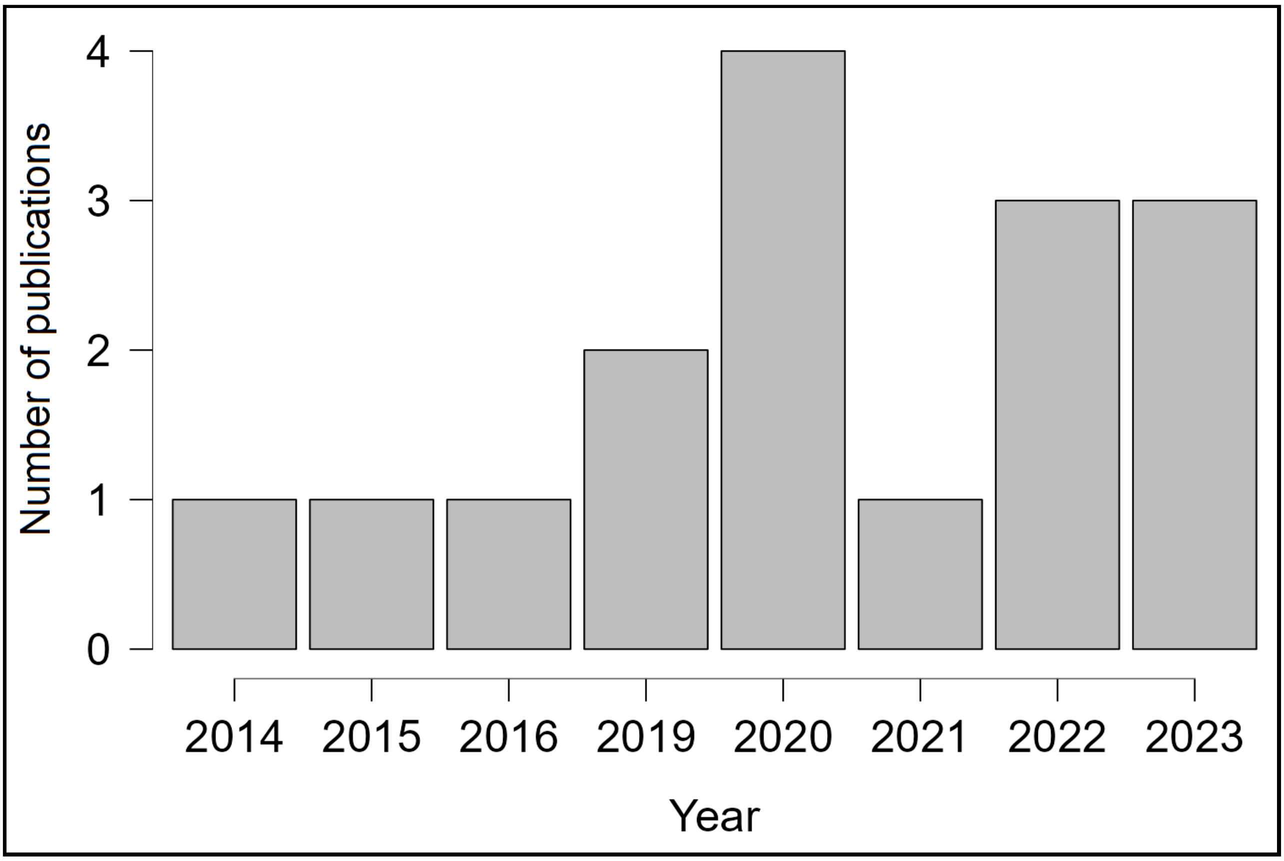

Figure 5. Number of publications per year

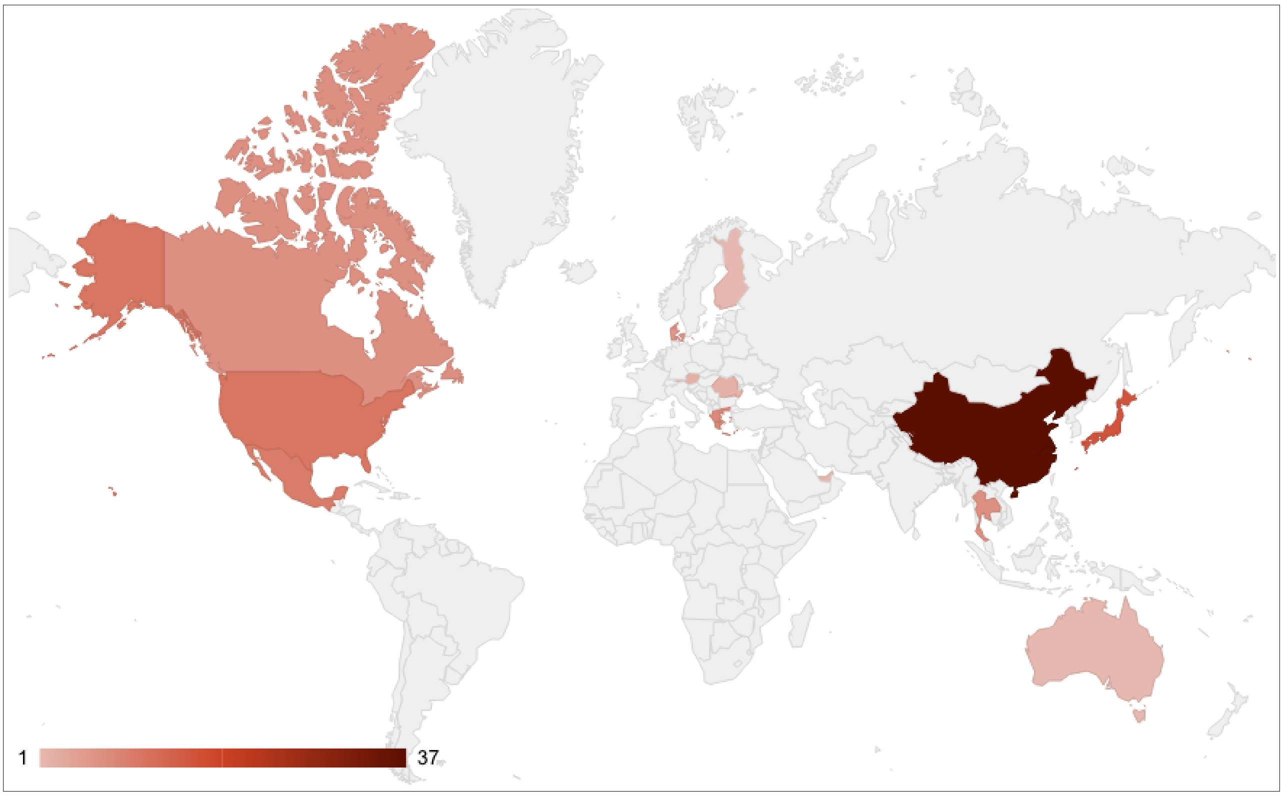

Figure 6. Number of authors affiliated with each country. Grey indicates 0 authors.

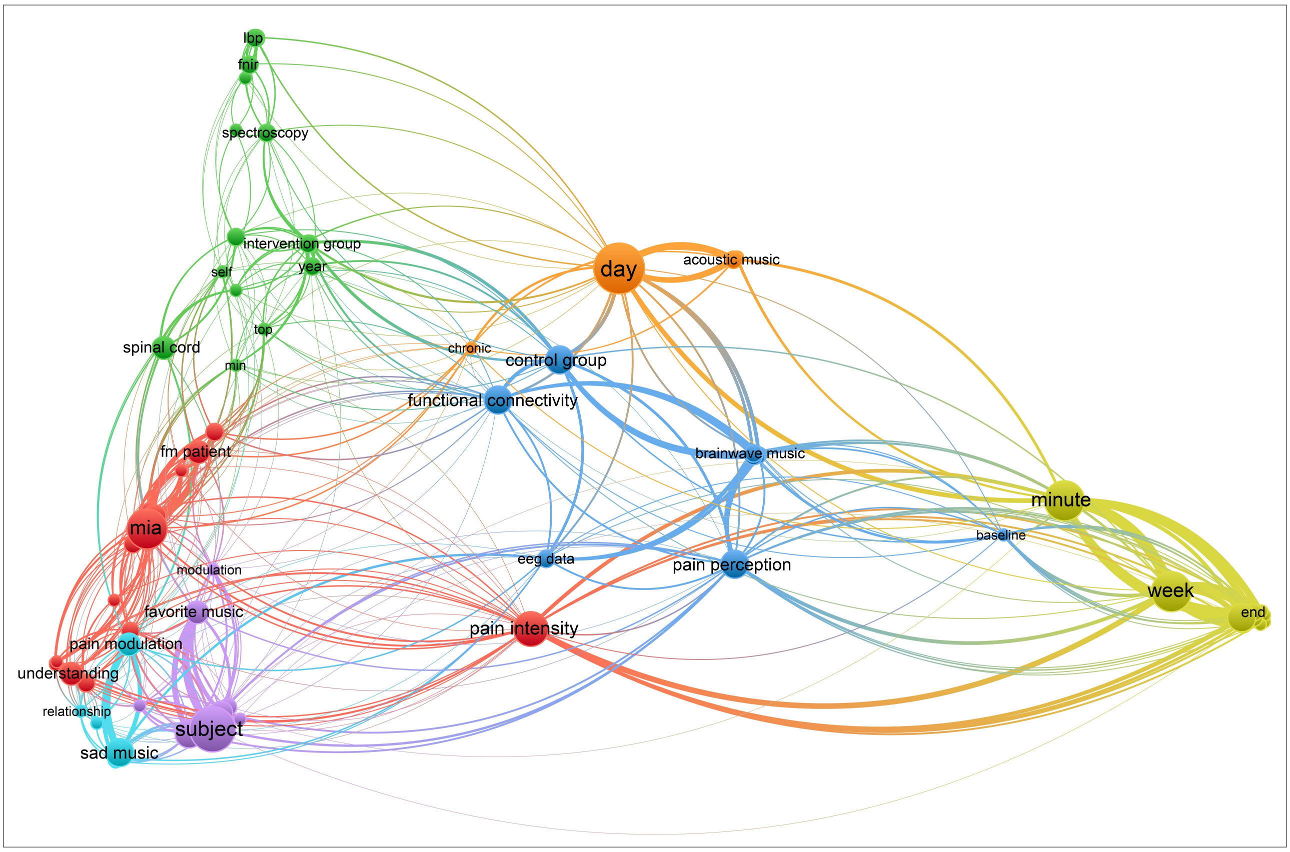

Figure 7. Network of words that frequently appear together in the abstracts of the 16 publications, created using VOSviewer. The size of each circle represents how many times the word occurs across all abstracts, in which the larger the size the higher the occurrence. The thickness of each of the lines connecting the circles represents how often these words co-occur within the same abstract. Minimum number of occurrences: 2. The 60% most relevant terms were selected. Items: 86. Clusters: 7. Links: 663. Total link strength: 2466. Weights: occurrences. Minimum strength: 0. Maximum lines: 1000.

The page count was not associated with the year of publication (r_s = 0.011, p = 0.967), number of authors (r_s = -0.304, p = 0.253), number of citations (r_s = 0.143, p = 0.598), Altmetric score (r_s = 0.392, p = 0.133), or the impact factor of the journal (r_s = 0.461, p = 0.073). The number of citations was associated with the year of publication (r_s = -0.900, p < 0.001; i.e. the older the publication the more citations it had obtained), the impact factor of the journal (r_s = 0.584, p = 0.018), and the Altmetric score (r_s = 0.576, p = 0.020), but not the number of authors (r_s = 0.337, p = 0.202). The Altmetric score was associated with the impact factor of the journal (r_s = 0.598, p = 0.014), but not with the year of publication (r_s = -0.492, p = 0.053) or the number of authors (r_s = 0.098, p = 0.719).

3) Neurosynth meta-analysis

The regions that have been reported in fMRI studies to be related to pain can be seen in Figure 8. The regions that have been reported in fMRI studies to be related to music can be seen in Figure 9. The overlap of the pain and music activation networks can be seen in Figure 10. In this figure, we can see that there is an overlap of activations (pink areas) in the following regions: left and right cerebellum, hippocampi, amygdalae, insula, superior temporal gyri, superior and inferior frontal gyri, supplementary motor area, left thalamus, right cingulate cortex, right nucleus accumbens, and inferior parietal lobules. In other words, these regions respond to both pain and music and thus may be involved in music-induced analgesia.

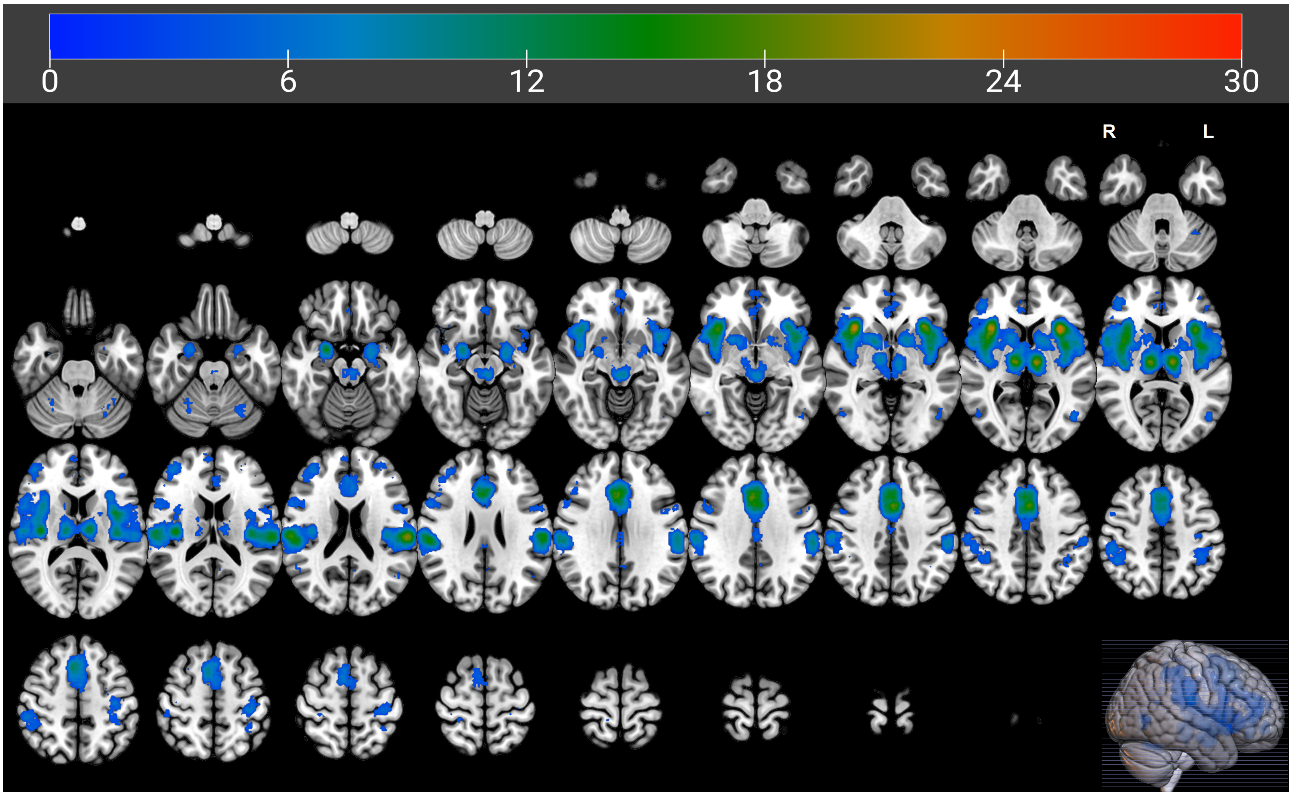

Figure 8. Brain activations related to the term “pain”, derived from a uniformity test map generated in Neurosynth.

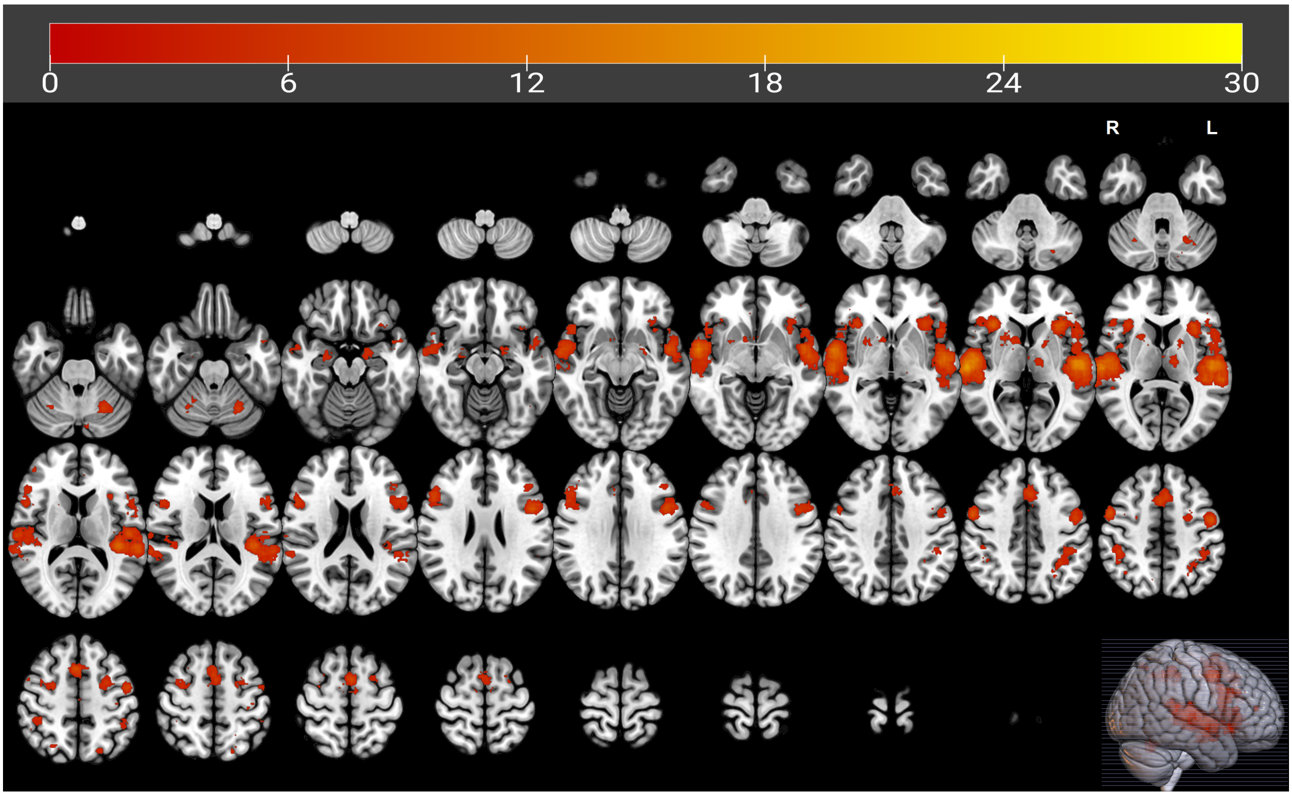

Figure 9. Brain activations related to the term “music”, derived from a uniformity test map generated in Neurosynth.

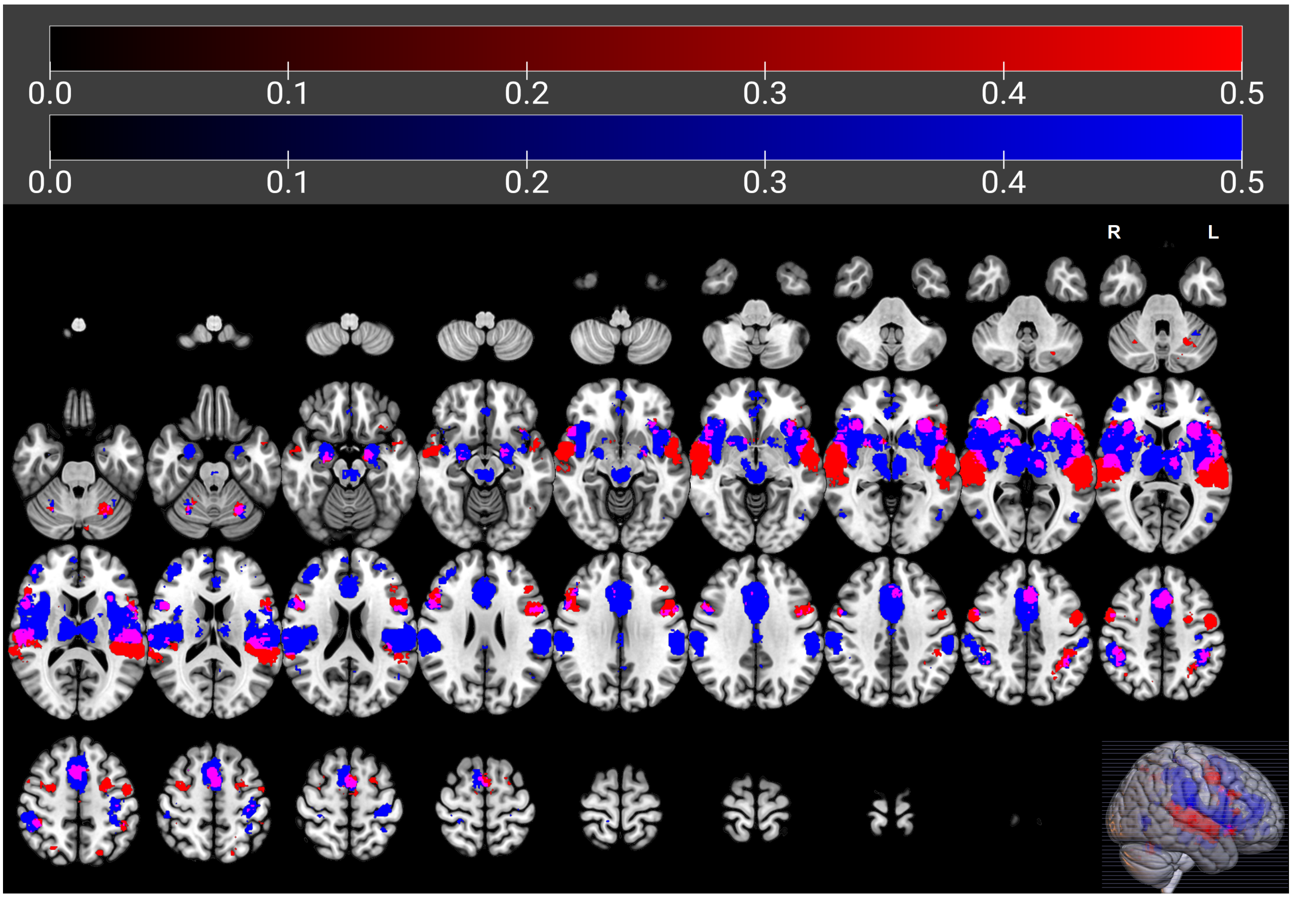

Fig. 10. Overlap of “music” (red) and “pain” (blue) activations. The overlap is shown in pink.

Discussion

Research on the brain regions involved in music-induced analgesia remains limited. The studies identified in the systematic literature review have shown that changes in the activity and connectivity of and between many brain regions occur when listening to music while experiencing a painful stimulus (see Tables 3 and 4). Similar regions were also identified in the overlap of pain and music activations based on fMRI data from Neurosynth.

Table 3. Brain regions that show a change in their activity when participants are listening to music while experiencing pain.

Lobe/Anatomical area	**Subregion**	**The activity of these regions after listening to music**	**How many studies found this region?**
Limbic	Cingulate gyrus (mainly anterior cingulate cortex)	decreased/ increased/altered	4
	Right nucleus accumbens	altered	1
Frontal	Dorsolateral prefrontal cortex (BA 9, 46)	decreased/altered	3
	Anterior prefrontal cortex (BA10)	decreased	2
	Right orbitofrontal cortex	altered	1
	Left superior frontal gyrus	increased	1
	Prefrontal cortex	altered	2
	Supplementary motor area/cortex (BA 6)	decreased/altered	3
	Primary motor cortex	decreased/altered	2
	Inferior frontal gyrus	altered	1
	Not specified	increased	1
Temporal	Posterior temporal lobe	altered	1
	Bilateral middle temporal gyrus	altered	1
	Bilateral fusiform gyrus	altered	1
	Left superior temporal gyrus	altered	1
	Left primary auditory cortex	altered	1
	Right parahippocampal gyrus	altered	1
	Right inferior	increased	1

	temporal gyrus		
Parietal	Primary somatosensory cortex	decreased/altered	3
	Right supramarginal gyrus	increased	1
	Precuneus	increased/altered	2
	Not specified	increased	2
Occipital	Left secondary visual association cortex	altered	1
	Not specified	increased	2
Diencephalon	Ventral posterolateral thalamus	altered	1
	Pulvinar	altered	1
	Right hypothalamus	altered	1
Cerebellum	Not specified	altered	2
Brainstem	Dorsolateral pontine tegmentum	altered	1
	Ventral tegmental area	altered	1
	Periaqueductal grey area	altered	1
	Rostral ventromedial medulla	altered	1
Left insula	Not specified	altered	1

These are the regions that were found in the 16 studies of the systematic literature review.

Table 4. Brain regions between which there is a change in connectivity when participants are listening to music while experiencing pain.

Regions	Connectivity
Pain matrix	Decreased
Pain matrix ↔ Right precuneus, right posterior cingulate gyrus, right orbitofrontal cortex	
Left anterior cingulate cortex ↔ Right superior temporal gyrus	
Left anterior cingulate cortex ↔ Right posterior superior temporal gyrus, right superior parietal lobe	

<table>
<tr><th>Regions</th><th>Connectivity</th></tr>
<tr><td>Left angular gyrus ↔ Right precuneus</td><td rowspan="4"></td></tr>
<tr><td>Left angular gyrus ↔ Right anterior cingulate cortex, right supplementary motor cortex, precuneus, right precentral gyrus</td></tr>
<tr><td>Left angular gyrus ↔ Right precuneus, left superior frontal gyrus, right superior frontal gyrus, right posterior cingulate gyrus, right posterior middle temporal gyrus</td></tr>
<tr><td>Left insula ↔ Left primary motor cortex</td></tr>
<tr><td>Left amygdala ↔ Right middle frontal gyrus</td><td rowspan="3">Increased</td></tr>
<tr><td>Left angular gyrus ↔ Left caudate nucleus, right dorsolateral prefrontal cortex</td></tr>
<tr><td>Prefrontal, parietal, and occipital regions</td></tr>
<tr><td>Right insular cortex ↔ Posterior cingulate cortex / precuneus</td><td rowspan="3">Altered</td></tr>
<tr><td>Hippocampus ↔ Thalamus</td></tr>
<tr><td>Insula ↔ Amygdala</td></tr>
</table>

These are the regions that were found in the 16 studies of the systematic literature review. Each row contains the findings of one study

There are many reasons why the above brain regions may be implicated in music-induced analgesia. First, many of these regions are related to processing emotions, e.g. the amygdala, insula, nucleus accumbens, orbitofrontal, and cingulate cortex (Murray, 2007; Salgado and Kaplitt, 2015; Journée et al., 2023; Rolls, 2023; Zhang, Deng and Xiao, 2024). Pain usually induces negative mood, whereas music usually induces positive mood or acts as a rewarding stimulus. The process of perceiving pain and then listening to music during the painful stimulus likely alters the emotions one feels and therefore a reduced pain sensation, through altered activity in these regions.

Second, many of these regions are related to attention. The effect of music on pain may be through distraction. An fMRI study showed that the anterior cingulate cortex and dorsolateral prefrontal cortex seem to be involved in attention shifting (Kondo, Osaka and Osaka, 2004). Compared to healthy controls, adults with ADHD (attention deficit hyperactivity disorder) have been found to have a smaller prefrontal cortex and anterior cingulate cortex (Seidman et al., 2006). Distraction has been shown to lead to reduced activity in the amygdala, left insula, and right inferior parietal lobe, but increased activity in prefrontal and cingulate regions (McRae et al., 2010). In healthy subjects receiving a painful stimulus, distraction led to decreased functional connectivity between the anterior insula and medial prefrontal cortex (Stankewitz et al., 2018); in the study of Stankewitz and colleagues (2018), distraction was induced using the Stroop task (Stroop, 1935), a classic neuropsychological task in which incongruent colour words are shown and the participant is asked to either read the word (e.g. to say BLUE when shown "BLUE") or say the colour of the word (e.g. to say BLACK when shown "BLUE"). An increase in functional connectivity between the left insula and right prefrontal cortex was found when healthy subjects searched for neutral targets in the presence of negative emotional distractors in complex everyday life visual scenes (Pedale, Macaluso and Santangelo, 2019).

Third, the involvement of certain brain regions in music-induced analgesia may partly reflect their role in stress reduction. An fMRI study found increased activity in the dorsolateral prefrontal cortex, anterior cingulate cortex, hippocampus, parahippocampal gyrus, precentral and postcentral gyrus during meditation (Lazar et al., 2000). In a PET (positron emission tomography) study, relaxation was associated with increased activity in the anterior cingulate cortex (Critchley, 2001).

Fourth, the superior temporal gyrus is the region where auditory information is primarily processed (specifically Heschl's gyrus) (Fullerton and Pandya, 2007). Interestingly, a study found that this gyrus may also be important for the memory exaggeration of the motivo-affective component of a painful event (Houde et al., 2020). Changes in the volume of this gyrus have been found in maltreated children, adolescents with PTSD (post-traumatic stress disorder), children and adolescents with generalised anxiety disorder, and adolescents with a history of suicide attempt and major depressive disorder compared to healthy controls (De Bellis, Keshavan, Frustaci, et al., 2002; De Bellis, Keshavan, Shifflett, et al., 2002; Pan et al., 2015); these conditions are often associated with depression, stress, and anxiety. This gyrus also seems to be involved in perceiving emotions when looking at faces (Radua et al., 2010).

Fifth, those brain regions may have been found because many of them are involved in processing information relating to the self. For example, the prefrontal cortex and cingulate cortex were more activated when adjectives were judged to describe the self rather than somebody else (Zhu et al., 2007). In particular, a meta-analysis showed that the perigenual anterior cingulate cortex seems to be involved in self-processing (Qin and Northoff, 2011). In a study in which healthy subjects were asked to decide whether social situations were caused by themselves or someone else, activation in the precuneus was found to correlate with self-attribution (Cabanis et al., 2013).

Implications

Reporting a comprehensive list of brain regions that have been related to music-induced analgesia is useful in many ways. First, it enables the identification of a potential brain network that if altered (e.g. using brain stimulation invasively or non-invasively) could lead to reduced pain perception. This could be a potential treatment for people with acute or chronic pain, e.g. due to cancer or any type of pain that is resistant to medication such as central post-stroke pain (see Hosomi, Seymour and Saitoh, 2015). Second, it may contribute to theories on top-down modulation of pain perception by cognitive-affective stimuli. Third, it may help develop personalised pain treatments in which digital platforms that use music and neurofeedback could be adjusted according to the patient's brain lesions, in order to alleviate their pain. Fourth, it reveals gaps in the literature that would need to be filled by conducting further research.

Limitations

There are not so many original articles yet examining brain regions involved in music-induced analgesia. Therefore, the systematic literature review was not able to have a homogenous group of studies using similar neuroimaging techniques in order to decipher whether the brain regions involved in music-induced analgesia differ depending on various pain characteristics, such as the type of pain, its cause, its duration, or its response to pharmaceutical agents.

Some of the studies in the literature review only examined certain brain regions that were determined a priori by the researchers. For example, the study by Antioch and colleagues (2020) only focused on activity in the anterior cingulate cortex. Also, in the three fNIRS studies, probes were placed only over certain cortices. Specifically, in the first and second fNIRS study they were placed only over the right and left frontal cortices, and in the third fNIRS study they were placed over the left and right primary motor and somatosensory cortices. Thus, potential activity in other cortices (e.g. the parietal, temporal or occipital cortices) could not be detected.

Other caveats are related to pain perception. Pain is subjective and this is an important limitation in studies trying to examine it. Also, not all studies ensured participants' abstinence from substances that can affect pain perception, such as caffeine, or nicotine. Although Du and colleagues (2022) ensured that participants did not take these substances shortly before the experiment, not all other studies followed their approach.

The participants of the studies that were included in the literature review varied quite a lot in their age. This could affect which brain regions are found to be associated with music-induced analgesia because of two main factors. First, because pain tolerance can differ depending on one's age (Lue et al., 2018; González-Roldán et al., 2020) and thus the changes in pain scores pre- vs post- music-listening may have been affected by differences in pain tolerance. Second, during healthy ageing, changes can occur in the connectivity between key nodes of the pain pathway (González-Roldán et al., 2020) and in the brain's structural integrity (Oosterman and Veldhuijzen, 2016).

The music interventions varied a lot across the studies of the literature review. This is beneficial because if there is a specific region associated with music-induced analgesia, then it would have been found across all these studies (i.e. irrespective of the exact musical piece that was presented). However, it is disadvantageous because the vast differences across pieces of music could, to a small or large extent, have affected which brain regions were activated. For example, tempo, loudness, type of music, duration of the piece, how much the participant liked it, whether it induced the "chill" effect, how much the participant understood the piece (which can be affected by the level to which they have studied music), how often they have listened to the piece previously, and what memories (if any) it induced. Many of the studies included in this review had "no sound" as the control condition. However, arguably this may not be the ideal control condition. For example, studies could include, as a control condition, sounds that are not musical, such as a monotonous voice talking.

Future directions

The regions that have been reported in the above studies are derived from non-lesion studies and are therefore inherently correlational. In order to identify which brain regions are necessary and which are just epiphenomenal, lesion studies will need to be conducted. No studies were found that used a lesion approach. In other words, no study examined stroke patients or patients with a tumour to investigate the brain regions that are associated with music-induced analgesia. Therefore, a causal association could not be made, nor any lesion symptom mapping or lesion network mapping analysis could be conducted. Two example approaches of using a causative rather than a correlational approach are the following. First, a study could examine a group of stroke patients with pain who after listening to music do not experience any relief in their pain versus a group of stroke patients with pain who after listening to music do experience relief in their pain. Then one could analyse the location of the patients' lesions e.g. doing a lesion overlap of each group and then conduct a subtraction anaysis. Otherwise, if the music-induced pain relief is measured as a continuous variable, one could also do lesion symptom mapping or lesion network mapping. Second, studies using tDCS or TMS could induce transient inhibition of brain regions that seem (from studies using a correlational approach) to be involved in music-induced analgesia and examine whether the music-induced pain relief does not occur upon stimulation of those regions. Otherwise, tDCS or TMS could be used to increase the function of these brain regions. In this case, one could examine whether the pain relief induced by music is greater in the "on" compared to the "off" condition.

More original studies are needed to examine which brain regions are important for the pain-reducing effect evoked by listening to music. These studies need to be more rigorous and comprehensive than what has been conducted so far. For example, they could examine many different types of pain and many different types of music. This will allow us to delve deeper into multiple factors that could alter music's effect on pain-responsive brain regions. By understanding these mechanisms, in the future, we could enhance the ability of music to reduce pain sensation.

Conclusions

This thesis includes the first systematic literature review and bibliometric analysis examining brain regions associated with music-induced analgesia. Many of the regions that were found to be related to music-evoked pain relief in the systematic literature review were also found when overlapping "pain" and "music" activations using Neurosynth. These included the cerebellum, left insula, superior temporal gyri, dorsolateral prefrontal cortices, supplementary motor area, primary somatosensory cortices, thalami, hippocampi, cingulate gyri, and right nucleus accumbens. Further clinical research is needed to confirm these findings and enrich our understanding of how the human brain allows music to act as an analgesic agent.

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Appendix

The author has no conflicts of interest to declare