School of Physiotherapy and Exercise Science

Interactions between Manipulation Induced Pain Modulation and Conditioned Pain Modulation Analgesia

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Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)* – updated March 2014. The proposed research studies received human research ethics approval from the Curtin University Human Research Ethics Committee (Approval Numbers: HRE2016-0181-01, HRE2016-0175, and HRE2017-0198-02).

Signature:

[Ahmad Muhsen]

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Abstract

Endogenous analgesia (EA) is modulated through multiple central inhibitory and facilitatory mechanisms to limit perception of pain. Evidence suggests that these EA mechanisms can be activated through the phenomena of conditioned pain modulation (CPM) and manipulation induced pain modulation (MIPM). These forms of natural analgesia appear to share similar neurophysiological mechanisms, although with some individual variations. Although the immediate effects of MIPM in musculoskeletal pain have been established (e.g. in conditions such as lateral epicondylalgia (LE)), there is still a limited understanding about exactly how MIPM exerts its analgesic effect. The overall objective of this research was to determine whether, in individuals with LE, CPM and MIPM analgesia are associated and the extent to which the analgesic responses of each were augmented when combined with other interventions.

A series of four experimental studies (one reliability study and three main studies) were included in this thesis. LE was used as the clinical model of musculoskeletal pain where there is already evidence for the MIPM having an effect. This facilitated valid comparisons of the analgesia produced by CPM and MIPM. The protocols for CPM and MIPM assessment were identified with reference to existing literature. For CPM the analgesic response was induced with a noxious cold pressor test (CPT) whereas the MIPM analgesic response was induced by a pain-free oscillatory cervical lateral glide (CLG) technique. Analgesic responses were primarily measured using pressure pain threshold (PPT) at local and distant sites by a single investigator. PPT was assessed at baseline, during, and post CPT for CPM and CLG for MIPM. For MIPM, secondary outcome measures of pain free grip (PFG) and upper limb neurodynamic test with radial nerve bias (ULNDT-RN) were also measured pre and post CLG.

An initial reliability study (N=11 and N=10) was conducted to establish the reliability of repeated PPT measures at the wrist and elbow (Study 1, Chapter 3). It also aimed to assess the pattern of CPM analgesia over a one hour period to calculate the time required for PPT to return to baseline value. This was important to determine the washout period between the CPM and MIPM assessment protocols applied in Studies 2 - 4. The data from this study were also used to calculate the minimal sample size required for each main study. For the wrist test site only, the PPT test-retest protocol was conducted followed by the CPM assessment protocol with a 10 minute rest period in between in a single testing session. For the elbow test site, the PPT test-retest protocol was conducted on a separate session. In the PPT test-retest protocol, PPT was measured at baseline, at 1 minute, at 2 minutes and at 5 minutes over the wrist and elbow test sites over 2 days. In the CPM assessment protocol, PPT measures were obtained over the wrist test site only at baseline pre CPT, at 1 minute during CPT, and at 1 minute, 5 minutes, 15 minutes, 30 minutes, 45 minutes, and 60 minutes post CPT. The study demonstrated an excellent reliability for PPT at the wrist and elbow test sites with intra-class correlation coefficients (ICCs) of 0.991 and 0.986, respectively. Linear mixed model analysis showed that the CPM analgesic effect returned to baseline value after 5 minutes post immersion. The PPT data from the elbow test site (i.e. effect size difference) were included in the sample size calculation.

Next, a quasi-experimental single-group repeated measures study (N=70) was conducted with the main aim to determine the association between CPM and MIPM analgesia in people with LE (Study 2, Chapter 4). A secondary aim was to determine whether there was a difference in the level of MIPM analgesia between CPM responders and non-responders, defined as those individuals who had a post-stimulus increase in PPT greater than the standard error of the mean for the sample. The CPM assessment protocol was applied first, followed

by the MIPM assessment protocol in a single session with a 15 minute rest period in between. PPT measures were collected from the wrist and elbow of the symptomatic LE side pre, during, and post the cold pressor test (CPT) for CPM and at the same time-points for the cervical lateral glide (CLG) mobilisation for MIPM. Pre and post CLG, PFG and ULNDT-RN were also assessed. Participants were assigned post hoc into two CPM groups: responders (n=62) and non-responders (n=8), using a previously calculated literature based cut-off value of meaningful CPM effect. Linear mixed models were used to analyse the differences in CPM and MIPM analgesic responses, with participants showing a significant increase in PPT, PFG and ULNDT measures (i.e. higher levels of analgesia) both during and post CPT and CLG ($p<0.001$ for all). There were significant moderate and positive partial correlations (r: 0.40–0.54, $p<0.001$) between CPM and MIPM analgesia (measured by PPT) over different time points measured at the two test sites. Univariate regression analysis showed that CPM analgesia significantly predicted MIPM analgesia (adjusted R^2: 73%-85%, $p<0.001$). CPM responders demonstrated significantly higher levels of analgesia during (wrist: $p=0.033$, elbow: $p=0.021$) and post (wrist: $p=0.017$, elbow: $p= 0.014$) MIPM compared to CPM non-responders, although with no significant between-group differences in PFG ($p=0.083$) and ULNDT-RN ($p=0.653$). The association between CPM and MIPM analgesia suggests that the two forms of EA are related and may potentially be mediated by similar underlying neurophysiological mechanisms. These study findings laid the foundations for the subsequent two studies (Studies 3 and 4), where the EA systems were manipulated using psychological and physical interventions.

For Study 3 (Chapter 5), a randomised between-group controlled trial (N=68) was conducted to evaluate the influence of an enhanced research assistant / participant empathetic interaction on CPM and MIPM analgesia in

participants with LE. Participants were randomly allocated to either the enhanced empathetic or the neutral interaction group (n=34 each group). All participants were initially evaluated for CPM and MIPM analgesia (using the same assessment protocols applied in Study 2) in a single session prior to the main test session. For 15 minutes at the start of the main test session and in the 15 minute rest between CPM and MIPM protocols, participants received either enhanced empathetic and positive or neutral (business-like) interactions from a professionally trained role play actor, who performed the role of a research assistant (RA). All CPM and MIPM assessment was completed in a neutral manner by the main investigator, who only entered the research room for these aspects of the study. At the end of the session, participants were asked to complete the Consultation and Relational Empathy (CARE) measure to rate the overall interaction they experienced with the RA. The RA was similarly asked to evaluate the quality of the interactions they conveyed using a quality of session scale. The enhanced empathetic interaction group reported significantly higher CARE measure scores ($p<0.001$) than those reported by the neutral interaction group, signifying a clear distinction in participant perception between both types of interaction. Linear mixed models were used to assess any differences in CPM and MIPM responses between interaction groups. Participants in both groups showed a significant increase in all PPT measures for both CPM and MIPM and in MIPM secondary outcome measures ($p<0.001$ for all). However, the enhanced empathetic interaction group demonstrated significantly higher levels of analgesia than the neutral interaction group during (wrist: $p<0.001$, elbow: $p<0.001$) and post CPM (wrist $p=0.002$, elbow: $p=0.002$) and post MIPM (wrist $p=0.004$, elbow: $p<0.001$) test sites. There were no significant differences between groups in PFG ($p=0.398$) and ULNDT-RN ($p=0.668$) measures. The correlation data also suggested that enhanced empathetic interaction positively influences CPM and MIPM analgesic responses to a similar extent in people with LE.

Finally, in Study 4 (Chapter 6), a randomised between-group controlled trial (N=68) was conducted to establish the immediate effect of two different aerobic exercise intensities on CPM and MIPM analgesia in participants with LE. As with the psychological study, this study secondarily investigated the association between CPM/MIPM analgesia and aerobic exercise induced analgesia (EIA). Participants were randomly allocated to one of two aerobic exercise intensity groups, moderate and high (n=34 per group). These aerobic exercise intensities were determined based on individual age-related target heart rate (HR): the moderate group exercised at 50% of maximum HR while the high group exercised at 75% maximum HR. A cycle ergometer with linked HR monitor was used. Each participant was required to complete two 15 minute cycling sessions at either moderate or high intensity depending on group allocation, on two separate days with a three day rest in between. Immediately after each aerobic exercise session, all participants were individually assessed for either CPM or MIPM in a random order. CPM and MIPM protocol followed the same methodology used in Study 2. Data were analysed using linear mixed models, partial correlations, and univariate regression. Participants in both groups showed a significant increase in all PPT measures for CPM and MIPM at both test sites and at both time-points during and post (all $p<0.001$) as well as for PFG ($p<0.001$), and ULNDT-RN ($p<0.001$). There were also significant differences in EIA between the exercise groups, as measured by the change in PPT from pre to post aerobic exercise ($p<0.001$ for all). However, the high aerobic intensity group demonstrated significantly higher levels of analgesia in all PPT measures for CPM and MIPM at the wrist ($p<0.001$) and elbow ($p<0.001$), and for ULNDT-RN ($p<0.001$), although not for PFG ($p=0.052$). There were significant large and positive partial correlations between EIA and CPM (r: 0.90–0.93, $p<0.001$) and between EIA and MIPM analgesia (r: 0.68–0.86, $p<0.001$) over different time points measured at both test sites. EIA was a significant predictor of both CPM analgesia (adjusted R^2:

92%-95%) and MIPM analgesia (adjusted R^2: 73%-93%). The study showed that an acute bout of high intensity aerobic exercise significantly enhanced the analgesic effect of CPM and MIPM in a patient population with LE. The correlational results also may suggest that aerobic exercise, CPM and MIPM activate similar descending inhibitory mechanisms to mediate their analgesic effects.

The above studies found that CPM and MIPM have similar patterns of analgesic responses that are significantly associated and comparably manipulated by an enhanced empathetic interaction and by aerobic exercise interventions. These findings show that CPM and MIPM provide sufficient stimulus for activation of endogenous descending pain inhibitory systems and so may share similar neuro-physiological mechanisms. There may also be an overlap with EIA. The results highlight the potential utility of CPM in forecasting MIPM outcomes. This may improve our knowledge about the nature of MIPM analgesia and therefore guide clinical practice towards more effective treatment. The final two studies show that enhanced empathetic interaction and aerobic exercise both potentiate the CPM and MIPM analgesic effects in a patient population with LE. This suggests that, in a clinical setting, analgesia may be enhanced by ensuring that a patient has a positive and empathetic experience when visiting a clinician and adding an aerobic element before other physical interventions.

It must be noted that these investigations did not attempt to investigate the analgesic effects of CPM and MIPM analgesia over a longer follow-up period and for optimal clinical value this needs to be studied. Follow-up studies with other chronic pain conditions would also clarify whether these finding can be more widely applied. In addition, given the evidence regarding the likely involvement of serotonergic and noradrenergic systems in the endogenous descending inhibitory pathways in CPM and MIPM analgesia, it is anticipated

that the CPM and MIPM analgesia might be further enhanced using a pharmacological intervention that accesses the same pain modulatory systems (e.g. duloxetine). Further research in these areas and future animal studies evaluating the mechanisms of both forms of analgesia in a similar manner are recommended.

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Publications and Conference Presentations related to this thesis

Muhsen, A, Moss, P, Gibson, W, Walker, B and Wright, A 2017, 'The influence of a psychological intervention on conditioned pain modulation in participants with tennis elbow', Mark Liveris Research Student Seminar 2017, Curtin University, Perth, WA, Australia.

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Muhsen, A, Moss, P, Gibson, W, Walker, B, Schug, S, Jacques, A and Wright, A 2018, 'The association between the conditioned pain modulation and manual therapy analgesia in participants with lateral epicondylalgia', *The Clinical Journal of Pain*, vol. 35, no. 5, pp. 435-442.

Muhsen, A, Moss, P, Gibson, W, Walker, B, Schug, S, and Wright, A 2019, 'The association between the conditioned pain modulation and manual therapy analgesia in participants with lateral epicondylalgia', The World Confederation for Physical Therapy (WCPT) Congress 2019, Geneva, Switzerland.

Muhsen, A, Moss, P, Gibson, W, Walker, B, Schug, S, and Wright, A 2019, 'The effect of aerobic exercise on conditioned pain modulation and manual therapy analgesia in participants with lateral epicondylalgia', The World

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Muhsen, A, Moss, P, Gibson, W, Walker, B and Wright, A 2019, 'The influence of empathetic interaction on conditioned pain modulation and manual therapy analgesia in participants with lateral epicondylalgia', submitted to *The Clinical Journal of Pain.*

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Abbreviations

ACC	Anterior Cingulate Cortex
α2-AR	α2-Adrenergic Receptors
AP	Antero-Posterior
CLBP	Chronic Low Back Pain
CLG	Cervical Lateral Glide
CPM	Conditioned Pain Modulation
CPT	Cold Pressor Test
DNIC	Diffuse Noxious Inhibitory Control
DPN	Diabetic Polyneuropathy
EA	Endogenous Analgesia
EIA	Exercise Induced Analgesia
EMG	Electro-myography
ESSA	Exercise and Sport Science Australia
FA	Fitness Australia
5-HT	5-Hydroxytryptamine (serotonin)
FM	Fibromyalgia
fMRI	functional Magnetic Resonance Imaging
GABA	γ-Aminobutyric Acid
HRmax	Maximum Heart Rate
IBS	Irritable Bowel Syndrome
ICC	Intra-class Correlation Coefficient
IFC	Interferential Current
kPa/s	kilopascal/second
LBP	Low Back Pain
LE	Lateral Epicondylalgia
MIPM	Manipulation Induced Pain Modulation
MOR	μ-opioid receptor
NA	Noradrenaline
NRI	Norepinephrine Reuptake Inhibitor
NRM	Nucleus Raphe Magnus
OA	Osteoarthritis
PAG	Periaqueductal Gray
PFC	Prefrontal Cortex
PFG	Pain Free Grip
PPT	Pressure Pain Threshold
RA	Research Assistant
RA	Rheumatoid Arthritis
RVM	Rostral Ventromedial Medulla

SC	Skin Conductance
SMA	Sports Medicine Australia
SNL	Spinal Nerve Ligated
SNRI	Serotonin and Noradrenaline Reuptake Inhibitor
SNS	Sympathetic Nervous System
SRD	Subnucleus Reticularis Dorsalis
SSRIs	Selective Serotonin Reuptake Inhibitors
TPT	Thermal Pain Threshold
ULNDT-RN	Upper Limb Neurodynamic Test (Radial Nerve biased)
VAS	Visual Analogue Scale
WDR	Wide Dynamic Range

Chapter 1: **Introduction**

The overall objective of this thesis was to improve our understanding of two important forms of endogenous analgesia (EA): that induced by conditioned pain modulation (CPM) and by manipulation induced pain modulation (MIPM). Secondarily, the aim was to determine whether these analgesic responses were associated, and whether they were similarly influenced by psychological and physical interventions designed to manipulate the analgesic responses.

MIPM encompasses the pain relieving effects of manual therapy interventions applied by the clinician to improve range of movement, reduce resistance, and decrease pain (Schmid et al. 2008). It has been effectively used in the treatment of various musculoskeletal conditions such as knee osteoarthritis (OA) (Moss, Sluka & Wright 2007), hip OA (MacDonald et al. 2006), low back pain (LBP) (Childs et al. 2004), neck pain (Garcia et al. 2016; Hidalgo et al. 2017) and lateral epicondylalgia (LE) (Vicenzino et al. 2001). Evidence from recent systematic reviews supports the effectiveness of manual therapy for reducing pain (Voogt et al. 2015) and improving clinical outcomes in several musculoskeletal conditions (Clar et al. 2014; Coulter et al. 2018; Heiser, O'Brien & Schwartz 2013; Martins et al. 2016; Xu et al. 2015). It has been hypothesised that MIPM exerts its analgesia by activating endogenous descending inhibitory mechanisms (Wright 1995), in which serotonergic and noradrenergic systems are likely to be key players (Skyba et al. 2003).

CPM is commonly described as 'pain inhibits pain' (Lebars, Dickenson & Besson 1979). Growing evidence suggests that CPM is a reliable measure of EA and potentially a predictive tool for pain related therapeutic outcomes (Kennedy et al. 2016). CPM assessment typically involves application of a measurable noxious test stimulus before and during and/or after a painful

conditioning stimulus applied remotely. CPM can be evoked using a range of different painful conditioning stimuli including heat, cold, electrical, ischaemic and others (Yarnitsky 2015). There is also compelling evidence from animal (Bannister et al. 2017; Bannister et al. 2015) and human (Niesters et al. 2014; Yarnitsky et al. 2012) studies that CPM-induced analgesia is mediated via supra-spinal descending mechanisms involving serotonergic and noradrenergic systems. It is therefore suggested that CPM and MIPM analgesia may share common neurophysiological mechanisms. This raises queries as to whether they stimulate the same or different systems, whether individuals who respond well to CPM will also show a good response to MIPM, and whether their analgesic effects are positively enhanced when combined with additional interventions that may influence response.

Chapter 2 considers the salient aspects of literature pertaining to CPM and MIPM analgesia and evidence of centrally mediated descending neurophysiological mechanisms, relevant methodological considerations, and factors influencing analgesic responses. This chapter particularly considers the evidence for shared descending pain inhibitory mechanisms that potentially mediate both forms of EA.

The thesis then describes a series of experimental studies (Figure 1.1) that evaluate the analgesia associated with CPM and MIPM using well-established assessment protocols. Both CPM and MIPM assessment protocols used pressure pain threshold (PPT) as the main outcome measure to quantify the immediate analgesic responses elicited during each test protocol. It was important therefore to conduct an initial reliability study (Study 1, Chapter 3) to ensure that repeated PPT measures were not influenced by random errors that could potentially pose a threat to the studies' validity (Fitzmaurice 2002).

In the subsequent investigations (Studies 2 and 3) CPM and MIPM assessment protocols were applied in a single session. An additional aim of the first study was therefore to determine the duration of a measurable CPM effect to assist in determining test order for CPM and MIPM as well as the time required for suitable rest period between protocols in order to ensure no confounding carry-over effects. In addition, the data from the first study were essential to calculate the minimum sample size required in subsequent studies.

Chapter 4 (Study 2) describes a quasi-experimental one-group study (N=70) investigating the association between CPM and MIPM analgesia in a sample population with LE. The study also compared the levels of MIPM analgesia between those who exhibited a CPM response (CPM responders) and those who did not exhibit CPM response (CPM non-responders).

In the subsequent two studies (Studies 3 and 4), both CPM and MIPM analgesia were manipulated using two experimental paradigms which aimed to enhance descending pain modulation. Chapter 5 (Study 3) reports on a randomised between-group controlled trial (N=68) comparing the effect of enhanced empathetic or neutral interactions on CPM and MIPM analgesia in participants with LE (Study 3). In Chapter 6 (Study 4), a randomised between-groups controlled trial (N=68) was carried out to evaluate the influence of moderate versus high intensity aerobic exercise on CPM and MIPM analgesia also in a patient population with LE. This study also assessed whether there was an association between CPM/MIPM analgesia and aerobic exercise-induced analgesia (EIA).

Chapter 7 (the final chapter) outlines the overall findings of the studies included in this thesis, addresses areas for future research and summarises the original contribution to knowledge offered by this work.

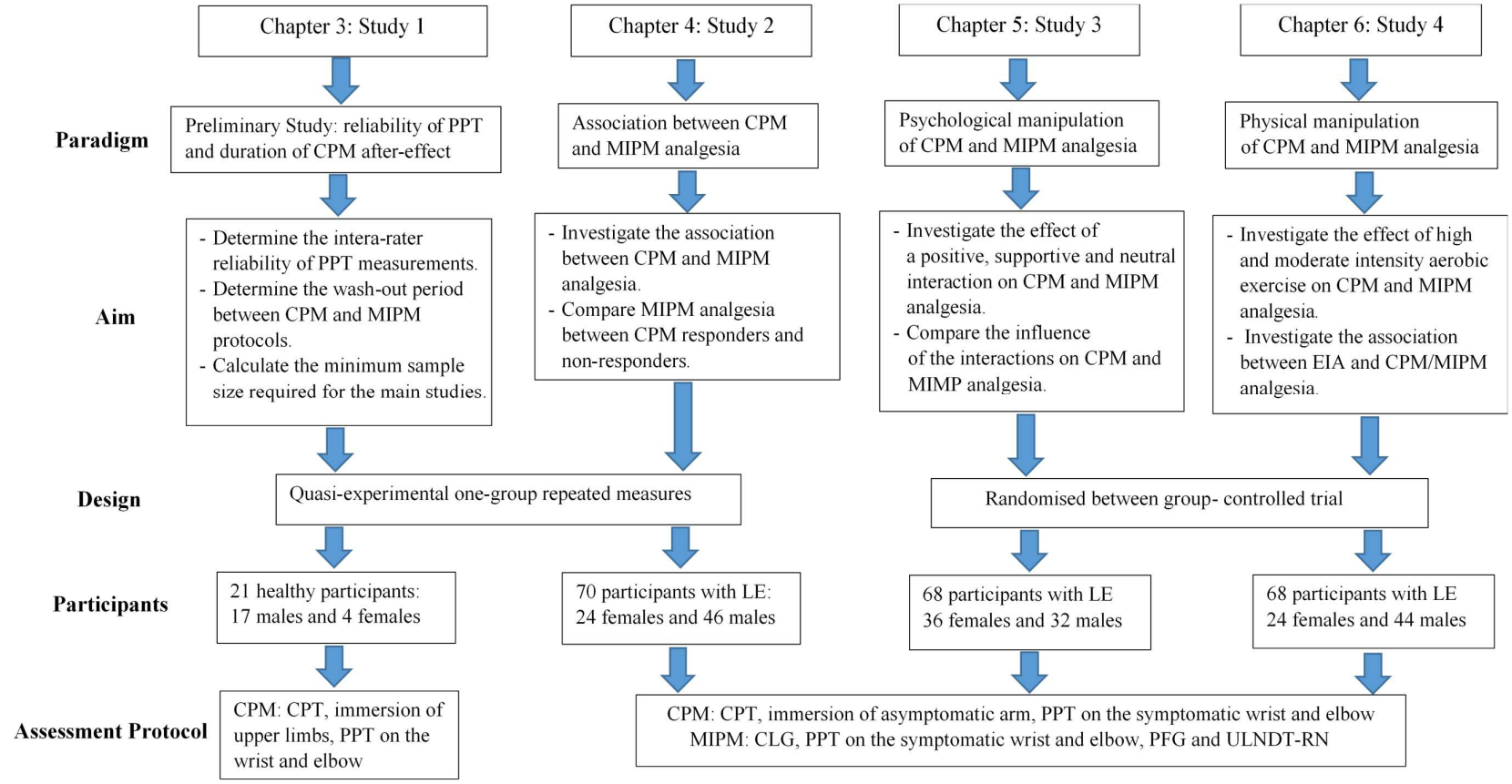

Figure 1.1 Methodologies and main aims of the studies. CPM: Conditioned Pain Modulation, MIPM: Manipulation Induced Pain Modulation, LE: Lateral Epicondylalgia, CPT: Cold Pressor Test, PPT: Pressure Pain Threshold, CLG: Cervical Lateral Glide, PFG: Pain Free Grip, ULNDT-RN: Upper Limb Neurodynamic Test-Radial Nerve bias, EIA: Exercise-induced Analgesia.

Chapter 2: **Background**

2.1. **Central Pain Modulation**

Our understanding about the neurophysiological mechanisms of pain modulation is relatively well established and is known to involve the interaction between multiple cortical and spinal pathways. Peripheral nociceptive signals are primarily transmitted via nociceptive afferent neurons (i.e. Aδ and C fibres) to the spinal cord dorsal horn (Millan 2002). Myelinated Aδ fibres convey immediate and well-localised pain whereas unmyelinated C fibres transmit dull aching and more diffuse pain (Yam et al. 2018). These nociceptive neurons form synapses with second order neurones in the spinal cord to transmit nociceptive stimuli to the brain for processing. This process leads to activation of multiple neural structures and networks to modulate nociception (Millan 2002; Yam et al. 2018). The descending modulation systems exert inhibitory or facilitatory effects on the incoming nociceptive signals at the dorsal horn of the spinal cord to attenuate or augment perception of pain, respectively (Heinricher et al. 2009; Ossipov, Dussor & Porreca 2010). The net influence of descending modulation on the dorsal horn is mediated by the equilibrium of inhibition and facilitation (Calvino & Grilo 2006).

The periaqueductal gray (PAG) region in the brain is believed to play a central role in modulation of pain at the spinal cord dorsal horn via relays in the rostral ventromedial medulla (RVM) (Kwon et al. 2014), which in turn provides direct descending projections to the spinal cord dorsal horn (Porreca, Ossipov & Gebhart 2002). Evidence suggests that PAG-RVM system pain modulation is 'bidirectional', since controlling both pain facilitation and inhibition is a major part of its function (Ossipov, Morimura & Porreca 2014). RVM bidirectional modulation is mainly orchestrated via two types of pain modulatory neurons (Fields, Heinricher & Mason 1991): ON-cells and OFF-

cells that are thought to activate descending nociceptive facilitation and inhibition, respectively (Carlson et al. 2007). It has also been found that descending modulation of pain is mediated in the spinal cord dorsal horn through release of the neurotransmitters serotonin (5-hydroxytryptamine; 5-HT) (Klintschar 2012; Ossipov, Morimura & Porreca 2014) and noradrenaline (NA) (Cui et al. 1999). Depending on the type of spinal receptors activated, 5-HT can induce excitatory or inhibitory effects (Cui et al. 1999) via presynaptic or postsynaptic mechanisms (Kwon et al. 2014). Activation of serotonergic 5-HT2 and 5-HT3 receptors mediates pain facilitation, while activation of 5-HT7 and 5-HT2A receptors induces inhibition (Bannister & Dickenson 2017). NA has also been shown to be both a facilitatory and inhibitory neurotransmitter (Bannister & Dickenson 2017). NA can facilitate nociception through activation of spinal α1-adrenergic receptors (Budai, Harasawa & Fields 1998) but can also induce pain inhibition via activation of spinal α2-adrenergic receptors (α2- AR) (Pertovaara 2006). The NA pathway can also facilitate pain inhibition by inhibiting presynaptic release of excitatory neurotransmitters from the central terminals of primary nociceptors and by supressing postsynaptic spinal pain-relay neurons (Pertovaara 2006).

Research has also shown that several cortical centres, the so called "pain matrix" (Apkarian et al. 2005), are activated in response to nociceptive stimuli (Mazzola et al. 2012). This matrix interacts with the PAG-RVM system to influence pain modulation (Heinricher et al. 2009). For example: the primary (S1) and secondary (S2) somatosensory cortices are involved in the sensory discrimination of pain (Lithwick, Lev & Binshtok 2013); the amygdala is involved in pain related to negative emotions and memories (Li et al. 2013); the anterior cingulate cortex (ACC) is involved in affective and attentional elements of pain (Peyron, Laurent & Garcia-Larrea 2000) as well as empathy (Lamm, Decety & Singer 2011) and social (exclusion) pain (Yanagisawa et al.

2011). The insula, which plays a role in the emotional experience of pain, works with the ACC in feeling empathy for another's pain (Lamm, Decety & Singer 2011), and with somatosensory cortices in the sensory discrimination component of pain (Peyron, Laurent & Garcia-Larrea 2000). The insula may also have a role in the coping element of pain (Lithwick, Lev & Binshtok 2013). The prefrontal cortex (PFC) is involved in the emotional component and the cognitive assessment of pain (Lithwick, Lev & Binshtok 2013). Pain processing therefore involves multiple cortical areas that interact to determine whether the nociceptive stimulus is painful or not, and the degree of pain that is experienced.

2.2. **Conditioned Pain Modulation**

Central pain modulation encompasses multiple pain inhibitory and facilitatory mechanisms that modulate the perception of noxious stimuli. The outputs of the central pain pathways responsible for pain inhibition are broadly termed endogenous analgesia (EA).

One of the most widely investigated EA mechanisms is generally termed diffuse noxious inhibitory control (DNIC). This is the widely recognized concept that pain inhibits pain (Reinert, Treede & Bromm 2000). The term was first coined by Lebars, Dickenson and Besson (1979) during their early experiments on animals. They observed that inhibition of spinal cord dorsal horn neurons and trigeminal nuclei neurons occurred in response to distantly applied nociceptive stimuli in sedated rats. In 1989, Talbot, Duncan and Bushnell showed that a DNIC-like mechanism was also present in humans. Research has since referred to this mechanism using a range of different terms, such as DNIC, DNIC-like, pain-evoked hypoalgesia, counter-irritation, heterotopic noxious counter-stimulation. For consistency, Yarnitsky and colleagues (2010) recommended the use of Conditioned Pain Modulation

(CPM) as a term to distinctly define the DNIC phenomenon in humans and to limit the use of DNIC to describe a specific lower brainstem neurophysiological mechanism in animal research. Therefore, in the following section, for clarity the term DNIC will refer to the EA phenomenon in animals while CPM will be used to describe the human EA phenomena.

2.3. **Neurophysiology**

There is considerably more literature that explore the neurophysiology of DNIC than CPM. DNIC involves a cortically influenced spinal-bulbo-spinal neural circuit acting through inhibition of wide dynamic range (WDR) neurons in the spinal dorsal horn (Lebars, Dickenson & Besson 1979). A noxious conditioning stimulus is transmitted via Aδ and C fibres to the spinal WDR neurons that send supra-spinal input to the subnucleus reticularis dorsalis (SRD) in the caudal medulla (Lewis, Rice & McNair 2012). The SRD directs a diffused descending inhibition via the dorsolateral funiculi to the dorsal horn of the spinal cord to inhibit WDR neurons across multiple spinal levels (Lewis, Rice & McNair 2012; Villanueva, Bouhassira & LeBars 1996), which in turn inhibits the painful stimulus.

It has been shown that DNIC exerts its hypoalgesic effect on pain via an opioidergic central pathway. Willer, Lebars and Debroucker (1990) used naloxone hydrochloride to investigate the involvement of the opioidergic system in DNIC among 9 healthy participants using electrical stimuli as a test stimulus. The stimuli were applied distally on the right sural nerve, with noxious hot water bath immersion of the non-dominant hand used as a conditioning stimulus. Two minutes post hot water immersion, there was a complete inhibition of the RIII reflex in the biceps femoris that took 6-9 minutes to return to its pre-testing level. Participants were then randomly allocated into either a naloxone or saline group. Five minutes post intravenous

injection of naloxone, the analgesic effects were totally blocked. These anti-analgesic effects continued till 50 minutes post injection. Saline injection, however, produced no such blocking of DNIC-induced analgesia. These observations were similar to study findings with rats (Lebars et al. 1981), where DNIC was reduced after the naloxone administration. However, several studies reported that CPM is partially affected (Sprenger, Bingel & Buchel 2011) or completely unaffected (Edwards, Ness & Fillingim 2004; Hermans et al. 2018; Peters et al. 1992) by naloxone suggesting non-opioid pain mechanism. Collectively, these data suggest the findings of the involvement of the endogenous opioid system in the expression of DNIC analgesia are mixed.

It has also been postulated that DNIC exerts its effect via rostral brainstem networks (Villanueva 2009) mediated by serotoninergic (Bannister et al. 2017) and noradrenergic (Bannister et al. 2015) descending neurons. The RVM, including the nucleus raphe magnus (NRM) serotonergic cells, receives direct inputs from the PAG and then sends inhibitory signals downwards to WDR neurons (in laminae I, II, V) in the spinal dorsal horn (Calvino & Grilo 2006), where WDR neuron inhibition is mediated by neurons releasing the neurotransmitters 5-HT (Liu et al. 2007) and NA (Pertovaara 2006). 5-HT may induce an inhibitory effect on pain through direct action on the second order neurons (Radhakrishnan et al. 2003). It can also facilitate spinal interneurons release of several inhibitory mediators, which may inhibit release of glutamate from the primary afferent neurons, and consequently lead to pain inhibition (Yoshimura & Furue 2006). The NA inhibitory mechanisms have been outlined above (see central pain modulation).

Recent pharmacological studies on animals provide evidence for the important role of serotoninergic and noradrenergic inhibitory pathways in DNIC. Bannister et al. (2015) investigated the DNIC effect in naïve (n=12),

sham ligated (n=6) and spinal nerve ligated (SNL) (n=18) rats. DNIC was measured through application of von Frey filaments on the hind paw during ipsilateral noxious ear pinch. The resulting neuronal action potentials were recorded for 5 seconds before and during ear pinch, with maximum reduction in WDR neuronal firing representing the DNIC effect. The naïve and sham-operated (control) rats were then injected with spinal atipamezole (an α2-adrenergic receptors (AR) antagonist) or subcutaneous yohimbine (an α2-AR antagonist) to block the action of α2-AR. The SNL animals (n=18) were injected with ondansetron (a 5-HT3 receptor antagonist) to block the 5-HT3 descending facilitatory effect. The DNIC effect was assessed at baseline and after drug administration. At baseline (pre-injection), the control groups showed a significant reduction in neuronal response indicating an efficient DNIC effect, but it was absent in the SNL group. While the DNIC effect was abolished after injecting the control with atipamezole or yohimbine, it was restored in SNL rats in response to topical ondansetron injection, to a degree similar to that observed in the control. The authors then attempted to augment the inhibitory noradrenergic control in the SNL rats through intrathecal reboxetine (a norepinephrine reuptake inhibitor, NRI) or systemic tapentadol (an NRI and a μ-opioid receptor (MOR) agonist) administration. The DNIC effect was re-established after intrathecal reboxetine or systemic tapentadol administration. The authors concluded that the DNIC effect was potentially mediated by α2 -AR (noradrenergic) mechanisms.

In another experiment, Bannister et al. (2017) investigated the function of 5-HT in DNIC expression in sedated naïve (control) and SNL rats using the same DNIC protocol they applied in their original study (Bannister et al. 2015). The DNIC effect was recorded pre and post administration of the following drugs: single application of selective serotonin reuptake inhibitors (SSRIs) citalopram or fluoxetine, or joint application of SSRI plus 5-HT7 receptor

antagonist SB269970, or SSRI plus α2-AR antagonist atipamezole. Pre drug administration, DNIC effect was observed in control, but not in SNL rats. In contrast to systematic application, following spinal administration of SNL animals with SSRIs citalopram or fluoxetine the DNIC effect was restored. When the same animals were then injected with 5-HT7 receptor antagonist SB269970, the restored DNIC effect was abolished. Joint application of SSRI plus the α2-AR antagonist atipamezole produced no DNIC effect (i.e. no significant inhibition of WDR firing). The authors suggested that serotonergic 5-HT7 receptors were involved in mediating the (inhibitory) effect of DNIC in SNL rats after spinal SSRI application. They also proposed that the inhibitory effect of DNIC was mediated through α2-AR mechanisms. These findings from animal studies suggest the involvement of serotonergic and noradrenergic mechanisms in the pain modulation of DNIC in animal models.

Similar to DNIC in animals, there is robust pharmacological evidence that CPM in humans exerts its action via serotoninergic and noradrenergic inhibitory pathways. Duloxetine, a selective 5-HT and NA reuptake inhibitor, produces its analgesic effects by inhibiting the re-uptake of 5-HT and NA in the descending pain inhibitory neurons, thereby increasing the concentration of NA and 5-HT available to inhibit nociceptive transmission in the spinal cord (Iyengar et al. 2004). Yarnitsky et al. (2012) examined the relationship between CPM effect and duloxetine efficacy in thirty diabetic neuropathy patients. CPM was measured using contact heat and von Frey filament as test stimuli and hot water immersion as a conditioning stimulus. Participants received one week of placebo, followed by one week of 30mg/day duloxetine, and then 4 weeks of 60 mg/day. Overall, pain scores during contact heat significantly improved with duloxetine. However, when the results of individual participants were analysed, patients with less efficient CPM showed a better improvement with the drug than those patients with efficient CPM, who

showed no benefit from duloxetine. The authors proposed that duloxetine produced its effect among patients with inefficient CPM through reinstating the descending inhibitory control mechanism which was intact among those with efficient CPM.

Another study by Niesters et al. (2014) investigated the effect of Tapentadol, a combined MOR agonist and NRI, on CPM in diabetic polyneuropathy (DPN) patients. To induce CPM, heat pain applied on the non-dominant forearm was used as the measurable test stimulus and cold water immersion of the foot and lower leg was used as the conditioning stimulus. Patients were randomly allocated to Tapentadol therapy or placebo for 4 weeks. CPM was measured at baseline and on the last day of week 4. Pain scores were monitored on a weekly basis over 4 weeks. At baseline, no CPM effect was detected in either group. After 4 weeks, both groups showed a significant CPM effect, with a greater pain relief (i.e. reduction in pain scores) and greater CPM effect reported for those receiving Tapentadol. The authors concluded that Tapentadol restored CPM effect through stimulation of descending inhibitory systems, in which the noradrenergic system plays a key role.

It has been proposed that CPM in humans is mediated by autonomic cardiovascular mechanisms. Chalaye et al. (2013) demonstrated that CPM effect was positively associated with blood pressure increase in response to the cold pressor test (CPT) in healthy pain free individuals. A similar finding was also reported in patients with fibromyalgia (FM) (Chalaye et al. 2014), indicating that a baroreceptor mechanism is possibly involved in producing the CPM response.

Recent human imaging research demonstrated that CPM expression is influenced by several higher cortical centres (Brock et al. 2012; Piche, Arsenault & Rainville 2009; Sprenger, Bingel & Buchel 2011) such as S1, PFC,

and ACC (Knudsen et al. 2018), thalamus, insula, S2, medulla, and the amygdala (Sprenger, Bingel & Buchel 2011). La Cesa et al. (2014) examined the association between the cold pressor test (CPT) and PAG activation among twelve healthy participants using functional magnetic resonance imaging (fMRI). The CPT was applied to the left hand while the participants were lying flat in the fMRI machine. In response to the CPT, fMRI revealed a prominent co-activation of PAG bilaterally and other central neural structures, including: bilateral, middle and superior frontal gyrus, ACC and thalamus, left insula, right inferior frontal gyrus, and left inferior temporal gyrus. These results indicate that several cortical structures are involved in the perception of cold pressor pain and in mediating the CPM-induced hypoalgesia.

2.4. **CPM Efficiency**

CPM testing typically involves application of a painful 'test stimulus', during or after a distant painful 'conditioning stimulus' (Nir & Yarnitsky 2015). CPM effect is defined as the difference between the 'test stimulus' values before and during or after the 'conditioning stimulus' application. Many studies have demonstrated that a normal response involves a reduction in the painfulness of the test stimulus following application of the conditioning stimulus (Bouhassira et al. 2003; Graven-Nielsen et al. 2002; Reinert, Treede & Bromm 2000). In the case of pressure pain threshold (PPT), a positive CPM response is represented by an increase in the PPT measure. It is proposed that this reflects a normally efficient CPM.

Lewis, Rice and McNair (2012), in their systematic review and meta-analysis, concluded that several chronic pain conditions are associated with an inefficient CPM response. Patients with irritable bowel syndrome (IBS) demonstrated an increased heat pain (test stimulus) sensitivity in the hand in response to foot cold water immersion (conditioning stimulus) (King et al.

2009). A similar response was observed in FM patients (Julien et al. 2005). In these cases, it is almost a reverse response of hyperalgesia rather than analgesia following the conditioning stimulus. Less efficient CPM was also highly correlated with more reports of past pain experience in pain-free healthy individuals (Edwards, Fillingim & Ness 2003). Yarnitsky (2015) acknowledges that the less efficient CPM seen in chronic pain conditions appears to imply a dysfunctional pain modulation system. However, he also proposes that that the less efficient CPM in chronic pain syndromes is instead the by-product of a pain modulatory system that is already working optimally, meaning that no further increase in CPM can be demonstrated (Yarnitsky 2015).

2.4.1. Protocols for testing CPM

The CPM literature has described different CPM testing protocols (Pud, Granovsky & Yarnitsky 2009). Test stimulus modalities can include contact heat, mechanically-induced pressure, electrical stimulation, chemical stimuli (Nir & Yarnitsky 2015; Yarnitsky 2015) or ischemic pain (Fujii, Motohashi & Umino 2006). Different pain measurement parameters have also been used such as pain threshold, rating of supra-threshold pain and rating of temporal summation pain (Pud, Granovsky & Yarnitsky 2009). With respect to conditioning stimuli, these may include contact heat, or the most frequently used cold water immersion, the so called cold pressor test (CPT), or hot water immersion (Nir & Yarnitsky 2015; Pud, Granovsky & Yarnitsky 2009; Yarnitsky 2015). The most pronounced analgesic effect was observed in CPM paradigms using cold water immersion pain (or cold pressor test) to inhibit a test stimulus of PPT (Oono et al. 2011) and therefore this protocol was used in the current research. The test stimulus can be applied alone and then concurrently with the conditioning stimulus (parallel protocol), or directly after the conditioning stimulus ends (sequential protocol). The test stimulus is

applied at an anatomically distant site from the conditioning stimulus, preferably using one upper and lower limb site (ipsilateral or contralateral), though using only upper limb sites is acceptable and may be more practical (Yarnitsky 2015).

Lewis et al. (2012) have shown that CPM testing is a reliable measure for EA function using the CPT as the conditioning stimulus and PPT as the test stimulus. In their systematic review, Kennedy et al. (2016) have also shown that CPM using CPT and PPT is reliable, with a good (ICC: 0.6 – 0.75) to excellent (ICC: >0.75) inter-session reliability that was reported in 50% of studies. They concluded that the reliability of measuring CPM response is primarily determined by methods of CPM testing, stimulation parameters, and study population.

2.4.2. Cognitive and psychological influences and CPM

There is evidence to suggest that manipulation of cognitive elements can modify CPM effect. Nir et al. (2012) investigated the effect of expectancy reassurance on CPM in 48 healthy men. Participants were randomly allocated into four groups. Group 1 and 2 represented placebo and nocebo groups, respectively. Group 3 and 4 served as controls (for groups 1 and 2) and received no cognitive manipulation. Contact-heat applied to the dominant forearm was used as a test stimulus, and hot water immersion applied to the non-dominant (left) hand was used as a conditioning stimulus. Both placebo and nocebo groups had an anaesthetic cream applied to the left hand. The placebo group was informed that the cream would reduce the conditioning stimulus heat pain but the nocebo group was informed that the cream would increase the heat pain. Group 3 and 4 underwent the same protocol as groups 1 and 2 but without cognitive manipulation. CPM response was evaluated before and post cognitive manipulation. Compared to other groups, the

placebo group showed a significant reduction in the conditioning stimulus pain, and therefore a CPM effect. In contrast, the nocebo group significantly demonstrated an increase in the conditioning stimulus pain so no CPM effect and a hyperalgesic response. It therefore appears that CPM analgesic effect is influenced by the perceived painfulness of the conditioning stimulus pain instead of its actual pain intensity. This also suggests that CPM effect is open to manipulation of the person's expectations.

Cormier, Piche and Rainville (2013) likewise examined the influence of expectations on CPM anti-nociceptive effect among 64 healthy volunteers. In this study, CPM was assessed using electrical stimulations of the right sural nerve as a test stimulus and a noxious cold pack applied on the contralateral forearm as a conditioning stimulus. The participants were equally allocated into 4 groups: control, expectation, hyperalgesia, or hypoalgesia. The control group received simple instructions. The expectation group were asked to rate the extent that they thought the intensity of electrical stimulus pain would be increased or decreased in response to cold pack application. The hyperalgesia group was clearly instructed that the conditioning cold pack would increase the electrical test stimulus pain whilst the hypoalgesia group was informed that the cold pack would reduce the electrical stimulation pain. A priori expectations were significantly correlated with the extent of CPM analgesia produced. Compared to all other groups, the hyperalgesia group demonstrated a significant increase in test stimulus pain in response to the suggestion of increased pain. The hypoalgesia group CPM analgesia was comparable to that observed in expectation and control groups. Thus the verbally initiated expectations via suggestions was only and significantly different in the hyperalgesia groups. The lack of power could explain these study findings. Therefore, this study highlights the influence of cognitive

manipulation by suggestion on CPM responses that still require further research to fully uncover.

Gougeon et al. (2016) also studied the role of empathy in influencing CPM during three experimental conditions: pain condition, self-observation condition, and spouse-observation condition. In the pain condition participants were video recorded while immersing their forearm in a cold water bath (7°C). They were asked to rate their pain and unpleasantness levels 2 minutes post immersion on 0-100 scale. The participants were then randomly assigned into either self- or spouse-condition on two separate days. In the self-observation condition, the forearm was immersed in a warm water bath (20°C) (not likely to directly induce CPM) for 2 minutes while watching themselves in the film recorded on the first day. In addition to rating their average pain and unpleasantness levels, pain rating during seeing themselves in pain in the video was recorded. In the spouse-observation condition, participants observed the video of their spouse's pain experience while immersing their forearm in warm water. Again, the participants rated the average pain and unpleasantness levels of themselves and of the person they watched in the video. Both self-observation and spouse-observation conditions showed a significant CPM effect, even in the absence of a painful conditioning stimulus. Amongst the female participants only, high empathy responses correlated with greater CPM effect.

Several studies have investigated the association between psychological traits and CPM response, although the results are inconsistent. Weissman-Fogel, Sprecher and Pud (2008) found a significant correlation between catastrophizing personality and reduced CPM in healthy individuals. Similar findings were reported by Goodin et al. (2009) that catastrophizing coexisted with inefficient CPM. In another study, Goodin et al. (2013) found a strong correlation between higher reports of optimism and more efficient CPM.

However, Nahman-Averbuch et al. (2016b) demonstrated no significant correlation between anxiety and catastrophizing levels and CPM effect. They also found that other factors such as novelty seeking and reward dependence had no influence on CPM, but harm avoidance trait was strongly correlated with reduced CPM effect. Granot et al. (2008) also investigated the effect of the personality traits of anxiety and catastrophizing on CPM-induced analgesia. They found no effect of anxiety and catastrophizing levels on the magnitude of CPM analgesia induced. These studies therefore showed inconsistent findings on the influence of personality traits on CPM efficiency.

Nahman-Averbuch et al. (2016a) have recently conducted a thorough meta-analysis using 37 studies to explore the association between CPM and personality factors of anxiety, depression and catastrophizing in both pain and pain free participants. The primary analysis showed no significant associations between CPM and these psychological factors but the secondary analysis interestingly found a specific correlation between test stimuli used in CPM testing and individual psychological factors. Pressure stimulus was associated with anxiety, heat stimulus with depression, and electrical stimulus with pain catastrophizing. The authors attributed this modality-specific correlation to the multifaceted nature of CPM, in which several mechanisms mediate its effect, such as noradrenergic and serotonergic, cortical, and autonomic systems.

2.4.3. Aerobic exercise and CPM

The effect of exercise on reducing pain is widely understood. The phenomenon was originally investigated by Black et al. (1979) and it has been described in both animals and humans (Koltyn 2000). Exercise has been also been shown to be an effective modality in the management of pain in several chronic conditions, such as FM (Busch et al. 2007), chronic neck pain, OA, RA,

and chronic low back pain (CLBP) (Geneen et al. 2017). Moreover, exercise has been shown to be effective in preventing recurrences of CLBP (Choi et al. 2010) and limiting the development of chronic musculoskeletal pain conditions (Landmark et al. 2013).

The inhibitory effect of exercise on pain perception is called exercise induced analgesia (EIA) (Koltyn 2002). EIA has been observed in response to several types of exercise, including aerobic exercise (Hoffman et al. 2007), isometric exercise (Kosek & Lundberg 2003) and resistance exercise (Focht & Koltyn 2009). EIA is associated with reduced pain sensitivity which is usually assessed by PPT (Naugle et al. 2014), cold (Ruble et al. 2005), heat (Staud, Robinson & Price 2005; Vaegter et al. 2018), electrical stimuli (Vaegter et al. 2018) or temporal summation of late thermal sensations (Vierck et al. 2001). EIA has been observed at local and remote sites (Naugle, Fillingim & Riley 2012), with more pronounced analgesia measured at the local sites (Vaegter, Handberg & Graven-Nielsen 2014).

Several mechanisms have been proposed to explain EIA. The endogenous opioid analgesia system is the most investigated mechanism that explains the widespread EIA following exercise (Naugle, Fillingim & Riley 2012; Vaegter et al. 2018). Research demonstrated elevated plasma levels of β-endorphin following aerobic exercise in healthy individuals (Rahkila et al. 1988; Rahkila et al. 1987). Research studies have presented mixed findings on the effect of naloxone on EIA as it blocked (Haier, Quaid & Mills 1981) and did not block EIA (Droste et al. 1991), indicating that other non-opioid mechanisms may also be involved in EIA.

Serum levels of 5-HT were also shown to be elevated in response to exercise in healthy active, compared to inactive, participants (Steinberg et al. 1998), and in patients with CLBP (Sokunbi, Watt & Moore 2007) and FM (Valim et al.

2013). Further, high intensity aerobic exercise was also found to increase serum levels of NA (Bahr et al. 1991). These data suggest that exercise activates serotonergic and noradrenergic mechanisms to produce analgesia.

Similar to CPM, EIA has been shown to be associated with cardiovascular and blood pressure responses (Koltyn & Umeda 2006). Pain perception was negatively correlated with blood pressure following exercise in a sample of healthy men and women (Koltyn et al. 2001). Exercise may initiate a baroreceptor mechanism that activates central pain inhibitory pathways (Dworkin et al. 1994) suggesting a potential mechanism for EIA.

Another possible mechanism modulating EIA is an endocannabinoid mechanism (Dietrich & McDaniel 2004). In a study by Koltyn et al. (2014), EIA measured by PPT was positively associated with a significant elevation in circulating endocannabinoids. In the same study, a reduction in thermal heat temporal summation following exercise was significantly associated with an increase in endocannabinoids plasma levels. Endocannabinoids exert an inhibitory feedback mechanism that limits the release of glutamate at synapses transmitting nociceptive signals (Piomelli 2003).

The intensity level for aerobic exercise required to induce EIA is still unclear. A number of previous studies have shown strong hypoalgesic responses after both moderate and high intensity aerobic exercise (Naugle et al. 2014; Vaegter, Handberg & Graven-Nielsen 2016). Naugle et al. (2014) compared the acute hypoalgesic effects of stationary cycling at 70% VO2max and 50% VO2max among 27 healthy volunteers. Both intensities of aerobic exercise induced significant hypoalgesic effects, with a greater hypoalgesia effect after cycling at 70% VO2max. However, other studies reported a significant EIA after high, but not moderate, intensity aerobic exercise (Hoffman et al. 2004; Vaegter, Handberg & Graven-Nielsen 2014). Therefore, the evidence is inconsistent

regarding the exact aerobic exercise intensity necessary to induce significant EIA.

The influence of aerobic exercise on chronic pain is also still unclear. In their systematic review, Cunha et al. (2016) reported that the positive hypoalgesic effect of exercise was consistent in some chronic pain conditions (e.g. rheumatoid arthritis and knee osteoarthritis), but it was unspecified in others (e.g. FM, temporomandibular disorders, painful DPN). This inconsistency in pain responses may be attributed to intact EA pathways in some but not all chronic pain states (Vaegter, Handberg & Graven-Nielsen 2016). The authors (Cunha et al. (2016)) concluded that further investigations are required to clearly identify the effect of aerobic exercise EIA in chronic pain conditions. This project therefore explored the effect of aerobic exercise in a patient population with chronic lateral epicondylalgia (LE) that has not been previously investigated.

It has been shown in healthy pain-free individuals that acute bouts of aerobic exercise positively influence CPM analgesia (Meeus et al. 2015; Naugle, Fillingim & Riley 2012) and that greater CPM efficiency is more likely to be associated with higher levels of EIA (Lemley, Hunter & Bement 2015; Vaegter, Handberg & Graven-Nielsen 2016). Vaegter et al. (2015) examined the hypoalgesic effects of 15 minutes of bicycling exercise at an intensity of 75% VO2max and cold immersion/CPT among active and inactive healthy participants. While the active group showed higher levels of EIA and more efficient CPM effect, as measured by PPT than the inactive group, the extent of analgesia induced by CPM and aerobic exercise in both groups was positively correlated. The association between enhanced CPM effect and increased physical activity level is further supported by Flood et al. (2017), who demonstrated greater CPM analgesia among athletes compared to non-athletes. In this investigation, the influence of 15 minutes stationary cycling at

75% of maximum heart rate (HRmax) and 50% HRmax, which has previously elicited strong EIA levels (Naugle et al. 2014), on CPM analgesia was investigated in people with LE.

2.5. **Manipulation Induced Pain Modulation**

Manipulation induced Pain Modulation (MIPM) is a form of EA associated with manual therapy treatments. Wright (1995) has suggested that MIPM is a multifactorial phenomenon exerting its analgesic effect through several neurophysiological mechanisms. He has proposed that manipulative therapy induces analgesia through facilitation of chemical changes within the environment of peripheral nociceptors, stimulation of peripheral joint repair, activation of neuro-segmental pain modulation systems, and stimulation of descending endogenous anti-nociceptive pathways and non-specific placebo effects. Similarly, Bialosky et al. (2009) also presented a broad model demonstrating the potential multisystem features of the manipulative therapy effect. They have hypothesized that manual therapy may trigger different neurophysiological responses, including hypoalgesia, neuromuscular reflex responses, autonomic, endocrine, and placebo responses mediated by peripheral, spinal, and supraspinal systems. Similar to the model originally proposed by Wright (1995), they suggested that the interplay between these mechanisms is what produces the manual therapy effect, rather than it being induced by an individual system in isolation.

PPT has been used to measure the analgesic effects of spinal and peripheral joint mobilisation and manipulation, with increased PPT values denoting a reduction in the perceived pain at the test location, or hypoalgesia. Voogt et al. (2015) have recently conducted a systematic review to study MIPM effects. Of the 13 randomized studies included in their analysis, 10 demonstrated a significant increase in PPT post manual therapy suggesting a clear MIPM

effect. Three studies also used PPT to objectively detect both local and remote analgesic changes post manual therapy treatment. However, the authors (Voogt et al. 2015) reported that thermal pain threshold (TPT) demonstrated no significant effects for manual therapy treatments.

2.5.1. Evidence of central pain modulatory mechanisms

There is evidence to suggest that descending pain inhibitory systems (central mechanisms) likely play a fundamental role in mediating the analgesic effect of MIPM (Vicenzino et al. 1995). It has been proposed that manual therapy activates afferent neuronal inputs that stimulate the central nervous system to inhibit pain through descending modulation (Souvlis, Vicenzino & Wright 2004). It is thought that the midbrain PAG has an important function in controlling the effects of descending analgesia in both animals (Reynolds 1969) and humans (Hosobuchi, Adams & Linchitz 1977). Reynolds (1969) elicited a strong analgesic effect in rats through direct electrical stimulation of midbrain PAG that was enough to perform laparotomy surgery without anaesthesia. Stimulation of the dorsal PAG in rats was associated with mechanical hypoalgesia, sympathetic excitation and increased muscle activity (Lovick 1991). In a human study, Hosobuchi, Adams and Linchitz (1977) showed that stimulation of the central grey area in people with intractable pain was associated with analgesia. In the view of these findings, the PAG may potentially play a role in mediating the analgesic effects of manual therapy in humans (Sterling, Jull & Wright 2001; Wright 1995).

2.6. Widespread effect of MIPM

2.6.1. Animal research

Animal studies have shown that manual therapy induces widespread effects in areas beyond the mobilised joint or spinal segment, suggesting a central

mechanism (Sluka et al. 2006; Sluka & Wright 2001). Sluka and Wright (2001) showed that knee joint mobilisation decreased experimentally induced ankle and foot hyperalgesia induced by joint inflammation. They investigated the anti-hyperalgesic effect of ipsilateral knee joint mobilisation, in the form of a grade III end range knee extension associated with anterior to posterior tibial translation, on ankle joint inflammatory dynamic hyperalgesia induced by intra-joint capsaicin injection in 31 superficially sedated rats. There were three intervention groups: 3-minue mobilisation group received 3 repetitions of 1-minute mobilisation with 30 second rest intervals in between, 9-minute mobilisation group received three repetitions of 3-minute mobilisation and 15-minute mobilisation group received three 5-minute mobilisations with 30-seccond rest intervals in between. Two control groups were also included: the first group received the same manual contact and manipulative treatment that was used in the 9-minute mobilisation group but without gliding movements being made, and the second control group received the same treatment as the first control but without a manual contact being applied. Mechanical withdrawal thresholds were measured using von Frey filaments applied to the sole of the foot at baseline, at 30 minutes, 1 hour, and 2 hours post induction of inflammatory hyperalgesia into the left ankle joint, and at 5, 10, 15, 30, 45 minutes and 1 hour after knee mobilisation. Secondary hypoalgesia appeared within 2 hours, and lasted for 4 hours, post capsaicin injection. In comparison with the control groups, the 9-minute and 15-minute mobilisation groups showed elevated mechanical withdrawal thresholds relative to baseline readings, which continued for 30 minutes post-mobilisation. There was a complete anti-hyperalgesic effect of 9 minutes and 15 minutes after ipsilateral knee mobilisations on foot and ankle joint hyperalgesia secondary to capsaicin injection. This distant anti-nociceptive effect of proximal joint mobilisation is possibly mediated by supra-spinal mechanisms.

In another animal study, Sluka et al. (2006) investigated the effect of joint mobilisation on experimentally induced hyperalgesia after joint and muscle inflammation in rats. The rats were first randomly assigned into mobilisation and non-mobilisation control groups. Bilateral inflammatory hyperalgesia was elicited in both groups by injecting one gastrocnemius muscle or one knee joint with 3% carrageenan and 3% kaolin/carrageenan, respectively. The knee joint on the ipsi-lateral side of injection was mobilised with a Maitland grade III extension combined with an antero-posterior (AP) tibial glide for three minutes with a 30-second rest in between. Mechanical withdrawal threshold of the paw was established at baseline prior to inflammatory injection, at 1, 2, and 4 weeks post-inflammation, and then at 15, 30, 45, and 60 minutes post knee mobilisation. The study found that mechanical withdrawal thresholds were bilaterally reduced 1, 2, and 4 weeks post knee or muscle inflammation. After knee joint mobilisation over the same period, there was a bilateral elevation in mechanical withdrawal thresholds in rats with muscle inflammation. The mechanical withdrawal thresholds, however, were only elevated after inflamed knee joint mobilisation at 4 weeks, and no change was observed at 1 or 2 weeks. It was therefore hypothesised that unilateral knee joint mobilisation induced bilateral hypoalgesic effects by triggering central EA systems.

2.6.1.1. **Human research**

Similar to animal studies, human studies have shown that manual therapy produced widespread effects observed at distant body areas (de Camargo et al. 2011; Fernandez-Carnero, Fernandez-de-las-Penas & Cleland 2008). Moss, Sluka and Wright (2007) examined the initial effect of a large amplitude AP knee joint mobilisation on pain and function among 38 participants with knee osteoarthritis. In the experimental condition, 3 sets of 3 minutes of knee mobilisation were applied with 30 second rest intervals in between. The

placebo condition received manual contact similar to that used in the mobilisation condition but without a gliding action occurring. The control condition received no treatment or manual contact. PPT was measured over the most tender point at the medial aspect of the treated knee and over the medial aspect of the heel on the same side. Compared to placebo and control conditions, the experimental condition showed an immediate and significant increase in PPT measurements both locally at the knee and at a distant ipsilateral heel site. The remote anti-nociception effect induced by knee mobilisation, indicated by the immediate increase in PPT at the heel, could potentially be mediated by central mechanisms.

Fernandez-Carnero, Fernandez-de-las-Penas and Cleland (2008) investigated the immediate effect of a single cervical upslope manipulation (thrust) C5-6 level on PPT, TPT and pain free grip (PFG) in subjects with LE. The effect of cervical manipulation was compared to manual contact only without a thrust. The study found a significant increase in PPT bilaterally and ipsilateral PFG on the symptomatic side with no effect on TPT. In a more recent study, de Camargo et al. (2011) applied the C5-6 technique in patients with mechanical cervical pain and found a significant increase in PPT over the deltoid muscles on both sides. These findings support the hypothesis that manual therapy induces widespread effects that may be mediated by descending inhibitory pathways.

2.6.1.2. **Concurrent MIPM and sympathetic excitation**

Several studies have investigated the correlation between MIPM and sympathetic excitation, which again suggests activation of central pathways (Chiu & Wright 1996; Sterling, Jull & Wright 2001; Vicenzino, Collins & Wright 1996; Vicenzino et al. 1995). Sterling, Jull and Wright (2001) investigated the associated effects of cervical mobilisation on pain, sympathetic, and motor

responses among 30 participants with an insidious onset of cervical pain. Three conditions were investigated: a grade III unilateral PA C5/6 mobilisation, a placebo manual contact over C5/6, and a control condition without manual contact. The cervical mobilisation condition, compared with placebo and the control condition, exhibited an elevated PPT over the mobilised C5/6 segment, an immediate hypoalgesic effect represented by reduced resting subjective pain rating (visual analogue scale, VAS), a significantly elevated skin conductance (SC) denoting a selective sympathetic effect, and decrease in superficial cervical flexors electro-myography (EMG) signals, likely suggesting an improved deep neck flexors activity, during the cranio-cervical flexion test. The concurrent effect of mobilisation-induced hypoalgesia, sympatho-excitation and improved motor function may support the hypothesis that MIPM is mediated by descending neuronal systems controlled by the PAG.

In patients with chronic LE, Vicenzino et al. (1998b) examined the link between the immediate analgesia post mobilisation and centrally-driven sympathoexcitation. The participants received three treatment conditions: a grade III oscillatory cervical lateral glide (C5/6) mobilisation, a placebo condition where manual contact at the C5/6 segment was provided without gliding movements, and a control condition with no manual contact. The cervical mobilisation condition achieved a greater improvement in PPT, pain free range of movement in the upper limb neurodynamic test (radial nerve biased) (ULNDT-RN), PFG, SC, and blood flux of the skin over the lateral elbow than the placebo or control conditions. The skin temperature and blood flux of the glabrous skin of the hand reduced while TPT had no significant change. This study showed that cervical mobilisation induced analgesia at the elbow together with sympathoexcitation changes such as an increase in SC in the upper limb. In a similar study, Vicenzino et al. (1998a) showed that

analgesia and sympatho-excitation effects, such as increased heart rate, respiratory rate and blood pressure, and motor responses, were simultaneously induced in response to cervical spine mobilisation. This close association between the MIPM and sympatho-excitation responses suggests a role for EA systems (similar to DNIC/CPM) in producing manual therapy analgesia.

Similar to spinal manual therapy, a peripheral mobilisation with movement technique was used to produce concurrent hypoalgesic and sympatho-excitatory effects in people with LE. Paungmali et al. (2003) investigated the effect of a mobilisation with movement technique on pain and sympathetic system responses among 24 participants with chronic LE. The experimental condition received 10 repetitions of Mulligan's manual lateral glide and gripping a hand dynamometer, with a 15 second rest in between. The placebo condition had only a manual contact over the elbow without gliding, but with pain-free gripping movements. The control condition received no manual contact, but only pain-free gripping. Compared to placebo and control conditions, the treatment condition showed a significant increase in PPT, PFG, heart rate, and blood pressure, but without a significant change in thermal pain threshold (TPT). All skin sympathetic nervous system (SNS) measures of conductance, blood flux, and temperature were stimulated in response to elbow mobilisation only. These findings demonstrated that peripheral mobilisation induced pain inhibition was associated with sympatho-excitation, comparable to that observed with spinal manipulation.

2.6.2. Imaging studies and joint mobilisation

2.6.2.1. **Animal research**

fMRI studies in animals show central nervous system changes in response to joint mobilisation. Malisza et al. (2003b) used lumbar spinal cord fMRI to study

the effect of subcutaneous and intra-joint capsaicin injection on the spinal cord neuronal activity, and the effect of joint mobilisation on these neural responses post-hyperalgesia induction in anaesthetized rats. Capsaicin was injected into the plantar aspect of the right hind-paw or into the lateral right ankle joint. Three experimental groups were included. The first was right hind-paw injection without joint mobilisation, the second was right ankle joint injection without joint mobilisation, and the third was right ankle joint injection with 9-minute mobilisation post-injection. In the second group, a light touch stimulation was applied to the plantar surface of the right hind-paw 4 hours post injection using a nylon tip. The third group received light touch stimulation 2 hours post-ankle injection and immediately post joint mobilisation. Knee joint mobilisation ipsilateral to the injection site, in the form of rhythmical flexion and end range extension associated with AP tibial translation was applied for 3 minutes, and repeated 3 times with one-minute rest in between. fMRI detected a noticeable neural activation in spinal cord segments S2-L3 in response to capsaicin-induced hyperalgesia in the hindpaw and ankle, with a greater activation found in the ankle injection groups, specifically in the ipsilateral spinal dorsal horn area. fMRI showed a decrease in the amount of activation in the spinal cord neural activation after knee joint mobilisation. This fMRI study shows that knee joint mobilisation reduces the neuronal activity in spinal cord areas activated by capsaicin-induced hyperalgesia in an animal model.

These central nervous system changes were further examined by Malisza et al. (2003a). They replicated their previously described spinal cord fMRI study, but with using fMRI to investigate the effect of hyperalgesia induced by capsaicin injection on cortical responses, and the effect of ipsilateral knee joint mobilisation on these brain changes after induction of hyperalgesia in anaesthetized rats. In all injected animals, fMRI detected an obvious activation

of several cortical regions involved in the pain experienced in response to capsaicin-induced hyperalgesia, specifically the bilateral anterior cingulate and frontal cortices, and the contralateral sensory motor cortex, with a more substantial activation reported post subcutaneous capsaicin hind-paw injection. Similar brain regions were activated in response to mechanical allodynia and secondary hyperalgesia induced post capsaicin intra-articular joint injection. Compared to other groups, the knee mobilisation group showed tendencies toward decreased activation of the brain regions involved in pain processing in response to knee mobilisation. These fMRI studies suggest that manual therapy analgesia is modulated via central anti-nociceptive pathways.

2.6.2.2. **Human research**

Imaging studies in humans have started to investigate potential central nervous system changes controlling the pain inhibitory effects of MIPM analgesia. More recently, alterations in cortical excitability responses have been visualised in fMRI in response to non-painful pressure in pain free subjects (Mansour et al. 2018). fMRI detected cortical activation of medial parts of the postcentral gyrus (S1) bilaterally, S2, posterior parts of the insular cortex, different parts of the cingulate cortex, and the cerebellum during a centrally applied PA glide over the lumbar spine vertebrae (L1, L3, and L5) in 10 healthy volunteers (Meier et al. 2014). Sparks et al. (2013) also used brain fMRI to detect brain activity changes in response to mechanical pain made by von Frey filaments application to the cuticle of the index finger, and the effect of a thoracic thrust manipulation on these cerebral responses in 10 healthy participants. During the fMRI scanning, temporal summation of pain was produced by von Frey filaments application at a frequency of 1 Hz for a period of 15 seconds, with 15 seconds rest intervals in between, in blocks of 10 cycles (5 minutes). This was followed by a mid-thoracic thrust application in the

supine position. The participants were then immediately re-scanned using fMRI concurrently with von Frey filament stimulations. An 11-point numeric pain rating scale was used immediately post-mechanical stimulations, pre and post thoracic manipulation. The cortical hemodynamic change pre and post thoracic manipulation was measured by blood oxygenation level-dependent fMRI. The results showed a reduction in cerebral activity levels in the pain neuro-matrix (i.e. cortical structures, including S1, S2, insula, and ACC) post thoracic manipulation, that was correlated to a significant decrease in perceived pain ratings. Despite the absence of a control group, this fMRI study presented evidence suggesting involvement of central endogenous pathways in pain inhibition post-thoracic manipulation.

Gay et al. (2014) also investigated the immediate change in functional cortical connectivity in response to three types of manual therapy in an experimentally induced low back pain model. After completing an exercise injury protocol to produce acute low back pain, a sample of previously healthy volunteers were randomly allocated into three manual therapy experimental conditions: chiropractic spinal manipulation (thrust), spinal mobilisation (non-thrust), or therapeutic touch. Participants then underwent a resting state fMRI scan prior to intervention. Following manual therapy interventions, participants underwent a second resting state fMRI. All three manual therapy interventions equally resulted in reduction in low back pain. Additionally, all manual therapy interventions were associated with immediate changes in functional cortical connectivity, including a reduction in functional connectivity between S1 and posterior insular cortex and an increase in functional connectivity between posterior cingulate and anterior insular cortices, and affective and descending pain modulatory areas (insular cortex and PAG). These immediate changes in functional cortical connectivity after manual therapy may explain the neurophysiological mechanism of MIPM

analgesia. Further research is required to investigate these functional cortical changes in patients with pain conditions.

2.6.3. Pharmacological Studies

2.6.3.1. **Human research**

Evidence from pharmacological studies suggests that opioid analgesia is not likely to be involved in manual therapy analgesia in humans (Paungmali et al. 2004; Vicenzino et al. 2000; Zusman, Edwards & Donaghy 1989) and in animals (Skyba et al. 2003). It was shown that systemic administration of naloxone did not antagonise the immediate analgesia induced by spinal manual therapy analgesia (Vicenzino et al. 2000). Similarly, in their randomised control trial, Paungmali et al. (2004) examined the effect of intravenous injection of naloxone on a Mulligan mobilisation with movement technique among 18 individuals with LE. In comparison to placebo (saline injection) and control (cannula insertion without injection), naloxone did not reverse the analgesic effect of peripheral mobilisation of the elbow. These research findings indicate that opioid analgesia is unlikely to be a neurophysiological mechanism explaining MIPM analgesia. They support the notion that MIPM analgesia is potentially mediated by non-opioid mechanisms.

2.6.3.2. **Animal research**

Skyba and colleagues (2003) used a rat model of inflammatory pain to demonstrate the important role of descending inhibitory pathways in producing the initial effects of mobilisation induced analgesia. They aimed to define the types of spinal neurotransmitters involved in the manual therapy pain relieving effect in anaesthetized rats. Capsaicin injection into the ankle was used to establish hyperalgesia in the ankle and foot region. Optimal hyperalgesia was established after 2 hours. After induction of hyperalgesia,

knee joint mobilisation in the form of flexion and end range extension associated with AP tibial translation was applied for 3 minutes, and repeated three times with 1 minute rest in between. In different groups of rats, bicuculline, naloxone, yohimbine and methysergide, were spinally administered to block spinal γ-aminobutyric acid (GABA) receptors, opioid receptors, α2-adrenergic receptors (α2-AR) and 5-HT1/2 receptors, respectively. Mechanical withdrawal thresholds of the hindpaw plantar surface were assessed using von Frey filaments at baseline and 2 hours post capsaicin injection, and at 15, 30, 45 and 60 minutes post knee mobilisation. Capsaicin induced a reduction in mechanical withdrawal threshold. This effect was reversed by mobilisation of the knee joint, demonstrating a significant analgesic or anti-hyperalgesic effect. Intrathecal administration of the α2-AR antagonist, yohimbine and the 5-HT receptor antagonist, methysergide partially blocked and completely blocked this analgesic effect. Blocking GABA and opioid receptors produced no effect on the analgesia induced by knee mobilisation. In a further experiment, 5HT1A, 5-HT2A, and 5-HT3 receptors antagonists were given, namely NAN-190, ketanserin, and MDL-72222, respectively. The findings from this experiment showed that blockade of the 5-HT1A receptor completely abolished the analgesic effect of manual therapy. They concluded that segmental pain modulation mechanisms involving GABA and the opioid systems do not contribute to the analgesic effect of manual therapy. They also concluded that spinal serotonergic and noradrenergic receptors linked to descending serotonergic and noradrenergic neurons play a key role in mediating manipulation-induced analgesia.

These data from human and animal research provide evidence that manual therapy activates central endogenous pathways, which are non-opioid, to mediate its immediate pain relieving effects. The evidence also suggests that MIPM can be widespread, as indicated by increasing PPT at distant body

regions, and occurring concurrently with sympatho-excitation responses. In addition, pharmacological studies have further helped explain the neurophysiological analgesic effects of MIPM, through which MIPM activates central pain inhibitory mechanisms, where the PAG potentially has a central role, involving serotonergic and adrenergic, rather than opioidergic systems. These studies, taken together with evidence from imaging studies that demonstrate the involvement of supraspinal regions in the analgesic effects of MIPM, provide clear evidence that central pain mechanisms are potentially the most plausible explanation for MIPM analgesia.

2.6.4. Psychological factors influencing MIPM analgesia

While psychological factors (e.g. placebo) are inadequately investigated in manual therapy, it appears that placebo is influential in conventional or alternative therapies dealing with musculoskeletal pain, such as massage and acupuncture. Kalauokalani et al. (2001) randomly allocated 135 CLBP participants into 2 groups receiving acupuncture or massage treatments for 10 weeks. Prior to randomization, participants were asked to rate their expectations for the usefulness of each interventions on a scale of 0 to 10. The modified Roland Disability scale was the main functional outcome measure used at 10 weeks. They found that participants with higher expectation for massage and having massage had significantly better outcomes than those participants with higher expectations for acupuncture and having massage, and vice versa. This study suggested that expectation for helpfulness of a treatment was significantly associated with better clinical outcomes. Therefore, in a similar way, placebo may exert its analgesic effects in manual therapy, via supraspinal analgesic mechanisms.

A patient's expectations about manual therapy effectiveness was shown to be influential in determining the extent of their response to the treatment. Bishop

et al. (2013) in their secondary analysis of a clinical trial using thrust manipulation and exercise to treat neck pain found that expectations of patients for the effectiveness of physiotherapy treatments have a considerable effect on outcomes. Out of 140 patients, in excess of 80% expected moderate symptom relief, prevention of disability, increased activity levels and getting better sleep. Of manual therapy modalities, both manipulation and massage had the maximum percentage of patients expecting these treatments to considerably relieve their cervical pain. At 1 month, lower likelihood of reporting a successful effect was demonstrated by patients who were uncertain of achieving full pain relief as compared to those who predicted full relief. The likelihood of success was decreased by believing that manipulation would help and not receiving manipulation in comparison with believing manipulation would help and receiving manipulative. The study concludes that expectation of help among patients with neck pain strongly affects clinical outcomes.

Bialosky et al. (2008) studied the impact of expectation of pain reduction on the analgesic effect of lumbar spine manipulation on painful heat stimulation among three groups of asymptomatic volunteers. The positive expectation group was instructed that the spinal manipulation, 'is a very effective form of manipulation used to treat LBP and we expect it to reduce your perception of heat pain'. The negative group was given the opposite instruction involving expectation of increased heat pain. The neutral expectation group was advised that the manipulation treatment has, 'an unknown effect' on their heat pain perception. The negative expectation group showed a substantial increase in pain response to thermal sensitivity testing, while no effect was observed in pain perception in the other groups.

2.7. **Therapeutic interaction**

The therapeutic relationship between a patient and therapist, or the so called patient-therapist interaction, can be generally expressed as a sense of partnership, warmth, and support between therapist and patient in the clinical setting (Ackerman & Hilsenroth 2003). Effective patient-therapist interaction may involve a positive connection (or rapport) between the patient and therapist developed through respect, empathy, trust, and verbal and non-verbal communications (Pinto, Ferreira & Oliveira 2012).

Evidence from a growing body of research indicates that the patient-therapist interaction is associated with positive treatment outcomes such as lower pain levels, decreased disability, and greater clinical satisfaction (McGilton et al. 2009). Hall et al. (2010) conducted a systematic review of quantitative studies to investigate the effect of the patient-therapist interaction on several clinical outcomes (including pain, disability, quality of life, depression, adherence, and satisfaction with treatment) in physical rehabilitation. In their analysis, they included thirteen studies from different fields of rehabilitation (including brain, musculoskeletal, and cardiac). The authors found a positive association between patient-therapist interaction (alliance) and the clinical outcomes in rehabilitation. A more recent systematic review by Lakke and Meerman (2016) examined the influence of the therapeutic alliance (i.e. patient-therapist interaction) on pain and physical functioning in patients with musculoskeletal pain. The authors included five studies (one randomised controlled trial (RCT) and four cohort studies) involving 1,041 patients with chronic musculoskeletal pain. In this review, positive therapeutic interaction was a significant predictor of reduced pain and enhanced physical functioning in chronic musculoskeletal pain.

Research also suggests that patient-therapist interaction can be manipulated to modify clinical pain. A recent study by Fuentes, Armijo-Olivo and Funabashi (2014) manipulated the therapist-patient interaction (enhanced or limited) to investigate the pain relieving effect of a single session of interferential current (IFC) (sham or active) on CLBP. Compared to the other groups, the group that received active IFC with enhanced interaction experienced the most significant pain relief on the numerical pain scale. There was also a significant increase in PPT for both the active and sham IFC groups combined with enhanced interaction. The authors concluded that an enhanced interaction positively influences clinical outcomes when combined with active IFC in the treatment of CLBP.

The effect of experimental manipulation of the patient-therapist interaction is not clear. Mistiaen et al. (2016) performed a comprehensive systematic review of randomised and quasi-randomised controlled trials to assess the effects of different types of experimentally manipulated patient-practitioner interaction on pain. 51 studies with a total of 5079 patients were included in their analysis. Three types of therapeutic interaction intervention were identified: cognitive care, empathetic (emotional) care and procedural preparation. Overall, there was a significant, but small, effect of therapeutic interaction on pain. Positive suggestion and informational preparation seemed to reduce pain while negative suggestion appeared to increase pain. In relation to empathetic care, the authors reported that the included studies were of poor quality, in which various types of interactions were combined and as a result the selective effect of empathetic interaction could not be completely isolated. Therefore, the empathetic interaction had a weak and indirect effect on reducing pain although the level of evidence was very low. In the light of the reviewed research studies, the effective elements of the therapeutic interaction could not be clearly identified.

2.8. **Summary**

Clinical research has demonstrated that individuals with dysfunctional EA system, manifested as less efficient CPM, are more likely to experience chronic pain. Accordingly, understanding the role of descending modulatory pathways in chronic musculoskeletal pain may lead to finding new therapies.

Recent research evidence also suggests that both CPM and MIPM represent an adequate stimulus for activating descending pain inhibitory pathways. Literature also suggests the initial pain relieving effect of CPM and MIPM may be mediated by common neurophysiological mechanisms in the EA systems in which serotonergic and adrenergic systems have an important function. This apparent neuro-physiological link between CPM and MIPM is reinforced by the fact that their analgesic responses can be affected by psychological and pharmacological interventions that exert an influence on EA. This raises the possibility that individuals who demonstrate a functional response to CPM could also consistently show a good response to MIPM. Therefore, clinicians can potentially utilise CPM test to identify MIPM responders and MIPM non-responders and, thus, customise treatment plan for each individual patient. Evidence also provides an excellent base from which to investigate the possibility of enhancing either CPM and/or MIPM analgesic effects by combining them with other treatment modalities (i.e. empathetic interaction and aerobic exercise) to potentiate management of musculoskeletal pain.

The overall objective of this thesis was to investigate whether CPM and MIPM could exhibit similar patterns of analgesic responses through a series of experimental paradigms targeted to facilitate the function of the endogenous descending pain inhibitory (modulation) systems. These experimental paradigms looked at the association between CPM and MIPM analgesic response and then manipulated their analgesic effects using psychological and

physical interventions, through enhanced empathetic interaction and aerobic exercise, respectively. Each of these experimental paradigms are considered separately in the following chapters.

In this investigation, LE has been used as a clinical model for testing as the analgesic effect of MIPM in LE is firmly confirmed (de Camargo et al. 2011; Fernandez-Carnero, Fernandez-de-las-Penas & Cleland 2008; Vicenzino et al. 1998a; Vicenzino et al. 1998b; Vicenzino, Collins & Wright 1996). This has rendered the comparison with CPM reasonable, where its efficiency in LE is yet to be demonstrated. Additionally, compared to other chronic musculoskeletal pain conditions, LE can be seen as a 'clean' musculoskeletal condition where pain experience is less likely to be confounded by other variables of chronic pain (e.g. chronic pain medications).

Chapter 3: **Study One**

The Reliability of pressure pain threshold and duration of conditioned pain modulation after-effect

3.1. Introduction

In a series of preliminary studies, conditioned pain modulation (CPM) and manipulation therapy induced pain modulation (MIPM) analgesic responses will be assessed using established CPM (Locke et al. 2014) and MIPM (Vicenzino, Collins & Wright 1996) assessment protocols, respectively. Both protocols will use as the main outcome pressure pain threshold (PPT) measured by a handheld digital algometer. Previous investigations have shown a relatively high reliability for PPT (Balaguier, Madeleine & Vuillerme 2016; Paungmali et al. 2012; Smidt et al. 2002) in assessment of pressure hyperalgesia (Wright, Thurnwald & Smith 1992). Waller et al. (2015) reported excellent inter-rater and intra-rater intra-class correlation coefficients (ICCs) of PPT, ranging from 0.92-0.95 and 0.80-0.99 respectively, when tested over 4 different body sites. However, this level of reliability is dependent upon tester skills. Therefore, the was a need for the specific investigator in this thesis to evaluate his own test-retest reliability

A CPM protocol using the cold pressor test (CPT) and PPT, as the conditioning and testing stimuli respectively, has been demonstrated to be the most effective method to induce an efficient CPM effect (Oono et al. 2011). CPM analgesic effect is exhibited by the degree of PPT elevation in response to the CPT. This protocol requires repeated PPT measures (at baseline, at 1 minute, at 3 minutes and at 5 minutes) and so it is important to demonstrate the reliability of repeated PPT measurements within the timeframe of the testing protocol.

Previous research has reported different durations for the length of time that the CPM effect lasts. Willer, De Broucker and Le Bars (1989) found that the elevated PPT from the conditioning stimulus took between 6-9 minutes to return to baseline levels. However, Tuveson, Leffler and Hansson (2006) reported that CPM lasted 30 minutes after conditioning stimulus removal whilst Graven-Nielsen et al. (1998) reported a one hour latency. Therefore, there is uncertainty around the duration of CPM after-effect that warrants further investigation and therefore it was important to specifically assess the duration of CPM response using the methodology supplied in other studies in this thesis.

The initial aim of this study was to therefore to determine the reliability of repeated PPT measurements. The second aim of the study was to determine the duration of a measurable (meaningful) CPM effect to assist in determining a suitable rest period before any assessment of MIPM effect would occur in future studies. The final aim was to provide data to facilitate the calculation of the sample size required for the design of the subsequent studies reported in this thesis.

3.2. **Methods**

3.2.1. Participants

In this study two separate groups of pain-free participants (N = 11 and N = 10) were recruited through advertisements on noticeboards in the Bentley area, Perth, Western Australia. To ensure that only pain-free subjects were included, all participants were asked to fill out a screening questionnaire prior to commencing the study. Potential participants were required to be between 18-70 years of age. Participants were excluded if they presented with:

- History of chronic pain conditions (e.g. fibromyalgia, irritable bowel syndrome, temporomandibular dysfunction, migraines)
- Neurological or sensory dysfunction (especially in the upper limbs)
- History of chronic musculoskeletal pain (e.g. arthritis, chronic low back pain)
- Contraindications to cold application (i.e. Reynaud's disease, diabetes)
- Current or long-term use of pain medication or anti-depressants
- Inability to communicate in English

All testing was carried out at the Physiotherapy Clinic (Building 404), School of Physiotherapy and Exercise Science, Curtin University. The study was approved by Curtin University Human Research Ethics Committee (HREC) (HRE2016-0181-01). All participants gave written informed consent before commencing testing.

3.2.2. Procedure

A single group pretest/posttest design was used in this two-part study. Eleven healthy participants attended a single test session where they underwent a PPT test-retest protocol for the wrist site (Phase 1) followed by a CPM testing protocol (Phase 2), with a rest period of 10 minutes in between. On a separate session, 10 healthy participants completed the Phase 1 test-retest protocol for the elbow site. The experimental protocols were performed by the same investigator. All instructions were standardized (Figure 3.1).

3.2.3. Outcome measures

3.2.3.1. **Pressure pain threshold (PPT)**

For both the first (wrist test-retest and CPM duration) and second (elbow test-retest only) sub-studies, PPT was assessed using a hand-held digital pressure algometer (Somedic, Sweden), modified with a footswitch rather than the standard hand switch control (Locke et al. 2014). A 1 cm^2 algometer tip was applied perpendicularly over the marked site by the assessor and the pressure stimulus was applied at a standard rate of 40 kPa/s. The digital algometer used had an on-screen dial to facilitate standardizing the rate of application. Participants were instructed to press the footswitch at the moment they perceived the pressure began to have become painful. The standardised wrist test site was identified and marked at the mid-point on the posterior aspect of the right wrist 2 cm proximal to the wrist crease (Locke et al. 2014). The standardized elbow site was identified and marked at a point on the lateral aspect of the right elbow, 2 cm distal to the lateral epicondyle. For all testing, participants sat on a chair of adjustable height so the right forearm was comfortably positioned in pronation on a table. The test procedure was first conducted at the left forearm for familiarization. For each test site, three PPT measurements were then taken on the right forearm with 15-20 seconds intervals between each. PPT measures were the pressure values (kPa) recorded from the algometer.

3.2.4. Testing protocols

For the first sub-study PPT test-retest protocol at the wrist was followed by CPM protocol, with a 10 minute rest period in between. For the second sub-study, only PPT test-retest at the elbow was carried out (Figure 3.1).

3.2.4.1. **PPT test-retest protocol**

The assessor measured PPT using an electronic digital algometer (Somedic AB, Sweden) as described above. Measurements were taken at the test site (wrist for sub-study 1 and elbow for sub-study 2) at baseline, at 1 minute, at 3 minutes and at 5 minutes. Three PPT measurements were taken at each time point with a 15-20 seconds interval between each. Mean values were then used in analysis. (Figure 3.1 a)

3.2.4.2. **Conditioned pain modulation (CPM) testing protocol**

PPT was used as the test stimulus and measurements were carried out in the manner described above.

The cold pressor test (CPT) was used as the conditioning stimulus to elicit the CPM response. The left (non PPT-tested) hand was submerged to 10 cm above the wrist crease in a cold water bath with temperature maintained at 7°C, for a period of 2 minutes (Locke et al. 2014). The water bath contained a mix of water and ice and a circulating pump ensured uniformity of water temperature at the skin. A thermometer was used to monitor water temperature throughout the testing. PPT at the right wrist site was tested at baseline prior to CPT, after 1 minute during immersion (CPT) to calculate CPM response, and then at various time points post immersion (1 minute, 5 minutes, 15 minutes, 30 minutes, 45 minutes, and 60 minutes) to determine the time point at which PPT returned to the baseline value. At each time point, PPT was measured three times with 15-20 second rest intervals in between. The mean value of the three measurements at each time point was used for statistical analysis (Figure 3.1 b).

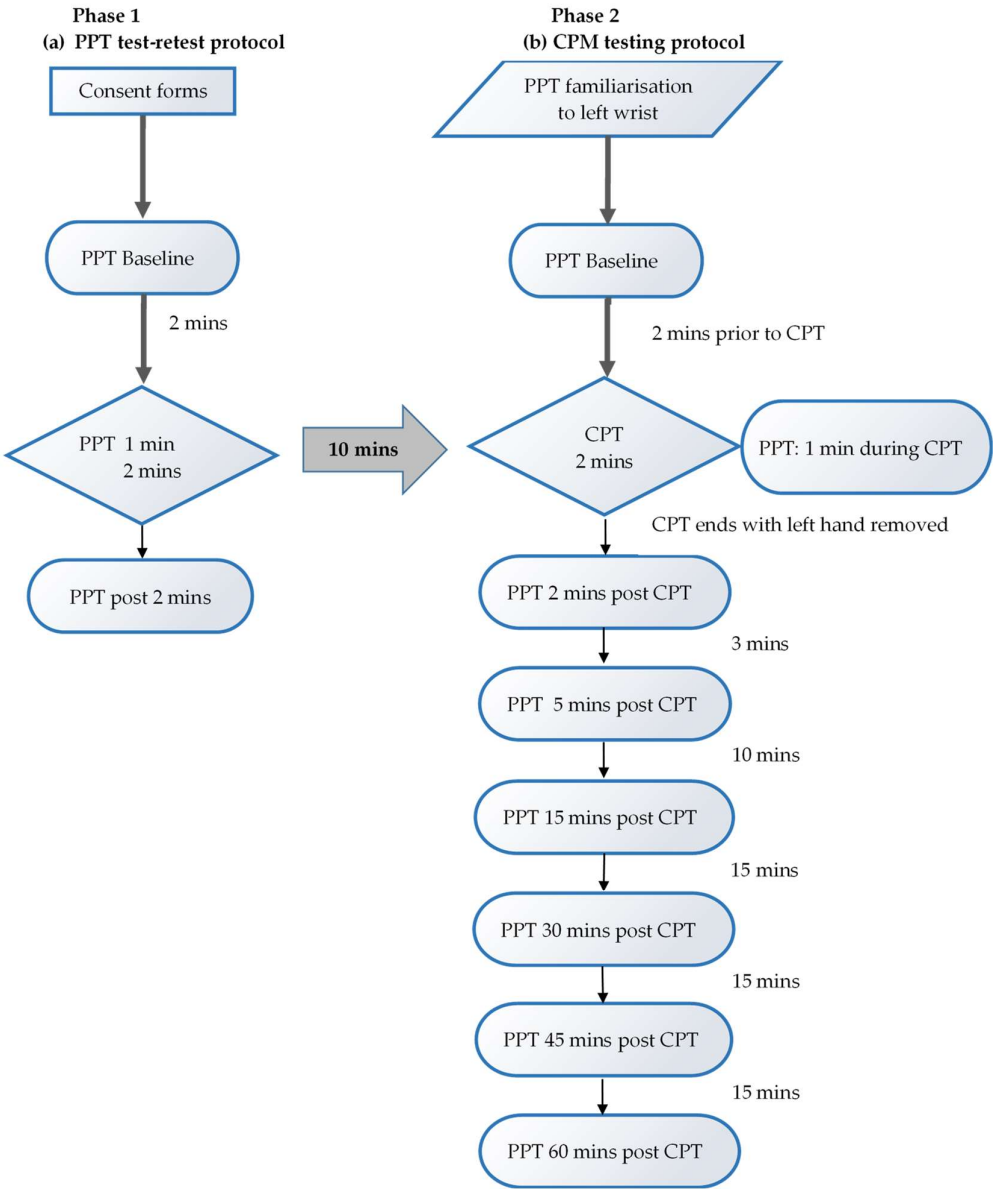

Figure 3.1 Preliminary study with testing protocols: PPT test-retest (a) and CPM testing protocols (b).

3.2.5. Data analysis

For all analyses, $P<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS Statistics Version 24.0 (IBM Corp., Amonk, NY, USA) and Stata/IC (version 15.0: StataCorp LLC, TX).

3.2.5.1. **Reliability testing**

For PPT reliability, the intra-class correlation coefficient (ICC) of the mean value for each time point in the PPT test-retest protocol (baseline, at 1 minute, at 2 minutes and at 5 minutes) was calculated at the wrist (for sub-study 1) and at the elbow for sub-study 2. The intra-rater reliability for each site was calculated using an ICC for consistency under a two way-mixed effects model, using the average of the 4 measures obtain by the single rater: ICC (3,4).

3.2.5.2. **Assessment of duration of CPM after-effect**

To determine at which time-point the CPM response returned to baseline, mean PPT values obtained at each time point post CPT at the right wrist site were evaluated using a linear mixed regression model with random participant effects. The mean PPT percentage increase from baseline at each time point was also compared to the percentage increase determined for meaningful CPM effect as determined by Locke et al. (2014). In Locke et al. (2014) study, CPM effect was considered meaningful if the percentage increase in wrist PPT from baseline was greater than the standard error of measurement (SEM) for repeated PPT measures. The authors computed the SEM for each time point using the formula SD x √(1-ICC), where ICC represented the intra-class correlation coefficient of the mean value for each time point. They then added the SEM to the PPT mean value for each time point to indicate the maximum upper value of normal variation in repeated PPT measures. They then transformed each value to a percentage change value by dividing it by the PPT mean value. The mean of these percentage change values represented the meaningful CPM effect (105.28%). The time point at which there was no significant difference between mean PPT values and baseline mean PPT values and where the mean percentage increase in PPT was

less than the meaningful CPM effect (5.29%) was designated as the limit of any analgesic response.

3.2.5.3. **Sample size calculations**

Sample size calculations were conducted using Stata/IC (version 15.0: StataCorp LLC, TX). Calculations of the required sample size were based on means and standard deviations of PPT measured at the elbow site for a power of 0.80 with a p value of 0.05. Descriptive statistics of the mean and standard deviation for each time point in the PPT test-retest protocol using the elbow site (baseline, at 1 minute, at 2 minutes and at 5 minutes) were calculated and then pooled. The minimal clinical important difference (MCID) in PPT at the elbow was based on data from a major clinical trial comparing corticosteroid injections and physiotherapy management of tennis elbow (Coombes et al. 2013). The MCID was considered to be 88 kPa (Coombes & Vicenzino 2017; personal communication). In determining our sample size, we used a difference value of 50 kPa with the pooled standard deviation calculated.

3.3. **Results**

3.3.1. Reliability analysis for PPT at the wrist site

In the first test cohort for the wrist site study, two females and 9 males participated. All participants were able to complete the wrist PPT test-retest protocol measurements, except for one male whose PPT measurements at minute 5 was not taken accidentally. Therefore, data for 10 participants (age range: 20-40 years, mean: 31.2, SD: 6.2) were included in the wrist site reliability analysis.

ICC analysis using PPT mean value at the wrist site at each time point showed excellent intra-rater reliability: ICC (3,4) = 0.991 (Table 3.1).

Table 3.1 Intra-class Correlation Coefficients at the wrist test site

		95% CI		F Test with True Value 0			
	ICC	Lower Bound	Upper Bound	Value	df1	df2	P
Single Measures	0.963	0.907	0.990	105.535	9	27	<0.001
Average Measures	0.991	0.975	0.997	105.535	9	27	<0.001

ICC: Intra-class Correlation Coefficient, CI: confidence interval, df: degree of freedom. Level of significance, <0.05

3.3.2. Reliability analysis for PPT at elbow site

In the second cohort, two females and 8 males participated. All participants were able to complete the elbow PPT test-retest protocol measurements. Therefore, data for 10 participants (age range: 21-43 years, mean: 31.5, SD: 6.8) were included in the reliability analysis.

ICC analysis using PPT mean value at the elbow site at each time point also showed excellent intra-rater reliability: ICC (3,4) = 0.986 (Table 3.2).

Table 3.2 Intra-class Correlation Coefficients at the elbow test site

		95% CI		**F Test with True Value 0**			
	ICC	Lower Bound	Upper Bound	Value	df1	df2	P
Single Measures	0.946	0.869	0.985	71.701	9	27	<0.001
Average Measures	0.986	0.963	0.996	71.701	9	27	<0.001

ICC: Intra-class Correlation Coefficient, CI: confidence interval, df: degree of freedom. Level of significance, <0.05

3.3.3. Assessment of duration of CPM after-effect

All participants from the first sub-study (2 females and 9 males) were able to complete phase 2 of the study and therefore 11 data sets were included in the analysis. The differences in PPT across time points from baseline are presented in Table 3.3. A linear mixed model showed that mean PPT measured at 1 minute during immersion and 1 minute post immersion increased significantly relative to baseline (P values: <0.001 and 0.002, respectively). This indicates a significant CPM effect above the meaningful CPM cut-off value of 5.29% (Locke et al. 2014) at these time points. There was however no significant difference in PPT measures taken at 5 minutes (P=0.103), 15 minutes (P=0.258), 30 minutes (P=0.198), 45 minutes (P=0.715) and 60 minutes (P=0.252) post immersion when compared to baseline measure. The pattern of PPT values (Figure 3.2) therefore demonstrated that the values returned to baseline levels below 5.29% from 5 minutes post immersion.

Table 3.3 Mixed regression models for PPT values across 7 time points: predicted marginal means: differences between time points relative to baseline.

Time point	Mean	95% CI (mean)	p
Baseline (Pre)	219.27	180.41 – 258.14	-
1 minute During	369.39	330.53 - 408.26	**< 0.001**
1 minute Post	260.97	222.10 - 299.84	**0.002**
5 minutes Post	241.33	202.47 - 280.20	0.103
15 minutes Post	234.57	195.71 - 273.44	0.258
30 minutes Post	236.67	197.80 - 275.53	0.198
45 minutes Post	224.21	185.35 - 263.08	0.715
60 minutes Post	234.78	195.89 - 273.62	0.252

PPT: pressure pain threshold, CI: confidence interval.
Level of significance, <0.05

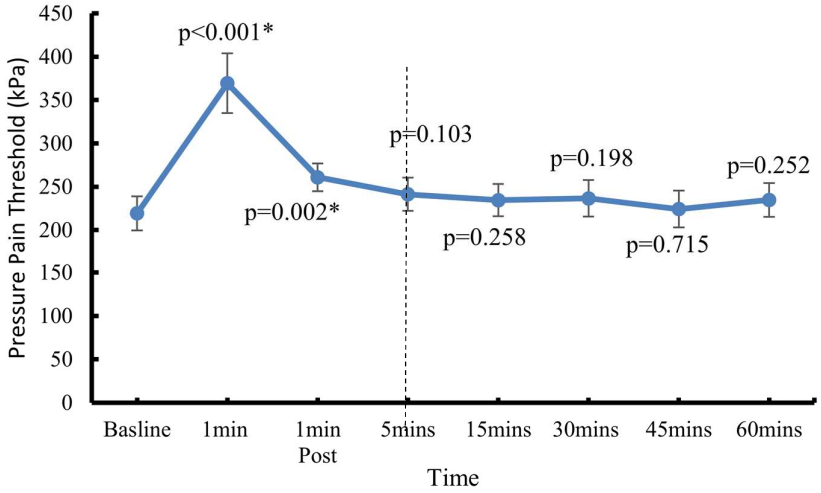

Figure 3.2 CPM pattern of analgesic responses (PPT) at different time points

3.3.4. Sample size calculations

PPT data at the elbow site for 10 participants (2 females and 8 males) were used in the analysis (Table 3.4). The pooled mean of 307.21 kPa and the pooled standard deviation of 73.22 kPa were calculated. In determining our sample size we used a difference value of 50 kPa (Coombes & Vicenzino 2017; personal communication) with the pooled standard deviation of 73.22 kPa resulting in an effect size difference of 0.68. An a priori power analysis (alpha = 0.05, beta = 0.80) indicated a required sample size of 68 (34 per group).

Table 3.4 Descriptive statistics for PPT measured at the elbow test site

	Minimum	Maximum	Mean	SD
Baseline PPT	235.67	468.00	307.07	66.90
1 minute	233.33	495.67	307.90	77.17
3 minutes	244.00	480.33	310.03	71.23
5 minutes	222.33	490.00	303.83	77.56

PPT: pressure pain threshold, SD: standard deviation

3.4. **Discussion**

The results of the PPT test-retest protocol demonstrated high intra-rater reliability when measuring PPT at 4 time points. Locke et al. (2014) in their 10 subject pilot study demonstrated high intra-rater reliability (ICC=0.949). A study with a larger sample of healthy volunteers by Waller et al. (2015) also showed that intra-rater ICCs ranged from 0.81 to 0.97 at the wrist site. Vicenzino et al. (2001) also reported an excellent level of reliability (ICC=0.95) at the elbow site. The ICC results of these studies are comparable to the ICC results of 0.991 and 0.986 at the wrist and elbow sites, respectively, in this reliability study. Despite this comparability of ICC values, our study demonstrated higher ICC values denoting higher degree of consistency in PPT measurements.

This study also assessed the pattern of CPM analgesic response as measured by PPT over a one-hour time period in a group of healthy pain-free individuals. During CPT, all participants exhibited a CPM effect as determined by the meaningful CPM cut-off value of 5.29% calculated by Locke et al. (2014). PPT measurements returned to baseline levels and below the 5.29% value by 5 minutes post immersion. This is in accordance with Fujii, Motohashi and Umino (2006) study that showed that the CPM effect lasted 5 minutes after removing the conditioning stimulus. In contrast to these findings, other studies have demonstrated a more prolonged CPM after-effect lasting for 30 minutes (Tuveson, Leffler & Hansson 2006) and up to 60 minutes (Graven-Nielsen et al. 1998). However, these studies used very different conditioning stimuli to induce CPM over longer periods of time than the current study, which involved a 2-minute CPT conditioning stimulus. To inhibit pressure pain, Tuveson, Leffler and Hansson (2006) used an ischemic pain model with pressure cuff inflation applied for about 10 minutes while Graven-Nielsen et al. (1998) administered hypertonic saline for 15 minutes.

These variations in the conditioning stimulus and time-frame used to induce endogenous analgesia could be the reason for these differences in the CPM durations. Further, the Locke et al. (2014) study showed that some participants still demonstrated a CPM effect at 5 minutes but did not investigate the pattern of CPM effect beyond 5 minutes post CPT. Therefore, this study further explored the duration of analgesic effect following CPM testing (using PPT as a testing stimulus and CPT as a conditioning stimulus) that has not been explicitly investigated in previous research.

Finally, the sample size calculated (N=68) that will be used in the subsequent studies (i.e. Studies 3 and 4) is higher than any sample size used in previous studies looking at the effect of manual therapy on musculoskeletal dysfunction. The elbow site was chosen for sample size calculation since PPT will be used as the main outcome measure to quantify the manual therapy effect in lateral epicondylalgia (LE), which will be used as a model for musculoskeletal pain in the subsequent studies.

3.5. **Conclusion**

This study established a high level of intra-rater reliability for PPT measured at both the wrist and elbow sites using a digital handheld algometer. It also found that a CPM analgesic response is induced during and 1-minute post a CPT conditioning stimulus but that this response returned to baseline levels by 5 minutes post stimulus completion. The findings of this study will be used to determine the duration of the rest period between CPM and MIPM assessment protocols, and the required minimum sample size that will be used in the subsequent studies described in this thesis.

Chapter 4: **Study Two**

Association between the analgesic effects of CPM and MIPM

4.1. Introduction

Perception of noxious stimuli is modulated by pain inhibitory and facilitatory mechanisms in the central nervous system. Endogenous analgesia (EA) generally involves multiple central circuits that modulate pain inhibition. Diffuse noxious inhibitory controls (DNIC) is one of the most extensively studied forms of EA and it involves the phenomenon of pain inhibiting pain (Lebars, Dickenson & Besson 1979; Reinert, Treede & Bromm 2000). DNIC involves a cortically mediated spinal-bulbo-spinal inhibitory pathway acting through inhibition of wide dynamic range (WDR) neurons in the dorsal horn of the spinal cord (Lebars, Dickenson & Besson 1979). There is also compelling evidence that the descending inhibitory component of the DNIC pathway is mediated via neural networks located in the rostral brainstem, involving serotoninergic and noradrenergic descending neurons (Bannister et al. 2017). It is recommended to use the term Conditioned Pain Modulation (CPM) to specifically define the DNIC phenomenon in humans (Yarnitsky et al. 2010). Data from early research suggested that DNIC analgesia involves an opioid mediated mechanism (Bouhassira, Villanueva & Le Bars 1992; Le Bars, Willer & De Broucker 1992; Willer, Le Bars & De Broucker 1990). However, more recent research has demonstrated that the CPM response in humans is partially reversed (Sprenger, Bingel & Buchel 2011) or not affected (Hermans et al. 2018) by naloxone, suggesting that there may be a limited role for opioid neurotransmitters in CPM.

CPM has been used as a reliable measure for EA efficiency (Kennedy et al. 2016). A less efficient CPM effect is associated with chronic pain states,

implying dysfunctional pain modulatory mechanisms (Yarnitsky 2015). However, the absence of CPM response has also been observed in some healthy individuals (Locke et al. 2014).

Another form of EA is Manipulation Induced Pain Modulation (MIPM). Wright (1995) has suggested that MIPM is a multifaceted phenomenon exerting its analgesic effects through activation of several mechanisms. It is proposed that in the clinical setting it is the interaction between these systems that produces the MIPM effect, rather than a particular system in isolation (Bialosky et al. 2009; Wright 1995).

Several studies have shown a close association between MIPM following cervical joint mobilisation and centrally-mediated sympatho-excitation in patients with chronic lateral epicondylalgia (LE) (Chiu & Wright 1996; Sterling, Jull & Wright 2001; Vicenzino et al. 1998b; Vicenzino, Collins & Wright 1996; Vicenzino et al. 1995). In the same way, changes in sympathetic nervous system function (e.g. increased heart rate, increased blood pressure) were significantly positively associated with CPM response in pain-free healthy individuals (Chalaye et al. 2013) and in a patient population with fibromyalgia (Chalaye et al. 2014). This concurrent association of sympathetic responses with MIPM and CPM suggests a role for central pain modulatory mechanisms in producing the analgesia associated with MIPM and CPM (Vicenzino et al. 1998b).

Data from pharmacological studies has also shown that CPM and MIPM share similar neurophysiological mechanisms. Systemic or local administration of an α1-adrenoceptor agonist (Makino et al. 2010), systemic administration of a selective α2-adrenergic receptors (α2-AR) agonist (Sanada et al. 2009) or 5-HT7 (5-hydroxytryptamine 7) receptor antagonist SB269970 (Bannister et al. 2017) inhibited DNIC/CPM responses. Likewise, MIPM analgesia was partially

blocked by intrathecal injection of an α2-AR antagonist while a 5-HT (serotonin) receptor antagonist completely blocked the analgesic effect of MIPM (Skyba et al. 2003). Spinal blockade of γ-aminobutyric acid (GABA) or opioid receptors however did not affect MIPM analgesia (Skyba et al. 2003). These data suggest that CPM and MIPM analgesia is potentially mediated by descending serotonergic and noradrenergic mechanisms.

Reports on the association between different naturally induced forms of analgesia are limited. The current available evidence shows that CPM is positively associated with exercise induced analgesia (EIA) (Lemley, Hunter & Bement 2015; Vaegter et al. 2015). To date there has been no study assessing the association between CPM and MIPM analgesia.

The initial aim of this study was to assess the association between the analgesic effects of CPM and MIPM in patients with LE. The second aim was to investigate whether there was a difference in MIMP effect between those who demonstrated and who did not demonstrate a clear CPM effect. LE was used as a clinical model as the effect of MIPM in LE (Vicenzino et al. 1998b) has been previously established.

4.2. **Methods**

4.2.1. Null hypotheses

1. There will be no difference between time points in the level of CPM and MIPM analgesia detected by measures of PPT at the wrist and elbow.

2. There will be no difference between the level of CPM and MIPM analgesia overtime (CPM vs MIPM measures).

3. There will be no correlation between the level of MIPM and CPM analgesia as detected by measures of PPT at the wrist and elbow.

4. There will be no difference in the level of MIPM analgesia overtime between those participants who do and those who do not exhibit a CPM response (CPM responders vs non-responders).

4.2.2. Study design

This was a quasi-experimental single-group, pretest-posttest study design conducted in one testing session. Curtin University Human Research Ethics Committee approved the study (HREC project approval number: HRE2017-0198-02). The study was also registered with the Australia New Zealand Clinical Trials Registry (ANCTR) (ID number ACTRN12617000218392). On the study testing day, all participants were given a more detailed description of the study in the form of a Participant Information Sheet. Written informed consent was obtained from all participants prior to commencing testing.

4.2.3. Participants

A convenience sample of 70 volunteers with LE was recruited through Curtin Radio advertisements, a specialised clinical trials recruitment agency, adverts on social media and in sports clubs and a range of musculoskeletal and sports physiotherapy clinics in Perth. Inclusion criteria (Haker & Lundeberg 1990) and exclusion criteria were as follows:

4.2.3.1. **Inclusion criteria**

- Aged 18 years or older
- Unilateral elbow pain > 6 weeks duration reproduced on at least two of the following tests:
  - Palpation of the lateral epicondyle
  - Isometric testing of the wrist extensors

- Middle finger extension test
- Passive stretch of wrist extensors
- Resisted hand gripping using a dynamometer
- Upper limb neurodynamic test-radial nerve bias (ULNDT-RN)

4.2.3.2. **Exclusion criteria**

- Neurological and radicular dysfunctions
- History of fracture/surgery in the forequarter (past 2 years)
- History of generalized arthritis
- Steroid injection into the elbow (preceding 6 weeks)
- Contraindications to cold application
- Inability to communicate in English
- Current use of antidepressants for > 12 weeks

Potential participants were initially contacted via phone. They were questioned about LE diagnosis, age, history of pain, and the exclusion criteria (see above) to ensure that they had LE. To further confirm that the eligibility criteria were met, a thorough clinical examination, including the diagnostic tests outlined in the inclusion criteria, of all participants was carried out by a single assessor prior to commencing the study. All testing was carried out at the Physiotherapy Clinic, Curtin University. Participants were asked to avoid taking pain medications 24 hours prior to testing and to avoid any additional physiotherapy treatment and other physical treatments (e.g. chiropractic or acupuncture) on the testing day. A $20 voucher was given to each participant to help pay for travel or parking.

4.2.4. Pain-related outcome measures

4.2.4.1. **Pressure pain threshold (PPT)**

PPT was measured using an electronic digital algometer (Somedic AB, Sweden) with slightly modified methodology (Coombes, Bisset & Vicenzino 2015; Locke et al. 2014). PPT has been shown to have a high intra-rater reliability with excellent intra-class correlation coefficient (ICCs: 0.81-0.99) when measured at 4 different body sites (Waller et al. 2015) and more particularly when used for assessment of pain in LE (ICC > 0.86) (Fernandez-Carnero et al. 2009). ICCs of 0.991 and 0.986 were demonstrated at the wrist and elbow sites, respectively, by the current researcher (i.e. the same single assessor) during preliminary reliability testing (Chapter 3). The assessor identified the most tender point at the lateral aspect of the affected elbow by palpation. The assessor also identified a mid-point on the posterior aspect of the wrist, 2 cm proximal to the wrist crease. These measurement sites were then marked. For the CPM assessment protocol, a modified pressure algometer with a footswitch control was used to assess PPT (Locke et al. 2014). The participant was sitting on a chair of adjustable height so the forearm was comfortably positioned in pronation on a table. A 1 cm^2 algometer tip was applied perpendicularly over each marked site by the assessor and the pressure stimulus was applied at a standard rate of 40 kPa/s. The participant was instructed to press the footswitch control at the moment they perceived the pressure becoming painful. Using a footswitch enabled participants to place one hand in the cold water and still respond to the pressure stimulus. For the MIPM assessment protocol the participant was comfortably lying supine on a plinth and a pressure algometer with the same handswitch control was used for testing. PPT measures were the pressure value (kPa) recorded from the algometer. The test procedure was first conducted at the unaffected forearm for familiarization. Three PPT measurements were taken at each site

on the symptomatic side with 10-15 seconds intervals between each. Mean values were used in analysis.

4.2.4.2. **Pain free grip (PFG)**

Pain on gripping is a clinical sign of LE (Vicenzino et al. 1998b). Pain free grip (PFG) refers to the amount of grip force that can be applied prior to the onset of pain (Paungmali et al. 2003). PFG was measured with an electronic digital dynamometer (MIE, Medical Research Ltd.) using standard methodology (Coombes, Bisset & Vicenzino 2015). It has been demonstrated to be both a reliable (ICC > 0.97) (Smidt et al. 2002) and valid (Paungmali et al. 2003) measure used in patients with LE. The participant was lying supine with the affected arm by their side, positioned in elbow extension and forearm pronation. The participant was then requested to squeeze the dynamometer handles until they first felt their lateral elbow pain, and then to stop the squeezing action. The PFG force value was then recorded from the digital display. The PFG test was performed three times with 10-20 seconds rest intervals in between. The average value was used for analysis.

4.2.4.3. **Upper limb neurodynamic test with radial nerve bias (ULNDT-RN)**

The upper limb neurodynamic test with radial nerve bias (ULNDT-RN) has been used to assess primarily neural mobility of the forequarter (Butler 2000). Pain free range of motion in the test is restricted in patients with LE (Yaxley & Jull 1993). The participant's symptomatic arm was progressively positioned in scapular depression and protraction, elbow extension, internal rotation, forearm pronation, wrist and finger flexion. Scapular depression was sustained while performing the test. The arm was slowly taken into shoulder abduction. The participant was instructed to say 'now' to indicate the onset of pain with this movement and the arm was returned to the start position. The shoulder abduction range at the onset of pain was measured using an M180

twin axis electrogoniometer (Penny & Giles, United Kingdom) positioned over the anterior shoulder (Vicenzino, Collins & Wright 1996). Three readings were taken with 20-30 seconds intervals in between. The average of these readings was used for analysis.

4.2.5. Assessment protocols

4.2.5.1. **Conditioned pain modulation (CPM) assessment protocol**

Test stimulus: PPT was used as the test stimulus, using an electronic digital algometer (Somedic AB, Sweden) as outlined above. Participants were seated on a chair of adjustable height so the affected forearm was comfortably positioned in pronation on a table. PPT was then tested as outlined above on the two marked locations of the affected arm at baseline prior to cold water immersion, after 1 minute during immersion, and 1 minute post immersion. At each time point, PPT was measured three times with 10-15 seconds rest intervals in between. The mean value of the three measurements at each time point was used for analysis.

Conditioning stimulus: The Cold Pressor Test (CPT) was used as a conditioning stimulus to elicit the CPM response. The unaffected hand was submerged 10 cm above the wrist crease in a cold water bath, with temperature maintained at 10°C for a period of 2 minutes (Hoffken et al. 2017). The water bath contained a mix of water and ice and it was supplied with a circulating pump to ensure uniformity of water temperature at the skin. Separate PPT measures were obtained for the wrist and elbow sites.

4.2.5.2. **Manipulation induced pain modulation (MIPM) assessment protocol**

The existence of a MIPM effect was assessed using a very similar protocol to CPM testing.

Test stimulus: PPT was the test stimulus. The measures of PPT at both test sites were carried out at baseline, during (i.e.at the start of the third minute of treatment) and immediately after the conditioning stimulus (C5/6 cervical lateral glide). Testing was performed with the participants lying supine on a plinth. The PFG test and ULNDT-RN bias test were performed pre and post MIPM to provide additional measures of the MIPM effect.

Mobilisation stimulus: a grade III passive oscillatory, contralateral lateral glide (CLG) mobilisation of the C5/6 motion segment of the cervical spine was used to induce MIPM (Vicenzino, Collins & Wright 1996). The participant was comfortably lying supine with arms by their side and instructed to report if they felt any discomfort or pain during execution of the mobilisation. In contrast to CPM this conditioning stimulus should be painless (Vicenzino et al. 1999). The therapist (experienced in manual therpy) cradled the occiput and neck above the C5/6 segment and applied a grade III passive oscillatory CLG directed towards the unaffected upper limb at an appropriate rate that would be generally used in a normative clinical practice. The CLG stimulus was performed for 60 seconds, and was repeated three times, with 60 seconds rest periods in between (5 minutes total) (Vicenzino, Collins & Wright 1996). Separate PPT measures were obtained for the wrist and elbow sites and the PFG and ULNDT measures were completed pre and post mobilisation.

4.2.6. Tennis elbow specific assessment instrument (PRTEE)

The Patient Rated Tennis Elbow Evaluation (PRTEE), a condition-specific assessment instrument, was used to measure both pain (5 items) and functional disability levels (10 items) on a scale of 0-10 experienced during daily activities, work, and sports over the preceding week (Macdermid 2005). Responses were aggregated to give one overall score of 0 (no pain or disability) to 100 (worst possible pain and disability). Participants completed the PRTEE

in a paper and pencil format. PRTEE is a reliable (Overend et al. 1999; Rompe, Overend & MacDermid 2007) and valid (Vincent et al. 2013) measure for evaluation of pain and function in tennis elbow (or LE) pathology.

4.2.7. Procedure

After clinical examination and eligibility criteria were confirmed, each participant was asked to attend for CPM and MIPM assessment protocols in a single session. The CPM assessment protocol was initially conducted followed by the MIPM assessment protocol with a rest period of 15 minutes in between to control for any carryover effect. This time interval was determined based on findings from our preliminary Study (Chapter 3: approval number: HRE2016-0181). The cold pressor test was administered as described above. The CLG was delivered by one of three experienced musculoskeletal physiotherapists who received adequate training prior to the initial testing to ensure consistent administration of the technique. All instructions were standardized. (See Figure 4.1).

4.2.8. Sample size calculation

Sample size calculations were generated using Stata/IC (version 15.0: StataCorp LLC, TX). The aim of the study was to determine the correlation between cross sectional PPT measures obtained for MIMP (PPT^{MIPM}) and CPM (PPT^{CPM}) assessment protocols. As there is no current literature that quantifies the correlation between PPT^{MIPM} and PPT^{CPM}, we estimated that the correlation coefficient between these variables would be 0.35, just above the minimum effect size required to detect a sizeable correlation (Cohen 1992). In determining our sample size, we set alpha at 0.05 and power at 80% to detect at least a correlation coefficient of 0.35. Therefore, the minimum required sample size for a one-sample correlation test was 62, based on a two-tailed test.

4.2.9. Statistical analysis

For all analyses, $P<0.05$ was considered statistically significant. Data were analysed using Stata/IC (version 15.0: StataCorp LLC, TX). Demographic data were analysed using descriptive statistics. Frequency distributions and percentages were obtained for categorical variables (i.e. gender and elbow tested). Depending on normality, means and standard deviations (SD) or medians and interquartile ranges (IQR) were calculated for continuous variables (i.e. age, duration and PRTEE score). Univariate group comparisons between CPM groups (responders vs non-responders) included $\chi 2$ and Fisher exact tests for categorical comparisons, and independent t-tests or Mann-Whitney U tests for continuous variables, as appropriate.

All outcome data were evaluated for normality using Shapiro-Wilk tests and graphical review. Non-normally distributed data were transformed using natural logarithms (PPT) or square roots (PFG and ULNDT-RN).

To test null hypotheses 1 (i.e. there will be no difference between time points in the level of CPM and MIPM analgesia detected by measures of PPT at the wrist and elbow) and 2 (i.e. there will be no difference between the level of CPM and MIPM analgesia overtime (CPM vs MIPM measures)), measures of CPM and MIPM responses were first obtained for the wrist and elbow sites. Separate linear mixed models with random participant effects were then used to test these hypotheses.

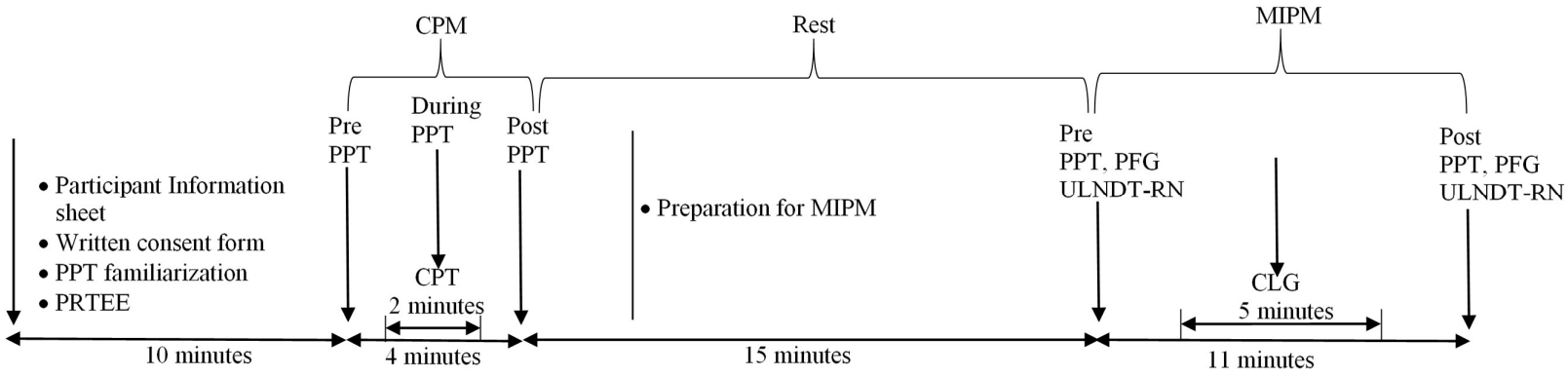

Figure 4.1 Testing session. PPT: pressure pain threshold, CPM: conditioned pain modulation, CPT: cold pressor test, PRTEE: patient rated tennis elbow evaluation, PFG: pain free grip, ULNDT-RN: upper limb neurodynamic test- radial nerve, CLG: cervical lateral glide.

To test null hypothesis 3 (i.e. there will be no correlation between MIPM and CPM analgesic effects), the Pearson partial correlation coefficient (r) was used to measure the strength and direction of the linear relation between CPM (explanatory variable) and MIPM PPT measures (dependent variable) whilst controlling for baseline CPM and MIPM PPT measures. The strength of the partial correlations were interpreted according to the guidelines defined by Cohen (1988): (small: $0.10 \leq r \leq 0.29$; medium: $0.30 \leq r \leq 0.49$; large: $0.50 \leq r \leq 1.0$). Univariate linear regression models were then used to calculate regression coefficients (B), and their 95% confidence intervals (CI) and p-values, and adjusted coefficients of determination (adj. R^2) to evaluate the association between CPM (explanatory variable) and MIPM (dependent variable) across different time points. The baseline CPM and MIPM PPT measures were identified as potential confounders and therefore these were controlled for in the regression analyses.

To test null hypothesis 4 (i.e. there will be no difference in the level of MIPM analgesia overtime between those participants who do and those who do not exhibit a CPM response (CPM responders vs non-responders), participants were initially assigned post hoc into two groups, based on whether or not they demonstrated a meaningful CPM effect at the wrist test site. Locke at al. (2014) considered CPM effect clinically meaningful if the percentage increase in PPT was greater than the inherent measurement error. The meaningful CPM cut-off value of 5.3%, previously calculated by Locke et al. (2014) in pain free healthy individuals, was used to classify participants into two groups: CPM responders and CPM non-responders. Therefore, participants with a CPM effect above 5.29% were classified as CPM responders and those with a CPM effect below this percentage were classified as CPM non-responders since their response did not exceed the inherent measurement variability. Linear mixed models with random participant effects were used to explore between-group

overtime differences in MIPM analgesia by computing the interaction between group and time, whilst adjusting for PRTEE and gender in the analyses.

4.3. **Results**

A total of 70 participants met the eligibility criteria and participated in the study. All volunteers received both CPM and MIPM assessment protocols and were analysed with regards to all outcome measures. Based on the meaningful CPM cut-off value (Locke et al. 2014), out of the 70 participants, 62 participants were considered as CPM responders while 8 participants (11%) were categorized as CPM non-responders. Characteristics of the participants and the CPM groups are summarised in Table 4.1. (See also Figure 4.2: Consort Diagram).

Table 4.1 Descriptive summaries for the research sample and by CPM groups

*Data summarised as Mean (SD) unless otherwise specified**

Demographic		Sample (N=70)	Responders (n=62)	Non-responders (n=8)	p
Gender *n (%)**	F	24 (34.3)	20 (32.3)	4 (50.0)	0.269
	M	46 (65.7)	42 (67.7)	4 (50.0)	
Elbow affected/tested *n (%)**	L	33 (47.1)	30 (48.4)	3 (37.5)	0.422
	R	37 (52.9)	32 (51.6)	5 (62.5)	
Age *(years)*		46.20 (10.6)	46.9 (10.0)	41.1 (14.0)	0.150
Duration *(years) med IQR**		0.67 (0.42, 1.5)	0.67 (0.4, 1.5)	1.3 (0.8, 2.3)	0.152
PRTEE		38.73 (16.4)	39.08 (17.1)	36 (9.6)	0.458

F: female, M: male, L: left, R: right, PRTEE: patient rated tennis elbow evaluation questionnaire, med: median, IQR: interquartile range. Level of significance, $p<0.05$

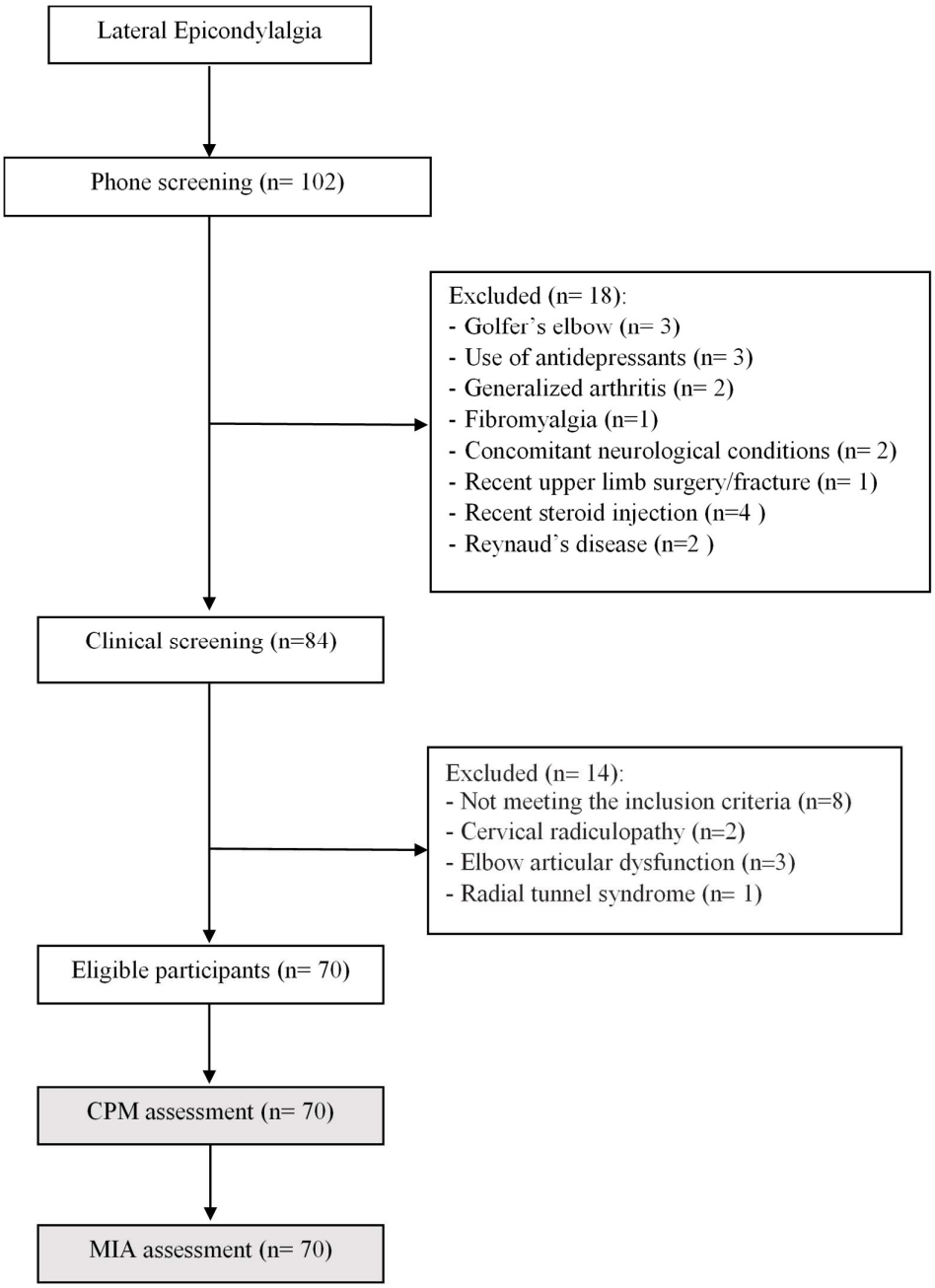

Figure 4.2 Consort Diagram. Flow of participants during the recruitment process

4.3.1. Demographics

The demographic characteristics of the whole research sample are shown in Table 4.1. There were no significant differences (P>0.05) in the demographic characteristics of participants in each of the CPM responder and non-responder groups (11% of the sample) (i.e. gender (P=0.269), affected elbow tested (P=0.422), age (P=0.150), duration of tennis elbow condition (P=0.152)).

4.3.2. PRTEE

Both CPM groups showed no statistical difference in the PRTEE score (P=0.458, >0.05). The PRTEE score was 39.08 points (SD=17.1) reported for the CPM responders group and 36.0 points (SD=9.6) for the CPM non-responders group.

4.3.3. Analgesic effect of CPM and MIPM

PPT was used as the main objective outcome measure to quantify the analgesic responses produced by CPM and MIPM. The overall differences in CPM and MIPM analgesia between time points are presented in Table 4.2. Participants demonstrated a significant increase in PPT measured at wrist and elbow sites during and immediately post CPM and MIPM (p<0.001). There was also a significant increase (p<0.001) in MIPM secondary outcome measures (PFG and ULNDT-RN) immediately post the CLG.

4.3.4. Comparison of CPM and MIPM analgesia

There were significant differences between CPM and MIPM analgesia measured at the wrist (p<0.001) and elbow (p<0.001) during the CPM and MIPM interventions, with higher levels of analgesia measured during CPM. The mean increase in analgesic levels (PPT) during CPM and MIPM was 198.85 kPa and 124.50 kPa, respectively. However, no differences were detected at

both testing sites post CPM (mean 120.15 kPa) and MIPM (mean 122.83 kPa) (Wrist: p=0.569, elbow: p=0.839). (See Figure 4.3).

4.3.5. The correlation between MIPM and CPM analgesic effects

Changes in PPT measures induced by both MIPM and CPM assessment protocols were used to quantify the analgesic effects. The partial correlation values for the association between PPT measures for MIPM and CPM at each assessment time point are presented in Table 4.3. The partial Pearson correlation coefficient (r) values show statistically significant, moderate and positive linear relationships between CPM PPT and MIPM PPT measures at different time points (r: 0.40 – 0.54, $p<0.001$). This implies that higher levels of CPM PPT analgesia are associated with higher levels of MIPM PPT. The regression analysis shows that CPM PPT is a significant predictor of MIPM PPT ($p<0.001$) measured at both sites over different time points. The adjusted coefficient of determination (adj. R^2) values range between 0.73 and 0.85. This indicates that, based on this research sample, between 73% and 85% of the variability in MIPM PPT is explained by CPM PPT values obtained at particular time points.

4.3.6. Comparison between CPM responders and CPM non-responders levels of MIPM analgesia

There were significant differences in MIPM analgesia between both CPM groups overtime, with significantly higher levels of MIPM analgesia observed for the CPM responders group measured at the wrist (during: p=0.033, post: p=0.017) and elbow (during: p=0.021, post: 0.014). No between-CPM group differences were observed for the PFG (p=0.083) and ULND-RN measures (p=0.653). (Table 4.4. See also Figure 4.4).

Table 4.2 Mixed regression models for CPM and MIPM responses (predicted marginal means): overall differences between time points.

Test/ measurement	pre CPM/MIMP		During CPM/MIPM		Post CPM/MIPM		Pre to During CPM/MIPM	Pre to Post CPM/ MIPM
	Mean	*95%CI*	Mean	*95%CI*	Mean	*95%CI*	*p*	*p*
CPM Wrist PPT	540.60	*494.18 - 587.02*	742.47	*696.05 - 788.88*	654.84	*608.42 - 701.25*	**<0.001**	**<0.001**
CPM Elbow PPT	275.82	*256.85 - 296.19*	465.95	*433.91 - 500.36*	396.71	*369.42 - 426.00*	**<0.001**	**<0.001**
MIPM Wrist PPT	534.48	*491.02 - 577.94*	664.13	*620.67 - 707.59*	657.60	*614.14 - 701.06*	**<0.001**	**<0.001**
MIPM Elbow PPT	310.54	*283.60 - 337.48*	433.55	*406.61 - 460.49*	434.04	*407.10 - 460.98*	**<0.001**	**<0.001**
PFG	198.24	*174.65 - 221.82*	**-**	**-**	245.80	*222.21 - 269.38*	**-**	**<0.001**
ULNDT- RN	13.35	*11.87 - 14.84*	**-**	**-**	20.76	*19.28 - 22.25*	**-**	**<0.001**

CPM: conditioned pain modulation, MIPM: manipulation induced pain modulation, CI: confidence interval, PPT: pressure pain threshold, PFG: pain free grip, ULNDT-RN: upper limb neurodynamic test-radial nerve bias. Level of significance, $p<0.05$

Table 4.3 Correlations and regression models for CPM and MIPM analgesia within different time points adjusted for baseline PPT

CPM PPT vs. MIPM PPT	Partial correlation coefficient (r)	Regression coefficient (B)	Standard Error (B)	95%CI (B)	Adjusted R-squared (R^2)	p (r)	p (B)	p (F-test)
CPM PPT Wrist During vs. MIPM PPT Wrist During	0.44	0.55	0.14	0.28 - 0.82	0.82	**<0.001**	**<0.001**	**<0.001**
CPM PPT Elbow During vs. MIPM PPT Elbow During	0.45	0.47	0.11	0.24 - 0.70	0.73	**<0.001**	**<0.001**	**<0.001**
CPM PPT Wrist Post vs. MIPM PPT Wrist Post	0.40	0.43	0.12	0.19 - 0.68	0.85	**<0.001**	**0.001**	**<0.001**
CPM PPT Elbow Post vs. MIPM PPT Elbow Post	0.54	0.47	0.09	0.29 - 0.65	0.82	**<0.001**	**<0.001**	**<0.001**

CPM: conditioned pain modulation, MIPM: manipulation induced pain modulation, PPT: pressure pain threshold, 95%CI: 95% confidence interval. Level of significance, $p<0.05$

Table 4.4 Mixed regression models for MIPM predicted marginal means, adjusted for PRTEE and gender: Differences in MIPM responses between (CPM responder and CPM non-responder) groups overtime.

Test/ measurement	CPM group	pre MIPM		During MIPM		Post MIPM		Pre to During MIPM	Pre to Post MIPM
		Mean	*95%CI*	Mean	*95%CI*	Mean	*95%CI*	*p*	*p*
MIPM Wrist PPT	Non-responders	555.67	*439.99 - 671.36*	635.63	*519.95 - 751.32*	623.26	*507.57 - 738.94*	**0.033**	**0.017**
	Responders	531.75	*490.53 - 572.96*	667.81	*626.59 - 709.02*	662.03	*620.82 - 703.25*		
MIPM Elbow PPT	Non-responders	318.10	*244.29 - 391.91*	394.85	*321.04 - 468.66*	392.27	*318.45 - 466.08*	**0.021**	**0.014**
	Responders	309.56	*283.25 - 335.87*	438.54	*412.23 - 464.85*	439.43	*413.12 - 465.73*		
PFG	Non-responders	225.37	*164.89 - 285.86*	-	-	246.75	*186.26 - 307.24*	-	0.083
	Responders	194.74	*173.18 - 216.29*	-	-	245.67	*224.12 - 267.22*		
ULNDT-RN	Non-responders	11.54	*7.23 - 15.85*	-	-	18.46	*14.15 - 22.76*	-	0.653
	Responders	13.59	*12.05 - 15.12*	-	-	21.06	*19.52 - 22.59*		

CPM: conditioned pain modulation, MIPM: manipulation induced pain modulation, 95%CI: 95% confidence interval, PPT: pressure pain threshold, PFG: pain free grip, ULNDT-RN: upper limb neurodynamic test-radial nerve bias. Level of significance, $p<0.05$

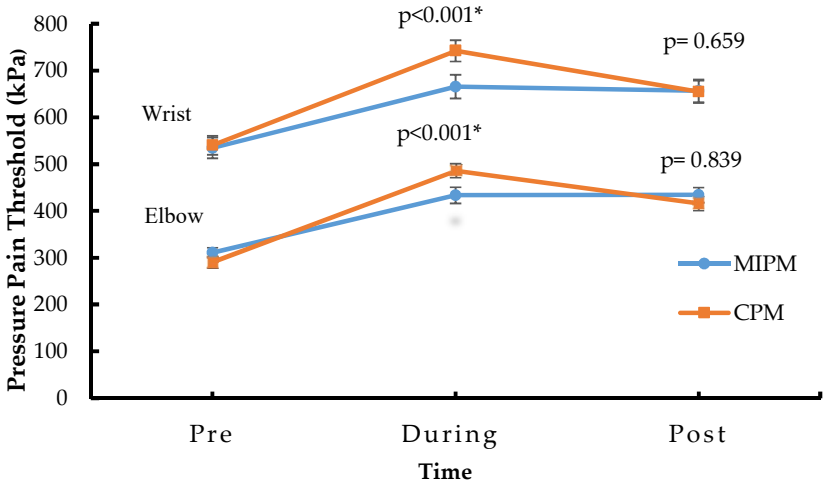

Figure 4.3 CPM and MIPM predicted marginal means: Differences in PPT between CPM and MIPM over time. *Level of significance p<0.05

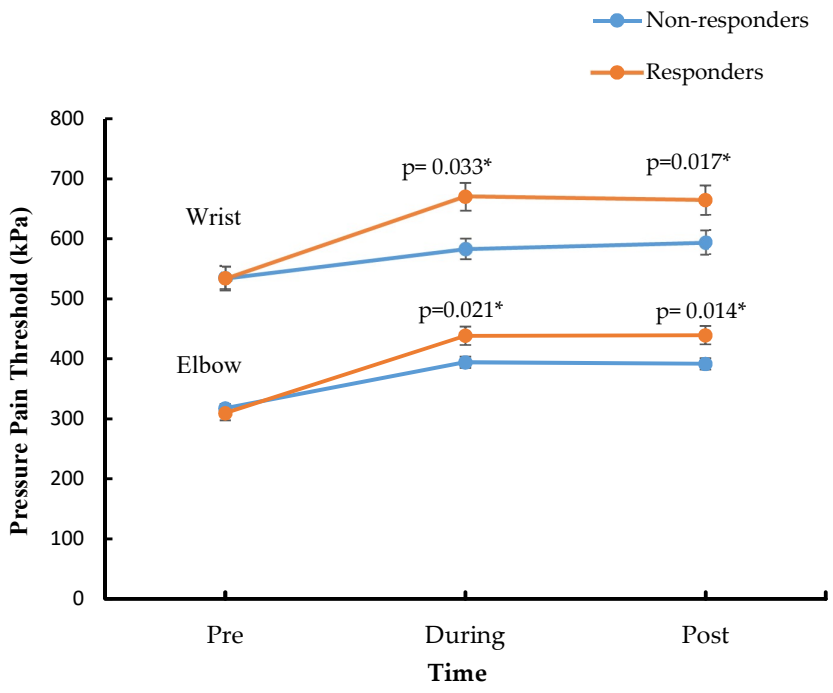

Figure 4.4 MIPM predicted marginal means, adjusted for PRTEE and gender: Differences in MIPM PPT (analgesia) between CPM groups (responders and non-responders) over time. *Level of significance <0.05

4.4. **Discussion**

This is the first study to investigate the association between CPM and MIPM analgesia. The group demonstrated a significant increase in PPT during and post CPM and MIPM indicating an analgesic response to both stimuli measured at different time points over two testing sites. The results showed significant differences between the levels of CPM and MIPM analgesia measured at the wrist and elbow during, but not post, CPM and MIPM. There was also a significant association between the CPM and MIPM analgesia in a sample population with LE. Lastly, the results showed a significant difference in the levels of MIPM analgesia (PPT) between CPM responders and CPM non-responders. This has allowed for a valid comparison with CPM, where its effect needs to be investigated.

In this study LE was chosen as a clinical model based on a number of considerations. Several studies have previously demonstrated the analgesic effect of MIPM (i.e. CLG) in LE (de Camargo et al. 2011; Fernandez-Carnero, Fernandez-de-las-Penas & Cleland 2008; Vicenzino et al. 1998a; Vicenzino et al. 1998b; Vicenzino, Collins & Wright 1996). This has allowed for a valid comparison with CPM, where its effect needs to be investigated.

This study showed for the first time an intact CPM response in people with LE, represented by a significant increase in PPT measures during and post the cold pressor test (CPT). This is in accordance with recent research findings of preserved CPM response reported for other chronic musculoskeletal conditions such as chronic local back pain (Gerhardt et al. 2017), patello-femoral pain (Rathleff et al. 2017), long term trapezius myalgia (Leffler, Hansson & Kosek 2002). The functional CPM response found in this LE sample is also similar to the positive CPM response observed in pain-free healthy populations (Locke et al. 2014; Pud, Sprecher & Yarnitsky 2005), suggesting

unaltered endogenous inhibitory mechanisms in LE. However, a recent CPM study by Lim, Sterling and Vicenzino (2017) reported an impaired CPM effect in patients with LE when compared to healthy controls. The difference in the CPM responses reported in both studies may be explained by variations in the testing parameters used. The Lim, Sterling and Vicenzino (2017) study used contact thermal heat as the conditioning stimulus to stimulate CPM responses. Our CPM protocol however used CPT as a conditioning stimulus and that has been found to induce the most pronounced analgesic effect when used with PPT as a testing stimulus (Oono et al. 2011). In pain free healthy controls, Lim, Sterling and Vicenzino (2017) reported a 19.02 (SD=27.49) % to 24.75 (SD=26.21) % change in PPT, for the dominant and non-dominant arm respectively, during thermal pain compared to a 35.80 (SD=26.26)% change reported by Locke et al. (2014) during CPT. Our LE study sample demonstrated a percentage change in PPT of 40 (SD=19.91)% and 71 (SD=33.79)% at the wrist and elbow sites, respectively, during CPT. This suggests there may be a weaker CPM effect in response to contact thermal heat relative to CPT and this may provide a reason for the less efficient CPM in the LE group in the Lim, Sterling and Vicenzino study. Further, almost 11% of LE patients in our study sample were classified as CPM non-responders, which is comparable to 10% reported by Locke et al. (2014). Altogether, these data are highly indicative of efficient CPM in LE found in our study. Although Lewis, Rice and McNair (2012) have suggested that these methodological differences do not have a significant impact on CPM activation in many chronic pain states, their influence on the CPM effect in LE is not fully established and accordingly it requires further investigation.

Consistent with earlier studies evaluating the analgesic effects of cervical manual therapy in LE (de Camargo et al. 2011; Fernandez-Carnero, Fernandez-de-las-Penas & Cleland 2008; Vicenzino et al. 1998b; Vicenzino,

Collins & Wright 1996), this study showed a significant immediate increase in PPT at the elbow and improvements in PFG and ULNDT-RN after CLG. This study is also the first to report a positive increase in PPT values over the ipsilateral wrist in LE indicating a widespread effect of MIPM (i.e. CLG). A similar pattern of MIPM responses was reported by Moss, Sluka and Wright (2007) locally at the knee and remotely at the ipsilateral heel after knee mobilisation. This suggests that central inhibitory mechanisms may be involved in MIPM analgesia (Vicenzino et al. 1998b).

There is a lack of research studies investigating the association between different forms of EA. In this respect, research has been limited to investigating the association between CPM and exercise induced analgesia (EIA) in a pain-free healthy population (Lemley, Hunter & Bement 2015; Vaegter et al. 2015). Courtney et al. (2016) enhanced the CPM response via the addition of MIPM in patients with knee osteoarthritis (OA) but these authors did not examine the association between CPM and MIPM. Therefore, to the best of our knowledge, this is the first study to investigate the association between CPM and MIPM in people with musculoskeletal pain.

The study demonstrated a significant association between PPT measures over the wrist and elbow during and post CPM and MIPM. While PPT significantly increased during and post CPM and MIPM, the levels of CPM analgesia during CPT were significantly higher than the levels of MIPM analgesia during CLG suggesting stronger analgesic responses associated with the cold conditioning stimulus (CPT), which is painful, compared to the non-painful CLG. These results indicate that both CPM and MIPM may share similar neurophysiological mechanisms, but with a clear distinction in the exact mechanism identified for each paradigm, that requires further research to elucidate.

The study results showed that there were between-group differences in MIPM analgesia between CPM responders and CPM non-responders. This means that participants with a clear CPM response showed a stronger response to MIPM than those who exhibited a limited CPM effect. This supports the theory that both CPM and MIMP analgesia are mediated by similar endogenous systems. Despite the small number of CPM non-responders (n=8) found in this cohort compared to CPM responders (n=62), the demographic characteristics and PRTEE scores of both CPM groups were equivalent. There were no significant between-group differences in PFG and ULNDT-RN responses although the PFG measure approached significance. Although not significant, the PFG between-group-difference approached significance (p=0.083) that could be attributed to type II error due to small sample size of the non-responder group. Therefore, we anticipate that differences in these measures might become significant with a larger sample of CPM non-responders.

Recent imaging studies in humans provided an opportunity to visualize cortical activity accompanying CPM and MIPM analgesia. (La Cesa et al. 2014) reported that activity in several cortical structures was revealed by functional magnetic resonance imaging (fMRI) in response to cold water hand immersion in healthy participants, including: medial parts of the postcentral gyrus (S1) bilaterally, the secondary somatosensory cortex (S2), posterior parts of the insular cortex, different parts of the cingulate cortex, and the cerebellum. Cortical activity was also shown in other areas during CPM such as: thalamus, medulla, the amygdala (Sprenger, Bingel & Buchel 2011), supplementary motor area and prefrontal cortex (Piche, Arsenault & Rainville 2009). In the same way, Gay et al. (2014) found that MIPM analgesia was associated with immediate changes in functional cortical connectivity of S1, posterior insular cortex, posterior cingulate cortex, and the periaqueductal grey region in experimentally induced low back pain. Other brain areas such as S2, premotor

and supplementary areas, the amygdala, insula, anterior cingulate cortex (ACC), thalamus (Sparks et al. 2013), anterior cerebellum, and middle frontal cortex (Boendermaker et al. 2014) are also active during manual therapy. These data suggest that both CPM and MIPM analgesia are mediated by similar cortical structures, which supports the hypothesis of potentially shared supra-spinal mechanisms responsible for both forms of analgesia.

There is also pharmacological evidence suggesting that CPM and MIPM induced analgesia is mediated by serotonergic and noradrenergic endogenous analgesic mechanisms. In a diabetic neuropathy model of pain, CPM effect was reinstated in patients with less efficient CPM by the selective serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor, duloxetine (Yarnitsky et al. 2012), and in another study by a combined μ-opioid receptor (MOR) agonist and noradrenaline reuptake inhibitor (NRI), Tapentadol (Niesters et al. 2014). In an animal neuropathic pain model, blockade of α2-adrenergic receptors (AR) in intact animals through α2-AR antagonists, spinal atipamezole or subcutaneous yohimbine, abolished the DNIC/CPM effect, but it was augmented in spinally injured animals after intrathecal administration of a norepinephrine reuptake inhibitor (NRI), reboxetine, or systemic injection of an NRI and a μ-opioid receptor (MOR) agonist, tapentadol (Bannister et al. 2015). Some studies have shown that CPM-induced analgesia was not affected by naloxone (an opioid antagonist) administration in humans (Edwards, Ness & Fillingim 2004; Hermans et al. 2018; Peters et al. 1992) suggesting a non-opioid form of analgesia. Other human studies have however demonstrated that naloxone partially (Sprenger, Bingel & Buchel 2011) or completely reversed CPM analgesia (Pertovaara et al. 1982; Willer, Le Bars & De Broucker 1990). Therefore, the current evidence on the involvement of opioid pathways in CPM analgesia is inconclusive. In human MIPM models, administration of naloxone (an opioid antagonist) did not block spinal (Vicenzino et al. 2000;

Zusman, Edwards & Donaghy 1989) or peripheral (Paungmali et al. 2004) MIPM analgesia. This suggests that non-opioid mechanisms are likely to be involved in MIPM analgesia. In an animal study, Sluka and Wright (2001) showed that knee joint mobilisation decreased ankle hyperalgesia induced by joint inflammation in an animal model of articular pain. Skyba et al. (2003) used the same pain model and reported that intrathecal administration of the α2-AR antagonist, yohimbine partially blocked and the 5-HT receptor antagonists, methysergide and NAN-190 completely blocked the analgesic effect of joint mobilisation. They also showed that intrathecal administration of naloxone did not block the MIPM response. They concluded that spinal serotonergic and noradrenergic receptors linked to descending serotonergic and noradrenergic neurons play a key role in mediating MIPM. These data suggest CPM/DNIC and MIPM analgesia activates endogenous pain mechanisms involving serotonergic and noradrenergic pathways in the central nervous system. There appears to be some variation between the two forms of EA in terms of the degree to which the analgesic effect is blocked or reversed by naloxone.

Data from human and animal research suggest that both the cold pressor test (CPT) and the cervical lateral glide (CLG) mobilisation activate central mechanisms, to mediate their analgesic effects. The research evidence also suggests that MIPM and CPM analgesia are widespread effects, as indicated by changes in PPT detected at a remote body sites. In addition, both forms of analgesia are influenced by pharmacological agents that can abolish or enhance CPM or MIPM analgesia through their effect on serotonergic and adrenergic, systems. These data, when taken together with the evidence from imaging trials on the involvement of supra-spinal centers in the analgesic effects of CPM and MIPM, provide evidence that central pain modulation mechanisms are potentially involved in CPM and MIPM. Some variation in

the specific mechanism of modulation may exist, as suggested by the differences in response to naloxone administration and the potential differentiation of the two phenomena as opioid and non-opioid forms of analgesia.

4.5. **Clinical implications**

The association between both forms of analgesia was evaluated to improve our understanding of EA analgesia. The study provides strong evidence of the analgesic effects of MIPM in immediately reducing pain in LE. This research has also improved our knowledge of the mechanism of action of MIPM. This study will therefore lay the foundation for future clinical trials that will investigate/compare the impact of different treatment interventions on CPM and MIPM responses. Additionally, there is a prospect of using CPM as a prognostic test to potentially identify individuals who do or do not respond to MIPM interventions. This would help clinicians to individualise their patients' management plans accordingly.

4.6. **L**imitations

First, this study was designed to assess the correlation between CPM and MIPM only. Therefore, it did not allow for manipulation of CPM and MIPM analgesia. As a result, neither the assessor nor the participants were blinded. In addition, we could not make a conclusion on casual inference as to which form of analgesia (i.e. CPM, MIPM) would be influenced by the other. Second, this study included only participants with tennis elbow. Thus, the external validity of the findings may not be applied to other chronic musculoskeletal conditions. Future research would need to investigate whether there are similar patterns of CPM and MIPM analgesia found in other clinical conditions. Third, there was a chance that the CPM and MIPM responses were

affected by the assessor interaction during testing. However, all instructions were standardised and communications with the participants were kept to the minimum. Fourth, the study assessed short term changes in CPM and MIPM analgesic responses. It would therefore be worthwhile to examine these changes over a longer follow-up period.

4.7. **Conclusion**

The present study showed that CPM and MIPM analgesic responses were significantly correlated in a sample population with LE. The study also demonstrated that there were between-group over time differences in the level of MIPM analgesia between CPM responders and CPM non-responders. This suggests that both forms of EA share similar neuro-physiological mechanisms, potentially involving descending serotonergic and noradrenergic systems.

Chapter 5: **Study Three**

Influence of empathetic interaction on CPM and MIPM analgesia

5.1. **Introduction**

A positive therapeutic interaction is essential for the delivery of clinical care (Hassan, McCabe & Priebe 2007). Therapeutic interaction involves an emotional bond and joint agreement between therapists and their patients in relation to treatment goals and interventions (Bordin 1979). This requires the therapist to positively connect with patients (Adnoy Eriksen et al. 2014), through development of rapport (Crowden 2013), respect (Egan 2014), empathy and trust (Crowden 2013), and collaboration (Morley & Cashell 2017). A positive therapeutic interaction has been shown to improve patient engagement in therapy, patient satisfaction and treatment effectiveness (Fuertes et al. 2007; Fuertes et al. 2017). In order to optimise outcomes it is therefore vital to foster a patient-centered interaction (Broady 2014; Hebblethwaite 2013) which explicitly focuses on features such as empathy, trust, respect and collaboration.

Previous research has identified various aspects of an enhanced therapeutic interaction (Di Blasi et al. 2001). In their review, Mistiaen et al. (2016) classified patient-therapist interaction into three main components: cognitive care, emotional care and procedural preparation. Cognitive care involves manipulating patient's expectations to produce a positive, neutral or negative therapeutic outcome. Emotional care includes interventions intended to improve the perceived empathy of the clinician and so put patients at ease. This can encompass strategies such as continuous verbal support and reassurance (Faymonville et al. 1997), active listening (Fuentes et al. 2014), showing friendliness and warmth (White et al. 2012), encouraging a sense of

control (Lang et al. 2000), using non-verbal strategies (eye contact, head nodding, smiling) (Vangronsveld & Linton 2012), and explaining questions clearly (White et al. 2012). Procedural preparation deals with arrangements made to facilitate therapeutic interventions, such as information giving, procedural instructions, and relaxation (Mistiaen et al. 2016). Mistiaen et al. (2016) reported that manipulating these components in experimental settings can influence patients' perception of their pain. They have concluded however that more research is necessary to distinguish the most influential components.

Recent research has shown that manipulating cognitive factors such as expectation can alter pain perception in experimental settings, either positively or negatively. Wang et al. (2008) reported a significant increase in postoperative pain (i.e. nocebo) after abdominal hysterectomy in patients who received negative suggestions about patient-controlled analgesia. Nir et al. (2012) investigated the effect on conditioned pain modulation (CPM) of placebo (positive) and nocebo (negative) suggestions about the effects of anaesthetic cream in healthy participants. The placebo group showed a reduction in the conditioning stimulus pain, and therefore a CPM effect. In contrast the nocebo group demonstrated an increase in the conditioning stimulus pain so no CPM effect and a hyperalgesic response. In another study, Cormier, Piche and Rainville (2013) investigated the impact of verbally initiated positive or negative expectations on CPM analgesia. Compared to the control group that received simple instructions, the nocebo group demonstrated an increase in pain in response to the suggestion that cold application would be painful, while the placebo group showed a reduction in the test stimulus pain as a result of suggestion of decreased pain. This highlights the importance of cognitive influences on a CPM response.

The influence of cognitive factors on manual therapy analgesia has not been widely investigated. With respect to spinal manipulation, Bialosky et al. (2008) studied the impact of expectation (positive, negative, neutral) of analgesia on the analgesic effect of lumbar spine manipulation, evaluated using a painful heat stimulus in asymptomatic volunteers. The positive expectation group was informed that lumbar manipulation 'is a very effective form of manipulation used to treat low back pain (LBP) and we expect it to reduce your perception of heat pain'. The negative expectation group was given the opposite instruction, that manipulation would increase their perception of heat pain, while the neutral group was informed that manipulation had 'an unknown effect' on heat pain perception. The negative expectation group showed a substantial increase in pain response during thermal sensitivity testing (i.e. a nocebo response), while no effect was observed on pain perception in the positive or neutral expectation groups. Expectation may have an influence on manipulation induced pain modulation (MIPM), however, that effect does not appear to be as consistent as it is for CPM.

The current evidence indicates that a good therapeutic interaction may have a positive effect on pain and disability levels (Lakke et al. 2009) and satisfaction (Hall et al. 2010). Fuentes et al. (2014) recently investigated the effect of patient-therapist interaction on pain responses in patients with chronic low back pain (CLBP) after a single session that involved either sham or active interferential current (IFC)). The authors found a significant improvement in pressure pain threshold (PPT) in both active and sham groups that received an enhanced interaction. The active group also reported improved analgesia (measured on a numerical pain scale) following IFC. However, other existing evidence of the impact of empathetic interaction on clinical pain is inconsistent and weak (Mistiaen et al. 2016). To date, there have been no studies investigating the

influence of an enhanced, empathetic interaction on pain in musculoskeletal physiotherapy in general, and on CPM and MIPM analgesia in particular.

This study aimed to evaluate, in individuals with tennis elbow, the effect of a positive, supportive empathetic interaction, compared to a neutral interaction, on a person's hypoalgesic response as measured by CPM and MIPM analgesia. Where an effect was observed the study evaluated whether the effect was similar for CPM and MIPM analgesia. Tennis elbow was used as the clinical model since evidence for the analgesic effect of cervical manual therapy in lateral epicondylalgia (LE) is well established (Vicenzino et al. 1998a; Vicenzino et al. 1998b; Vicenzino, Collins & Wright 1996) and there has been some published data evaluating CPM analgesia in this clinical group (Lim, Sterling & Vicenzino 2017).

5.2. Methods

5.2.1. Null Hypotheses

1. There will be no difference between time points (i.e. during CPM, and post CPM and MIPM) relative to baseline in the level of CPM and MIPM analgesia detected by measures of PPT at the wrist and elbow.

2. There will be no difference in the level of CPM and MIPM analgesia overtime between those participants who receive an enhanced empathetic interaction and those who receive a neutral interaction

5.2.2. Study design

A randomised, controlled between-group experimental design was used. Eligible participants were randomised to receive either an enhanced empathetic interaction (active) condition or a neutral interaction (control) condition in one single session (see experimental conditions).

5.2.3. Randomisation

A randomisation sequence was computer-generated and held by a researcher who was not otherwise involved in the study. Prior to commencing the testing session, the research assistant (RA) actor contacted the holder of the allocation schedule to ascertain the group allocation for each participant.

5.2.4. Participants

In this study, a sample of 68 volunteer participants with LE, (aged between 18 and 60 years) were recruited from Perth, Western Australia between March 2017 and April 2018 through Curtin Radio advertisements, adverts on social media and sports clubs, via a range of musculoskeletal and sports physiotherapy clinics and through a specialised clinical trials recruitment agency. Inclusion criteria (Haker & Lundeberg 1990) and exclusion criteria were as follows:

5.2.4.1. **Inclusion and exclusion criteria**

Inclusion and exclusion criteria were as indicated in Chapter 4, Section 4.2.3.

Participants were initially contacted via phone to screen for eligibility and to provide a brief explanation regarding the study protocols and requirements. Additional information about the study was provided via email. To confirm the eligibility criteria were met, a thorough clinical examination of all participants was carried out by the primary investigator prior to commencing the study. All testing was carried out at the Physiotherapy Clinic, School of Physiotherapy and Exercise Science, Curtin University. Participants were asked to abstain from taking pain medications 24 hours prior to initial testing and to avoid any additional physiotherapy treatment and other physical treatments (e.g. chiropractic or acupuncture) on the testing day.

Curtin University Human Research Ethics Committee approved the study (HREC approval number: HRE2016-0175). On the testing day, all participants were given a more detailed description of the study in the form of a Participant Information Sheet. Written informed consent was obtained from all participants prior to commencing testing. Each participant was provided with a $20 voucher to help pay for travel or parking.

5.2.5. Pain related measures

Pressure pain threshold (PPT), pain free grip (PFG) and the upper limb neurodynamic test with radial nerve bias (ULNDT_RN) measures were obtained using the same methodology described in Chapter 4, Section 4.2.4. All measures were obtained in triplicate. PPT measures were obtained at the wrist and elbow test sites.

All participants were also required to complete the Patient Rated Tennis Elbow Evaluation (PRTEE) as described in Chapter 4, Section 4.2.6.

5.2.6. Procedure

All participants attended a single test session where they underwent a CPM protocol and a MIPM protocol, with either enhanced or neutral interactions as described below. A rest period of 15 minutes was provided between protocols (Figure 5.1). This rest period was based on findings from the initial Study, (approval number: HRE2016-0181, Chapter 3) to control for any carry-over effect of CPM on MIPM. Both CPM and MIPM testing protocols were performed by the same investigator, who was blinded to the experimental group of each participant. The interaction between the assessor and all participants was standardised. The enhanced/neutral interactions were all provided by a professional role play actor, playing the part of an additional research assistant (RA).

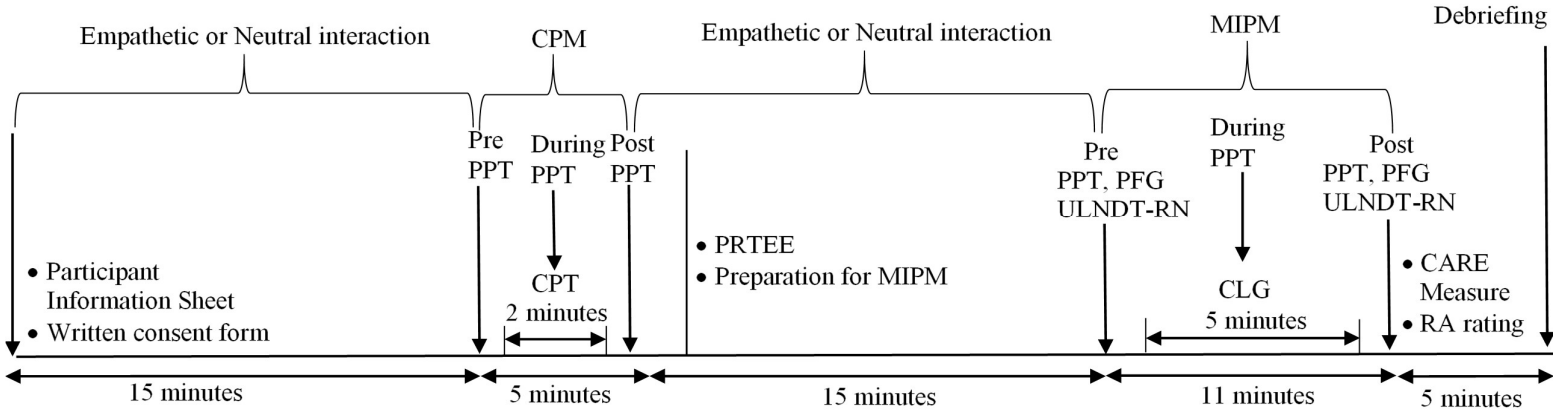

Figure 5.1 Testing session. PPT: pressure pain threshold, CPM: conditioned pain modulation, CPT: cold pressor test, PRTEE: patient rated tennis elbow evaluation, PFG: pain free grip, ULNDT-RN: upper limb neurodynamic test- radial nerve, CLG: cervical lateral glide.

At the start of the test session, the participant was greeted by the RA actor. The participants gave written informed consent in the presence of the RA actor. The main investigator then entered the room to confirm the LE diagnosis, and then left. The RA actor initially spent 15 minutes of either enhanced or neutral interaction with the participant, as described below. After 15 minutes of enhanced/neutral interaction, the main investigator entered the room to conduct the CPM protocol, and then left. The participant was then given a 15 minute rest period, during which the RA actor resumed the enhanced/neutral interaction with the participant. After the rest period, the investigator returned to the room to conduct the MIPM assessment protocol. Following completion of the experiment, all participants were thanked for participation and received a debriefing session by the main investigator, in the presence of the RA actor, to explain to them the purpose of the study and the role of the RA actor in both experimental conditions. Any questions were also answered.

5.2.7. Assessment protocols

5.2.7.1. **Conditioned pain modulation (CPM) protocol**

Test stimulus: PPT was used as the test stimulus, using an electronic digital algometer (Somedic AB, Sweden) as outlined below. Participants were seated on a chair of adjustable height so the affected forearm was comfortably positioned in pronation on a table. PPT was then tested on three occasions on the wrist and elbow sites of the affected arm described below: at baseline prior to cold water immersion; at 1 minute during immersion; and at 1 minute post immersion. At each time point, PPT was measured three times at each site with 10-15 second rest in-between. The mean value of the three measurements at each site was used for analysis.

Conditioning stimulus: The Cold Pressor Test (CPT) was used as a conditioning stimulus to elicit a CPM response. The unaffected hand was

submerged to 10 cm above the wrist crease in a cold water bath, (maintained at 10°C) for a period of 2 minute (Hoffken et al. 2017). The water bath contained a mix of water and ice and had a circulating pump to ensure uniformity of water temperature at the skin.

5.2.7.2. **Manipulation induced pain modulation (MIPM) protocol**

The presence of a MIPM effect was assessed using a very similar protocol to CPM.

Test stimulus: PPT at both the wrist and elbow test sites was used as the test stimulus. Baseline PPT was assessed at both test sites and immediately after the manual therapy stimulus (C5/6 cervical lateral glide (CLG)). Testing was performed with the participants lying supine on a plinth. The pain-free grip (PFG) and Upper Limb neurodynamic-radial nerve (ULND-RN) bias tests were also performed pre and post MIPM to provide additional measures of the MIPM effect (described below).

Mobilisation stimulus: a grade III passive oscillatory, contralateral lateral glide (CLG) mobilisation of the C5/6 motion segment of the cervical spine was used to induce MIPM (Vicenzino, Collins & Wright 1996). The participant was comfortably lying supine with arms by their side and instructed to report if they felt any discomfort or pain during execution of the mobilisation. In contrast to CPM, this mobilisation stimulus was intended to be painless (Vicenzino et al. 1999). The therapist cradled the occiput and neck above the C5/6 segment and applied a grade III passive oscillatory CLG directed towards the unaffected upper limb. The CLG stimulus was performed for 60 seconds, and was repeated three times, with 60-second rest periods in between (5 minutes total) (Vicenzino, Collins & Wright 1996).

5.2.8. Experimental conditions: enhanced and neutral interactions

Both enhanced and neutral interaction conditions were provided by the RA actor at two time-points during the test session: 15 minutes at the start of the session before the CPM assessment protocol and 15 minutes during the rest-period between CPM/MIPM protocols (Figure 5.2). The RA actor remained in the room during the period that the main investigator spent conducting the assessment protocols but undertook some administrative activities and did not directly interact with the participant.

5.2.8.1. **Enhanced empathetic interaction condition**

The RA actor engaged in a very positive, supportive and empathic interaction with the participant. The actor's interaction was carefully controlled to include features that were likely to enhance empathy. The RA actor was very positive and enthusiastic about their assistance with the project and supportive about the participants' LE condition. They established good rapport with the participant through use of positive communication strategies and body language such as: assuming open posture, maintaining appropriate eye contact, head nodding, being friendly and warm, using the person's name, listening to them without interruption, showing an interest in their life and interests, asking about the impact of LE on them, and they used appropriate disengagement to smoothly transition the discussion from one topic to another or to initiate procedural activities as required.

5.2.8.2. **Neutral interaction condition**

In the 15 minutes before the CPM protocol, the RA actor spent 5 minutes on normal, business-like interactions with the participant. The actor greeted and briefly advised the participant about the study without being particularly positive, supportive, or enthusiastic in relation to the study. The actor's

interaction was carefully controlled so as not to include features that were likely to enhance empathy (i.e. none of the above). There was then a 10 minute interval during which the participant was asked to rest and the RA actor completed some administrative tasks and minimized interaction with the participant. The RA actor did not initiate conversation but politely and concisely answered questions when asked. They made minimal eye-contact, showed more interest in their laptop or phone and concerned themselves with their own issues. In the rest period, 15 minutes before the MIPM protocol conducted, there was only a short discussion and only minimal interaction with the RA actor as before.

5.2.9. Intervention integrity

The actor was given a detailed script explaining the key attitudes that should be portrayed during each period of time on each testing day. The professional role play actor underwent a comprehensive coaching session prior to the start of the experiment, in which they were trained to perform the enhanced empathetic and neutral interactions by the research team, including a simulation expert.

5.2.10. Audit of actor interactions

The actor's adherence to experimental procedures was audited by a member of the research team during randomly selected testing sessions, to ensure intervention fidelity. Actor interactions with participants from both groups were observed and recorded on several occasions during testing. During neutral interactions it was observed that the actor engaged with the participant only minimally. If initiated by the actor, interactions were almost entirely instructional. For example, requesting that the participant complete a questionnaire, informing the participant that the investigator would return in

a certain amount of time. If conversation was initiated by the participant, the actor replied politely but briefly and used closed body language to demonstrate that they did not wish to engage further. In contrast, during the enhanced interactions, the actor used open body language to demonstrate interest in the participant. The actor also actively engaged the participant in conversation throughout the time periods when the investigator was not in the room. This conversation focused on the individual participant, for example, chatting about their interests or work. Although not all participants in the enhanced group were easy to engage, it was observed that there was a clear difference in actor interactions between the enhanced and neutral groups.

5.2.11. Empathetic interaction outcome measure

At the end of the testing session, and in the absence of the RA actor, all participants were asked by the main investigator to complete the Consultation and Relational Empathy (CARE) Measure (Mercer et al. 2004) to rate the overall interaction they experienced with the Research Assistant (RA). It included 10 items rated on a 5 point scale (poor=1, excellent=5) that were summed to give a total score out of 50. A maximum of 2 'does not apply' responses were permitted and these were substituted by the mean average score of other responses (Mercer et al. 2004). The CARE Measure has been validated for assessment of empathetic interaction in primary (Mercer et al. 2008) and secondary (Mercer & Murphy 2008) care, and in rehabilitation settings (Kersten, White & Tennant 2012). It has been shown to have a high reliability (Cronbach's α=0.92) and an excellent validity (mean r=0.85) compared to other measures of empathy (Mercer et al. 2004).

5.2.12. Actor Evaluation

The RA actor was also required to rate how well they were able to deliver an enhanced or neutral interaction session with the participants using a quality of session scale: (1-10; unsatisfactory to excellent).

5.2.13. Sample Size calculation

Sample size calculations were conducted using Stata/IC (version 15.0: StataCorp LLC, TX). Based on data from a large clinical trial comparing corticosteroid injections and physiotherapy management of tennis elbow (Coombes et al. 2013) the minimal clinically important difference (MCID) in pressure pain threshold at the elbow was considered to be 88 kPa (Coombes & Vicenzino 2017; personal communication). In determining our sample size we used a difference value of 50 kPa (just above half of the MCID), with a pooled standard deviation of 73.22 kPa (based on our Pilot Study data, Chapter 3) resulting in an effect size difference of 0.68. An a priori power analysis (alpha = 0.05, beta = 0.80) indicated a required sample size of 68 (34 per group).

5.2.14. Statistical analysis

Data were analysed using Stata/IC (version 15.0: StataCorp LLC, TX). For all analyses, $P<0.05$ was considered statistically significant. Descriptive statistics were based on frequency distributions for categorical data (i.e. gender and elbow tested) and means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous data (age, duration CARE, RA rating and PRTEE), depending on normality. Univariate group comparisons between intervention groups included $\chi 2$ and Fisher exact tests for categorical comparisons, and independent t-tests or Mann-Whitney U tests for continuous outcomes.

All outcome data were evaluated for normality using Shapiro-Wilk tests and graphical review. Non-normally distributed data were transformed using natural logarithms (PPT: CPM and MIPM Wrist) or square roots (MIPM Elbow PPT, PFG and ULNDT-RN).

Linear mixed models with random subject effects were used to calculate the overall differences (relative to baseline) between time points (all participants) and between groups overtime for CPM and MIPM outcomes (i.e. PPT, PFG and ULNDT-RN). The respective marginal means, 95% confidence intervals (CI), and p-values of these differences were calculated. The analysis was adjusted for CARE, RA rating and sex.

Number needed to treat (NNT) analysis was also performed for each interaction group to compare CPM and MIPM effect using an online NNT calculator (Herbert 2013). We defined a difference of 50 kPa (the value used in our sample size calculations) between the pre and post PPT measures obtained for CPM and MIPM protocols as a clinically positive outcome.

5.3. **Results**

A total of 68 participants met the eligibility criteria and participated in the study. There were no drop-outs. All participants received the intended interaction intervention for their group (n=34 per group), and all data were analysed. Characteristics of the participants are summarised by group in Table 5.1.

5.3.1. Demographics

There were no significant differences ($p>0.05$) in the characteristics of participants in each of the experimental groups (i.e. affected elbow tested ($p=0.097$), age ($p=0.950$) and duration of tennis elbow condition ($p=0.738$).

Although there was a greater number of females in the enhanced interaction group, the gender difference did not reach significance (p=0.112).

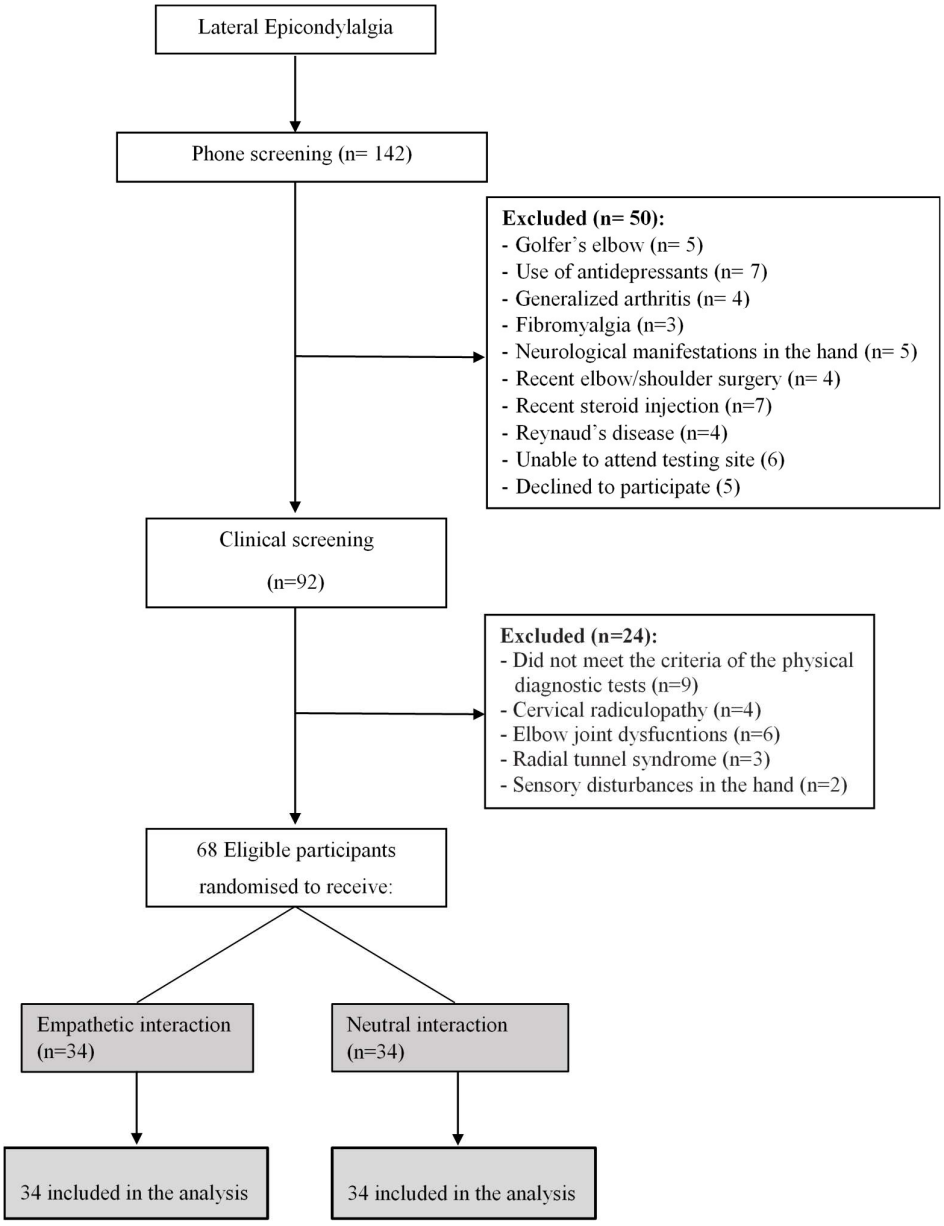

Figure 5.2 Consort Diagram. Flow of participants during the recruitment process.

5.3.2. Self-reported measures

5.3.2.1. **Patient Reported Tennis Elbow Evaluation (PRTEE)**

There was no statistically significant difference between groups in the PRTEE scores (p=0.203, >0.05). The mean PRTEE score was 37.1 points (SD=17.7) for the neutral interaction group and 42.5 points (SD=17.1) for the enhanced interaction group.

Table 5.1 Descriptive summaries for the research sample by intervention groups.
*Data are presented as mean and standard deviation (SD) unless otherwise specified**

		Neutral n=34 *Mean (SD)*	Enhanced n=34 *Mean (SD)*	p
Gender n (%)*	F	15 (44.1)	21 (61.8)	0.112
	M	19 (55.9)	13 (38.2)	
Elbow tested n (%)*	L	8 (23.5)	14 (41.2)	0.097
	R	26 (76.5)	20 (58.8)	
Age (years)		50.8 (11.2)	50.6 (9.6)	0.950
Duration (years) median, (IQR)*		0.6 (0.3, 2.1)	0.5 (0.3, 2.0)	0.738
PRTEE		37.1 (17.7)	42.5 (17.1)	0.203
CARE Measure		27.5 (12.6)	43.8 (7.2)	**<0.001**
RA rating of rapport (1-10 scale)		8.0 (1.7)	8.8 (1.5)	0.052

F: female, M: male, L: left, R: right. IQR: interquartile range, PRTEE: patient rated tennis elbow evaluation, CARE: consultation and relational empathy measure, RA: research assistant. Level of significance, p<0.05

5.3.2.2. **Empathetic interaction outcome measures**

At the end of the interaction there was a significant statistical difference in the CARE Measure score (p<0.001) between groups, with the enhanced group reporting higher empathy: neutral (27.5, SD=12.6), enhanced (43.8, SD=7.2).

The RA rating of the delivery of sessions was close to significant (p=0.052) suggesting more effective delivery of the enhanced interaction sessions although the scores for both groups were high (8.8/10, SD 1.5 compared with 8.0/10, SD 1.7) suggesting that the professional actor believed that sessions were delivered appropriately.

5.3.3. Between-time points (all participants)

5.3.3.1. **PPT**

CPM and MIPM protocols used change in PPT as the main objective outcome measure to compare participants' analgesic response to neutral or enhanced interactions. The overall differences between time-points for all participants are presented in Table 5.2. Both interaction groups (all participants) demonstrated a significant analgesic effect (increase in PPT), at both wrist and elbow sites for CPM (baseline to during (wrist: 88.31; elbow: 87.57, $p<0.001$) and baseline to immediately post CPM (wrist: 41.56; Elbow: 37.59, $p<0.001$), and for MIPM (baseline to post MIPM (wrist: 56.41; elbow: 67.07, $p<0.001$).

5.3.3.2. **PFG and ULNDT-RN**

PFG and ULNDT-RN were used as a secondary outcome measures of analgesic effect of MIPM (Table 5.2). All participants exhibited a significant increase in PFG ($p<0.001$) and ULNDT-RN ($p<0.001$) following CLG in MIPM.

5.3.4. Time x group interaction effects

5.3.4.1. **PPT**

Table 5.3 shows that there were significant group x time interaction effects for PPT change at both test sites during CPM (wrist: $p<0.001$; elbow: $p<0.001$), post CPM (wrist: $p<0.001$; elbow: $p=0.002$) and post MIPM (wrist: $p=0.004$; elbow:

p<0.001). In each case, higher levels of analgesia were observed for the enhanced interaction group (during CPM mean 113.80 kPa, post CPM mean 54.80 kPa, post MIPM mean 78.29 kPa) compared to the neural group (during CPM mean 62.08 kPa, post CPM mean 24.35 kPa, post MIPM mean 45.20 kPa). (Figure 5.3)

5.3.4.2. **PFG and ULNDT-RN**

There were no significant group x time interaction effects for change in PFG (p=0.398) or ULNDT-RN (p=0.668). (Table 5.3)

5.3.5. Number needed to treat

The number need to treat (NNT) values for CPM (baseline to post) and MIPM (baseline to post) analgesic effect outcomes were also calculated, with a change in PPT of 50kPa or more considered a positive outcome. Table 5.4 shows that there were a greater number of positive outcomes for the enhanced interaction group than for the neutral interaction group. NNT values were lower for the elbow site for both protocols. The lowest NNT was for MIPM effect at the elbow (2.13) indicating a greater influence of the enhanced interaction for this measure.

5.4. **Discussion**

The results showed that both groups demonstrated a significant analgesic response measured at both the local elbow and more distant wrist sites. There was also a significant difference in PPT between both groups over time with the enhanced empathetic interaction group demonstrating higher levels of analgesia compared to the neutral interaction group. Participants' evaluation of the session also clearly distinguished the enhanced and neutral interaction

conditions. In addition, there was a higher number of positive outcomes for the enhanced empathetic interaction group.

This is the second study in this thesis to demonstrate a positive CPM effect in a patient population with LE. The finding of efficient CPM in LE is consistent with other research in patients with pain states such as: chronic local back pain (Gerhardt et al. 2017) and long term trapezius myalgia (Leffler, Hansson & Kosek 2002). An efficient CPM response has also been reported in pain-free healthy samples (Locke et al. 2014; Pud, Sprecher & Yarnitsky 2005), which supports the finding that the endogenous inhibitory system is functional in LE. This differs from findings of Lim, Sterling and Vicenzino (2017) as discussed in Chapter 4.

Similar to the previous study (Chapter 4) and other published research (as discussed in Chapter 4, Section 4.4), participants in this study showed an immediate analgesic effect in response to MIPM and CPM at both test sites. There was also a significant overall increase in MIPM secondary outcome measures of PFG and ULNDT-NR. This is in agreement with previous research in the same clinical group (Vicenzino et al. 1998a; Vicenzino et al. 1998b; Vicenzino, Collins & Wright 1996). However, there were no significant difference in PFG and ULNDT-RN between both interaction groups. The study was powered to detect the difference in PPT (the primary outcome) which could explain the lack of statistical difference between the interaction groups in these secondary outcome measures. However, further studies are required to particularly investigate the effect of empathetic interaction on these secondary outcome measures of MIPM analgesia.

The results indicated that the enhanced interaction group scored higher on the CARE Measure as compared to the neutral interaction group. This higher score is an indication that the positive and empathetic interactions of the RA

actor when dealing with the participants in the enhanced interaction group were effective. This between-group difference in the CARE Measure scores confirms the RA actor interaction with the enhanced group was clearly distinct from the neutral group from the participants' perspective. The RA rating of the effective delivery of the interaction sessions approached significance ($p=0.052$) with a rating for the enhanced interaction group of 8.8/10 indicating that the actor found it somewhat easier to deliver the enhanced interaction than it was to deliver the more limited, neutral interaction (8/10). The relatively high score for both measures however suggests that overall the two different types of interaction were appropriately and adequately delivered.

The current study found that an empathetic interaction improved analgesia produced by both CPM and MIPM in an experimental setting. However, this finding is not consistent with a recent systematic review of randomised and quasi-randomised controlled trials conducted by Mistiaen et al. (2016). The authors analysed 14 studies to measure the effect of empathetic manipulation on clinical pain. The authors reported that these studies were poor quality, and various types of interactions were combined. The majority of these studies showed no evidence of the direct influence of empathy on pain, while 4 studies demonstrated a weak effect on pain. The authors concluded that the effect of empathetic interaction on pain was not strong and the level of evidence was very low. Thus, to our knowledge, this is the first well-designed randomised controlled study that focuses on the positive effect of empathetic interaction on pain relief in musculoskeletal physiotherapy.

A number of recent studies have highlighted the importance of psychological influences on CPM responses. Gougeon et al. (2016) studied the role of empathy in influencing CPM during three experimental conditions: pain condition, self-observation condition, and spouse-observation condition. Both the self-observation and spouse-observation conditions showed

Table 5.2 Mixed regression models for CPM and MIPM responses: predicted marginal means adjusted for the CARE Measure, RA rating and sex: overall differences between time points (all participants).

	Pre CPM/MIMP		During CPM		Post CPM/MIPM		Pre to During CPM	Pre to post CPM/MIPM
	Mean	*95%CI*	Mean	*95%CI*	Mean	*95%CI*	*p*	*p*
CPM Wrist PPT	358.58	*332.74 - 386.43*	444.81	*412.75 - 479.35*	399.26	*370.49 - 430.26*	**<0.001**	**<0.001**
CPM Elbow PPT	238.06	*222.01 - 255.27*	324.79	*302.89 - 348.27*	276.21	*257.59 - 296.19*	**<0.001**	**<0.001**
MIPM Wrist PPT	369.53	*340.69 - 400.82*	**-**	**-**	425.39	*392.18 - 461.41*	**-**	**<0.001**
MIPM Elbow PPT	268.13	*248.53 - 288.48*	**-**	**-**	335.13	*313.17 - 357.83*	**-**	**<0.001**
PFG	165.13	*149.29 - 181.76*	**-**	**-**	197.61	*180.25 - 215.77*	**-**	**<0.001**
ULNDT-RN	12.63	*11.26 - 14.08*	**-**	**-**	17.94	*16.30 - 19.66*	**-**	**<0.001**

CPM: conditioned pain modulation, MIPM: manipulation induced pain modulation, 95% CI: 95% confidence interval, PPT: pressure pain threshold, PFG: pain free grip, ULNDT-RN: upper limb neurodynamic test-radial nerve bias. Level of significance, $p<0.05$

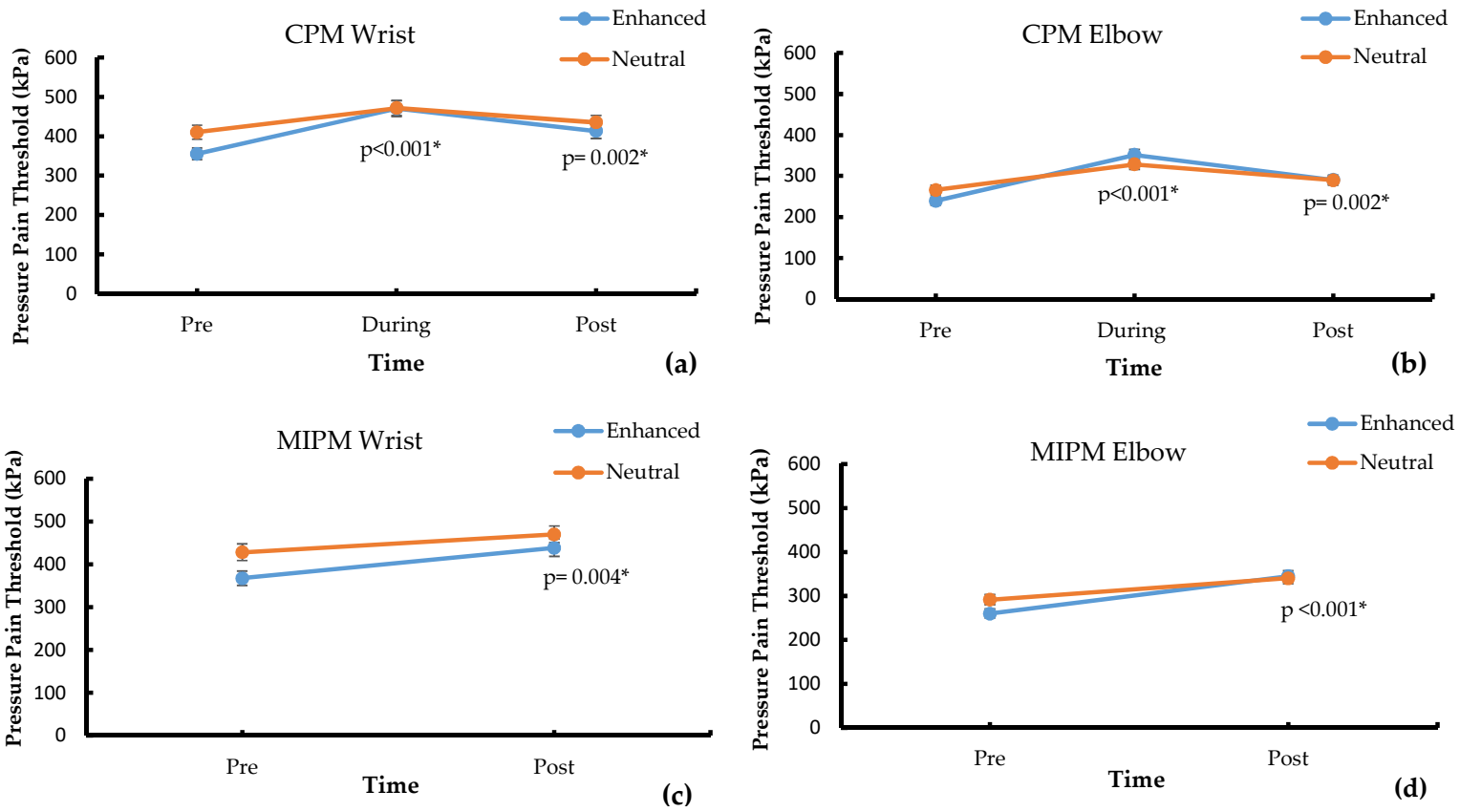

Figure 5.3 CPM and MIPM PPT predicted marginal means, adjusted for CARE, RA rating and sex: overtime differences between enhanced and neutral interaction groups. There were significant differences in CPM (a and b) and MIPM (c and d) analgesia, with higher levels of analgesia observed for the enhanced empathetic interaction group at both test sites. Levels of significance <0.05*.

Table 5.3 Mixed regression models for CPM and MIPM responses: predicted marginal means adjusted for CARE, RA rating and sex: differences between enhanced and neutral interaction groups over time.

Test/ measurement	Interaction group	pre CPM/MIMP		During CPM		Post CPM/MIPM		Pre to During CPM	Pre to Post CPM/ MIPM
		Mean	*95%CI*	Mean	*95%CI*	Mean	*95%CI*	*p*	*p*
CPM Wrist PPT	Enhanced	341.81	302.31 - 386.47	452.09	399.85 - 511.15	395.46	349.77 - 447.12	**<0.001**	**0.002**
	Neutral	376.17	332.71 - 425.32	437.65	387.08 - 494.82	403.09	356.51 - 455.75		
CPM Elbow PPT	Enhanced	226.06	201.72 - 253.34	335.54	299.40 - 376.03	276.38	246.62 - 309.74	**<0.001**	**0.002**
	Neutral	250.70	223.70 - 280.95	314.38	280.53 - 352.32	276.05	246.32 - 309.36		
MIPM Wrist PPT	Enhanced	349.86	306.09 - 399.88	_	_	417.83	365.56 - 477.57	_	**0.004**
	Neutral	390.32	341.49 - 446.12	_	_	433.09	378.91 - 495.01		
MIPM Elbow PPT	Enhanced	252.81	222.02 - 285.59	_	_	337.62	301.89 - 375.35	_	**<0.001**
	Neutral	283.91	251.23 - 318.59	_	_	332.64	297.18 - 370.10		
PFG	Enhanced	144.47	120.61 - 170.48	_	_	172.41	146.24 - 200.73		0.398
	Neutral	187.17	159.86 - 216.63	_	_	224.52	194.51 - 256.69		
ULNDT-RN	Enhanced	12.09	9.94 - 14.46	_	_	17.13	14.54 - 19.93		0.668
	Neutral	13.18	10.93 -15.65	_	_	18.77	16.06 - 21.70		

CPM: conditioned pain modulation, MIPM: manipulation induced pain modulation, PPT: pressure pain threshold, PFG: pain free grip, ULNDT: upper limb neurodynamic test- radial nerve bias 95%CI: 95% confidence interval. Level of significance, P<0.05

Table 5.4 Number need to treat analysis (NNT)

Measurement of analgesia (PPT)	Empathetic interaction (no. of positive outcomes*)	Neutral interaction (no. of positive outcomes)	NNT
CPM Wrist	14	8	5.67
CPM Elbow	16	9	4.86
MIPM Wrist	21	13	4.25
MIPM Elbow	28	12	2.13

PPT: pressure pain threshold, CPM: conditioned pain modulation, MIPM: manipulation induced pain modulation. *An outcome was considered positive if there was a change in PPT of 50kPa or more.

significant CPM effects, even in the absence of a painful conditioning stimulus. The authors in their study investigated the impact of participants' empathy on CPM in response to emotional triggers. Our study however examined the effect of empathetic interaction on CPM responses and this has not been previously investigated. The current study therefore provides new data in relation to the effect of manipulating the empathetic component of the patient/therapist interaction on CPM response.

Evidence from previous research also suggested that enhanced therapeutic interactions with patients is significantly associated with better clinical outcomes (Hall et al. 2010; O'Keeffe et al. 2016). A recent study by Fuentes et al. (2014) manipulated the therapist-patient interaction (enhanced, limited) to investigate the pain relieving effect of a single session of interferential current (IFC) (sham, active) on chronic low back pain (CLBP). Compared to other groups, the group that received active IFC with an enhanced interaction experienced the most significant pain relief on a numerical pain scale. There was also a significant increase in PPT for both groups (sham, active) when combined with an enhanced interaction. The authors concluded that enhanced

interactions positively influenced clinical outcomes when combined with active IFC in the treatment of CLBP. This is in agreement with the findings from our study that the enhanced empathetic interaction significantly improved the elbow pain in LE. Although Fuentes et al. manipulated the enhanced interaction through verbal and nonverbal behaviours and empathy, they measured expectancy, but not the empathetic, component of therapeutic interactions. Our study however specifically manipulated the empathetic interactions and appropriately assessed the interaction using the CARE Measure.

We used the number needed to treat (NNT) analysis to compare the influence of the interactions on CPM and MIPM effects. An NNT value of 2.13 for PPT change at the elbow following MIPM is a strong indication of the added value of empathetic interaction to potentially reduce pain in musculoskeletal practice. However, the extent of achieving these potential benefits in different musculoskeletal models is unpredictable and as a result it warrants additional study.

5.5. **Clinical implications**

The result of this study suggest that patient's perception of a clinician's empathy is associated with improvement in objective analgesic response. Clinicians are often encouraged to be more empathetic as part of a client centered approach to achieve better patient outcomes. This notion is based on evidence from the business sphere, where clients will be more satisfied with the service they receive if they have an enhanced interaction with the service provider (Fuertes et al. 2007; Fuertes et al. 2017). Our study findings therefore provide objective evidence to support the use of enhanced interaction with patients to reduce their pain in any clinical encounter.

5.6. **Limitations**

There are several potentially limiting factors in this study that need to be taken into consideration. First, there was a difference in the gender balance between the groups, with the enhanced interaction group having more females (63.6%) than the neutral interaction group (45.5%). This might explain the lower baseline PPT threshold values recorded for this group, as females tend to have lower PPT values than males (Fillingim et al. 2009; Racine et al. 2012; Skovbjerg et al. 2017). However, statistically the group gender difference was not significant ($p=0.112$). Having said that, gender was also controlled for in the analysis.

Although interacting for 15 minutes prior to CPM and MIPM protocols was sufficient to induce significant analgesic responses in the enhanced interaction group in people with LE, it remains unclear whether higher levels of analgesia or a positive effect on PFG and ULNDT would have been achieved with a longer enhanced interaction. Equally, only the immediate analgesic responses of CPM and MIPM were measured. Although, in this study we tried to investigate the degree of CPM and MIMP analgesia induced by a short term interaction, it would be useful to gather more information on the pattern of CPM and MIPM analgesic responses gathered over longer follow-up periods.

It must be noted that participants underwent diagnostic screening with the same assessor who conducted the CPM and MIPM protocols. While it is acknowledged that this additional interaction might affected treatment responses, it was highly standardised, as neutral as possible and kept to a minimum.

5.7. **Conclusion**

The current study showed that a single session of enhanced empathetic interaction positively influenced CPM and MIPM analgesic responses in people with LE. Results, however, showed that both interaction groups demonstrated high levels of natural analgesia following CPM and MIPM protocols. Although this increase in CPM and MIPM responses is not necessarily linked to improvement in clinical pain outcomes, CPM and MIPM may share similar neurophysiological mechanisms when activating endogenous descending pain inhibitory systems. Further research is recommended into the effect of a longer period of enhanced empathetic intervention on CPM and MIPM analgesia and into the exact mechanisms through which CPM and MIPM exert their effects.

Chapter 6: **Study Four**

The influence of aerobic exercise on CPM and MIPM analgesia

6.1. **Introduction**

Exercise is a key physiotherapeutic modality that has been shown to improve physical (Kaleth et al. 2013), cognitive and psychosocial function (Kennedy et al. 2016), and life expectancy (Wen et al. 2011). In people with chronic pain, exercise has been shown to improve depression and mood alterations (Hauser et al. 2010) and to reduce fatigue and sleep disturbance (Langhorst et al. 2013). Further, exercise has been shown to be effective in the management of pain associated with chronic musculoskeletal conditions (Ambrose & Golightly 2015). For example, exercise has been shown to prevent the development (Landmark et al. 2013) and subsequent recurrence of chronic low back pain (Choi et al. 2010).

Exercise has also been widely shown to reduce pain sensitivity, a phenomenon termed 'exercise induced analgesia' (EIA) (Koltyn 2000, 2002). EIA has been reported following aerobic (Vaegter, Handberg & Graven-Nielsen 2014), isometric (Hoeger Bement et al. 2008), and resistance exercise (Focht & Koltyn 2009), using a range of pain related modalities (e.g. pressure, thermal or electrical stimuli) (Vaegter et al. 2018). In the case of aerobic exercise, EIA is induced when performed at moderate to high intensity (Vaegter, Handberg & Graven-Nielsen 2014). Naugle, Fillingim and Riley (2012) compared the immediate effect of high (75% VO2max) and moderate (50%% VO2max) intensity aerobic exercise, elicited by stationary cycling, on the magnitude of EIA in healthy participants. The results showed that high intensity exercise induced greater levels of EIA than moderate intensity exercise, suggesting a dose-response relationship. In contrast, several other studies have reported a significant EIA response after high intensity aerobic exercise only (Hoffman et

al. 2004; Vaegter, Handberg & Graven-Nielsen 2014). Thus, the optimal intensity for eliciting a significant EIA response needs further investigations.

While EIA has been clearly demonstrated in healthy individuals (Koltyn 2000; Naugle, Fillingim & Riley 2012), the evidence for EIA induction in chronic pain conditions is ambiguous. In their review, Cunha et al. (2016) concluded that EIA is functional in some chronic musculoskeletal pain states (e.g. osteoarthritis (OA), rheumatoid arthritis (RA)) but is impaired in others (e.g. fibromyalgia (FM), chronic whiplash disorders). This discrepancy in EIA responses between chronic pain conditions could be attributed to a preserved endogenous analgesia (EA) system across the chronic pain groups with functional EIA. Equally it may be that subgroups within the same pain condition exhibit differing levels of EIA (i.e. low pain sensitivity vs. high pain sensitivity subgroups), data that is not captured if only group means are reported (Vaegter, Handberg & Graven-Nielsen 2016). Consequently, further studies are required to clarify the effect of aerobic exercise on EIA in chronic pain conditions.

There is some evidence to suggest that aerobic exercise activates endogenous analgesic mechanisms similar to those implicated in conditioned pain modulation (CPM) and manipulation induced pain modulation (MIPM) analgesia. Cardiovascular and blood pressure changes (i.e. a rise in pulse rate and blood pressure) were shown to concurrently occur with EIA (Koltyn & Umeda 2006), CPM (Chalaye et al. 2013; Chalaye et al. 2014), and MIPM (Chiu & Wright 1996; Sterling, Jull & Wright 2001; Vicenzino et al. 1998b; Vicenzino, Collins & Wright 1996; Vicenzino et al. 1995). Similarly, serotonergic mechanisms have been reported as being important for EIA (Soares, Naffah-Mazzacoratti & Cavalheiro 1994; Steinberg et al. 1998), CPM (Yarnitsky 2015), and MIPM (Skyba et al. 2003). Naloxone (an opioid antagonist) did not reverse MIPM analgesia (Paungmali et al. 2004; Vicenzino et al. 2000; Zusman,

Edwards & Donaghy 1989), suggesting a non-opioid mechanism. However, the effect of naloxone on CPM and EIA is inconclusive: some studies show that naloxone reversed EIA (Haier, Quaid & Mills 1981) and CPM analgesia (King et al. 2013; Pertovaara et al. 1982; Willer, Le Bars & De Broucker 1990); while other studies report no reversal (EIA: (Droste et al. 1991); CPM: (Edwards, Ness & Fillingim 2004; Hermans et al. 2018; Peters et al. 1992)). Consequently, there is some ambiguity regarding the involvement of the opioid system in EIA and CPM. Further research to elucidate the exact mechanisms involved in each form of EA is needed.

Functional EIA has been shown to be associated with efficient CPM analgesia (Lemley, Hunter & Bement 2015; Vaegter, Handberg & Graven-Nielsen 2014; Vaegter et al. 2015). Fingleton, Smart and Doody (2017) compared EIA responses in patients with knee OA between those with efficient and inefficient CPM. EIA was induced by 5 minutes of isometric knee extension followed by 4-10 minutes of aerobic cycling (cycling exercise was terminated if the knee pain exceeded 3/10 irrespective of reduced workload). The efficient CPM group showed a functional EIA response, while the inefficient CPM group showed a dysfunctional EIA response, both during and post aerobic and isometric knee exercises. Further, in a comparison between groups of inactive and active healthy volunteers, Vaegter et al. (2018) compared between the EIA induced after 15 minutes of high intensity aerobic cycling (75% VO^2max) and CPM analgesia. Higher levels of EIA and stronger CPM effect were demonstrated by the active group, although EIA and CPM analgesia were positively associated in both groups.

Based on these findings, it may be hypothesized that a similar association may exist between EIA and MIPM analgesia. It may also be that there is potential for MIPM analgesia to be potentiated by a preliminary period of aerobic exercise. Exercise and manual therapy are often combined within a

multimodal program to reduce pain in conditions such as chronic low back pain (Chan, Mok & Yeung 2011; Childs et al. 2004; Cleland et al. 2009; Hallegraeff et al. 2009). However, these studies have not specifically examined the immediate combined effect of aerobic exercise and manual therapy on chronic pain.

The first aim of this randomized, controlled study was to compare the immediate effect of a single session of moderate or high intensity aerobic exercise using a cycle ergometer on pain in a patient population with lateral epicondylalgia (LE). The second aim was to determine whether aerobic exercise potentiates CPM and MIPM analgesia, and whether it affects both CPM and MIPM responses to a similar degree. The third aim was to assess the association between EIA and CPM and MIPM analgesia.

6.2. **Methods**

6.2.1. Null hypotheses

1. There will be no difference in the magnitude of exercise induced analgesia (EIA) between those participants who receive moderate intensity aerobic exercise and those who receive high intensity aerobic exercise.

2. There will no difference between time points (i.e. during and post CPM and MIPM) in the level of CPM and MIPM analgesia, relative to baseline, detected by measures of PPT at the wrist and elbow (all participants).

3. There will be no difference in the magnitude of CPM and MIPM analgesia between those participants who receive moderate intensity aerobic exercise and those who receive high intensity aerobic exercise.

4. There will be no correlation between magnitudes of EIA and MIPM and CPM analgesia as detected by measures of PPT at the wrist and elbow.

6.2.2. Study design

A randomised, controlled between-group experimental design was used in this study. Eligible participants were randomised to receive either moderate intensity aerobic exercise (control condition) or high intensity aerobic exercise (active condition) during two separate test sessions. (See protocol description)

6.2.3. Randomisation

A randomisation sequence was computer-generated and held by the Physiotherapy Clinic supervisor at Curtin University, who was not involved in delivery of care or assessment of outcomes for the study. Randomisation was stratified for males and females. Prior to commencing each testing session, a research assistant contacted the holder of the allocation schedule to ascertain group allocation for each participant. This research assistant conducted the aerobic exercise sessions. The primary investigator (AM) who undertook all outcomes testing remained blind to group allocation throughout the study.

6.2.4. Participants

A gender stratified convenience sample was used to recruit 68 participants with LE, aged between 18 and 60 years, from Perth, Western Australia. Recruitment took place from October 2017 until June 2018 through Curtin Radio advertisements, adverts in sports clubs, via a range of musculoskeletal and sports physiotherapy clinics and through a specialised social media clinical trials recruitment agency.

6.2.5. Eligibility criteria

Inclusion (Haker & Lundeberg 1990) and exclusion criteria were as outlined in Chapter 4, Section 4.2.3. Participants were excluded if they were found ineligible for aerobic exercise intervention.

Participants were initially contacted via phone to screen for eligibility and to provide a brief explanation of the study protocol. Additional information about the study was provided via email. Prior to commencing the study, each participant underwent a thorough clinical examination, carried out by the primary investigator to confirm eligibility. Participants were also required to complete the Adult Pre-exercise Screening System (APSS) tool, a tool developed by Exercise and Sport Science Australia (ESSA), Fitness Australia (FA), and Sports Medicine Australia (SMA) to assess participants' eligibility and safety for aerobic exercise testing (Norton 2012). All testing was carried out at the Physiotherapy Clinic, School of Physiotherapy and Exercise Science, Curtin University. Participants were asked to abstain from taking pain medications 24 hours prior to initial testing and to avoid any additional physiotherapy treatment or other physical treatments (e.g. physical exercise, aerobic exercise, chiropractic or acupuncture) 3 days before and on the testing day.

Curtin University Human Research Ethics Committee approved the study (HREC project approval number: HRE2017-0198-02). The study was also prospectively registered with the Australia New Zealand Clinical Trials Registry (ANCTR) (ID number ACTRN12617000219381). Written informed consent was obtained from all participants before the start of testing.

6.2.6. Procedure

After confirming eligibility, the primary investigator tested all participants for pressure pain threshold (PPT) at both elbow and wrist test sites, as described below, and then left the room. These PPT values were used as the baseline value for EIA calculations (Baseline 1). Following baseline PPT measurement, the aerobic exercise session was then conducted under the supervision of a research assistant who had received training in the exercise protocol. Participants were allocated to receive either moderate (50% HRmax) or high intensity (75% HRmax) aerobic exercise based on the randomisation schedule. Each participant completed two sessions, both at the same exercise intensity, separated by three days. Following the completion of the cycling exercise, the primary investigator re-entered the room and conducted either a CPM or a MIPM assessment protocol, in a random order. In both cases, a second set of PPT measures (Baseline 2) were taken before the CPM or MIPM stimulus was applied. These measures provided an indication of the EIA effect and constituted a baseline measure to assess the CPM or MIPM response. Additional sets of PPT measures were then taken during and post CPM and MIPM stimuli respectively, as described below. All PPT assessments was performed by the primary assessor, who remained blind to the experimental group of each participant. (Figure 6.1)

6.2.7. Pain-related outcome measures

Pain-related measures of pressure pain threshold (PPT), pain free grip (PFG) and the upper limb neurodynamic test with radial nerve bias (ULNDT_RN) measures were measured using the same methodology outlined in Chapter 4, Section 4.2.4. All measures were obtained in triplicate. PPT measures were assessed at the wrist and elbow test sites.

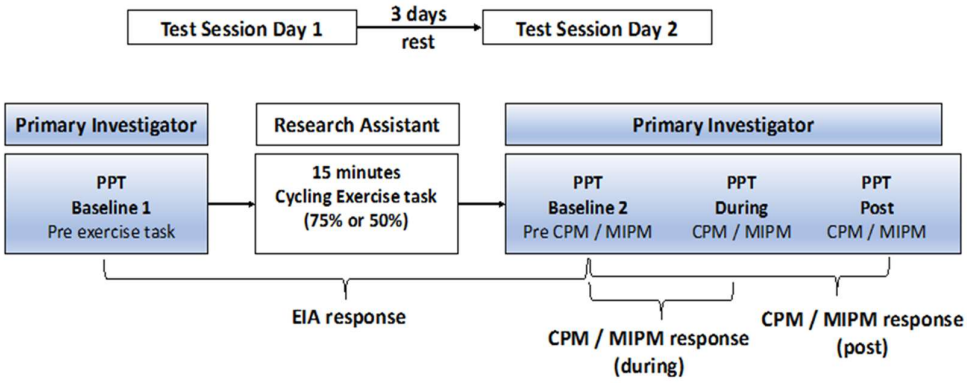

Figure 6.1 Testing session with inhibitory assessment protocols. PPT: pressure pain threshold, CPM: conditioned pain modulation, MIPM: manipulation induced pain modulation

6.2.8. Assessment protocols

Conditioned pain modulation (CPM) and manipulation-induced pain modulation (MIPM) assessment protocols were performed using the same methodology described in Chapter 4, Section 4.2.5. The mobilisation stimulus was carried out by an experienced practitioner who was different from the main investigator. The change in PPT at each test site from Baseline 1 (pre-exercise task) to during and post conditioning and mobilisation stimuli was considered as the CPM and MIPM analgesic effects, respectively.

6.2.9. Exercise-induced analgesia (EIA)

EIA was calculated as the change in PPT at each test site from pre-exercise (Baseline 1) to pre-conditioning stimulus (CPM) or mobilisation stimulus (MIPM), depending on test day (Baseline 2).

6.2.10. Tennis Elbow specific assessment instrument

At test session one, before physical testing, all participants were asked to complete the Patient Rated Tennis Elbow Evaluation (PRTEE) as described in Chapter 4, Section 4.2.6.

6.2.11. Physical activity assessment

Participants were also asked to complete at baseline the Global Physical Activity Questionnaire (GPAQ) (World Health Organization 2005) to evaluate their physical activity levels. This is a 16-question self-report questionnaire measuring the typical weekly time spent on three main domains of physical activities (work, transport and recreation) and sedentary behaviour. The total GPAQ score was calculated using the GPAQ guidelines (World Health Organization 2005) to analyse the data. The total amount of physical activity expressed as Metabolic Equivalents (MET)-minute/week was used for analysis. The GPAQ was shown to be a reliable measure (moderate to substantial strength, Kappa: 0.67-0.73) of physical activity, with a moderate to strong concurrent validity (0.45 to 0.65) compared to the International Physical Activity Questionnaire (IPAQ) and a poor to fair criterion validity (0.06 to 0.35) (Bull, Maslin & Armstrong 2009).

6.2.12. Experimental conditions

The method described here is based on a study by Naugle et al. (2014). Participants completed two separate stationary cycling sessions, both at either high or moderate intensity (randomly allocated) and for 15 minutes duration. The primary investigator was not present in the room at any time during the exercise sessions. Before starting the first session, a target heart rate (THR) was calculated for each participant by the study research assistant, based on age-predicted maximal heart rate (HRmax), where maximal HR = 220-age (Fox &

Naughton 1972). THR for those in the high intensity group was determined using the formula maximal HR × 75%. THR for those in the moderate intensity group was calculated as maximal HR × 50%.

All participants completed their exercises sessions using a cycle ergometer (828E Ergometer, Monark, Vansbro, Sweden). The cycle seat post was individually adjusted so that the participant's knee remained at approximately 5° flexion when the pedal was at the bottom of a revolution, with the ankle held in neutral. Heart rate was monitored during exercise using a chest heart rate monitor (Monark Heart Rate Monitor, Monark Exercise AB), which was fitted at the start of the session. The targeted exercise intensity level was achieved through adjusting the speed and the resistance of the cycle ergometer. Participants started the exercise session by warming up for 5 minutes. For the first two minutes, participants cycled at low intensity (HR = 40%-45% maximal HR) to familiarise themselves with the cadence. The resistance was then gradually increased over the next three minutes to reach the desired THR by the end of the first 5 minutes. Participants then continued cycling for the following 10 minutes while maintaining the exercise intensity at THR. Heart rate was continuously monitored to stay within a range of 10% above and 5% below the THR. Every five minutes during the cycling session participants were instructed to rate their perceived exertion (RPE) using the Borg-Scale (6-20) (Borg 1998). Heart rate (beats/minute) and workload (in watts) were recorded every minute during the first five minutes and every 30 seconds and one minute, respectively, during the main exercise session. Mean RPE, HR and workload data collected during the 10 minutes of the high aerobic intensity was used for the analysis.

6.2.13. Sample Size calculation

Sample size was calculated using the same methodology described in Chapter 5, Section 5.1.2.13. A priori power analysis (alpha = 0.05, beta = 0.80) indicated a required sample size of 68 (34 per group).

6.2.14. Statistical analysis

Data were analysed using Stata/IC (version 15.0: StataCorp LLC, TX). For all analyses, $p<0.05$ was considered statistically significant. Descriptive statistics were based on frequency distributions for categorical data (gender and elbow tested) and means and standard deviations (SD) (age, PRTEE and RPE) or medians and interquartile ranges (IQR) for continuous data (duration of LE, GPAQ, HR, workload). Univariate group comparisons between intervention groups at baseline and during exercise sessions included χ^2 and Fisher exact tests for categorical comparisons, and independent t-tests or Mann-Whitney U tests for continuous outcomes, as suitable.

All outcome data were evaluated for normality using Shapiro-Wilk tests and graphical review. Non-normally distributed data (PPT, PFG, ULNDT-RN) were transformed using natural logarithms.

For hypotheses 1, 2 and 3, linear mixed models with random subject effects were used to calculate the overall differences (relative to baseline PPT measures) between time points (all participants) and between exercise groups over time for EIA, CPM and MIPM outcome variables (i.e. PPT, PFG and ULNDT-RN). The respective marginal means, 95% confidence intervals (CI), and p-values of these differences were calculated. The analysis was controlled for PRTEE, GPAQ and sex.

For hypothesis 4, partial correlations and univariate regression models were run to determine the relationships between EIA (i.e. independent variable)

and CPM and MIPM analgesia (i.e. dependent variables), measured both during and post cold water immersion / mobilisation stimuli at both test sites. The strength of the correlations were interpreted according to the guidelines defined by Cohen (1988): (small: $0.10 \leq r \leq 0.29$; medium: $0.30 \leq r \leq 0.49$; large: $0.50 \leq r \leq 1.0$). Univariate regression models were used to calculate regression coefficients (B), and their 95% confidence intervals (CI) and p-values. The adjusted coefficients of determination (adj. R^2) were also calculated in order to determine the proportion of variability in CPM /MIPM PPT (dependent variable) that is explained by post cycling PPT (EIA, explanatory variable). Due to the anticipated between-individual variability in PPT, baseline PPT (Baseline 1) was identified as a potential confounder for the association and therefore it was adjusted for in the partial correlations and regression analyses.

6.3. **Results**

A total of 68 participants met the eligibility criteria and participated in the study. All volunteers were randomly allocated into each group (n=34), received the intended aerobic exercise interventions, completed both CPM and MIPM assessment sessions, and were analysed with regards to outcomes (Figure 6.2). Characteristics of all participants are summarised by group in Table 6.1.

6.3.1. Demographics

There were no significant differences between exercise groups ($p>0.05$) in demographic characteristics of participants: gender ($p=1.00$), affected elbow tested ($p=1.00$), age ($p=0.571$) and duration of tennis elbow condition ($p=0.551$). There were equal numbers of females 12 and males 22 in each aerobic exercise group.

6.3.2. Self-reported measures at baseline

6.3.2.1. **PRTEE**

There was no statistical difference in the PRTEE scores between exercise groups (p=0.960, >0.05): mean PRTEE scores 37.59 (SD=14.44) for the moderate intensity aerobic group; 37.78 (16.79) points for the high intensity group.

6.3.2.2. **GPAQ**

The GPAQ scores were also not significantly different between groups (p=0.883): moderate intensity group 3090 MET-minute/week, (IQR=1660-5760; high intensity group 2960 MET-minute/week, (IQR=1440-5720).

6.3.3. Exercise intensity measurements during cycling tasks

There were statistically significant differences between the exercise groups during their two cycling sessions in exercise intensity measurements (Table 6.2). As anticipated, the high intensity group maintained significantly higher HR (beats/minute, p<0.001) and workload (Watts, p<0.001) and reported significantly higher perceived exertion (Borg, p<0.001).

6.3.4. Between time points differences (all participants)

6.3.4.1. **PPT**

Both aerobic exercise groups (all participants) exhibited a significant increase in all PPT measures for both CPM and MIPM protocols) at the wrist and elbow sites from Baseline 1 (pre cycling) to: Baseline 2 (immediately post cycling - EIA effect) p<0.001 for both sites; during CPM p<0.001 both sites, and during MIPM p<0.001 both sites; and immediately post both CPM and MIPM, p<0.001 both protocols and both sites). (Table 6.3)

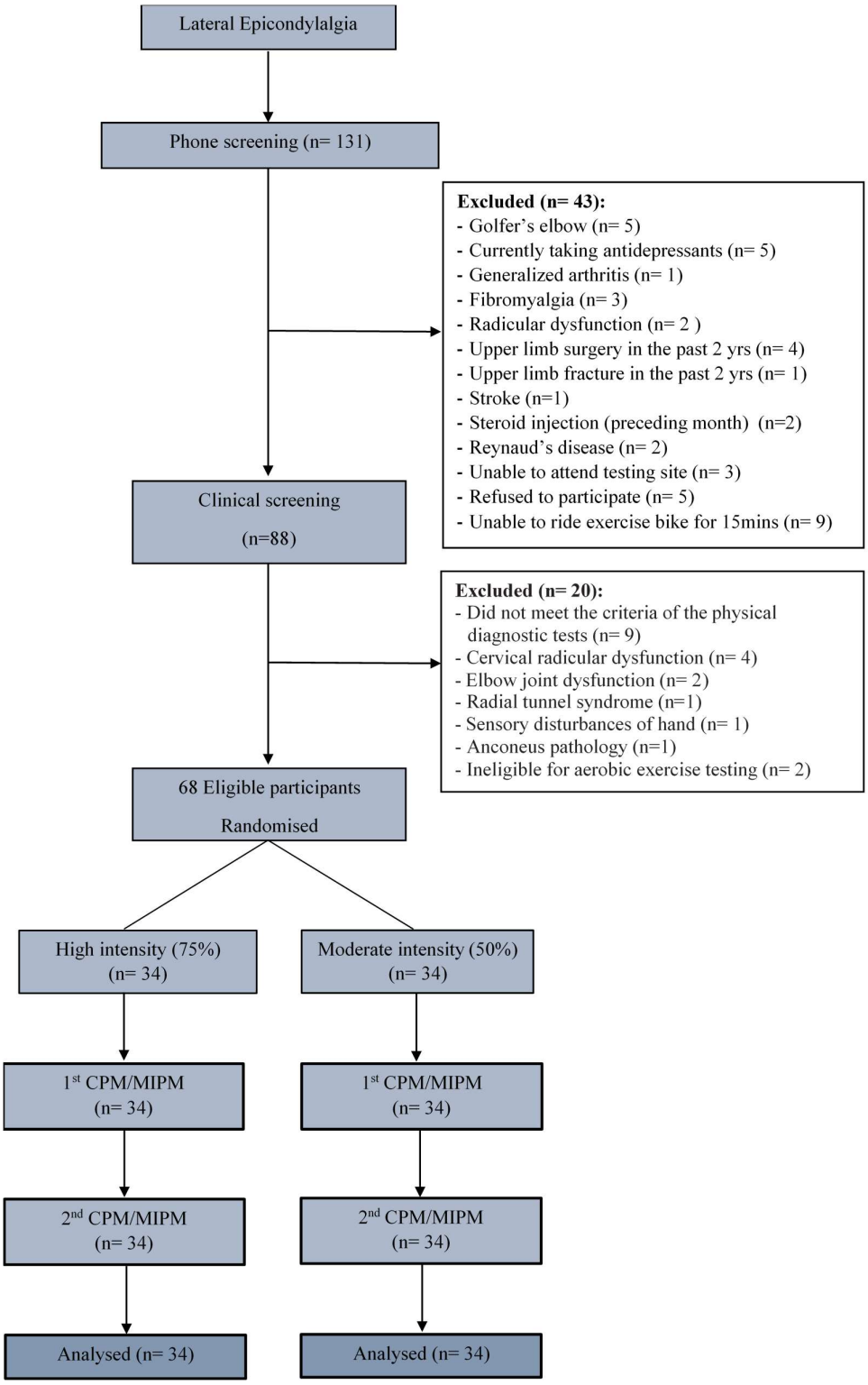

Figure 6.2 Consort diagram illustrating overall experimental procedure

Table 6.1 Descriptive summaries for the research sample by intervention groups.
*Data are presented as mean and standard deviation (SD) unless otherwise specified**

		Sample (N=68)	Moderate intensity (n=34)	High intensity (n=34)	p
Gender *n (%)**	F	24 (35.29)	12 (35.29)	12 (35.29)	1.000
	M	44 (64.71)	22 (64.71)	22 (64.71)	
Elbow tested *n (%)**	L	29 (42.65)	15 (44.12)	14 (41.18)	1.000
	R	39 (57.35)	19 (55.88)	20 (58.82)	
Age *(year)*		46.47 (9.62)	45.80 (9.57)	47.14 (9.77)	0.571
Duration *Median (IQR)(year)**		0.67 (0.42, 1.5)	0.58 (0.38, 2)	0.67 (0.50, 1.50)	0.551
PRTEE		37.68 (15.54)	37.59 (14.44)	37.78 (16.79)	0.960
GPAQ *Median (IQR)** *(MET-min/week)*		3090 (1650, 5740)	3090 (1660, 5760)	2960 (1440, 5720)	0.883

F: female, M: male, L: left, R: right, PRTEE: patients rated tennis elbow evaluation, GPAQ: general physical activity questionnaire, MET: metabolic equivalent. IQR: interquartile range, SD: standard deviation. Level of significance, $p<0.05$.

6.3.4.2. **PFG and ULNDT-RN (MIPM protocol only)**

PFG and ULNDT-RN were used as secondary measures of the analgesic effect of MIPM. Both aerobic exercise groups exhibited a significant increase in PFG ($p<0.001$) and ULNDT-RN ($p<0.001$) from pre to post MIPM (Table 6.3).

Table 6.2 Exercise intensity measurements for each exercise group during CPM and MIPM assessment session
Data summarised as median (IQR) (except RPE data summarised as mean (SD))

Exercise descriptor	Moderate intensity (n=34)	High intensity (n=34)	*p*
CPM cycling			
HR	89.65 (85.9, 95.3)	134.75 (126, 144.2)	**<0.001**
Workload	31.6 (21, 55.8)	112.6 (83.8, 158.7)	**<0.001**
RPE (6-20)	9.68 (2.15)	13.29 (1.79)	**<0.001**
MIPM cycling			
HR	89.95 (84.8, 97.4)	134.65 (126.9, 140.9)	**<0.001**
Workload	39.55 (59.2, 23.6)	104.45 (73.8, 154.7)	**<0.001**
RPE (6-20)	10.26 (1.82)	13.34 (1.81)	**<0.001**

HR: heart rate (beats/minute), workload (watt), RPE: rating of perceived exertion (Borg), IQR: interquartile range, SD: standard deviation. Level of significance $p<0.05$

6.3.5. Between-group differences over time (group x time interaction effect)

6.3.5.1. **PPT**

There were significant group x time interaction effects for PPT both at the elbow and the wrist test sites at Baseline 2 (immediately post cycling) ($p <0.001$), during CPM ($p <0.001$), during MIPM ($p <0.001$), post CPM ($p <0.001$) and post MIPM ($p <0.001$). Significantly higher levels of PPT (analgesia) were measured for the high intensity exercise group at both sites across all time-points (Table 6.4 and Figure 6.3). The percentage change in PPT (kPa) from Baseline 1 (pre cycling) to each time-point at

both test sites for each exercise group is shown in Figure 6.4. There was an increase in PPT (decreased sensitivity) for both exercise groups, for all inhibitory protocols (EIA, CPM and MIPM), but this analgesic effect was considerably greater in the high intensity exercise group. This analgesic effect was consistently greater at the affected elbow rather than the wrist site, for all protocols. Further, there was a clear additive analgesic effect for both CPM and MIPM after exercise (on EIA). For example, for the high intensity group, the percentage increase in PPT at the elbow improved from 72.70% immediately following exercise to 125.50% during CPT, and to 119.60% during mobilisation. Data additionally show that whereas the CPM effect started to reduce immediately post CPT completion, it continued to increase immediately following mobilisation.

6.3.5.2. **PFG and ULNDT-RN**

There was a significant group x time interaction effect for change in ULNDT-RN ($p<0.001$) but this did not quite reach significance for PFG ($p=0.052$) (Table 6.4).

6.3.6. Between-group differences over time (group x time interaction effect) whilst controlling for Baseline 2

The same analysis performed above was conducted without including Baseline 1 data and controlling for differences in Baseline 2 data (See Table 6.5). There were significant group x time interaction effects for PPT both at the wrist test sites during ($p <0.001$) and post ($p <0.001$) CPM and MIPM. While the over time differences between both groups for PPT at the elbow region were significant post CPM ($p=0.016$), during MIPM ($p=0.037$) and post MIPM ($p=0.010$), the difference was not significant during CPM ($p=0.335$). The high intensity group demonstrated significantly higher levels of CPM and MIPM analgesia (PPT) at both test sites across all times points, except for the PPT measured during CPM at the elbow region. When controlling for Baseline 2 in this analysis, the analgesic responses become more variable at the elbow compared to those at the wrist that have been consistent across all time points in the both analyses.

6.3.7. The correlation between EIA and CPM analgesia

There were significant positive and large partial correlations between PPT values measured post aerobic exercise (EIA) and PPT values during ($p<0.001$) and post ($p<0.001$) cold water immersion (CPM), with Pearson correlation coefficients (r) ranging between 0.90 and 0.93. The subsequent regression analyses showed that EIA is a significant predictor of CPM PPT measured at both test sites during ($p <0.001$) and post cold water immersion ($p <0.001$). The adjusted coefficient of determination (adj. R^2) values range between 0.92 and 0.95. This indicates that, based on this research sample, between 92% and 95% of the variability in CPM PPT measures is explained by the EIA response. The correlation and regression analyses of the association between EIA and CPM analgesia, adjusting for baseline PPT values, are presented in Table 6.6.

6.3.8. The correlation between EIA and MIPM

The partial correlation and regression analyses for the association between PPT values measured post aerobic exercise (EIA) and PPT measured during and post the mobilisation stimulus (MIPM) are presented in Table 6.7. Significant positive, large partial correlations were seen between EIA and MIPM analgesia measured during ($p<0.001$) and post ($p<0.001$) the mobilisation stimulus (r values range between 0.68 and 0.86). The regression analyses, adjusting for baseline PPT, show that EIA is a significant predictor of MIPM PPT measured at both sites during ($p <0.001$) and post mobilisation ($p<0.001$). The adj. R^2 values range between 0.73 and 0.93. This indicates that based on this cohort between 73% and 93% of the variability in MIPM PPT measures is explained by the EIA response.

Table 6.3 Mixed regression models for CPM and MIPM responses: predicted marginal means adjusted for PRTEE, GPAQ and sex: overall differences between time points (all participants).

	Baseline 1 (pre-cycling)		Baseline 2 (pre CPM/MIMP)		During CPM/MIPM		Post CPM/MIPM		Baseline 1 to Baseline 2 (EIA effect)	Baseline 1 to During CPM/ MIPM	Baseline 1 to Post CPM/ MIPM *pre-post MIPM
	Mean	*95%CI*	Mean	*95%CI*	Mean	*95%CI*	Mean	*95%CI*	*p*	*p*	*p*
CPM Wrist PPT	494.48	*463.60 - 527.42*	609.44	*571.38 - 650.04*	731.70	*686.00 - 780.44*	671.62	*629.68 - 716.36*	**<0.001**	**<0.001**	**<0.001**
CPM Elbow PPT	274.91	*255.48 - 295.83*	390.16	*362.58 - 419.83*	502.50	*466.98 - 540.73*	446.02	*414.49 - 479.95*	**<0.001**	**<0.001**	**<0.001**
MIPM Wrist PPT	490.32	*458.38 - 524.48*	590.88	*552.39 - 632.05*	665.31	*621.97 - 711.66*	682.20	*637.76 - 729.73*	**<0.001**	**<0.001**	**<0.001**
MIPM Elbow PPT	270.36	*248.64 - 293.97*	382.17	*351.47 - 415.54*	469.71	*431.99 - 510.74*	479.45	*440.94 - 521.32*	**<0.001**	**<0.001**	**<0.001**
PFG			216.72	*201.52 - 233.08*			255.71	*237.77 - 275.00*			**<0.001***
ULNDT-RN			13.27	*12.08 - 14.58*			20.16	*18.36 - 22.15*			**<0.001***

CPM: conditioned pain modulation, MIPM: manipulation induced pain modulation, PPT: pressure pain threshold, PFG: pain free grip, ULNDT: upper limb neurodyn test-radial nerve bias, 95%CI: 95% confidence interval. Level of significance, p<0.05

Table 6.4 Mixed regression models for CPM and MIPM predicted marginal means, adjusted for PRTEE, GPAQ and sex: differences between moderate and high intensity aerobic groups over time.

Measurement	Exercise group	Baseline 1 (pre-cycling)		Baseline 2 (pre CPM/MIMP)		During CPM/MIPM		Post CPM/MIPM		Baseline 1 to Baseline 2 (EIA effect)	Baseline 1 to During CPM/ MIPM	Baseline 1 to Post CPM/ MIPM *pre-post MIPM
		Mean	*95%CI*	Mean	*95%CI*	Mean	*95%CI*	Mean	*95%CI*	*p*	*p*	*p*
CPM Wrist PPT	Moderate	508.02	*468.15 - 551.28*	544.29	*501.58 - 590.65*	629.67	*580.25 - 683.29*	579.15	*533.70 - 628.47*			
	High	481.31	*443.54 - 522.30*	682.39	*628.83 - 740.50*	850.27	*783.55 - 922.69*	778.86	*717.74 - 845.19*	**<0.001** (EIA)	**<0.001**	**<0.001**
CPM Elbow PPT	Moderate	286.16	*260.51 - 314.34*	340.80	*310.25 - 374.37*	433.97	*395.06 - 476.70*	378.63	*344.69 - 415.92*			
	High	264.11	*240.43 - 290.12*	446.66	*406.61 - 490.64*	581.86	*529.70 - 639.16*	525.40	*478.30 - 577.14*	**<0.001** (EIA)	**<0.001**	**<0.001**
MIPM Wrist PPT	Moderate	498.29	*457.13 - 543.15*	541.02	*496.34 - 589.73*	571.79	*524.57 - 623.27*	578.57	*530.78 - 630.66*			
	High	482.48	*442.63 - 525.92*	645.33	*592.03 - 703.43*	774.11	*710.18 - 843.81*	804.38	*737.95 - 876.80*	**<0.001** (EIA)	**<0.001**	**<0.001**
MIPM Elbow PPT	Moderate	271.23	*244.06 - 301.43*	325.75	*293.11 - 362.02*	387.81	*348.96 - 430.99*	392.90	*353.54 - 436.65*			
	High	269.48	*242.49 - 299.49*	448.36	*403.44 - 498.28*	568.91	*511.91 - 632.25*	585.07	*526.45 - 650.21*	**<0.001** (EIA)	**<0.001**	**<0.001**
PFG	Moderate			212.30	*191.71 - 235.11*			243.09	*219.51 - 269.21*			
	High			221.24	*199.77 - 245.00*			268.99	*242.90 - 297.89*			**0.052***
ULNDT-RN	Moderate			12.05	*10.67 - 13.63*			16.70	*14.77 - 18.88*			
	High			14.62	*12.93 - 16.52*			24.35	*21.54 - 27.53*			**<0.001***

CPM: conditioned pain modulation, MIPM: manipulation induced pain modulation, PPT: pressure pain threshold, PFG: pain free grip, ULNDT: upper limb neurodynamic test- radial nerve bias, 95%CI: 95% confidence interval. *pre-post MIPM. Level of significance, p<0.05

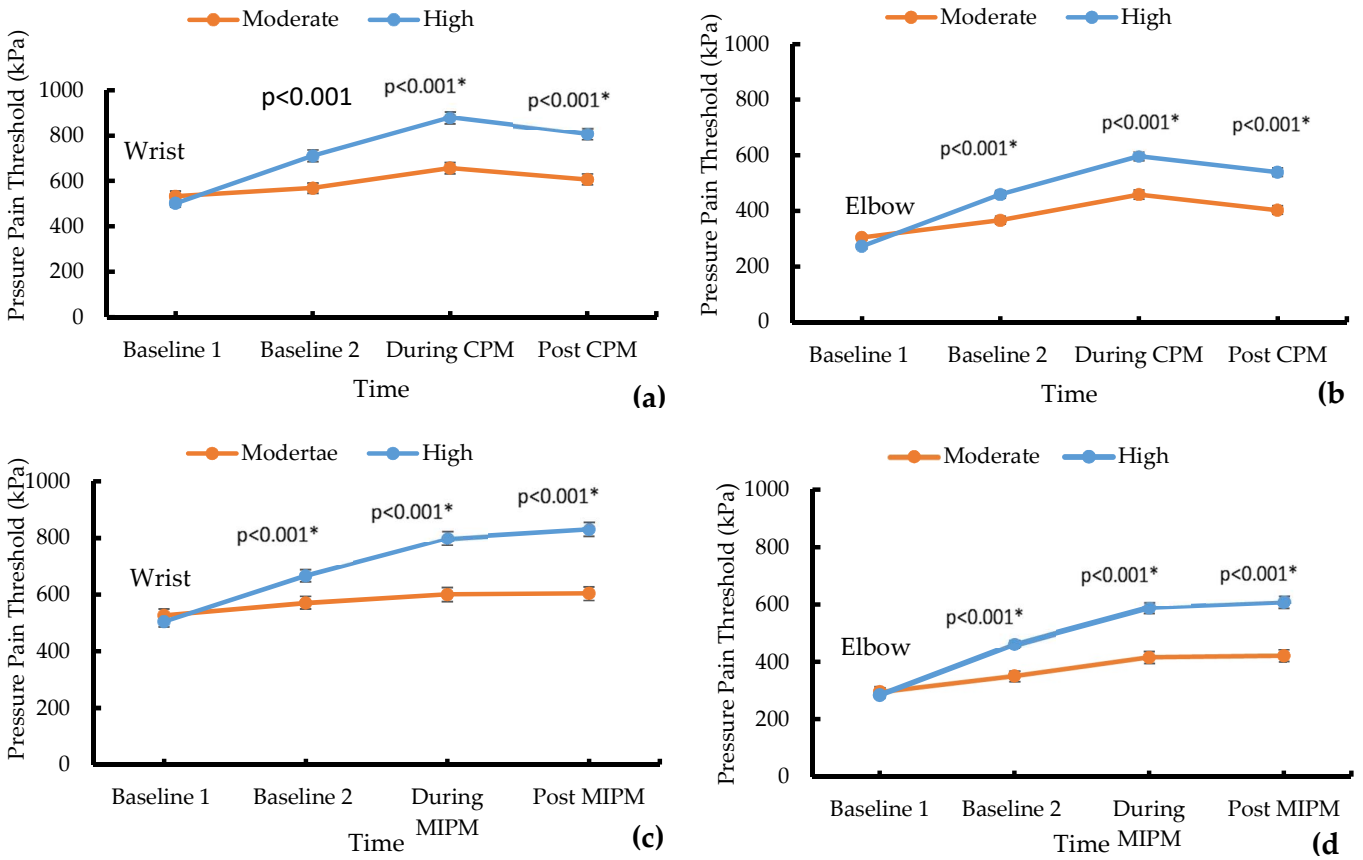

Figure 6.3 Significant group x time interaction effects for PPT both at the wrist (a and c) and the elbow (b and d) test sites, with higher PPT values measured for the high intensity aerobic exercise group at baseline 2 (post cycling), during CPM/MIPM, post CPM/MIPM. Level of significance, p<0.05*

Table 6.5 Mixed regression models for CPM and MIPM predicted marginal means, adjusted for Baseline 2 (dropping Baseline 1), PRTEE, GPAQ and sex: differences between moderate and high intensity aerobic groups over time.

	Exercise intensity group	Baseline 2 (pre CPM/MIMP)		During CPM/MIPM		Post CPM/MIPM		Baseline 2 to During CPM/ MIPM	Baseline 2 to Post CPM/ MIPM *pre-post MIPM
		Mean	*95%CI*	Mean	*95%CI*	Mean	*95%CI*	*p*	*p*
CPM Wrist PPT	Moderate	544.30	*502.32 - 589.79*	629.67	*581.10 - 682.29*	579.15	*534.48 - 627.55*	**<0.001**	**<0.001**
	High	682.38	*629.75 - 739.41*	850.27	*784.69 - 921.33*	778.86	*718.79 - 843.95*		
CPM Elbow PPT	Moderate	340.83	*310.58 - 374.02*	434.00	*395.49 - 476.26*	378.66	*345.06 - 415.54*	0.335	**0.016**
	High	446.62	*406.99 - 490.11*	581.82	*530.19 - 638.48*	525.36	*478.74 - 576.52*		
MIPM Wrist PPT	Moderate	541.02	*497.58 - 588.25*	571.79	*525.88 - 621.71*	578.57	*532.11 - 629.07*	**<0.001**	**<0.001**
	High	645.33	*593.52 - 701.67*	774.11	*711.97 - 841.70*	804.34	*739.80 - 874.61*		
MIPM Elbow PPT	Moderate	325.76	*294.68 - 360.13*	387.83	*350.81 - 428.75*	392.92	*355.42 - 434.37*	**0.037**	**0.010**
	High	448.34	*405.55 - 495.65*	568.89	*514.60 - 628.92*	585.05	*529.21 - 646.78*		
PFG	Moderate	212.30	*191.71 - 235.11*	-	-	243.09	*219.51 - 269.21*	-	0.052
	High	221.23	*199.77 - 245.00*	-	-	269.00	*242.90 - 297.89*		
ULNDT-RN	Moderate	12.05	*10.66 - 13.63*			16.70	*14.77 - 18.88*		**<0.001**
	High	14.62	*12.93 - 16.52*			24.35	*21.54 – 27.53*		

CPM: conditioned pain modulation, MIPM: manipulation induced pain modulation, PPT: pressure pain threshold, PFG: pain free grip, ULNDT: upper limb neurodynamic test- radial nerve bias, 95%CI: 95% confidence interval. *pre-post MIPM. Level of significance, p<0.05

Table 6.6 Regression models for EIA and CPM analgesia within different time points adjusted for baseline PPT

^{EIA} PPT (time point) vs. ^{CPM} PPT (time point)	Partial correlation coefficient (r)	Regression coefficient B	Standard error (B)	95%CI (B)	Adjusted R^2	p (r)	p (B)	p (F-test)
^{EIA} PPT Wrist vs. ^{CPM}PPT Wrist During	0.90	0.70	0.04	0.62 - 0.79	0.94	**<0.001**	**<0.001**	**<0.001**
^{EIA} PPT Elbow vs. ^{CPM}PPT Elbow During	0.92	0.88	0.05	0.79 - 0.98	0.92	**<0.001**	**<0.001**	**<0.001**
^{EIA} PPT Wrist vs. ^{CPM} PPT Wrist Post	0.90	0.72	0.04	0.63 - 0.80	0.95	**<0.001**	**<0.001**	**<0.001**
^{EIA} PPT Elbow vs. ^{CPM} PPT Elbow Post	0.93	0.86	0.04	0.77 - 0.94	0.93	**<0.001**	**<0.001**	**<0.001**

CPM: conditioned pain modulation, MIPM: manipulation induced pain modulation, PPT: pressure pain threshold, 95%CI: 95% confidence interval. Level of significance, $P<0.05$

Table 6.7 Regression models for EIA and MIPM analgesia within different time points adjusted for baseline PPT

EIA PPT (time point) vs. MIPM PPT (time point)	Partial correlation coefficient (r)	Regression coefficient B	Standard error (B)	95%CI (B)	Adjusted R^2	p (r)	p (B)	p (F-test)
EIA PPT Wrist vs. MIPM PPT Wrist During	0.86	0.60	0.05	0.51 - 0.69	0.93	**<0.001**	**<0.001**	**<0.001**
EIA PPT Elbow vs. MIPM PPT Elbow During	0.68	0.58	0.08	0.42 - 0.73	0.73	**<0.001**	**<0.001**	**<0.001**
EIA PPT Wrist vs. MIPM PPT Wrist Post	0.86	0.59	0.04	0.51 - 0.68	0.93	**<0.001**	**<0.001**	**<0.001**
EIA PPT Elbow vs. MIPM PPT Elbow Post	0.86	0.75	0.05	0.64 - 0.85	0.89	**<0.001**	**<0.001**	**<0.001**

CPM: conditioned pain modulation, MIPM: manipulation induced pain modulation, PPT: pressure pain threshold, CI: confidence interval. Level of significance, $p<0.05$

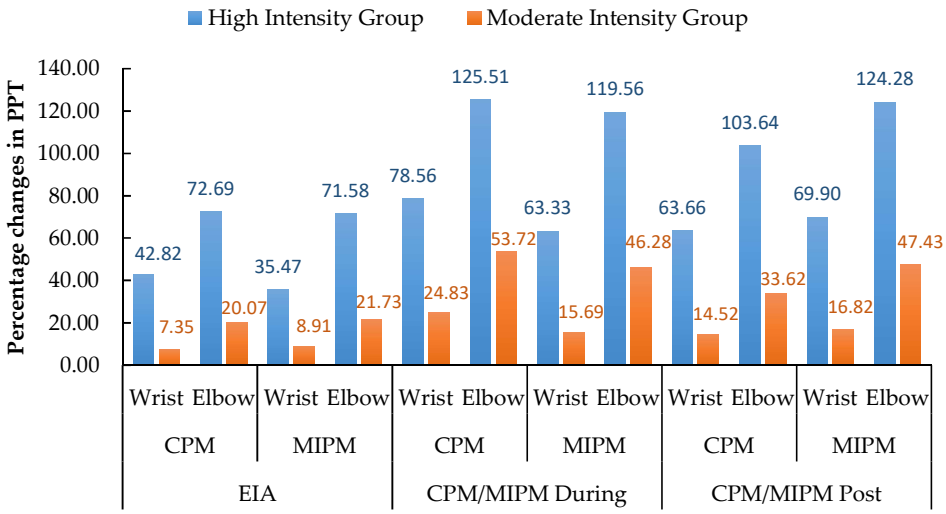

Figure 6.4 Percentage change in PPT at the wrist and elbow from Baseline 1 (pre-cycling) to each time-point: post cycling (EIA effect), during CPM/MIPM, post CPM/MIPM.

6.4. **Discussion**

This study showed that participants with lateral epicondylalgia (LE) demonstrated a significant increase in PPT (analgesic response) at both a local (elbow) and more distant test site immediately post aerobic exercise indicating an exercise induced analgesia (EIA) response, regardless of exercise intensity. Participants also showed a significant CPM and MIPM response immediately following both moderate and high intensity aerobic exercise. Significantly higher levels of analgesia as indicated by higher PPT measures were however seen for the high intensity aerobic exercise group at each time-point post exercise and during CPM and MIPM testing. The study further showed that the EIA response was significantly correlated with the analgesic response induced by both CPM and MIPM.

To our knowledge, this is first study to investigate the effect of aerobic exercise on pain sensitivity in LE. The results showed a significant increase in PPT at

the wrist and elbow and therefore a significant generalised hypoalgesic effect of exercise-induced analgesia (EIA). This supports other studies reporting a significant EIA response following aerobic exercise in healthy participants (Kodesh & Weissman-Fogel 2014; Koltyn 2000; Naugle, Fillingim & Riley 2012) and in chronic pain conditions such as rheumatoid arthritis (Meeus et al. 2015), and chronic low back pain (Hoffman et al. 2004; Meeus et al. 2010). In further agreement with previous studies, our study showed significant EIA responses at remote non-exercising locations (i.e. wrist and elbow) (Koltyn et al. 1996; Naugle et al. 2014). This appears to indicate a generalised pain inhibitory effect (Vaegter et al. 2015). However, it must be noted that other research has reported a dysfunctional EIA response after aerobic exercise (i.e. increase rather than decrease in pain sensitivity) in chronic fatigue syndrome (Meeus et al. 2010) and other chronic pain conditions such fibromyalgia (Meeus et al. 2015) and chronic whiplash associated disorder (Van Oosterwijck et al. 2012). It may therefore be that the effect of aerobic exercise on pain sensitivity, and thus the functionality of endogenous analgesia varies between chronic pain conditions (Vaegter, Handberg & Graven-Nielsen 2016) and possibly even between individuals with the same condition (Fingleton, Smart & Doody 2017). This requires further investigation.

This study was similar to the previous studies (Chapters 4 and 5) and other published research (as discussed in Chapter 4, Section 4.4), that demonstrated an efficient CPM effect in a patient population with LE. This however contradicts findings from a study by Lim, Sterling and Vicenzino (2017) as previously discussed in the same section.

Further, all participants in this study showed an immediate and efficient MIPM effect following cervical lateral glide (CLG) that is in agreement with previous studies (Chapter 4 and 5) and other research reports outlined in Chapter 4, Section 4.4. This reduction in pain sensitivity away from the site of

intervention suggest that central mechanisms are implicated in MIPM analgesia (Vicenzino et al. 1998a).

In this study CPM analgesia was also demonstrated at distant (and contra-lateral) wrist and elbow regions. The parallel temporal (i.e. pre and post CPT/CLG) and spatial (i.e. at the wrist and elbow) patterns observed for both CPM and MIPM analgesia (and EIA) may indicate that they are potentially mediated by similar neurophysiological mechanisms. However, further clarification is needed across a range of healthy and clinical populations.

The findings of this study indicated reduced pressure pain sensitivity (EIA) after both moderate (50% HRmax) and high intensity (75% HRmax) aerobic cycling, although with a greater hypoalgesic effect induced after high intensity exercise. This is consistent with Naugle et al. (2014) who showed a similar increase in PPT after similar exercise protocols in healthy, pain free individuals and it has also been reported in chronic pain states such as fibromyalgia (Newcomb et al. 2011). However, other studies have reported a significant increase in PPT only after high intensity aerobic exercise (Hoffman et al. 2004; Vaegter, Handberg & Graven-Nielsen 2014). Possible reasons for this discrepancy could be related to methodological differences such as lack of controls and unmasking of assessors in these earlier studies. Our study specifically addressed these issues by including a control comparison and maintaining strict assessor blinding.

The finding from our study of a strong significant correlation between MIPM and EIA, to the best of our knowledge has not be previously reported. However, the correlation between CPM and EIA in participants with LE shown in our study is in agreement with other recent findings in pain-free individuals (Lemley, Hunter & Bement 2015; Vaegter et al. 2015), although the correlations in our study were stronger. Again there were methodological

differences between studies in the CPM protocol used. In Lemley, Hunter and Bement (2015), CPM effect was assessed using pressure pain threshold at the finger as the test stimulus and cold water immersion of the foot as the conditioning stimulus. Vaegter et al. (2015) applied a similar CPM protocol to ours but used different PPT test sites, measuring at exercising and non-exercising muscles (biceps and quadriceps) whereas our study measured PPT at remote, non-exercising, sites (wrist and lateral epicondyle). Although CPM analgesia has previously been found to predict EIA (Ellingson et al. 2014; Lemley, Hunter & Bement 2015; Stolzman & Bement 2016), our study appears to be the first to show that an aerobic EIA model predicts both CPM and MIPM analgesia. This implies that participants who exhibited higher levels of EIA demonstrated greater analgesia during and post CPM and MIPM. This also suggests the possibility that MIPM analgesia may be enhanced by a preliminary bout of aerobic exercise.

CPM as a mechanism was previously proposed to mediate EIA by Ellingson et al. (2014). The authors compared the responses to pain sensitivity following three exercise sessions: painful, non-painful and quiet rest. In the painful exercise session, the authors used pressure cuffs to induce quadriceps muscle pain (as a conditioning stimulus) to inhibit heat pain sensitivity (test stimulus). A significant EIA (reduced pain sensitivity to heat) was induced during both painful and non-painful aerobic exercise sessions, with higher levels of EIA observed after the painful aerobic exercise. As EIA was induced after non-painful exercise, the authors suggested that CPM could partially contribute to EIA. Our exercise protocol only assessed perceived exertion rather than pain during the aerobic exercise and therefore we do not have sufficient data to assess whether any of the exercise was painful, although none of the participants spontaneously reported exercise related pain (some did report pain related to sitting on the saddle and holding the bike handle bars). None

the less, significantly stronger CPM analgesia was induced in the current study after high intensity exercise compared with moderate intensity, exercise suggesting a greater additive effect of CPM and MIPM on EIA when the exercise is more strenuous. Future studies could be directed towards further evaluating the potential for additive or synergistic analgesic effects when combining exercise with CPM or MIPM.

The comparable multi-segmental effects of EIA, CPM and MIPM suggest a potential overlap in the neurophysiological mechanisms. Evidence from several studies suggest that EIA is mediated by a non-opioid mechanism. In human studies, aerobic exercise has been shown to activate both sympathetic responses (i.e. increased HR and blood pressure) and analgesia (Koltyn & Umeda 2006), as has CPM (Chalaye et al. 2013; Chalaye et al. 2014), and MIPM (Chiu & Wright 1996; Sterling, Jull & Wright 2001; Vicenzino et al. 1998a; Vicenzino et al. 1998b; Vicenzino, Collins & Wright 1996; Vicenzino et al. 1995). Further, an elevation in levels of serotonin after aerobic exercise has been reported (Soares, Naffah-Mazzacoratti & Cavalheiro 1994; Steinberg et al. 1998). Serotonin has similarly been found to be involved in both CPM (Yarnitsky 2015), and MIPM (Skyba et al. 2003) analgesia. In support of this, administration of naloxone (an opioid antagonist) has been shown not to reverse the analgesia induced by aerobic exercise (Droste et al. 1991), CPM (Edwards, Ness & Fillingim 2004; Hermans et al. 2018; Peters et al. 1992), or MIPM (Paungmali et al. 2004; Vicenzino et al. 2000; Zusman, Edwards & Donaghy 1989), suggesting a non-opioid mechanism. However, other studies have reported that naloxone did reverse the analgesia induced after aerobic exercise (Haier, Quaid & Mills 1981; Janal et al. 1984; Olausson et al. 1986), or CPM (King et al. 2013; Pertovaara et al. 1982; Willer, Le Bars & De Broucker 1990) suggesting an involvement of the endogenous opioid system. The extent

to which opioidergic mechanisms are involved in EIA, CPM or MIPM-induced analgesia is therefore still unclear and warrants further investigation.

6.5. **Clinical implications**

Clinicians should consider assessment of EIA in chronic pain populations when utilising manual therapy or aerobic exercise as a treatment option to enhance descending analgesia. A simple aerobic exercise task (even at moderate intensity only) could be applied to calculate EIA and so predict the extent to which a manual therapy intervention may reduce pain in an individual with chronic pain. Equally, aerobic exercise could be used to potentiate MIPM analgesia. This would be clinically valuable for those clinicians who often combine different treatment modalities to manage musculoskeletal pain.

6.6. **Limitations**

There are some limitations for this study that must be acknowledged. First, this study did not include a non-exercising control group, although a previous study by our research group (reported in Chapter 4) has shown a strong CPM and MIPM response in people with LE without any intervention. Second, the true intensity of aerobic cycling sessions was not objectively measured using an exhaustive laboratory fitness test (such as VO2max) but it was estimated using a vicarious age-predicted HRmax calculation. Perceived and objective exercise intensity was closely monitored during the exercise session using the Borg RPE and HR. This allowed for adequate differentiation between the moderate and high intensity levels of exercise, as shown by the differences in values between groups. Third, the study did not assess the impact of psychological factors on EIA (e.g. expectation of the effect of exercise, pain catastrophizing) that needs to be considered in the interpretation of the results.

It must be acknowledged that the findings of this study cannot be generalised to other chronic musculoskeletal pain populations other than LE. Finally, the study only measured the immediate effects of a single session of aerobic exercise on CPM and MIPM analgesia. Therefore, there is uncertainty about whether similar results would be demonstrated over longer follow-ups, following single or multiple aerobic exercise sessions. It is recommended to address these issues in future research.

6.7. **Conclusion**

The present study demonstrated that a single session of aerobic cycling exercise reduced pressure pain sensitivity in people with LE. It also showed that high intensity aerobic exercise enhanced CPM and MIPM analgesic responses. Further, EIA responses were significantly correlated with CPM and MIPM responses in this group with LE, and the level of EIA response was predictive of the level of CPM and MIPM response. This suggests that there may be an overlap in the neurophysiological mechanisms mediating EIA, CPM and MIPM.

Chapter 7: **Discussion**

The primary objective of this thesis was to improve our knowledge and understanding of the relationship between CPM and MIPM analgesia through a series of experimental studies aiming to explore and highlight similarities and differences in the patterns of the analgesic responses to CPM and MIPM. This thesis has presented a series of four studies. The first study (Chapter 3) established the reliability of PPT (the main outcome measure) measurements over the assessment timeframe for the subsequent studies, the duration of CPM after-effect to determine the rest period between CPM and MIPM protocols, and the minimal sample size necessary for the subsequent studies. This was followed by a quasi-experimental one-group, repeated measures study (Study 2, Chapter 4) investigating the extent of CPM and MIPM analgesic effect in a sample of participants with LE and the association between the two phenomena. This study also investigated whether there was a difference in MIPM analgesia between CPM responders and non-responders. Study 3 (Chapter 5) was a randomised controlled trial (RCT) comparing the effect of an enhanced empathetic interaction to that of a neutral (business-like) interaction on CPM and MIPM analgesia in participants with LE. The final study (RCT) compared the EIA effect of moderate and high intensity aerobic cycling in people with LE and examined its potential additive analgesic effect on CPM and MIPM analgesia. The study also assessed associations between levels of analgesia induced by aerobic exercise, CPM and MIPM.

7.1. **The analgesic effect of CPM and MIPM**

The studies presented in Chapters 4, 5 and 6 of this thesis are the first studies to consistently show an increase in homotopic (ipsilateral) PPT at the elbow and wrist, denoting a functioning CPM effect and MIPM effect, and indicating

that pain inhibitory systems function effectively in people with LE. One recent study (Lim, Sterling & Vicenzino 2017) conflicts with these findings in reporting that a CPM response was impaired in the same clinical group. The difference between these findings may be attributed to methodological differences in the CPM protocol used. This was discussed in detail in Chapter 4 (Section 4.4). As far as MIPM effect is concerned, the current work has also confirmed findings from previous literature regarding the effectiveness of the CLG mobilisation technique in reducing elbow pain in LE. In addition the studies have provided a new finding that CLG has a widespread analgesic effect in LE, demonstrating increased PPT also at the pain-free ipsilateral wrist.

The findings from these studies demonstrated that CPM and MIPM share similar patterns of response whilst also differing in several aspects. Robust multi-segmental increases in PPT measures (wrist and elbow) during and post CPT and CLG were seen in both the CPM and MIPM protocols and across all studies. Higher levels of CPM and MIPM analgesia were observed at the wrist compared to the elbow in Studies 2 and 3. However, the analgesic responses were higher at the elbow test site compared to the wrist test site in Study 4. This finding is hard to explain and it would need to be clarified with additional data. Further, the increase in PPT and thus the analgesic response, was significantly greater during CPM than during MIPM (assessed in Study 2). CPT is an intense and potentially painful stimulus (Yarnitsky 2015) while the CLG mobilisation is pain free (Vicenzino et al. 1999). CPT acts as a stressor that suddenly triggers autonomic nervous system responses and leads to release of noradrenaline (Silverthorn & Michael 2013). On the other hand, CLG is a relaxing stimulus (similar to massage) that increases general well-being responses and release of serotonin (5-HT) (Field et al. 2005). This could explain the stronger analgesic responses associated with CPM compared to MIPM.

Similar patterns of analgesic responses during CPM and MIPM were observed in the empathetic interaction study (Study 3) and the aerobic exercise study (Study 4). While there was no significant difference between the levels of CPM and MIPM analgesia post CPT and CLG mobilisation (assessed in Study 2), the pattern of analgesic response reduced rapidly after the CPT stimulus while it remained relatively steady after the CLG mobilisation. Therefore, while the MIPM analgesia appears to be less than for CPM, its effect is longer lasting

Despites these differences in the patterns of CPM and MIPM analgesia, both CPM and MIPM appear to share similar temporal (i.e. during and after CPM/MIPM) and spatial manifestations (i.e. wrist and elbow). This suggests that they could be potentially mediated by common neurophysiological mechanisms but with some differences in the individual modulatory pathway. This requires further exploration. Moreover, these observations are based on the immediate analgesic responses measured at defined time points assessed during these investigations. Therefore, it is unknown how and in what way they will differ over a longer timeframe (i.e. after a single session of CPM or MIPM) in people with LE. Further research measuring these analgesic responses over a longer follow-up period in this patient population is warranted.

7.2. **The analgesic effect of aerobic exercise**

In the aerobic exercise study (Study 4), for the first time in people with LE an acute bout of aerobic cycling was shown to produce an analgesic effect (increase in PPT) at remote test sites not being activated during the exercise (wrist and elbow). This finding indicates that the EIA response is intact in this sample of patients with LE. Although it is notable that both exercise intensities induced EIA, compared to moderate intensity cycling, high intensity cycling produced higher levels of analgesia, indicating a dose response relationship.

The remote effect of aerobic exercise indicates that central pain inhibitory systems play a role in EIA (Vaegter et al. 2015). These findings were based on the immediate influence of a single 15 minute aerobic exercise session at a specific intensity. Further research is recommended into the effect of multiple aerobic exercise sessions on EIA.

7.3. **The Association between different forms of endogenous analgesia**

An important finding in the association study (Study 2) and the aerobic exercise study (Study 4) was the significant association in people with LE between the natural forms of analgesia under investigation. Study 2 reported significant moderate and positive association between CPM and MIPM analgesia. This association was measured at the wrist and elbow sites during and post CPT (CPM) and CLG mobilisation (MIPM). Previous investigations were confined to the association between CPM analgesia and EIA (Lemley, Hunter & Bement 2015; Vaegter et al. 2015). Another important finding was that the strong positive association between aerobic EIA and CPM, and between aerobic EIA and MIPM in Study 4. The association between CPM analgesia and EIA was larger in the aerobic exercise study than that described by Lemley, Hunter and Bement (2015) and Vaegter et al. (2015). This variation may be attributable to differences in methodological factors related to study design, testing parameters, and research sample recruited. However, additionally Study 4 found a strong association between EIA and MIPM analgesia, a new finding that has not been previously reported.

Previous studies have also reported that CPM analgesia is predictive of EIA (Ellingson et al. 2014; Lemley, Hunter & Bement 2015; Stolzman & Bement 2016), a finding that was replicated in the current study. To our knowledge though, the association study (Study 2) is the first study to show that CPM is

a significant predictor of MIPM analgesia, and the aerobic study (Study 4) is the first to report that EIA is a significant predictor of both CPM and MIPM analgesia. These findings provide further evidence that CPT, CLG, and aerobic exercise may activate similar pain modulatory mechanisms involving the descending inhibitory pathways. Further studies verifying similar findings in different patient populations should be carried out.

Findings from the aerobic exercise study showed that aerobic exercise induced an analgesic response at the wrist and elbow, a similar manifestation (temporal and spatial) to that reported for CPM and MIPM. These observations enable us to hypothesise that these natural forms of EA may be mediated by common neurophysiological mechanisms in the central nervous system. These findings suggest the potential use of CPM to predict response to MIPM in the clinical setting when considering manual therapy as a treatment option for musculoskeletal pain. Further long term clinical trial studies in this area are recommended.

7.4. **CPM responders and non-responders analysis**

The association study (Study 2) highlighted the importance of individual variations in CPM response by demonstrating that participants can be divided into two distinct CPM groups: responders and non-responders. The CPM responders group exhibited more robust MIPM analgesia compared to the CPM-non-responders. This finding further supports the link between CPM and MIPM analgesia, suggesting again that they may be controlled by common descending inhibitory systems.

Although the proportion of CPM-non responders in this study was very small (11.4%) compared with CPM responders (88.6%), the difference in MIPM analgesia between both CPM groups was statistically significant. This indicates that responders vs non-responders analysis is a sensitive and robust

method (Rankin & Stokes 1998) for assessing the effectiveness of pain interventions. The CPM responders and non-responders analysis could be also applied to EIA in future studies.

7.5. **Effect of psychological and physical manipulation on CPM and MIPM**

This study provided evidence, for the first time, that both CPM and MIPM analgesia can be enhanced by both psychological and physical manipulation. In Study 3, the enhanced empathetic interaction group experienced significantly higher levels of CPM and MIPM analgesia compared with the neutral interaction group. This study supports the potential clinical benefit of a positive patient-therapist interaction in enhancing analgesia. Further studies are required to evaluate whether creating a more positive clinical interaction might result in better clinical outcomes from more prolonged periods of treatment.

In Study 4, the high intensity aerobic cycling group exhibited significantly higher levels of CPM and MIPM analgesia than the moderate intensity group. This study provides further evidence that high intensity aerobic exercise can be used as an additive intervention to enhance pain-relieving treatments in patients with chronic musculoskeletal pain, and is shown for the first time in LE. However, the extent to which these positive effects last is currently unknown. Therefore, there is a need to conduct further studies investigating the change in these analgesic responses over longer periods.

Based on these findings, it appears that enhanced empathetic interaction and high intensity cycling can both potentiate CPM and MIPM analgesia in a similar way. Again, this provides an indication that both CPM and MIPM analgesia may be mediated by common mechanisms linked to the descending pain modulatory systems.

7.6. **Summary of limitations**

- LE was used as a clinical model to represent other conditions with chronic pain. Owing to the complexity of chronic pain states, the generalisability of the findings of the studies in this thesis to other chronic pain conditions is limited.

- Due to the experimental nature of these studies, there may be questions about the extent of applicability of the findings to clinical settings.

- Only short term analgesic responses of CPM and MIPM were measured in these studies. Therefore, the pattern of these analgesic responses over longer follow-up periods cannot be determined.

- Although communications with the participants were standardised at all times in these studies, the influence of participants' expectations on their analgesic responses and/or instructions could not be ruled out. This was particularly relevant to Studies 1 (the reliability study) and 2 (the association study) where CPM and MIPM analgesia was not manipulated by an additional intervention.

- The association study (Study 2) was a single-arm trial that investigated the association between CPM and MIPM analgesia. This design (quasi-experimental) is associated with threats to internal validity (bias) such as lack of randomisation and the potential regression to the mean (Harris et al. 2006). However, the study was mainly intended to find the association between CPM and MIPM analgesia as a starting point before introducing the experimental manipulation in the subsequent study (the empathetic interaction study, Study 3). There were efforts made to minimise possible sources of bias such as: ensuring adequate sample size, using clear-cut inclusion and exclusion criteria, and

administering the experimental procedure and data collection in a consistent way.

- Studies 3 and 4 (the empathetic interaction study and the aerobic exercise study, respectively) used post-test only control group design. So neither group was pretested for CPM or MIPM. While pre-intervention (baseline) CPM and MIPM assessments would allow for better understanding of the differential effects of the intervention observed, pre-intervention assessment of CPM and MIPM responses could have influenced participants' analgesic responses during the intervention studies (empathetic interaction and aerobic exercise).

- Study 3 sought to compare between the influence of two types of interaction on CPM and MIPM analgesia. Although there was a statistical difference in CARE Measure scores between the groups, a more distinct difference between the interaction interventions could have been achieved by subgrouping people using a cut-off value of the CARE score. This was not performed since an appropriate cut-off value of the CARE Measure has not been determined.

- In Study 2 and 3, MIPM always came after CPM (i.e. order effect), it is possible that the effects of MIPM were systematically influenced by the preceding CPM – it may have enhanced (or limited) the MIPM response. However, the sufficient washout period (determined in Study 1) followed the CPM protocol should have minimised this effect. Further, statistical models also dealt with CPM and MIPM data separately.

- In Study 4, CPM and MIPM protocols were assessed over 2 test days, with an interval of 3 days, and randomised to eliminate possible order effect. While the CPM after-effect was determined in Study 1, the

washout out period after the MIPM or EIA protocols was not determined. The duration of the rest period was decided based on clinical judgment that 3 days would be the minimum reasonable time for an adequate recovery (associated with less chance for dropouts and reduced post exercise soreness) before starting the second aerobic exercise session. Additionally, this was based on previous studies (Moss, Sluka & Wright 2007; Vicenzino et al. 1998b; Vicenzino, Collins & Wright 1996) where at least 24 hours was allowed between mobilisation conditions.

7.7. **Recommendations for future research**

Taking into consideration the findings presented in this thesis, some important areas for future work have been highlighted below:

- In the light of the positive results achieved in this series of studies (i.e. Studies 2, 3, 4) using LE, equivalent clinical trials are necessary to evaluate whether a similar influence on CPM and MIPM endogenous analgesia could be obtained in different chronic musculoskeletal states.

- In these studies, short term analgesic responses (PPT) of CPM and MIPM were evaluated. It would be important from a clinical point of view to determine what changes would occur in the pattern of analgesic responses over longer follow-ups.

- The current thesis explored the one-hour effects of a single CPM session (Study 1). The MIPM effects from a single session could also be explored in a similar way in future research. For Study 4, this would clearly rule out possible carryover effects from MIPM protocol to CPM protocol.

- Results from Study 2 suggest that CPM could potentially be a useful predictor for MIPM response in the clinical setting. Pre manual therapy CPM assessment could also be used to identify responders and non-responders in advance of treatment. It would be useful of conduct a longer term study to determine if CPM testing could accurately identify MIPM responders and non-responders.

- Studies 3 and 4 assessed CPM and MIPM analgesia in response to empathetic interaction and aerobic exercise interventions, respectively. Future studies could assess pre-interventions CPM and MIPM and then allow a period of time before conducting post-interventions CPM and MIPM protocols to reduce the effect of testing.

- In Study 4, the influence of a single session of aerobic exercise on LE and CPM and MIPM analgesia was assessed. It would be beneficial to investigate the effect of a course of multiple aerobic exercise sessions on EIA, CPM and MIPM analgesia.

- It would also be appropriate to consider undertaking a future study using a pharmacological intervention such as duloxetine, a selective 5-HT and NA reuptake inhibitor (SNRI) (Lyengar et al. 2004) to evaluate the influence it has on CPM and MIPM analgesia. An appropriate musculoskeletal model for testing would need to be identified where there is already some evidence for the effect of duloxetine and at least one of the interventions (i.e. CPM and MIPM). Using the same methodologies, participants could attend for CPM and MIPM assessment protocols before and following a course of duloxetine therapy or a control intervention. The patterns of analgesic responses to CPM and MIPM could then be analysed to determine whether duloxetine could effectively enhance MIPM.

- In this thesis, similar variations in the patterns of CPM and MIPM analgesia were observed in a series of experimental paradigms to support the hypothesis that CPM and MIPM analgesia is mediated by descending inhibitory systems. However, due to ethical considerations differential control of the system (i.e. involvement of serotonergic and adrenergic pathways) cannot be investigated in humans. One area of future research is to apply the same methodologies in a pharmacological trial using an animal model (e.g. rats). Selective serotonergic reuptake inhibitors/agonists and/or noradrenergic receptors agonists/antagonists could then be systemically or intrathecally injected to investigate/manipulate the DNIC/CPM and MIPM analgesic effects in an equivalent way, to determine whether the responses are blocked by similar pharmacological interventions.

7.8. **Original contribution to knowledge**

- The reliability and duration of CPM effect in Study 1 provided essential data related to the reliability of PPT measurements at the wrist and elbow sites, and for the first time, the duration of the meaningful CPM effect, and sample size calculations that had a methodological significance to the subsequent studies.

- The association study (Study 2) is the first study to find an intact CPM effect in people with LE.

- Study 2 was also the first study to report a difference in MIPM analgesia based on (CPM effect) responders vs non-responders analysis for a different form of analgesia.

- Study 2 was also the first to report a remote analgesic response (PPT) in response to CPM and MIPM over the asymptomatic ipsilateral wrist in LE.

- Study 2 also provided the first evidence of an association between CPM and MIPM analgesia in people with musculoskeletal pain and first to report the use of CPM to predict MIPM analgesia.

- The empathetic interaction study (Study 3) was the first study to selectively assess and manipulate the therapist (RA)/patient interaction to objectively show the positive influence of an enhanced empathetic interaction on CPM and MIPM analgesia in participants with LE.

- The aerobic exercise study (Study 4) was the first study to investigate the analgesic effect of aerobic exercise in LE and to show the positive multi-segmental aerobic EIA in this clinical group.

- Study 4 was the first study to investigate and demonstrate an association between EIA and MIPM.

- Study 4 also showed the positive influence of high intensity aerobic exercise on CPM and MIPM analgesic responses in participants with LE.

- Study 4 was also the first study to demonstrate that aerobic EIA is predictive of both CPM and MIPM analgesia in participants with LE.

- The studies in this thesis show that analgesia induced by CPT, CLG and aerobic exercise exhibits similar patterns of analgesic responses suggesting that there is likely to be a considerable overlap between the neurophysiological mechanisms mediating each form of EA.

- In clinical practice clinicians tend to combine interventions to obtain greater positive treatment outcomes. The findings in this thesis support the use of this (multimodal) approach to manage clinical pain conditions, in that there is evidence for enhanced analgesic responses as a result of combining different modalities.

7.9. **Conclusions**

Repeated PPT measures (Chapter 3) showed excellent intra-class correlational coefficients (ICCs: 0.991 and 0.986) at two test sites: the wrist and elbow, respectively. The CPM pattern of analgesic responses showed that PPT returned to baseline measurement after 5 minutes post cold water immersion.

The association study (Chapter 4) demonstrated an immediate significant increase (relative to baseline) in all CPM and MIPM measures of analgesia over different time points. PPT measures of CPM and MIPM were significantly, moderately and positively associated at the elbow and wrist. CPM analgesia was shown to significantly predict MIPM analgesia consistently at both test sites. There was also a significant difference in MIPM analgesia between CPM responders and non-responders, with higher levels of analgesia measured for CPM responders. However, there was no significant difference between both CPM groups in the secondary outcome measures of MIPM. That finding is likely attributable to the difference in the sample size between responders (n=62) and non-responders (n=8). The results of this study suggested that CPM and MIPM may activate similar neurophysiological mechanisms in the descending inhibitory system.

The RCT manipulating the RA/participant interaction (Chapter 5) found that all participants experienced an immediate significant increase in CPM and MIPM analgesia (including PFG and ULNDT-RN). However, higher levels of CPM and MIPM analgesia were demonstrated at the wrist and elbow sites

(excluding PFG and ULNDT-RN) for those participants who were in the enhanced empathetic interaction group. The study concluded that a single session of enhanced empathetic interaction significantly potentiated the CPM and MIPM analgesia (in a similar way). This suggests that when CPM and MIPM analgesic effects are combined with enhanced empathetic interaction they produce an increased analgesic effect. These results may indicate that both forms of analgesia induced by CPM and MIPM are potentially accessing the same central pain control systems in the descending pathways.

The final RCT manipulating the intensity of aerobic exercise showed that both aerobic exercise groups (i.e. the high and moderate intensity) demonstrated an immediate significant increase in EIA, CPM and MIPM analgesia at both test sites. However, significantly higher levels of analgesia (i.e. EIA, CPM and MIPM analgesia, excluding PFG) were reported for the high intensity aerobic exercise group. EIA analgesia was significantly and positively associated with MIPM and CPM analgesia. EIA was found to be a significant predictor of CPM and MIPM analgesia. The results of this study indicate that a single bout of high intensity exercise (similarly) enhanced the CPM and MIPM analgesic responses. It also suggests a common link between the neurophysiological mechanisms in the descending system mediating the initial analgesic effect of aerobic exercise, CPT and CLG mobilisation.

This series of experimental studies provide further evidence that CPM and MIPM produce natural forms of EA. They appeared to have comparable analgesic responses as demonstrated in these investigations. They also appeared to be similarly influenced (enhanced) by psychological (enhanced empathetic) factors and physical interventions (aerobic exercise). These observations (combined with the available research evidence) suggest that CPM and MIPM may share similar underlying neurophysiological mechanisms in the central descending pain inhibitory systems. Further

research should be carried out to investigate this possibility in suitable animal models.

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Appendices

Appendix 1: Curtin Human Research Ethic (HREC) Approvals

Curtin University

Office of Research and Development

GPO Box U1987
Perth Western Australia 6845

Telephone +61 8 9266 7863
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Web research.curtin.edu.au

13-Jun-2017

Name: Tony Wright
Department/School: School of Physiotherapy and Exercise Science
Email: T.Wright@curtin.edu.au

Dear Tony Wright

RE: Amendment approval
Approval number: HRE2016-0181

Thank you for submitting an amendment request to the Human Research Ethics Office for the project **A pilot study: Assessment of meaningful CPM effect and pattern of analgesic responses in pain-free normal participants**.

Your amendment request has been reviewed and the review outcome is: **Approved**

The amendment approval number is HRE2016-0181-01 approved on 13-Jun-2017.

The following amendments were approved:
Phase 1: PPT test-retest protocol In addition to the right wrist test site, a point on the right elbow will be used as a measurement site, approximately 2.5 cm distal to the lateral epicondyle. Measurements at each test site (i.e. wrist and elbow) will be taken at baseline, at 1 min, at 3 min and at 5 min. Three PPT measurements will be taken at each time point with a 10-15 seconds intervals between each. Mean values will then be used in analysis.

Any special conditions noted in the original approval letter still apply.

Standard conditions of approval

1. Research must be conducted according to the approved proposal
2. Report in a timely manner anything that might warrant review of ethical approval of the project including:
   - proposed changes to the approved proposal or conduct of the study
   - unanticipated problems that might affect continued ethical acceptability of the project
   - major deviations from the approved proposal and/or regulatory guidelines
   - serious adverse events
3. Amendments to the proposal must be approved by the Human Research Ethics Office before they are implemented (except where an amendment is undertaken to eliminate an immediate risk to participants)
4. An annual progress report must be submitted to the Human Research Ethics Office on or before the anniversary of approval and a completion report submitted on completion of the project
5. Personnel working on this project must be adequately qualified by education, training and experience for their role, or supervised
6. Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, that bears on this project

7. Changes to personnel working on this project must be reported to the Human Research Ethics Office
8. Data and primary materials must be retained and stored in accordance with the Western Australian University Sector Disposal Authority (WAUSDA) and the Curtin University Research Data and Primary Materials policy
9. Where practicable, results of the research should be made available to the research participants in a timely and clear manner
10. Unless prohibited by contractual obligations, results of the research should be disseminated in a manner that will allow public scrutiny; the Human Research Ethics Office must be informed of any constraints on publication
11. Ethics approval is dependent upon ongoing compliance of the research with the Australian Code for the Responsible Conduct of Research, the National Statement on Ethical Conduct in Human Research, applicable legal requirements, and with Curtin University policies, procedures and governance requirements
12. The Human Research Ethics Office may conduct audits on a portion of approved projects.

Should you have any queries regarding consideration of your project, please contact the Ethics Support Officer for your faculty or the Ethics Office at hrec@curtin.edu.au or on 9266 2784.

Yours sincerely

[redacted]

Dr Catherine Gangell
Manager, Research Integrity

Curtin University

Office of Research and Development

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Perth Western Australia 6845

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Web research.curtin.edu.au

03-Aug-2016

Name: Anthony Wright
Department/School: School of Physiotherapy and Exercise Science
Email: T.Wright@curtin.edu.au

Dear Anthony Wright

RE: Ethics approval
Approval number: HRE2016-0175

Thank you for submitting your application to the Human Research Ethics Office for the project **A comparison of conditioned pain modulation and manipulation induced pain modulation effects in participants with tennis elbow**.

Your application was reviewed through the Curtin University low risk ethics review process.

The review outcome is: **Approved**.

Your proposal meets the requirements described in National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)*.

Approval is granted for a period of one year from **03-Aug-2016** to **02-Aug-2017**. Continuation of approval will be granted on an annual basis following submission of an annual report.

Personnel authorised to work on this project:

Name	Role
Muhsen, Ahmad AARM	
Wright, Anthony A	
Moss, Penny	
Gibson, William	

Standard conditions of approval

1. Research must be conducted according to the approved proposal
2. Report in a timely manner anything that might warrant review of ethical approval of the project including:
    - proposed changes to the approved proposal or conduct of the study

- unanticipated problems that might affect continued ethical acceptability of the project
- major deviations from the approved proposal and/or regulatory guidelines
- serious adverse events

3. Amendments to the proposal must be approved by the Human Research Ethics Office before they are implemented (except where an amendment is undertaken to eliminate an immediate risk to participants)
4. An annual progress report must be submitted to the Human Research Ethics Office on or before the anniversary of approval and a completion report submitted on completion of the project
5. Personnel working on this project must be adequately qualified by education, training and experience for their role, or supervised
6. Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, that bears on this project
7. Changes to personnel working on this project must be reported to the Human Research Ethics Office
8. Data and primary materials must be retained and stored in accordance with the Western Australian University Sector Disposal Authority (WAUSDA) and the Curtin University Research Data and Primary Materials policy
9. Where practicable, results of the research should be made available to the research participants in a timely and clear manner
10. Unless prohibited by contractual obligations, results of the research should be disseminated in a manner that will allow public scrutiny; the Human Research Ethics Office must be informed of any constraints on publication
11. Ethics approval is dependent upon ongoing compliance of the research with the Australian Code for the Responsible Conduct of Research, the National Statement on Ethical Conduct in Human Research, applicable legal requirements, and with Curtin University policies, procedures and governance requirements
12. The Human Research Ethics Office may conduct audits on a portion of approved projects.

Special Conditions of Approval

Please include the first sentence of the HREC statement in recruitment materials (Curtin University Human Research Ethics Committee (HREC) has approved this study (HREC number XX/XXXX)

This letter constitutes ethical approval only. This project may not proceed until you have met all of the Curtin University research governance requirements.

Should you have any queries regarding consideration of your project, please contact the Ethics Support Officer for your faculty or the Ethics Office at hrec@curtin.edu.au or on 9266 2784.

Yours sincerely

[redacted]

Dr Catherine Gangell
Manager, Research Integrity

Curtin University

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12-Jun-2017

Name: Tony Wright
Department/School: School of Physiotherapy and Exercise Science
Email: T.Wright@curtin.edu.au

Dear Tony Wright

RE: Amendment approval
Approval number: HRE2017-0198

Thank you for submitting an amendment request to the Human Research Ethics Office for the project **The influence of aerobic exercise on conditioned pain modulation (CPM) and manual therapy induced pain modulation (MIPM)**.

Your amendment request has been reviewed and the review outcome is: **Approved**

The amendment approval number is HRE2017-0198-02 approved on 12-Jun-2017.

The following amendments were approved:
Study One: Association between the analgesic effects of CPM and MIPM,
In the manipulation induced pain modulation (MIPM) assessment protocol, additional PPT measurement will be conducted during cervical mobilisation at the start of third minute of the intervention.

Any special conditions noted in the original approval letter still apply.

Standard conditions of approval

1. Research must be conducted according to the approved proposal
2. Report in a timely manner anything that might warrant review of ethical approval of the project including:
   - proposed changes to the approved proposal or conduct of the study
   - unanticipated problems that might affect continued ethical acceptability of the project
   - major deviations from the approved proposal and/or regulatory guidelines
   - serious adverse events
3. Amendments to the proposal must be approved by the Human Research Ethics Office before they are implemented (except where an amendment is undertaken to eliminate an immediate risk to participants)
4. An annual progress report must be submitted to the Human Research Ethics Office on or before the anniversary of approval and a completion report submitted on completion of the project
5. Personnel working on this project must be adequately qualified by education, training and experience for their role, or supervised
6. Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, that bears on this project

7. Changes to personnel working on this project must be reported to the Human Research Ethics Office
8. Data and primary materials must be retained and stored in accordance with the Western Australian University Sector Disposal Authority (WAUSDA) and the Curtin University Research Data and Primary Materials policy
9. Where practicable, results of the research should be made available to the research participants in a timely and clear manner
10. Unless prohibited by contractual obligations, results of the research should be disseminated in a manner that will allow public scrutiny; the Human Research Ethics Office must be informed of any constraints on publication
11. Ethics approval is dependent upon ongoing compliance of the research with the Australian Code for the Responsible Conduct of Research, the National Statement on Ethical Conduct in Human Research, applicable legal requirements, and with Curtin University policies, procedures and governance requirements
12. The Human Research Ethics Office may conduct audits on a portion of approved projects.

Should you have any queries regarding consideration of your project, please contact the Ethics Support Officer for your faculty or the Ethics Office at hrec@curtin.edu.au or on 9266 2784.

Yours sincerely

[redacted]

Dr Catherine Gangell
Manager, Research Integrity

Appendix 2: Conference Oral Presentations

- The Mark Liveris Research Student Seminar, on 28 September 2017 at Curtin University, Perth, WA.

The influence of a psychological intervention on conditioned pain modulation in participants with tennis elbow

Presented by:	Ahmad Muhsen, School of Physiotherapy and Exercise Science
Course:	Doctor of Philosophy
Supervisor	Professor Tony Wright, School of Physiotherapy and Exercise Science
A/Supervisors	Dr Penny Moss, School of Physiotherapy and Exercise Science
	Dr Will Gibson, School of Physiotherapy, University of Notre Dame

Background: Conditioned Pain Modulation (CPM) refers to a reduction in pain perception of a painful stimulus applied to one body part in response to application of a distant noxious stimulus. Recent research evidence suggests that CPM activates endogenous pain inhibitory systems to produce a natural form of analgesia. We sought to determine if a psychological intervention based on an empathetic interaction and an enhanced expectation of analgesic effect might have a positive influence on the degree of CPM that individuals with a musculoskeletal pain problem might experience.

Purpose: The main purpose of this study was to evaluate the impact of an enhanced research assistant/research participant interaction on CPM analgesic responses in a patient population with tennis elbow.

Methods: 66 participants with tennis elbow from Western Australia were recruited for the study. They were initially assigned into two groups, the enhanced interaction (n=33) and normal interaction groups (n=33). The enhanced /normal interactions were all under the control of a professional role play actor, playing the part of a research assistant. The actor was trained to provide a very empathetic and positive interaction with the research participants (enhanced interaction) or a very neutral business like interaction (neutral interaction). Participants' ratings of the interaction were determined using the Consultation and Relational Empathy (CARE) Measure. At the start, the research assistant spent 15min interacting with the participants. Immediately after the interaction, a blinded assessor (ICC (3,4)=0.99) measured pressure pain threshold (PPT) at the elbow and wrist of the symptomatic side before, during and after immersing the other arm in a bath of cold water (10°C) to evoke the CPM response. Linear mixed models were used to evaluate differences in CPM response between the interaction groups, controlling for the CARE measure and baseline PPT.

Results: There was a significant difference in the CARE scores ($p<0.001$) between the interaction groups. There was also a significant increase in PPT for all participants during CPM ($p<0.001$) and immediately post CPM ($p<0.001$), with higher level of analgesia observed for the enhanced empathetic interaction group during ($p<0.001$) and post CPM (0.002) at the elbow and wrist compared to the neutral group. A similar pattern of change in PPT was demonstrated at both measurement sites (wrist and elbow) during and immediately post CPM.

Conclusion: The current study showed that an empathetic interaction and an enhanced expectation of analgesia positively influence CPM pain responses in people with tennis elbow. Further research is recommended into the effect of a longer term of psychological intervention on CPM analgesia.

- The 1st International Conference of Indonesian Physiotherapy Association (ICIPA), presented on 14 August 2018 in Bali, Indonesia. Awarded a certificate for the best conference oral presenter.

THE INFLUENCE OF EMPATHETIC INTERACTION ON CONDITIONED PAIN MODULATION AND MANUAL THERAPY ANALGESIA IN PARTICIPANTS WITH LATERAL EPICONDYLALGIA

Muhsen A [1,2*], Moss P [1], Gibson W [3], Walker B [4], Wright A [1]

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2 School of Physical and Occupational Therapy, The Hashemite University, Zarqa, Jordan
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Abstract

Introduction: Conditioned Pain Modulation (CPM) and Manual Therapy (MT) produce a natural form of analgesia. The objective of this research was to investigate the impact of empathetic interaction on CPM and MT analgesia in patients with Lateral Epicondylalgia (LE). **Methods:** In a double-blind randomised clinical trial, 68 participants with LE were randomly and equally assigned into two groups: the empathetic and neutral interaction groups. The interactions were all under the control of a professional role play actor, playing the part of a research assistant (RA). CPM was initially assessed and followed by MT in a single session. The RA spent 15min before CPM and MT assessment interacting with the participants. Immediately after interactions, a blind assessor measured pressure pain threshold (PPT) at the symptomatic side before cold pressor test (CPT) and cervical contralateral lateral glide (CCLG), during CPT, and immediately after CPT and CCLG. Linear mixed models were used to evaluate differences in CPM and MT responses between the groups. **Results:** There was a significant difference in the CARE scores between the interaction groups. Both groups showed a significant increase in all PPT measured for CPM and MT. Although there was no significant between-group difference in the PPT values (no time), there was a significant between-group difference over time, with higher levels of analgesia observed for the enhanced interaction group. **Conclusion:** A single session of empathetic interaction positively influence CPM and MT analgesia in people with LE. This supports the use of empathetic interaction with patients to reduce their pain in clinical encounter. Further research is recommended into the effect of long term empathetic interaction on CPM and MT responses.

Key words: Conditioned pain modulation, empathetic interaction, manual therapy analgesia

- The World Confederation for Physical Therapy (WCPT) Congress 2019, presented on 13, May 2019, in Geneva, Switzerland.

Abstract Preview - Step 3/4

Printversion

Primary topic: Musculoskeletal: upper limb

Title: **THE ASSOCIATION BETWEEN CONDITIONED PAIN MODULATION AND MANUAL THERAPY ANALGESIA IN PARTICIPANTS WITH LATERAL EPICONDYLALGIA**

Author(s): Muhsen A[1], Moss P[2], Gibson W[6], Walker B[4], Schug S[5], Wright A[5]

Institute(s): [1]*Curtin UniversityUniversity, School of Physiotherapy and Exercise Science, Perth, Australia,* [2]*Curtin University, School of Physiotherapy and Exercise Science, Perth, Australia,* [3]*University of Notre Dame Australia, School of Physiotherapy, Fremantle, Australia,* [4]*Murdoch University, School of Health Professions, Perth, Australia,* [5]*University of Western Australia, Department of Anaesthesiology, Perth, Australia,* [6]*Curtin University, School of PHysiotherapy and Exercise Science, Perth, Australia*

Text: **Background:** Endogenous Analgesia (EA) generally involves multiple central circuits that modulate pain inhibition. Recent research evidence suggests that Conditioned Pain Modulation (CPM) and Manual Therapy (MT) activate EA mechanisms to mediate their analgesic effects. The association between the CPM and MT analgesia has not been previously investigated.
Purpose: The main aim of this study was to assess the association between CPM and MT analgesia in patients with Lateral Epicondylalgia (LE). We also sought to investigate whether there was a difference in MT analgesia between those who did and who did not demonstrate a clear CPM effect (i.e. CPM responders and non-responders).
Methods: In a quasi-experimental single-group pretest-posttest study design, 70 participants with LE were initially assessed in a single session for CPM followed by MT with 15 minute rest in between. A single assessor (ICC (3,4)=0.99) measured pressure pain threshold (PPT) at the elbow and wrist of the symptomatic side before, during, and after cold water immersion (10°C) of the other arm and contralateral cervical lateral glide (CLG) mobilisation. Based on the level of CPM response, participants were assigned post hoc into two CPM groups: responders and non-responders. Linear mixed models (LMDs) were used to evaluate differences in CPM and MT responses between time points in both groups. Pearson partial correlations and regression analyses were also used to examine the association between CPM and MT PPT measures whilst controlling for baseline PPT measures. Separate LMDs were then used to evaluate differences in MT analgesia overtime between CPM groups controlling for Patient Rated Tennis Elbow Evaluation (PRTEE) scores and gender.
Results: Both CPM responder and non-responder groups demonstrated significant increase in PPT measures during and post CPM and MT over the wrist and elbow testing sites ($p < 0.001$). There were also significant moderate positive partial linear correlations (r: 0.32-0.53, $P < 0.05$) between CPM and MT PPT measures. The regression analyses showed that CPM PPT was a significant predictor of MT PPT ($p < 0.001$) measured at both sites over different time points and the models explained between 71% and 89% variability in MT PPT. Lastly, there were significant differences in MT PPT measures between CPM groups overtime, during and post CLG mobilisation ($P = 0.014$-0.033), with significantly higher MT PPT responses observed at both testing sites among CPM responders.
Conclusion(s): The study showed that CPM and MT analgesic responses were significantly correlated in a sample population with LE. CPM responders demonstrated significantly higher levels of MT analgesia compared to CPM-non responders. This suggests that both forms of analgesia share similar neuro-physiological mechanism. Further research is recommended into longer term changes of CPM and MT analgesia and in various musculoskeletal pain conditions.
Implications: The study provides strong evidence of the analgesic effects of CLG in immediately reducing pain in LE. It has also improved our knowledge of the mechanism of action of MT. This study will therefore lay the foundation for future clinical trials that will investigate/compare the impact of different treatment interventions on CPM and MT responses.
Key-Words: conditioned pain modulation, lateral epicondylalgia, manual therapy analgesia
Funding acknowledgements: PhD project funded by the Hashemite University, Jordan. Also supported by the School of Physiotherapy and Exercise Science, Curtin University.

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Abstract Preview - Step 3/4

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Primary topic: Musculoskeletal: upper limb

Title: **THE EFFECT OF AEROBIC EXERCISE ON CONDITIONED PAIN MODULATION AND MANUAL THERAPY ANALGESIA IN PARTICIPANTS WITH LATERAL EPICONDYLALGIA**

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Text: **Background:** Recent research evidence suggests that Conditioned Pain Modulation CPM and Manual Therapy (MT) produce a natural form of analgesia. They appear to share similar neuro-physiological mechanisms involving activation of endogenous analgesia (EA) systems. We propose a paradigm to positively influence the levels of CPM and MT analgesia thorough a period of aerobic physical exercise in individuals with a musculoskeletal pain state.
Purpose: To determine the effect of moderate and high intensity aerobic exercise on CPM and MT analgesic responses in a patient population with Lateral Epicondylalgia (LE).
Methods: A gender stratified convenience sample of 68 participants with LE was recruited for this study. Pressure pain threshold (PPT) was initially measured at the elbow and wrist of the symptomatic side. Participants were then randomly allocated to receive either moderate (50% HRmax, n=34) or high intensity (75% HRmax, n=34) aerobic exercise (without crossover) using a cycle ergometer. Each participant was required to complete two 15min aerobic exercise sessions at the same intensity. All participants were then assessed for CPM and MT analgesic responses in a random order, in two separate test sessions (i.e. two study days) separated by three days. PPT responses were measured at baseline, immediately after the completion of the aerobic exercise, during, and after immersing the other arm in a cold water bath (10°C) (CPM) and during and after cervical lateral glide (CLG) mobilisation. All PPT responses were obtained from the two testing sites by the same main investigator (ICC (3,4)=0.99), who was blinded to the exercise group allocation. Linear mixed models were used to evaluate differences in CPM and MT responses between the exercise groups, controlling for the patient rated tennis elbow evaluation (PRTEE) scores, global physical activity questionnaire (GPAQ) scores and gender.
Results: Both aerobic exercise groups demonstrated a significant increase in PPT measured at wrist and elbow sites immediately post cycling (EIA), during and immediately post cold water immersion and CLG ($P < 0.001$). There were significant differences in PPT measures between the groups overtime, with higher levels of analgesia observed for the high intensity group during ($P < 0.001$) and post ($P < 0.001$) cold water immersion (CPM) and CLG (MT) measured over the wrist and elbow sites.
Conclusion(s): A 15min session of aerobic exercise positively influences CPM and MT analgesia in people with LE. Further research is recommended into the effect of long term high intensity aerobic exercise on CPM and MT responses.
Implications: This study has improved our understanding of mechanisms of action of MT analgesia. The addition of aerobic exercise can potentiate MT analgesia in clinical settings.
Key-Words: aerobic exercise, conditioned pain modulation, manual therapy analgesia
Funding acknowledgements: PhD project funded by the Hashemite University, Jordan. Also supported by the School of Physiotherapy and Exercise Science, Curtin University.

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