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Does temporarily altering visual perception of limb size have a modulatory effect on deep-tissue pain? A repeated-measures within-subjects randomised study.

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Abstract

Previous research has suggested that looking at a painful body part has an analgesic effect on experimental pain. Furthermore, it has been demonstrated that magnifying the size of the viewed part has a greater analgesic effect, while minifying the perceived size of the body part reduces the analgesia. These studies involved the application of a noxious stimulus to the skin, inducing pain that is perceived superficially. It is believed that most clinical pain is likely contributed to by noxious information from deep tissues and is certainly more commonly perceived as deep (below the skin surface). Research on clinical populations has also supported the idea that visualisation of the painful body part is analgesic, however the effects of magnification and minification are opposite to those seen with an experimental pain paradigm. While a number of mechanisms might explain these differences it is possible that the modulatory effect of vision is different for pain that is perceived superficially to that which is perceived deeply.

Here we explore the effects of visualisation and visual enlargement on experimental deep tissue pain of the anterior thigh. All participants undertook a bout of high load eccentric exercise to induce delayed onset muscle soreness. Twenty four hours later those participants who reported at least a moderate level of muscle soreness were tested in a four phase randomised cross-over experiment. We measured pain intensity during the performance of a standardised quadriceps contraction under four different visual conditions, namely: normal visualisation of the thigh; magnified visualisation of the thigh; visualisation of the contralateral uninjured thigh and visualisation of a neutral object. Contrary to previous research on superficially perceived pain, we found no difference in pain intensity across any of the four conditions. These results demonstrate that visualisation does not have an analgesic effect on experimental deep tissue pain, suggesting that different modulatory factors exist for superficial and deep experimental pain. It also proposes the notion that visualisation may only have a modulatory effect on experimental pain when visual feedback offers a significant contribution to the perception of safety of the

stimulated structure. Visualisation provides clear information that all is well with the skin but less credible evidence that all is well with deep structures, however this hypothesis remains to be tested.

Declaration of Authorship

I declare that this thesis is my own work and has not been submitted in any form for another degree or diploma at any University or other Institute of a tertiary education.

Information derived from published and unpublished work of others has been acknowledged in the text with references provided for that material.

Candidate Name: Megan van Selm

Candidate's signature:

Date: 1 November 2016

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CHAPTER ONE: INTRODUCTION

1.1 Topic and Purpose

Chronic pain has a debilitating impact not just on the lives of the sufferers, but also on the broader Australian community. It is one of Australia's most widespread health issues, costing the economy over \$34.3 billion annually (MBFFoundation, 2007). In 2003, the medical cost of managing lower back pain alone in Australia was \$A 1.02 billion, which was relatively insignificant compared to the societal cost of \$A 8.5 billion (Walker, Muller, & Grant, 2003). Chronic pain affects almost one in three Australians (Blyth et al., 2001) and is often accompanied by mental disorders such as depression, anxiety and suicide attempts (Twillman, 2007). Although our understanding of pain is constantly evolving and improving, much remains unknown regarding pain mechanisms, particularly the host of factors which interact to modulate the perceived pain experience. As a result the effects of most common treatments are modest and the burden of pain continues to escalate.

To date, several experiments have investigated the modulatory effect of visualisation on pain using a paradigm of delivering noxious stimulation to the skin (Diers et al., 2013; Longo, Betti, Aglioti, & Haggard, 2009; Mancini, Longo, Kammers, & Haggard, 2011; Osumi et al., 2014) . These studies have helped to indicate the potential analgesic effect of visualisation and to suggest strategies that might be useful in the management of clinical pain (Diers, Loffler, Zieglsberger, & Trojan, 2015; Wand et al., 2012). However, there are a number of important differences between pain arising from experimental stimulation of the skin and clinical pain. One distinction is that it is thought that noxious information arising from deep tissues make a more significant contribution to the emergent pain experience than noxious information from the skin (Bove, Zaheen, & Bajwa, 2005). One important step in determining if visualisation evoked analgesia might be a useful clinical tool is to investigate if the phenomenon holds true for pain evoked from noxious deep tissue stimulation.

This study is novel in that it will explore experimental pain mediated by input from deep tissues, in particular to see whether factors which have been shown to have modulatory effects on pain evoked by superficial tissue stimulation influence pain evoked by deep tissue stimulation in the same way. Firstly, it will investigate whether visualisation of the painful body part affects the perceived intensity of pain. Secondly, it will attempt to establish whether visual magnification of the body part has any further effect on the perceived pain level, as has been demonstrated in superficial experimental pain.

The primary purpose of this study is to establish whether vision and visual magnification modulate pain perception and in so doing to better understand the mechanisms modulating pain perception when deep tissues are nociceptively activated, as these may assist our approaches to management of clinical pain states.

1.2 Background

Traditionally the experience of pain was believed to be synonymous with nociception. Pain was regarded as a linear sensory experience dependant only on A Delta and C nociceptive fibres transmitting impulses to a “pain” centre in the brain (Melzack, 1996), that is pain was thought to reside within the peripheral tissues and blocking nociception was seen as the fundamental therapeutic approach. Over the last four decades our understanding of pain has been revolutionised, with nociception now seen as only one component of the emergent pain experience. Indeed it is now clear than nociception is neither necessary nor sufficient for the production of pain. Pain does not exist within the tissues but is created by the brain (Moseley, 2007).

Pain emerges into consciousness when the brain decides that the body’s tissues are under threat and action is required (Moseley & Flor, 2012). This involves the processing, scrutinising and modulation of multiple information sources at a number of levels throughout the neuraxis (Moseley, 2007) and importantly emphasises that the management of pain has multiple targets. Essentially, anything that decreases the individual’s perception of danger to the tissues has the potential to moderate the pain experience. The multi-sensory emergent nature of pain is highlighted by recent work demonstrating the importance of visual input on modulating the pain experience.

Longo et al. (2009) showed in healthy volunteers that observation of the body part while an unseen painful stimulus is applied topically to that body part has an analgesic effect compared to observation of a neutral object. They adopted the term “non-informative analgesia” as the stimulus is not visualised, ruling out the opportunity of attributing the analgesic effect to the observation of the agent responsible for noxious stimulation. Similar results were observed by Diers et al. (2013) in a chronic back pain population. Visual feedback of the patients’ own backs reduced the perceived intensity of experimentally induced pain. Diers et al. (2015) expanded the concept of visual analgesia by observing it in a chronic back pain population, in this case demonstrating that the intensity and unpleasantness of the subjects’ habitual

perceived back pain could be reduced by subjects watching their back on a video screen.

However, the effect of visualisation on perceived pain is not yet beyond doubt. Subsequent to the design of our study, research with contrasting results has emerged. Valentini, Koch, and Aglioti (2015) recorded an analgesic effect only when viewing the hand was combined with the hand crossing the midline. No analgesia was experienced with visualisation alone. Torta, Legrain, and Mouraux (2015) did not observe visual analgesia at all either when subjects viewed a mirror image of their hand or when they viewed their hand directly. Clearly more work is needed to explore the effect of visualisation on pain intensity.

The effects of visual distortion of body size on pain perception have also been explored. Mancini et al. (2011) proposed a dose-response relationship to visual analgesia. With magnification of the perceived size of the body part an increased analgesic effect was observed whereas minification of the body part reduced the analgesic effect.

Subsequent to these findings Osumi et al. (2014) suggested that an analgesic effect to a magnified view of the body part is not necessarily a standard response. Exploring possible factors associated with modulation of pain by visual distortion of size, Osumi et al. (2014) used a mirror to reflect and augment the size of the viewed hand while applying a topical noxious heat stimulus to the unviewed hand. Subjects who exhibited a higher pain threshold under the enlarged hand condition were also found to experience more vivid somatosensory perception and reported that they felt “nothing special” in response to the view of the enlarged limb. The subjects who demonstrated a lower pain threshold under the enlarged condition did not show any significant difference in two-point discrimination and responded that they felt unpleasant emotions towards the view of the enlarged hand. This study suggests that specific factors are associated with modulation by visualisation and visual distortion of size. Their study introduces some of these factors however investigation to explore further conditions for an effect by visualisation is warranted.

In contrast to the positive effects of magnification observed by Mancini et al. (2011), Moseley, Parsons, and Spence (2008) demonstrated an augmented pain response to a magnified view of the upper limb in the case of chronic regional pain syndrome (CRPS) patients and an analgesic response to the minified view of the limb. Ramachandran, Brang, and McGeoch (2009) found a similar analgesic response to minification of the reflection of the intact limb (which was perceived as the phantom limb) in a patient with phantom limb pain.

The studies by Longo et al. (2009), Mancini et al. (2011), Diers et al. (2013) and Osumi et al. (2014) involved the application of noxious stimuli to the skin of subjects. We still know relatively little about modulatory factors influencing clinical pain states and whether the findings of studies involving experimental topical noxious stimuli can be extrapolated to the clinical environment. There are a number of important differences between pain arising from noxious stimuli applied to the skin and pain arising from noxious stimuli from deeper tissues. One distinction is that it is thought that noxious information arising from deep tissues make a more significant contribution to the emergent pain experience in clinical pain states than noxious information from the skin (Bove et al., 2005). An important step in determining if visual analgesia might be a useful clinical tool is to investigate if the phenomenon holds true for pain evoked from experimental deep tissue stimulation. A better understanding of deep tissue pain could potentially assist us to target treatment of chronic pain conditions more appropriately.

1.3 Development of this Research Study

In the previously-mentioned experimental studies, pain has been induced through topically applied noxious input. The resultant superficially felt pain is potentially very different to clinical pain for a number of reasons, one of which is that clinical pain is thought to be more commonly associated with noxious input from deeper structures. This study was developed with a view to generate deep tissue pain in normal subjects' quadriceps muscles by inducing delayed onset muscle soreness (DOMS), and then to investigate the effects of visualisation and visual distortion of size, in the form of magnification, on pain perception. An experimental healthy population was used in order to minimise extraneous influences that clinical states introduce.

Many of the experimental studies which have demonstrated the existence of visual analgesia and analgesic responses to visual distortion of body size have made use of mirror boxes to allow for "non-informative" noxious stimulation (Longo et al., 2009) and for manipulation of perceived size of the limb. It has recently been suggested that use of the mirror box may induce an analgesic effect rather than the visualisation component of these experiments per se. The proposed mechanism underlying this mirror-box analgesia may involve a degree of conflict (introduced by the mirror) between a subject's proprioceptive, somatosensory and visual representations (Torta et al., 2015), the added attentional processes that embodiment of the reflected image might entail or simply the greater novelty of viewing a reflected image. In light of this possibility, we used magnifying glasses to visually distort the view of the limb rather than concave and convex mirrors positioned on a mirror-box. This excluded the possibility of the reflected image contributing to "visual analgesia".

Given the ambiguity of previous findings and the lack of visualisation-analgesia studies in deep tissue our hypotheses were:

1. Visualisation of the painful body part will have an effect on deep tissue pain
2. Pain perception will be modified by visual distortion of the size of the viewed quadriceps muscle, in the form of magnification.

As part of our study we included the use of the short version of the Pain Anxiety Symptom Scale (PASS-20) (Appendix 1) and the Pain Sensitivity Questionnaire (PSQ) (Appendix 2). These have both been shown to be reliable predictors for the development of chronic pain (Lance M. McCracken & Dhingra, 2002; Ruscheweyh, Marziniak, Stumpfenhorst, Reinholz, & Knecht, 2009). The researchers felt it would be worthwhile to explore for any interaction between pain anxiety, trait sensitivity and pain during the various visual conditions. Modifying the subjects' view of their thigh, particularly in the case where the view of the thigh was obstructed by a neutral object, had the potential to affect their anxiety levels and this in turn could have had some impact on their perceived pain levels.

1.4 Potential Significance

Recent research results indicate that visualisation can potentially modulate pain perception and furthermore visual distortion of body size can further modify the pain experience. However, the direction of the effect is at this stage disputed, as contrasting findings have been observed both within experimental conditions involving superficial pain and in clinical populations. This study attempted to establish whether visualisation of the painful body part has an effect on experimental deep tissue pain, and if so, whether this was in the direction of analgesia. Secondly, this study explored whether visual distortion of body size impacts pain perception, specifically magnification of the viewed body part. Exploration of deep tissue pain is necessary as most clinical pain is believed to involve noxious input from tissues deeper than the skin. The results of this study could form the basis for future therapy targeting chronic deep tissue pain; that of manipulating multisensory input (such as vision) to modulate the pain experience.

CHAPTER TWO: LITERATURE REVIEW

2.1 Past Concepts of Pain

Until the 1960's, pain was believed to be a specific sensory modality, comprising peripheral receptors and unique, afferent neural pathways, terminating in a distinct centre in the brain. It was paralleled to modalities such as vision or hearing. Nociceptors were thought to detect noxious stimuli in the periphery and convey impulses, to the "pain centre" in the brain. The intensity of perceived pain was thought to reflect only the extent of tissue damage in the periphery (Melzack, 1996) and the blocking of nociception was seen as the primary therapeutic approach.

In 1965 Melzack and Wall started to question the traditional linear concept of pain as it did not explain complex pain phenomena such as causalgia. They presented the Gate Control Theory, a theory that small fibre nociceptive pathways responsible for signalling pain (C fibres) were inhibited by concomitant large fibre inputs signalling touch or other modalities (A β). Nociception was believed to be modulated peripherally at a spinal level, before ascending to evoke the perception of pain (Melzack, 1996). This was one of the first concepts proposing modulation of pain, and led to further investigation of this phenomenon.

Over the past four decades, our concepts of mechanisms underlying pain have evolved radically to the point where we now believe pain to be a complex interaction of multiple inputs creating a subjective, multidimensional, emergent experience (Grieve & Schultewolter, 2014). This complex perception is reflected in the current definition of pain provided by the International Association for the Study of Pain (IASP): "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey & Bogduk, 2012).

2.2 The Neuroanatomical Pathways of Nociception

2.2.1 Peripheral nociception.

Peripheral sensory nerves are responsible for conveying afferent signals to the spinal cord and ultimately the brain thus allowing for a conscious perception of the peripheral event that is taking place (van Griensven, 2005). Receptors transduce stimuli allowing transmission of a signal along the afferent fibre. These receptors can be specialized responding only to a specific stimulus, or they can be polymodal responding to various types of stimuli. Mechanoreceptors are sensitive only to mechanical stimulation such as pressure, touch, vibration etc. Chemoreceptors will only be activated by particular chemicals, and thermoreceptors will only be stimulated by changes in temperature.

In mammals, most discriminative light touch sensation is mediated by the A β low-threshold mechanoreceptors. Specialized A β low-threshold mechanosensory receptor end organs are classified into several different subtypes based on their structure. These include Meissner's corpuscles, Pacinian corpuscles, lanceolate endings and Ruffini corpuscles (Fleming & Luo, 2013).

Meissner's corpuscles have an extremely low threshold for activation, responding to an indentation of the skin of less than 10 μ m. Meissner's corpuscles have relatively small receptive fields and are most sensitive to low intensity stimuli (Fleming & Luo, 2013). They are therefore sensitive to light touch, and although they can be found all over the skin, they are concentrated in sensitive regions such as the finger tips and lips. Pacinian corpuscles sense vibration and the fine texture of objects, while the A β low-threshold mechanoreceptors innervating hair follicles are lanceolate endings. Ruffini corpuscles act as stretch receptors, and appear to work with other proprioceptors to sense the position of the fingers and hands.

Thermosensation is another sensory modality of the skin. Besides contributing to the temperature perception of an external stimulus it also contributes to the identification of an object through touch, by providing information about the

temperature of that object. Thermosensation is an important mechanism which contributes to the maintenance of a homeostatic condition in the body and it provides a protective function by detecting noxious hot or cold stimuli. Cutaneous thermosensation is mediated by a variety of primary afferent nerve fibres that transduce, encode and transmit thermal information. Specialized thermoreceptors are embedded in the free nerve endings of afferent fibres. Six “families” of thermoreceptors, known as transient receptor potential (TRP) ion channels, have been identified, whose activity depends on the temperature of the environment. Each of these receptor types is only activated over a particular range of temperatures, but together the receptors detect a full range of temperatures from noxious cold to noxious heat. Some of the thermoreceptors are specific to temperature only, while some of the thermoreceptors detect mechanical and chemical changes too, making them polymodal receptors (Schepers & Ringkamp, 2009).

Nociceptors are sensory receptors that detect noxious stimuli. They can be highly specialized responding only to injury and inflammation, but they can also be relatively unspecialized, known as “polymodal”, responding to extreme and potentially damaging mechanical, thermal and chemical stimuli. Despite each neural afferent having specialized receptors, once all these receptors are activated, the process of converting a specific stimulus into an electrical signal and conducting it along the length of the nerve to the specific synapses at the dorsal horn, is identical (van Griensven, 2005).

In a resting state, a voltage difference or “potential” exists across the membranes of nerve axons, creating an overall positive external environment compared with the negative interior. This is generated by active “ion pumps” in the membranes separating the positive sodium and potassium ions from the negative chloride ions. Ion channels in the cell membranes can be opened by mechanical force (in the case of mechanoreceptors), by specific chemicals known as ligands (in the case of chemoreceptors and thermoreceptors), or by direct depolarisation via an externally applied electrical charge. When these ion gates open, there is a rush of negative electrons through the gates as a result of the voltage across the membrane changing

the electrical charge of the nerve locally. Once this charge reaches its threshold, an action potential is created which results in the adjacent ion gates opening and the same cycle of depolarisation beginning there. This continues along the axon membrane allowing an electrical impulse to be carried along the nerve to its synapse. This process reflects the notion that impulses are generated in an 'all-or-nothing' fashion; the stimulus has to be sufficiently intense (noxious) to initially open the ion channels which will then propagate its own electrical impulse. Once depolarised, the membrane is restored to its normal resting state by the ion pumps. The stronger the stimulus, the more frequently action potentials will be generated, a process referred to as rate encoding. This entire process of converting a specific stimulus into an electrical impulse is known as transduction, whilst the impulse travelling along the nerve is referred to as transmission (van Griensven, 2005).

This transmission of information via electrical impulses from the peripheral tissues to the central nervous system results in a conscious perception of events occurring in the peripheral tissue. Two types of afferent fibres exist for transmitting nociceptive signals; unmyelinated C fibres and myelinated A Delta fibres. Both are relatively thin which means they conduct signals more slowly than other sensory afferents, but because of the presence of the myelin sheath, the A Delta fibres convey the impulses faster than the C fibres. This myelin sheath originates from the Schwann cells in the peripheral nervous system and the oligodendroglial cells in the central nervous system. The myelin insulates the axon, however it is not continuous along the entire length of the axon. There are spaces between the cells, termed Nodes of Ranvier, where the axon membrane is left exposed. These nodes are critical to the conduction of the impulse along the axon because the membrane underlying the myelin cannot undergo depolarisation and so this can only occur at the Nodes of Ranvier. The impulse therefore hops along the axon from node to node and is termed saltatory conduction. This conduction occurs at a much faster rate than the conduction of an impulse along an unmyelinated membrane via depolarisation of each adjacent segment of the membrane. Transmission along an A Delta fibre occurs at 4-36m/s, while that along C fibres occurs between 0.4-3m/s (van Griensven, 2005).

The receptors at the terminals of the afferents are specific to the fibre type. Polymodal receptors, which are stimulated by chemical, thermal or mechanical stimuli, are generally associated with C fibre types. Mechanical nociception tends to be transmitted by A Delta fibres while thermal nociception is subserved by both A Delta and C fibres. As a result of the different conduction speeds, receptor field sizes and the speed of accommodation of these two fibre types, we are able to perceive different qualities in the nature of one noxious stimulus. The A Delta fibres tend to give rise to the perception of a short-lived, sharp pain while the C fibres generally evoke a more diffuse aching or burning with longer-lasting effects. (van Griensven, 2005).

Once a nociceptive afferent has been sufficiently stimulated to trigger an action potential, stored neuropeptides in the peripheral terminals of the neuron, such as substance P and Calcitonin Gene Related Peptide (CGRP), are released into the local tissues from whence the stimulus arose. This has the effect of causing vasodilation of the local capillaries and stimulation of mast cells to release histamine. Together, these effects result in an increased collection of interstitial fluid as the plasma leaks from the permeable blood vessels. The histamine also has a sensitising effect on the nerve endings in the area by lowering the membrane potential, facilitating depolarisation and generation of action potentials. Besides the neuropeptide being released when a nociceptor is activated, antidromic impulses are also generated. Most of the impulses travel proximally along the fibre tract towards the spinal cord, but antidromic impulses are those that stray from the general direction of the current, to flow down branches of the same fibre tract toward other peripheral terminals. When these impulses arrive at the terminals further neuropeptides are released in this vicinity which will in turn have a vasodilatory effect and cause increased amounts of histamine to be released from mast cells into this new area. This in turn, increases local inflammation. The area may appear red and the increase in blood flow to the area increases the local temperature. Swelling results from oedema in the extravascular space and this can further induce pain due to the stretching and distortion of the tissue.

2.2.2 Spinal cord.

The dorsal horn of the spinal cord is the ultimate target and relay station for the primary nociceptive afferents and the impulse conveyed by them. The dorsal horn is comprised of six distinct layers according to the specific modalities that the afferent neurons, which terminate there, convey. Despite the distinct laminae, there are branched collateral connections between lamina layers which are likely to allow for 'cross-talk' between nociceptive and non-nociceptive afferents at this level. It is thought these potential connections may play a role in pain modulation (Basbaum & Jessel, 2000).

Second order neurons in lamina I (marginal layer) are primarily nociceptive specific neurons that respond only to noxious and thermal stimuli, receiving input from afferent A Delta and C fibres, which synapse directly with them in the dorsal horn. These are known as nociceptive-specific neurones (NS neurones). Some of the neurones respond to a variety of stimuli and are known as wide-dynamic range neurones. Lamina V contains wide-dynamic range neurones which ascend to the brain stem and the thalamus. A β and A Delta fibres synapse in lamina V, so the neurons are activated by both noxious and non-noxious stimuli in this lamina. The neurons in this lamina have dendrites which extend into lamina I and are activated by the afferent C fibres which terminate in lamina I. It is within lamina V that the visceral and somatic nociceptors converge which could potentially explain the phenomenon of referred pain (Basbaum & Jessel, 2000).

Lamina II (substantia gelatinosa) is made up of tightly-packed interneurons activated by noxious and non-noxious stimuli, having both an excitatory and an inhibitory function. The majority of neurons in lamina II receive information from sensory dorsal root ganglion cells as well as descending dorsolateral fasciculus (DLF) fibres. This lamina is believed to be important for the modulation of sensory/nociceptive input. Interneurones sensitive only to the A β neurones that synapse with them are concentrated in lamina III and IV and VI. They carry predominantly non-noxious

information and are arranged topographically according to the receptive fields of the afferent neurones. Some of the dendrites of lamina IV project to lamina II and possibly contribute to its modulatory function (Basbaum & Jessel, 2000). Lamina VII, found in the ventral horn, is polysynaptic and responds to noxious and non-noxious stimuli. It also receives input from both sides of the body, unlike the dorsal horn laminae, which may explain the diffuse nature of some pain conditions.

Laminae I and V appear to be the laminae which play a direct role in the transmission of nociceptive signals up the spinal cord, while the other laminae potentially contribute to pain modulation, which occurs mainly in lamina II, via their cross-links with that lamina. Glutamate and substance P are the excitatory neurotransmitters released by the C and A Delta fibres in the dorsal horn to facilitate the transmission (Basbaum & Jessel, 2000).

The nociceptors synapse with spinal interneurons and the ascending fibres of the spinal cord in laminae I and V within the dorsal horn of the spinal cord. From here the ascending nociceptive signals are transmitted up the spinal cord to higher centres for processing through five tracts.

The spinothalamic tract relays impulses to the thalamus. The axons cross the midline then ascend in the anterolateral white matter to the thalamus. The medial and lateral nuclei of the thalamus are primarily involved in nociception. Fibre tracts that project to the lateral nuclear group and the nuclear neurons, have small receptor fields and appear to play a role in the localisation of pain. The medial nuclei assist in processing nociceptive information and have projections which extend into the various cortical areas, such as the insular cortex, cingulate gyrus and the basal ganglia. The cingulate gyrus is part of the limbic system and is thought to be involved in the processing of the emotional component of a pain experience. The insular cortex contributes to the internal body response to the pain experience via the autonomic nervous system (Basbaum & Jessel, 2000).

The spinoreticular tract relays information in the anterolateral white matter of the spinal cord to both the thalamus and the reticular formation, a neural network in the

brainstem which regulates the cardiovascular system, respiratory system and the sleep-wake cycle. The reticular formation is also responsible for posture, balance and motor function. In contrast to the spinothalamic tracts, these axons do not cross the midline. The spinomesencephalic tract axons run in the anterolateral quadrant and the dorsal part of the lateral funiculus, and is thought to contribute to the affective component of pain via its projections to the amygdala via the mesencephalic reticular formation and periaqueductal grey matter. The cervicothalamic tract fibres arise from the lateral white matter of the upper two cervical segments. They terminate in the cuneate and gracile nuclei of the medulla. These nuclei participate in the sensation of fine touch and proprioception. Finally, the spinohypothalamic tract projects to supraspinal autonomic control centres which regulate neuroendocrine and cardiovascular responses (Basbaum & Jessel, 2000).

2.2.3 Brain structures involved in pain perception.

Recent developments in structural and functional imaging methods have revolutionised neuroscience providing researchers with a better understanding of the organisation and behaviour of the brain. Structural imaging examines anatomical structure while functional imaging reveals physiological activity within particular tissues using tracers to reflect their spatial distribution within the body. Hemodynamic imaging methods rely on the fact that cerebral blood flow and neuronal activation are coupled. When an area of the brain is in use, blood flow to that region also increases. This method of imaging has allowed us to establish which areas of the brain are involved in pain perception. Electroencephalography (EEG) and magnetoencephalography (MEG) are other forms of functional imaging which are useful for demonstrating temporal sequencing and time delays in brain activation (Apkarian, Bushnell, Treede, & Zubieta, 2005). EEG is a monitoring method to record electrical activity in the brain, while MEG is a technique used to map brain activity by recording magnetic fields produced by electrical currents occurring with brain activity.

According to Basbaum and Jessel (2000) there are regions in the cerebral cortex which respond exclusively to nociceptive input. These authors believed these to be found in the somatosensory cortex, the cingulate gyrus and insular cortex. However a review by Legrain, Iannetti, Plaghki, and Mouraux (2011) disputed this and proposed that the areas that were once thought of as nociceptive specific are better thought of as salient specific. Nociception is just one of many types of salient information that gives rise to a particular salient specific neurosignature. Event-related brain potentials (ERPs) elicited in response to a salient stimulus involve three processes, namely the detection, localisation and reaction to a salient and potentially dangerous physical threat. These processes involve a wide range of sensory integration, such as visual and proprioceptive perception, not solely the processing of nociceptive input so the ERPs noted reflect this multisensory integration. Various brain centres have displayed ERPs in response to a salient noxious stimulus, hence contributing to the processing of nociceptive input and the ultimate perceived pain experience (Legrain et al., 2011).

The primary somatosensory cortex (S1), secondary somatosensory cortex (S2) and the posterior portion of the insular cortex (IC) are commonly and concurrently activated following noxious stimulation, unlike that observed with tactile stimulation, where the IC and S2 are activated only after processing of the stimulus in S1. The S2 and IC are therefore primary receiving regions for nociceptive input to the brain. These regions are thought to contribute to the sensory-discriminative functions of pain. The organisation within the S1 appears to follow the same somatotopy as observed for tactile input, however the evidence of this existing in S2 as well has not yet been established (Apkarian et al., 2005).

As presented in the systematic review by Apkarian et al. (2005) one study demonstrated that visceral and cutaneous noxious input both led to activations in S1, S2, anterior cingulate cortex (ACC) and IC, but the exact area within the regions differed for the two types of pain. This suggests that there are potentially sub-regions within the brain structures responsible for processing noxious stimuli from different types of tissue.

The prefrontal cortex (PFC), is a heterogeneous brain area with the various gyri contributing to cognitive, emotional and memory function. The PFC, as well as parietal association areas, are involved in the cognitive components of pain perception such as memory or stimulus evaluation (Apkarian et al., 2005).

While the posterior IC is involved in the sensory nature of pain perception, the anterior IC is part of the limbic system and is more closely linked anatomically and functionally to the PFC. and hence appears to contribute to the emotional, cognitive and memory related aspects of pain perception (Apkarian et al., 2005). The cingulate cortex, particularly the ACC is also a component of the limbic system, however it acts as an important interface between emotion and cognition, and is therefore involved in the cognitive-evaluative stages of pain processing. It is thought to be responsible for the affective-motivational component of pain (Apkarian et al., 2005).

Subcortical activations, particularly in the thalamus, basal ganglia, and cerebellum, have also been observed during noxious stimulation, as well as activity in the motor and pre-motor cortical areas. It is thought that the motor and pre-motor cortices may be involved in pain-evoked movements, altered motor patterns or suppression of movement in the presence of perceived pain (Apkarian et al., 2005).

Significant differences appear to exist between the parts of the brain involved in processing acute/experimental pain in normal subjects compared to the activation patterns seen in persistent clinical pain. Greater activation of the spinothalamic pathway, which transmits afferent nociceptive information through the thalamus to S1, S2, IC and ACC is observed with experimental pain induced in normal subjects, whereas with experimental pain induced in chronic clinical pain populations the proportion of activity in these primary sensory-evaluative areas is comparatively less, while the activation in the PFC is increased. As a result, it is postulated that the nociception transmission through the spinoparabrachial, spinohypothalamic and spinoreticular tracts is likely to increase. The emphasis shifting towards augmented PFC activity in the chronic pain conditions suggests a greater component of emotional and cognitive processing associated with the chronic pain state, and reduced sensory

processing. Thalamus activity is seen to increase temporarily as pain persists, but over time the activity actually diminishes. Decreased stimulus-related activity has been observed in this structure in chronic pain sufferers (Apkarian et al., 2005). A study using various brain imaging techniques confirmed a reduction in the anatomical size and function of the thalamus associated with chronic pain conditions, in particular, trigeminal neuralgia. This was proposed to impact on the thalamocortical circuitry resulting in persistent pain (Henderson et al., 2013).

2.3 Modulation of Pain

Under normal circumstances it is generally assumed that our perception of pain is coupled with the amount of noxious information being received from peripheral tissue. However, pain is a complex phenomenon. Nociceptive input is modulated by various factors at various levels which can allow for the production of a very different pain experience which is not reflective of what is actually occurring at the tissue level, in fact nociception is neither sufficient nor necessary to produce the experience of pain (Butler & Moseley, 2013). Modulation appears to occur in the periphery at the nociceptor terminals, within the dorsal horn of the spinal cord, and in supraspinal centres.

2.3.1 Peripheral modulation of pain.

Peripheral nociceptors may be sensitised and even activated by certain stored chemicals released from the terminals and local tissue cells. This is known as *peripheral sensitisation*. Some of the substances that lower the threshold of nociceptors include histamine, which is released by damaged mast cells, and bradykinin, a chemical also released by damaged cells. These lower the threshold and bring about more regular depolarisation, and once this occurs nociceptors release stored neuropeptides, such as substance P which act directly on the local capillaries causing vasodilation, resulting in oedema. This process is termed neurogenic inflammation as it is induced by nociceptor stimulation. Substance P is an excitatory neurotransmitter thought to be related to the transmission of pain information into the central nervous system at the dorsal horn. Substance P also sensitises the receptors in the periphery by causing undamaged mast cells to release more histamine. Reverse-flowing antidromic neural impulses also serve to further sensitise the local nociceptors and even those adjacent to injured areas, by resulting in the release of neuropeptides (Basbaum & Jessel, 2000).

The reduction in the threshold of these peripheral nociceptors underlies primary hyperalgesia, an increased pain experience to a noxious stimulus as a result of the increased sensitivity in the peripheral nociceptors (Woolf & Decosterd, 1999).

2.3.2 Modulation of pain in the spinal cord.

2.3.2i The dorsal horn.

Modulation of pain also appears to occur within the spinal cord at the level of the dorsal horn. Inhibition of nociception occurs through the Gate Control mechanism, while facilitation of nociception occurs through the process of central sensitisation (Basbaum & Jessel, 2000). Furthermore, the descending pain modulatory system appears to be able to modulate pain in the dorsal horn in both an inhibitory or facilitatory direction as a result of activity in pain-related brain regions, linked to the dorsal horn by a network of neurons (Zusman, 2002).

Central Sensitisation

In response to nociceptor input dorsal horn neurons exhibit changes which can profoundly alter sensitivity by increasing membrane excitability, facilitating synaptic strength and even decreasing inhibitory influences in dorsal horn neurons (Latremoliere & Woolf, 2009). This state of temporary hyperexcitability can progress to a lasting state in the dorsal horn neurons. Together these processes are known as central sensitisation (Basbaum & Jessel, 2000). Central sensitisation comprises two distinct phases.

The earlier stage of central sensitisation

The first phase is the early phosphorylation-dependent and transcription-independent phase. To induce central sensitization, C fibres terminals in somatic or

visceral tissue must undergo intense, repeated or sustained noxious stimulation (Latremoliere & Woolf, 2009). This results in rapid changes in glutamate receptor and ion channel properties (Latremoliere & Woolf, 2009). A fast augmentation of excitatory glutamatergic synapses in the superficial dorsal horn strengthens nociceptive transmission and recruits non-nociceptive input to the pathway. This is achieved by phosphorylation of numerous receptor and ion channel targets that lead to changes in threshold and an increase in the release of glutamate, substance P and CGRP. (Latremoliere & Woolf, 2009). This process is known as windup. It is perceived as an increase in pain intensity over time while a noxious stimulus is applied. Windup disappears within tens of seconds of the end of the stimulus train as the membrane potential returns to its normal resting level (Latremoliere & Woolf, 2009).

Once phosphorylated in the process described above, protein kinase-C (PKC) decreases inhibitory transmission at the segmental level by reducing gamma amino-butyric acid (GABA) inhibition and the descending inhibition driven from the periaqueductal grey matter (PAG). Disinhibition leaves dorsal horn neurons more susceptible to activation by excitatory inputs including non-nociceptive A-fibres.

Elevation in intracellular calcium is also a major trigger of central sensitisation, activating multiple calcium-dependent kinases that act on receptors and ion channels to increase synaptic efficacy. Sustained release of glutamate by peripheral nociceptive activity and the neuropeptides substance P and CGRP leads to sufficient membrane depolarization to force magnesium ions (Mg^{2+}) to leave the N-methyl-D-aspartate receptor (NMDAR) pores, whereupon glutamate binding to the receptor generates an inward current of calcium ions (Ca^{2+}) into the neuron. The increase in Ca^{2+} concentration then activates numerous intracellular pathways, such as the extracellular signal-related kinase (ERK) that can contribute to the maintenance of central sensitization. Once activated, the ERK cascade results in changes in the threshold and activation kinetics of NMDA and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, boosting synaptic efficacy. A key feature of acute activity-dependent central sensitization is that it typically lasts for tens of

minutes to several hours in the absence of further nociceptor input (Latremliere & Woolf, 2009).

A peripheral stimulus is required initially to trigger central sensitisation, but once sensitized, noxious, non-noxious (e.g. A β stimulation) or even no stimulus can initiate an impulse in second order dorsal horn neurons. This is termed stimulus-generated pain hypersensitivity. The second-order neurones have a large number of “subliminal” connections with surrounding areas. Prior to sensitization a normal somatotopic map and sensory specificity is maintained, however following sensitization these connections start to respond more readily (Zusman, 2002). Clinically, this may present as hyperalgesia (known as secondary- or centrally-mediated hyperalgesia), tactile allodynia, temporal summation, referred pain, hypersensitivity to thermal stimuli and even spontaneous pain at the stimulated site, but also at adjacent areas and even spreading to normal, more distant tissues (Basbaum & Jessel, 2000). Central sensitisation may also result in an increased duration of the painful experience, longer than would be expected from a particular stimulus.

This increase in sensitivity noted in the early stage of central sensitization is protective, because it helps healing by limiting use of an injured body part until the injury is fully repaired (Latremliere & Woolf, 2009). The hypersensitivity state is usually fully reversible, returning ultimately to its normal resting state, termed “basal sensitivity” (Woolf, 2011). It becomes pathological when central sensitization is maintained in the absence of active peripheral pathology (Latremliere & Woolf, 2009).

The later stages of central sensitisation

In cases of sustained noxious input or sustained high perceived threat, central sensitisation may persist. Different transcription-dependent changes are required for longer-lasting effects, and these generally do not occur in response only to brief

nociceptor activity but are the consequence of sustained input due to peripheral inflammation and nerve injury (Latremoliere & Woolf, 2009), though sustained descending excitatory input from higher centre may produce the same outcome (Bee & Dickenson, 2008). This later transcription-dependent phase drives synthesis of the new proteins responsible for the longer-lasting form of central sensitization observed in several pathological conditions. For example, ERK can lead to the activation of the transcription factor cAMP response element-binding protein (CREB) which drives expression of genes producing a long-lasting strengthening of the synapse (Latremoliere & Woolf, 2009). Also, as a result of peripheral inflammation the expression of centrally-acting neurotransmitters is increased, lowering the threshold allowing for more frequent or easily activated dorsal horn neuron depolarisation (Basbaum & Jessel, 2000).

Central sensitization represents not only a state in which pain can be triggered by less intense inputs but in which the central sensitization itself can be maintained by a lower level or different kind of input. Ongoing activity in C-fibres, even at levels that do not initiate central sensitization in normal conditions, is sufficient to maintain central sensitization once it has been induced for prolonged periods (Latremoliere & Woolf, 2009).

Gate Control

This nociceptive-inhibitory phenomenon involves the activation the A β fibres. Non-nociceptive A β (for perception of sensation) and nociceptive A Delta and C fibres converge onto common neurons in laminae I and V of the dorsal horn. Interneurons found in laminae I and II of the dorsal horn release inhibitory neurotransmitters, such as GABA, enkephalin or dynorphin (endogenous opioid neurotransmitters). When activated, these neurotransmitters bind to μ -opioid receptors on the axons of incoming C and A-delta fibres carrying pain signals from nociceptors activated in the periphery. The activation of the μ -opioid receptor inhibits the release of substance P from these incoming first-order neurons and, in turn, inhibits the activation of the

second-order neuron that is responsible for transmitting the pain signal up the spinothalamic tract to the ventroposteriolateral nucleus (VPL) of the thalamus (Pertovaara & Almeida, 2006). Thus, by selectively stimulating the A β fibres it appears we can reduce the input from the nociceptive A Delta and C fibres in these laminae. The use of transcutaneous electrical nerve stimulation (TENS) is based, in part, on the Gate Control Theory. It is important to note that an analgesic effect is only created if the A β stimulation is in an anatomically similar region to the area of the nociceptor stimulation, as the respective afferents are required to converge at the same level in the dorsal horn in order to establish this “gating control” of pain (Basbaum & Jessel, 2000). The A β fibres are not directly activated by noxious stimuli, however they appear to contribute to the perception of the quality of the noxious stimulus. Therefore, in summary, activation of A β fibres contributes to perception of stimulus quality but also appears to attenuate it.

2.3.2ii The descending pain modulatory system

A network of neurons exists in the spinal cord linking the pain-related brain regions to the dorsal horn. This network modulates nociception at the dorsal horn, as a result of brain activity in these areas. Activation of the neurons can induce both an excitatory and inhibitory effect on nociception, with the overall effect being the net result of the facilitatory and inhibitory influences. Under normal circumstances this appears to be inhibitory however this balance can be easily influenced by various factors (Zusman, 2002)

Nuclei involved in descending pain modulatory system

The PAG, located in the mesencephalon around the Sylvius aqueduct, exerts a powerful pain modulatory action. Afferent fibres from the spinothalamic tract synapse at the PAG. Neural traffic from the PAG is connected to the spinal cord via the rostral ventromedial medulla (RVM). The RVM is a group of neurons located close

to the midline on the floor of the medulla oblongata. The RVM includes the nucleus raphe magnus (NRM) and adjacent reticular formation, including the nucleus gigantocellularis pars and paragigantocellularis ventralis, all of which project directly to the spinal cord. The PAG sends efferent connections to the nucleus raphe magnus when it is stimulated by opiates (Pertovaara & Almeida, 2006). Both the PAG and RVM receive direct afferent projections from the spinal dorsal horn and, thus, they may control the ascending nociceptive input by a simple feedback mechanism.

The rostral ventromedial medulla (RVM) sends descending inhibitory and excitatory fibres to laminae I, II and V of the dorsal horn spinal neurons. Three categories of neurons have been identified in the RVM: “Off-cells” which are inhibitory; “on-cells” which are facilitatory/nociceptive; and neutral cells which show no response to nociceptive input (Pertovaara & Almeida, 2006). That the spinal cord pain pathway neurons can assert a nociceptive and antinociceptive influence indicates the bidirectional nature of the brainstem descending modulatory system.

The NRM receives descending afferents from the periaqueductal grey, the paraventricular hypothalamic nucleus, central nucleus of the amygdala, lateral hypothalamic area, parvocellular reticular nucleus and the prelimbic, infralimbic, medial and lateral precentral cortices. All of these brain areas influence the main function of the nucleus raphe magnus, that is, pain modulation. Projections extend to the dorsal horn of the spinal cord to directly inhibit nociception. When stimulated, the nucleus raphe magnus releases serotonin, a neurotransmitter which suppresses nociceptive input.

Inhibition

The descending inhibitory systems can impose an inhibitory effect on the ascending nociceptive signals but they can also serve to “focus” the painful signal by suppressing the surrounding extraneous neuronal activity, thereby reducing the level of “noise” in the nervous system (Zusman, 2002). Diffuse noxious inhibitory control neurons are

located in the caudal medulla (Lewis, Kersten, McCabe, McPherson, & Blake, 2007). Activation of these neurones is the mechanism by which the diffuse noxious inhibitory control system (DNIC) produces a top-down inhibitory effect on a painful stimulus. Descending inhibitory systems will serve to mask the “noise” of underlying pain when a “new” painful stimulus is applied in order to help focus the new painful stimulus (Zusman, 2002). Although DNIC involves a descending inhibitory influence, it has been postulated that the net effect of DNIC is clarification of pain perception evoked by the most threatening noxious stimulus (Pertovaara & Almeida, 2006). Clinical studies indicate that in patients with fibromyalgia a reduction of DNIC potentially contributes to hyperalgesia (Pertovaara & Almeida, 2006).

The descending inhibitory tracts and nuclei may be activated by various mechanisms. Descending pain inhibitory pathways have an important role in the ascending–descending circuitry, providing negative feedback control of nociceptive signals at the spinal cord level. Therefore, full activation of descending inhibition is observed only under painful conditions (Pertovaara & Almeida, 2006). Higher brain centres associated with cognition, motion, mood and behaviour recruit descending pain modulatory pathways. Some centrally-acting analgesic drugs are effective by inducing activation of descending pain inhibitory pathways (Pertovaara & Almeida, 2006).

The dorsolateral funiculus appears to be the main pathway for descending pain inhibitory systems between the RVM and dorsal horn (Zusman, 2002). There are several ways in which the descending inhibitory tracts suppress nociceptive signals:

1. Neurotransmitters released from descending axons may block the ascending nociceptive signal by producing a hyperpolarization of spinal relay neurons (Pertovaara & Almeida, 2006).
2. Descending pathways may also suppress nociceptive signals due to action on central terminals of primary afferent fibres (presynaptic inhibition). These terminals have receptors specific to the inhibitory neurotransmitters released in the descending spinal cord (Pertovaara & Almeida, 2006).

3. Gate Control theory of pain. The axons of the neurons within the dorsolateral funiculus terminate on inhibitory interneurons in the dorsal horn of the spinal cord. These interneurons, in addition to being subject to the segmental influence of peripheral origin in the Gate Control mechanism, may therefore also be subject to an activation of central origin. The interneurons in the dorsal horn exert their inhibitory effect by releasing endogenous opioids that act on specific receptors located both in the terminals of the primary nociceptive afferents and directly on the converging neurons, that is, pre-and post-synaptic inhibition.

Activation of projections from the PAG to the brainstem nuclei (RVM and locus coeruleus) and then to the dorsal horn of the spinal cord, involve neurotransmitters such as opioids, noradrenalin, and serotonin which have modulatory (both excitatory and inhibitory) influences on spinal cord afferent neurons. Opioids are strong analgesics which work at various sites within these descending tracts, preventing the passage of nociceptive signals through the dorsal horn and into higher levels of the brain where the perception of pain is generated (Basbaum & Jessel, 2000).

Facilitation

The nucleus reticularis gigantocellularis (NGC) in the medulla appears to be the origin of the descending facilitatory system. Activation in the NGC also appears to suppress the function of the inhibitory “off cells” in the RVM via inhibitory interneurons. A pathway exists between the dorsal reticular nucleus of the medulla and the dorsal horn of the spinal cord, which amplifies afferent nociceptive input and possibly contributes to central sensitization (Zusman, 2002).

2.3.3 Supraspinal modulation of pain.

There is evidence from functional magnetic resonance imaging (fMRI) studies showing that processing of nociception involves the activation of a diffuse network of transmitting fibre tracts and brain centres that are not exclusively devoted to pain

(Jabbur & Saadé, 1999). These centres receive afferent nociceptive input via multiple routes (Bushnell, Čeko, & Low, 2013). Prior to the production of the final pain experience the ascending afferent nociceptive signals are modulated supraspinally. A large number of brainstem, diencephalic (thalamic and hypothalamic) and telencephalic (cortical and sub-cortical) structures modulate pain through descending projections to the spinal dorsal horn, and in most cases their descending pain modulation effect is relayed through the PAG and the RVM (Pertovaara & Almeida, 2006).

There is substantial evidence for pathways from these “pain-involved” cortical and subcortical regions to both the PAG and RVM to facilitate this supraspinal modulation (Zusman, 2002) and input from these centres most likely influences the balance of inhibitory versus facilitatory effects of the descending modulatory tracts. The RVM and PAG in the brainstem and the descending modulatory pain tracts play a pivotal top-down role in modulating the afferent nociceptive input prior to higher-order processing. These mechanisms of pain modulation influence the ultimate pain experience (Tracey & Mantyh, 2007).

Connections between forebrain structures and the nuclei within the brainstem, particularly the RVM and PAG, have been identified. These include the ACC, IC and certain subcortical amygdala and hypothalamic nuclei (Zusman, 2002). Connections from higher centres of processing such as the S1, S2, posterior parietal, and insular cortices converge on the ACC together with connections from the prefrontal cortex (which is concerned with planning a response to the painful stimulus). The ACC, therefore, plays a major role in the integration of the sensory, affective, attentional, cognitive and emotional components of pain. Through its direct and indirect connections with the RVM and PAG, the ACC influences the descending modulatory system in a bi-directional manner and helps to explain how cognitions, beliefs, emotions, context and attention can influence our perception of pain (Zusman, 2002). Particular personality traits, emotional states and cognitive styles lend themselves to the amplification and persistence of perceived pain via these connections from cortical /subcortical brain regions to the brainstem (Zusman, 2002).

2.4 Interaction between Pain and Emotional Factors

Various pain-related pathways in the brain are responsible for different aspects of the pain experience. With recent advances in imaging we have been able to recognise various parts of the brain associated with the processing of the emotional component of a pain experience, and the various parts of the brain which appear to be activated by emotional states and exhibit a top-down modulatory effect on the afferent information. The ACC and the insula are part of the limbic system of the brain which is primarily involved in a person's emotional state. These regions are important for encoding the emotional components of pain (pain affect). They are linked directly to the PAG, and are commonly termed the "medial system" (Tracey & Mantyh, 2007). The amygdalae are almond-shaped nuclei in the temporal lobe of the brain, and are also part of the limbic system. They play an important role in emotional behaviour. Nociceptive afferent inputs through the spino-parabrachio-amygdala pathway probably contribute to pain-induced changes in affective behaviour. Likewise, the connections from the amygdala to the PAG and RVM may be involved in mediating the influence of emotions on pain. Stressful situations like physical exercise, exposure to extreme temperatures, fight, fear and pain may induce a decrease in pain sensitivity, a phenomenon called stress-induced analgesia. The hypothalamus is likely involved in stress-induced analgesia (Pertovaara & Almeida, 2006).

The emotional component of the pain experience is powerful. Studies have shown that a noxious stimulus is not actually required to activate pain pathways and even to perceive pain, if a subject is adequately emotionally "primed". This occurred in subjects while they were merely observing other individuals in pain (Lamm, Decety, & Singer, 2011). Also, when "emotionally primed" the subject's perceived pain levels to a noxious stimulus was reported to be higher than without the priming (Loggia, Mogil, & Bushnell, 2008).

It is difficult to induce a psychological state of anxiety/depression in the experimental environment and hence experiments are limited to inducing sadness or a depressed mood in subjects. In a study by Borna et al. (2010) subjects underwent a "sad" mood

induction process by means of reading “Velten-type” statements (commonly used to induce moods in psychological experiments) along with sad background music. They were deemed to have experienced a sad mood induction if they achieved a greater than 40% increase in their depressed mood score. The subjects were exposed to a noxious thermal stimulus and the brain activation patterns compared to those observed when the subjects were exposed to the same stimulus in a “neutral mood”. The results indicated that the induction of depressed mood augments the ratings of pain unpleasantness. The major difference noted using fMRI was the increased activity in the greater inferior frontal gyrus and amygdala in those subjects who reported the largest increase in pain unpleasantness. This demonstrates a potential link between changes in emotion control mechanisms and enhancement of pain. The researchers suggest that this may explain how depressed mood and chronic pain may co-occur (Berna et al., 2010).

Anxiety and depression are together referred to as “emotional distress” as it is often difficult to separate the two states diagnostically, particularly in children. The psychological states of anxiety and depression have been clinically demonstrated to augment the pain experience. It appears this is likely to be due to the increased attention focussed on the pain. For example, one study showed that subjects who were predisposed to anxiety and who were fearful of dental intervention both expected and experienced more pain than non-anxious subjects during restorative dental procedures (Klages, Kianifard, Ulusoy, & Wehrbein, 2006). Depressive disorders often accompany persistent pain (Tracey & Mantyh, 2007) and currently it is unclear which condition precedes the other. In an fMRI study of patients with fibromyalgia activation in amygdala and anterior insula differentiated patients with and without major depression, however the exact connections between pain and depression have not yet been determined (Giesecke et al., 2005).

2.5 Interaction between Pain and Cognitive Factors

The interaction between pain and cognitive factors has similarly undergone significant investigation. Studies have revealed that cognitive processes can influence pain behaviours and disability levels (Moseley, 2007). Cognitive processes appear to activate the superior parietal lobe, the insula and the S1 somatosensory cortex which is consistent with the role of these regions in pain sensation, rather than in pain affect. They are collectively termed the “lateral system” (Bushnell et al., 2013). These centres are linked to the ACC, PAG and RVM and thereby contribute to modulation of pain-evoked activity via the descending modulatory system (Zusman, 2002).

Attentional focus seems to have a significant effect on acute pain perception. Through their experiments, Miron, Duncan, and Bushnell (1989) demonstrated that changes in the direction of attention alter the ability to discriminate noxious heat stimuli. They further provided evidence that both the speed and accuracy of detecting changes and the intensity and unpleasantness in noxious heat stimuli are decreased when the subject attends to another stimulus modality. Focus towards the nociceptive stimulus increases the pain experience while distraction decreases pain (Miron et al., 1989). Moseley (2007) reported contrasting effects of attention. The modulatory effect that attention has on pain perception seems to depend on the underlying threat value of the pain to that individual, and the measure of control the individual has over that pain. Nevertheless, despite the differences in direction of effect, there appears to be a strong modulatory effect of attention on the pain experience (Moseley, 2007).

Pain distracts our attention from current activity. The amount it interrupts our attention is dependent on the intensity of pain or the perceived threat value. This turns our concentration towards the pain, which may result in a psychological state of hypervigilance (Vlaeyen, Crombez, & Goubert, 2007). In ongoing clinical pain states hypervigilance, which is characterised by excessive attention towards sensory information, augments our perception of pain (Vlaeyen et al., 2007) and has been

shown to explain some of the variance in pain severity and serve as a potential barrier to resolution in persistent pain problems.

Attribution, anticipation and anxiety are cognitive factors that reflect aspects of a subject's sense of control over a painful experience. In general, people with pain often seek to attribute their symptoms to a specific cause or diagnosis. As pain becomes more persistent, there is often no clear, physiological explanation for their symptoms. This leads to a sense of loss of control which has been demonstrated to augment the pain experience. In a study investigating the effect of a depressive-attribution style in healthy male subjects, causal attributions for negative events were measured using the attribution style questionnaire (ASQ). A moderate correlation was demonstrated between the perceived pain intensity (PPI) of the electrical skin stimulus and the ASQ. Following uncontrollable stress exposure, the PPI increased significantly and there was a higher correlation between PPI and the ASQ (Müller, 2013). Anticipation and anxiety (as a trait) have also been shown to modulate the pain experience. Anticipating pain is adaptive and important to prevent potential injury. In an fMRI study, brainstem responses during anticipation and processing of thermal noxious stimuli were investigated. The intensity of perceived pain was shown to increase as the anticipation/ anxiety prior to the noxious stimulus heightened (Fairhurst, Wiech, Dunckley, & Tracey, 2007).

Pain catastrophisation has been defined as a maladaptive "exaggerated negative mental set brought to bear during actual or anticipated painful experience", and is thought to encompass the factors of helplessness, magnification and rumination (Sullivan et al., 2001). Others have emphasised that catastrophising about pain also encompasses "worrying about a major negative consequence from a situation, even one of minor importance" (Turner, Jensen, & Romano, 2000). Catastrophisation contributes to the pain experience and is associated with higher pain rating in both experimental and clinical studies. Individuals registering high scores on the pain catastrophisation scale report more intense pain (Sullivan et al., 2001), more severe depression and anxiety (Keefe, Brown, Wallston, & Caldwell, 1989), show higher levels of pain behaviour and disability (Sullivan, Lynch, & Clark, 2005) and have been

shown to predict higher perceived post-operative pain levels (Pavlin, Sullivan, Freund, & Roesen, 2005). It has been proposed that attention to pain underlies catastrophisation. This has been substantiated by neuroimaging data revealing increased activation in the cortical regions implicated in attention, vigilance and awareness.

Expectation is the state of looking forward or anticipating a future occurrence. It is the degree of probability that something will occur. Recently, the placebo modulatory effect on pain was investigated as a form of inducing expectation (of relief) using a molecular imaging approach. The researchers confirmed that placebo analgesic effects are mediated by endogenous opioid activity on μ -opioid receptors. These observations were extended to confirm that prefrontal mechanisms can trigger the opioid release within the brainstem during expectancy to influence the descending pain modulatory system and subsequently modulate pain perception (Wagner et al., 2007).

2.6 Multisensory Integration

Besides the influence of cognition and emotion on our perception of pain, the intensity of pain may be influenced by the interaction from other sensory modalities, such as tactile, nociceptive, auditory, olfactory, gustatory, and visual input. This phenomenon is known as multisensory modulation (Haggard, Iannetti, & Longo, 2013). There has been significant interest in exploring the influence of multisensory integration on the experience of pain.

2.6.1 Modulatory effects of tactile activity on pain perception.

The Gate Control mechanism of pain modulation discussed above, is a well-known example of multisensory modulation, whereby interactions between touch and nociceptive afferent stimuli at various levels, including the spinal cord, thalamus and cortex, reduce the intensity of pain perceived (Melzack, 1996).

2.6.2 Modulatory effects of nociceptive activity on pain perception.

The DNIC system is another example of multisensory modulation of pain, this time with acute nociception as the sensory input having a modulatory effect on underlying pain.

2.6.3 Modulatory effects of auditory activity on pain perception.

The effects of different auditory input on pain tolerance and pain intensity have been investigated by various groups. Music in different forms has been the most commonly described auditory input.

Mitchell, MacDonald, and Brodie (2006) used experimentally induced cold pressor pain to compare the effects of subject-preferred music to two types of distracting

stimuli; mental arithmetic (a cognitive distraction) and humour (which may emotionally engage us in a similar manner to music). Preferred music listening was found to significantly increase pain tolerance time in comparison to the cognitive task and in comparison to humour. Ratings of pain intensity on a visual analogue scale and the pain rating index were not significantly different between the three distractions. So the investigators concluded that preferred music distracts attention from experimental pain significantly more than an affectively-neutral arithmetic task to allow for an increased tolerance time but not significantly more effectively than humour. The music used in this study was self-chosen and familiar, and therefore, individual preferences and familiarity could enhance the drive to listen attentively to the music and thus act as a distractor from the pain. The results also showed that preferred music provides a significantly greater feeling of control over a painful experience than a humorous distraction (Mitchell et al., 2006). These results were corroborated by work from the same group showing that familiar music increases pain tolerance more than unfamiliar music (Mitchell et al., 2006).

Roy, Peretz, and Rainville (2008) developed a hypothesis that the mechanism underlying this established music-induced analgesia is mediated by the valence of the emotions induced by the music. Positive valence refers to the intrinsic attractiveness of the music while negative valence refers to the averseness. The results of this experiment varied from the above-mentioned in that the researchers found that the intensity of pain was affected, rather than just the subject's pain tolerance. In their study, only the pleasant excerpts of music significantly reduced pain intensity and unpleasantness of a thermal stimulus, compared with unpleasant music and the silent control condition. Pain reduction was negatively correlated to the subjects' reports of pleasantness of music. These results supported their proposal that pleasant music reduces pain more than unpleasant music (Roy et al., 2008).

Subsequently, in a study involving a clinical population of fibromyalgia patients, pain ratings and timed-up-and-go tests were assessed while the subjects listened to self-chosen, relaxing, pleasant music versus a control group who listened to an even/flat noise (termed "pink noise"). The experimental group demonstrated a significant

reduction in pain ratings and improved functional mobility compared with the results from the control group. The investigators went on to explain that the improved functional mobility was not related to an improved motor rhythm derived from a faster rhythm in the music because the effects were noted even if the music was played before the mobility assessment rather than during the test (Garza-Villarreal et al., 2014).

Villarreal, Brattico, Vase, Ostergaard, and Vuust (2012) extended the above findings and demonstrated that valence of music alone is not an effective pain modulator. In their study an active distraction of a cognitive arithmetic task reduced pain more than the passive distractions with low arousal such as unfamiliar but pleasant music and unfamiliar but pleasant environmental sounds. Arousal refers to the physiological or psychological state of being awake or reactive to a stimulus. Although less effective than the cognitive task, the environmental sounds and music still had an analgesic effect and they reduced pain similarly to each other. Pain intensity was significantly correlated with valence and arousal (Villarreal et al., 2012). Therefore, valence and arousal are two interrelated emotional mechanisms that appear to be clearly linked to the analgesic effect of music.

Pud and Sapir (2006) explored the influences of auditory stimulation and cognitive tasks on intensity of pain perception of normal subjects to a heat stimulus. A non-music auditory stimulus in the form of a sinusoidally modulated speech-like signal was used. In this experiment, there was a significant difference in the visual analogue scale (VAS) ratings of the heat stimulus when the heat stimulus was applied in isolation, as opposed to being applied in conjunction with the auditory stimulus or with the auditory stimulus plus the cognitive task. The VAS rating dropped when there was competing sensory input/processing, demonstrating a significant influence of auditory +/- cognitive processing on the pain experience (Pud & Sapir, 2006).

Dobek, Beynon, Bosma, and Stroman (2014) investigated the neural mechanisms underlying music-induced analgesia using fMRI. Noxious thermal stimulation was applied while subjects listened to their favourite music, or no music. Subjective pain

ratings were recorded while the spinal cord, brainstem and brain was scanned. In both the pain and pain with music condition neural activity was noted in areas consistent with previous experiments involving pain perception, however the pain with pleasurable music condition also involved activity in the limbic, frontal and auditory regions. This condition also demonstrated activity in the regions involved in the descending pain modulatory system, namely the dorsolateral prefrontal cortex (DLPFC), PAG, RVM, and the dorsal grey matter of the spinal cord. This gives a clear indication of the connections between auditory and pain perception and helps to explain the mechanisms underlying music-induced analgesia; namely activation of the descending inhibitory pathways.

2.6.4 Modulatory effects of olfaction on pain perception.

Raudenbush, Koon, Meyer, Corley, and Flower (2004) investigated whether odours could modulate subjects' pain ratings and pain tolerance levels. Via a nasal cannula, they exposed the subjects to low-flow oxygen, peppermint odour plus oxygen, or jasmine odour plus oxygen while they underwent a cold pressor test. Subjects reported pain levels using a 0-10 scale every 30 sec, up to a maximum of 5 minutes. Following the cold pressor test, subjects also completed questionnaires related to mood (POMS), workload (NASA-TLX), and anxiety (STAI). The results indicated that peppermint and jasmine odour significantly decreased ratings of pain and increased overall pain tolerance. The questionnaires clearly reported positive influences by the odour conditions on the mood, workload and anxiety levels of subjects. Physiological changes were also observed. Oxygen saturation levels improved, pulse rate increased and blood pressure decreased during odour administration (Raudenbush et al., 2004).

The positive effects of odour on pain intensity ratings were supported by a recent study by Bartolo et al. (2013). They used the nociceptive withdrawal reflex (NWR), a defensive, protective response to a noxious stimulus as a reliable indicator of spinal nociception in humans, to explore the modulatory effects of odour on pain perception. They compared a pleasant odour, an unpleasant odour and a neutral

odour. The results indicated that both the NWR magnitude and subjective pain ratings were reduced by odours evoking pleasant sensations and increased by odours evoking unpleasant sensations. From this experiment, the investigators were unable to establish whether olfactory-modulation of pain exists as a result of direct connections between the primary olfactory enthorhinal cortex and spinal cord neurons or whether the modulation occurs indirectly by cognition, mood, anxiety, emotion, memories (Bartolo et al., 2013).

A separate investigation aimed to establish whether odour-analgesia was related to hedonics of pleasantness or to a quality of the odour, specifically sweetness. The researchers assessed the effects on pain ratings and pain tolerance during application of a sweet-smelling odour, a pleasant odour, an unpleasant odour, and no odour. Again pain was evoked using a cold pressor test. The results indicated that odour sweetness rather than pleasantness increased pain tolerance. This may be through associative learning, through the frequent pairing of odours with sweet tastes. These results, however, dispute the findings of the above-mentioned studies in that odour itself was found to have no effect on pain intensity ratings. (Prescott & Wilkie, 2007).

2.6.5 Modulatory effects of gustation on pain perception.

Variable results have been observed when the modulatory effect of gustation on pain has been explored. This is particularly evident when the results of studies involving infant populations are compared to adult populations.

In an experiment on newborns undergoing heel-stick procedures, pain was measured under four gustatory conditions: (a) water-moistened pacifier, (b) sugar-coated pacifier, (c) 2 cc of a 12% oral sucrose solution, or (d) control. Pain measures were duration of cry, vagal tone, and salivary cortisol levels. The results indicated that the babies with the sugar-coated pacifiers cried significantly less and they demonstrated significantly lower vagal tone than the babies in the other conditions. This difference was observed for fifteen minutes after the procedure. This suggests that the concentrated form of sucrose in the sugar-coated pacifier possibly modulated the pain experience. We cannot attribute the findings to the pacifier because one of the

other conditions involved the use of a water-moistened pacifier, which made no significant difference (Greenberg, 2002). That the 12% oral sucrose solution didn't have a significant analgesic effect is likely to be due to the differences in concentration between the sugar-coated pacifier and the sucrose solution. The results from a review of studies examining the analgesic effects of sweet-tasting solutions for infants concurred with these findings (Harrison, Bueno, Yamada, Adams-Webber, & Stevens, 2010).

Contradictory results are observed when the analgesic effect of sucrose is studied in adults. A more recent study compared modulatory effects of sweet, bitter and tasteless gelatine in the mouth of subjects who had experimental jaw muscle pain evoked by injection of hypertonic saline into the masseter muscle. The subjects continuously rated pain intensity as well as mood and unpleasantness/pleasantness of the conditioning stimuli. The gustatory stimuli failed to generate a robust change on the scores of emotions. No effects on pain intensity were observed during sweet or bitter gustatory stimuli. Based on pre-existing knowledge that emotions have an important modulatory effect on pain perception, the investigators concluded that the lack of pain intensity modulation during exposure to varied tastes was likely due to a lack of modulatory effects of gustation on emotions and the limbic system, and subsequently on the pain experience (Horjales-Araujo, Finnerup, Jensen, & Svensson, 2013).

2.6.6 Modulatory effects of vision on pain perception.

2.6.6i Modulatory effects of vision on pain perception in a healthy population.

Anticipation of pain in response to a visual stimulus appears to have a modulatory effect on perceived pain. Visual input in peripersonal space modulates neural processes involved in predicting pain. One study showed that pain unpleasantness ratings were higher when the subject observed a needle approaching an embodied artificial hand, as opposed to a Q tip approaching the hand. The researchers felt the

expectation of pain was likely to have been responsible for the subjects' increased pain unpleasantness perception (Höfle, Hauck, Engel, & Senkowski, 2012).

A study by Martini, Perez-Marcos, and Sanchez-Vives (2013) showed that pain thresholds to a thermal stimulus were modified by changing the colour of an embodied virtual arm between blue, red and green. The subject's pain threshold was lower when the virtual image was seen as red compared with when it turned blue. The visual input had a significant modulatory effect on the perceived pain which the investigators attributed to a top-down cognitive process of understanding the meaning of the visual input i.e. that red is associated with warmth and blue with cold. When the noxious thermal stimulus was associated with a red visual cue it was perceived as being hotter and hurt more than when the same stimulus was associated with a blue cue.

Visualisation of one's own body part while a painful stimulus is applied is a form of multisensory modulation which has attracted a lot of attention recently. The intensity of perceived pain can be affected by the content of visual input. In a study by Longo et al. (2009) subjects looked into a mirror aligned with the midline of their body at either a reflection of their left hand, another person's left hand or at a reflection of a neutral object. The reflection of their left hand created the illusion that they were observing their right hand. The use of the mirror enabled the investigators to apply a painful stimulus to the right hand while the subject observed the illusion of their right hand but without the subject actually observing the application of that stimulus. In other words, the stimulus remained "non-informative". After a 60 second induction period where the subject looked passively at the object reflected in the mirror, laser stimulation was used to selectively activate the nociceptive A Delta and C fibres, without activating mechanoreceptive afferents. Subjective pain ratings, using the VAS were collected while the stimulus was applied to compare any differences between visualising the painful body part and visualising a neutral object. A questionnaire was administered following each testing condition to determine what exactly the subject felt they were looking at in the mirror. Both the subjective ratings of perceived pain by the participant to cutaneous laser stimulation and the maximum

level of laser stimulation achieved reflected a reduction in perceived pain when the participant viewed their own hand, in contrast to viewing a neutral object. A variation of this experiment was included in the study where another person's hand was reflected in the mirror instead of the subject's. This part of the experiment demonstrated that the analgesic response is specific to observing one's own hand, as opposed to another person's hand. A second variation was also included which involved the subject looking directly at the right hand or at an object rather than a reflection of the left hand or object respectively. This part of the experiment was included to investigate the proposed mechanism underlying the analgesic effect; that of conflicting proprioceptive, sensory and visual representations produced by the mirror inhibiting pain. When the mirror was removed, the analgesic effect was still noted. The researchers therefore excluded this mechanism as the possible explanation behind the analgesic effect (Longo et al., 2009).

It appears that pain and touch respond in contrasting ways to non-informative vision of a body part during noxious stimulation. Non-informative vision of the hand increases tactile acuity (Kennett, Taylor-Clarke, & Haggard, 2001), while in the experiment by Longo et al. (2009) pain ratings were lower with non-informative vision of the body part during noxious stimulation. A proposed explanation by Longo et al. (2009) for their experimental observations involved the visual-activation of GABAergic interneurons. GABA is a major neurotransmitter within the descending inhibitory system, thereby reducing perceived pain as a result of cross-modal modulation/inhibition. They cited the work of Kennett et al. (2001) who reported enhanced tactile acuity by visual modulation of somatosensory GABAergic neurotransmitters. Thus, they suggested that GABAergic interneurons are a likely effector of both improved tactile acuity and analgesia during this non-informed vision of the body part (Longo et al., 2009).

It is also proposed that visual perception of one's own body results in functional coupling between visual and parietal areas that may subserve multisensory inhibitory mechanisms. Longo, Iannetti, Mancini, Driver, and Haggard (2012) investigated the neural correlates underlying visual analgesia. They used fMRI to assess the neural

activity of the brain during the visual analgesia phenomenon that they had previously described. They used an infra-red laser to stimulate the cutaneous nociceptors of normal subjects' right hands, under two conditions. They compared the subjective pain ratings and the regional brain activity, while the subject was stimulated looking at a neutral object versus looking at their own hand. The visual analgesic effect was confirmed with analysis of the subjective pain ratings. The fMRI clarified the regions of the brain associated with visual perception, namely the bilateral posterior parietal cortices (PPC), lateral occipital and superior parietal cortices. Extensive activations bilaterally within the S1, S2, anterior insula, posterior insula, ACC and midcingulate cortex were observed during pain stimulation compared to a resting state. Therefore, there was little overlap between this and the pattern of activation noted during the visual perception. One common region that was activated in both scenarios, however, was the basal ganglia, particularly the caudate nucleus and the putamen. Thus the basal ganglia may provide the link between the visual system and nociceptive system to allow for pain modulation and subsequent visual analgesia. Their findings suggest that visually-induced analgesia does not result from a reduction in overall cortical responses to the painful stimulus but rather appears to be as a result of the activation of visual or bimodal visuo-tactile cells in the secondary somatosensory cortex (posterior parietal cortex). The investigators propose that sensory input such as vision causes these cells to activate inhibitory interneurons in the early somatosensory areas (S1 and thalamus) - regions associated with the perception of pain. This was evident from the increased connectivity (i.e. functional coupling) observed between posterior parietal nodes of the visual body network and the structures comprising the pain matrix such as SII, anterior and posterior insula, and anterior cingulate cortex. This appears to occur much more quickly than the structural reorganizational changes associated with the development of chronic pain. Importantly, the pain experience was shown to be an emergent result of connectivity between multiple regions of the brain, rather than a direct read-out of nociceptive stimulation, within a specific pain matrix.

In 2015 Valentini et al. (2015) found that a vision induced analgesic effect was only observed when the viewed body part was placed across the midline. Direct vision of the hand (as opposed to the mirror-box used in the study by Longo et al. (2009)) in an uncrossed position alone and crossing the midline alone did not induce an analgesic effect, while together they did influence the intensity of the pain perceived. The analgesic effect observed with vision of one's own body in a crossed position may be due to the augmented cognitive processing required to resolve the conflict between body-centred representation of the visual input and the egocentric spatial frame of reference. This would suggest that a combination of mismatched proprioceptive and visual representations may be worth incorporating into a pain management plan.

Torta et al. (2015), suggested that the mirror-box, that was used in several previous studies to avoid the confounding effect of viewing the noxious stimulator, may contribute to the reported visual analgesia. They used a heat laser stimulator on the skin of the hand to compare the effects of "direct" vision of the hand versus vision of an illusion of the hand via a mirror-box on the intensity of pain ratings and on the event-related potentials (ERPs) elicited by nociceptive and non-nociceptive stimuli. They were unable to demonstrate visual analgesia or any effect on pain unpleasantness when viewing the hand either directly through a glass panel or a mirror-image of the hand, compared to when viewing a neutral object. They ruled out the possibility of the interposed glass causing the lack in observed visual analgesia by repeating the experiment. They compared pain ratings when observing the hand directly as opposed to through the glass panel and there was no significant difference observed. However, they did observe greater nociceptive ERPs during vision of a neutral object compared to the hand, and greater non-nociceptive ERPs during vision of the hand compared to a neutral object. The researchers stated that the changes in brain activity were unlikely to be linked to the concept of "visual analgesia" reported by Longo et al. (2009), as there was no change in perceived intensity observed in this experiment. This study raises further questions about what specific factors need to be in place to bring about visual analgesia.

2.6.6ii Modulatory effects of vision on pain perception in a clinical population.

There are some indications that clinical pain *may* be subject to some of the same integration across multi-sensory modalities as seen with experimental pain. Wand et al. (2012) used a mirror with lower back pain patients to allow them to view their backs during pain-provoking lumbar spine movements. The view of their backs during movement proved to have an analgesic effect, demonstrating that visual analgesia potentially exists for clinical pain. The researchers did not investigate if magnification or minification of the viewed body part affected the analgesia.

Diers et al. (2015) supported these findings in a chronic back pain population. Using real-time video feedback, subjects' perceived pain intensity was reduced compared to viewing a neutral object, a video of another person of the same sex's back or a static picture of their own back. The authors cited Longo et al. (2009) to explain their results, suggesting that the increase in the sense of agency by monitoring the painful body part would augment the subject's body awareness potentially giving rise to top-down pain reduction. There was no significant difference in reported pain unpleasantness. Interestingly, an analgesic effect was also noted when the subjects were tested with their eyes closed, however the authors feel that there were likely to be two different mechanisms underlying these effects. In conclusions, Diers et al. (2015) proposed that real-time video feedback of movement could be a simple and beneficial treatment modality to incorporate into the management plans of chronic pain patients.

Visualisation was also documented to have an effect in a paper which describes a study, focussed mainly on improving two point discrimination (TPD) training success. Moseley and Wiech (2009) explored the effects of coupling visualisation of the painful body part with TPD training in a CRPS population, as opposed to TPD training alone.

Using a mirror-box to reflect the unaffected arm, there was a greater reduction in TPD threshold and pain levels post-training in the visualisation condition compared to the controls, however only the TPD difference lasted until the 2 day follow-up measurement. The pain relief was short-lived.

2.6.6iii Effects of visual distortion of size on pain perception in a healthy population.

Exploration of the effects of visual distortion of size on perceived pain has also gained momentum recently. Mancini et al. (2011) measured heat-pain threshold changes to assess the effect of visual analgesia under three different visual conditions. A mirror box was used to create the illusion of the ipsilateral hand, while that hand was stimulated with a thermal laser behind the mirror. In this experiment the visual condition was altered by replacing the normal mirror with a convex or concave mirror to produce a magnified or minified reflection respectively. The subjects were given a 10-minute adaptation period in which they focussed on the reflected image. A fake laser probe was applied to the reflected hand to prevent perceptual conflict. Questionnaires were used after each condition to check that the mirror had induced the illusion of the hidden hand, that the various mirrors were effective in generating variances in the perceived size of the reflected hand and to monitor base skin temperatures. Pain threshold was assessed by asking subjects to press a pedal at the moment the heat stimulus became painful. This same experiment was then repeated but the hand to be reflected was placed inside a wooden box, so the reflected image was a neutral object instead of their hand, and the three visual conditions repeated again. The results of these experiments confirmed the findings of non-informative visual analgesia which was established in the previous experiment. But this experiment went on to show that visual enlargement of the hand enhanced analgesia and visual reduction of the hand decreased analgesia. This suggests a dose-response relationship to analgesia. With magnification of the perceived size of the body part, there was an increased analgesic effect, and vice versa.

A distinctive difference between the methods of pain ratings collected in this experiment and those used by Longo et al. (2009) is that the subjects had to push a pedal the moment they perceived the stimulus as painful, while Longo et al. (2009) used VAS pain ratings. These ratings would be generated after potential modulation by cognitive, emotional and multisensory influences but the pedal mechanism better isolates the sensory-discriminative component of the pain before modulation comes in to play. Despite this, similar effects were observed, which demonstrates that visualising the body part modulates the sensory-discriminative component of the pain experience in the early somatosensory areas (Mancini et al., 2011).

One explanation for the mechanism underlying non-informative visual analgesia and for the increased analgesic effect noted when the body part is magnified is that there is increased attention turned toward the body part, which would have cognitive modulatory (inhibitory) effects on the pain experience. However, that a reduction in analgesia is observed in the minified condition disputes this as there is also likely to be increased attention drawn towards a body part that is viewed as unusually small.

Osumi et al. (2014) showed that visual analgesia and analgesia due to visual distortion of size of the affected body part are not necessarily standard responses. They explored the factors associated with modulation of pain by using the magnifying mirror-box technique employed by Mancini et al. (2011). Subjects were divided into two groups according to their pain threshold responses to the magnified condition. Subjects who displayed a higher threshold to the thermal stimulus also displayed more vivid somatosensory perception (two-point discrimination) and presented with a neutral emotional response to the view of the magnified hand. Subjects who displayed a lower pain threshold in response to the magnified condition were separated into the “low-threshold” group and this response was found to be associated with no significant difference between TPD in actual and enlarged size conditions, and with a more negative impression of the magnified image of the hand compared to the “high threshold” group. There was also a strong negative correlation between the differences in feelings towards the enlarged hand and the Body Attitude Questionnaire (BAQ) scores in both conditions.

While interesting and compelling, these above-mentioned studies were performed on healthy populations, using experimentally-induced cutaneous pain. The methodology employed only inflicted noxious stimuli in superficial structures. Most clinical pain presenting to physiotherapists are likely to be contributed to by noxious input from deep tissues (Bove et al., 2005), so exploration of the effects of visual distortion of size on deep tissue pain and clinical pain conditions is important.

2.6.6iv Effects of visual distortion of size on pain perception in a clinical population.

An exploratory experiment, using real-time video capture of subjects' hands, was able to manipulate the perceived size of painful and non-painful parts of the hand in an attempt to modulate pain experienced by twenty osteoarthritis sufferers (Preston & Newport, 2011). The study demonstrated that both stretching and shrinking the painful parts of the hand had an analgesic effect, halving the pain in 85% of the subjects. This effect was not witnessed when the entire hand or non-painful parts were stretched or shrunk (Preston & Newport, 2011). It is interesting that the analgesic effect was observed in both the shrunken and enlarged conditions. The authors propose that two distinct mechanisms could underlie these two effects, with the possibility that placebo could play a role in them. This research demonstrated that visual distortion of size has a modulatory effect on perceived clinical pain and that the use of visual illusions created using real-time video may be a potentially beneficial form of treatment for chronic pain sufferers.

A study by Moseley et al. (2008) revealed contrasting effects of visualisation and visual distortion of size in a clinical population of subjects with CRPS of a unilateral upper limb. Under four visual conditions, a small sample size of ten subjects watched their painful arm while they performed a program of ten hand movements at a pre-determined and standardised speed and amplitude. The four conditions involved looking at their arm: 1) normally, 2) through clear glass, 3) through magnifying binoculars, and 4) through minifying binoculars. The results indicated that the

magnified view of the limb significantly increased the perceived pain and extended the time for return to resting pain levels. Pain was least when they viewed the minified image of their arm during movements and recovery to pre-task pain was quickest under this condition (Moseley et al., 2008).

Working with an upper limb amputee suffering from significant phantom limb pain Ramachandran et al. (2009) were able to alleviate the phantom sensation and phantom pain of the elbow, wrist and proximal palm leaving the distal palm and digit pain unaffected. This was achieved by the subject attempting to perform symmetrical movements of both upper limbs while observing a reflection of the intact limb in a mirror-box. They explored changing the perceived size of the phantom limb with magnifying and minifying lenses, and found that magnification condition made no difference to the resting phantom pain, while shrinking the size of the phantom limb dramatically reduced the perceived pain. When the subject shut his eyes his pain returned immediately. This experiment confirmed in a clinical population the “visual analgesic” effect proposed by Longo et al. (2009) however, as reported by Moseley et al. (2008) the effects of visual distortion of size were in contrast to those found by Mancini et al. (2011). Perhaps the difference lies in the clinical pain populations studied.

Several significant differences exist between chronic and acute pain mechanisms (Phillips & Clauw, 2011). These may explain the different findings. In CRPS subjects the size and territory of the brain region which represents the affected limb has been seen to change (Lewis et al., 2007). Also, an impaired body image and sense of ownership have been linked to chronic pain syndromes (Lewis et al., 2007). These findings may well underlie the variances in effects noted. An alternative explanation may be the significant differences which appear to exist between superficial and deep tissue pain. Comparison between superficial and deep pain mechanisms is therefore warranted and necessary.

2.7 Deep versus Superficial Pain

Pain that arises from noxious stimulation of deep tissues appears to be quite different to pain that arises from noxious cutaneous stimulation, not only subjectively but also from a neuroanatomical and mechanistic perspective.

Witting, Svensson, Gottrup, Arendt-Nielsen, and Jensen (2000) compared pain from noxious skin stimulation to pain from noxious muscle stimulation, using equal stimuli of capsaicin. This study showed that cutaneous pain varied significantly to intramuscular pain in several ways. They found the quality of cutaneous pain to be commonly described as sharp, while muscle pain to be described as dull, throbbing, and less intense. Cutaneous pain tends to be well localised which is important for protection. A fast motor response can often remove an external noxious stimulus. Muscle pain was observed to be less localised (Witting et al., 2000). A separate study noted that while muscle pain is difficult to localise, pain arising from other deep structures, such as periosteum and fascia was actually well localised (Staff, 1988).

Peripherally, if the stimulus is strong enough, muscle pain can result in referred pain to subcutaneous structures distant to the site of the stimulus and the muscle being stimulated, while superficial pain does not demonstrate this phenomenon (Witting et al., 2000). Viscera were also shown to refer pain, however they appear to refer pain only to the skin (S Mense & Simons, 2001). Another observation was that the pain experience was reported to last longer when muscles are stimulated compared with when superficial tissues are exposed to the same painful stimulus (Witting et al., 2000).

At the spinal level, muscular pain differs from cutaneous pain in that the excitatory effects of unmyelinated A δ afferent fibres from muscle are subject to a strong segmental inhibition by myelinated A β afferent fibres. This inhibition is not observed with activation of the cutaneous C fibres (S. Mense, 2003).

In the central nervous system, nociceptive signals from muscle and skin are processed differently. The afferent nociceptive fibres from muscular tissue terminate in the

ventral PAG while those from the skin terminate in the lateral PAG (Keay & Bandler, 1993). A separate study showed there is not one specific region in the brain activated by muscle pain however the S2 was specifically activated by nociceptive cutaneous stimuli (Uematsu, Shibata, Miyauchi, & Mashimo, 2011). These differences that have been observed in the processing of superficial and deep nociception may explain the variance seen in the descending modulation of deep and superficial nociceptive signals.

Activity in the descending pain-modulatory pathways was found to influence the superficial and deep tissue nociceptor afferents differently. Spinal neurons with afferent input from deep tissues were observed to be located in the superficial dorsal horn and in and around lamina V, and were more strongly affected by the descending inhibition than cutaneous input to the same neuron (Yu & Mense, 1990). It was also observed that when descending pain-modulating pathways were experimentally interrupted, the observed activity in the ascending nociceptive pathways distal to the site of interruption is not equal between the cutaneous and deep nociceptor afferents. The activity was higher in neurones with input from deep nociceptors than in cells mediating cutaneous nociception (S. Mense, 2003). The two mechanisms are affected differently when descending inhibition is disrupted.

These differences demonstrate why the findings of experiments involving cutaneously-induced pain should not be directly applied to deep tissue pain. It appears that deep tissue and superficial tissue mediated pain mechanisms are considerably different from each other.

2.8 Summary of Literature Review

Over the past four decades, our concepts of mechanisms underlying pain have evolved radically to the point where we now believe pain to be a complex interaction of multiple inputs creating a subjective, multidimensional, emergent experience (Breen, 2002).

Nociceptors are sensory receptors that detect noxious stimuli. They respond to extreme and potentially damaging mechanical, thermal and chemical stimuli. The dorsal horn of the spinal cord is the ultimate target and relay station for the primary nociceptive afferents and the impulses conveyed by them. Despite the distinct laminae within the dorsal horn, there are branched collateral connections which are likely to allow for 'cross-talk' between nociceptive and non-nociceptive afferents at this level. It is thought that these potential connections may play a role in pain modulation (Basbaum & Jessel, 2000).

According to Basbaum and Jessel (2000) there are regions in the cerebral cortex which respond exclusively to nociceptive input. However a review by Legrain et al. (2011) disputed this and proposed that the areas that were once thought of as nociceptive specific are better thought of as salient specific. Nociception is just one of many types of salient information that gives rise to a particular salient specific neurosignature. ERPs elicited in response to a salient stimulus involve three processes, namely the detection, localisation and reaction to the salient and potentially dangerous physical threat

Nociceptive input is modulated by various factors at various levels which can allow for the production of a very different pain experience which is not only reflective of what is occurring at the tissue level. Modulation appears to occur in the periphery at the nociceptor terminals, within the laminae of the dorsal horn, and in supraspinal centres.

Besides evidence of the influence of cognition and emotion on our perception of pain, the intensity of pain may be influenced by the interaction from other sensory

modalities, such as tactile, nociceptive, auditory, olfactory, gustatory, and visual input. This phenomenon is known as multisensory modulation (Haggard et al., 2013). There has been significant interest in exploring the influence of multisensory integration on the pain experience, particularly vision, over the past several years.

Longo et al. (2009) showed that observation of the actual body part while an unseen painful stimulus is applied topically to that body part has an analgesic effect, as opposed to observation of a neutral object. They adopted the term “non-informative analgesia” as the stimulus is not visualised. This experiment was carried out in a healthy population.

Wand et al. (2012) used a mirror with lower back pain patients to allow them to view their backs during pain-provoking lumbar spine movements. The view of the subjects’ backs during movement proved to have an analgesic effect.

Diers et al. (2015) supported Wand et al. (2012) findings by observing visual analgesia in a chronic back pain population, demonstrating that the intensity of perceived back pain could be reduced by subjects simply watching their backs on a video screen.

However, Torta et al. (2015) did not observe visual analgesia when subjects viewed a mirror image of their hand or their hand directly, when compared to a neutral object. Valentini et al. (2015) recorded an analgesic effect only when viewing the hand was combined with the hand crossing the midline. No analgesia was experienced with visualisation alone in their study.

The effects of visual distortion of body size on pain perception have also been explored, with mixed results. Mancini et al. (2011) proposed a dose-response relationship to visual analgesia. With magnification of the perceived size of the body part an increased analgesic effect was observed whereas minification of the body part reduced the analgesic effect. Preston and Newport (2011) also reported a significant analgesic effect when the size of the view of the painful part of the hand in osteoarthritic sufferers was altered using real-time video.

More recent findings by Osumi et al. (2014) have suggested modulation of pain by visualisation is not a definitive response and is associated with certain conditions being in place. They found that subjects' somatosensory vividness (TPD) was reduced and a neutral emotional response was displayed by the subjects who demonstrated a higher pain threshold in the enlarged condition compared to the actual size condition. Subjects with strong obsessiveness towards the shape and appearance of their own bodies (as reflected by the BAQ scores) displayed negative feelings towards the magnified mirror visual feedback and these factors were found to be associated with a reduction in pain threshold in the magnified condition.

These articles suggest that visualisation, and particularly visual magnification of the painful body part might have some therapeutic value in the management of clinical pain states, although findings by Moseley et al. (2008) and Ramachandran et al. (2009) in CRPS patients and phantom limb pain patients respectively contradict these. They observed a modulatory effect of visual distortion of size however this was in the opposite direction to Mancini et al. (2011). Mechanisms underlying these two unique chronic pain syndromes may, however, operate differently and account for the different results observed.

The studies by Longo et al. (2009), Mancini et al. (2011) and Osumi et al. (2014) involved the application of noxious stimuli to the skin of subjects. It is thought that most clinical pain is contributed to by noxious stimuli from deeper tissues. Despite this, to date there have been no studies researching the effects of visualisation and visual distortion of size on experimental deep tissue pain. These questions are the topic of this thesis:

1. Does visualisation of the painful body part have an effect on deep tissue pain?
2. Will pain perception be modified by visual distortion of the size of the viewed quadriceps muscle, in the form of magnification?

CHAPTER THREE: PILOT STUDY

This study investigated the stability of the outcome measures used to assess experimental deep tissue pain in the form of Delayed Onset Muscle Soreness (DOMS). We also required data obtained from the pilot study to inform the power calculation for the primary study.

Eccentric exercise is a well-established method of inducing deep tissue soreness (Cheung, Hume, & Maxwell, 2003; Law et al., 2008). The exact mechanisms underpinning the pain experienced are not yet fully described, however DOMS is viewed as the perceptual correlate of a muscle adaptive process (Malm, 2001) induced by a novel bout of loaded, lengthening eccentric contractions. Typically delayed soreness peaks between 24 and 48 hours post exercise reaching complete resolution by day five to seven post exercise (Abraham, 1977)

While DOMS as an endogenous model of deep tissue pain has been widely used as an experimental methodology utilised to investigate deep pain, there is a dearth of information regarding the stability of the pain responses evoked during DOMS perception. Currently there are no data on the temporal reliability of the pain responses to movement or mechanical stimulation. This study therefore investigated the reliability of repeated evoked pain responses (over the course of 1 hour) to a standardised contraction in a DOMs affected muscle. Further, this pilot study provided data that informed the power calculations of the main study project.

Observation over the period of one hour was chosen as this was anticipated to be the length of time required for the testing procedure in the second session of the primary study. If the intensity of pain was demonstrated to remain constant then any changes in intensity experienced in the second session of the primary study could not be attributed to time and could therefore be attributed to the various visual conditions experienced by the subjects.

3.1 Study Design and Methodology

A repeated-measures within-subjects design was used in this pilot project. Ethics approval was obtained from the HREC of The University of Notre Dame Australia (Reference number: 014036F) and all participants provided written informed consent.

DOMS was induced in either the left or right quadriceps muscle of involved participants. A key feature of the primary study in this project was the requirement to be able to observe the sore body part. Quadriceps and forearm extensors were therefore considered ideal in this regard (as opposed to Triceps or Gastrocnemius for example). Test exercise revealed inconsistency in the level of DOMS induced in the forearm muscles, therefore this study focussed on DOMS in quadriceps muscle. The non-dominant limb was chosen for DOMS induction to standardise our procedure and also because the non-dominant limb was likely to be less conditioned than the dominant limb and hence yield more consistent delayed onset soreness responses.

3.1.1 Participants.

Ten healthy volunteers participated in this project. The researchers worked directly within their personal networks to identify individuals to participate in this study. Inclusion criteria for the pilot study: aged between 18 and 50 years, proficient in written and spoken English and the ability to provide informed written consent. Participants were excluded if they suffered ongoing lumbar spine problems, experienced abnormal tenderness to palpation of the soft tissues of the thigh, presented with reduced or excessive knee or hip movement, had suffered leg pain that required a visit to a health care professional within the previous 12 months or had sustained a fracture or dislocation of the leg within the last five years. They were also excluded if they had any ongoing medical or neurological conditions, consumed regular anticoagulant medication or medications known to influence pain sensitivity

(e.g. painkillers, anti-inflammatories, anti-depressants) or if they had recently trained the quadriceps with eccentric strength exercises (within the previous six months).

3.1.2 Experimental procedure.

Each subject attended two sessions 48 hours apart.

Session one.

The purpose of the 1st session was to collect subject demographics and to guide the subject through an exercise protocol which had been developed to induce DOMS in the non-dominant quadriceps muscle.

At the first visit, subjects received a Plain Language Statement which explained the process of the study and the implications of their participation. Informed consent was obtained and basic demographic information collected. The procedure of the study was explained, the subject's maximal isometric knee extension strength was determined, and they were then supervised in a one-on-one manner by the researcher through the exercise protocol aimed at inducing DOMS.

3.1.2i Maximal isometric knee extension strength.

The participant's maximal isometric strength of the non-dominant quadriceps muscle was established. This was performed with the subject in a seated position with knees and hips flexed to 90 degrees and feet flat on the floor. The subject extended the non-dominant knee until they were at a point 10° off full knee extension. The assessor then positioned a hand-held dynamometer against the anterior aspect of the distal tibia, just proximal to the talo-crural joint line. The subject was asked to attempt to extend the knee into full extension while the assessor resisted this action, resulting in a maximal isometric contraction. Once the dynamometer registered the

greatest force generated during the contraction the machine produced a “beep” sound which indicated the reading had been taken and the subject could relax. This was repeated 3 times to ensure consistency, with the average of these three scores being used to establish the sandbag weights required for resistance in the testing session (see “Testing procedure”).

3.1.2ii Exercise protocol to induce DOMS.

The participants undertook a protocol aimed at inducing DOMS in the non-dominant quadriceps muscle group. This involved the subject performing 150 repetitions, leaning backwards as far as possible in a slow and controlled manner from a half kneeling position (see Figure 1), then returning to the start position with assistance from the researcher.



Figure 1. Exercise starting position

This figure illustrates the half kneeling position assumed during DOMS-inducing exercise session.

The direction and speed of the backward lean was controlled by eccentric lengthening of the quadriceps muscle on the side the subject was kneeling on. The researcher acted as a 'spotter' during the eccentric component of the task to ensure safety. The 150 repetitions were divided into five sets of 30 repetitions, and the 30 repetitions were performed as three sets of ten. Subjects had a 30 second break between each set of ten repetitions and a two-minute break between each of the five sets.

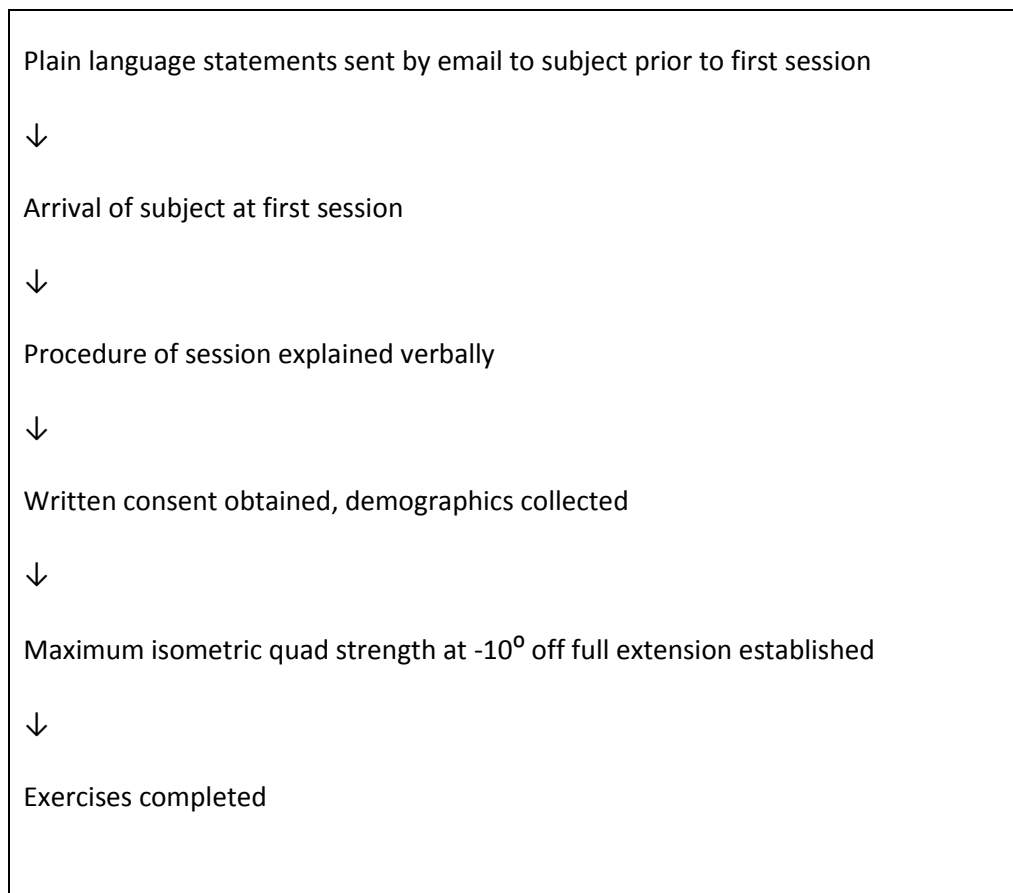


Figure 2. Flow diagram to represent sequence of events at subjects' first visit.

Session two.

The 2nd session took place 48 hours later. The purpose of this session was to determine subject eligibility to participate in the study and to assess the levels of pain evoked at 15 minute intervals with a view to establishing the stability of the outcome measures used to assess experimental deep tissue pain in the form of DOMS.

Subject's completed a validated Likert scale and then, if included in the study, underwent the testing procedure.

3.1.2iii Likert scale.

Upon arrival at the 2nd session, 48 hours later, subjects were asked to complete a previously validated Likert scale of delayed onset muscle soreness that recorded their perception of soreness experienced at that moment in time (see Appendix 3 for the full data Collection template) (Slater, Arendt-Nielsen, Wright, & Graven-Nielsen, 2005). They needed to score ≥ 3 to be included in the testing procedure.

1	A light soreness in the muscle felt only when touched/ a vague ache
2	A moderate soreness felt only when touched/ a slight persistent pain
3	A light muscle soreness while walking up and down stairs
4	A light muscle soreness when walking on a flat surface
5	A moderate muscle soreness, stiffness or weakness while walking
6	A severe muscle soreness, stiffness or weakness that limits my ability to move

Figure 3. Modified Likert Scale of muscle soreness

(Andersen, Arendt-Nielsen, Svensson, Danneskiold-Samsøe, & Graven-Nielsen, 2008). This scale was used by each subject to reflect their level of soreness at the second session.

3.1.2iv Testing procedure: evoked pain during DOMS.

The testing involved the subject performing quadriceps contractions at 15 minute intervals across the period of one hour and rating the pain evoked by these standardised contractions. Pain was rated using a numerical rating scale (NRS). Immediately following each standard contraction the participant was shown a 10cm

long NRS with zero anchored by 'no pain' and 10 with 'maximum pain'. Participants provided one NRS score following each contraction. Participants were placed in a seated position; feet flat on floor, hips and knees flexed to 90°. The load for each subject was standardised by calculating 40% of the average force recorded during the maximal isometric contractions completed during session one 48 hours previously. A sandbag of this established weight was attached to the distal tibial using a Velcro strap. The researcher then passively extended the affected knee joint. From this position the subject was then verbally guided to perform a controlled lowering of the foot towards the floor, allowing flexion of the knee toward 90° over the period of 3 seconds. This movement required eccentric lengthening contraction of the DOMS affected quadriceps muscle. This procedure was repeated three times and between each of the three repetitions the assessor extended the knee passively, returning it to the starting position of full knee extension. The visual conditions were identical across each test period in that the subjects looked straight ahead focussing on the same object during each repetition. After three contractions the sandbag was removed and the subjects were given a 15 minute washout period. This process was completed at the 15 minute mark, 30 minute mark, 45 minute mark and 60 minute mark (four sets of three contractions in total).

If, during the testing process, the subject rated their pain consistently as zero out of ten on the NRS, then the subject was excluded from the study.

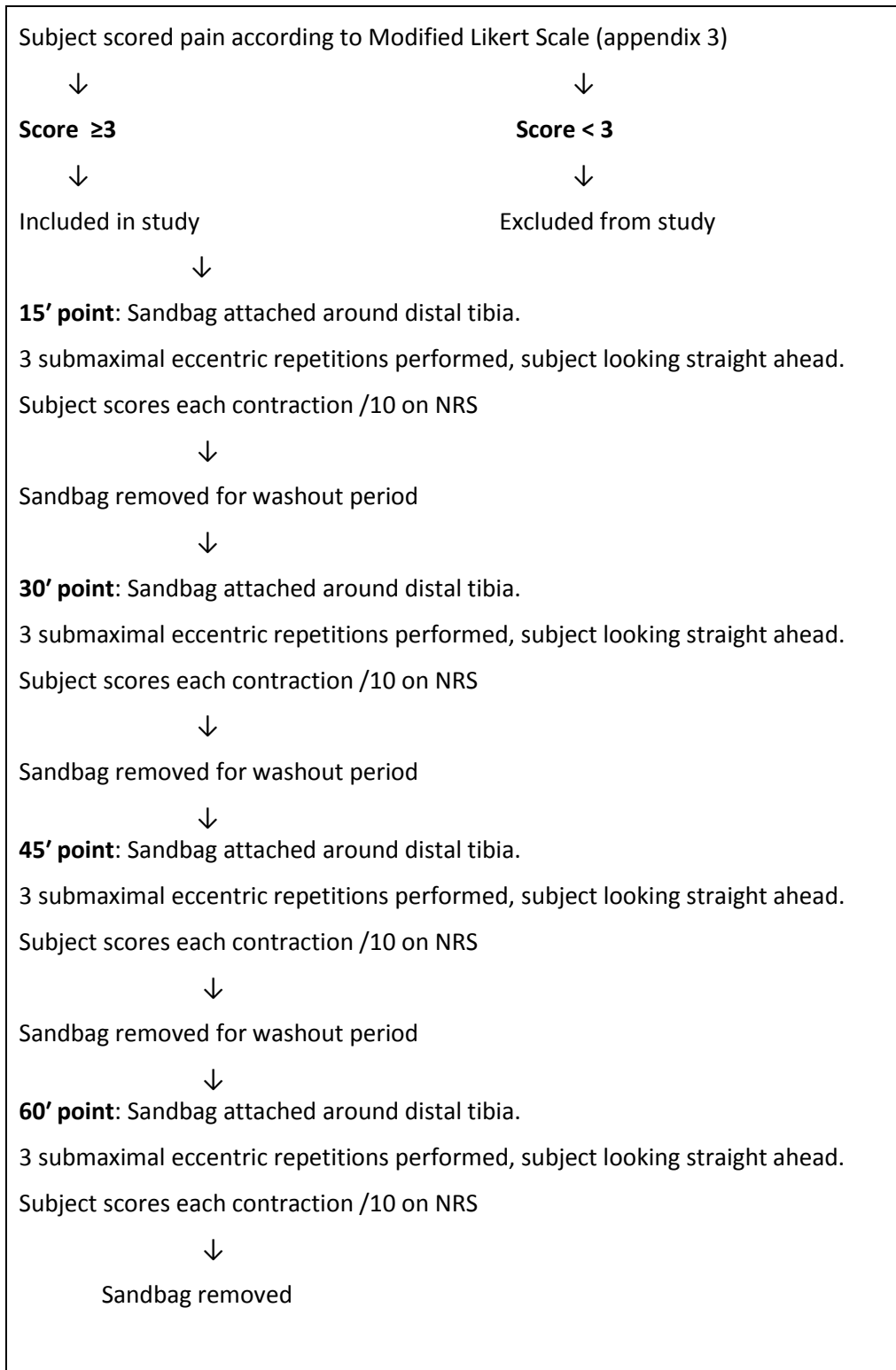


Figure 4. Flow diagram to represent sequence of events at subjects' second visit.

3.1.3 Ethical considerations.

Experimental induction of pain in human subjects is obviously fraught with ethical considerations. It is important that any pain induced is transient and does not represent injury or damage to tissues. In essence, the primacy of benefits outweighing risks has to be respected.

To fulfil these requirements in this research study it was decided to induce DOMS, which is a usual response to unaccustomed exercise that includes a preponderance of eccentric muscle actions.

With any form of exercise, there may be some risk of sustaining a musculoskeletal injury. The researchers believed that the risk of injury in this case was highly unlikely due to the type of exercise that was to be performed and the fact that the conditions would be controlled under the direct guidance of a Physiotherapist. The DOMS would likely cause some short-term discomfort (peaking at approximately 48 hours) in the thigh muscles of the non-dominant leg, before starting to dissipate. However previous research has shown that there are no long-term adverse effects from DOMS; in fact DOMS has been shown to be of benefit to the musculotendinous unit in the long-run, and high load eccentric exercise is used in the rehabilitation of common musculoskeletal conditions such as tendinopathy (Alfredson, 2003). In some cases and under some conditions DOMS has been shown to be of benefit to the participant in terms of longer term muscle development and function (Brockett, Morgan, & Proske, 2001). Thus, while exercise in this study was very specific, it was also very well controlled with the perception of soreness dissipating within a short period of time (e.g. maximum of seven to ten days) and protecting the muscle from subsequent DOMS from the same stimulus for up to six weeks.

Participation in the study was only accepted if there was very minimal risk associated with undertaking the tests involved and that the participant satisfied the criteria for participation. The subjects were free to stop the testing and withdraw from the study at any time and to withdraw any unprocessed data previously supplied.

If any adverse events arose, the chief-investigator was to arrange Physiotherapy or Medical management at location which is convenient for the participant at the expense of the co-investigator. The participant's condition was to be closely followed-up and monitored by the co-investigator. There were no foreseeable risks to the researchers.

The benefit of conducting this research was that a better understanding of the mechanisms of deep tissue pain would be gained, and this in turn could potentially contribute to treatment modalities targeting pain. As explained, this knowledge was gained at very low risk to the subjects. This study received Ethical approval by the Human Research Ethics Committee of the The University of Notre Dame Australia, Fremantle (Reference number: 014036F) (Appendix 5).

3.2 Data Analysis

3.2.1 Exploration of data and tests for normality.

Descriptive statistics were used to present demographic information and pain intensity scores following each contraction for each condition. Normality of distribution was assessed by visual inspection of Q-Q plots and further investigated with Shapiro-Wilk tests for normality. All results were reported as Mean \pm SD. A p -value of <0.05 was considered to represent statistical significance. All data were analysed using IBM SPSS Statistics 23.0 software. A statistician was consulted to assist with this process.

3.2.2 Stability of pain scores over the period of an hour.

A one-way repeated measures ANOVA was performed to compare pain scores (NRS) across the hour i.e. at 15 minutes, 30 minutes, 45 minutes and 60 minutes.

3.2.3 Reliability of pain intensity ratings across the period of an hour.

Temporal reliability of pain intensity across the four trials was evaluated using a two-way mixed model intraclass correlation co-efficient $ICC_{(3,1)}$ with absolute agreements. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity.

3.2.4 Sample size and minimal detectable difference size calculations.

The within-subject difference in mean pain intensity ratings (NRS) across the four time points was estimated and used as the minimal detectable change in the power calculation for the primary study.

3.3 Results

3.3.1 Exploration of data and tests for normality.

A total of ten subjects (three males, seven females) volunteered to participate. The mean age was 40.5 years \pm 2.80. Every participant rated their pain at a level of three or greater on the Modified Likert Scale at the beginning of Session two (Appendix 3), which meant every subject could be included in the testing component of the experiment.

The lowest pain score reported across the four testing sessions was 1 out of 10 and the highest was 8.5. The mean pain score and standard deviations across the four contraction repetitions are listed in Table 1 below. Visual inspection of boxplots of each test occasion indicated no outliers and Shapiro-Wilks test for normality demonstrated a normal distribution for all tests ($p > .05$).

Time	Mean \pm SD
15 minutes	4.37 \pm 2.34
30 minutes	4.10 \pm 2.02
45 minutes	4.20 \pm 2.26
60 minutes	4.23 \pm 2.26

Table 1. Mean and Standard Deviations of NRS pain scores across contractions

3.3.2 Stability of pain scores over the period of an hour.

A one-way repeated measures ANOVA was conducted to determine whether there were statistically significant differences in NRS rating across the four testing occasions. Mauchly's test of sphericity was not significant ($p > .05$) indicating the assumptions of sphericity had been met. The NRS ratings did not change significantly over time ($F_{3,27} = .459, p = .713$) with mean pain scores listed in Table 1 above.

3.3.3 Reliability of pain intensity ratings across the period of an hour.

In the two way mixed model intraclass coefficient calculation with absolute agreements for the four testing occasions, the sample was deemed the random effect while the repeated rating by the individual was considered the fixed effect. The $ICC_{(3,1)} = .987$ indicated extremely high reliability across the testing occasions.

3.3.4 Sample size and minimal detectable difference size calculations.

Based on data from the pilot study we estimated a within-subject difference in means of 0.3 on the pain intensity NRS. This was used as the threshold for determining the minimal detectable change in the power calculation for the primary study. The power of a cross-over design using a minimal detectable difference of 0.3 achieved 90% power when a minimum of 17 subjects were recruited, the standard deviation of the mean difference was 0.34 and the significance level was set at 0.05. It was decided that we should oversample by three subjects in the primary study to give a total sample of 20 subjects which would increase the power to 96%.

The results of the power calculations used to establish the required sample size for the primary study are documented and further explained in the “Results” section of Chapter Four.

3.4 Discussion

This pilot study provided two important contributions to this project and potentially the wider body of literature in which DOMS as an investigative tool in deep-tissue pain mechanisms is employed.

Firstly, the reliability of NRS pain intensity scores (to an evoked stimulus) over the period of one hour was demonstrated. An ICC of 0.987 indicates very high reliability. This information was crucial to enable valid interpretation of our primary study results.

On exploration of the literature regarding DOMS, it appears that there have been no previous studies investigating the within-session reliability of pain outcome measures. Many studies involving DOMS have investigated the effectiveness of certain treatment modalities on DOMS; for example the influence of vibration prior to exercise (Bakhtiary, Safovi-Farokhi, & Aminian-Far, 2007) or the effect of low-dose pulsed ultrasound administered daily post-exercise (Aytar et al., 2008; Howatson, Van Someren, & Hortobagyi, 2007). Many studies have been conducted as randomised controlled trials (RCTs) involving an intervention and a control group, with pain scores prior to the DOMS-inducing exercise session being compared to pain scores on consecutive days afterwards up to one week post-exercise. Pressure pain threshold at specified points along the muscle is a pain outcome measure assessed in some of these studies (Bakhtiary et al., 2007; Howatson et al., 2007; Olsen, Sjøhaug, van Beekvelt, & Mork, 2012). Another outcome measure used regularly is the visual analogue scales that consists of a 100 mm line with “no soreness” at one end and “unbearably painful” at the other, or similar, to determine muscle soreness in response to mechanically-evoked pain. This could be in the form of a stretch on the muscle (Aytar et al., 2008; Howatson et al., 2007) or use of the sore muscle (Matsuda, Kan, Uematsu, Shibata, & Fujino, 2015). These outcome measures would have taken a minimum of a few minutes to assess or observe, and it has merely been assumed that the pain scores would have remained constant over that testing period. However this has never been proven. This pilot study has now provided this evidence, particularly for pain which is evoked mechanically as in this pilot study, which in turn

assists to validate the results of previous studies which have conducted their testing over a period of time lasting up to one hour.

Some studies have used eccentric exercise-induced muscle soreness to investigate properties of a specific muscle group. In a study by Binderup, Arendt-Nielsen, and Madeleine (2010), the heterogeneity of the development of muscle hyperalgesia within the trapezius muscle was demonstrated by mapping the pressure-pain sensitivity throughout the muscle 24 hours after eccentric exercises were performed to induce muscle soreness. Fernández-Carnero et al. (2010) also mapped topographical pressure pain sensitivity. In this case it was around the lateral elbow of subjects who had exercise-induced lateral epicondylalgia in order to help establish and implicate the extensor carpi radialis brevis muscle belly in lateral epicondylalgia. Whilst threshold values are conceptually separate from evoked pain responses, the high temporal stability of the pain scores established through this pilot study, add weight to conclusions drawn from studies involving topographical mapping of various properties of muscles affected by DOMS.

To date, most studies investigating potential treatment modalities for DOMS have involved control and experimental groups as opposed to within-subject, repeated measures designs. Our study has demonstrated reliability of the within-session self-reported pain outcomes, allowing for the use of this design in future repeated-measure studies. DOMS is already frequently used as an experimental form of pain and as research into pain evolves the use of DOMS is likely to escalate as an ethical, safe and effective form of experimental deep tissue pain. It is therefore imperative that this reliability has been established for both the currently used RCT designs as well as potential future repeated-measures within-subject designs.

Secondly, the within-subject mean difference was calculated and used as the threshold for determining the minimal detectable change for the primary study. This was established to be 0.3 on a NRS scale. This value was used to assist us in calculating the sample size required in the primary study. Furthermore it also provides a threshold value below which changes in NRS may be considered 'noise' or natural

variance between individuals but above which may be interpreted as representing actual change in scores. Prior to this study, the value of this was largely unknown or assumed information.

3.5 Conclusion

This pilot study succeeded in establishing the stability of the movement-evoked pain responses during DOMS perception over the course of one hour. This was imperative to ensure valid analysis of our primary study data. Furthermore, this contributes to previous research involving DOMS whereby temporal stability of mechanically-evoked pain responses during DOMS has previously merely been assumed.

Based on data from the pilot study we estimated a within-subject difference in means of 0.3 on the pain intensity NRS. This was used as the threshold for determining the minimal detectable change in the power calculation for the primary study. Furthermore, this figure could be used in future research as a quantifiable threshold value to assist in determining significant effect sizes.

The sample size calculation for the primary study was based on a minimal detectable mean difference of 0.3 and on a standard deviation of the within-subject mean difference being 0.34. It was established that 17 subjects in the primary study to achieve 90% power (see section 4.2 for more detail on the sample size calculations).

CHAPTER FOUR: PRIMARY STUDY

This study attempted to establish whether visualisation of the painful body part has an effect on experimental pain induced by stimulation of deep tissue, and if so, whether this was in the direction of analgesia. Secondly, this study explored whether visual distortion of body size impacts pain perception, specifically magnification of the viewed body part. Exploration of deep tissue pain is necessary as most clinical pain is believed to be contributed to by noxious information from tissues deeper than the skin (Bove et al., 2005). Therefore the results of this study could potentially be more clinically relevant than the findings of studies involving experimental superficial pain, upon which our hypotheses were based.

This study has made use of “direct” visualisation of the thigh. For both the condition involving normal vision of the thigh and the condition involving a magnified view of the thigh the subject will observe their thigh directly, albeit through magnifying glasses in the magnified condition. This avoids the use of the mirror box which is the mechanism that Torta et al. (2015) has proposed to be responsible for the visual analgesia described by Longo et al. (2009), eliminating this as a potential confounder.

4.1 Study Design and Methodology

A repeated-measures within-subjects randomised experiment was carried out at The University of Notre Dame Australia, Fremantle. This study received ethics approval from the HREC of The University of Notre Dame Australia (Reference number: 014036F) and all participants provided written informed consent.

Variances in eye sight meant that it was not possible to use a consistent strength of magnifying lens in the magnified condition as the view of the thigh would not be in focus for some of the subjects. The testing position and strength of magnifying glasses was therefore slightly variable between subjects. The strength of the magnifying glasses ranged from +1.5 to +3.5. The strongest magnification possible was used whilst still maintaining clear focus of the thigh. The process to establish the appropriate glasses strength and thigh position will be explained in detail in the “Establishing the testing position” section below.

4.1.1 Participants.

A cohort of 20 healthy individuals were recruited using a general email advert and a snowball sampling technique of the students and staff of The University of Notre Dame Australia. Due to the fact that some of the subjects were current students of the School of Physiotherapy, there was the possibility of bias being an issue. To mitigate this problem, the author ensured that none of the subjects were her current students, and each participant was clearly advised that they may withdraw at any stage of the study with no consequences.

Inclusion criteria for the primary study were identical to those of the pilot: aged between 18 and 50 years, proficient in written and spoken English and the ability to provide informed written consent. Participants were excluded if they suffered ongoing lumbar spine problems, experienced abnormal tenderness to palpation of the soft tissues of the thigh, presented with reduced or excessive knee or hip

movement, had suffered leg pain that required a visit to a health care professional within the previous 12 months or had sustained a fracture or dislocation of the leg within the last five years. They were also excluded if they had any ongoing medical or neurological conditions, consumed regular anticoagulant medication or medications known to influence pain sensitivity (e.g. painkillers, anti-inflammatories, anti-depressants) or if they had recently trained the quadriceps with eccentric strength exercises (within the previous six months). An exclusion criterion unique to the primary study was any participant who required glasses to obtain normal vision. The magnified condition in the primary study was established by fitting the subject with a pair of magnifying glasses. This would have been physically impossible to do if they were already wearing glasses. Wearing contact lenses at the time of testing was acceptable as long as the subject had normal vision with the lenses in situ.

4.1.2 Experimental procedure.

Each participant attended two sessions, 48 hours apart.

Session one.

The purpose of the first session was to obtain subject demographics, to establish a suitable test position for the 2nd session for each subject, to complete two questionnaires and to guide subjects through an exercise protocol aimed at inducing DOMS.

On arrival, subjects received a Plain Language Statement, written informed consent was obtained and basic demographic information collected. The procedure of the study was explained to the subjects and they were asked to complete the short-form Pain Anxiety Symptoms Scale (PASS-20) questionnaire (see Appendix 1) and the Pain Sensitivity Questionnaire (PSQ) (see Appendix 2). The researchers felt it would be worthwhile to explore for any interaction between pain anxiety, trait sensitivity and

pain during the various visual conditions, hence the inclusion of these questionnaires. Thereafter the subject's maximal isometric knee extension strength was assessed and the test position established in preparation for the 2nd session. Finally the subjects underwent the exercise protocol aimed at inducing DOMS.

4.1.2i Maximal isometric knee extension strength.

The assessor used a hand-held dynamometer to establish the maximum force each participant could generate with an isometric quadriceps contraction. This process was identical to that done in the pilot study- performed in a seated position, with the knee extended to 10° off full extension. The subject was instructed to extend the knee maximally against the resistance of the dynamometer until the "beep" sound was heard. The maximum force generated during the contraction was recorded on the dynamometer and documented. This was repeated three times for consistency and the average score used to calculate the amount of resistance required during the testing session (see 4.1.3vii Testing procedure)

4.1.2ii Establishment of testing position.

During the first session the assessor sought to establish an appropriate test position and the maximal magnification strength which could be used during the testing process of the second session. Subjects were seated on a narrow desk, leaning back comfortably against a wall for back support. Each subject donned the strongest magnifying glasses (+3.5) and looked at their thigh to see if the thigh was in clear focus. If not, they flexed their hip bringing their knee up towards their head. They were instructed to stop at the point where the thigh came into focus. If the subject was unable to focus clearly on the thigh at any point through their comfortable range of hip flexion then the glasses with 0.5 less magnification strength was attempted next. The same procedure was repeated until the subject was able to find an appropriate pair of glasses and the exact position of their thigh to achieve clarity.

Once the correct magnifying strength and thigh position had been established the magnification strength and hip flexion angle was documented and used consistently for all four visual conditions in the testing session. The angle of hip flexion ranged between 90° and 140° between the subjects.

4.1.2iii Exercise protocol to induce DOMS.

The participant undertook exactly the same protocol as in the pilot study aimed at inducing DOMS in the non-dominant quadriceps muscle group. They were closely monitored and the movement was controlled by the researcher.

4.1.2iv PASS-20.

The PASS-20 consists of 20 items and measures fear and anxiety responses specific to pain. Subjects were asked to circle one number from 0 which represents “never” to 5 which represents “always” for each situation described. The total score out of 100 was established by calculating the sum of all the items. This questionnaire took 5-10 minutes to complete.

4.1.2vi PSQ.

The PSQ consists of 17 items. Each item describes a daily life situation and asks the subject to rate how painful this would be for them on a scale of 0 to 10. There are normally non-painful situations serving as sensory references interspersed between a variety of types of painful situations e.g. hot, sharp etc. The PSQ-total score was calculated as the average rating of items 1, 2, 3, 4, 6, 7, 8, 10, 11, 12, 14, 15, 16, and 17 (all but the three non-painful items). This questionnaire took between 5-10 minutes to complete.

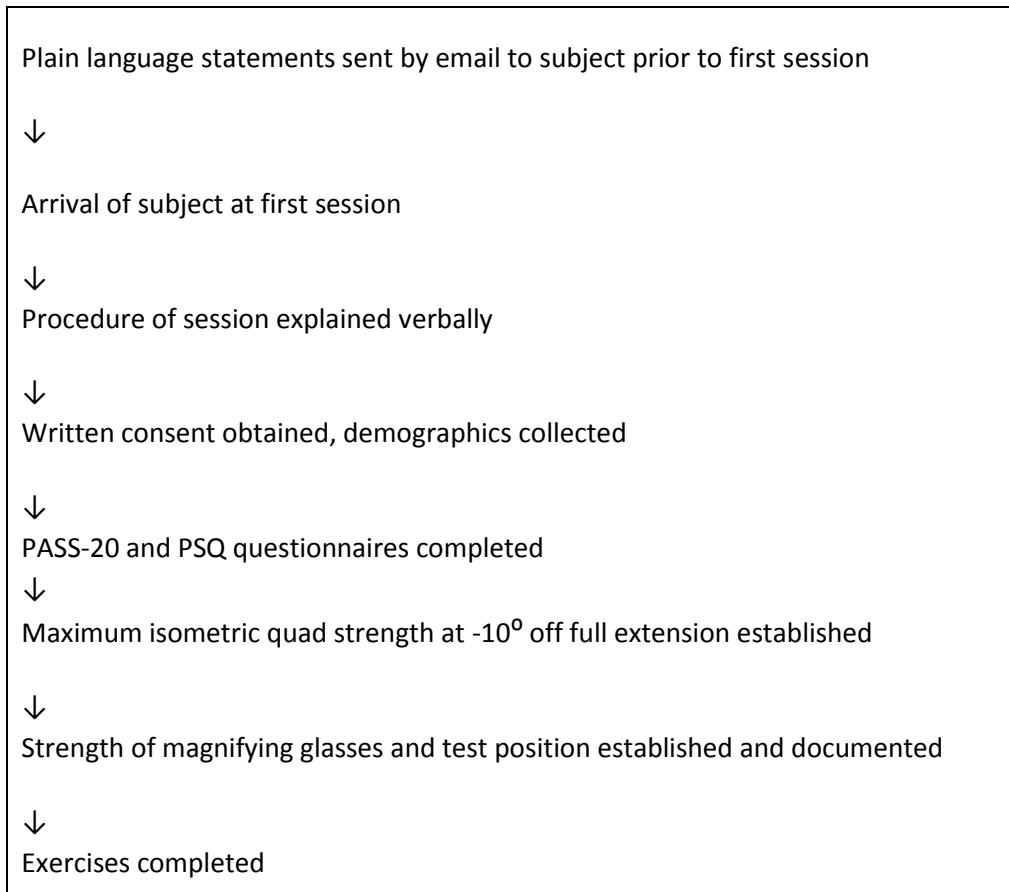


Figure 5. Flow diagram to represent sequence of events at subjects' first visit.

Session two.

The 2nd session was attended 48 hours after the 1st session. The purpose of the 2nd session was to determine the subject's eligibility for continuation in the study, establish the randomisation order of exposure for that subject to the four visual conditions and then to perform the testing. Eligibility to participate was established with the subject completing a previously validated Likert scale of delayed onset muscle soreness.

4.1.2vi Likert scale.

At the 2nd session following the DOMS induction in session one, subjects completed a previously validated Likert scale of delayed onset muscle soreness that recorded

their perception of soreness they were experiencing at that moment in time. They needed to score ≥ 3 and fulfil all other inclusion criteria to be included into the study (see Appendix 4 for full data Collection template).

1	A light soreness in the muscle felt only when touched/ a vague ache
2	A moderate soreness felt only when touched/ a slight persistent pain
3	A light muscle soreness while walking up and down stairs
4	A light muscle soreness when walking on a flat surface
5	A moderate muscle soreness, stiffness or weakness while walking
6	A severe muscle soreness, stiffness or weakness that limits my ability to move

Figure 6. Modified Likert Scale of muscle soreness.

(Andersen et al., 2008).

4.1.2vii randomisation of exposure to visual conditions.

Eligible subjects were assigned the next participant number and this was recorded on the data capture sheet. They were asked to open the particular sealed envelope which corresponded to the participant number they had been assigned. Inside was a letter: A, B, C or D which matched one of four particular sequences of order of exposure to the visual conditions. The letters had been randomly generated by computer using Excel software and the four sequences had been derived using a Latin Square design. Once the order of exposure to the visual conditions had been established the testing procedure began.

4.1.2viii Testing procedure: evoked pain during DOMS.

Testing was performed at the 2nd session 48 hours after the 1st session. The testing involved the subject performing quadriceps contractions under load at 15 minute intervals, under various visual conditions and rating the pain evoked by these standardised contractions. This process was completed at the 15 minute mark, 30 minute mark, 45 minute mark and 60 minute mark.

The four visual conditions we investigated were:

- Visualisation of the thigh without visual manipulation
- Visualisation of the thigh with magnifying glasses
- Visualisation of the contralateral thigh
- Visualisation of a neutral object

“Visualisation of the thigh without visual manipulation” involved the subject merely observing the mid-thigh of the affected leg, positioned in their pre-established testing position. A sandbag was fitted to the distal tibia at the start of the fixation period. The load of the sandbag was standardised by calculating 40% of the average force recorded during the maximal isometric contractions completed during session one, 48 hours previously. This was attached to the distal tibia using a Velcro strap at the commencement of each fixation period and only removed at the start of the washout period. The same sandbag was used for each of the four conditions.

“Visualisation of the thigh with magnifying glasses” was the condition used to create the magnified image of the affected thigh. Again, subjects observed the mid-thigh of the affected leg, but this time they observed the thigh through magnifying glasses. On completion of the testing process during the magnified condition, subjects were asked to rate the degree of magnification they were experiencing while wearing the glasses using the “Scale of perceived enlargement”, prior to the sandbag being removed for the wash-out period.

“Visualisation of the contralateral thigh” involved the subjects observing the mid-thigh of the unaffected limb while the subject was still set up in the testing position. The affected limb was hidden from view by a box that was fitted over it. The box was also covered by a towel to ensure no visualisation of the affected thigh.

The final condition, “Visualisation of a neutral object”, made use of a box as the neutral object. A box was placed over the affected thigh to hide the view of the thigh. The limb was maintained in the identical set-up position and the sandbag was fitted to the distal tibia throughout the fixation and testing procedure as per the other three conditions. The subject was asked to focus on the box for that condition.

The fixation period lasted five minutes and was aimed at allowing the subject to adapt to the new visual condition. Following this period, the subjects performed the quadriceps contractions against the load of the sandbag. The researcher passively extended the affected knee joint. From this position the subject was verbally guided to perform a controlled lowering of the foot towards the floor, allowing flexion of the knee toward 90° over the period of 3 seconds. This movement required an eccentric lengthening contraction of the DOMS-affected quadriceps muscle. This procedure was repeated three times and between each of the three repetitions the assessor extended the knee passively, returning it to the starting position of full knee extension. Pain was rated using an 11-point numerical rating scale (NRS) with 0 reflecting no perceived pain and 10 reflecting the worst possible pain. Pain was rated by the participant immediately following each standard contraction. After three contractions the sandbag was removed and the subjects were given a five minute washout period. This process was repeated for all four visual conditions.

If the subject rated their pain consistently as zero out of ten on the NRS, then the subject was excluded from the study.

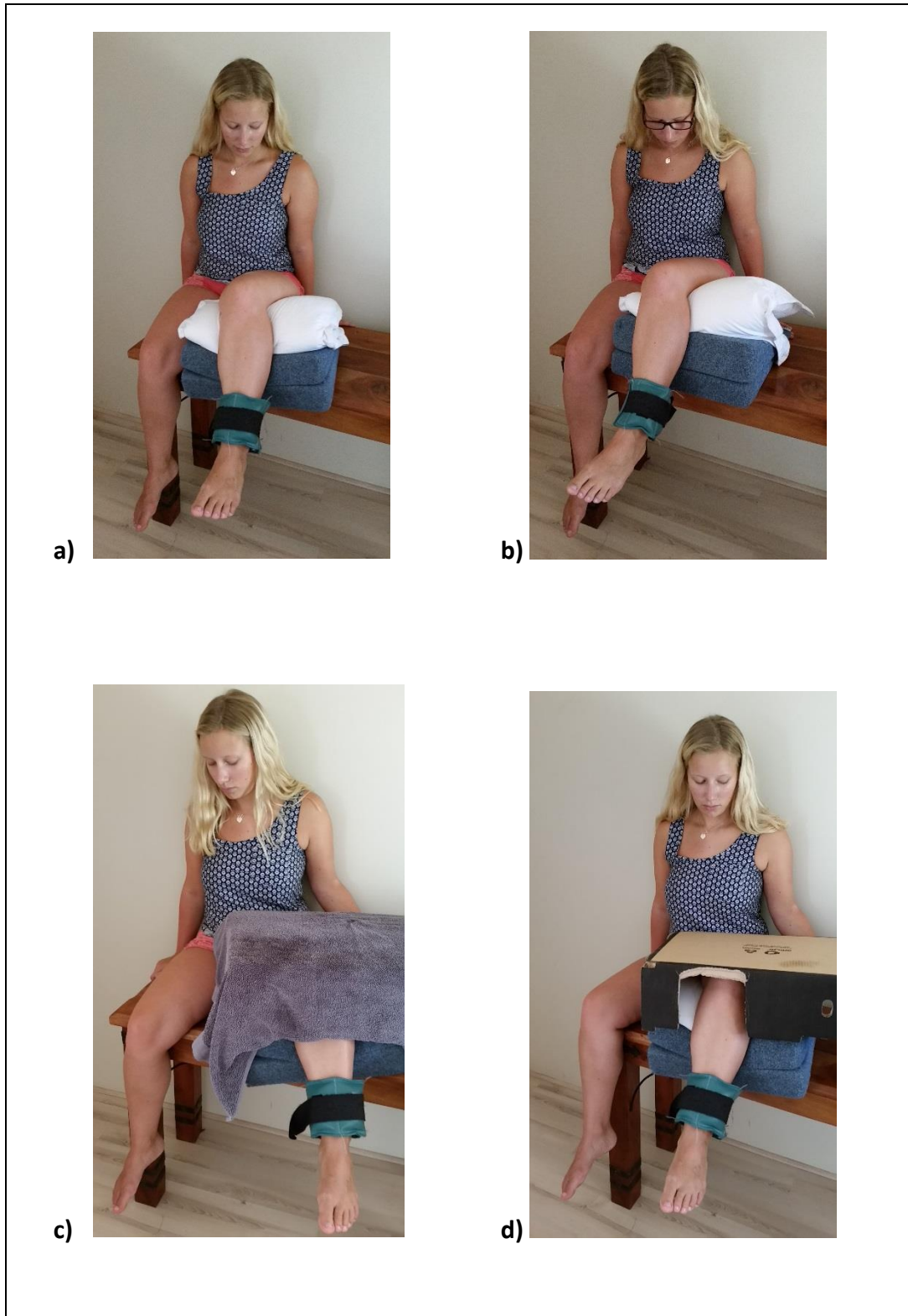


Figure 7. The four visual conditions.

This figure illustrates the four visual conditions we investigated; namely the effect of a) normal vision b) magnified condition c) vision of contralateral thigh d) vision of neutral object on the perceived level of pain.

4.1.3viii Scale of perceived enlargement.

Varying strengths of magnifying glasses had to be used to accommodate for differences in people's eyesight. Following the eccentric contractions performed with the magnifying glasses on, to ensure that visual manipulation of leg size by the glasses had been effective, the subjects estimated the effect of the glasses using a nine-point scale. The subjects were asked to rate the degree of magnification they perceived prior to removing the glasses, using the following scale:

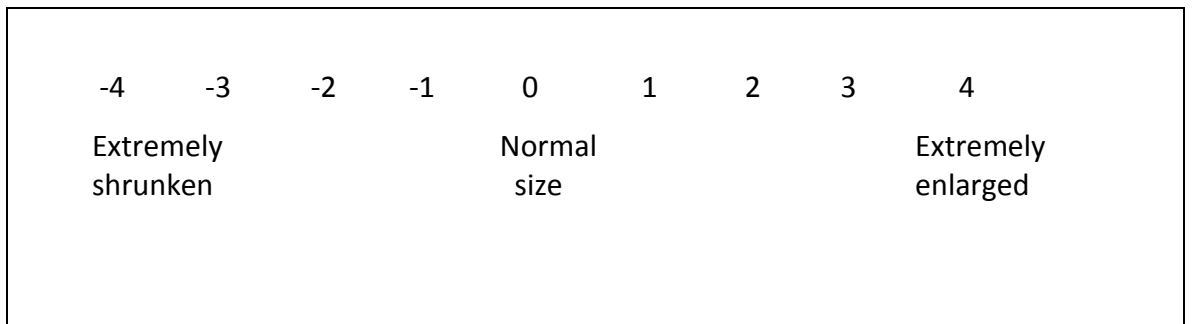


Figure 8. Scale of Perceived Enlargement.

This scale was used by the subjects during the magnified condition to estimate the effect of magnification induced by wearing the glasses.

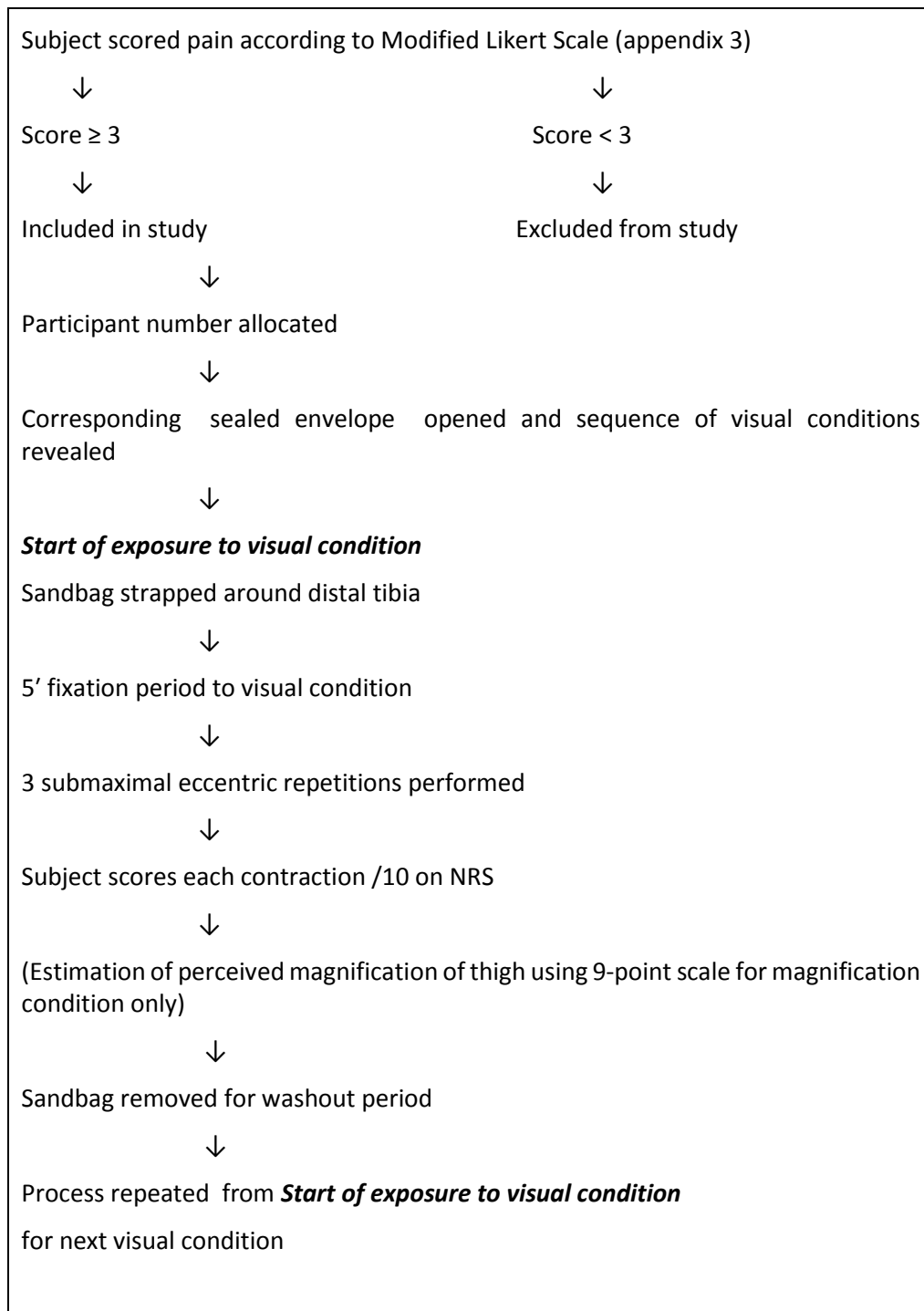


Figure 9. Flow diagram to represent sequence of events at subjects' second visit.

4.2 Data Analysis

4.2.1 Sample size calculation.

Based on data from the pilot study, the within-subject difference in means in pain intensity ratings (NRS) over the hour was estimated to be 0.3 and this was used as the threshold for determining the minimal detectable change in the power calculation for the primary study. The power of a four phase cross-over design using a minimal detectable difference of 0.3 achieved 90% power when a minimum of 17 subjects were recruited, the standard deviation of the mean differences was 0.34 and the significance level was set at 0.05. We oversampled by three subjects in the primary study to give a total sample of 20 subjects which increased the power to 96%.

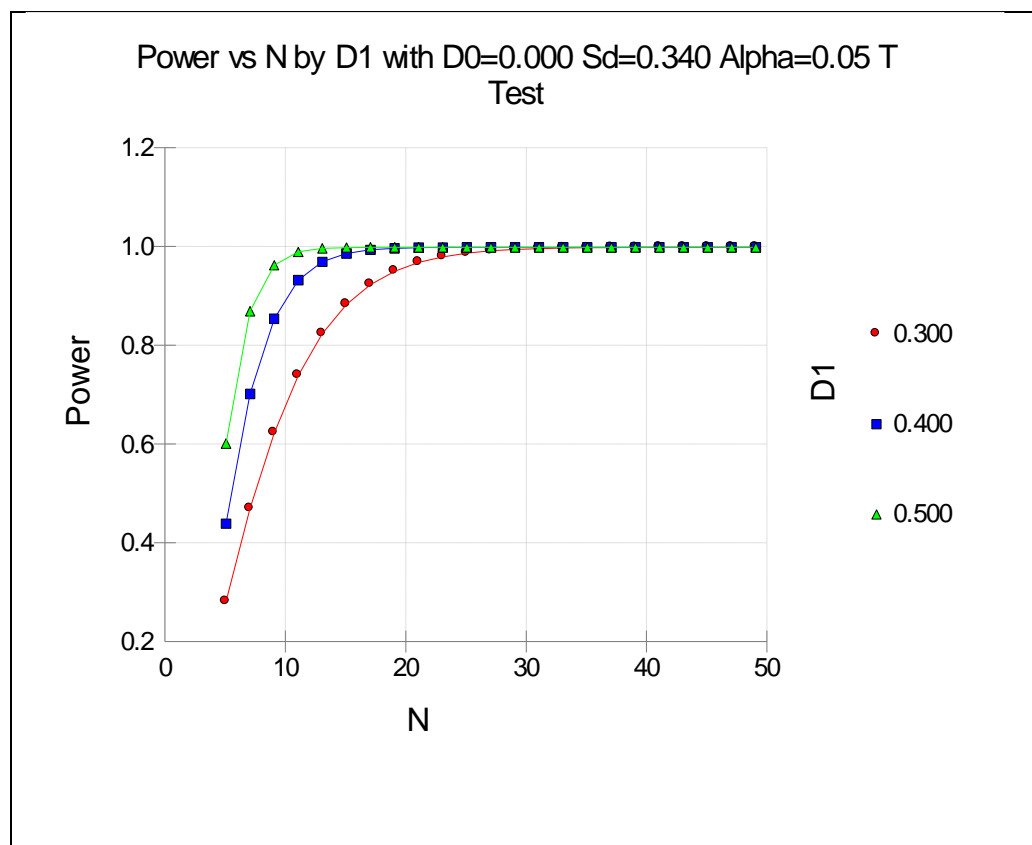


Figure 10. Graph to establish sample size required in Primary Study.

This graph gives the sample size for three different values of the mean difference and the impact on Power (0.3, 0.4 and 0.5). A sample size of 20 retains a power of greater than 80% in all three cases.

4.2.2 Exploration of the data and tests for normality.

Descriptive statistics were used to present demographic data, pain ratings for each experimental condition and results from the PASS-20 and PSQ. Normality of distribution was assessed by visual inspection of Q-Q plots and further investigated with Shapiro-Wilk tests for normality. All results were reported as Mean \pm SD. A p value of $<.05$ was considered to represent statistical significance. All data were analysed using IBM SPSS Statistics 23.0 software.

4.2.3 Methodological checks.

4.2.3i Effectiveness of the glasses used to magnify the image of the thigh.

Descriptive statistics were used to report the results of the nine-point scale to establish the effectiveness of the glasses used to produce an enlarged image of the affected thigh during the “magnified” condition. A score of 0 would indicate that the thigh is perceived as being the same size as normal, with increasing positive scores indicating increasing degrees of perceived enlargement.

4.2.3ii Exploration of potential confounding variables.

The effects of co-variates on the primary dependent variable were analysed using a general linear model (repeated measures) with the relevant covariate included. Age, trait pain sensitivity (PSQ) and trait pain anxiety (PASS-20) were treated as covariates within the model whilst gender and order effect were treated as between-subject factors.

4.2.4 Hypothesis testing.

4.2.4i Effects of vision on pain perception.

A general linear model (repeated measures) was used to test the primary hypotheses. Pain intensity rating was the dependent variable and the visual condition was the independent variable with four levels (neutral object, visualisation of contralateral thigh, normal visualisation of thigh, magnified visualisation of thigh). Covariates and between-subject factors found to be statistically significant were adjusted for in the overall general linear model test.

4.3 Results

4.3.1 Exploration of the data and tests for normality.

A total of 22 subjects were recruited from staff and students at The University of Notre Dame Australia. One participant was excluded at the start on the first session as he did not meet the inclusion criteria (he was taking regular analgesia for cervical spine-related pain). A second was excluded at the end of the second session as he recorded no pain with any eccentric contraction during any of the experimental conditions. Twenty participants met all inclusion criteria and were included in the analyses. All participants completed all experimental conditions and there were no missing data.

Of the 20 participants 8 were male and 12 female. The average age was 26.45 years \pm 7.0 with a range from 20 to 47 years. The average PSQ score was 2.58 \pm 0.76. This score would be classified as a low trait sensitivity score (Kim et al., 2015). The average PASS-20 scores for our study was 17 \pm 15.14. Again, this would be classified as a low pain-related anxiety score (Abrams, Carleton, & Asmundson, 2007).

At the start of the second session the average score on the Modified Likert scale representing pain intensity during the previous 24 hours was 3.9 \pm 0.54, with a range

of 3 (the minimum entry criteria) to 5. This meant that every participant was eligible to continue with the testing procedure and could be included in the study.

Shapiro-Wilks tests for normality demonstrated the majority of the data was not normally distributed and there were several outliers across three out of the four conditions. In order to meet the assumptions behind the general linear model (repeated measures) the data were log-transformed. All further analysis of the primary dependent variable was performed on this new log-transformed data. Log-transformation resulted in the majority of the data being normally distributed (Shapiro-Wilks test $p > 0.05$) and a significant loss of outliers (only one outlier for one condition).

4.3.2 Methodological Checks.

4.3.2i Effectiveness of the glasses used to magnify the image of the thigh.

The average “Effect of Magnification” questionnaire score was 1.8 ± 0.6 , with a minimum value of 1.0 and a maximum value of 3.0, indicating the glasses to be effective in producing an enlarged image of the thigh. A score of 0 would indicate that the thigh is perceived as being the same size as normal, with increasing positive scores indicating increasing degrees of perceived enlargement.

4.3.2ii Exploration of potential confounding variables.

Age, PSQ and PASS-20 were individually included as covariates in the general linear model (repeated measures). All analysis demonstrated that assumptions of sphericity were met. There was no significant interaction between the condition and age, ($F=.357_{(3,54)}$, $p=.784$). Analysis of PSQ and condition demonstrated no interaction ($F=1.596_{(3,54)}$, $p=.201$). Lastly, PASS-20 and condition similarly demonstrated no interaction ($F=1.331_{(3,54)}$, $p=.274$).

Gender and order effect were explored as between-subject factors in the general linear model (repeated measures). There was no interaction between gender and condition ($F=0.098_{(3,54)}$, $p=.961$). A main effect for order by condition was found ($F=2.111_{(9,48)}$, $p=.047$) however post-hoc pair-wise comparisons were not statistically significant ($p>0.05$ for all comparisons).

4.3.3 Hypothesis testing.

4.3.3i Effect of vision on pain perception.

The mean pain intensity reported under each of the visual conditions can be found in Table 2. To determine if pain intensity varied between the visual conditions a general linear model (repeated measures) on the log-transformed data across all four visual conditions was used. As there was no evidence of an interaction between order, age, gender, PASS-20 or PSQ and condition, treatment effects were estimated unadjusted for these factors. A significant main effect of visual condition on pain score (NRS) was found ($F=2.797_{(3,57)}$, $p=.048$). However Bonferroni corrected post-hoc pairwise comparisons demonstrated no significant difference between any conditions, indicating that pain intensity was not significantly influenced by visual condition. We therefore accept the null hypothesis that vision and visual distortion of size in the form of magnification have no significant effect on the intensity of perceived experimental deep tissue pain.

Condition	Mean ± SD
Neutral object	2.68 ± 1.16
Contralateral thigh	2.73 ± 1.48
Normal vision of thigh	2.60 ± 1.65
Magnified view of thigh	3.05 ± 1.57

Table 2. Mean and Standard Deviations of NRS pain scores across the four conditions.

4.4 Discussion

4.4.1 Summary of main findings.

The aim of this project was to examine whether visualisation of the painful body part has an effect on experimental deep tissue pain in a healthy population. Secondly, we set out to determine if visual distortion of size, in the form of magnification, had a further effect on the perceived pain.

Recent studies investigating visual analgesia in response to observation of a superficial noxious stimulus led to the first hypothesis: that visualisation of the painful body part could influence deep tissue pain. Since results of these studies have been mixed the direction of the effect could not be predicted with confidence.

Studies investigating the effect of visual distortion of size on perceived pain in both clinical and non-clinical populations have also reported contrasting results. Our study aimed to establish the effect of magnification of the painful viewed body part on deep tissue pain in a healthy population. We hypothesised that visual magnification would produce an effect on the intensity of perceived pain, again without being able to predict the direction of the effect.

Contrary to our first hypothesis we found that direct visualisation of the painful body part, which in this case was the anterior thigh, had no significant effect on pain intensity ratings of experimental deep tissue pain. Furthermore, visual distortion of size in the form of magnification had no significant effect on perceived pain levels in a healthy population.

When we explored for potential confounding variables, the covariates of age, pain sensitivity and trait anxiety did not demonstrate any significant interactions with the visual conditions and neither did gender and order effect when explored as between-subject factors.

4.4.2 Relationship to existing literature.

This is a novel study. There are no similar studies against which our study can be directly compared since no previous studies have investigated the effects of vision and visual distortion of size on experimental, deep tissue pain. Our hypotheses were based on the findings of experiments involving noxious stimuli applied cutaneously to induce experimental, superficial pain in healthy subjects and on studies involving clinical populations. Significant differences appear to exist between the underlying mechanisms and the presentation of superficial and deep pain. With this in mind, we anticipated but could not confidently predict a visual analgesic effect on deep tissue pain. In our study vision had no effect on perceived pain.

Our findings contradict those of Longo et al. (2009), who demonstrated an analgesic effect of visualisation on superficially-induced experimental pain in a healthy population. Although both studies involved experimental pain, a major difference between the two studies is that our study involved noxious stimulation of deep tissue while that of Longo et al. (2009) involved superficial stimulation. It is possible that the analgesic effect to visualisation observed when the cutaneous tissues were stimulated is optimised as the tissues being stimulated are directly observable and visualisation could reduce the threat value of the pain by providing the individual with information that all is well with the stimulated tissue. This is in contrast to deep tissue stimulation where only the overlying skin can be observed however the actual tissue affected cannot be visualised directly so adding visual input would not have significant informative value in terms of perception of safety of the stimulated structure. A further important difference is the different method of visualisation employed in the two studies. It has been proposed that the visual analgesic effects observed in the experiment by Longo et al. (2009) may be more as a result of viewing a reflected image than due to the effects of vision (Torta et al., 2015). Torta et al. (2015) investigated their proposal by comparing pain intensity ratings of superficial noxious stimuli with subjects observing their hand directly, an illusion of their hand via the use of a mirror-box and a neutral object. There were no significant differences noted across the different conditions and no visual analgesia was observed under any

of the conditions. Our findings would tend to support those of Torta et al. (2015) as our study excluded the use of a mirror box and no effect was observed.

Our findings also support some of the observations of Valentini et al. (2015), who did not observe a visual analgesic effect when the hand was situated on the normal side of the body. They only found visual analgesia of experimental, superficial pain to exist when the limb was placed on the contralateral side of the midline. In our current study, we did not explore the effects of vision coupled with crossing the midline on deep tissue pain, but our results concur in that we did not observe visual analgesia when the limb was observed in its regular ipsilateral position.

When we compare our study to those which investigate the effects of vision in clinical populations, our results differ. Both Wand et al. (2012) and Diers et al. (2015) observed analgesic effects with vision of the back in chronic back pain sufferers. Wand et al. (2012) made use of a mirror to allow subjects to view their backs, while Diers et al. (2015) used real-time video feedback. Perhaps the mechanism driving the effects observed in both these experiments was similar to that underlying the observations in the experiments which used a mirror-box (that of possible conflict between the somatosensory, visual and proprioceptive representations requiring higher cognitive processing levels with resultant pain inhibition). Our study made use of direct visualisation i.e. no reflected images were generated and no analgesic effect was observed. An alternative and very plausible explanation for the positive findings in response to visualisation may be due to the particular part of the body which is involved. In both these studies the part visualised i.e. the back, is a region of the body which is not readily visible to the subject. It was evident that the introduction of visual feedback from the back region made a significant difference to the perceived pain intensity. In our study, the affected body part is body part that is usually visible to the subject so the novelty and additional information provided by visualisation would have been minimal.

With regards to our second hypothesis proposing that visual magnification of a painful body part would induce an effect on pain, the results of this study differ from

Mancini et al. (2011) upon which the hypothesis was formulated. Our study found no significant effect of the visual magnification condition although Mancini et al. (2011) did note an analgesic effect. A major difference between the two studies is that Mancini et al. (2011) employed a topical noxious stimulus which induced superficial pain, while our study involved deep tissue stimulation. The linear relationship between pain perception and visual magnification that was demonstrated by Mancini et al. (2011) was less consistently demonstrated by Osumi et al. (2014) in that only the subjects who displayed more vivid tactile perception demonstrated an increase in pain thresholds to the magnified condition (the “high” threshold group). The “low” threshold group, demonstrating a lower pain threshold, displayed a negative emotional response to the enlarged view and no TPD change. Again, the pain induced in this experiment was perceived superficially. These findings contrast those in our present study where no analgesia nor any effect of magnification was observed. Mancini et al. (2011) and Osumi et al. (2014) both made use of mirror-boxes to enlarge the view of the limb and this variance in methodology could be a contributing factor to the different results obtained between the studies, as has been suggested by Torta et al. (2015). An alternative explanation is that superficial pain mechanisms vary from deep pain mechanisms and that researchers and clinicians should avoid extending the results of studies involving superficial experimental pain to experimental deep pain or clinical pain presentations (S. Mense, 2003; Uematsu et al., 2011; Witting et al., 2000). The question remains whether findings of studies such as ours (involving experimental deep tissue pain) can be generalised to clinical chronic pain presentations.

Moseley et al. (2008) found a significant effect of visual distortion of size in a CRPS population. Minification and magnification using binoculars reduced and augmented the pain respectively. The findings of Ramachandran et al. (2009) tend to support this in a phantom limb pain population. Visual analgesia was demonstrated using a mirror-box, and although no effect was observed in the magnified condition, there was a significant analgesic effect with minification. These findings contrast the results of the experiments by Mancini et al. (2011) and ourselves. This may highlight the

difference between experimental and clinical pain presentations but it could also exist because CRPS and phantom limb pain are unique and extreme chronic pain experiences in which the visual appearance of the painful area is greatly disrupted (Birklein, Riedl, Claus, & Neundörfer, 1998; Harden et al., 1999) and visual manipulation, particularly in the form of normalisation, is likely to have a powerful threat-reducing effect.

The PASS-20 is a brief version of the original PASS-40 and has been shown to be a good reflection of the PASS-40 (Roelofs et al., 2004). Both these measures assess four distinct components of pain anxiety: cognitive anxiety (catastrophic thinking), fearful thinking about pain and anticipated negative consequences related to pain, escape and avoidance behaviour, and physiological anxiety (heightened arousal) (Watt, Stewart, Moon, & Terry, 2010). If desired, subscale scores for these components can be determined by summing particular items in the questionnaire together for each component of pain anxiety. In this study we were more interested in a general pain anxiety score so we used the total scores for our analyses. During the “neutral object” visual condition of the present study, the subject’s view of their painful thigh was obstructed by the box. This could have potentially reduced the level of perceived control the subject had over their painful body part and induced a measure of subsequent fear or heightened anticipation of pain (one of the components of pain anxiety). Pain anxiety has been found to be associated with augmented pain perception (L. M. McCracken & Gross, 1998) however our results did not demonstrate a significant interaction between the PASS-20 scores and the pain scores during the “neutral object” visual condition. In previous studies, the majority of individuals classified as having “high” pain-related anxiety have been shown to have PASS-20 total scores greater than 30 (Abrams et al., 2007). The average PASS-20 scores for our study was 17 ± 15.14 , which is well below that threshold. It should be noted, however, that the population involved in this experiment was a collection of physiotherapy students who had received education in the mechanisms underlying pain perception, and thus were likely to present with relatively lower pain anxiety levels than the general public.

When we explored for possible interactions between trait pain sensitivity (reflected by the PSQ questionnaire) and the reported pain scores during the various visual conditions no significance was apparent. There have been significant correlations reported between PSQ scores and experimental pain intensity ratings in healthy subjects (Ruscheweyh et al., 2009). PSQ scores have also been reported to be significantly associated with pain anxiety and fear scores (Nelson & Massey, 2013). With no significant pain intensity ratings being observed across any of the visual conditions in the current study, and no interactions demonstrated between trait anxiety and pain scores, we did not expect to observe a significant finding between the pain sensitivity and the pain scores across any of the visual conditions either. Our results confirmed our expectations.

4.4.3 Clinical implications and contributions.

This thesis makes an original contribution to knowledge as no previous studies have investigated the modulatory effects of visualisation or visual magnification on deep, experimental pain. These effects have previously been explored in experimental superficial pain and clinical populations although it has remained unclear whether we could extrapolate the results of previous studies to acute deep tissue pain. Previous studies have also yielded contrasting effects making it difficult to predict with confidence the direction of the effects on deep tissue pain. As highlighted in the previous section (section 4.4.2) various hypotheses could explain the results of each of those studies. Combining the findings of previous research and those in our study some common themes start to evolve which appear to be able to consistently explain the various findings.

Clinical populations in which visualisation and visual distortion of size have had an effect appear to be those in which the condition involves significant visible physical changes to the affected area. In a CRPS population, such as that researched by Moseley et al. (2008), changes in the subjects' hair and nail growth can be seen, as well as swelling, excessive sweating or dry skin. In a phantom limb pain patient such

as that studied by Ramachandran et al. (2009), there is a significant visual change with the absence of a limb. The introduction of visual feedback would have allowed subjects to normalise the perceived appearance of their limb and this is likely to have reduced fear associated with the pain contributing to the analgesic effects observed. Our study involved experimental pain in the form of DOMS. DOMS is likely to have been experienced regularly by our cohort of healthy subjects in the past. Ethically, we were obliged to disclose that the type of pain induced was merely a transient pain. These factors would have contributed to the lack of threat associated with the DOMS pain inflicted on them. Furthermore there were no physical changes or observable abnormalities associated with the pain induced in the subjects, so the impact of visual input would have been minimal compared to the visual input which normalised the CRPS or phantom limb subjects' perception of their limb appearance. This would help to explain our negative findings.

It appears that visual analgesia also depends on the body part affected. If a body part is usually not visible to the subject then visual feedback is likely to have a greater impact than visualisation of a body part that is usually readily visible. Supporting this proposal, would be the findings of Wand et al. (2012) and Diers et al. (2015) who demonstrated analgesic responses in chronic back pain patients with the subject's visualisation of their backs. Although there may not be visible changes to the appearance of the back, the back is a region of the body which is not readily visible to the subject and the introduction of visual feedback from this region is likely to have provided participants with information about the state of their back that is not normally accessible to them. Our study indirectly supports this notion too. We can usually see our anterior thigh easily so adding visual feedback doesn't add information or reduce the threat value of the perceived pain.

That Longo et al. (2009) and Mancini et al. (2011) observed analgesic effects of visualisation and visual distortion of size respectively, of readily observable body parts such as the hand, may be explained by the fact that the pain induced in their studies was topical. Visualisation would have enhanced the subjects' sense of safety by relieving any fears of injury resulting from the perceived noxious stimulus, and in

turn inducing an analgesic effect. This proposal would also explain the lack of effect observed in our present study. The pain induced was deep tissue pain. The tissues affected were not directly observable so there was not the same sense of safety and control to be gained as there was by observing topical pain. Furthermore, research suggests that the nature and underlying mechanisms of topical pain and deep tissue pain differ significantly (S. Mense, 2003; Uematsu et al., 2011; Witting et al., 2000). As a result one should not automatically expect a common modulatory phenomenon to exist for both types of pain.

The main aim of this study was to explore the mechanisms underlying deep experimental pain. The priority was not to source new treatment options, although favourable findings to visualisation or visual magnification may have informed future treatment. From a clinical perspective, it appears that “direct” visualisation and “direct” visual magnification may not be useful for acute pain management programs in the case of pain perceived in body parts that are readily observable. Visualisation is more likely to have a greater impact on body parts which cannot usually be seen such as the lower back. This hypothesis would be supported by the results observed by Wand et al. (2012) and Diers et al. (2015). The likely mechanism underlying this analgesia is the “de-threatening” effect that visual input would have on a body part that cannot usually be seen. Also, from a clinical perspective, visual analgesia is likely only to exist for pain which associated with altered body perception or physical changes to the appearance of that body part, as observed by Ramachandran et al. (2009), Moseley et al. (2008) and Preston and Newport (2011). All these studies manipulated the visual feedback serving to normalise the perception of that body part and in so doing maybe increase the sense of safety and provide evidence that all is well with that body part and consequently modulate the pain experience. Visualisation is unlikely to have any impact on pain whereby the overall appearance of the body part remains normal. This notion is supported by the results of Torta et al. (2015) and by our study.

CHAPTER FIVE: LIMITATIONS, RECOMMENDATIONS AND CONCLUSION

5.1 Limitations

Ethically, there is a limitation to the amount of pain that can be inflicted on or induced in subjects, and by the ways in which this pain can be induced. A widely used means of inducing transient, endogenous experimental pain is via the DOMS phenomenon. It induces an acceptable level of pain, although the pain level may be below those pain levels experienced by the clinical population, especially those with chronic pain. Also, the pain induced is experimental. Ideally, studying a clinical population would be more relevant but it is very difficult to standardise subjects and testing procedures as clinical pain states vary significantly from one individual to the next. The necessary constraints to ensure internal validity of the research would limit sample size. These limitations led to the decision to induce DOMS to represent deep tissue pain. Recognising that we cannot completely apply the results to clinical pain, the study does serve to give us a better understanding of the behaviour and mechanisms underlying deep tissue pain, which may be beneficial.

One should consider the type of pain that was induced, the effect that our belief systems have on our pain perception and the potential effect this could have on visual analgesia. The majority of the population recruited for this study were physiotherapy students. These subjects are likely to have a greater interest in physical activity and hence have been exposed to DOMS of the lower limbs more frequently than a regular population. This frequent exposure to DOMS is likely to have reduced any pain-associated fear. Through their curriculum the students are likely to have developed a comprehensive understanding of pain mechanisms. Understanding their pain would further minimise their fear. It is probable that a reduction of the fear/ threat value associated with the pain would reduce perceived pain levels. It was imperative, therefore, to include the modified Likert scale to ensure that the subjects were experiencing adequate pain levels prior to the testing procedure.

5.2 Recommendations

“Direct” visualisation alone did not influence pain rating in our study, however several studies involving experimental superficial pain (Longo et al., 2009; Mancini et al., 2011; Osumi et al., 2014) and those involving clinical pain populations (Moseley et al., 2008; Ramachandran et al., 2009) have noted visual analgesic effects using “indirect visualisation” (albeit in opposing directions). Use of a mirror-box has allowed this “indirect visualisation”. With this in mind, it may be worthwhile exploring whether a mirror-box has any effect on deep tissue pain. Researchers would need to be mindful that if DOMS is to be used as the experimental deep tissue pain, a muscle group needs to be chosen that is both easily visible by the subject (for example, the gastrocnemius is difficult to observe due to its dorsal location) and easy to situate alongside a mirror to induce an illusion. If an effect is noted while using the mirror box, it could be likely that the mechanism underlying this effect involves the introduction of a degree of conflict between visual, sensory and proprioceptive representations which requires augmented cognition to decipher, in turn affecting and inhibiting perceived pain levels. Depending on the direction of the effect, the mirror box could potentially be incorporated as a useful clinical tool for managing clinical pain.

Our study was initiated prior to the publication of findings of Valentini et al. (2015) and Osumi et al. (2014), who have not been able to reproduce the consistent visual analgesic results observed by Longo et al. (2009) and Mancini et al. (2011). Valentini et al. (2015) did not use a mirror-box and could only get an analgesic effect with vision of the body part when it was combined with the affected limb crossing the midline. Taking this into account, it may also be worthwhile to include a “crossed midline condition” as another visual condition to the experiment suggested above.

To explore visual analgesia in experimental, deep tissue pain, another study involving the use of real-time video feedback to produce an image of the affected body part, would be informative. Real-time video feedback has successfully induced visual analgesia in clinical populations studied by Diers et al. (2015) and Preston and Newport (2011). It has the potential to be a very practical treatment modality. It

could be used on all parts of the body (unlike the mirror- box) and would not involve the subjects crossing the midline (which is difficult to achieve with some body parts). The image could also be easily manipulated to increase or decrease the size of the viewed body part in order to normalise the subjects' perception of their limb size if these are found to be helpful.

Combining the findings of our current studies and other relevant research it is apparent that visualisation may only have a modulatory effect on pain when visual feedback offers a significant contribution to the generation or maintenance of perceived pain; in pain associated with visible changes to the affected tissues (or perceived to have physical changes in appearance), pain perceived in tissues which are directly visible (such as the skin as opposed to deeper tissues) or pain perceived in body parts that are not readily visible (such as the lumbar spine). With this in mind, it would be worthwhile inducing experimental deep tissue pain in healthy volunteers in a body part that is not readily visible, such as the back, buttock or hamstring regions, and exploring the effects of visualisation on the perceived pain intensity, in order to substantiate the proposal that visualisation has a modulatory effect only when the visual input, or lack thereof, plays a significant role in the generation or maintenance of pain.

It would be also be worthwhile observing the effects of visual manipulation in a population of chronic pain sufferers involving body parts that are readily visible and that do not involve noticeable physical changes to the body part, but are perceived to have physical changes in appearance, that is the subject has a dysfunctional cortical representation of that body part. It would be interesting to establish whether normalising their perception via visual feedback has an impact on pain. Subsequent to the writing of this literature review a recent and relevant study has been published. Healthy subjects demonstrated physiological changes in the form of skin conductance response (SCR) to topical painful stimuli with the simultaneous use of embodied virtual images of the affected body part. SCR is reflective of the autonomic nervous system's response to painful stimuli. Typically, stronger responses of SCR are observed for stimuli that are processed by the brain as more painful. The size of the

embodied virtual image was manipulated and the changes in SCR were found to be inversely proportional to the size of the image, as long as the image was believed to be the subject's own body. Besides affecting pain processing and subsequently the SCR, the embodied virtual image did not result in any changes to the conscious experience of pain, that is the pain intensity rating of this superficial, experimental pain (Romano, Llobera, & Blanke, 2016). It may be worthwhile repeating a similar experiment of virtual embodiment but this time with a population of chronic pain sufferers in which the cortical representation of their affected part has been altered. Virtual embodiment would be easier to implement than the traditional mirror-box and the images could be easily manipulated to help normalise the subject's perception of their affected body part.

5.3 Conclusion

The aim of the present experiment was to investigate, firstly, whether visualisation of the painful body part has an effect on acute deep tissue pain in a healthy population, and secondly, to determine if visual distortion of size, in the form of magnification, has a further effect on the perceived pain, and if so, whether this is in the direction of analgesia.

We found that visualisation of the painful body part had no significant effect on pain intensity ratings of experimental deep tissue pain. Furthermore, there was no significant effect of visual magnification on perceived pain levels.

The findings of this study have highlighted that experimental superficial, experimental deep and chronic pain mechanisms appear to have different modulatory factors. The results of our study together with the studies explored in this literature review suggest that effects of visualisation and visual distortion of size are likely to be limited to specific circumstances; when there are significant visual changes to the appearance of a body part associated with the perceived pain or when the pain is perceived in a body part that is not usually observed so visual feedback has a major impact. We suggest that the augmented sense of safety and control that visualisation introduces to topical pain explains the analgesic effect, contrasting the lack of effect noted in our study involving “unobservable” deep tissue pain.

This study has contributed to a better understanding of the effects of visualisation as a modulatory factor in acute deep tissue pain, however it is important to note that only “direct” vision and “direct” visual magnification of the painful limb were tested against control conditions. Conditions coupling visualisation with the use of a mirror box, real-time video or subjects’ limbs crossing the midline were not explored. Subsequent to the data collection for this study, it has become evident that these factors could potentially contribute to visual analgesia. Further studies to investigate the effects of these conditions coupled with visualisation or visual distortion of size on deep tissue pain are warranted, as well as studies to explore the effects of

visualisation on experimental deep tissue pain in body parts that are not readily visible or clinical pain in which there is an altered cortical representation of that body part.

Finally, as a result of this study, we can state with some confidence that acute deep tissue pain appears not to be affected by “direct” visualisation or “direct” visual magnification of the overlying skin of a body part which is usually readily observable. We further recommend that it is not worthwhile including this in a management plan for painful conditions of these regions.

Appendix 1: PASS – 20

(Lance M. McCracken & Dhingra, 2002)

Individuals who experience pain develop different ways to respond to that pain. We would like to know what you do and what you think about when in pain. Please use the rating scale below to indicate how often you engage in each of the following thoughts or activities.

Circle one number from 0 (NEVER) to 5 (ALWAYS) for each item.

1. I think that if my pain gets too severe, it will never decrease.

0 1 2 3 4 5

2. When I feel pain, I am afraid that something terrible will happen.

0 1 2 3 4 5

3. I go immediately to bed when I feel severe pain.

0 1 2 3 4 5

4. I begin trembling when engaged in activity that increases pain.

0 1 2 3 4 5

5. I can't think straight when I am in pain.

0 1 2 3 4 5

6. I will stop any activity as soon as I sense pain coming on.

0 1 2 3 4 5

7. Pain seems to cause my heart to pound or race.

0 1 2 3 4 5

8. As soon as pain comes on, I take medication to reduce it.

0 1 2 3 4 5

9. When I feel pain, I think that I may be seriously ill.

0 1 2 3 4 5

10. During painful episodes, it is difficult for me to think of anything else besides the pain.

0 1 2 3 4 5

11. I avoid important activities when I hurt.

0 1 2 3 4 5

12. When I sense pain I feel dizzy or faint.

0 1 2 3 4 5

13. Pain sensations are terrifying.

0 1 2 3 4 5

14. When I hurt I think about the pain constantly.

0 1 2 3 4 5

15. Pain makes me nauseous (feel sick to my stomach).

0 1 2 3 4 5

16. When pain comes on strong I think I might become paralysed or more disabled.

0 1 2 3 4 5

17. I find it hard to concentrate when I hurt

0 1 2 3 4 5

18. I find it difficult to calm my body down after periods of pain.

0 1 2 3 4 5

19. I worry when I am in pain.

0 1 2 3 4 5

20. I try to avoid activities that cause pain.

0 1 2 3 4 5

Thank you for completing this questionnaire.

Appendix 2: Pain Sensitivity Questionnaire

(Sellers, Ruscheweyh, Kelley, Ness, & Vetter, 2013)

This questionnaire contains a series of questions in which you should imagine yourself in certain situations. You should then decide if these situations would be painful for you and if yes, how painful they would be.

Let 0 stand for no pain; 1 is an only just noticeable pain and 10 the most severe pain that you can imagine or consider possible.

Please mark the scale with a cross on the number that is most true for you. Keep in mind that there are no “right” or “wrong” answers; only your personal assessment of the situation counts. Please try as much as possible not to allow your fear or aversion of the imagined situations affect your assessment of painfulness.

1. Imagine you bump your shin badly on a hard edge, for example, on the edge of a glass coffee table.

How painful would that be for you?

0 1 2 3 4 5 6 7 8 9 10

not at all painful

most severe pain imaginable

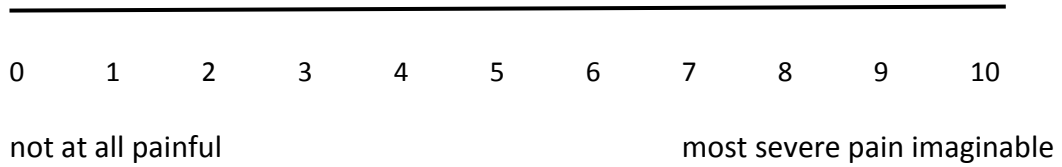
2. Imagine you burn your tongue on a very hot drink. How painful would that be for you?

0 1 2 3 4 5 6 7 8 9 10

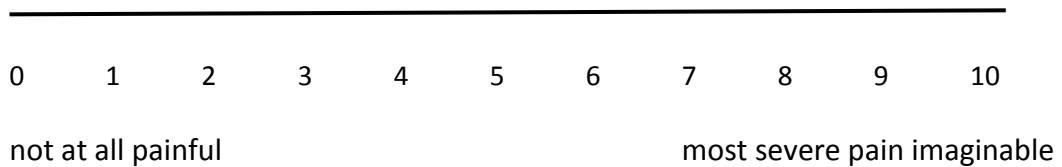
not at all painful

most severe pain imaginable

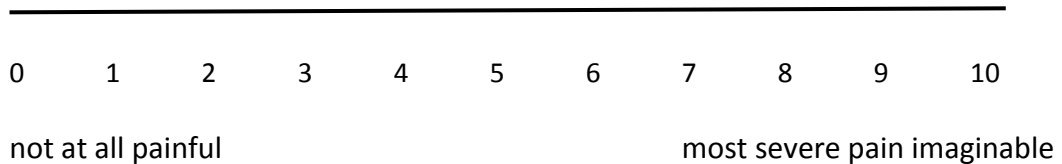
3. Imagine your muscles are slightly sore as the result of physical activity. How painful would that be for you?



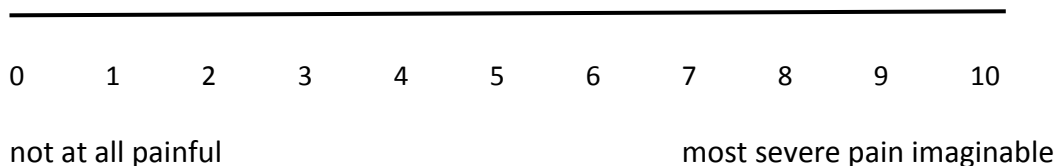
4. Imagine you trap your finger in a drawer. How painful would that be for you?



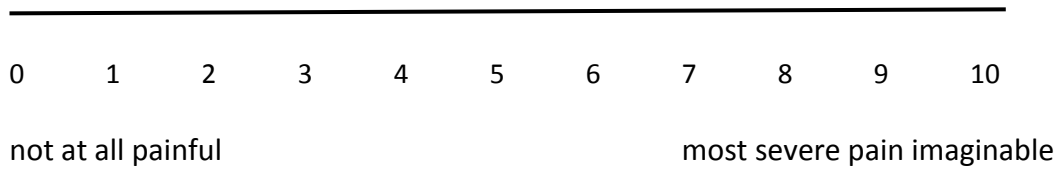
5. Imagine you take a shower with lukewarm water. How painful would that be for you?



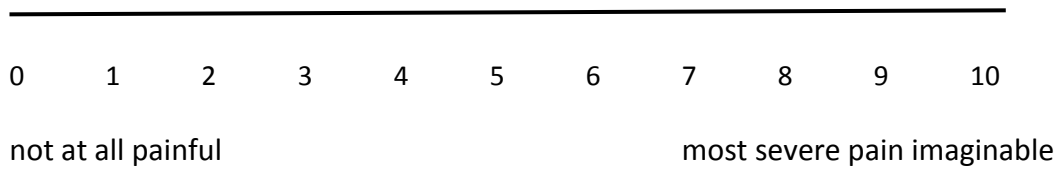
6. Imagine you have mild sunburn on your shoulders. How painful would that be for you?



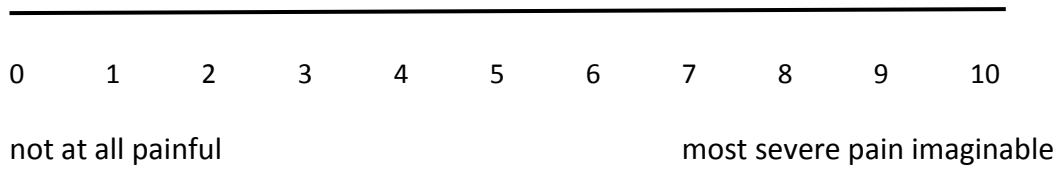
7. Imagine you grazed your knee falling off your bicycle. How painful would that be for you?



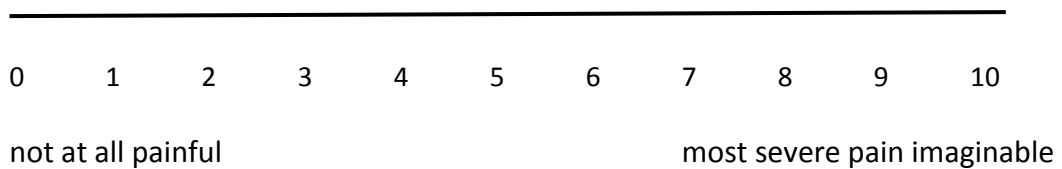
8. Imagine you accidentally bite your tongue or cheek badly while eating. How painful would that be for you?



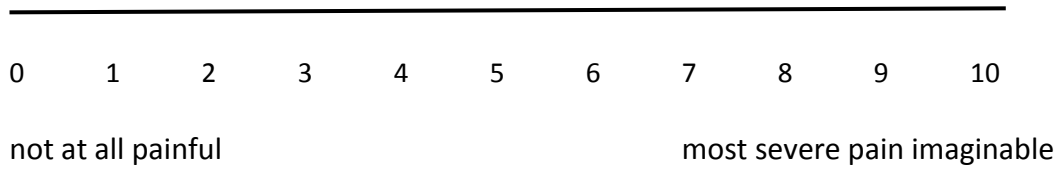
9. Imagine walking across a cool tiled floor with bare feet. How painful would that be for you?



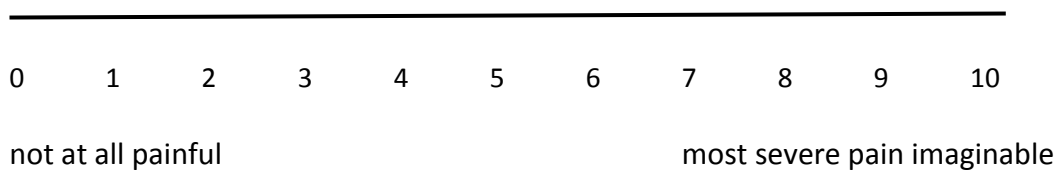
10. Imagine you have a minor cut on your finger and inadvertently get lemon juice in the wound.



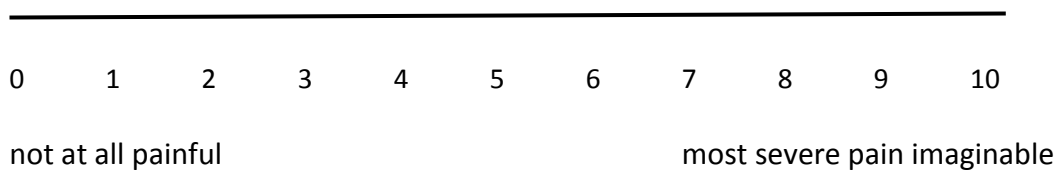
11. Imagine you prick your fingertip on the thorn of a rose. How painful would that be for you?



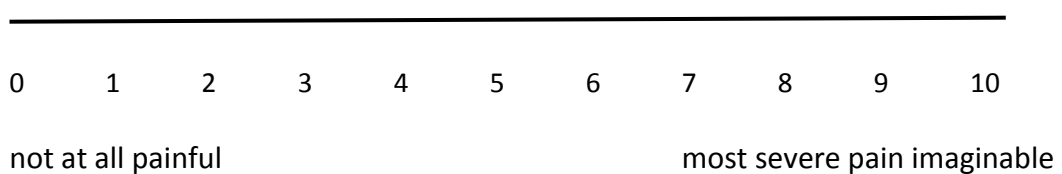
12. Imagine you stick your bare hands into an esky filled with icy water for a couple of minutes. How painful would that be for you?



13. Imagine you shake hands with someone who has a normal grip. How painful would that be for you?



14. Imagine you shake hands with someone who has a very strong grip. How painful would that be for you?



15. Imagine you pick up a hot pot by inadvertently grabbing its equally hot handles. How painful would that be for you?

0 1 2 3 4 5 6 7 8 9 10

not at all painful most severe pain imaginable

16. Imagine you are wearing sandals and someone with heavy boots steps on your foot. How painful would that be for you?

0 1 2 3 4 5 6 7 8 9 10

not at all painful most severe pain imaginable

17. Imagine you bump your elbow on the edge of a table
 (“funny bone”). How painful would that be for you?

0 1 2 3 4 5 6 7 8 9 10

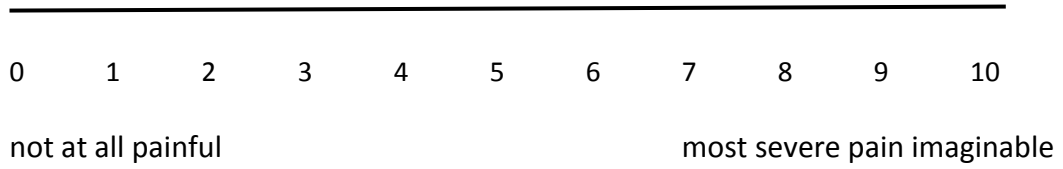
not at all painful most severe pain imaginable

18. Imagine you pick up a hot pot by inadvertently grabbing its equally hot handles. How painful would that be for you?

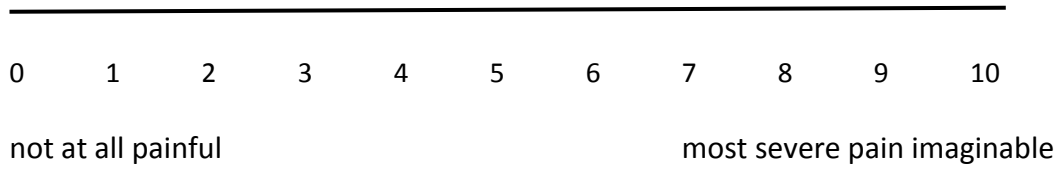
0 1 2 3 4 5 6 7 8 9 10

not at all painful most severe pain imaginable

19. Imagine you are wearing sandals and someone with heavy boots steps on your foot. How painful would that be for you?



20. Imagine you bump your elbow on the edge of a table (“funny bone”). How painful would that be for you?



Appendix 3: Data Collection Pilot Study

SESSION 1:

Date: _____

Time: _____

Maximum isometric quadriceps contraction at -10 knee extension

Test 1	
Test 2	
Test 3	
Average	
40% of average	

ACTION	SET 1	SET 2	SET 3	SET 4	SET 5
10 reps					
30 sec rest					
10 reps					
30 sec rest					
10 reps					
2 min break					

SESSION 2:

Modified Likert Scale of muscle soreness (Andersen et al., 2008)	
Date:	
Time:	
1	A light soreness in the muscle felt only when touched/ a vague ache
2	A moderate soreness felt only when touched/ a slight persistent pain
3	A light muscle soreness while walking up and down stairs
4	A light muscle soreness when walking on a flat surface
5	A moderate muscle soreness, stiffness or weakness while walking
6	A severe muscle soreness, stiffness or weakness that limits my ability to move

Does subject fulfil inclusion criteria? _____

Subject number: _____

	OUTCOMES: (NRS pain score /10)			
Date:	5 mins	15 mins	25 mins	35 mins
Time:				
Eccentric Quadriceps contraction NRS –test 1				
Eccentric Quadriceps contraction NRS- test 2				
Eccentric Quadriceps contraction NRS- test 3				

Appendix 4: Data Collection Research Study

SESSION 1:

Date: _____

Time: _____

Maximum isometric quadriceps contraction at -10 knee extension

Test 1	
Test 2	
Test 3	
Average	
40% of average	

Glasses magnification which allows focussed but magnified view of thigh: _____

Position of leg for best focus Leg weights in situ: _____

ACTION	SET 1	SET 2	SET 3	SET 4	SET 5
10 reps					
30 sec rest					
10 reps					
30 sec rest					
10 reps					
2 min break					

SESSION 2:

Modified Likert Scale of muscle soreness (Andersen et al., 2008)	
Date:	
Time:	
1	A light soreness in the muscle felt only when touched/ a vague ache
2	A moderate soreness felt only when touched/ a slight persistent pain
3	A light muscle soreness while walking up and down stairs
4	A light muscle soreness when walking on a flat surface
5	A moderate muscle soreness, stiffness or weakness while walking
6	A severe muscle soreness, stiffness or weakness that limits my ability to move

Does subject fulfil inclusion criteria? _____

Subject number: _____

	OUTCOMES: (NRS pain score /10)			
	test 1	test 2	test 3	test 4
Date:	5 mins	15 mins	25 mins	35 mins
Time:				
VISUAL CONDITION - neutral object (X), contralateral leg (CL), Normal (N), magnified (M)				
Weights strapped around ankle				
5 minute fixation time- subject to made aware that they will need to estimate width of thigh after fixation testing				
Eccentric Quadriceps contraction NRS –test 1				
Eccentric Quadriceps contraction NRS- test 2				
Eccentric Quadriceps contraction NRS- test 3				
“Effect of Magnification” Scale- done just prior to removal of glasses in magnified condition				
Weights removed from ankle prior to washout period				
5 minute washout period				

Appendix 5: Letter Granting Ethical Approval



THE UNIVERSITY OF
NOTRE DAME
A U S T R A L I A

20 May 2014

Associate Professor Ben Wand
School of Physiotherapy
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CRICOS PROVIDER CODE: 01032F

Dear Ben,

Reference Number: 014036F

Project title: "Does temporarily altering visual perception of limb size have a modulatory effect on deep pain perception?"

Your response to the conditions imposed by the university's Human Research Ethics Committee, has been reviewed and based on the information provided has been assessed as meeting all the requirements as mentioned in the *National Statement on Ethical Conduct in Human Research* (2007). Therefore, I am pleased to advise that ethical clearance has been granted for this proposed study.

All research projects are approved subject to standard conditions of approval. Please read the attached document for details of these conditions.

On behalf of the Human Research Ethics Committee, I wish you well with your study.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'Natalie Giles'.

Dr Natalie Giles
Research Ethics Officer
Research Office

cc: Prof Peter Hamer, Dean, School of Physiotherapy;
A/Prof Shane Patman, SRC Chair, School of Physiotherapy

Glossary of Abbreviations

ACC	anterior cingulate cortex
AMPA receptors	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ASQ	attribution style questionnaire
BAQ	Body Attitude Questionnaire
Ca ²⁺	calcium ions
CGRP	Calcitonin Gene Related Peptide
CREB	cAMP response element-binding protein
CRPS	Chronic Regional Pain Syndrome
DLF	dorsolateral fasciculus
DLPFC	dorsolateral prefrontal cortex
DNIC	diffuse noxious inhibitory control system
DOMS	delayed onset muscle soreness
EEG	Electroencephalography
ERK	extracellular signal-related kinase
ERP	Event-related brain potential
FMRI	functional magnetic resonance imaging
GABA	gamma amino-butyrlic acid
IASP	International Association for the Study of Pain
IC	insular cortex
ICC	inter class correlation co-efficient
Minification	process of reducing something only in appearance, not in physical size
MEG	magnetoencephalography
Mg ²⁺	magnesium ions

NGC	nucleus reticularis gigantocellularis
NMDAR	N-methyl-D-aspartate receptor
NRM	nucleus raphe magnus
NWR	nociceptive withdrawal reflex
PAG	periaqueductal grey matter
PASS-20	pain anxiety symptoms scale questionnaire
PFC	prefrontal cortex
PKC	protein kinase-C
PPC	posterior parietal cortices
PPI	perceived pain intensity
RVM	rostral ventromedial medulla
S1	somatosensory cortex
S2	secondary somatosensory cortex
SCR	Skin conductance response
TENS	transcutaneous electrical nerve stimulation
TRP	transient receptor potential
VAS	visual analogue scale
VPL	ventroposteriolateral nucleus

References

- Abraham, W. M. (1977). Factors in delayed muscle soreness. (Facteurs de l' endolorissement musculaire differe). *Medicine & Science in Sports*, 9(1), 11-20.
- Abrams, M. P., Carleton, R. N., & Asmundson, G. J. (2007). An exploration of the psychometric properties of the PASS-20 with a nonclinical sample. *Journal of Pain*, 8(11), 879-886 878p.
- Alfredson, H. (2003). Chronic midportion Achilles tendinopathy: an update on research and treatment. *Clinics in Sports Medicine*, 22(4), 727-741.
- Andersen, H., Arendt-Nielsen, L., Svensson, P., Danneskiold-Samsøe, B., & Graven-Nielsen, T. (2008). Spatial and temporal aspects of muscle hyperalgesia induced by nerve growth factor in humans. *Experimental Brain Research*, 191(3), 371-382. doi:10.1007/s00221-008-1531-5
- Apkarian, A. V., Bushnell, M. C., Treede, R. D., & Zubieta, J. K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain*, 9(4), 463-484.
- Aytar, A., Tüzün, E. H., Eker, L., Yürük, Z. Ö. B., gcaron, Daşkapan, A., & Akman, M. N. (2008). Effectiveness of low-dose pulsed ultrasound for treatment of delayed-onset muscle soreness: A double-blind randomized controlled trial. *Isokinetics & Exercise Science*, 16(4), 239-247.
- Bakhtiary, A. H., Safavi-Farokhi, Z., & Aminian-Far, A. (2007). Influence of vibration on delayed onset of muscle soreness following eccentric exercise. *British Journal of Sports Medicine*, 41(3), 145-148.
- Bartolo, M., Serrao, M., Gamgebeli, Z., Alpaidze, M., Perrotta, A., Padua, L., . . . Sandrini, G. (2013). Modulation of the human nociceptive flexion reflex by pleasant and unpleasant odors. *Pain (03043959)*, 154(10), 2054-2059. doi:10.1016/j.pain.2013.06.032
- Basbaum, A. I., & Jessel, T. M. (2000). *Principles of Neural Science* (4th edition ed.). New York: McGraw-Hill.
- Bee, L. A., & Dickenson, A. H. (2008). Descending facilitation from the brainstem determines behavioural and neuronal hypersensitivity following nerve injury and efficacy of pregabalin. *Pain*, 140(1), 209-223. doi:10.1016/j.pain.2008.08.008
- Berna, C., Leknes, S., Holmes, E. A., Edwards, R. R., Goodwin, G. M., & Tracey, I. (2010). Induction of depressed mood disrupts emotion regulation neurocircuitry and enhances pain unpleasantness. *Biological Psychiatry*, 67(11), 1083-1090.
- Binderup, A. T., Arendt-Nielsen, L., & Madeleine, P. (2010). Pressure pain threshold mapping of the trapezius muscle reveals heterogeneity in the distribution of muscular

- hyperalgesia after eccentric exercise. *European Journal of Pain*, 14(7), 705-712 708p.
doi:10.1016/j.ejpain.2009.11.001
- Birklein, F., Riedl, B., Claus, D., & Neundörfer, B. (1998). Pattern of autonomic dysfunction in time course of complex regional pain syndrome. *Clinical Autonomic Research*, 8(2), 79-85. doi:10.1007/bf02267817
- Blyth, F. M., March, L. M., Brnabic, A. J. M., Jorm, L. R., Williamson, M., & Cousins, M. J. (2001). Chronic pain in Australia: a prevalence study. *Pain*, 89(2-3), 127-134. doi:[http://dx.doi.org/10.1016/S0304-3959\(00\)00355-9](http://dx.doi.org/10.1016/S0304-3959(00)00355-9)
- Bove, G. M., Zaheen, A., & Bajwa, Z. H. (2005). Subjective Nature of Lower Limb Radicular Pain. *Journal of Manipulative & Physiological Therapeutics*, 28(1), 12-14. doi:10.1016/j.jmpt.2004.12.011
- Breen, J. (2002). Transitions in the concept of chronic pain. *Advances in Nursing Science*, 24(4), 48-59.
- Brockett, C. L., Morgan, D. L., & Proske, U. (2001). Human hamstring muscles adapt to eccentric exercise by changing optimum length. *Medicine & Science in Sports & Exercise*, 33(5), 783-790.
- Bushnell, M. C., Čeko, M., & Low, L. A. (2013). Cognitive and emotional control of pain and its disruption in chronic pain. *Nature Reviews Neuroscience*, 14(7), 502-511. doi:10.1038/nrn3516
- Butler, D. S., & Moseley, G. L. (2013). *Explain pain* (Vol. Second). Adelaide;Adelaide, S.A.; Noigroup Publications.
- Cheung, K., Hume, P. A., & Maxwell, L. (2003). Delayed Onset Muscle Soreness: Treatment Strategies and Performance Factors. *Sports Medicine*, 33(2), 145-164.
- Diers, M., Loffler, A., Zieglgansberger, W., & Trojan, J. (2015). Watching your pain site reduces pain intensity in chronic back pain patients. *Eur J Pain*, 18(10), 765.
- Diers, M., Zieglgansberger, W., Trojan, J., Drevensek, A. M., Erhardt-Raum, G., & Flor, H. (2013). Site-specific visual feedback reduces pain perception. *Pain*. doi:10.1016/j.pain.2013.02.022
- Dobek, C. E., Beynon, M. E., Bosma, R. L., & Stroman, P. W. (2014). Music modulation of pain perception and pain-related activity in the brain, brainstem, and spinal cord: an fMRI study. *J Pain*, 28(14), 00822-00820.
- Fairhurst, M., Wiech, K., Dunckley, P., & Tracey, I. (2007). Anticipatory brainstem activity predicts neural processing of pain in humans. *Pain*, 128(1-2), 101-110.
- Fernández-Carnero, J., Binderup, A. T., Ge, H., Fernández-de-las-Peñas, C., Arendt-Nielsen, L., & Madeleine, P. (2010). Pressure pain sensitivity mapping in experimentally induced lateral epicondylalgia. *Medicine & Science in Sports & Exercise*, 42(5), 922-927 926p. doi:10.1249/MSS.0b013e3181c29eab

- Fleming, M. S., & Luo, W. (2013). The anatomy, function, and development of mammalian A beta low-threshold mechanoreceptors. *Frontiers in Biology*, *8*(4), 013-1271.
- Garza-Villarreal, E. A., Wilson, A. D., Vase, L., Brattico, E., Barrios, F. A., Jensen, T. S., . . . Vuust, P. (2014). Music reduces pain and increases functional mobility in fibromyalgia. *Frontiers in Psychology*, *5*(90).
- Giesecke, T., Gracely, R. H., Williams, D. A., Geisser, M. E., Petzke, F. W., & Clauw, D. J. (2005). The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. *Arthritis and Rheumatism*, *52*(5), 1577-1584.
- Greenberg, C. S. (2002). Practice applications of research. A sugar-coated pacifier reduces procedural pain in newborns. *Pediatric Nursing*, *28*(3), 271-277.
- Grieve, K., & Schultewolter, D. (2014). Chronic pain: current issues and opportunities for future collaborations. *British Journal of Healthcare Management*, *20*(12), 563-567.
- Haggard, P., Iannetti, G. D., & Longo, M. R. (2013). Spatial sensory organization and body representation in pain perception. *Current Biology: CB*, *23*(4), R164-R176. doi:10.1016/j.cub.2013.01.047
- Harden, R. N., Bruehl, S., Galer, B. S., Saltz, S., Bertram, M., Backonja, M., . . . Stanton-Hicks, M. (1999). Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive? *Pain*, *83*(2), 211-219. doi:10.1016/s0304-3959(99)00104-9
- Harrison, D., Bueno, M., Yamada, J., Adams-Webber, T., & Stevens, B. (2010). Analgesic Effects of Sweet-Tasting Solutions for Infants: Current State of Equipoise. *Pediatrics*, *126*(5), 894-902. doi:10.1542/peds.2010-1593
- Henderson, L. A., Peck, C. C., Petersen, E. T., Rae, C. D., Youssef, A. M., Reeves, J. M., . . . Gustin, S. M. (2013). Chronic pain: lost inhibition? *The Journal of neuroscience*, *33*(17), 7574.
- Höfle, M., Hauck, M., Engel, A. K., & Senkowski, D. (2012). Viewing a needle pricking a hand that you perceive as yours enhances unpleasantness of pain. *Pain*, *153*(5), 1074-1081. doi:10.1016/j.pain.2012.02.010
- Horjales-Araujo, E., Finnerup, N. B., Jensen, T. S., & Svensson, P. (2013). Differential effect of visual and gustatory stimuli on experimental jaw muscle pain. *European Journal of Pain*, *17*(6), 811-819. doi:10.1002/j.1532-2149.2012.00253.x
- Howatson, G., Van Someren, K., & Hortobagyi, T. (2007). Repeated Bout Effect after Maximal Eccentric Exercise. *International Journal of Sports Medicine*, *28*(7), 557-563.
- Jabbur, S. J., & Saadé, N. E. (1999). From electrical wiring to plastic neurons: evolving approaches to the study of pain. *Pain, Suppl 6*, S87-S92.
- Keay, K. A., & Bandler, R. (1993). Deep and superficial noxious stimulation increases Fos-like immunoreactivity in different regions of the midbrain periaqueductal grey of the rat. *Neuroscience Letters*, *154*(1-2), 23-26.

- Keefe, F. J., Brown, G. K., Wallston, K. A., & Caldwell, D. S. (1989). Coping with rheumatoid arthritis pain: catastrophizing as a maladaptive strategy. *Pain*, *37*(1), 51-56.
- Kennett, S., Taylor-Clarke, M., & Haggard, P. (2001). Noninformative vision improves the spatial resolution of touch in humans. *Curr Biol*, *11*(15), 1188-1191.
- Kim, H.-J., Lee, J.-I., Kang, K.-T., Chang, B.-S., Lee, C.-K., Ruscheweyh, R., . . . Yeom, J. S. (2015). Influence of pain sensitivity on surgical outcomes after lumbar spine surgery in patients with lumbar spinal stenosis. *Spine (03622436)*, *40*(3), 193-200 198p. doi:10.1097/brs.0000000000000699
- Klages, U., Kianifard, S., Ulusoy, O., & Wehrbein, H. (2006). Anxiety sensitivity as predictor of pain in patients undergoing restorative dental procedures. *Community Dentistry & Oral Epidemiology*, *34*(2), 139-145.
- Lamm, C., Decety, J., & Singer, T. (2011). Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. *Neuroimage*, *54*(3), 2492-2502. doi:10.1016/j.neuroimage.2010.10.014
- Latremoliere, A., & Woolf, C. J. (2009). Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*, *10*(9), 895-926.
- Law, L. A. F., Evans, S., Knudtson, J., Nus, S., Scholl, K., & Sluka, K. A. (2008). Massage reduces pain perception and hyperalgesia in experimental muscle pain: a randomized, controlled trial. *Journal of Pain*, *9*(8), 714-721 718p.
- Legrain, V., Iannetti, G. D., Plaghki, L., & Mouraux, A. (2011). The pain matrix reloaded: a salience detection system for the body. *Progress in Neurobiology*, *93*(1), 111-124.
- Lewis, J. S., Kersten, P., McCabe, C. S., McPherson, K. M., & Blake, D. R. (2007). Body perception disturbance: a contribution to pain in complex regional pain syndrome (CRPS). *Pain*, *133*(1-3), 111-119.
- Loggia, M. L., Mogil, J. S., & Bushnell, M. C. (2008). Empathy hurts: compassion for another increases both sensory and affective components of pain perception. *Pain*, *136*(1-2), 168-176. doi:10.1016/j.pain.2007.07.017
- Longo, M. R., Betti, V., Aglioti, S. M., & Haggard, P. (2009). Visually induced analgesia: seeing the body reduces pain. *The Journal Of Neuroscience: The Official Journal Of The Society For Neuroscience*, *29*(39), 12125-12130. doi:10.1523/jneurosci.3072-09.2009
- Longo, M. R., Iannetti, G. D., Mancini, F., Driver, J., & Haggard, P. (2012). Linking pain and the body: neural correlates of visually induced analgesia. *The Journal Of Neuroscience: The Official Journal Of The Society For Neuroscience*, *32*(8), 2601-2607. doi:10.1523/jneurosci.4031-11.2012
- Malm, C. (2001). Exercise-induced muscle damage and inflammation: fact or fiction? *Acta Physiologica Scandinavica*, *171*(3), 233-239.
- Mancini, F., Longo, M. R., Kammers, M. P., & Haggard, P. (2011). Visual distortion of body size modulates pain perception. *Psychol Sci*, *22*(3), 325-330. doi:10.1177/0956797611398496

- Martini, M., Perez-Marcos, D., & Sanchez-Vives, M. V. (2013). What Color is My Arm? Changes in Skin Color of an Embodied Virtual Arm Modulates Pain Threshold. *Frontiers in human neuroscience*, 7, 438. doi:10.3389/fnhum.2013.00438
- Matsuda, Y., Kan, S., Uematsu, H., Shibata, M., & Fujino, Y. (2015). Pain-Related Brain Activity Evoked by Active and Dynamic Arm Movement: Delayed-Onset Muscle Soreness as a Promising Model for Studying Movement-Related Pain in Humans. *Pain Medicine*, 16(8), 1528-1539.
- MBFFoundation. (2007). *The high price of pain: the economic impact of persistent pain in Australia*. University of Queensland.
- McCracken, L. M., & Dhingra, L. (2002). A short version of the Pain Anxiety Symptoms Scale (PASS--20): Preliminary development and validity. *Pain Research & Management*, 7(1), 45-50.
- McCracken, L. M., & Gross, R. T. (1998). The role of pain-related anxiety reduction in the outcome of multidisciplinary treatment for chronic low back pain: preliminary results. *Journal of Occupational Rehabilitation*, 8(3), 179-189 111p.
- Melzack, R. (1996). Gate control theory: on the evolution of pain concepts. *Pain Forum*, 5(2), 128-138.
- Mense, S. (2003). What is different about muscle pain? *Schmerz*, 17(6), 459-463. doi:10.1007/s00482-003-0264-4
- Mense, S., & Simons, D. (2001). *Muscle Pain. Undersanding Its Nature, Diagnosis, and Treatment* (P. Darcy Ed.): Lipincott Williams & Wilkins.
- Merskey, H., & Bogduk, N. (2012). IASP Taxonomy - IASP. Retrieved from <http://www.iasp-pain.org/Taxonomy?navItemNumber=576>
- Miron, D., Duncan, G. H., & Bushnell, M. C. (1989). Effects of attention on the intensity and unpleasantness of thermal pain. *Pain*, 39(3), 345-352.
- Mitchell, L. A., MacDonald, R. A., & Brodie, E. E. (2006). A comparison of the effects of preferred music, arithmetic and humour on cold pressor pain. *European Journal of Pain*, 10(4), 343-351.
- Moseley, G. L. (2007). Reconceptualising pain according to modern pain science. *Physical Therapy Reviews*, 12(3), 169-178. doi:10.1179/108331907x223010
- Moseley, G. L., & Flor, H. (2012). Targeting cortical representations in the treatment of chronic pain: a review. *Neurorehabilitation And Neural Repair*, 26(6), 646-652. doi:10.1177/1545968311433209
- Moseley, G. L., Parsons, T. J., & Spence, C. (2008). Visual distortion of a limb modulates the pain and swelling evoked by movement. *Curr Biol*, 18(22), R1047-1048. doi:10.1016/j.cub.2008.09.031

- Moseley, G. L., & Wiech, K. (2009). The effect of tactile discrimination training is enhanced when patients watch the reflected image of their unaffected limb during training. *Pain (03043959)*, *144*(3), 314-319. doi:10.1016/j.pain.2009.04.030
- Müller, M. J. (2013). Depressive attribution style and stressor uncontrollability increase perceived pain intensity after electric skin stimuli in healthy young men. *Pain Research & Management*, *18*(4), 203-206.
- Nelson, D., & Massey, A. (2013). Predictive utility of the pain sensitivity questionnaire. *The Journal of Pain*, *14*(4), S23. doi:10.1016/j.jpain.2013.01.101
- Olsen, O., Sjøhaug, M., van Beekvelt, M., & Mork, P. J. (2012). The Effect of Warm-Up and Cool-Down Exercise on Delayed Onset Muscle Soreness in the Quadriceps Muscle: a Randomized Controlled Trial. *Journal of Human Kinetics*, *35*, 59-68.
- Osumi, M., Imai, R., Ueta, K., Nakano, H., Nobusako, S., & Morioka, S. (2014). Factors associated with the modulation of pain by visual distortion of body size. *Frontiers in human neuroscience*, *8*(Journal Article), 137. doi:10.3389/fnhum.2014.00137
- Pavlin, D. J., Sullivan, M. J., Freund, P. R., & Roesen, K. (2005). Catastrophizing: a risk factor for postsurgical pain. *Clinical Journal of Pain*, *21*(1), 83-90.
- Pertovaara, A., & Almeida, A. (2006). Chapter 13 Descending inhibitory systems *Handbook of Clinical Neurology* (Vol. 81, pp. 179-192).
- Phillips, K., & Clauw, D. J. (2011). Central pain mechanisms in chronic pain states--maybe it is all in their head. *Best Pract Res Clin Rheumatol*, *25*(2), 141-154. doi:10.1016/j.berh.2011.02.005
- Prescott, J., & Wilkie, J. (2007). Pain Tolerance Selectively Increased by a Sweet-Smelling Odor. *Psychological Science (Wiley-Blackwell)*, *18*(4), 308-311. doi:10.1111/j.1467-9280.2007.01894.x
- Preston, C., & Newport, R. (2011). Analgesic effects of multisensory illusions in osteoarthritis. *Rheumatology*, *50*(12), 2314-2315.
- Pud, D., & Sapir, S. (2006). The effects of noxious heat, auditory stimulation, a cognitive task, and time on task on pain perception and performance accuracy in healthy volunteers: a new experimental model. *Pain (03043959)*, *120*(1-2), 155-160. doi:10.1016/j.pain.2005.10.029
- Ramachandran, V. S., Brang, D., & McGeoch, P. D. (2009). Size reduction using Mirror Visual Feedback (MVF) reduces phantom pain. *Neurocase (Psychology Press)*, *15*(5), 357-360. doi:10.1080/13554790903081767
- Raudenbush, B., Koon, J., Meyer, B., Corley, N., & Flower, N. (2004). Effects of Odorant Administration on Pain and Psychophysiological Measures in Humans. *North American Journal of Psychology*, *6*(3), 361-370.
- Roelofs, J., McCracken, L., Peters, M. L., Crombez, G., van Breukelen, G., & Vlaeyen, J. W. S. (2004). Psychometric evaluation of the Pain Anxiety Symptoms Scale (PASS) in chronic pain patients. *Journal of Behavioral Medicine*, *27*(2), 167-183 117p.

- Romano, D., Llobera, J., & Blanke, O. (2016). Size and Viewpoint of an Embodied Virtual Body Affect the Processing of Painful Stimuli. *J Pain*, *17*(3), 350-358. doi:10.1016/j.jpain.2015.11.005
- Roy, M., Peretz, I., & Rainville, P. (2008). Emotional valence contributes to music-induced analgesia. *Pain*, *134*(1-2), 140-147.
- Ruscheweyh, R., Marziniak, M., Stumpfenhorst, F., Reinholz, J., & Knecht, S. (2009). Pain sensitivity can be assessed by self-rating: Development and validation of the Pain Sensitivity Questionnaire. *Pain*, *146*(1-2), 65-74.
- Schepers, R. J., & Ringkamp, M. (2009). Thermoreceptors and thermosensitive afferents. *Neuroscience and Biobehavioral Reviews*, *33*(3), 205-212.
- Sellers, A. B., Ruscheweyh, R., Kelley, B. J., Ness, T. J., & Vetter, T. R. (2013). Validation of the English language pain sensitivity questionnaire. *Regional Anesthesia And Pain Medicine*, *38*(6), 508-514. doi:10.1097/AAP.000000000000007
- Slater, H., Arendt-Nielsen, L., Wright, A., & Graven-Nielsen, T. (2005). Sensory and motor effects of experimental muscle pain in patients with lateral epicondylalgia and controls with delayed onset muscle soreness. *Pain (03043959)*, *114*(1-2), 118-130. doi:10.1016/j.pain.2004.12.003
- Staff, P. H. (1988). Clinical consideration in referred muscle pain and tenderness. Connective tissue reactions. *European Journal of Applied Physiology Occupational Physiology*, *57*(3), 369-372.
- Sullivan, M. J., Lynch, M. E., & Clark, A. J. (2005). Dimensions of catastrophic thinking associated with pain experience and disability in patients with neuropathic pain conditions. *Pain*, *113*(3), 310-315.
- Sullivan, M. J., Thorn, B., Haythornthwaite, J. A., Keefe, F., Martin, M., Bradley, L. A., & Lefebvre, J. C. (2001). Theoretical perspectives on the relation between catastrophizing and pain. *The Clinical Journal of Pain*, *17*(1), 52-64.
- Torta, D. M., Legrain, V., & Mouraux, A. (2015). Looking at the hand modulates the brain responses to nociceptive and non-nociceptive somatosensory stimuli but does not necessarily modulate their perception. *Psychophysiology*, *52*(8), 1010-1018.
- Tracey, I., & Mantyh, P. W. (2007). The cerebral signature for pain perception and its modulation. *Neuron*, *55*(3), 377-391.
- Turner, J. A., Jensen, M. P., & Romano, J. M. (2000). Do beliefs, coping, and catastrophizing independently predict functioning in patients with chronic pain? *Pain*, *85*(1-2), 115-125.
- Twillman, R. (2007). Mental Disorders in Chronic Pain Patients. *Journal of pain & palliative care pharmacotherapy*, *21*(4), 13-19. doi:10.1300/J354v21n04_04
- Uematsu, H., Shibata, M., Miyauchi, S., & Mashimo, T. (2011). Brain imaging of mechanically induced muscle versus cutaneous pain. *Neuroscience Research*, *70*(1), 78-84.

- Valentini, E., Koch, K., & Aglioti, S. M. (2015). Seeing One's Own Painful Hand Positioned in the Contralateral Space Reduces Subjective Reports of Pain and Modulates Laser Evoked Potentials. *Journal of Pain*, *16*(6), 499-507. doi:10.1016/j.jpain.2015.02.003
- van Griensven, H. (2005). *Pain in Practice* (E. Ltd Ed. 1st ed.). Philadelphia, USA.: Butterworth, Heinemann, Elsevier.
- Villarreal, E. A., Brattico, E., Vase, L., Ostergaard, L., & Vuust, P. (2012). Superior analgesic effect of an active distraction versus pleasant unfamiliar sounds and music: the influence of emotion and cognitive style. *PLoS One*, *7*(1), 5.
- Vlaeyen, J. W. S., Crombez, G., & Goubert, L. (2007). The psychology of chronic pain and its management. *Physical Therapy Reviews*, *12*(3), 179-188.
- Wagner, K. J., Sprenger, T., Kochs, E. F., Tolle, T. R., Valet, M., & Willoch, F. (2007). Imaging human cerebral pain modulation by dose-dependent opioid analgesia: a positron emission tomography activation study using remifentanyl. *Anesthesiology*, *106*(3), 548-556.
- Walker, B. F., Muller, R., & Grant, W. D. (2003). Low back pain in Australian adults: the economic burden. *Asia Pac J Public Health*, *15*(2), 79-87.
- Wand, B. M., Tulloch, V. M., George, P. J., Smith, A. J., Goucke, R., O'Connell, N. E., & Moseley, G. L. (2012). Seeing it helps: Movement-related back pain is reduced by visualization of the back during movement. *The Clinical Journal of Pain*, *28*(7), 602-608. doi:10.1097/AJP.0b013e31823d480c
- Watt, M. C., Stewart, S. H., Moon, E., & Terry, L. L. (2010). Childhood learning history origins of adult pain anxiety. *Journal of Cognitive Psychotherapy*, *24*(3), 198-212 115p. doi:10.1891/0889-8391.24.3.198
- Witting, N., Svensson, P., Gottrup, H., Arendt-Nielsen, L., & Jensen, T. S. (2000). Intramuscular and intradermal injection of capsaicin: A comparison of local and referred pain. *Pain*, *84*(2-3), 407-412. doi:10.1016/s0304-3959(99)00231-6
- Woolf, C. J. (2011). Central sensitization: implications for the diagnosis and treatment of pain. *Pain*, *152*(3 Suppl), 18.
- Woolf, C. J., & Decosterd, I. (1999). Implications of recent advances in the understanding of pain pathophysiology for the assessment of pain in patients. *Pain*, *6*(7), S141-147.
- Yu, X. M., & Mense, S. (1990). Response properties and descending control of rat dorsal horn neurons with deep receptive fields. *Neuroscience*, *39*(3), 823-831.
- Zusman, M. (2002). Forebrain-mediated sensitization of central pain pathways: 'non-specific' pain and a new image for MT. *Manual Therapy*, *7*(2), 80-88.