# EFFECTS OF MUSIC ON THE PAIN RESPONSE IN THE CENTRAL NERVOUS SYSTEM USING FUNCTIONAL MAGNETIC RESONANCE IMAGING

By

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## Abstract

The oldest procedure for pain relief has been music, dated back to writings from ancient civilizations. There is abundant behavioural evidence to support music's pain relieving properties, however, studies to date have yet to investigate music-induced analgesia via imaging. Our first imaging study used thermal stimulation just below pain threshold in combination with various music stimuli, to determine whether music can affect neural activity in response to heat stimuli within brainstem and spinal cord regions. Differential responses to music stimuli were found within regions known for descending modulation, and familiar classical music had a unique effect on neural activity in these regions compared to unpleasant music, reverse music, and no music. This study confirmed that the emotional valence of music affects neural activity in the brainstem and spinal cord.

The second study used a well-defined pain paradigm applied with or without favorite music to study the neural activity responses in the brain, brainstem, and spinal cord using imaging. Subjective pain ratings were significantly lower when painful stimuli were administered with music than without music. The pain condition alone elicited neural activity in brain regions consistently activated during similar pain studies. Brain regions associated with pleasurable music listening were activated including limbic, frontal, and auditory regions when comparing music to non-music pain conditions. In addition, neural regions showed activity responses indicative of descending modulation when contrasting the two conditions. These regions include the projections of the spinothalamic tract, dorsolateral prefrontal cortex (DLPFC), periaqueductal grey (PAG), rostral ventromedial medulla (RVM), and the dorsal gray matter of the spinal cord. The

data suggest that music seems to engage mesolimbic and mesocortical brain regions to activate the descending pain modulation pathway. Lower subjective pain ratings corresponded to a greater suppression in the dorsal gray matter when listening to music. This is the first imaging study to characterize the neural response of pain and how it is mitigated by music listening, and brain and spinal fMRI are appropriate means to study pain processing and its modulation in the central nervous system.

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I thank you for your patience after all of this time, and so blessed that I am able to call you mine.

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For this reason Mary, I dedicate this to you; if you weren't here I would have never pulled through.
You made me see that life has immeasurable value; I will always be here, Dearest Mary,
"I love you".

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## List of Abbreviations

| | |
|---|---|
| **ACC** | anterior cingulate cortex |
| **ANOVA** | analysis of variance |
| **BOLD** | blood oxygenation-level dependent |
| **C6** | the 6$^{th}$ cervical spinal cord segment |
| **C8** | the 8$^{th}$ cervical spinal cord segment |
| **CNS** | central nervous system |
| **CSF** | cerebrospinal fluid |
| **DH** | dorsal horn |
| **DLPT** | dorsolateral pontine tegmentum |
| **DLPFC** | dorsolateral prefrontal cortex |
| **EPI** | echo-planar imaging |
| **fMRI** | functional magnetic resonance imaging |
| **GABA** | gamma-aminobutyric acid |
| **GLM** | general linear model |
| **GM** | gray matter |
| **LC** | locus coeruleus |
| **MR** | magnetic resonance |
| **MRI** | magnetic resonance imaging |
| **NAc** | nucleus accumbens |
| **NGC** | nucleus gigantocellularis |
| **NRM** | nucleus raphe magnus |
| **NTS** | nucleus tractus solitarius |
| **OFC** | orbitofrontal cortex |
| **PAG** | periaqueductal gray matter |
| **PBN** | parabrachial nucleus |
| **PCA** | principle components analysis |
| **PCC** | posterior cingulate cortex |
| **PET** | positron emission tomography |
| **PFC** | prefrontal cortex |
| **PMJ** | pontomedullary junction |

| | |
|---|---|
| **RF** | radio-frequency |
| **ROI** | region of interest |
| **RVM** | rostral ventromedial medulla |
| **SI** | primary somatosensory cortex |
| **SII** | secondary somatosensory cortex |
| **SC** | spinal cord |
| **SEEP** | signal enhancement by extravascular water protons |
| **SMA** | supplementary motor area |
| **TE** | echo time |
| **TR** | repetition time |
| **VPL** | ventral posterolateral thalamus |
| **VTA** | ventral tegmental area |

## Chapter 1

*One good thing about music, when it hits you, you feel no pain.-Bob Marley*

### INTRODUCTION

One therapeutic value of music is its ability to provide pain relief, known as music-induced analgesia [26]. Specifically, music-induced analgesia is described as an individual having a reduction in perceived pain after passive music listening. Music is a multi-faceted phenomenon that contains physical, emotional, cognitive, and social elements that affect people on an individual basis. As such, music has been used as a tool to promote physical and mental recovery for centuries. Music therapy can be defined as a controlled use of music to recover the physiological, psychological, and/or the emotional integration during treatment of a disability or illness [88]. There has been extensive research showing that music-induced analgesia can reduce stress, depression, and distress in people with acute and chronic pain [26]. A seminal study by Gardner [45] stated that 90% of 5000 patients undergoing dental surgery reported reduced pain while listening to music. This original finding has been replicated numerous times, and in a current review of 51 music-induced analgesia studies with over 3500 patients suffering from various types of pain, 70% had a greater probability of reporting at least a 50% decrease in pain and a reduction in opioid medications compared to control patients [26]. Furthermore, hospitalized patients have shown significantly reduced stress effects on physiological mechanisms such as heart rate and breathing, total mood scores, perceived anxiety, and pain states after music listening [98]. In summary, the literature has shown music's effectiveness in pain reduction over a wide diversity of clinical populations. However, it is still controversial as to how music specifically activates the nervous system to reduce

pain. It is generally agreed that some aspect(s) of the psychology of music is responsible for the pain reduction. Whether music reduces pain by directing attention away from a painful stimulus, or activates rewarding properties from an emotional stimulus, or whether there is another mechanism responsible, is still up for debate.

After years of extensive research on pain processing, it became widely accepted that nociceptive somatosensory information at the dorsal horn was not automatically processed at higher brain structures, but was modulated in the spinal cord. Unfortunately, most studies investigating music-induced analgesia have focused on the brain, due to the past inaccessibility of detecting spinal cord and brainstem neural activity. However, with the development of spinal functional magnetic resonance imaging (fMRI), we can now detect neural activity changes within structures of the descending pain analgesia system of the brainstem and spinal cord, which is necessary for our understanding of the entire process of pain modulation.

The goal of my thesis was to characterize the neural responses to pain in the central nervous system (CNS) and to assess how these responses were modulated by music-induced analgesia. This was achieved by means of fMRI of the brain, brainstem, and spinal cord. For the first time we were able to relate observable changes in neural function in the entire CNS to changes in pain perception that relate to music analgesia.

There are two studies described in the thesis. The purpose of the first study (Chapter 2) was to identify if modulation of neural activity as a result of musical stimuli could be detected in the brainstem and spinal cord using an innocuous heat stimulus. If music did modulate spinal cord and brainstem activity in response to innocuous heat, the second aim of this study was to determine if the activity is consistent with structures

involved in descending pain modulation. The purpose of the second study (Chapter 3) was to further clarify the role of the descending pain analgesia system in music-induced analgesia in the entire CNS. This study used finer constraints on participants, self-selected music choice, and a well-defined pain paradigm to create optimal conditions to study music-induced analgesia and account for potentially confounding variables related to pain studies. Overall, this thesis relates neural activity changes in the brain, brainstem, and spinal cord to changes in pain perception that relate to music-induced analgesia.

## 1.1 Pain Transmission

### *1.1.1 Nociceptors*

Pain is defined as an unpleasant sensory or emotional experience associated with actual or potential tissue damage (International Association for the Study of Pain). Pain is a highly subjective experience which contains both sensory-discriminative and motivational-affective dimensions [85], and is elicited by specialized nociceptors located throughout the body. The type of nociceptor and fibre activated (Aδ or C) influences the pain experience [65]. Pain can be described as either first pain or second pain, eliciting impulses in fast conducting Aδ fibers or slow conducting C fibers respectively. As Aδ fibers are myelinated, first pain is a transient and sharp response. First pain is also known as the sensory discriminative component of pain, and imaging studies show that stimulation of Aδ fibers specifically activates the primary and second somatosensory cortex [100]. In contrast, second pain is long lasting, non-discriminative, and described as a dull ache. The slower conduction velocity of second pain is due to the lack of myelin on C fibers. Second pain is largely responsible for the affective component of pain, and has

diffuse region activation throughout the brain including the anterior cingulate cortex (ACC) and second somatosensory cortex [100].

### *1.1.2 Anterolateral System*

Aδ and C fibers are present at the periphery and synapse directly or indirectly (through interneurons) in the dorsal horn (DH) of the spinal cord. This first bifurcation of these neurons forms the initial synapse of all the ascending pathways of the anterolateral system [79]. The anterolateral system conveys pain and temperature, as well as crude touch. The ascending pathways transport sensory information to the supraspinal structures in the brainstem and diencephalon by projection neurons [136]. Such target areas include cortical and limbic structures where the pain signal can be modulated [85]. There are three main pain pathways of the anterolateral system including the spinothalamic tract, the spinoreticular tract, as well as the spinomesencephalic tract.

#### 1.1.2.1 SPINOTHALAMIC TRACT

The spinothalamic tract is responsible for the location and perception of pain. It has nociceptive fibers that first terminate in the substantia gelatinosa of the DH via Lissauer's tract [81]. Lissauer's tract typically runs up or down two spinal cord segments before it branches off into the spinothalamic tract [103]. The 2$^{nd}$ order neuron tracts then ascend to the reticular formation of the medulla, the periaqueductal grey (PAG) of the midbrain, and the thalamus. From the thalamus, a 3$^{rd}$ order neuron terminates in the insula, the postcentral gyrus, as well as the other cortical areas that are not shown in figure 1.1A.

#### 1.1.2.2 SPINORETICULAR TRACT

The spinoreticular tract functions as the emotional aspect of pain (Figure 1.1B). The more medial spinoreticular tract originates in the DH, and ascends with the spinothalamic tract to the reticular formation of the medulla and pons [79]. In particular, this tract projects to the nucleus gigantocellularis (NGc), the lateral reticular nucleus, and the lateral parabrachial nucleus (PBN) of the reticular formation [25]. The dorsolateral pontine tegmentum (DLPT) is an important region in the pons that modulates nociception, which includes the locus coeruleus (LC), Kolliker-Fuse nucleus, and subcoeruleus, which receives input from both the PAG and RVM. The more lateral spinoreticular tract ascends to areas within the DLPT including the ventral subcoeruleus, Kölliker- Fuse nucleus, the LC, as well as the dorsal PBN [29].

#### 1.1.2.3 SPINOMESENCEPHALIC TRACT

Finally, the spinomesencephalic tract is known for the modulation of pain (Figure 1.1C). This tract originates in multiple areas of the spinal cord segment and most notably projects to the PAG and PBN, with projections also in the cuneiform nucleus (NCF), intercolliculus nucleus, and nucleus of Darkschewitsch for pain processing [79]. The spinomesencephalic tract also terminates in higher cortical structures, namely the amygdala, which allows for the influence of psychological variables (discussed in section 1.2).

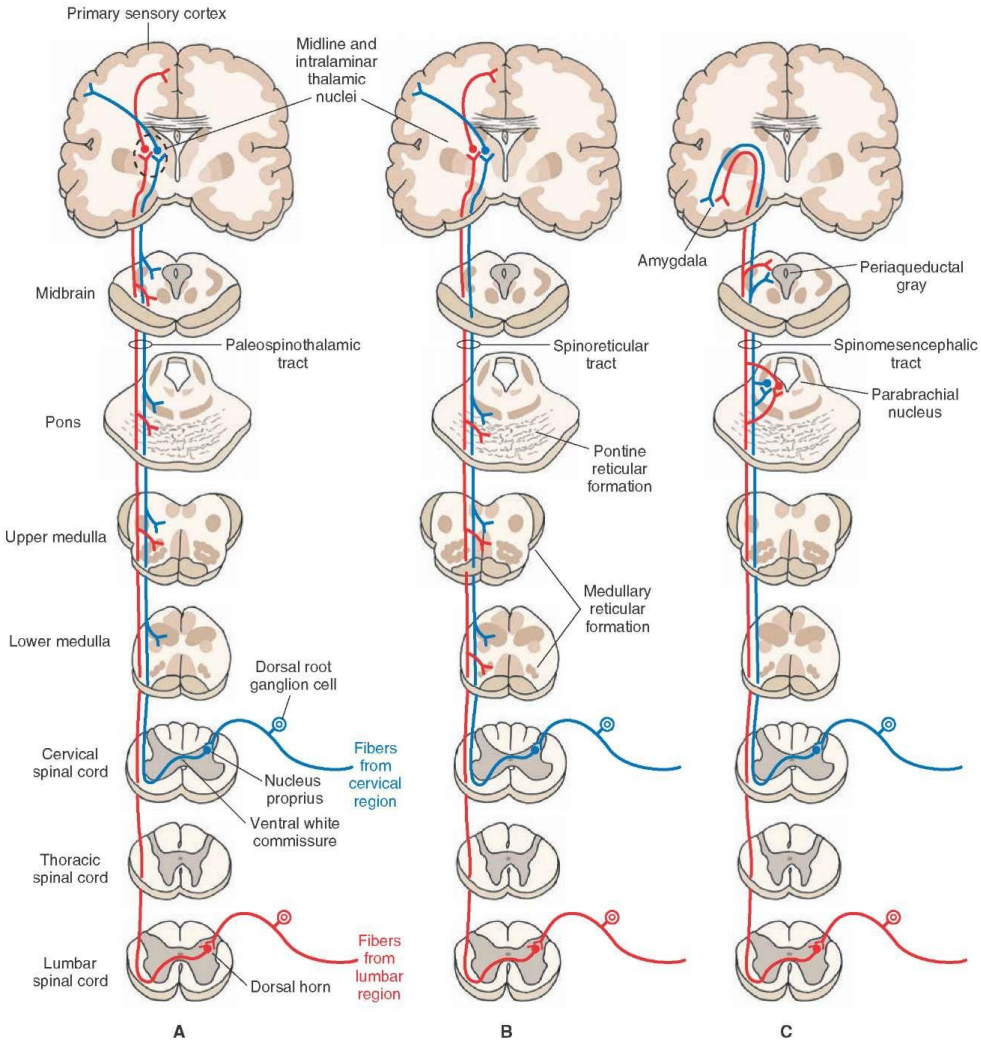


**Figure 1.1:** A) Spinothalamic tract with pain fibers passing through Lissauer's tract until they terminate in the substantia gelatinosa, where a second order neuron projects as the spinothalamic tract, with projections to the reticular formation, PAG, insula, and postcentral gyrus. B) Spinoreticular Tract with projections to the medullary and pontine reticular formation, as well as thalamic nuclei and cerebral cortex. C)Spinomesencephalic Tract with ascending axons terminating in the periaqueductal grey and amygdala, via the parabrachial nucleus. Reprinted by permission from Wolters Kluwer Publishing: [115], 2010.

## 1.2 Descending Pain Modulation

Pain modulation acts via the descending pain analgesia system, which contains ascending and descending pathways which act either to amplify nociceptive information (descending facilitation), or reduce nociceptive information (descending inhibition). The

two most well-known structures in the analgesia system are the midbrain periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM). Electrical stimulation or local injection of opioids into either structure induces antinociception in animals [76; 77; 107]. Antinociception and analgesia involve suppression of nociceptive information in the lower neuraxis, namely the dorsal horn of the spinal cord. The RVM directly projects to the dorsal horn via the dorsolateral funiculus [7; 53], while the PAG indirectly projects to the dorsal horn through the RVM [86]. Bilateral lesions to the dorsolateral funiculus block the effects of stimulus-produced analgesia and morphine by disrupting the descending inhibitory pathway [9].

The PAG also has extensive, reciprocal connections with limbic and forebrain structures including the hypothalamus, the pre-optic area, orbitofrontal cortex (OFC), and the amygdala [86]. These higher cortical connections allow for the influence of psychological variables on pain responses, such as pleasure, attention, and emotion. The PAG-RVM connections to forebrain structures act by either reducing or heightening noxious information that influences the dorsal horn level [133] (Figure 1.2).

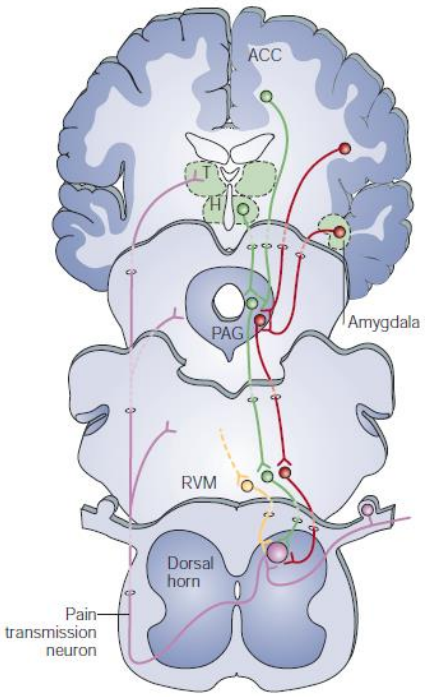


**Figure 1.2**: Outline of opioid sensitive pain-modulating circuit; anterior cingulate cortex (ACC), thalamus (T), hypothalamus, frontal cortex, periaqueductal grey (PAG), and rostral ventromedial medulla (RVM). Reprinted by permission from Macmillan Publishers Ltd: Nature [38], 2004.

### *1.2.1 Gate Theory of Pain*

The gate theory of pain was developed by Melzack and Wall [80] and suggests that pain impulses travel from the peripheral site of injury to the dorsal horn of the spinal cord, and are modulated before reaching the brain. Specifically, innocuous input can override noxious input within the dorsal horn, which prevents pain from travelling to supraspinal structures. The gate theory of pain demonstrates how an inhibitory local circuit neuron acts to process either mechanoreception or nociception depending on the strength of either input. If the innocuous stimulation is stronger, it produces presynaptic inhibition on nociceptor fibers via the inhibitory interneuron. Therefore, this presynaptic inhibition will stop the noxious information from reaching the brain. This explains why after you stub your toe, it helps to rub it.

### *1.2.2 Opioids and Pain Modulation*

There is overwhelming evidence that demonstrates opioid and dopamine involvement in processing pain and pleasure [70]. Endogenous opioids are important substrates for pain modulation because they induce pleasure and analgesia, and their receptors are abundant in the PAG and RVM. Directly injecting opioid agonists into either the PAG or RVM produces analgesia, conversely, applying the μ -opioid antagonist naxolone will block analgesia [41]. Dopamine can influence opioid levels, depending on its distribution. For example, phasic dopamine will increase opioid levels [108], whereas tonic dopamine can decrease opioid levels in the brain [60].

## 1.3 Principles of MRI

### *1.3.1 The MR Signal*

The dominant source of the magnetic resonance (MR) signal for biological imaging is the nucleus of the hydrogen atom. Hydrogen is found in water and lipids which are abundant in neural tissue. Inside the strong magnetic field of the MRI system, the neural tissue becomes weakly magnetized because the hydrogen nuclei are forced into alignment with the magnetic field (equilibrium). When the hydrogen nuclei are not in alignment with the static magnetic field, they precess (wobble) around the direction of the static field at a frequency that depends only on the field strength. The nuclei can be pushed out of alignment with the static field (out of equilibrium). By applying a brief, weak, pulse of a magnetic field that rotates at the exact same frequency as the precession. This pulse is known as the radio-frequency (RF) pulse, and the degree to which the hydrogen nuclei are rotated away from equilibrium is called the flip angle. The MR signal is produced in the receiver coil of the MRI system, as an electrical signal induced by the rotating magnetization of the hydrogen atoms. Following an RF pulse, the hydrogen nuclei slowly lose energy, while also precessing, and return back to equilibrium. This is known as relaxation, and occurs due to magnetic interactions between the hydrogen nuclei. Different tissues often have different relaxation times related to their water content, mobility of water within the tissues, and lipid content. These relaxation times are reflected by the strength of the MR signal as a function of time after the RF pulse. For example, adipose tissue and cerebrospinal fluid have very different relaxation times which allow us to distinguish them in images. In addition to the

effects of relaxation, the signal can decay quickly due to spatial variations in the magnetic field strength making nuclei precess at slightly different frequencies.

For imaging, spatial information is encoded into the signal by making the magnetic field strength vary with position. Additional magnetic fields are turned on briefly while the MR signal is recorded, so that the frequency of the signal depends on the position where it originates. These additional fields are generally made to vary linearly with position, in each of the 3 principal axis directions, and are called "magnetic field gradients".

A commonly-used method to increase the signal that can be detected is to reverse the effects of having different field strengths at different positions during imaging. By reversing the effects briefly, the MR signal is briefly increased, and this is called an "echo". One method of producing an echo is to apply a gradient in one direction, and then reverse it while the MR signal is recorded, so that the "echo" is formed while the signal is recorded. This is called a gradient-echo. Spin-echo imaging is another type of imaging that allows more time to measure the MR signal before it returns to equilibrium. This is carried out by applying a second RF pulse sometime after the first RF pulse. The first RF pulse is usually set at $90^0$, and the role of the second RF pulse is to invert the magnetization $180^0$ around any axis in the transverse plane. This cancels out any variations in the magnetic field, and as the nuclei return to equilibrium, and the spin-echo is formed. The time between the RF pulses is known as the repetition time (TR) and time from the initial RF pulse and the echo formation is defined as the echo time (TE). The amount of signal that is detected depends on the transverse relaxation time, $T_2$, and the echo time, TE, for a spin-echo. For a gradient echo, the signal depends on the effective

transverse relaxation time, $T_2$* which includes effects of both $T_2$ and non-spatially-uniform magnetic fields, and the echo time, TE. These two methods of making echoes, and two different relaxation times, are essential for functional MRI [120].

### *1.3.2 Specific Applications of MRI: functional MRI*

Functional MR imaging relies on several concepts that enable neural activity to be linked to the MRI signal strength. When a neuron receives inhibitory and/or excitatory input from other neurons, more oxygen is consumed for the increased metabolic demand. To supply more oxygen to the tissues, there is an increased blood flow to the area as well. The net effect is that there is an increase in oxygen in the neural tissue when the area is more active. When the iron in hemoglobin in blood is bound to oxygen, it has a much weaker magnetic effect than when the iron is not bound. The de-oxygenated iron in the blood makes the local magnetic field non-uniform, and reduces the MRI signal relaxation times. This key point is how the blood oxygenation-level dependent (BOLD) contrast is produced. The more uniform magnetic field due to the increased blood oxygen-level, alters the MR signal relaxation times, and produces increased MR signal intensity. The change in total energy metabolism of the tissues is closely related to the presynaptic input that includes both excitatory and inhibitory input. After an external stimulus is applied to the person in the MRI (ex: flash of light), the MR signal increase is slightly delayed (~2 seconds) from the onset of the stimulus and lasts approximately 20 seconds. This delayed response function is called the hemodynamic response function, as it is based on the changes in blood flow.

An alternative and supplemental contrast is known as signal enhancement by extravascular water protons (SEEP). This contrast is most notably used during spinal cord

imaging, and is coupled with the BOLD contrast. How SEEP functions depends on the role of astrocytes during neural activity changes. Astrocytes absorb glutamate from the synapse, and then convert the absorbed glutamate into glutamine. When a glutamate molecule is absorbed by the astrocyte, simultaneously three $Na^+$ ions, water, and one $H^+$ ion is transported into the astrocyte and one $K^+$ ion is transported out. The effect of water being taken up by the astrocyte from the blood vessels result in a local increase in tissue water content and is detected by the MR signal. All of these concepts are important when determining optimal imaging parameters for brain and spinal fMRI [120].

## 1.4 Using fMRI to Investigate Pain

### *1.4.1 Spinal fMRI*

Functional imaging studies on pain are essential to understand normal pain processing and pain modulation. Neuroimaging techniques such as fMRI have vastly progressed our knowledge of how neuronal structures process acute and chronic pain. Most fMRI studies focus on the brain, consequently, less is known about the pain matrix in the lower structures like the midbrain, brainstem, and spinal cord. The spinal cord has small physical dimensions and poor magnetic field homogeneity due to the motion of the cord and cerebral spinal fluid, which makes it harder to image than the brain. However over the past 15 years, imaging techniques have been developed to overcome these difficulties accordingly. Spinal fMRI uses spin echo imaging, which has been shown to produce optimal 3D image quality and contrast to noise ratio in the brainstem and spinal cord, at a resolution of 1.5 x 1.5 x 2 $mm^3$. Extensive method development has made spinal fMRI a reliable means to investigate brainstem and spinal cord activity.

Stroman (2009) used fMRI to image the cervical spinal cord and brainstem to view neural changes in response to thermal stimulation at a range of innocuous stimuli. This study demonstrated how activity in the ipsilateral dorsal gray matter (GM) shows the net result of sensory input from the periphery as well as modulation from the descending analgesia system via the RVM and from pain's emotional components via the locus coeruleus (LC). The activity in the ventral GM depended on the dorsal GM as well as descending modulation from emotional components via the pontine reticular formation. On the other hand, the contralateral ventral GM reflected input from the ipsilateral dorsal GM, via interneurons. Therefore, it is likely that intermediate/ventral activity is a result of descending modulation from the brainstem ipsilateral, but not contralateral, to the thermal stimulation. Also, this study showed that stimulus temperatures demonstrated an inhibition of pain responses with lower temperatures and sensory facilitation with stimulation at the warmest temperature. These results not only confirm anatomical knowledge of the pain pathway, but also confirm that the imaging methods are sensitive and reliable enough to detect pain transmission.

Spinal fMRI studies have also measured the neuronal activity corresponding to repeated innocuous and noxious thermal stimulation on the hand [24]. Innocuous thermal stimuli were set at 42 $^{\circ}$C while noxious stimuli were set at 46 $^{\circ}$C. Both types of thermal stimuli influenced activity in the PAG, RVM, and dorsal spinal cord. Noxious stimuli showed greater activity in the ipsilateral dorsal horn at C6, the ipsilateral PAG, and significantly lower activity in the contralateral olivary nucleus compared to innocuous stimuli. The locus coeruleus (LC) and RVM received higher input during the initial thermal stimulation which subsequently provides less input to the dorsal gray matter,

demonstrating descending modulation. The results of this study also showed that the subjective pain ratings and activation of the pain matrix are significantly correlated when transitioning from innocuous to noxious stimuli. Therefore, temperature intensity determines the strength of neural activity changes processed in the cord, and perceived pain ratings have parallel modulation.

Emotional and cognitive factors are known to influence subjective pain ratings, as well as related pain activity in spinal structures. Stroman et. al [122] found attention influenced neural activity in the spinal cord as thermal stimulation was applied to the hand. Since the ipsilateral dorsal GM registers sensory input, the activity of the dorsal GM represents the total net change of neural input from the periphery as well as higher cortical structures. There was significantly lower signal in the dorsal GM at the primary input to the cord when attending to the pain, compared to no response in this region when distracted by another cognitive task. In addition to the PAG and RVM, the dorsolateral pontine tegmentum (DLPT) contributes significantly to pain modulation and is composed of many nuclei including the locus coeruleus (LC). The LC is associated with arousal, anxiety, and stress while the nucleus gigantocellularis (NGc) receives ascending input from the spinoreticular tract and plays a critical role for affect in perceived pain. The LC and NGc both demonstrated significant activity that changed in response to thermal stimulation during all conditions. The reduction in input to the spinal cord dorsal GM was attributed to a change in descending modulation via the DLPT, particularly the LC. This study illustrated how cognitive factors, such as attention and distraction, can significantly change activity in structures involved with modulating thermal pain in the spinal cord.

### *1.4.2 Temporal Summation and Brain fMRI*

Temporal summation of pain is described as increased pain intensity and duration induced by repeating brief noxious stimuli [101]. When eliciting repeated, brief noxious stimuli to the Aδ myelinated fibers, the magnitude of the response is gradually reduced [101]. Price et al. [102] demonstrated that there was a greater membrane depolarization and more excitatory post synaptic potentials (EPSP) recruited during repeated noxious stimulation to C-fibers as opposed to Aδ fibers. However, this greater response can only be induced if the rate of stimulation is 0.3/second or more (Figure 1.3). Therefore, when applying repeated, brief noxious stimuli at a frequency of once every three seconds, the intensity and duration of the response amplifies in the dorsal horn due to C fibers. This phenomenon is known as temporal summation of second pain or "wind-up". Electrophysiology studies with animals have solidified our understanding of these pain mechanisms at the level of the periphery and dorsal horn of the spinal cord [55]. The "wind-up" model of pain is a useful paradigm to study pain not only for its intense response in the dorsal horn, but also that the noxious stimulation is tolerable to participants.

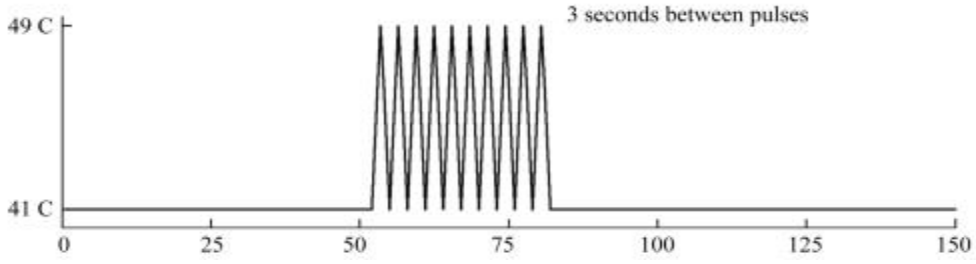


**Figure 1.3:** Thermal stimulation with heat pulses presented at a frequency of 0.33 Hz to induce temporal summation of the C fibers (Stroman works in progress).

In addition to electrophysiology studies, functional MRI studies have also investigated the effects of temporal summation in the brain. Staud et al. [117] exposed participants to various rates of noxious stimuli to induce "wind-up", and characterize its effects on the brain. Participants received six brief, hot stimuli at a rate of 0.33 Hz to produce "wind-up" and 0.17 Hz which is insufficient to produce wind-up. After each exposure, they gave subjective pain ratings on a scale from 0-100 with 0 being no pain, 20 as the pain threshold, and 100 as intolerable pain. They found that pain ratings during the 0.17 Hz pulse rate were initially 20 and increased to 30 by the $6^{th}$ pulse. On the other hand, pain ratings for the 0.33 Hz pulse rate increased to 45 ± 10 by the $6^{th}$ pulse. This significant increase in pain ratings for the faster pulse rate also demonstrated significant neural activity changes in the contralateral thalamus, somatosensory cortex, bilateral somatosensory association cortex, anterior and posterior insula, ACC, and supplementary motor areas compared to the slower pulse rate. This study demonstrates the effects of temporal summation in the brain, and our ability to study it using fMRI.

### *1.4.3 Temporal Summation and Spinal fMRI*

Recently, the Stroman laboratory has successfully replicated the pain rating results of Staud et al. [117] during pilot testing. Pilot studies have extended the brain imaging by Staud to imaging the brainstem and spinal cord. Results thus far illustrate activity in the ipsilateral dorsal horn of the spinal cord, contralateral ventral horn, and approximate areas of the RVM, nucleus tractus solitarius (NTS), and PAG. The higher rate of noxious stimuli (0.33 Hz) demonstrated significantly larger BOLD responses in these areas compared to the lower rate (0.17 Hz) (Figure 1.4). In addition, activity during

the higher presentation was more localized in the stimulated spinal cord segment. Therefore, this data is novel as it uses spinal fMRI to determine that temporal summation of pain produces stronger neural responses in the lower pain matrix.

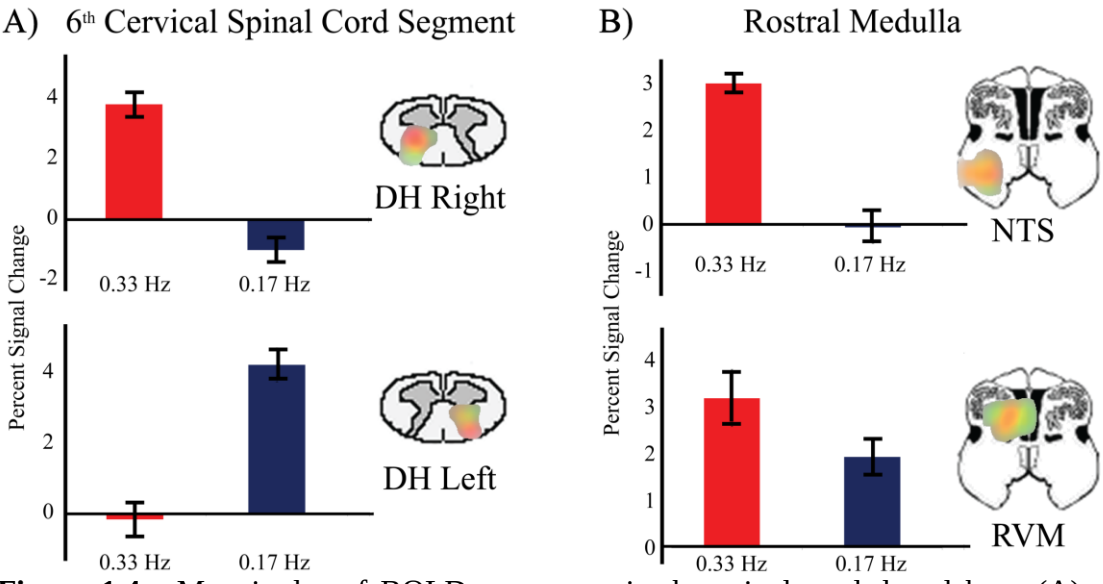


**Figure 1.4:** Magnitudes of BOLD responses, in the spinal cord dorsal horn (A), and rostral medulla (B). Hotter colours reflect the larger rostral-caudal extent of the region of interest in the dorsal horn (DH); nucleus tractus solitarius (NTS); rostral ventromedial medulla (RVM) (Stroman works in progress).

### 1.5 Attention-induced Music Analgesia

Music automatically captures one's attention and therefore can provide a distraction from pain, anxiety, or other negative stimuli [62]. Music can create strong mental imagery of many kinds, and is not restricted to musicians. Listening to music can allow the individual to escape into an imaginary world, and provide relief of pain or stress [4].

Attending to a painful stimulus can be demonstrated in activated brain regions via imaging. Bushnell et al. [23] asked participants to switch their attention between a painful stimulus and an auditory stimulus presented simultaneously. As the participants switched

their focus, the corresponding regions of their brain activation changed accordingly. Specifically, when attending to auditory tones as opposed to a painful stimulus, the primary auditory cortex was more active while the primary somatosensory cortex was less active. The opposite was true when concentrating on the painful stimulus. Tracey et al. [126] demonstrated the importance of the brainstem in attentional modulation of pain, specifically the PAG. When participants focused on colored lights as opposed to the heat pain, subjective pain scores significantly decreased in both intensity and aversiveness. Corresponding changes in the PAG were also evident, as the signal intensity had a lower percent signal change when attending to the colored lights than the heat pain. As the pain intensity rating increased, the fMRI signal change in the PAG increased. The behavioural and imaging results illustrate how the PAG modulates attention by decreasing its activity during a distraction, and conversely, increasing its activity during a focus on pain. Also, nociceptive neurons in the medullary dorsal horn of monkeys are more active when attending to noxious thermal stimuli than visual stimuli [22]. This evidence illustrates how attention plays an important role when processing pain in the brain, brainstem, and spinal cord. Namely, neural activity in the pain matrix is reduced when attending to a competing stimulus and is heightened when concentrating on the pain.

One structure involved with attention and pain in the brain is the anterior cingulate cortex (ACC). The ACC receives nociceptive inputs and regulates responses to noxious stimuli. Senapti et al. [114] concluded that electrical stimulation of the ACC induces a significant reduction of the spinal cord dorsal horn neurons to noxious stimuli. It is theorized that attentional and emotional components of pain are activated in separate areas of the ACC [131]. The posterior ACC may modulate attention by influencing the

sensory and/or response selection. The posterior ACC inputs to the lateral prefrontal cortex, parietal cortex, and premotor and supplementary motor areas. Conversely, the anterior ACC has been shown to be associated with the emotional response to pain, and its connections outflow to the amygdala, hypothalamus, anterior insula, hippocampus, PAG, nucleus accumbens (NAc), and the orbitofrontal cortex (OFC). It has been demonstrated that ACC lesions selectively reduce the affective component of neuropathic pain [67]. Therefore, it is theorized that the posterior ACC regulates pain intensity and the anterior ACC regulates pain unpleasantness[21].

Currently, research also suggests that attention can modulate pain through pain specific opiate-sensitive descending modulatory pathways [135]. The ACC has one of the highest densities of opioid receptors in the CNS [132], and has been shown to promote descending pain analgesia [56]. The opiate-sensitive pathway has been extensively studied, and projects from the frontal cortex, to the amygdala, PAG, and rostral ventromedial medulla (RVM), which act to modulate nociception at the dorsal horn of the spinal cord. Other brain studies propose that a distraction will decrease pain perception via the spinothalamic pain pathway [8].

## 1.6 Emotion-induced Music analgesia

### *1.6.1 Introduction*

Listening to music is a highly pleasurable experience, and most people engage in music listening for the emotion it induces [57]. By as early as nine months of age, infants can discriminate between happy and sad music [43], therefore, the ability to respond emotionally to music may be innate. Recently, there has been a strong focus on "basic

emotions", which proposes that emotional responses to music can be consistent across listeners of varying ages. These basic emotions are comprised of feelings of happiness, sadness, anger, and fear. As such, basic musical emotions may be both innate and universal, which is important when suggesting a neural circuit for processing music emotions [94]. Past studies have shown how pain can be modulated by emotions induced by a variety of stimuli [78; 130; 139]. These studies demonstrate that pleasant emotions generally decrease pain while unpleasant emotions generally increase pain. Classical music has been known to evoke strong emotions such as feelings of pleasure [57]. In regards to music-induced analgesia, thermal pain intensity and unpleasantness were significantly reduced while listening to pleasant music but not during unpleasant music [110].

### *1.6.2 Involuntary Reflexes*

Music is carried through our auditory channels, through to the thalamus and cortex. But music can arouse the autonomic nervous system without higher cortical involvement. Some physical responses to music involve involuntary reflexes, for example inducing "chills" from the emotional impact of music [18; 93], breathing more rapidly during an accelerated piece or unconsciously beating time to the music [4]. Involuntary physiological responses associated with the stress response, such as heart rate, breathing, blood pressure, sweating, and cortisol levels can be manipulated with different types of music. For example, quiet, repetitive music with a slow tempo has been used as an anxiolytic in many fields of nursing and medicine because it decreases blood pressure, heart rate, cortisol, and breathing rate [48; 61]. These involuntary physiological responses

are regulated by the hypothalamus, which is active during passive listening to pleasurable, classical music [84].

### *1.6.3 Brain fMRI Studies*

The first pivotal study that investigated the physiological responses to pleasurable music via imaging was Blood et al. [19]. Pleasurable music consisted of novel melodies composed of varying consonant chords, whereas unpleasant music was composed of varying dissonant chords both designed based on previous pilot studies. They found that cerebral blood flow changes in brain areas involved with reward, emotion, and arousal were activated when listening to pleasurable music. These areas include the ventral striatum, midbrain, amygdala, OFC, and ventral medial prefrontal cortex. However, the poor resolution of the positron emission tomography scans prevented showing nucleus accumbens (NAc) involvement. This study was the first to illustrate that music can activate emotion related structures.

Other fMRI studies since have confirmed activation of emotion related structures during pleasurable music listening. Blood and Zatorre [18] presented participants with their favorite music which induced highly pleasurable "chills" or commonly known as the "shivers-down-the-spine" experience. They also presented control pieces chosen by the experimenters. Chill intensity increases correlated with increases in cerebral blood flow in brain regions associated with reward and emotion, such as the insula, OFC, the ventral medial prefrontal cortex and the ventral striatum. As the intensity of the chills increased, there were correlated decreases in cerebral blood flow in the hippocampus and amygdala. Therefore, activation changed in central limbic structures. Similar amygdala activations

have been detected while non-musicians listened to pleasant music that was unfamiliar [20; 63], or familiar [84; 87].

### *1.6.4 Mesolimbic Dopaminergic Pathway*

The mesolimbic system, specifically the nucleus accumbens (NAc) and the ventral tegmental area (VTA), play a significant role in mediating reward induced analgesia [38]. Dopamine release in the VTA has been associated with opioid transmission in the NAc, which work together to modulate the brain's reward response and process pleasure-evoking stimuli [58]. Both the NAc and the ventral striatum have a rostrocaudal "hedonic gradient", where the rostral area will process pleasure while the caudal area will process pain. The neighboring location of pleasure and pain proposes functional connections between the two, where pleasure decreases pain and rewards induce analgesia [70].

Menon and Levitin [84] used non-musicians exposed to both familiar classical music and scrambled music to investigate the effects of valence on music. Both the familiar classical music and the scrambled music were identical in pitch, loudness, and timbre. The difference between the two was that scrambled music lacks temporal structure [33] or temporally driven expectations [72]. Passive listening to the familiar, pleasurable classical music activated the NAc, VTA, and the hypothalamus in accordance with Brown et al. [20], where they reported NAc response to passive listening with unfamiliar but pleasant music. There was also significant activation detected in the hypothalamus, which is responsible for modulating autonomic responses. The strong interactions between the frontal brain regions (OFC and inferior frontal cortex) and the mesolimbic reward regions (NAc and VTA) suggest a functional link between the "cognitive" and

"affective" components of music listening. Orbitofrontal cortex interactions could be related to cognitive reward, emotional control, and valence representation [14]. The reward response in the brain is associated with dopamine release in the VTA, which triggers opioid transmission in the NAc [58]. Since the NAc and VTA activation was significantly correlated, and pleasurable music is known to evoke opioid signaling and reduce medical opioid requirements [104], this evidence suggests that music may activate the mesolimbic reward regions. This study theorized that the mesolimbic dopaminergic pathways and frontal brain regions work together to process the emotional power of music into a rewarding response in the brain. However, one cannot determine whether the subcortical activations precede or follow cortical activations.

Recently Salimpoor et al. [111] provided direct evidence that intense pleasure experienced when listening to music is associated with dopamine activity in the mesolimbic reward system. Using fMRI and PET imaging simultaneously, they exposed participants to self-selected pleasurable music known to evoke a "chill" response, together with other participant's self-selected music. To ensure there was a difference in autonomic nervous system response between the two types of music, they also collected heart rate, respiration rate, electrodermal skin conductance, blood volume pulse amplitude and peripheral temperature data. Results illustrated endogenous dopamine release in the striatum during intense pleasurable responses to the music, known as "chills". Furthermore, they discovered a functional dissociation where the caudate was more involved during the anticipation of reward while the NAc was more involved in the peak emotional response to the music (Figure 1.5). These results demonstrate that not

only is dopamine released in the striatal system during peak emotional responses to music, but anticipation of the reward releases dopamine in the caudate as well.

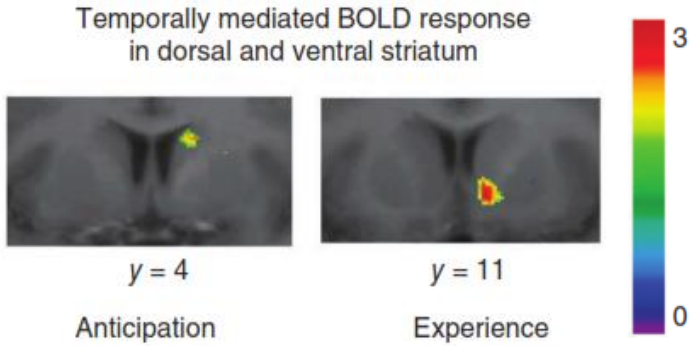


**Figure 1.5:** Hemodynamic response and dopamine activity were maximal in the dorsal striatum (caudate) during anticipatory phases, but shifted more ventrally to nucleus accumbens (NAc) during peak emotional responses. Adapted by permission from Macmillan Publishers Ltd: Nature [111], copyright 2011.

### *1.6.5 Lesion Studies*

There is overwhelming evidence suggesting that the NAc, amygdala, caudate, VTA, and hippocampus are active during pleasurable music listening. Lesion studies done by Gosselin et al. [49] showed that a patient with complete bilateral damage only to the amygdala showed selective loss of emotional processing, but not perceptual processing during music listening. Another lesion study showed that a patient with lesions of the left amygdala and left insula showed selective loss of intense, pleasurable experiences during music listening. Prior to the injury, the patient had the capacity to listen to music which would evoke chills. This capacity was lost after the lesion had occurred [51]. Studies have also found that people with reduced positive emotionality, like depression or post-traumatic stress disorder, show reduced hippocampal activity in response to music listening [64]. Koelsch [62] suggests that the anterior hippocampus plays a critical role in generating positive emotion, and that music has one of the greatest

powers in evoking hippocampal activity related to happiness. In summary, current research provides strong evidence that all major limbic and paralimbic brain structures are involved in the emotional processing of pleasant music illustrated in Figure 1.6 [94].

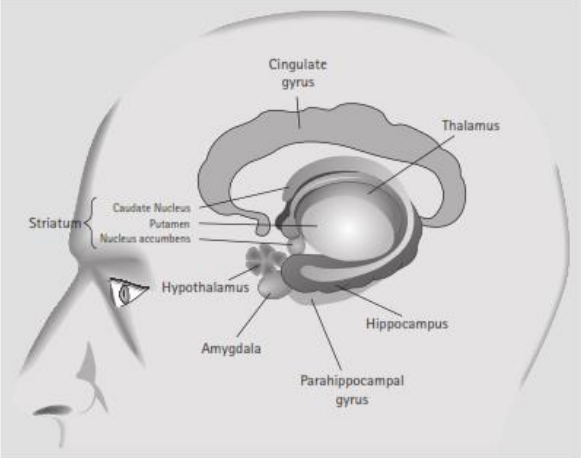


**Figure 1.6**: Deep brain structures of the limbic lobe involved in music listening. Reprinted by permission from Oxford University Press: [94], 2010.

### *1.6.6 Hormones, Neurotransmitters, & the Endocrine System*

When music's auditory information is received by the brain, neurotransmitter substances are released [1]. Endogenous opioids and morphines are released during music listening [47], and long-term effects of music listening has been shown to reduce the medical opioid requirements for patients [104]. Endogenous opioids mediate the whole pain network, and μ-opioid signaling induces pleasurable and analgesic effects in the brain. In addition, catecholamines are thought to be influenced by music listening, including norepinephrine, epinephrine, and dopamine. Norepinephrine and epinephrine are involved with regulating the autonomic nervous system in response to music. Dopamine controls arousal and is released during feelings of pleasure. Dopamine can influence opioid levels, depending on its distribution [60; 108]. Dopamine is released in response to passive music listening to evoke feelings of pleasure [84; 111]. Another neurotransmitter, gamma amino butyric acid (GABA), is thought be involved with the

relaxation response to music. Music may allow neurons to be more receptive to GABA, thereby slowing down neuronal activity and producing a relaxation response [1; 71].

### *1.6.7 Conclusion*

As mentioned above, the neural signature of pain and its mechanisms have been vastly studied in the human brain, with substantial animal studies examining brainstem and spinal cord pain processes. However, the literature has yet to study human pain processing in the entire central nervous system via imaging. Secondly, there has been much work investigating music and its influence on the brain, and there have been many behavioural studies demonstrating music-induced analgesia. Yet, behavioural studies such as respiration rate, electrodermal skin response, spinal nociceptive reflexes, and heart rate cannot demonstrate which neural structures are involved in music-induced analgesia. Therefore, the objective of our research is to investigate human pain processing in the entire central nervous system to provide the missing link between human and animal studies. Furthermore, we wish to see how pain is mitigated by passive music listening, and to study whether there are activity changes in structures known for descending pain modulation.

# Chapter 2

## Music Manipulation of Innocuous Heat Stimuli in the Spinal Cord

### 2.1 Introduction

Listening to pleasant music engages the limbic system, the prefrontal cortex, and the mesolimbic circuit to elicit a rewarding response in the brain [18; 20; 84; 111]. One factor associated with music's rewarding properties is the release of endogenous opioids, which induce pleasurable and analgesic effects on the nervous system [47]. Music-induced analgesia is defined as a reduction in perceived pain due to passive music listening. This treatment option has been used to reduce pain for thousands of years, because it is successful, accessible, free of side effects, and cost-effective [37]. The literature suggests that opioid release activates the descending analgesia system in the brainstem [38] which acts in a gate-control manner to inhibit pain processing in the spinal cord [80].

Emotional valence has also been shown to modulate pain in response to a variety of stimuli; pleasant emotions generally decrease pain whereas unpleasant emotions tend to increase pain [78; 130; 134; 139]. Music has an analogous effect, and pain is significantly reduced while listening to pleasant music but not during unpleasant music [54; 96; 110]. Furthermore, activation of specific paralimbic and neocortical brain regions, which are involved with pain perception, have been shown to be correlated with the degree of music pleasantness [19; 20]. Evidence also suggests that emotional valence can influence neural activity at the level of the spinal cord. Pleasant music was more effective at dampening the spinally mediated nociceptive flexion reflex than unpleasant

music [109]. Thus, the emotional valence of music seems to be an important factor to the modulation of pain.

However, current investigations have not isolated activity in brainstem and spinal cord regions known to be involved with the descending modulation system. There is no direct evidence for how pleasant or unpleasant music can influence neural activity in the spinal cord. Recent advances in functional neuroimaging now make it possible to study the descending analgesia pathway in the human spinal cord and lower brain structures [122]. Past fMRI studies have shown how innocuous and noxious thermal stimuli show similar activation in the brain [13], brainstem and spinal cord [24], and that these activations can be modulated during a cognitive task [122]. The purpose of this study is to use spinal fMRI to investigate whether or not neural activity in the brainstem and spinal cord, in response to a heat stimulus just below pain threshold, is influenced by musical stimuli. If music does modulate spinal cord and brainstem activity, the second aim of this study is to determine if the activity occurs in regions that are known to be involved in the descending analgesia pathway. With this information, we will develop a better understanding of the entire neural response during music-induced analgesia, beyond the role of the brain.

Here we report the results of functional MRI studies spanning the cervical spinal cord and brainstem, to investigate the influence of a variety of musical stimuli (pleasant, unpleasant, and reverse music) on the activity produced by an innocuous thermal stimulus on the hand. Furthermore, by varying the emotional valence of music, we can determine how music pleasantness plays a role in the sensory processing in the spinal cord and brainstem. We hypothesize that neural activity in response to thermal

stimulation will be modulated by music in regions associated with the descending analgesia pathway such as the periaqueductal grey (PAG), rostral ventromedial medulla (RVM), and the dermatome of stimulation.

## 2.2 Method

### *2.2.1 Participants*

Functional MRI of the brainstem and spinal cord was carried out using 18 healthy, English speaking, right-handed participants; age 19-30, 10 females. Participants were non-musicians, defined as never having received instruction on singing or playing an instrument, and never having received special musical education besides what is normally given in public schools [74]. The participants had no previous history of central nervous system disease or injury, were free from contra-indications for MRI safety (such as implanted pacemaker, neurostimulator, metallic implants, etc), and all gave informed consent prior to imaging. All research procedures were approved by the Queen's University Human Research Ethics Board.

### *2.2.2 fMRI Acquisition*

All imaging used a 3T whole-body MRI system (Siemens Magnetom Trio; Siemens, Erlangen, Germany) using blood oxygenation-level dependent (BOLD) contrast, and a contribution from signal enhancement by extracellular water protons (SEEP) contrast [118]. Initially, a set of localizer images were acquired with a fast gradient-echo sequence in three planes to provide a reference for slice positioning. Functional image data were acquired with a phased-array spine receiver coil, using a partial-Fourier, single-shot, fast spin-echo sequence, acquiring 84 phase encoding steps

(partial Fourier with ½ of k-space + 12 lines of oversampling, no oversampling in phase encoding direction). There were nine contiguous sagittal slices (2 mm thick, 0 gap between slices) imaged spanning from above the corpus callosum to below the C7/T1 intervertebral disc. The in-plane spatial resolution was 1.46 mm x 1.46 mm and the remaining imaging parameters were as follows; TE = 38 msec, TR = 9 sec, with spatial saturation pulses to eliminate signal anterior to the spine. The acquisition was repeated 45 times to produce a 6 minute 45 second time series.

### *2.2.3 Stimulus Presentation*

Thermal stimulation was applied to the glabrous skin of the right hand, corresponding to the C8 dermatome, and was produced using a Medoc TSA-II thermal sensory analyzer (Medoc Ltd, Haifa, Israel). Prior to imaging within the MRI system, each participant's heat-pain threshold was determined by incrementally raising the thermode temperature until the participant reported that it was painful. The temperature at which the participant reported pain was recorded as the heat-pain threshold. For the duration of the subsequent imaging, thermal stimulation was applied at 0.3 $^{\circ}$C below the measured heat-pain threshold. This temperature stayed constant throughout testing without the knowledge of the participant, so that this information did not influence the participants' pain ratings. Participants also wore MR-compatible headphones which played the music stimuli throughout the experiment. Before testing, a sound check was done with a designated classical music piece to ensure the quality and sound level was comfortable for each participant. Noise due to imaging remained constant throughout the experiments, and between participants, at 85 decibels. The MR compatible headphones are rated to attenuate noise in the MRI environment by +30 decibels.

There were three types of music used across repeated fMRI experiments including familiar classical ("pleasant", P) [72], reverse classical (R), and scrambled classical ("unpleasant", U). Both the familiar and scrambled music used for this study were rated in a prior study by participants on a 7 point pleasure scale, 0 being not at all pleasant and midpoint being neither pleasant nor unpleasant. The familiar classical music was rated significantly more pleasurable (6.13 ± 0.76) than scrambled music (2.35 ± 1.12), therefore the familiar classical music was used to induce pleasurable emotion for our experiment [84]. Scrambled music was used as an unpleasant stimulus, and was created by splitting the familiar music into 1 second excerpts and randomly reordering the excerpts within 20 seconds of their original position in the musical piece. Both the familiar classical music and the scrambled music were identical in pitch, loudness, and timbre, but differed in temporally driven expectations or melody [72].

### *2.2.4 Experimental Protocol*

Thermal stimulation was applied in a block paradigm with 4 blocks, separated by baseline periods at 32 °C. In addition to thermal stimulation, participants listened to two types of music, one of which was played for the first half of the fMRI time-series acquisition, and the other was played during the second half, as demonstrated in Figure 2.1. Pleasant music was played in the first half of each experiment, paired with either reverse classical music (neutral, PR), scrambled classical music (unpleasant, PU), or no music (PN) for the other half of the experiment. The pleasant music was composed of the same four well-known classical pieces used for each participant, and one piece was designated for each experiment (See appendix A). After each experiment, each participant reported subjective ratings for their temperature discomfort on a scale from 0-

10, with 0 being no discomfort at all to 10 being the worst discomfort imaginable. Participants gave two ratings for each block, one for the pleasant music (P) as well as one for the other type of music (R, U, N).

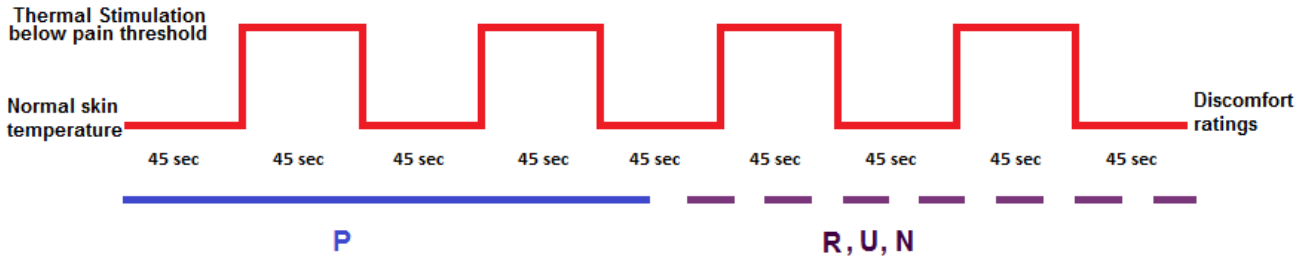


**Figure 2.1**: Paradigm per experiment, with thermal stimulation alternating from normal skin temperature to 0.3 °C below pain threshold every 45 seconds concurrent with a music stimulus switch half way through the experiment; pleasant (P), reverse (R), unpleasant (U), and no music (N). Two discomfort ratings were reported after each experiment.

## 2.3 Analysis

### *2.3.1 Preprocessing*

Functional MRI data were analyzed using custom-made software written in MatLab (The Mathworks Inc., Natick, MA), specifically for spinal cord and brainstem fMRI. For spatial normalization, to generate region masks, and to guide image co-registration, a total of nine reference lines were manually drawn on one volume of each set of time-series image data (Figure 2.2). Within the sagittal view of each data set, five lines were drawn along the anterior and posterior edges of the cord, around the edge of the pons, along the posterior medulla, as well as the top of the corpus callosum. In addition, there were four lines drawn on the coronal view to mark 1) the bottom of the pons 2) an extension through the middle of the image spanning the corpus callosum to the bottom of the pons and 3) right and left boundaries of the spinal cord. To fine tune the definition of the references lines even further, the Medical Image Registration Toolbox

(MIRT) was applied to function as a 3 dimensional non-rigid registration method [89; 90].

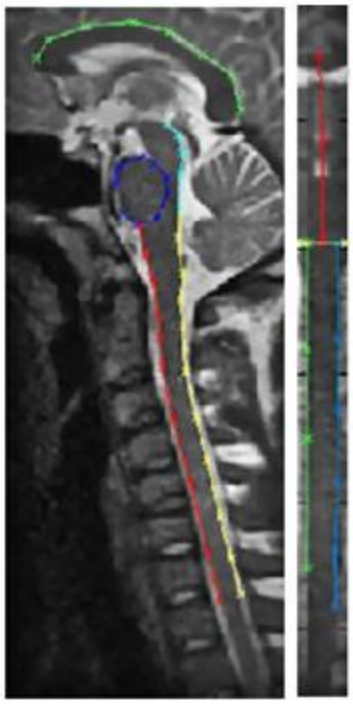

**Figure 2.2:** Sagittal (left) and coronal (right) view of a midline slice where nine reference lines were manually drawn for preprocessing (Stroman works in progress).

### *2.3.2 Statistical Analysis*

Data were analyzed by means of a general linear model analysis (GLM) with multiple basis functions. The GLM analysis uses a voxel by voxel analysis to decompose the signal intensity time series for each voxel into a weighted sum (β-value) of the model time series. Each basis function is linearly independent, and the combination of β-values provides the best fit to the measured signal changes in the fMRI data. The basis functions in this study included a model paradigm for the thermal stimulation convolved with the tissue response function, a constant function, a differential response, and the first two principle components of the time-series data for all voxels in the spinal cord and brainstem [42; 123; 137]. The differential response modeled how the response differed between the first and second halves of each experiment. Thus, the differential response

paradigm gave information on whether the response increase, decreased, or stayed the same when pleasant music (P) switched to a different stimulus (R, U, N) in the second half of each experiment. The first two principle components were included as regressors in the GLM analysis because they identify temporal patterns of variance in the time-series data that are common across all voxels, and are therefore likely to be attributable to physiological motion (Stroman works in progress). A region of interest (ROI) mask of the 3D representation of the cord and brainstem was applied to exclude outlying regions. Structured noise due to movement of the CSF and surrounding anatomy was not modeled in the GLM and thus these regions do not give information pertaining to the error rates within the cord. A random-effects group analysis was applied to determine the significance of the mean responses across all of the participants, relative to the variance of those responses. Therefore, the random-effects analysis was used to determine the consistent features of the areas of activity across participants for the group results.

**2.4 Results**

Neural activity in response to thermal stimulation during music listening was detected in all participants. All music conditions (PR, PU, PN) had significant components of the response that corresponded to the differential paradigm. Areas demonstrating differential activity include C8, the medulla, pons, and midbrain with significant differences between conditions demonstrated in regions of the left ventral horn of C8 and the dorsolateral pontine tegmentum (DLPT).

Brainstem activity exemplified neural activity changes among music conditions in terms of the differential response, as shown in Figure 2.3. In the PR music condition, there was an increase in percent signal change within regions of the rostral ventromedial

medulla (RVM) ($M$= 0.27, *S.E.M.* = 0.17), DLPT ($M$= 0.20, *S.E.M.* = 0.08) and periaqueductal grey (PAG) ($M$= 0.05, *S.E.M.* = 0.10). The PU condition demonstrated similar, but greater activity within the vicinity of the PAG ($M$= 0.22, *S.E.M.* = 0.10) and the DLPT ($M$= 0.40, *S.E.M.* = 0.07), with a small increase in activity in the RVM region ($M$= 0.03, *S.E.M.* = 0.15). However, the only significant differences in the differential response were found in the PN condition. A one-way analysis of variance (ANOVA) between subjects was conducted to compare the effect of music condition on the BOLD response within the DLPT [$F(2, 66) = 5.99$, $p < 0.01$]. A post hoc Tukey test showed that there was a significant suppression of activity in regions of the DLPT when comparing the PN to the PR condition at $p < 0.05$, as well as comparing the PN condition to PU condition at $p < 0.01$. Similar to the PR and PU condition, the PN condition also had increase in activity within the RVM ($M$= 0.11, *S.E.M.* = 0.17) and PAG ($M$= 0.39, *S.E.M.* = 0.16) (Table 2.1).

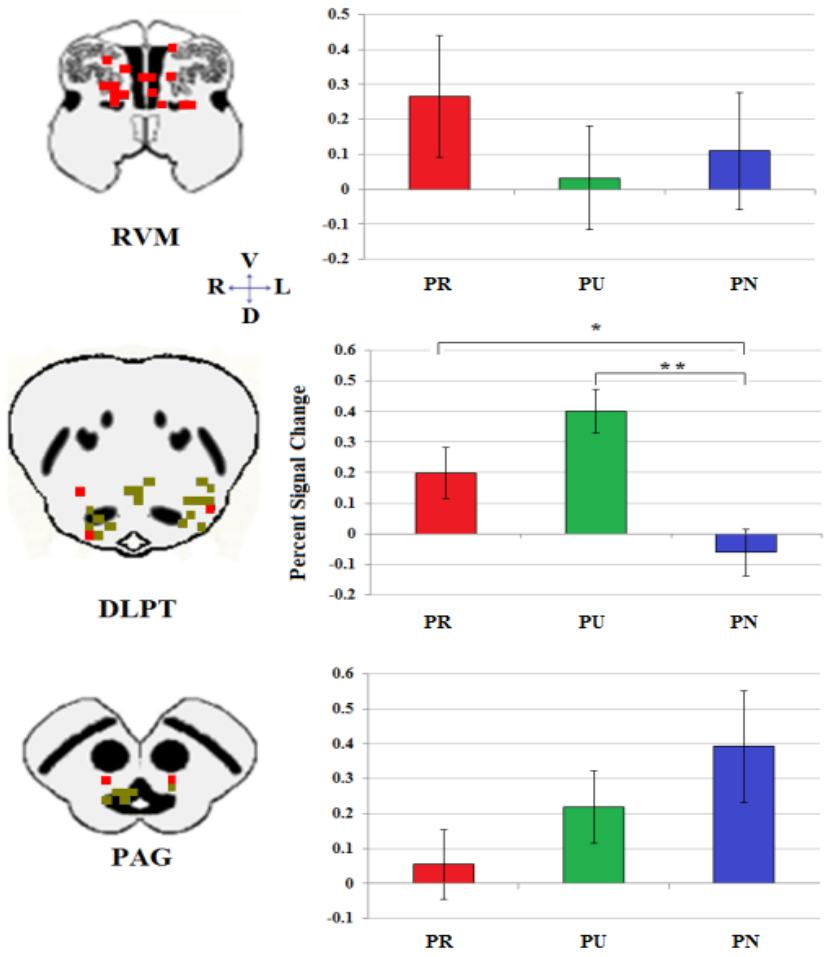


**Figure 2.3:** Magnitudes of differential BOLD responses within rostral medulla (top), pons (middle), and midbrain (bottom) for the PR (pleasant -reverse), PU (pleasant - unpleasant), and PN (pleasant-none) condition. Hotter colors represent the greater rostral-caudal degree of the region of interest in the rostral ventromedial medulla (RVM); dorsolateral pontine tegmentum (DLPT); and periaqueductal grey (PAG). *= P < 0.05, **= P < 0.01

Figure 2.4 demonstrates how regions within the 8$^{th}$ cervical spinal cord segment (C8) either showed greater activity (in percent signal change) or lesser activity during the differential response. In all music conditions, there was an increase in activity induced within the area of the ipsilateral dorsal horn of the spinal cord. There were varying degrees that the BOLD response increased determined by the music condition, including the PR condition (*M*= 0.69, *S.E.M.* = 0.24), the PU condition (*M*= 0.55, *S.E.M.* = 0.11),

and the PN condition (*M*= 0.04, *S.E.M.* = 0.25). Changes in the BOLD response were also detected in the vicinity of the contralateral ventral horn of C8 for each condition with an increase in activity for the PR condition (*M*= 1.29, *S.E.M.* = 0.73) and a corresponding decrease in activity for the PU condition (*M*= -0.61, *S.E.M.* = 0.45) and the PN condition (*M*= -1.06, *S.E.M.* = 1.08) (Table 1). A one-way ANOVA demonstrated significant differences between music conditions at $F(2, 21)= 3.451$, $p < 0.05$. Tukey post-hoc comparisons of the three groups indicated that activity in the surrounding area of the left ventral horn had significantly lower activity for the PN condition than the PR condition at $p < 0.05$. Table 2.1 represents a summary of the group results within the brainstem and spinal cord.

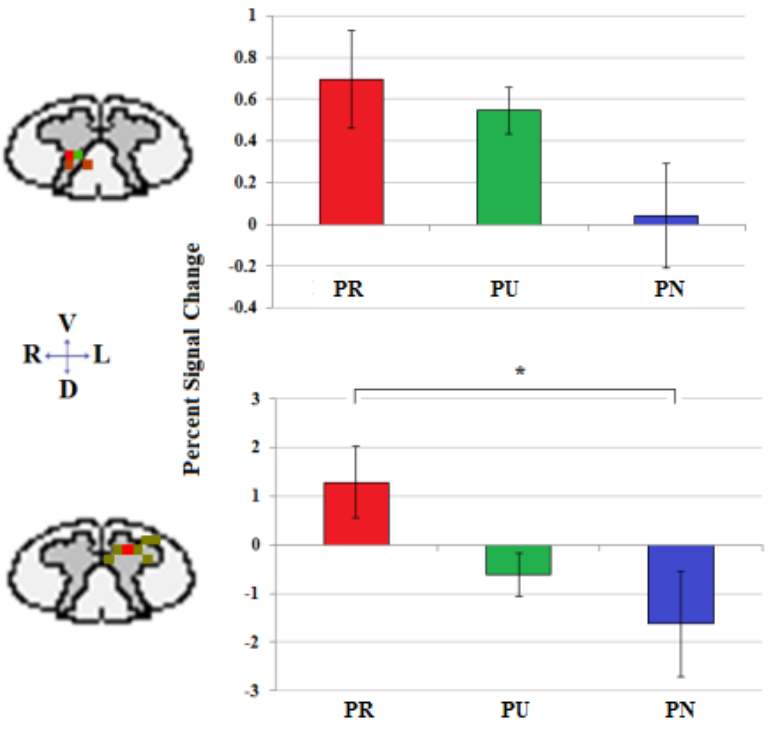


**Figure 2.4:** Magnitudes of the differential BOLD responses within the right dorsal horn (top) and left ventral horn (bottom) for the PR (pleasant -reverse), PU (pleasant - unpleasant), and PN (pleasant -none) condition. Hotter colors represent the greater rostral-caudal degree of the region of interest. *= $P < 0.05$

| Region of Interest | PR | | PU | | PN | |
|---|---|---|---|---|---|---|
| | Mean | S.E.M. | Mean | S.E.M. | Mean | S.E.M. |
| RVM | 0.27 | 0.17 | 0.03 | 0.15 | 0.11 | 0.17 |
| DLPT | 0.20 | 0.08 | 0.40 | 0.07 | -0.06 | 0.08 |
| PAG | 0.05 | 0.10 | 0.22 | 0.10 | 0.39 | 0.16 |
| C8 right dorsal | 0.70 | 0.24 | 0.55 | 0.11 | 0.04 | 0.25 |
| C8 left ventral | 1.29 | 0.73 | -0.61 | 0.45 | -1.06 | 1.08 |

**Table 2.1:** Overview of group results of the magnitudes of the differential BOLD response for regions of interest within the brainstem and spinal cord. For each music condition, the mean of the percent signal change and standard error of the mean (S.E.M.) is shown within the RVM, DLPT, PAG, and C8; PR (pleasant -reverse), PU (pleasant - unpleasant), and PN (pleasant -none) condition (n=18)

Thermal stimulation temperature throughout the trials was constant with an average of 45.6 ° C across participants (range: 44 - 47.8 ° C). Participants gave two subjective ratings of their discomfort relative to the thermal stimulation, on a scale from 1- 10, with 1 being no discomfort at all to 10 being the worst discomfort imaginable after each trial. One rating pertained to the pleasant music, while the other rating represented either reverse, unpleasant, or no music. During the PR condition, there was a decrease in mean pain ratings from pleasant music at 5.92 (*S.E.M.* = 0.57) to reverse music at 5.47 (*S.E.M.* = 0.60). In contrast, the PU condition had pleasant music at a rating of 4.77 (*S.E.M.* = 0.64) and increased to 5.25 (*S.E.M.* = 0.48) for unpleasant music, while pleasant music also increased from 5.37 (*S.E.M.* = 0.51) to 5.66 (*S.E.M.* = 0.72) during the PN condition. However, participants' ratings did not reach significant differences between music conditions when evaluated with a two-tailed, paired-sample t-test (Table 2.2).

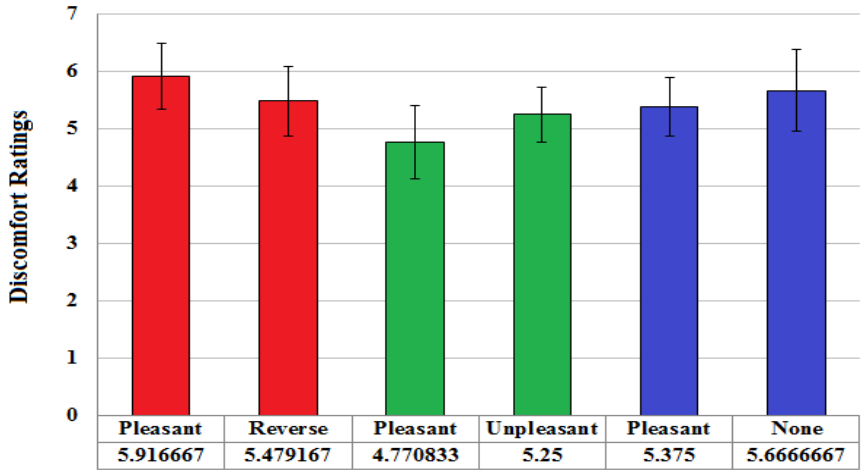


**Table 2.2:** Results of discomfort ratings by participants shown for each half of each music condition on a scale of 0-10, including the average rating and standard error of the mean for each music manipulation including the PR condition (red), the PU condition (green), and the PN condition (blue) (n = 18).

## 2.5 Discussion

The present study is the first of its kind to use imaging to detect alterations in neural responses in the brainstem and spinal cord to noxious thermal stimulation as a result of exposure to different musical stimuli. The spinal fMRI method used was sensitive enough to show neural activity changes during several variations of musical presentation. When one musical stimulus changed over to another musical stimulus half way through the block, neural activity changed accordingly. If the thermal stimulation temperature stays consistent, any difference in signal intensities can be contributed to the change in the music stimuli. If music did not influence activity within the brainstem and spinal cord, then activity would have remained constant between the first and second half of each trial. This would have been particularly evident when comparing pleasant music to no music. Due to the evidence that there was significant variation in activity as the musical stimuli changed, it can be concluded that music influences activity at the level of the brainstem and spinal cord.

The PAG, RVM, DLPT, and the dorsal gray matter (GM) of the spinal cord receive multiple inputs (excitatory and inhibitory) from the limbic system, the brainstem, and the periphery that influence their individual activity. The rostral ventromedial medulla (RVM) receives inputs from the PAG and directly projects to the dorsal horn via the dorsolateral funiculus[53]. The results demonstrate that the right dorsal horn GM and the PAG area have a reciprocal relationship where the larger the increase in activity within the vicinity of the dorsal horn, the smaller the increase in activity within the PAG area. Connectivity analysis based on spinal fMRI data with innocuous sensory stimuli has been used previously to show that the ipsilateral dorsal GM receives inhibitory input from the RVM [119]. As the PAG projects to C8 via the RVM, this may explain the findings comparing the PAG and C8 area (Figure 2.5). In addition, the contralateral ventral GM area demonstrated the largest percent signal changes in activity compared to all other regions of interest investigated. The contralateral ventral GM has been suggested to only receive input from the ipsilateral dorsal gray matter when using an innocuous heat stimulus [119]. If the contralateral ventral GM is solely influenced by the ipsilateral dorsal area, the lack of varying inputs may account for the strong activity changes within the contralateral ventral region. Also, ipsilateral dorsal and contralateral ventral GM area demonstrated the greatest differences between the PR and PN music conditions, which provide further evidence for the connectivity within C8.

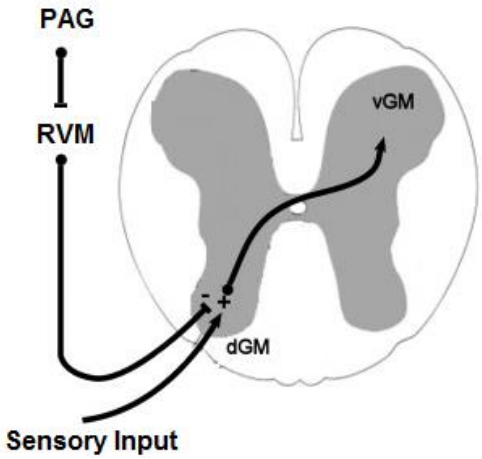


**Figure 2.5:** Summary of interpretation of activity involved in the eighth cervical segment (C8). The gray matter of the dorsal horn of the spinal cord (dGM) receives input from the periphery as well as input from the brainstem. The rostral ventromedial medulla (RVM) negatively projects directly to the dGM, and is influenced by inputs from the periaqueductal grey (PAG). Hence, the dorsal horn demonstrates the sum of activity from brainstem and peripheral input. The contralateral ventral gray matter (vGM) reflects local input from the ipsilateral dGM alone. *Figure adapted from* [119].

In accordance with previous studies, our results support the conclusion that emotional valence contributes to music modulation of thermal stimuli [84; 110]. During the PU condition, there was a differential increase in activity in regions of the ipsilateral dorsal horn, RVM, DLPT, and PAG, and a decrease within the contralateral ventral horn. Unpleasant music and pleasant music were identical in pitch, loudness, and timbre, but differed in the melodic or the emotional component of music [72]. Due to their identical auditory properties, the changes in activity between unpleasant and pleasant music may be explained by the differing emotional valence. Our results are in accordance with Roy et al. [109] which demonstrated that the emotional valence of music effects neural activity beyond the level of the brain.

The dorsolateral pontine tegmentum (DLPT) is an important component to descending modulation and contains various nuclei, one of the most important being the locus coeruleus (LC). It is theorized that the LC functions primarily on sensory processing and regulates arousal [17]. The LC also has prominent connections to the orbitofrontal cortex (OFC) and prefrontal cortex (PFC), which have shown to be active

when listening to pleasurable music [18; 19]. The LC also has extensive projections to the limbic system, thus, LC activity may reflect changes in the emotional valence of the music stimuli. The results demonstrate a significant increase in activity when pleasant music changed to reverse and unpleasant music, but significantly decreased during no music. Unpleasant music may serve as a stronger emotionally aversive stimulus than reverse music, resulting in larger activity changes in the DLPT area. As the no music condition cannot serve as an affective stimulus, this may perhaps explain the small decrease in the BOLD response. Therefore, the DLPT seems to serve an important role when processing different music stimuli accompanied by thermal stimulation.

One problem with attempting to isolate attentional and emotional influences during an fMRI study is that it is impossible to have complete control of the participant's mental state. Attention can waver away from the thermal and musical stimuli, and determining whether the participant is focusing on the thermode or the music cannot be accurately judged. Another important factor to consider is that different pieces of music have different sentimental value from one person to the next. This study was carried out with non-musicians to avoid mental schemas of music and further, only presented 4 different classical works shown to be familiar and pleasurable to the general public [72]. Despite these controls, the personal relevance and experience with a piece of classical music cannot be controlled for. However, music has been shown to release opioids and it is suggested that an opiate-sensitive descending pathway including the PAG, RVM, and spinal cord dorsal horn may be involved with both the emotional and/or attentional modulation of pain [39].

Because this study employed innocuous stimuli, there were no significant changes in subjective ratings when different musical stimuli were presented. Since the temperature chosen for each participant was 0.3 ° C lower than their individual pain threshold, the heat stimuli evoked discomfort as opposed to pain. This is in accordance with Roy et al. [110] where warmth perception was not affected by emotional valence of music but pain perception was. However, the thermal stimulation used was strong enough to elicit varying responses in regions known for descending modulation. Future studies will investigate the role of the brainstem and spinal cord in music-induced stimuli using noxious heat stimuli and how this compares to innocuous thermal stimulation.

This study identifies neural structures involved in music modulation within the brainstem and spinal cord, for the first time. The brainstem and spinal cord are necessary elements to consider when studying how pain and music are processed in the nervous system because they host structures involved in descending modulation. Spinal fMRI is a suitable tool to study music in the brainstem and spinal cord because it of its sensitivity and its non-invasive nature. This study demonstrates the involvement of the lower central nervous system in music modulation. More research is needed to accurately determine the brainstem and spinal cord's role in music-induced analgesia to improve the efficiency of music's analgesic use.

# Chapter 3
# Music manipulation of Noxious Heat Stimuli in the Brain, Brainstem, and Spinal Cord

## 3.1 Introduction

Pain is a highly subjective and unpleasant experience that can be mitigated by passive music listening, known as music-induced analgesia. Music-induced analgesia has been used as a treatment option for thousands of years, and behavioural studies investigating this phenomenon have demonstrated a decrease in subjective pain ratings [26]. Although there is much evidence to support the use of music for pain reduction, studies have yet to demonstrate its mechanisms of action. In recent investigations, imaging studies have illustrated how passive listening to pleasant music activates brain areas involved with reward, emotion, and arousal such as the limbic system, orbitofrontal cortex (OFC), cerebellum, and medial prefrontal cortex (PFC) [18; 19; 72]. Correspondingly, numerous pain studies using functional magnetic resonance imaging (fMRI) illustrate activity changes in the amygdala, anterior cingulate cortex (ACC), somatosensory cortex, insula, hypothalamus, and thalamus when a person is subjected to a painful stimulus [32; 97]. Music's pain relieving properties are hypothesized to suppress pain by activating the descending pain modulation system via opioids released during music listening [47]. The descending analgesia system is opioid-sensitive, and includes structures in the brain and brainstem which act to suppress nociceptive responses in the spinal cord [39]. However, the neural activity involved with music-induced analgesia has only been hypothesized thus far, which demonstrates the need for imaging studies to investigate the link between music and its influence on regions involved with pain.

Here, we investigate the neural mechanisms involved in music-induced analgesia by using fMRI of the brain, brainstem, and spinal cord in the same imaging session. Each participant was asked to bring their favorite selections of music of any genre, at least 215 seconds in length (Appendix B). Healthy participants were subjected to noxious heat stimuli and provided ratings of their perceived pain, while simultaneously listening to either their favorite pieces of music, or no music as a control. We anticipate that pleasant music will reduce the subjective ratings of pain, compared to when no music is presented. During the "music condition" (when music is presented), we hypothesize that activity will be reduced (compared to the no music condition) in areas known to be involved in pain processing such as the dorsal horn of the spinal cord (C6), the periaqueductal grey (PAG), and the rostroventromedial medulla (RVM). We also predict that there will be activity in brain regions thought to be involved with reward and emotion associated with passive music listening in the music condition. The objective of this study is to characterize the neural responses to music-induced analgesia throughout the entire central nervous system to further the evidence gained from behavioural studies, and to investigate whether the pain relieving properties of music act via the descending analgesia system.

## 3.2 Methods

### *3.2.1 Participants*

Healthy, female, non-musicians, aged 18-40 participated in this study (n=12). Non-musicians were defined as never having received instruction on singing or playing an instrument, and never having received special musical education besides what is normally given in public schools [74]. Compared to men, women are more sensitive to

thermal detection and thermal pain at the thenar eminence [66] and illustrate a greater response to music-induced analgesia [59]. We therefore restricted the participants in an effort to obtain the most consistent responses possible.

As pain perception and the opioidergic system can be influenced by the stage of menstrual cycle [35], participants were tested in the luteal stage of their menstrual cycle, occurring in the last two weeks of their natural cycle or cycle of oral contraceptives. Due to the influence of emotion and cognition on perceived pain, participants were also screened with a series of questionnaires to ensure no past history of psychiatric disorders and no current symptoms of depression or anxiety. Questionnaires included the Beck Depression Inventory[15], Spielberger's State-Trait Anxiety Inventory [116], the Crowne-Marlowe Social Desirability Scale [30], as well as the Pain Catastrophizing Scale [124] (Appendix D-G). Because alcohol and caffeine have demonstrated influences on emotions, alertness, and the blood oxygenation level dependent (BOLD) response [27], participants were asked to refrain at least 12 hours and 6 hours before the study respectively. The participants also had no previous history of central nervous system disease or injury, were free from contra-indications for MRI safety (such as implanted pacemaker, neurostimulator, metallic implants, etc), and all gave informed consent prior to imaging. This study was reviewed and approved by the institutional research ethics board.

### *3.2.2 Thermal Stimulation*

The method used to induce pain was a well-defined model which probes primarily C-fibre related pain responses [101; 117]. Thermal stimulation was administered on the thenar eminence of the right hand, corresponding to the C6 dermatome, and was

produced by a Medoc TSA-II thermal sensory analyzer (Medoc Ltd, Haifa, Israel). First, each individual was trained to recognize first and second pain, and to rate their second pain on a 100-point rating scale. First pain was described as an initial, sharp pain while second pain was a dull, throbbing pain that followed. The pain rating scale depicted verbal descriptors at 10, 20, 30…100 (no sensation, warm, a barely painful sensation, very weak pain, weak pain, moderate pain, slightly strong pain, strong pain, very strong pain, nearly intolerable pain, intolerable pain). This scale was visible to the participants throughout the psychophysical testing (Figure 3.1).

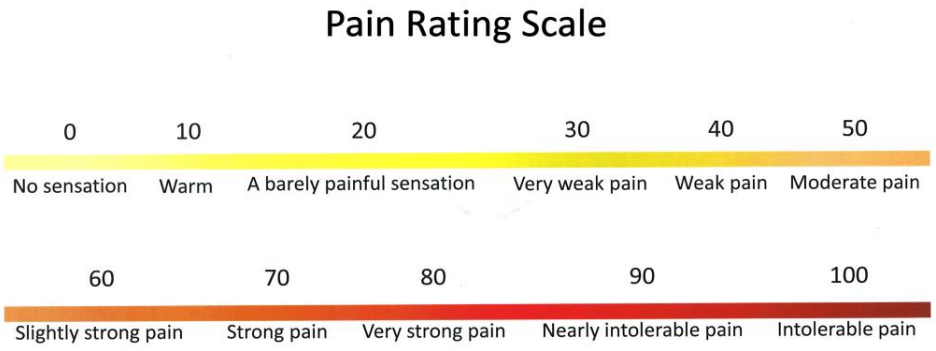


**Figure 3.1**: Pain rating scale used to rate pain perception of second pain

Participants experienced thermal stimulation in a "wind-up" paradigm consisting of 10 hot, brief, heat pulses applied at two different frequencies. The frequency of administration was 0.33 Hz (pulses every 3 seconds), which has been shown to produce temporal summation of pain [101]. A lower rate of stimulation was 0.17 Hz (every 6 seconds) was also employed that is not sufficient to produce temporal summation. The thermode was initially held at a warm adaptation temperature for 23 or 50 seconds, depending on the presentation's frequency rate. The pulses in temperature were composed of an 8 $^{\circ}$C increase over 1.5 seconds, then a drop back to the warm adaptation temperature within 1.5 seconds. The warm adaptation temperature and the peak

temperature were always 8 °C apart. However, these temperatures were calibrated based on individual pain sensitivity. The ten pulses used to distinguish the emergence of temporal summation were administered over 30 seconds (0.33 Hz) and 57 seconds (0.17 Hz), and were followed by 75 seconds at the warm adaptation temperature. In total, the wind-up paradigm was 155 seconds in length with a rest period of 2 minutes between each trial, allowing for the skin receptors to acclimate to room temperature (Figure 3.2).

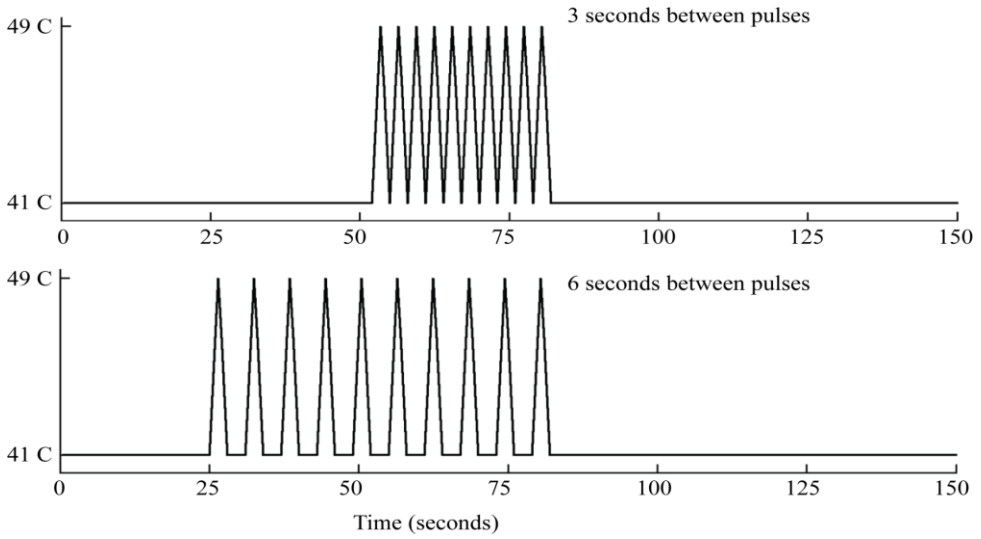


**Figure 3.2:** Thermal stimulation with heat pulses presented at a frequency of 0.33 Hz to induce temporal summation of the C fibers (top), as well as the frequency of 0.17 Hz that does not induce temporal summation (bottom). Every participant received an amplitude of 8 $^{0}$C, however the adaptation temperature (depicted as 41 °C) and peak temperature (depicted as 49 °C) was calibrated for each individual's pain sensitivity (Stroman works in progress).

### *3.2.2 Training Phase I*

Prior to imaging, participants had a training session in a "sham" MRI environment to become practiced with the study procedures and to ensure that the temperature could be calibrated to evoke the temporal summation effect. The training session took place in a "sham" MRI, which resembles the MRI environment without the

magnetic field. For the first phase, participants sat upright and gave pain ratings for one pulse, two pulses, and then multiple series of 10 pulses of noxious stimuli. Participants reported both the average and maximum pain felt across the 10 pulses. The series of 10 pulses were used to calibrate the warm adaptation and peak temperatures for each participant to induce wind-up. Calibration ceased when the participant consistently reported average pain ratings of approximately 60 for the 0.33 Hz ten-pulse trials. At the same temperature, participants typically reported average pain ratings of approximately 30 for the 0.17 Hz ten-pulse trials. Once these consistent ratings were established, participants were positioned supine inside the sham MRI with headphones on, to replicate the environment during fMRI studies.

### *3.2.3 Training Phase II*

While lying in the sham MRI, participants felt only the ten, 0.33 Hz pulses at the temperature which produced the consistent average pain ratings of 60. Unbeknownst to the participant, this temperature was consistent throughout testing. During each trial participants reported the average pain rating and the maximum pain rating throughout the 10 pulses. Each participant was asked to bring their favorite selections of music of any genre, which was at least 215 seconds in length. Testing was repeated with the painful stimulus presented, in five interleaved trials with their favorite music playing, and five trials without music. After each music trial, participants rated each music piece based on 4 criteria to provide further insight on the mood of the individual. The scales ranged from 0-10, and the dimensions included relaxed-tense, very sad-very happy, unpleasant-pleasant, and angry-calm. Therefore, participants reported a total of 4 ratings for each piece demonstrated in Figure 3.3. The pain and music rating scales were projected onto a

rear-projection screen outside of the MRI, which could be seen by the participant via a mirror positioned above their head.

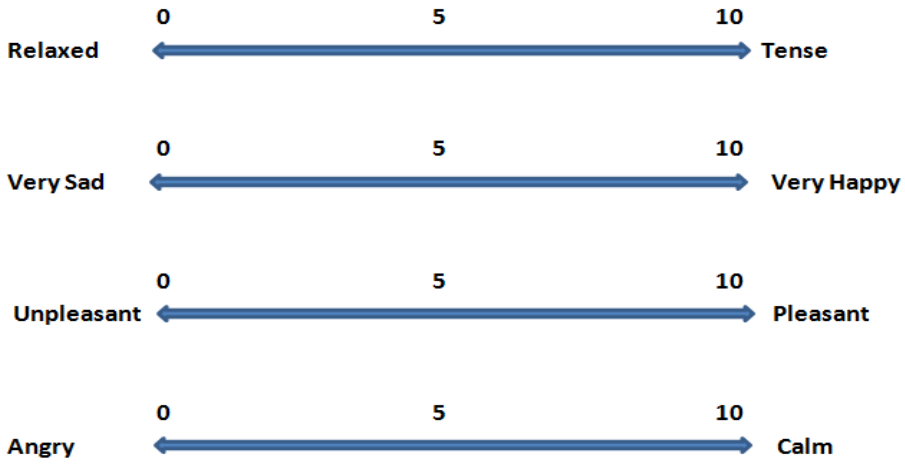


**Figure 3.3**: Rating scales used to rate perception of the music piece

### *3.2.4 Imaging Session*

The imaging session took place on a different day to avoid sensitization of the skin and reduce fatigue during the experiment. In the control room of the MRI facility, the temperature calibration was verified by applying 10 heat pulses to the thenar eminence of the right hand at rates of both 0.33 Hz and 0.17 Hz, and obtaining the average and maximum pain ratings for each. If the ratings did not match the ratings given during the training session, the calibration was re-established by adjusting the temperature slightly, as needed.

Before entering the MRI system, participants put on MR-compatible headphones which played their music selections throughout the experiment. Before scanning, a sound check was done with a designated classical music piece to ensure the quality and loudness was comfortable for each participant. Noise due to imaging stayed constant throughout the experiment, and between participants, at 85 decibels. The MR compatible

headphones provide passive noise attenuation by -30 decibels. Also, the MRI-compatible thermode (Medoc TSA-II) was positioned comfortably on the thenar eminence of their right hand held in place with cloth tape.

Participants were positioned supine on the MRI bed and entered the magnet head-first. All imaging was done with a 3T whole-body MRI system (Seimens Magnetom Trio; Siemens, Erlangen, Germany). Initially, a set of localizer images were acquired with a fast gradient-echo sequence in three planes to provide a reference for slice positioning. In addition, sagittal and coronal localizer images were acquired to allow for precise positioning of the participant for spinal fMRI. Trials alternated between pain applied with music and pain applied without music. Each imaging session contained eight spinal imaging blocks (4 music, 4 non-music) and four brain imaging blocks (2 music, 2 non-music). The experimental protocol was identical to the second half of the training phase, with the rating scales displayed to the participant in a similar manner (see Phase II).

Spinal functional image data were acquired with a phased-array spine receiver coil, using a half-Fourier, single-shot, fast spin-echo sequence (HASTE), acquiring 84 phase encoding steps (partial Fourier with ½ of k-space + 12 lines of oversampling, no oversampling in phase encoding direction). There were nine contiguous sagittal slices (2 mm thick, 0 gap between slices) imaged spanning from above the corpus callosum to below the C7/T1 intervertebral disc. The in-plane spatial resolution was 1.5 mm x 1.5 mm, with an echo time (TE) of 75 msec, and a repetition time (TR) of 6.75 sec per slice. This echo time has shown to provide the optimal contrast-to-noise ratio for spin-echo ($T_2$-weighted) imaging using BOLD contrast [121]. Across 4 repeated trials we acquired 92

imaging volumes for subsequent fMRI analysis in order to detect the influence of the music, or no music, on the responses to the noxious thermal stimulus.

Brain imaging data was acquired similarly to the spinal fMRI imaging protocol except that a 12-channel head coil was used. Imaging methods were based on established methods using gradient echo imaging with echo-planar imaging (EPI) spatial encoding. Transverse slices with a field of view (FOV) spanning 192 x 192 $mm^2$ with a 64 x 64 matrix were acquired to produce a 3 mm x 3 mm in-plane resolution. The slices were 3 mm thick to provide isotropic resolution, with a total of 43 slices acquired to span the entire brain and upper brainstem. Typical brain fMRI parameters (TR=3 sec, TE=30msec) were selected to provide optimal $T_2$*-weighted BOLD contrast. The brain and upper brainstem were imaged 51 times during each 155 second thermal stimulation trial. Three trials were carried out with each pain condition (music, no music), resulting in 153 volumes for each, for subsequent fMRI analysis.

### 3.3 Analysis

The spinal fMRI preprocessing steps and statistical analysis were identical to the previous study (see *2.3.1* and *2.3.2*). The brain fMRI data were analyzed using the statistical parametric mapping (SPM8) software package (Wellcome Dept. of Imaging Neuroscience). The image data were first converted into NifTI format, realigned, and co-registered with the slice timing corrected. The motion parameters from the co-registration helped to interpret residual motion effects (ex: steady-state magnetization). In addition, the data were smoothed with 5 mm FWHM Gaussian kernel and spatially normalized into MNI space. The GLM for brain analysis closely resembled the spinal fMRI basis functions (ex: stimulation paradigm convolved with the canonical HRF) as did the

random-effects group analysis. The T-scores were determined by use of a contrast-weights vector analysis within SPM8, where the β-value for every voxel from the first level analysis is multiplied by the contrast design matrix (such as to determine the difference in the responses, for example) and the mean and standard deviation is determined across the participants. The T-value is again the ratio of the mean contrasted values to the standard-error-of the mean. To aid in our identification of regions affected, we used the 'Atlas of the Human Brain' [75] and the Talairach Daemon Client (Version 1.1, Research Imaging Center, University of Texas Health Science Center, San Antonio, TX).

For the behavioural data, the mean pain ratings for both average and maximum pain categories were calculated across the 12 participants. A Student's two-tailed *t*-test was used to determine the significance of the differences between music and non-music conditions.

**3.4 Results**

Listening to music produced a reduction in subjective pain ratings, and differential activity in the brain, brainstem, and spinal cord as compared to the no music condition, as detailed below. Differences were found in brain areas involving limbic and paralimbic regions, frontal and temporal cortex, as well as midbrain and sensory cortex. Pain administered with music also produced differential activity in locations within close anatomical proximity to the rostroventromedial medulla (RVM), dorsolateral pontine tegmentum (DLPT) and the periaqueductal grey (PAG) area. Furthermore, differences exist between music and no music conditions in the BOLD responses in $6^{th}$ cervical spinal cord segment (C6).

*3.4.1 Subjective Ratings:*

On average, participants rated their self-selected music as being relaxed (*M*= 3.0, *S.E.M.* = 2.6), happy (*M*= 7.1, *S.E.M.* = 2.0), pleasant (*M*= 8.0, *S.E.M.* = 1.8), and calm (*M*= 7.3, *S.E.M.* = 2.2). Both the average and maximum pain ratings perceived during the music condition were significantly lower than the average and maximum pain ratings when no music was playing for the training session as well as the MRI session (two sample *t*-test, $p < 0.01$). During the training session, participants rated the average (54 ± 2.4) and maximum (62 ± 2.1) pain ratings in the music condition significantly lower than the average (59 ± 1.9) and maximum (67 ± 1.6) pain ratings without music. Similarly, during the MRI session the music condition had an average pain rating of 53.0 (*S.E.M.* = 2.8) and a maximum pain rating of 61 (*S.E.M.* = 2.8). Higher pain ratings were evident in the no music condition for average (57 ± 2.7) and maximum (65 ± 2.7) ratings (Table 3.1).

| Participant | Music | | Non-Music | |
|---|---|---|---|---|
| | Average | Max | Average | Max |
| 1 | 50 | 60 | 57 | 66 |
| 2 | 63 | 70 | 65 | 72 |
| 3 | 37 | 55 | 41 | 55 |
| 4 | 66 | 76 | 69 | 79 |
| 5 | 59 | 59 | 62 | 62 |
| 6 | 58 | 64 | 64 | 70 |
| 7 | 58 | 74 | 65 | 80 |
| 8 | 38 | 43 | 42 | 46 |
| 9 | 46 | 51 | 55 | 60 |
| 10 | 44 | 53 | 48 | 57 |
| 11 | 57 | 67 | 54 | 65 |
| 12 | 57 | 60 | 55 | 61 |
| **Average** | **53** | **61** | **57** | **65** |

**Table 3.1:** Average and maximum pain ratings across participants in the MRI session on a scale of 0-100 with music and without music.

### *3.4.2 Brain Results*

Brain imaging results indicated that there were significant differences in the BOLD response when pain was administered with music or without music (one-sample t-test). Both music and non-music conditions illustrated bilateral activations of the insula (BA 13), ventral anterior cingulate cortex (ACC, BA 24), anterior prefrontal cortex (PFC, BA 10), supplementary motor area (SMA, BA 6), as well as the cerebellum. The music condition alone portrayed bilateral activity in the inferior frontal gyrus (BA 47), medial prefrontal cortex (PFC, BA 8), hypothalamus, hippocampus, and supramarginal gyrus (BA 40) with the no music condition eliciting bilateral activity in the striate cortex, dorsal ACC (BA 32), and thalamus. Significant activity pertaining to music were also found in the right orbitofrontal cortex (OFC, BA 11), right nucleus accumbens, right caudate nucleus, and left amygdala all represented in Table 3.2 (*for Talairach coordinates, please see Appendix C*).

| | | Music | | Non-music | |
|---|---|---|---|---|---|
| | | Left | Right | Left | Right |
| ***Limbic Areas*** | **Insula (13)** | **10.0** | **5.2** | **6.1** | **5.3** |
| | **Nucleus Accumbens** | | **2.8** | | |
| | **Amygdala** | **2.8** | | | |
| | **Ventral Anterior Cingulate Cortex (24)** | **4.1** | **5.4** | **6.1** | **5.6** |
| | **Dorsal Anterior Cingulate Cortex (32)** | | | **6.1** | **3.9** |
| | **Ventral Posterior Cingulate Cortex (23)** | | | | **5.3** |
| | **Hippocampus** | **2.7** | **3.0** | | |
| | **Parahippocampal Gyrus (34)** | | **3.2** | **4.0** | **3.3** |
| ***Frontal Cortex*** | **Inferior Frontal Gyrus (47)** | **7.0** | **7.5** | **3.7** | |
| | **Dorsolateral Prefrontal Cortex (9)** | **4.5** | | **4.3** | |
| | **Medial Prefrontal Cortex (8)** | **4.5** | **4.5** | | **3.8** |
| | **Orbitofrontal Cortex (11)** | | **4.6** | | |
| | **Pars Opercularis *Broca's Area* (44)** | | | | **6.3** |
| | **Anterior Prefrontal Cortex (10)** | **4.7** | **7.8** | **3.6** | **5.0** |
| | **Supplementary Motor Area (6)** | **4.5** | **5.2** | **5.3** | **3.1** |
| ***Midbrain*** | **Caudate** | | **3.3** | **5.0** | **5.3** |
| | **Global Pallidus** | | | **7.2** | |
| | **Caudate Tail** | | | **5.6** | |
| | **Putamen** | | | **7.4** | **4.6** |
| | **Thalamus** | **4.7** | | **6.6** | **6.4** |
| | **Hypothalamus** | **3.8** | **3.1** | **3.8** | |
| ***Temporal Cortex*** | **Fusiform Gyrus (20)** | **4.1** | | | **4.4** |
| | **Middle Temporal Gyrus (21)** | | **4.5** | **8.3** | |
| | ***Superior Temporal Gyrus* (22)** | **6.6** | | | |
| | **Temporopolar Area (38)** | **4.7** | | | **5.1** |
| ***Other areas*** | **Supramarginal Gyrus (SII) (40)** | **4.6** | **7.0** | | **4.4** |
| | **Primary Somatosensory Cortex (3)** | | | **4.0** | |
| | **Precuneus (19)** | | | **4.1** | |
| | **Posterior Cerebellum** | **4.9** | **6.8** | **5.7** | **4.9** |
| | **Anterior Cerebellum** | **4.3** | **5.1** | **4.5** | **4.7** |

**Table 3.2:** T-score values for activations in the music + pain condition versus no music + pain condition for left and right brain hemispheres (one-sample t-test). After each brain region, the corresponding Brodmann area is shown in parentheses.

Furthermore, a paired *t*-test was conducted to test differences in the BOLD responses between conditions (Figure 3.4, Table 3.3). A comparison of responses to pain given with music to without music demonstrated significant activity in areas of the limbic system including the ventral tegmental area (VTA), right nucleus accumbens (NAc), left

insula (BA 13), bilateral dorsal ACC (BA 32), right ventral ACC (BA 24), and right parahippocampal gyrus (BA 36). Several areas also increased in the BOLD response within the frontal cortex, namely the right OFC (BA 11), left primary somatosensory cortex (SI, BA 3), bilateral dorsolateral PFC (BA 9), and right SMA (BA 6) among others. Significant differences were also found within the temporal cortex in areas of the bilateral middle temporal gyrus (BA 21), bilateral fusiform gyrus (BA 20/37), left superior temporal gyrus (BA 22), and left primary auditory cortex (BA 41). In addition, other brain areas which exhibited differences in between conditions included the right hypothalamus, cerebellum, pulvinar and ventral posterolateral (VPL) thalamus, bilateral precuneus (BA 19/7), and left secondary visual association cortex (BA 18).

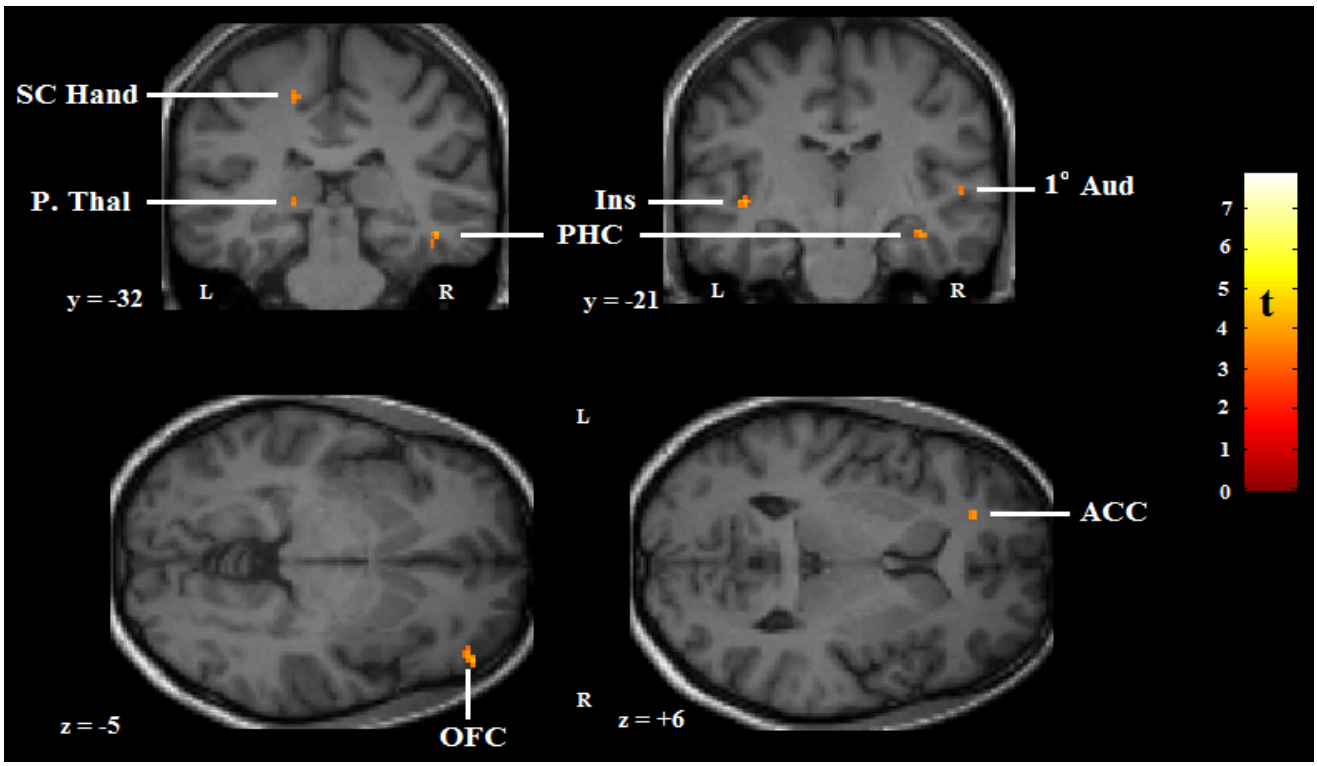


**Figure 3.4:** Neuroanatomical regions demonstrating the significant differences (t-scores) between the music + pain condition versus no music + pain condition (paired t-test, $p < 0.005$); somatosensory cortex of the hand (SC Hand); pulvinar thalamus (P. Thal); parahippocampal gyrus (PHC); insula (Ins); primary auditory cortex (1 ° Aud); orbitofrontal cortex (OFC); anterior cingulate cortex (ACC

| | LEFT | | | | RIGHT | | | |
|---|---|---|---|---|---|---|---|---|
| **Region** | x | y | z | t-score | x | y | z | t-score |
| *Limbic Areas* | | | | | | | | |
| **Insula (13)** | -40 | -23 | 2 | **4.2** | | | | |
| **Ventral ACC (24)** | | | | | 18 | -1 | 48 | **4.6** |
| **Dorsal ACC (32)** | -23 | 39 | 6 | **3.7** | 19 | 33 | 19 | **3.7** |
| **Parahippocampal Gyrus (36)** | | | | | 42 | -32 | -13 | **7.9** |
| **Ventral Tegmental Area** | 0 | -20 | -16 | **2.0** | | | | **2.0** |
| **Nucleus Accumbens** | | | | | 13 | 2 | -7 | **1.9** |
| *Frontal Cortex* | | | | | | | | |
| **Orbitofrontal Cortex (11)** | | | | | 37 | 47 | -13 | **3.1** |
| **Supplementary Motor Area (6)** | | | | | 22 | 16 | 58 | **5.0** |
| **Medial Prefrontal Cortex (10)** | | | | | 45 | 47 | -3 | **4.3** |
| **Dorsolateral Prefrontal Cortex (9)** | -18 | 36 | 20 | **3.6** | 29 | 34 | 23 | **4.0** |
| **Inferior Frontal Gyrus (47)** | | | | | 31 | -43 | -11 | **3.9** |
| **Pars Opercularis *Broca's Area* (44)** | -51 | 7 | 10 | **3.2** | | | | |
| *Temporal Cortex* | | | | | | | | |
| **Superior Temporal Gyrus (22)** | -43 | -25 | -3 | **3.4** | | | | |
| **Middle Temporal Gyrus (21)** | -59 | -7 | -7 | **3.6** | 46 | 0 | -18 | **3.2** |
| **Fusiform Gyrus (20/ 37)** | -38 | -15 | -24 | **4.6** | 40 | -8 | -22 | **7.1** |
| **Primary Auditory Cortex (41)** | | | | | 51 | -21 | 6 | **3.4** |
| *Other Areas* | | | | | | | | |
| **Primary Somatosensory Cortex (3)** | -18 | -27 | 46 | **4.6** | | | | |
| **Hypothalamus** | | | | | 9 | -8 | -10 | **3.0** |
| **Precuneus (19/ 7)** | 33 | -78 | 32 | **4.2** | 36 | -49 | 61 | **3.2** |
| **Secondary Visual Cortex (18)** | -28 | -82 | -7 | **3.2** | | | | |
| **Pulvinar Thalamus** | -17 | -32 | 3 | **3.6** | 19 | -30 | 14 | **3.5** |
| **Ventral Posterolateral Thalamus** | -21 | -19 | -3 | **3.4** | | | | |
| **Anterior Cerebellum** | -3 | -50 | -11 | **4.4** | 19 | -47 | -13 | **5.9** |
| **Posterior Cerebellum** | -17 | -44 | -32 | **5.7** | 32 | -58 | -32 | **4.8** |

**Table 3.3:** Talairach coordinates and t-score values for activations in the music condition compared to the no music condition. Coordinates are along left-right (x), anterior-posterior (y), and superior-inferior (z) represented in millimeters. After each brain region, the corresponding Brodmann area is shown in parentheses (paired t-test).

### *3.4.3. Brainstem Results*

Several brainstem regions had varying BOLD responses while a painful stimulus was applied with, or without, music as determined by region-of-interest analyses (Figure 3.5). The area of the rostroventromedial medulla (RVM) showed large activity when music was not playing ($M$= 1.4, *S.E.M.* = 0.3) compared to the small activity when music was playing ($M$= 0.6, *S.E.M.* = 0.5). Within the pons, the dorsolateral pontine tegmentum

(DLPT) area showed similar activity between conditions, with music producing slightly higher activity (*M*= 1.1, *S.E.M.* = 0.2) than no music (*M*= 0.9, *S.E.M.* = 0.3). Playing music resulted in significantly higher activity within the PAG region (*M*= 0.9, *S.E.M.* =0.4), whereas no music resulted in a smaller activity (*M*=-0.2, *S.E.M.* = 0.4).

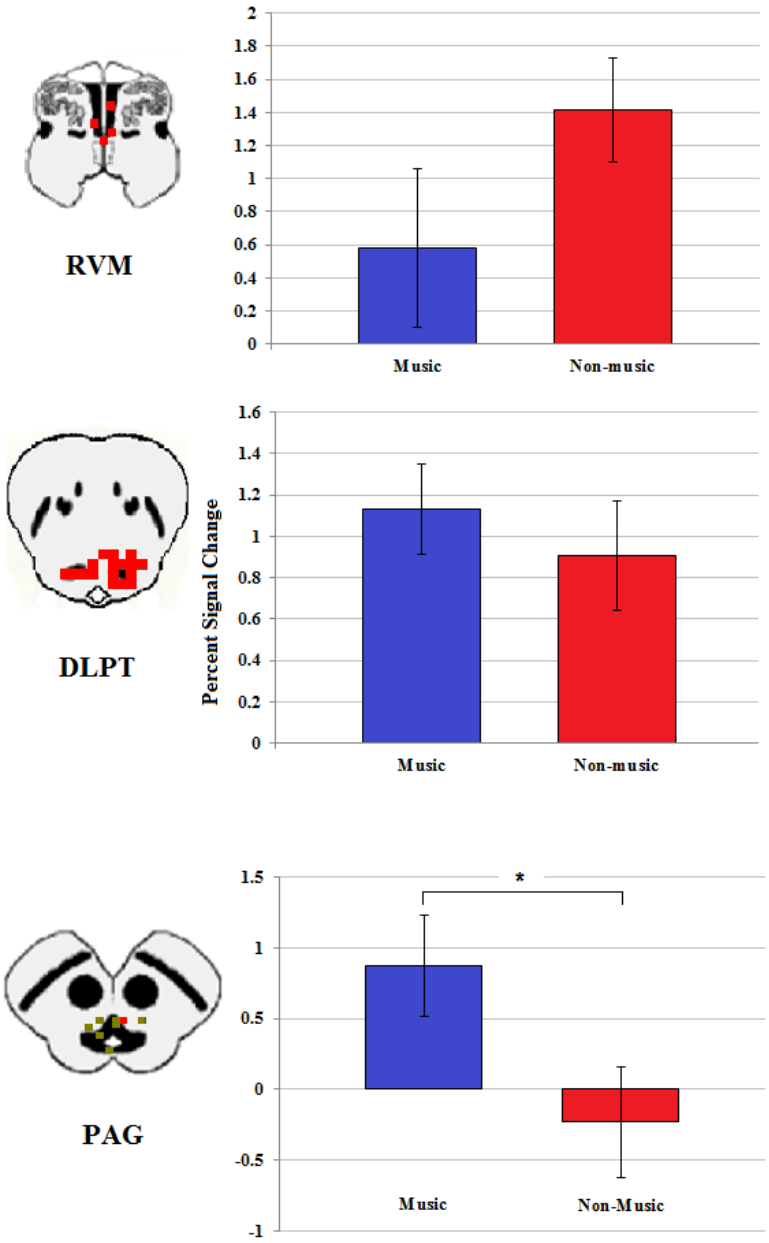


**Figure 3.5:** Magnitudes of BOLD responses within the rostral medulla (top), pons (middle), and midbrain (bottom) for music or no music conditions. Hotter colors represent the greater rostral-caudal degree of the region of interest in the vicinity of the rostral ventromedial medulla (RVM); dorsolateral pontine tegmentum (DLPT); and periaqueductal grey (PAG). *= P < 0.05

### *3.4.4 Spinal Cord Results*

As illustrated in figure 3.6, the music condition had a greater suppression in the region of the right dorsal horn of C6 (*M*= -3.4, *S.E.M.* = 1.8) than pain without music (*M*= -0.5, *S.E.M.* = 1.0). In contrast, the left ventral horn area demonstrated greater activity during the music condition (*M*= 1.4, *S.E.M.* = 0.8) than the non-music condition (*M*= 0.4, *S.E.M.* = 0.5). Summary of the brainstem and spinal cord results are found in table 3.4.

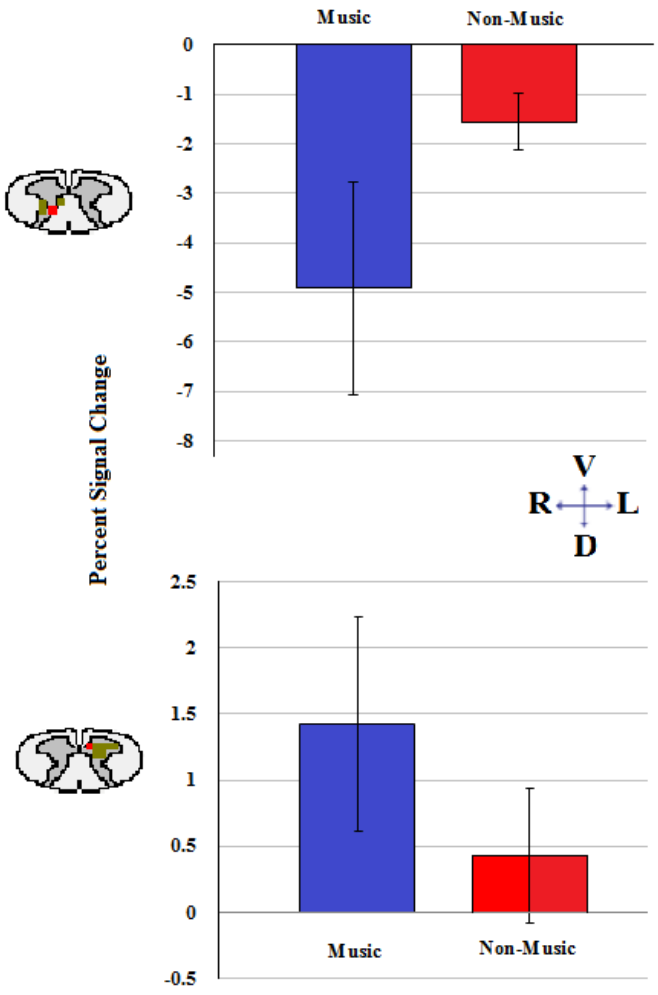


**Figure 3.6:** Magnitudes of BOLD responses within the regions of the C6 right dorsal horn (top) and left ventral horn (bottom) for pain with or without music. Hotter colors represent the greater rostral-caudal degree of the region of interest.

| Region of Interest | Music | | No Music | |
|---|---|---|---|---|
| | Mean | S.E.M. | Mean | S.E.M. |
| RVM | 0.6 | 0.5 | 1.4 | 0.3 |
| DLPT | 1.1 | 0.2 | 0.9 | 0.3 |
| PAG | -0.9 | 0.4 | -0.2 | 0.4 |
| C6 right dorsal | -3.4 | 1.8 | -0.5 | 1.0 |
| C6 left ventral | 1.4 | 0.8 | 0.4 | 0.5 |

**Table 3.4:** Overview of group results of the magnitudes of the BOLD response for regions of interest within the brainstem and spinal cord. For the music and no music condition, the mean of the percent signal change and standard error of the mean (S.E.M.) is shown within the RVM, DLPT, PAG, and C8 (n=12).

## Discussion

This is the first study to investigate the structures and mechanisms involved in music-induced analgesia within the entire central nervous system. Participants were asked to select their favorite music of any genre, and on average, participants chose music they rated as relaxed, happy, pleasant, and calm. Music shown to be the most effective at reducing pain is described as being pleasant [110], calm, and relaxing [48; 61]. Our behavioural results confirm that pain rating scores were significantly lower with music playing than without music playing, which is consistent with music-induced analgesia. Furthermore, imaging results demonstrated that the music condition was accompanied by activity in areas that process music stimuli, as well as areas of the descending pain analgesia system [86]. Because the pain stimulus remained constant within each individual, the differences detected between the music and non-music conditions can be attributed to the effect of music.

Our results demonstrate that pain administered without music elicited activity in the same brain areas shown to be consistently active in healthy participants in response to acute pain, also known as the “pain matrix” [97]. Studies show that the pain response

dependably activates the following brain regions: insula, secondary somatosensory area (SII), anterior cingulate cortex (ACC, BA 24), and bilateral thalamus. Other brain areas that have been identified in previous imaging studies of pain include the contralateral primary somatosensory cortex (SI), prefrontal cortex (PFC, BA 10), supplementary motor area (SMA, BA 6), striatum, and the cerebellum [97]. Our results support the observation that when pain is administered alone (without music), brain areas within the "pain matrix" are consistently activated. However, we also observed activity in brain areas that do not correspond with a pain response. The posterior cingulate cortex (PCC), medial temporal lobes, and precuneus also had strong BOLD changes in the no music condition, which may be explained by the initiation of the default mode network. Functional MRI studies have shown that the PCC and ventral ACC have greater BOLD responses during rest conditions than task conditions, and these responses are attributed to engagement of the default mode network [50]. Fransson and Marrelec [44] also discovered prominent functional interactions between the precuneus and medial temporal lobes to the default mode network. In the present study, during each 155 second trial, ten pain pulses were applied over a period of 30 seconds leaving over two minutes of rest at the warm adaptation temperature. As participants had no music to attend to, the default mode network may have been initiated during the rest condition and failed to disengage due to the repetitive nature of the task and study fatigue of the participant.

Comparison of the pain responses in the brain with music or without music, revealed differential activity in the limbic cortex, SI, and other brain regions involved with processing music and pain. These regions are consistent with areas of the brain previously implicated in emotion and reward circuitry that are associated with

pleasurable music listening. Such areas include the ventral tegmental area (VTA), nucleus accumbens (NAc), insula, ACC, right orbitofrontal cortex (OFC), parahippocampus, SMA, medial PFC, precuneus, thalamus, hypothalamus, and cerebellum [18; 63; 84; 87]. Therefore, our results indicate that regions prominently found during music listening were significantly activated during a contrast between the music and non-music condition. We also confirmed that areas known to participate in auditory processing of music such as the primary auditory cortex (BA 41), middle and superior temporal gyrus (BA 21/22), inferior frontal gyrus (BA 47), and Broca's area (BA 44) were activated during music listening [20; 63; 72; 74].

Apart from the activity within regions which process music, there were significant differences between the two conditions which correspond to pain modulation. The projected regions of the spinothalamic tract process the location and perception of pain. The initial region of the spinothalamic tract is the dorsal horn of the spinal cord and further projections include the medulla, PAG, contralateral ventral posterolateral (VPL) nucleus of the thalamus, contralateral insula, and contralateral S1. When the music condition was compared to the no music condition, there were differences in activity in the left insula, left VPL, as well as the left S1 corresponding to the right hand (BA 3). Bushnell et al. [23] indicated that S1 pain-related activity is highly modulated by cognitive factors such as attention. In addition, our contrast between the two conditions demonstrated activity in bilateral dorsolateral prefrontal cortex (DLPFC, BA 9), a region not found to be associated with music listening. The DLPFC is suggested to play an important role in pain reduction due to its proposed opioid sensitivity to influence supraspinal circuits [125], or by inhibiting orbitofrontal activity [73]. It has been shown

that repetitive stimulation of the DLPFC can increase pain tolerance in participants [125], and post mortem studies have shown a reduction in DLPFC gray matter density in people with chronic pain [5]. Therefore, pain modulation was demonstrated in the music condition by differences in activity within the spinothalamic tract as well as bilateral DLPFC activation compared to the no music condition.

During the music condition, the observed spinal cord and brainstem responses to the painful stimuli are consistent with descending pain modulation. The PAG is the site of origin of a descending pain-control pathway that relays to many sites in the brain and brainstem [85]. The music condition had a significantly greater increase in activity in the PAG area compared to the non-music condition. Consistent with Tracey et al. [126], the results demonstrated that increased PAG activity was concurrent with decreased pain intensity ratings.The rostral ventromedial medulla (RVM) directly inhibits neurons in the spinal cord dorsal horn via the dorsolateral funiculus [10]. Our results show activity in the RVM region corresponding with suppressions in the dorsal horn region of the sixth cervical segment (C6) to varying extents for both conditions. Numerous studies have demonstrated significant reduction of the spinal cord dorsal horn neurons to noxious stimuli when activating the descending pain analgesia system [40; 86; 114]. Suppression of dorsal horn neurons can also be produced by stimulation of the PAG [92]. According to our results the music condition demonstrated analogous activity of the descending analgesia system, as shown by the significantly greater activity of the PAG area coupled with the larger suppression in the dorsal horn region.

This study is novel as it provides evidence of the neural structures involved in music-induced analgesia, as well as characterizes neural activity involved with

descending modulation. When pain was administered while music was presented, perceived pain ratings were significantly reduced, with corresponding changes in activity in brain regions that process music and pain modulation. Brainstem and spinal cord structures showed similar activity to descending modulation, demonstrating activation of the PAG region with corresponding suppression within the dorsal horn region. Listening to pleasurable music induces dopamine release in the mesolimbic system [112], while evoking opioid signalling in the brain [47]. Subsequently, endogenous opioids may exert widespread analgesic effects by influencing several brain and brainstem regions within the descending analgesia pathway. The results of this study suggest that pleasurable music evokes opioid release which may act upon the limbic system, DLPFC, and PAG to activate the descending analgesia pathway. Subsequently, music suppressed activity in the dorsal horn of the spinal cord which resulted in reduced perceived pain ratings. However, whether music reduces pain specifically by attention or emotion, or if another mechanism is responsible, is still up for debate. Future studies may investigate the role of attention and emotion in descending modulation using brain and spinal fMRI to provide further insight into the neural underpinnings of music-induced analgesia. For the first time we have related observable changes in neural function to changes in pain perception that relate to music analgesia, which may improve the efficacy of music's widespread, clinical use.

## 4. Discussion

### *4.1 Main Conclusions*

The goal of this research was to provide insight into the neural processes involved in music-induced analgesia. There is overwhelming behavioural evidence to show that passive music listening can reduce perceived pain [26; 45; 98]. However there are no studies to date which investigate the neural structures involved in music-induced analgesia, demonstrating a major gap in the literature. Therefore, the objective of my thesis was to provide the first imaging studies on music-induced analgesia to characterise the neural response in the entire central nervous system. Pleasant music was compared to other musical stimuli and no musical stimuli in combination with heat, to determine pleasant music's unique effect on the nervous system. The two studies also probed both the sensory network and pain network to look at the similarities and differences between the two systems. Ultimately, these studies allowed us to relate observable changes in neural function to changes in pain perception in regards to music-induced analgesia.

The aim of the first study was to determine if neural activity in the brainstem and spinal cord changed in response to variations of music stimuli when applying a heat stimulus. Past studies have demonstrated that emotional and cognitive factors can influence subjective pain ratings as well as related pain activity using spinal fMRI [122]. Yet, there was no direct evidence that music could do the same. Therefore, we used different musical stimuli in combination with pleasant music, to discover that pleasant music had a unique effect on how thermal stimuli are processed in the brainstem and spinal cord. There were differential responses in the midbrain, pons, medulla, and spinal cord segment corresponding to the dermatome of stimulation when familiar classical

music (P) changed to either scrambled classical music (U), reverse classical music (R), or no music (N). The second aim of the study was to determine if the differential responses were consistent with structures involved in the descending modulation system, and the results illustrated that activity changes were evident in these areas of interest. Therefore, the first study demonstrated that spinal fMRI is sensitive enough to detect neural activity changes in response to pleasant music and thermal stimulation, and is an effective tool to study music-induced analgesia. Furthermore, pleasant music modulated thermal stimulation differently than other music stimuli or no music stimuli.

The second study investigated the pain response when participants listened to favorite music compared to no music, in the brain, brainstem, and spinal cord within a single imaging session. The results demonstrated a significant reduction in pain ratings when pain was administered with music as opposed to no music. According to our results, the pain condition alone demonstrated brain structures that are consistently activated during similar pain studies [97]. When comparing the music condition to the non-music condition, there were activations in brain regions associated with pleasant music listening, as well as descending modulation. Furthermore, the descending modulation system continued to be activated in brainstem and spinal cord structures. In comparison to the first study, using a painful stimulus induced larger activity changes in neural structures than with a thermal stimulus that is just below the pain threshold. In summary, decreased pain ratings and activation of the descending modulation system were evident in the music condition compared to the non-music condition.

### *4.2 Music Stimuli*

Many music stimuli were investigated between the two studies including pleasant music (P), unpleasant music (U), reverse music (R), favorite music, as well as no music (N). Favorite music seemed to be the most effective at reducing the pain, as pain ratings were significantly lower during favorite music than no music. Music shown in the literature to be the most effective at reducing pain is described as being pleasant [110], calm, and relaxing [48; 61]. When participants rated their favorite music selections, they described them as pleasant, calm, relaxing, and happy. Past studies have also shown that favorite music was more effective at reducing pain than non-preferred music [54]. Listening to music can allow an individual to escape into an imaginary world to provide pain relief [4], and it is possible that listening to favorite music can create stronger mental imagery than assigned music. The potential for mental imagery may explain the activations within the secondary visual cortex (BA 18) and the fusiform gyrus (BA 20/37) when listening to favorite music. In accordance with Blood and Zatorre [18], subjects listening to a self-selected music piece demonstrated larger BOLD activity within the visual cortex compared to a subject listening to an emotionally neutral control piece. Although the function of the fusiform gyrus remains unclear, research has demonstrated an increase in BOLD signal change when music was presented with an emotional picture as opposed to presenting the emotional picture without music [12]. Hence there may be strong mental imagery evoked when participants hear self-selected music, which may be more effective at reducing pain ratings. Also, the fusiform gyrus may play a role in processing auditory evoked mental imagery.

Unpleasant music and no music evoked higher discomfort ratings when compared to pleasant classical music, yet they were not significantly different. As the thermal stimulation was 0.3 °C below each individual's pain threshold the thermode emitted heat perceived as uncomfortable, as opposed to being perceived as painful. Roy et al. [110] found that warmth perception was not affected by pleasant or unpleasant music, but pain perception was. Thus, differences between emotional valence seems to significantly alter subjective pain ratings, but is not strong enough to significantly influence sensory ratings.

Pain modulation is affected by the emotional valence of music, where pain is significantly reduced while listening to pleasant but not unpleasant music [54; 96; 110]. The degree of music pleasantness is correlated with neural activity in paralimbic and neocortical brain regions involved with affective processing [19; 20]. Menon and Levitin [84] demonstrated that there was greater activation in the mesolimbic system when listening to familiar classical music rated as pleasant, compared to its scrambled counterpart rated as unpleasant. The scrambled versions of the pleasant music disrupted the musical structure or temporal coherence of the piece, which is described as its informational redundancy and expectation [46]. However, the psychoacoustic features such as pitch, loudness, and timbre between the two remained constant. Menon and Levitin [84] also demonstrated that there was no differential activation between the pleasant and unpleasant music in the primary and secondary auditory cortices, which are believed to process pitch, loudness [138], and timbre [83]. Therefore, pleasant classical music and its scrambled counterpart are well matched for psychoacoustic features but seem to differ in their rewarding and affective components of music, which make them good stimuli to use when investigating emotional valence. Our study used the same

stimuli, and results illustrated that there were differential activation increases in regions of the eighth cervical segment (C8), rostral ventromedial medulla (RVM), dorsolateral pontine tegmentum (DLPT), and periaqueductal grey (PAG) in the pleasant→unpleasant (PU) music condition. These brainstem and spinal cord regions are extensively connected to limbic and forebrain structures which process pleasure and emotion, and are known to be involved with descending modulation [86]. Hence, our pleasant music stimuli may have induced greater brain activations in the mesolimbic system [84], which resulted in smaller brainstem and cord activations in regions of the descending modulation system as compared to our unpleasant music stimuli. Previous literature has demonstrated that the emotional valence of music is processed beyond the brain [109], but this study is the first to suggest the location of the neural activity changes.

One major problem with investigating music-induced analgesia is that music listening is a highly subjective experience. When investigating regions of interest within the brainstem and cord, the error bars in both studies were comparably large which led to fewer significant differences between music conditions. Music preference is highly dependent on several factors such as individual differences, personalities [106], memory [95], and age [69]. The first study presented four classical music pieces which were previously rated as familiar and pleasant [72], however, each piece may have had a different sentimental value for each individual influenced by past memories, personality, and music preference. Thus for the second study, we asked participants to bring in their favorite music pieces due to the subjective nature of music enjoyment. However, new problems arose including different musical genres and lack of musical stimuli control across subjects, which may account for the variability in results for the second study.

Both studies used only non-musicians to avoid previous mental schemas of music, but due to the challenging nature of studying music, different confounding variables are present depending on which musical stimuli used.

### *4.3 Attention versus Emotion Debate*

It is still unclear whether music listening reduces pain specifically by evoking an emotional response or if music acts as a distracting stimulus, or whether there is an interaction between the two. Numerous studies demonstrate how listening to pleasant music activates limbic and forebrain structures [18; 19; 84], which results in analgesic opioid release [47]. When we administered pain with favorite music, there were increased activations in limbic and forebrain structures such as the NAc, VTA, hypothalamus, ventral anterior cingulate cortex (ACC, BA 24), orbitofrontal cortex (OFC), and hippocampus which coincide with the emotional rationale behind music-induced analgesia.

Conversely, there is also sufficient evidence to show that neural activity in regions that process pain, such as the primary somatosensory cortex (SI) and the dorsal gray matter (dGM) of the spinal cord, are reduced when attending toward a distracting stimulus, and are heightened when attending to the painful stimulus [8; 22; 23]. Attention is proposed to activate opiate-sensitive descending modulation pathways [135], and/ or decreases pain perception via the spinothalamic pain pathway [8]. Valet et al. [129] found that a distracting task reduced pain perception, and was associated with an increase in activity within dorsal ACC (BA 32), OFC, posterior thalamus, and PAG. In accordance with the distraction literature, our results also demonstrated increased activations within

the OFC, posterior thalamus, and PAG with a suppression of activity in SI and dGM during the music condition compared to the no music condition.

However, the dorsal ACC in our results had dissimilar activity when compared to the emotion and distraction literature. Our results illustrated that pleasant music and pain did not increase activation of the dorsal ACC, however other studies investigating pleasant music listening demonstrate an increase in activations in the dorsal ACC [18; 87]. In addition, the pain condition without music demonstrated greater activation within the dorsal ACC compared to with music, while previous pain imaging studies demonstrated smaller activations in the dorsal ACC during pain conditions without distraction compared to with distraction [129]. This opposition of activity suggests that the dorsal ACC may play a role in pain modulation involved in music-analgesia.

Separate areas of the ACC are suggested to be selectively activated for the attentional versus the emotional components of pain [131]. The ACC seems to be involved with the endogenous activation of the opioid system to regulate the sensory as well as the affective dimensions of pain [140]. The ventral ACC is consistently activated in pain studies, whereas the dorsal ACC is only occasionally activated [97], which suggests a possible functional dissociation between the two. Rainville [105] suggests that the consistency of ventral ACC activation is due to the primary affective value of a stimulus, also known as the primary biological significance of the pain, which gives the ventral ACC priority when engaging any type of pain responses. The dorsal ACC is suggested to reflect the secondary affective value attributed to stimuli, which would explain its presence in cognitive studies. Therefore, it seems that the ventral ACC is

present when pain is administered regardless of music's presence, whereas the dorsal ACC is influenced by whether or not music is present.

It is difficult to isolate emotional and attentional influences involved in music as it is impossible for the participants to fully concentrate on the music without being emotionally engaged by it. Conversely, it is unreasonable to assume that participants can be fully immersed in the emotional content of the music without attending to it. Also, the participant's attention can unknowingly waver from attending to the thermode to paying attention to the music, creating further complications. Future pain studies using spinal fMRI can investigate attention and emotion with different visual or auditory stimuli, and perhaps identify which specific pathways are involved with music-induced analgesia. Also, future studies may consider investigating the functional dissociation between the dorsal and ventral ACC in emotion versus cognition to provide insight on music-induced analgesia's mechanism of action.

### *4.4 Sensory versus Pain processing*

There are many similarities between sensory and pain processing of thermal stimuli. Studies have shown that nociceptive fibers do not show responses to thermal stimuli less than 45 ° C [68]. However, other evidence suggests that nociceptive fibers can be activated at 40- 42 ° C in primates [127], non-human primates [82], and humans [113]. Our first study used a thermal stimulus that was 0.3 ° C below each individual's heat-pain threshold, and participants gave subjective ratings of discomfort rather than pain. However, the average thermal stimulation temperature across the participants was 45.6 ° C, with a range from 44 - 47.8 ° C. Therefore, even though subjective ratings were

not painful, 14 out of the 18 participants had thermal stimulation of at least 45 ° C, which activates nociceptors. If nociceptors can be activated at 40- 42° C, all participants would have received stimuli which activated nociceptive fibers, as the lowest stimulation temperature was 44 ° C. Becerra et al. [13] used brain fMRI to compare activations between thermal stimuli at 41 ° C and 46 ° C. They found that all the same brain regions were significantly activated for both the 41 ° C and 46 ° C conditions. The 46 ° C stimuli showed a greater response in all brain regions compared to the 41 ° C stimuli, except in the somatosensory regions (SI and thalamus) which were the same. Also, Cahill and Stroman [24] used spinal fMRI to demonstrate that activity in the brainstem and spinal cord was greater during 46 ° C thermal stimulation than 42 ° C stimulation, and found the same neural regions were significantly activated for both temperatures. Therefore it seems that warm and painful thermal stimuli are processed similarly in the central nervous system, and that subjective pain ratings may not be indicative of nociceptor activation.

Both studies compared pleasant music versus non-music when applying a thermal stimulus, and produced similar activations within the brainstem and spinal cord. Results from both studies showed similar activity within the anatomical proximity of the dermatome of stimulation, RVM, and DLPT, with pain demonstrating a greater response (in percent signal change) compared to discomfort. Similar to Cahill and Stroman [24], both pain and discomfort activated the exact same brainstem and spinal cord regions, with pain demonstrating a larger response than discomfort. As the majority of participants had a thermal stimulation temperature sufficient to activate nociceptors, this may explain the similar response between brainstem and cord regions. However, there

was opposite activity within regions of the PAG for pain compared to discomfort. Activity within the PAG area was significantly greater when pain was applied with pleasant music than without music, while the PAG region demonstrated opposite activation during the discomfort study. The PAG region may reflect the subjective ratings given for each study. The PAG is directly influenced by forebrain and limbic inputs, and perhaps whether the subjective ratings were in the sensory or pain ranges affected how the PAG was activated. Thus, pain and discomfort demonstrate similar activity in the dermatome of stimulation, RVM, and DLPT when comparing pleasant music to non-music, but PAG activity may reflect the perception of the thermal stimulus.

### *4.5 The Mesolimbic System*

Music is a rewarding stimulus mediated by dopaminergic activity in the mesolimbic system [84; 111]. Previous imaging studies have demonstrated how music elicits highly pleasurable emotional responses, and activates mesolimbic and prefrontal circuits in the brain [18-20]. The mesolimbic system consists of several regions, namely the caudate nucleus and the nucleus accumbens (NAc). The NAc is involved in dopamine release from the ventral tegmental area (VTA), and also has extensive connections to the limbic system, including the amygdala, hippocampus, and hypothalamus (Figure 4.1) [52]. The mesolimbic system also has direct connections with the insula and anterior cingulate cortex (ACC) [52], which are involved in emotion processing. Brain areas in the frontal cortex are important for processing and appreciating rewarding stimuli, including the orbitofrontal cortex (OFC) and medial prefrontal cortex (PFC). There is a strong interaction between these mesocortical regions and the mesolimbic system during pleasant music listening, which suggests a functional link between the “cognitive” and

"affective" components involved with music listening [84]. Furthermore, interactions between the NAc and auditory cortices can reflect the rewarding value of music [112]. Recently, Salimpoor et al. [111] used positron emission tomography to demonstrate the time course of dopamine release when listening to pleasurable music. They found that the caudate was more involved with the anticipation of a peak emotional response, while the NAc was more involved with the peak response. In our second study, when participants listened to their favorite music while receiving a painful stimulus, there was activity in the right NAc as well as the right caudate nucleus. In addition, there was activation of the insula, medial PFC, OFC, amygdala, hypothalamus, hippocampus, and VTA which all have direct connections with the mesolimbic system. These results confirm findings from previous studies, and suggest that dopamine release in the mesolimbic and mesocortical circuits is associated with the rewarding nature of listening to pleasurable music.

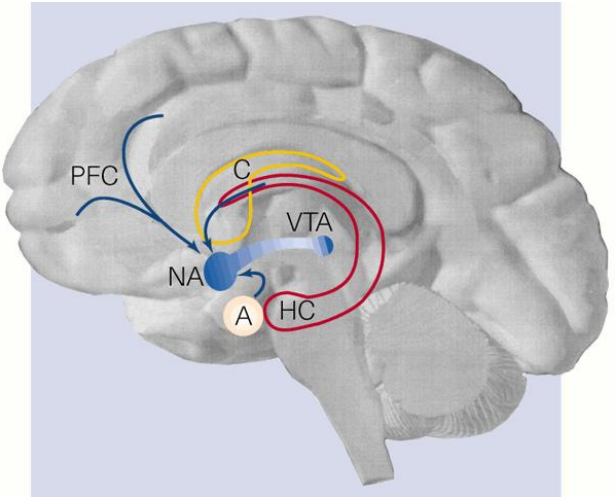


**Figure 4.1**: Dopaminergic pathways of the mesocorticolimbic system; nucleus accumbens (NA); ventral tegmental area (VTA); caudate (C); amygdala (A); prefrontal cortex (PFC). Reprinted by permission from Macmillan Publishers Ltd: Nature [128], 1999.

### *4.6 Opioid-sensitive Descending Pain Modulation*

The mesolimbic system plays an important role in reward-induced analgesia, especially the NAc and VTA [38]. When processing rewarding stimuli, dopamine is released from the VTA with an associated opioid transmission in the NAc [58]. Microinjection of opioids directly into the NAc has been shown to produce antinoception, while microinjection of an opioid antagonist into the NAc attenuates the antinociceptive effect of systemically administered morphine [34]. Furthermore, injecting morphine or cocaine into the mesolimbic system produces both reward and analgesia [2; 3]. Listening to pleasurable music induces dopamine release in the mesolimbic system [112], while evoking opioid signalling in the brain [47]. Long term music listening can even reduce medical opioid requirements of patient populations [104]. There is abundant evidence that illustrates opioid and dopamine release in processing pain and pleasure [70], and dopamine release can influence opioid levels [60; 108]. Opioids induce pleasure and analgesia, and have abundant receptors in the PAG, RVM, ACC, and dorsolateral prefrontal cortex (DLPFC) [41; 125; 132]. These regions are found in the descending pain modulation pathway, and the PAG-RVM connections to the brain act to suppress noxious information in the dorsal horn of the spinal cord [133].

When contrasting pain conditions with and without music, there were significant differences in brain activations associated with ascending pain pathways as well as descending pain modulation pathways. The ascending spinothalamic tract processes the location and perception of pain, which starts in the ipsilateral dorsal horn and projects to the contralateral ventral horn, medulla, PAG, contralateral insula, contralateral ventral posterolateral (VPL) thalamus, and the postcentral gyrus (SI). In our second study we

applied noxious heat to the cervical segment 6 (C6), corresponding to the right hand. When comparing pain administered with music to without music, there were significant differences in the right dorsal horn of C6, left ventral horn of C6, medulla, PAG, left insula, left VPL, and left SI corresponding to the right hand. Therefore, our results showed activity changes in all of the structures found in the ascending spinothalamic pathway when comparing pain given with or without music.

Comparisons between music and non-music pain conditions also demonstrated activations in structures found in the opioid-sensitive descending pain analgesia pathway. This pathway can be activated by opioid transmission in limbic areas such as the ACC and amygdala, as well as frontal cortical areas such as the OFC and DLPFC [38]. As shown in Figure 1.3, these brain areas project to the PAG and RVM to reduce nociceptive information in the dorsal horn. Our results contrasting the music to non-music condition demonstrated differential activity in bilateral ACC, right OFC, and bilateral DLPFC. The RVM had a greater activation during the non-music condition while the PAG had a significantly greater activation in the music condition. The activity of the dorsal horn reflects the input from the periphery as well as input from the brainstem, and the dorsal horn had a greater suppression of activity during the music condition compared to the non-music condition. The literature demonstrates how PAG activation corresponds with lower subjective pain ratings and a suppression in the dorsal horn when activating the descending pain analgesia pathway [40; 86; 92; 114]. Hence, our results demonstrated neural activity indicative of descending pain modulation. However, when contrasting music and non-music pain conditions, there was no significant detection of amygdala differences. As the amygdala is involved in emotion, pain processing, as well as its pain

modulation, this could explain why there were no large differences found between conditions. Also, a number of neuroimaging pain studies could not detect signal changes in the amygdala in response to pain or specific pain states [91], which may be due to the challenges of functional imaging of pain [31].

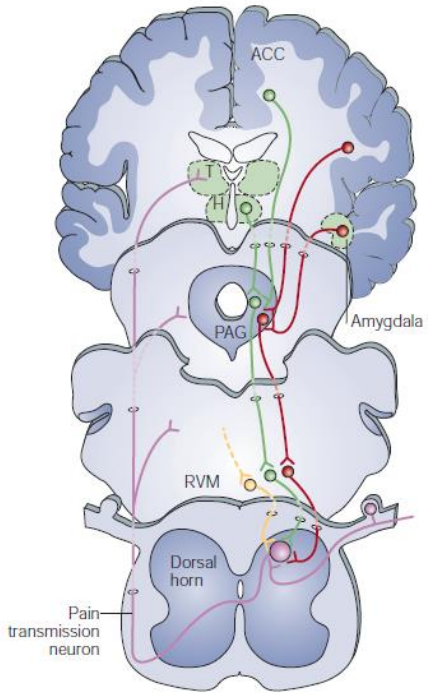


**Figure 1.3**: Outline of opioid sensitive pain-modulating circuit; anterior cingulate cortex (ACC), thalamus (T), hypothalamus, frontal cortex, periaqueductal grey (PAG), and rostral ventromedial medulla (RVM). Reprinted by permission from Macmillan Publishers Ltd: Nature [38], 2004.

### *4.7 Proposed Music-induced Analgesia Mechanism*

Based on our investigation and previous work in the literature, music-induced analgesia seems to work by evoking a rewarding response in the brain that activates the descending analgesia system. Music listening is a highly pleasurable experience and can have a large affective impact on an individual. Therefore, music is processed in various areas distributed throughout the brain including limbic areas, cortical regions, and reward-related mesolimbic circuits. Dopamine mediates the mesocortical and mesolimbic circuits to possibly trigger opioid release in the NAc during music listening.

Subsequently, endogenous opioids may exert widespread analgesic effects by influencing several brain and brainstem regions within the descending analgesia pathway. Information from limbic and cortical areas is received by the opioid-sensitive PAG, which activates serotonin-containing cells in the RVM [11]. Direct projections from the RVM to the dorsal horn, via the opioid-sensitive dorsolateral funiculus, are activated to inhibit dorsal horn activity. As nociceptive information is suppressed in the dorsal horn, subjective ratings of pain are reduced.

### *4.8 Significance of Work*

Chronic pain is a major public health problem that has significant consequences for affected individuals, the work force, and the health care system. According to Statistics Canada, about 1 in 10 Canadians between the ages of 12-44 experience chronic pain, while chronic pain affects 25-40% for those over 60. Currently, it is estimated that the cost of chronic pain in the United States is over $150 billion. The Canadian population expects a large increase in the number of seniors in the next 30 years, making it daunting problem for both individuals and society. Chronic pain patients commonly experience depression, sleep disturbance, and decreased overall physical and mental functioning which have significant effects on their occupation, personality, and social relationships. Most patients are prescribed opioid analgesics or non-steroidal anti-inflammatory drugs (NSAIDS) to manage their pain. However, chronic pain cannot be cured which forces patients to seek out alternative pain management therapies [6]. Over the past ten years, the use of alternative therapy has increased over 46% [36].

Using music to alleviate pain was first documented by the Greek civilization in circa 600 AD and currently, it is used with post-surgical patients, cancer patients,

labouring mothers, etc. worldwide [16; 48; 99]. Music is a highly effective source for pain management because it is cost-effective, easy to administer, free of side effects, non-invasive, and does not negatively interact with other medicine [26]. Patients subscribing to music-induced analgesia treatment have significant reductions in their opioid medications compared to control patients [26; 104]. This is important due to the major concern of opioid analgesic abuse in chronic pain patients, and offers another healthy strategy to treat pain [28]. In addition, most patients with chronic pain have comorbid depression symptoms. Research has shown how emotional music induces feeling of pleasure and dopamine release, which activates all major limbic and paralimbic brain structures. Studies have also demonstrated that music reduces depression in people with acute and chronic pain and generally enhances their mood [26]. Overall, music-induced analgesia is an efficacious treatment option for those suffering from chronic pain to reduce pain scores, improve mood scores, and reduce necessary medication, which all lead to a decreased cost on the health care system.

### *4.9 Final Conclusions*

Music engages the unique elements of the individual to provide a wealth of benefits such as improved well-being and pain relief. Today, there is ample evidence to support music's effectiveness in pain reduction over a wide diversity of clinical populations. However, the neural underpinnings of music-induced analgesia have not been fully theorized until now. This research describes the neural structures which process pain and music to provide pain reduction. Brain, brainstem, and spinal cord regions showed activity in response to listening to pleasurable music and descending pain modulation, with a corresponding decrease in subjective pain ratings. This is the first

imaging study to characterize the neural response to pain in the entire central nervous system, and to assess how these responses are modulated by music. Most studies examining the neural signature of pain in humans have focused on the brain, and have predominantly used animal models in the brainstem and spinal cord. However, the pain experience is complex and involves sensory, cognitive, and emotional components which depend on bi-directional communication with the cord. As such, brain fMRI in combination with spinal fMRI are appropriate means to non-invasively study pain processing in humans. Investigating descending pain analgesia is important to understand pain processing and how it can be mitigated. Future studies could determine the role of emotion and attention in descending analgesia to provide further insight into the mechanisms of music-induced analgesia, which may enhance the efficiency of the techniques for music-induced analgesia's widespread clinical use.

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## Appendix A: Classical Music Selection Chapter 2

| Composer | Title |
|---|---|
| Ludwig van Beethoven | Symphony no. 9 (Ode to Joy) |
| Ludwig van Beethoven | Symphony no. 5 |
| Johann Strauss II | The Blue Danube Waltz |
| Wolfgang Amadeus Mozart | Eine Kleine Nachtmusick |

## Appendix B: Participants Music Selection Chapter 3

| Composer/Artist | Title | Genre |
|---|---|---|
| Coldplay | Fix You | Alternative Rock |
| Cage | Depart from Me | Rap Rock |
| The Doors | The End | Raga Rock |
| Killswitch Engage | My Last Serenade | Metalcore |
| Slip Knot | Bloodstone Mix | Metalcore |
| Metric | Too Little Too Late | Indie Rock |
| The Lumineers | Stubborn Love | Indie Folk |
| Queens of the Stone Age | Make it wit chu | Alternative Metal |
| Hot Chip | The Warning | Electronic Indie Pop |
| Arctic Monkeys | If you were there, beware | Indie Rock |
| Yeah Yeah Yeahs | The Sweets | Indie Rock |
| Taylor Swift | State of Grace | Country |
| Lady Antebellum | Cold as Stone | Country |
| Carrie Underwood | Thank God for Hometowns | Country |
| Keith Urban | Stupid Boy | Country |
| Keith Urban | Making Memories of Us | Country |
| Enrique Ingelsias | I Like How It Feels | Hip Hop |
| Kelly Clarkson | What Doesn't Kill You | Pop Rock |
| LMFAO | Champagne Showers | Electronic Dance |
| Maroon 5 | Payphone | Pop Rock |
| Nicki Minaj | Starships | Dance |
| Rihanna | Diamonds | Rhythm & Blues |
| Ellie Goulding | Lights | Indie pop |
| Bruno Mars | Locked out of Heaven | Reggae Rock |
| Maroon 5 | One more Night | Pop Rock |
| David Guetta | Titanium | Pop, House |
| David Guetta | She Wolf | Electronic Dance |
| Florence & the Machine | Breath of Life | Baroque Pop |
| St. Lucia | All Eyes on You | Pop |
| Florence & the Machine | Cosmic Love | Baroque Pop |
| Taylor Swift | Jump then Fall | Country |
| Train | Hey Soul Sister | Pop Rock |
| Train | How to Save a Life | Pop Rock |
| James Blunt | Tears and Rain | Soft Rock |
| U2 | With or Without You | Rock |
| Joshua Radin | The Fear You Won't Fall | Acoustic folk |
| John Mayer | Gravity | Blues |
| The Postal Service | Such Great Heights | Indie Pop |
| Ed Sheeran | Give Me Love | Acoustic |
| The Beatles | Golden Slumbers | Rock |
| Hanson | Strong Enough to Break | Pop |
| Coldplay | Lost | Alternative Rock |
| Wintersleep | Weighty Ghost | Indie Rock |
| The Fray | Happiness | Rock |
| Hanson | This Time Around | Pop |
| Carrie Underwood | Cowboy Casanova | Country |
| Uncle Kracker | Smile | Rock |
| Johnny Reid | Let's Go Higher | Country |
| Elton John | Benny and the Jets | Rock |
| Taylor Swift | Forever and Always | Country |
| Taylor Swift | Sparks Fly | Country |
| Marianas Trench | Desperate Measures | Rock |
| Adele | One and Only | Gospel |
| Ed Sheeran | Kiss me | Folk |

## Appendix C: Tailarach Coordinates for Table 3.2

| | Music | | Non-music | |
|---|---|---|---|---|
| **Limbic Areas** | **Left x, y, z** | **Right x, y, z** | **Left x, y, z** | **Right x, y, z** |
| **Insula (13)** | -38, -21, 10 | 41, 10, 0 | -44, -11, 6 | 40, -1, -11 |
| **Nucleus Accumbens** | | 7, 16, -4 | | |
| **Amygdala** | -7, -5, -10 | | | |
| **Ventral Anterior Cingulate Cortex (24)** | -9, -5, 49 | 5, 26, -6 | -6, 27, 8 | 4, -8, 22 |
| **Dorsal Anterior Cingulate Cortex (32)** | | | -13, 22, 45 | 19, 43, -9 |
| **Ventral Posterior Cingulate Cortex (23)** | | | | 6, -25, 20 |
| **Hippocampus** | -31, -16, -19 | 13, -14, -17 | | |
| **Parahippocampal (34)** | | | -12, -14, -16 | 11, -4,-14 |
| | | 13, -15, -17 | | |
| **Frontal Cortex** | | | | |
| **Inferior Frontal Gyrus (47)** | -43, 34, -4 | 17, 22, -10 | -18, 21, -12 | |
| **Dorsolateral Prefrontal Cortex (9)** | -10, 49, 34 | | -25, 29, 23 | |
| **Medial Prefrontal Cortex (8)** | -15, 35, 42 | 36, 15, 52 | | 11, 46, 50 |
| **Orbitofrontal Cortex (11)** | | 23, 29, -12 | | |
| **Pars Opercularis *Broca's Area* (44)** | | | | 51, 3, 8 |
| **Anterior Prefrontal Cortex (10)** | -20, 42, 20 | 41, 47, -5 | -24, 40, 19 | 41, 39, 1 |
| **Pre-motor and Supplementary Motor Cortex (6)** | -11, 27, 54 | 47, -7, 7 | -20, 20, 61 | |
| **Midbrain** | | | | |
| **Caudate** | | 9, 16, -7 | -5, 0, 11 | 9, -1, 20 |
| **Global Pallidus** | | | -18, 1, -2 | |
| **Caudate Tail** | | | -23, -41, 12 | |
| **Putamen** | | | -29, 0, 1 | 23, 0, -5 |
| **Thalamus** | 0, -14, 20 | | -3, -26, 17 | 3, -2, 3 |
| **Hypothalamus** | -8, -2, -11 | 5, -7, -11 | -2, -10, -5 | |
| **Temporal Cortex** | | | | |
| **Fusiform Gyrus (20)** | -50, -30, -15 | | | 53, -32, -14 |
| **Middle Temporal Gyrus (21)** | | 42, -2, -11 | -42, -8, -7 | |
| ***Superior Temporal Gyrus* (22)** | -49, -4, 5 | | | |
| **Temporopolar Area (38)** | -43, 5, -10 | | | 40, 3, -15 |
| **Other areas** | | | | |
| **Supramarginal Gyrus (40)** | -48, -50, 53 | 41, 47, -5 | | 66, -38, 23 |
| **Primary Somatosensory Cortex (3)** | | | -60, -17, 29 | |
| **Precuneus (19)** | | | -38, -76, 36 | |
| **Claustrum** | | | -29, 0, 20 | |
| **Posterior Cerebellum** | -27, -52, -34 | 20, -65, -30 | -30, -74, -32 | 40, 39, 1 |
| **Anterior Cerebellum** | -3, -48, -7 | 19, -47, -16 | -3, -87, -26 | 15, -25, -13 |

## Appendix D: Charles D. Spielberger's State-trait Anxiety Inventory



**SELF-EVALUATION QUESTIONNAIRE** STAI Form Y-1

**Please provide the following information:**

Name_____Date_____S_____

Age_____ Gender (*Circle*) **M** **F** T_____

**DIRECTIONS:**

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel *right* now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

| | NOT AT ALL | SOMEWHAT | MODERATELY SO | VERY MUCH SO |
|---|---|---|---|---|
| 1. I feel calm | 1 | 2 | 3 | 4 |
| 2. I feel secure | 1 | 2 | 3 | 4 |
| 3. I am tense | 1 | 2 | 3 | 4 |
| 4. I feel strained | 1 | 2 | 3 | 4 |
| 5. I feel at ease | 1 | 2 | 3 | 4 |
| 6. I feel upset | 1 | 2 | 3 | 4 |
| 7. I am presently worrying over possible misfortunes | 1 | 2 | 3 | 4 |
| 8. I feel satisfied | 1 | 2 | 3 | 4 |
| 9. I feel frightened | 1 | 2 | 3 | 4 |
| 10. I feel comfortable | 1 | 2 | 3 | 4 |
| 11. I feel self-confident | 1 | 2 | 3 | 4 |
| 12. I feel nervous | 1 | 2 | 3 | 4 |
| 13. I am jittery | 1 | 2 | 3 | 4 |
| 14. I feel indecisive | 1 | 2 | 3 | 4 |
| 15. I am relaxed | 1 | 2 | 3 | 4 |
| 16. I feel content | 1 | 2 | 3 | 4 |
| 17. I am worried | 1 | 2 | 3 | 4 |
| 18. I feel confused | 1 | 2 | 3 | 4 |
| 19. I feel steady | 1 | 2 | 3 | 4 |
| 20. I feel pleasant | 1 | 2 | 3 | 4 |

## SELF-EVALUATION QUESTIONNAIRE

**STAI Form Y-2**

Name_____ Date_____

### DIRECTIONS

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you *generally* feel.

| | ALMOST NEVER | SOMETIMES | OFTEN | ALMOST ALWAYS |
|---|---|---|---|---|
| 21. I feel pleasant | 1 | 2 | 3 | 4 |
| 22. I feel nervous and restless | 1 | 2 | 3 | 4 |
| 23. I feel satisfied with myself | 1 | 2 | 3 | 4 |
| 24. I wish I could be as happy as others seem to be | 1 | 2 | 3 | 4 |
| 25. I feel like a failure | 1 | 2 | 3 | 4 |
| 26. I feel rested | 1 | 2 | 3 | 4 |
| 27. I am "calm, cool, and collected" | 1 | 2 | 3 | 4 |
| 28. I feel that difficulties are piling up so that I cannot overcome them | 1 | 2 | 3 | 4 |
| 29. I worry too much over something that really doesn't matter | 1 | 2 | 3 | 4 |
| 30. I am happy | 1 | 2 | 3 | 4 |
| 31. I have disturbing thoughts | 1 | 2 | 3 | 4 |
| 32. I lack self-confidence | 1 | 2 | 3 | 4 |
| 33. I feel secure | 1 | 2 | 3 | 4 |
| 34. I make decisions easily | 1 | 2 | 3 | 4 |
| 35. I feel inadequate | 1 | 2 | 3 | 4 |
| 36. I am content | 1 | 2 | 3 | 4 |
| 37. Some unimportant thought runs through my mind and bothers me | 1 | 2 | 3 | 4 |
| 38. I take disappointments so keenly that I can't put them out of my mind | 1 | 2 | 3 | 4 |
| 39. I am a steady person | 1 | 2 | 3 | 4 |
| 40. I get in a state of tension or turmoil as I think over my recent concerns and interests | 1 | 2 | 3 | 4 |

## Appendix E: Crowne-Marlowe Social Desirability Scale

### Social Desirability Scale

By Douglas P Crowne
and David Marlowe

Listed below are a number of statements concerning personal attitudes and traits. Read each item and decide whether the statement is true or false as it pertains to your personally. It's best to go with your first judgment and not spend too long mulling over any one question.

**1. Before voting I thoroughly investigate the qualifications of all the candidates.**

a. ○ True
b. ○ False

**2. I never hesitate to go out of my way to help someone in trouble.**

a. ○ True
b. ○ False

**3. It is sometimes hard for me to go on with my work if I am not encouraged.**

a. ○ True
b. ○ False

**4. I have never intensely disliked anyone.**

a. ○ True
b. ○ False

**5. On occasions I have had doubts about my ability to succeed in life.**

a. ○ True
b. ○ False

**6. I sometimes feel resentful when I don't get my way.**

a. ○ True
b. ○ False

**7. I am always careful about my manner of dress.**

a. ○ True

b. ○ False

**8. My table manners at home are as good as when I eat out in a restaurant.**

a. ○ True

b. ○ False

**9. If I could get into a movie without paying and be sure I was not seen I would probably do it.**

a. ○ True

b. ○ False

**10. On a few occasions, I have given up something because I thought too little of my ability.**

a. ○ True

b. ○ False

**11. I like to gossip at times.**

a. ○ True

b. ○ False

**12. There have been times when I felt like rebelling against people in authority even though I knew they were right.**

a. ○ True

b. ○ False

**13. No matter who I'm talking to, I'm always a good listener.**

a. ○ True

b. ○ False

**14. I can remember "playing sick" to get out of something.**

a. ○ True

b. ○ False

**15. There have been occasions when I have taken advantage of someone.**

a. ○ True

b. ○ False

**16. I'm always willing to admit it when I make a mistake.**

a. ○ True

b. ○ False

**17. I always try to practice what I preach.**

a. ○ True

b. ○ False

**18. I don't find it particularly difficult to get along with loudmouthed, obnoxious people.**

a. ○ True

b. ○ False

**19. I sometimes try to get even rather than forgive and forget.**

a. ○ True

b. ○ False

**20. When I don't know something I don't mind at all admitting it.**

a. ○ True

b. ○ False

**21. I am always courteous, even to people who are disagreeable.**

a. ○ True

b. ○ False

**22. At times I have really insisted on having things my own way.**

a. ○ True

b. ○ False

**23. There have been occasions when I felt like smashing things.**

a. ○ True

b. ○ False

**24. I would never think of letting someone else be punished for my wrong-doings.**

a. ○ True

b. ○ False

**25. I never resent being asked to return a favor.**

a. ○ True

b. ○ False

**26. I have never been irked when people expressed ideas very different from my own.**

a. ○ True

b. ○ False

**27. I never make a long trip without checking the safety of my car.**

a. ○ True

b. ○ False

**28. There have been times when I was quite jealous of the good fortune of others.**

a. ○ True

b. ○ False

**29. I have almost never felt the urge to tell someone off.**

a. ○ True

b. ○ False

**30. I am sometimes irritated by people who ask favors of me.**

a. ○ True

b. ○ False

**31. I have never felt that I was punished without cause.**

a. ○ True

b. ○ False

**32. I sometimes think when people have a misfortune they only got what they deserved.**

# Appendix F: Beck Depression Inventory

Roche

V 0477

**Beck Depression Inventory**

CRTN: ____ CRF number: ____ Page 14 patient inits: ____

**Baseline**

BDI-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

**Instructions:** This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

**1. Sadness**

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

**2. Pessimism**

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

**3. Past Failure**

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

**4. Loss of Pleasure**

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

**5. Guilty Feelings**

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

**6. Punishment Feelings**

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

**7. Self-Dislike**

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

**8. Self-Criticalness**

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

**9. Suicidal Thoughts or Wishes**

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

**10. Crying**

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

Subtotal Page 1

Continued on Back

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**11. Agitation**

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

**12. Loss of Interest**

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

**13. Indecisiveness**

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

**14. Worthlessness**

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

**15. Loss of Energy**

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

**16. Changes in Sleeping Pattern**

0 I have not experienced any change in my sleeping pattern.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1–2 hours early and can't get back to sleep.

**17. Irritability**

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

**18. Changes in Appetite**

0 I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than before.
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

**19. Concentration Difficulty**

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

**20. Tiredness or Fatigue**

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

**21. Loss of Interest in Sex**

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

3 4 5 6 7 8 9 10 11 12 A B C D E

_____ Subtotal Page 2
_____ Subtotal Page 1
_____ Total Score

NR15645

## Appendix G: Pain Catastrophizing Scale



**PCS-EN**

Client No.: _____ Age: _____ Sex: M(__) F(__) Date: _____

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

**0** – not at all **1** – to a slight degree **2** – to a moderate degree **3** – to a great degree **4** – all the time

***When I'm in pain ...***

1. ☐ I worry all the time about whether the pain will end.
2. ☐ **I feel I can't go on.**
3. ☐ **It's terrible and I think it's never going to get any better.**
4. ☐ **It's awful and I feel that it overwhelms me.**
5. ☐ **I feel I can't stand it anymore.**
6. ☐ I become afraid that the pain will get worse.
7. ☐ I keep thinking of other painful events.
8. ☐ I anxiously want the pain to go away.
9. ☐ **I can't seem to keep it out of my mind.**
10. ☐ I keep thinking about how much it hurts.
11. ☐ I keep thinking about how badly I want the pain to stop.
12. ☐ **There's nothing I can do to reduce the intensity of the pain.**
13. ☐ I wonder whether something serious may happen.

***...Total***

Updated 11/11

## Appendix H: MRI Safety Checklist

# Safety Screening Questionnaire for Studies involving Functional Magnetic Resonance Imaging:

**This must be completed before an MRI session is scheduled.**
Weight _____
Height _____
Are you in generally good health? _____

Do you consider yourself a musician? _____
(If "yes") How long have you played that instrument and/or received instruction? _____
Which hand do you write with? _____

Do you have a history of depression or anxiety or panic attacks? _____

Is English your first language? _____

Are you claustrophobic? _____
Are you a smoker? _____

Have you ever hand any injury to your spine or spinal cord? _____
Have you ever had any injury to your brain? _____

Are you currently taking any prescription medication(s)? (if "yes", please list)
_____

Do you have any implanted medical devices or any foreign material in your body? For example: pacemaker, neurostimulator, stent, artificial valve, cosmetic implants, vascular clips, dentures, artificial limb, bullet or shrapnel, object from construction accident, etc? (if "yes", please list) _____

Do you have, or had in the past, any neurological conditions?
_____

Do you have any history of seizures or panic attacks? _____

Do you have any history of cardiac-related problems such as heart disease, angina, fainting, dizziness, etc? _____

Have you ever had any surgery? (if "yes", please list) _____

Do you have any body piercing/jewellery that cannot be removed for the MRI scanning?
_____

Do you have any tattoos? _____

**Appendix I: Checklist for Participation in Study 2**

# Checklist for participation

## To prepare for participation

*Please attempt to follow the listed requests:*

- ❑ Avoided alcohol 12h prior to participating
  - ❑ If not _____
- ❑ Avoided caffeine 12h prior to participating
  - ❑ If not _____
- ❑ Avoided any recreational drug use
  - ❑ If not _____
- ❑ Ate proper meals at regular meal times
  - ❑ If not _____

## Please indicate if any of the following applies to you

### Exclusion

- ❑ Smoker
- ❑ In chronic pain
- ❑ Injured in any way
- ❑ Have a history of depression or anxiety or panic attacks

### Inclusion

- ❑ Female
- ❑ Age 18-48
- ❑ In the luteal (last 14 days) of the menstrual cycle at the time of study (best estimate)
  - ❑ Date of the end of the previous period _____