The sympathetic nervous system effects of spinal mobilisations in those with and without chronic low back pain

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Declaration

No portion of this work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institution of learning.

Dedication

To my husband and daughter (Ammar and Sara Bokhamseen)

To my father and mother (Hashem Almuslem and Zahra Bokhamseen)

Acknowledgment

I would like to express my sincere appreciation to my supervisory team Prof Michael Callaghan, Dr. Peter Goodwin, Dr. Emma Hodson-Tole and Mrs. Jackie Hindle for their constant support, help and assistance which have made the completion of this thesis possible. I would like to thank the participants who voluntarily participated in my studies. Many thanks go to University of Dammam (UOD) and the Saudi Cultural Bureau for the scholarship and the financial support to this project. Finally, I would like to express my gratitude to my husband (Ammar), daughter (Sara), and my family for their understanding, time and support.

Abstract

Background

Low back pain (LBP) is one of the most common musculoskeletal conditions encountered in clinical practice. Physiotherapists as well as other professionals in healthcare use manual spinal mobilisations to treat patients with LBP with the aim of reducing pain or/and stiffness and improving the range of motion. Although spinal mobilisations are widely used in the clinical sitting, the underlying mechanisms regarding its effectiveness remain largely unknown. The purpose of the current study was to examine the physiological responses of spinal mobilisations in terms of the hypoalgesic and SNS responses in those with and without LBP.

Methods

Phase 1 examined the test-re-test reliability of sympathetic and hypoalgesic measurements (n = 15). **Phase 2** was a pre-clinical study (single arm trial, n = 14) that investigated the hypoalgesic and sympathetic effects of thoracic mobilisation treatment in asymptomatic participants over a course of three sessions of mobilisation. **Phase 3** investigated the hypoalgesic and sympathetic effects of thoracic mobilisation treatment in patients with nonspecific chronic low back pain (NSCLBP) (n = 36) over a course of three sessions of mobilisation.

Results

Phase 1 demonstrated that the within-day test-retest reliability of skin conductance, skin temperature, heart rate, respiratory rate, systolic blood pressure and PPT measurements were excellent (ICCs of 0.77 to 0.99). On the other hand, the reliability of diastolic blood pressure and salivary alpha-amylase measurements were demonstrated to be fair to good (ICCs of 0.55 and 0.7, respectively). **Phase 2** revealed significant sympathoexitatory effects in terms of diastolic blood pressure (p=0.026), heart rate (p=0.005) and respiratory rate (p= 0.001) where there were insignificant results with regard to peripheral sympathetic measures (skin conductance and skin temperature). Significant hypoalgesic effects were evident in some locations, including distal areas, but not at all visits. **Phase 3** showed significant peripheral detectable sympathoexcitatory effects in the lower limbs in terms of increased skin conductance (p= 0.001) and decreased skin temperature (p= 0.001) following thoracic mobilisation that were not detected in asymptomatic participants.

Conclusion

This study demonstrated that patients with nonspecific low back pain are more peripheral sympathetic responsive to thoracic mobilisations than asymptomatic population suggesting that adaptive neuroplasticity, as well as dorsal horn and central processing, in the LBP patients, may be a feasible explanation of the results.

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List of abbreviations

°C = Celsius

1st DI = First dorsal interosseous muscle

ANOVA = Analysis of variance

ANS = Autonomic nervous system

AP = Anterior-to-posterior pressure

BMI = Body mass index

BP = Blood pressure

C5/6 = Facet joint between the fifth and the sixth cervical vertebrae

C6 = 6th cervical vertebrae

CI = Confidence intervals

CLBP = Chronic low back pain

CNS = Central nervous system

CSP = Chartered Society of Physiotherapy

D/K = Don't Know

DBP = Diastolic blood pressure

dlPAG = Dorsolateral periaqueductal grey

dmPAG = Dorsomedial periaqueductal grey

dPAG = Dorsal periaqueductal grey

ECG = Electrocardiogram

EDA = Electrodermal activity

g = Gram

GRADE = The Grading of Recommendations, Assessment, Development and Evaluations

GRC = Grey rami communicantes

GSR = Galvanic skin response

HPA = Hypothalamic–pituitary–adrenal axis

HR = Heart rate

HVLA = High velocity low amplitude

HVT = High-velocity thrust

Hz = Hertz

I = Grade one

ICC = Intraclass correlation coefficient

II = Grade two

III = Grade three

IV = Grade four

KFUH = King Fahad University Hospital

kg/m^2 = Kilogram per meter sequare

kPa = Kilopascals

L2 = Second lumbar vertebra

L3 = Third lumbar vertebra

L4 = Fourth lumbar vertebra

L4/5 = Facet joint between the 4^{th} and 5^{th} lumbar vertebrae

L5 = Fifth lumbar vertebra

LBP = Low back pain

lPAG = Lateral periaqueductal grey

LT = Left

MDC = Minimal detectable change

ml = millilitre

mmHg = Millimetres of mercury

MOB = Mobilisation

N = Newton

N/cm^2 = Newton per centimetre square

NICE = National Institute of Clinical Excellence

NPRS = Numerical Pain Rating Scale

NRM = Nucleus raphe magnus

NSCLBP = Nonspecific chronic low back pain

NSLBP = Nonspecific low back pain

PA = Posteroanterior

PAG = The periaqueductal grey

PNS = Parasympathetic nervous system

PPT = Pressure pain threshold

PRISMA = The Preferred Reporting Items for Systematic Reviews

RCT = Randomized controlled trial

Q-Q plot = quantile-quantile plot

RR = Respiratory rate

RT = Right

S = Seconds

S2 = Second sacral vertebra

S3 = Third sacral vertebra

S4 = Fourth sacral vertebra

sAA = Salivary alpha-amylase

SBP = Systolic blood pressure

SC = Skin conductance

SD = Standard deviation

SEM = Standard error of measurement

SMT = Spinal manual therapy

SNAG = Mulligan sustained apophyseal glide

SNS = Sympathetic nervous system

SPSS = The Statistical Package for Social Scientists

SR = Skin resistance

SRD = Smallest real difference

ST = Skin temperature

T1 = First thoracic vertebra

T12 = 12th thoracic vertebrae

T2 = Second thoracic vertebra

T3 = 3rd thoracic vertebrae

T4 = 4th thoracic vertebrae

T6 = Sixth thoracic vertebrae

TPT = Thermal pain threshold

U/m = Unite per minute

U/ml = Unit per millilitre

Ul = Microliter

V = Voltage

VAS = Visual Analogue Scale

vlPAG = Ventrolateral periaqueductal grey

vPAG = Ventral periaqueductal grey

WRC = White rami communicantes

Chapter one

Introduction

Low back pain (LBP) is one of the most common musculoskeletal conditions that has a relatively high incidence both in the United Kingdom and worldwide (Lidgren, 2003; Dunn and Croft, 2006). Between 49% and 70% of people suffer from LBP at some point in their lifetime (Koes et al., 2001; Koes and Van Tulder, 2006). Maxfarlane et al. (2006) reported that more than one-third of the UK population is affected each year. During the first 4–6 weeks of LBP, 58% of the patients report rapid improvement; however, recovery is often incomplete (Pengel et al., 2003). For most sufferers, persistent pain and associated disability may last for months, and a small proportion of patients may even become severely disabled (Koes et al., 2006). Moreover, recurrence is common over the next 12 months in those with completely resolved pain (Henschke et al., 2009). Maniadakis and Gray (2000) reported that in 1998, out of the total cost of LBP healthcare, approximately £600 million was spent on physiotherapy and other allied fields. LBP is one of the most common musculoskeletal conditions encountered in clinical practice (Krismer and Van Tulder, 2007). Multiple systematic reviews have indicated the beneficial effects of manual therapy in treating spinal pain conditions (Koes et al., 2001; Gross et al., 2002; Assendelft et al., 2003; Assendelft et al., 2004; Bronfort et al., 2004; Cleland et al., 2005; Chou and Huffman, 2007). Physiotherapists as well as other professionals in healthcare use manual therapy to treat patients with LBP with the aim of reducing pain or/and stiffness and improving the range of motion (Bronfort et al., 2004). Manual therapy includes physical techniques that are applied to patients by the therapist in the form of either manipulation or mobilisation. Manual therapy has been shown to have hypoalgesic and sympathetic effects in asymptomatic populations and patients with cervical pain (Vicenzino et al., 1998; Sterling et al., 2001; Perry and Green, 2008; Jowsey and Perry, 2010; Krouwel et al., 2010).

Spinal manual therapy (SMT) is widely applied in the clinical setting to treat musculoskeletal pain (Krouwel et al., 2010). However, the mechanisms underlying

its effectiveness remain largely unknown (Sterling et al., 2001; Hegedus et al., 2011). Over the last two decades there has been increasing interest in the neurophysiological responses of the sympathetic nervous system (SNS) to SMT. Several studies have measured sympathetic nervous system responses but research on the lumbar area of the spine is very limited. To date there are no reported studies on any patient population (Perry and Green, 2008; Jowsey and Perry, 2010; Krouwel et al., 2010). In contrast, the neurophysiological effects of spinal manipulation have undergone intense scrutiny (Thomson et al., 2009).

The overall aim of this thesis was therefore to explore the hypoalgesic and sympathetic effects of spinal mobilisation in asymptomatic and symptomatic populations with nonspecific chronic low back pain (NSCLBP). In addition, this thesis aimed to inform future research by providing evidence of SNS and pain responses to specific mobilisation treatment techniques.

The following outlines the topics covered in this thesis: In Chapter 2, the literature related to neurophysiological responses to spinal mobilisation is critically reviewed. Chapter 3 represents a systematic review of randomised controlled trials that assess the effectiveness of spinal mobilisation in terms of the hypoalgesic and SNS responses in healthy populations or in patients with spinal pain. Chapter 4 outlines the methods used for sympathetic and hypoalgesic measurements in the studies conducted in this thesis; with Chapter 5 reporting the test-re-test reliability of these measurements in asymptomatic participants (n = 15). Subsequently I investigated the effects of mobilisation treatment on these variables in asymptomatic populations and patients with NSCLBP. Chapter 6 reports a pre-clinical study (single arm trial, n = 14) that investigated the hypoalgesic and sympathetic effects of thoracic mobilisation treatment in asymptomatic participants over a course of three sessions of mobilisation. Chapter 7 outlines a clinical study (single arm trial, n = 36) that investigated the hypoalgesic and sympathetic effects of thoracic mobilisation treatment in patients with NSCLBP over a course of three sessions of mobilisation. Finally, Chapter 8 discusses the results of all three studies, highlights their original contribution to the available knowledge, and identifies areas for further research.

Chapter Two

Review of literature related to low back pain and spinal mobilisation

2.1. Definition and classification of low back pain

Dionne et al.'s (2008) definition of LBP is internationally accepted:

Pain between the inferior margin of the 12th rib and the inferior gluteal folds that is bad enough to limit usual activities or change the daily routine for more than one day. This pain can be with or without pain going down to the leg. This pain does not include pain from feverish illness or menstruation.

Over the last two decades, a number of attempts have been made to classify LBP with the aim of assisting heterogenic patient populations and easing the decision-making process (O'Sullivan, 2005). The literature in the area of LBP physiotherapy mostly uses the Quebec task force classifications system that provides a logical classification approach of LBP disorders within a biopsychosocial framework (Abenhaim et al., 2000; Waddell, 2004). Both red and yellow flags (psychological and/or social factors) are considered under this framework. This system classifies LBP disorders as 'specific LBP' with a determined patho-anatomical causative factor (e.g. systemic inflammatory disorders, ankylosing spondylitis, disc prolapse, fracture, malignancy, and infection) and 'non-specific low back pain' (NSLBP) (defined as soreness, tension or/and stiffness over the lower area of the back without a specific possible cause [NICE, 2009]). Further delineation of acute (up to 6 weeks of symptoms), sub-acute (4–12 weeks of symptoms) and chronic low back pain (CLBP) (>12 weeks) has also been provided by this classification system (Koes et al., 2010).

Eighty-five per cent of CLBP disorders (where back pain lasts for longer than 12 weeks) are classified as nonspecific with no known diagnosis (O'Sullivan, 2005). A further classification has been made for these disorders based on the area of the pain and defined as radicular in nature or somatic referred (Abenhaim et al., 2000). However, this classification does not consider the underlying mechanism of the pain

disorder; this means that the selection of an appropriate intervention is difficult, which limits the value of this classification system in a clinical sitting (Padfield and Butler, 2002).

2.2. Physiotherapy treatment of nonspecific chronic low back pain

There is ongoing debate about the best intervention for NSCLBP that is perhaps the result of diagnostic imprecision (Savigny et al., 2009). The National Institute of Clinical Excellence (2016) recommended that manual therapy be offered to patients with nonspecific low back pain but only as part of multi-modal treatment packages.

A complete examination by a physiotherapist is essential to make a decision about whether physiotherapy is appropriate for the patient or not. In the first meeting between a LBP patient and a physiotherapist, a study of the patient's subjective history is made, with a focus on the localisation of symptoms, the aggravating and ameliorating factors, past medical history, general health and history of past and present episodes of symptoms (Petty, 2011). Specific questions to rule out any serious pathological conditions are also asked, based on which the patient may be referred to other health professionals (Greenhalgh and Selfe, 2006). Furthermore, an insight into some factors that may affect recovery is important when taking the subjective history of the patient, such as the perception of the problem, functional limitations, and physical or psychological factors (Petty, 2011).

Following the subjective examination, a physical (objective) examination is performed based on the information gained. Normally, objective examination of the spine involves:

-Manual palpation of the lumbar and sacral areas to assess inflammation, tenderness and segmental hypomobility and dysfunction.

-Physiological movement assessment to determine which movements can be performed by patients,

-Accessory movement assessment to examine gliding movements of the joints during physiological movements that require external force and cannot be performed by the patient alone (Maitland et al., 2005),

-Other tests for assessment of nerves or muscles that may reproduce the patients' symptoms.

Based on the results of complete examination by a physiotherapist, a decision is made about whether manual therapy is appropriate for the patient or alternative treatment or further investigation is required. However, little research has been conducted to assess which CLBP patients would benefit from spinal manual therapy (Bronfort et al., 2004). It has been suggested that manual therapy can be recommended for CLBP patients who are free from any contraindications for this intervention (e.g. history of cancer, direct trauma, pain at rest, loss of bladder or bowel control and progressive neurological deficit). Spinal manual therapy may not be the best choice for CLBP patients with psychosocial factors or patients who are physically deconditioned and cannot increase their activity (ICSI, 2006).

2.3. Spinal manual therapy

Spinal manual therapy (SMT) is a frequently used treatment for NSLBP by healthcare professionals such as physiotherapists, chiropractors and osteopaths (Bronfort et al., 2004). A number of systematic reviews of the literature have indicated the efficacy of SMT in the treatment of spinal pain (Gross et al., 2002; Bronfort et al., 2004; Cleland et al., 2005; Miller et al., 2010). Several reviews examined the role of manual therapy as a management of CLBP. Most of these reviews reported that manual therapy is effective for NSCLBP in terms of pain and functional measures (Koes et al., 2001; Assendelft et al., 1995). A Cochrane review found that spinal manual therapy is moderately superior to sham manual therapy for CLBP (Chou and Huffman, 2007). Recent international guidelines for the management of chronic low back pain recommended spinal manual therapy as a beneficial management for NSLBP patients (Savigny et al., 2009). However, Flynn et al. (2002) recognised that manual therapy should not be expected to be efficacious intervention for all LBP patients.

Manual therapy includes physical techniques that are applied to patients by the therapist in the form of either manipulation or mobilisation. Manipulations are high-velocity thrust (HVT) techniques used to treat spinal pain. HVT techniques are usually applied at the end of the joint range and sometimes accompanied by a

'popping' sound. On the other hand, mobilisation is defined as a low-velocity, non-thrust passive movement, which is applied to a joint within or at the limit of the joint range (Maitland et al., 2005; Clinical Guidelines for the Physiotherapy Management of Persistent Low Back Pain, 2006). Moreover, mobilisation may be accompanied by active movements, such as mobilisation with movement techniques that was devised by Mulligan (1999). However, although the effects of spinal manipulation have undergone intense scrutiny, spinal mobilisation has received relatively little attention in comparison (Thomson et al., 2009). Furthermore, a large proportion of those investigations on spinal mobilisation have not looked at the neurophysiological effect of the mobilisation as a single treatment (Koes et al., 1992; Dishman and Bulbulian, 2001).

2.3.1 Passive mobilisation techniques

In 1965, Geoffrey Maitland was among the first physiotherapists to educate practitioners of mobilisation techniques that were applied to a joint in the form of graded oscillatory forces (Banks, 2010). These techniques are commonly used in clinical practice with the aim of reducing pain or/and stiffness and improving the range of motion. For example, Gracey et al. (2002) reported that Maitland mobilisations are used by 42% of physiotherapists to treat LBP. However, the underlying mechanisms regarding its clinical effectiveness are unknown (Vicenzino et al., 1998 and 1996; Sterling et al., 2001; Coronado et al., 2012).

The posteroanterior (PA) spinal mobilisation technique is one of the most commonly used passive manual techniques in clinical practice (Jull, 2000; Magarey et al., 2004). It is described as the application of pressure to the spinous process (central PA) or transverse process (unilateral PA) of the spinal vertebrae by the therapist by either the thumbs (thumb grip) or the heel of the hand (pisiform grip) (Maitland, 2005; Snodgrass et al., 2006). It is a low-velocity force directed from the posterior to anterior area of a single vertebra (Maitland, 2014).

The aim of mobilisation techniques applied by physiotherapists is to decrease pain or stiffness and/or increase the range of motion. The treatment dose depends on the aim of the treatment. Physiotherapists take into account a number of factors when selecting a specific technique such as the stage of the symptoms (acute or chronic),

the nature of the problem, the irritability and severity of the symptoms, the association between pain and stiffness based on the physical examination, pain mechanism, patient's expectations and biopsychosocial factors (Maitland, 2005).

The amplitude and number of courses of mobilisation depend on multiple parameters, and the treatment course is designed such that the optimal level of efficacy can be achieved (Table 2.1).

Table 2.1. Parameters for determining the mobilisation treatment dose

Position	The patient can be in the prone position with the spine in extension, flexion, rotation, or lateral flexion, or a combination of positions (McCarthy, 2010).
Level of treatment	Maitland et al. (2014) recommended mobilising according to the symptomatic level (the most comparable level) as identified by the physical assessment.
Grade	Maitland et al. (2014) described four grades of mobilisation (I, II, III and IV): -Grade I: movement of small amplitude within the initial range (soft resistance) -Grade II: movement of large amplitude within the available range (soft resistance) -Grade III: movement of large amplitude associated with firm resistance -Grade IV: movement of small amplitude associated with firm resistance.
Direction of mobilisation force	This refers to the inclination of the mobilisation force, such as medial, lateral, cephalad or caudal (McCarthy, 2010).
Rhythm	The rhythm can be either staccato or slow and smooth (Petty, 2011).
Rate	Typically, a frequency of 1 Hz (one oscillation/second) to 2 Hz (two oscillations/second) (Souvlis et al., 2004) is used. The frequency can also be quasi-static (0 oscillations) (Petty, 2011).
Duration	This refers to the length of time of the applied mobilisation. Normally, three sets of 30 seconds to 1 minute are applied (Maitland, 2005).
Reproduction of symptoms	Mobilisation may be performed at the point before that where the symptoms are reproduced or at the point where the symptoms are partially or fully reproduced (based on the desired effect) (Petty, 2011).

However, there are not enough studies on the optimum mobilisation parameters and the efficacy of treatment (Pentelka et al., 2012).

2.4. Understanding the mechanism of action of spinal mobilisation

Even though there is sufficient evidence to support the effective use of spinal mobilisations in the treatment of musculoskeletal conditions such as NSCLBP, the mechanisms behind it remain largely unknown (Vicenzino et al., 1998 and 1996; Khalsa et al., 2006; Coronado et al., 2012). A comprehensive understanding of these mechanisms is crucial for multiple reasons. The successful outcomes reported in recent studies are dependent on the identification of likely respondents rather than identification of a specific lesion (Flynn et al., 2002). Responders to mobilisations may be identified by the clustering of signs and symptoms (Flynn et al., 2002; Cleland et al., 2007). Although this proposed direction would be helpful in clinical practice, clinical outcomes cannot be predicted based on the signs and symptoms alone (Bialosky et al., 2009). On the other hand, if the mechanisms behind the mobilisations are understood, it would be possible to identify the predictive factors, based on which future clinical decisions to identify responders could be made (Flynn et al., 2002). Furthermore, establishing the mechanisms of mobilisation could increase its acceptance in clinical practice. Therefore, healthcare providers might be able to use these techniques more appropriately if they are aware of their mechanisms of action (Bialosky et al., 2009).

The therapeutic effects of mobilisation, especially decrease in pain after spinal mobilisation, are explained by theories, such as the gate-control mechanism (stimulation by non-noxious input is able to close the gate to painful input) along with other biomechanical effects (Melzack and Wall, 1965; Evans, 2002). Recently, there has been an increase in the number of studies supporting the neurophysiological mechanism, and the spinal and supraspinal mechanisms are the most commonly accepted (Schmid et al., 2008; Hegedus et al., 2011; Kingston et al., 2014; Voogt et al., 2014). Based on the findings of various investigations, it was proposed that a multi-system, centrally coordinated response is the mechanism underlying the therapeutic effects of mobilisation (Vicenzino et al., 1998; Evans, 2002). Several studies have identified other changes associated with spinal mobilisation, such as alterations in certain vasomotor, sudomotor and cutaneous measures; these findings indicate that spinal mobilisations may initiate SNS responses (Wright and Vicenzino,

1995; McGuiness et al., 1997; Vicenzino et al., 1999; Souvlis et al., 2000; Sterling et al., 2001; Cleland et al., 2004; Jowsey and Perry, 2010). These responses of the SNS have been demonstrated in parallel with pain modulation responses following mobilisation in animal and human studies (Sterling et al., 2001; Grayson et al., 2012). However, these findings have not been confirmed in patients with LBP. Therefore, this thesis focuses on pain modulation (hypoalgesic effect) and SNS responses to passive spinal mobilisation in individuals with and without LBP. In order to explain these neurophysiological responses to spinal mobilisation, the subsequent literature review will focus on somatosensory innervation of the spine, explaining how spinal mobilisation is understood to act as a physiological stimulus.

2.5. Somatosensory input from the spine

2.5.1. Cervical spine

Ligaments, capsules, paraspinal musculature, intervertebral discs and other structures of the cervical spine are innervated with afferent nerves, which project either directly or indirectly to different levels of the neural axis (Bolying and Jull, 2004). The vestibular, optic and sympathetic systems are related to the cervical spine, and these systems play a role in the production of a multifaceted neurophysiological response to the afferent input that occurs during spinal mobilisations. Touch and movement stimulate both cutaneous receptors and deeper tissue receptors such as the muscle spindle, during the application of spinal mobilisation (Bolton, 1998). Furthermore, paciniform corpuscles are common in the joint capsule on the external surface of the vertebrae, while Golgi tendon organs are located at the musculotendinous junction (Bolton and Tracey, 1992). The afferents from the receptors terminate in the spinal cord: cutaneous afferents synapse in laminae I–IV, afferents from the zygapophysial joint synapse in laminae I and II, and low-threshold afferents from the muscles terminate in the ventral horn as well as laminae IV–VI (Bolton, 1998). The primary afferent from the cervical spine projects higher through the dorsal column–medial lemniscal, spinothalamic and somatosensory pathways to the medulla nuclei, including the vestibular nuclei and ipsilateral cuneate nucleus, which provides afferent information, both nociceptive and proprioceptive, to the contralateral thalamus, cerebellum and sensorimotor

cortex (Bolton, 1998; Bolton and Tracey, 1992). Therefore, the stimulation of this multifaceted afferent input of the cervical spine is usually associated with a number of postural reflexes, such as opticokinetic, vestibulocollic and cervicocollic reflexes, which are responsible for eye movements, head movements and head on body movements, as well as the appropriate physiological responses to these movements (Bolying and Jull, 2004).

2.5.2. Thoracic and lumbar spine

Similar types of receptors as found in the zygapophysial joints are located in the thoracic and lumbar spines as well as in the cervical spine (McLain and Pickar, 1998). Although both type I and II fibres are found, as well as free nerve endings, their numbers are lower than those in the cervical spine and large receptive fields (McLain and Pickar, 1998). However, the connections for afferents from the lumbar spine in the spinal cord differ from those of the cervical spine, particularly afferents from muscle spindles (Bolying and Jull, 2004). Keirstead and Rose (1988) found that unlike certain supraspinally projected cervical afferents, lumbar connections are monosynaptic with motoneurons. As a result, the neurophysiological effects on the activation of lumbar spine afferents might be different.

In summary, the previous section indicates that movement of the vertebral column and its surrounding structures during spinal mobilisation can lead to activation of multiple receptors and the generation of afferent input that projects either to the spinal cord or beyond the spinal cord to reach supraspinal neurons (Pickar, 2002). The following section will describe the anatomy of the sympathetic and parasympathetic divisions of the ANS and their location with respect to the spine.

2.6. The autonomic nervous system

2.6.1. Anatomical divisions of the autonomic nervous system

It has been shown over the last two decades that elements of the ANS could be used to objectively measure physiological changes that occur during therapeutic treatments. The following section will describe the anatomy of the ANS and how changes in this system can be captured; moreover, these changes will be explained

in relation to known theories regarding the mechanism of action of spinal mobilisation.

Although parasympathetic nervous system (PNS) and the SNS interact with each other in the nervous system, they function as one unit (Benarroch, 2006). The internal environment of the body is controlled by the ANS, which supplies cardiac muscles, smooth muscles, glands and the viscera (Benarroch, 2006). The SNS and the PNS represent the two anatomical and topographical divisions of the ANS (Figure 2.1). The SNS is the larger part that plays a catabolic role in regulating the internal state of the body by increasing heart rate, expending energy and directing circulation from the peripheral regions of the body toward the centre (Goldberg, 2010). On the other hand, the PNS has an anabolic role that involves slowing down the heart rate, absorbing nutrition and conserving energy (Goldberg, 2010). The SNS and PNS exit the CNS at various sites to reach structures that they supply with their endings. These two complementary systems usually have opposite functions in each part of the body, as their terminals are either cholinergic or adrenergic.

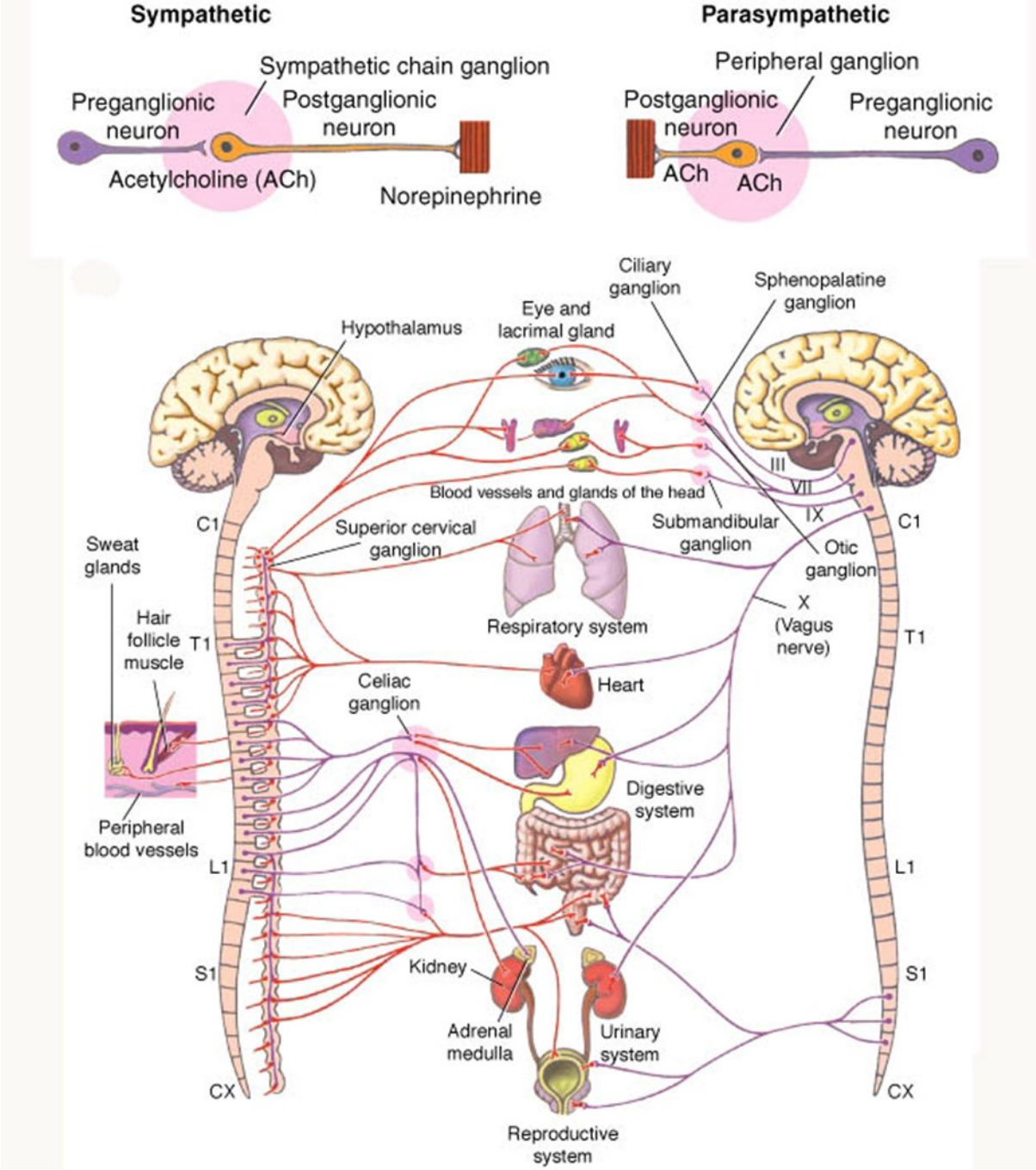


Figure 2.1. Anatomical divisions of the autonomic nervous system (Thomas, 2007).

Neurons of the ANS are classified into afferent, connector and efferent neurons. The receptors of the viscera are the origin of afferent impulses to the CNS. The efferent pathway consists of the ganglia that lie outside the CNS and is composed of the pre- and post-ganglionic neurons. These ganglia are located along the spine from the T2 to L4 anterolateral to vertebral bodies (Goldberg, 2010).

There are differences in the points at which the SNS and PNS connect with the CNS. The PNS nerves that protrude from the spinal nerves include cranial nerves III, VII, IX and X and sacral nerves S2, S3 and S4. Therefore, nerves of the PNS are described as having 'craniosacral outflow'. On the other hand, sympathetic nerves are described as having 'thoracolumbar outflow', as they are represented by spinal nerves T1 to L2 (Benarroch, 2006).

The SNS, being larger than the PNS, is distributed widely throughout the body and innervates the muscular walls of many blood vessels, piloerection muscles and cutaneous sweat glands. The SNS is activated in emergencies and causes redistribution of blood to the heart and the brain from the periphery, which results in sweating and arrest of digestion (Snell, 2010). As the activity of sweat glands is sympathetically controlled, Fowles (1974 and 1986) suggested that the activity of sweat glands was an ideal measure of SNS activity. The SNS consists of efferent nerve pathways from the spinal cord, two ganglionated sympathetic trunks, branches, plexuses and regional ganglia (Benarroch, 2006).

Motor pathways of the ANS have synapses within autonomic ganglia. The axons traveling from the CNS to such ganglia are called preganglionic axons, while the neurons forming the ganglia and the axons connecting them to the target organ are called postganglionic axons. Anatomically, the parasympathetic ganglia are located close to the target peripheral organ, so their postganglionic fibres are short. On the other hand, the sympathetic ganglia lie some distance away from the target organ (close to the spinal cord), so their postganglionic fibres are relatively long (Snell, 2010).

The lateral horn of the grey matter in the spinal cord (T1 to L2 segments) contains the cells bodies of preganglionic sympathetic neurons (Figure 2.2). At the level of the spinal cord where the cell bodies exist, the preganglionic sympathetic axons exit through the ventral roots of the spinal nerve. Following this, the preganglionic sympathetic axons enter the ventral ramus of the spinal nerve that leaves the ventral ramus just beyond the intervertebral foramen and forms a branch called the white rami communicantes (WRC) that enters the adjacent sympathetic trunk. Then, preganglionic sympathetic neurons either end or travel within the trunk upward or

downward. Preganglionic neurons that travel from the WRC at the lower thoracic and lumbar levels within the sympathetic trunk tend to assume a downward course toward the lower lumbar and sacral levels prior to their ending. Next, preganglionic neurons synapse in the sympathetic ganglia where the postganglionic cell bodies exist. After synapsing, the postganglionic neuronal axons exit the trunk; alternatively, before synapsing, they may assume a downward or upward course through the trunk (Palastanga et al., 1994). There are three paths via which postganglionic sympathetic neurons exit the sympathetic trunk. Most of them join a ventral ramus, while others follow arteries or form branches that travel directly to the viscera or the plexus. Postganglionic neurons leave the sympathetic trunk by joining a ventral ramus to form a branch called the grey rami communicantes (GRC). This branch leaves the trunk at every spinal level where the WRC leaves the spine, that is, from T1 to L2. Therefore, only ventral rami at the level of T1–L2 are connected to the sympathetic trunk by WRC and GRC.

After the postganglionic neurons join the ventral ramus, most of them assume a distal course within the ramus. Through the course of the ventral and dorsal rami, the postganglionic neurons reach their targets, including blood vessels of the joints or muscles, blood vessels in the skin (where cutaneous branches are related), and muscles related to piloerection or sweat glands in the skin (some of these neurons pass along the course of cutaneous branches of the somatic nerves).

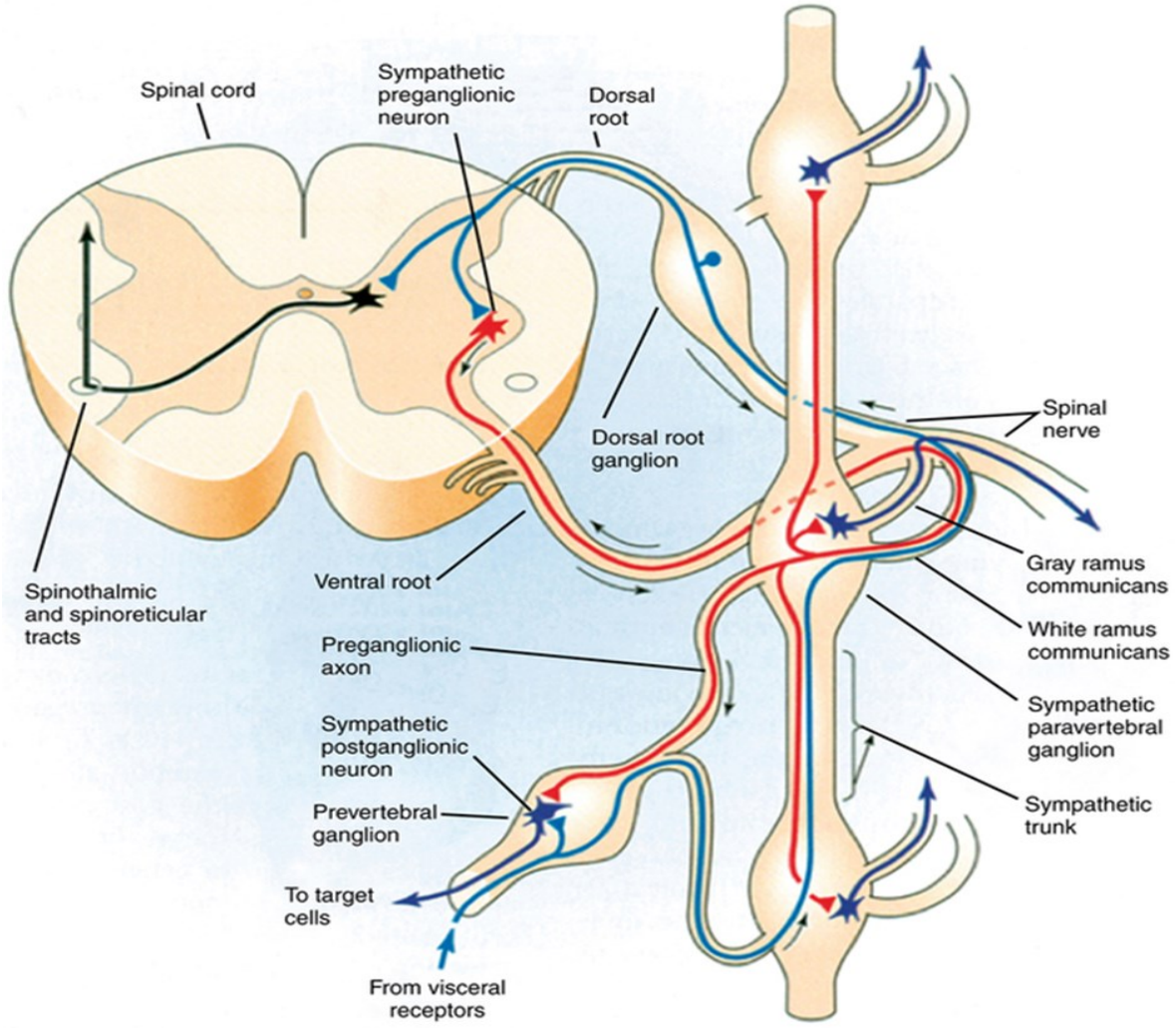


Figure 2.2. Anatomy of the preganglionic and postganglionic sympathetic nerve fibers and synapses (Boron and Boulpaep, 2005).

In summary, this section presented the anatomy of the sympathetic and parasympathetic divisions of the ANS and their location with respect to the spine. The following section will discuss the proposed neurophysiological mechanisms of action of spinal mobilisation and their potential relevance to the decrease in pain that is observed after spinal mobilisation.

2.7. Proposed neurophysiological mechanism of action of spinal mobilisation

Pain is one of the main indicators for spinal mobilisation. Although the clinical outcomes of spinal mobilisation are widely known, the underlying mechanisms are unclear (Vicenzino et al., 1998 and 1996; Sterling et al., 2001; Coronado et al., 2012). An increasing number of studies have demonstrated that the effect of

mobilisation goes beyond biomechanical changes, and these studies have proposed various neurophysiological theories to explain the clinical benefits of mobilisation (Krouwel et al., 2010; Willett et al., 2010; Pentelka et al., 2012). These theories suggest that spinal mobilisation has the ability to activate a number of neurophysiological responses in the central and peripheral nervous system (Bialosky et al., 2009).

Pain processing can be influenced by the peripheral healing process that occurs as a result of inflammation in cases of musculoskeletal injuries (Bialosky et al., 2009). Joint mobilisation may directly influence the interaction between peripheral nociceptors and inflammatory mediators. In fact, some authors have reported changes in the blood levels of endogenous cannabinoids, serotonin, anandamide and B-endorphine following joint mobilisation (McPartland et al., 2005; Degenhardt et al., 2007). Moreover, a study by Teodorczyk-Injeyan et al. (2006) showed that there was a significant decrease in the level of blood and serum cytokines in the mobilisation group in comparison with the control and sham group. The reduction of these inflammatory mediators following mobilisation may affect their interaction with peripheral nociceptors and influence pain processing (Bialosky et al., 2009).

Pain is transmitted to the substantia gelatinosa in the dorsal horn of the spinal cord by slow-conducting fibres (unmyelinated C and myelinated A delta fibres). Then, the nociceptive afferents are modulated via the midbrain and thalamus to the cortical level (Bolying and Jull, 2004). Melzack and Wall (1965) were some of the first researchers to appreciate that pain gating (stimulation by non-noxious input is able to close the gate to painful input) could be affected by the descending control systems projected from the supraspinal centres to the spinal cord. They described how the nociceptive information toward the brain can be reduced by the mechanism of pain gating that occurs when A beta fibres (large-diameter, fast-conducting fibres) inhibit A delta and C-fibres (small-diameter, slow-conducting fibres) in the substantia gelatinosa. It has been suggested that mobilisation may stimulate the pain gate mechanism (Wyke and Polacek, 1975; Souvlis et al., 2004). Sensory inputs such as touch and non-threatening inputs often trigger the gate control mechanism (Melzack and Wall, 1965). Multiple structures are moved by mobilisation, such as joints, nerves, muscles and skin. Therefore, the related afferents are stimulated, including

articular, muscular, cutaneous and neurovascular afferents (Souvlis et al., 2004). As a result, mechanoreceptors elicit discharges that are transmitted by A beta fibres (large diameter) to the spinal cord, resulting in a decrease in pain awareness by decreasing the input from nociceptors (Wyke and Polacek, 1975). However, this preferential ability of the spinal mobilisation toward stimulation of the low threshold mechanoreceptors apart from high threshold neurons has been questioned (Zusman, 1986). Zusman (1986) argued that the proposed hypoalgesic responses of spinal mobilisation might be the result of the suggested ability of the repetitive movement during the application of mobilisation to decrease activity of joint afferents.

George et al. (2006) and Bialosky et al. (2009) tried to explore whether there is a link between the hypoalgesic effects of SMT and the pain gate mechanism. These researchers measured the effect of spinal manipulation (HVT) on the activity of A and C fibres by sensory quantitative testing. Following SMT, they observed a reduction in dorsal horn excitability that was represented by reduction of C nerve fibre-mediated temporal summation. However, this was present only in areas that were supplied by the lumbar nerves and not the upper levels of the spine. These findings indicate that the dorsal horn of the spinal cord mediates local hypoalgesia. Another study by Malisza et al. (2003) used functional MRI to examine the effect of knee mobilisation in rats. Their results indicate that the hypoalgesia observed after mobilisation may be mediated at the spinal cord level, as the pain-associated areas of the spinal cord showed reduced activity. However, mobilisation is thought to produce an input that may extend beyond the spinal cord to the supraspinal levels of the CNS and modulate nociceptive information from the efferents (McGuiness et al., 1997; Vicenzino et al., 1999; Souvlis et al., 2000; Sterling et al., 2001; Cleland et al., 2004; Souvlis et al., 2004; Jowsey and Perry, 2010)

The presence of descending modulatory circuits is another proposed mechanism of induced hypoalgesia. Through this mechanism, numerous neurotransmitters have been observed to function in areas of the CNS, including the anterior cingular cortex, the amygdala, the periaqueductal grey (PAG) and the rostral ventromedial medulla, and result in modulation of pain output (Peyron et al., 2000; Moulton et al., 2005; Sawynok, 2015). These neurotransmitters include endogenous opioids,

vasopressin, endocannabinoids, adenosine, oxytocin and serotonin (Sawynok, 2015). It has also been shown that endocannabinoids and endogenous opioids are involved in mediating the hypoalgesia resulting from human touch and a placebo stimulus (Zubieta et al., 2005; Benedetti et al., 2011).

Much work has focused on the PAG area and the nucleus raphe magnus (NRM). Both animal and human studies have demonstrated that the PAG area of the midbrain is the key to the descending control system and endogenous hypoalgesic mechanisms (Hosobuchi et al., 1977; Cannon et al., 1982). Reynold (1969) first began research into this theory and conducted a study which demonstrated that electrical stimulation in the midbrain PAG area of rats could produce profound hypoalgesia. He found that this hypoalgesic effect was sufficient to compensate the effect of anaesthesia in the surgery. Further animal studies showed that the PAG area has a columnar structure, which includes ventrolateral (vlPAG), lateral (lPAG), dorsomedial (dmPAG) and dorsolateral (dlPAG) subdivisions (Bolying and Jull, 2004). Research has found that stimulation of the vPAG area in rats produces multiple effects, including hypoalgesia that is opioid in nature, freezing of movement and inhibition of the SNS (Farkas et al., 1998; Jansen et al., 1998). This state of hypoalgesia exhibits tolerance with repeated stimulation, and before it becomes apparent, it requires a significant period of peripheral stimulation (Cannon et al., 1982; Morgan and Leibeskind, 1987; Takeshige et al., 1992). On the other hand, stimulation of the dPAG area in rats produces a non-opioid form of hypoalgesia, movement facilitation and sympatho-excitation effects (Farkas et al., 1998; Jansen et al., 1998). The onset of this type of hypoalgesia is generally more rapid than that of vPAG-stimulated hypoalgesia (Wright, 1995). Based on all these findings, it has been suggested that the dPAG area coordinates responses to nociceptive stimuli, whereas the vPAG area activates the opioid system. Therefore, the descending pain inhibitory systems, and most importantly, the PAG area, are crucial for coordinating the responses of different systems, including the SNS, the nociceptive system and the motor system, in order to integrate the behavioural responses to stimuli such as pain and stress (Fanselow, 1991; Lovick, 1991).

In conjunction with these findings, Field and Basbaum (1989) reported that two individual projection systems exist from the PAG area to the spinal cord, which

primarily use different neurotransmitters. Projections from the vPAG area via the NRM use serotonin as a serotonergic neurotransmitter, whereas projections from the dPAG area via the nucleus gigantocellularis, paragigantocellularis and paragigantocellularislateralis use noradrenaline, which is described as being noradrenergic (Fields and Basbaum, 1989). Moreover, Kuraishi et al. (1983 and 1990) demonstrated that the serotonergic system is important with regard to morphine-induced hypoalgesia against thermal nociceptive stimuli, whereas the noradrenergic system is more important in stimulating morphine-induced hypoalgesia related to stimuli of a mechanical nociceptive nature.

Kuraishi (1990) found that nociceptive transmission in the spinal dorsal horn can be inhibited by the descending noradrenergic system, which also inhibits the release of substance P that is evoked by peripheral mechanical stimulation. This has led Wright (1995) to the assumption that activation of the descending pathways from the dPAG area is responsible for the immediate hypoalgesic effects of SMT, which are mediated by the SNS pathways. Therefore, it is hypothesised that if spinal mobilisation stimulates the dPAG area, the resultant hypoalgesia is accompanied by SNS responses (Jowsey and Perry, 2010).

On the other hand, from an anatomical perspective, the paravertebral ganglia and sympathetic trunk are believed to account for the SNS response following spinal mobilisation (Peterson et al., 1993; Kingston et al., 2014). The sympathetic chain and associated ganglia expand along the spine, starting at the upper cervical level and moving downward toward the coccyx (Palastanga et al., 2006). Thus, mobilisation at any spinal level may stimulate local sympathetic fibres (Jowsey and Perry, 2010). This theory forms the basis of the regional bias theory, according to which various spine levels produce various sympathetic responses. Harris and Wagnon (1987) reported sympathetic excitation in the form of decreased skin temperature (ST) following thoracic manipulation versus sympathetic inhibition in the form of increased ST following lumbar and cervical manipulation.

In summary, according to the neurophysiological mechanisms proposed so far, spinal mobilisation has the potential to initiate neurophysiological responses in the central and peripheral nervous system (Bialosky et al., 2009). The

neurophysiological mechanism is brought about via interaction between the autonomic nervous system and the pain system at several levels in the body, including the peripheral regions, the dorsal horn of the spinal cord, the brain stem and the fore brain (Benarroch, 2001). Such a multi-centre centrally coordinated response following spinal mobilisation has been reported in multiple studies (Willett et al., 2010; Pentelka et al., 2012). The following section will present a literature review of the studies that have reported hypoalgesic and SNS responses to spinal mobilisations.

2.8. Hypoalgesic changes following spinal mobilisation

Several studies have examined the immediate effects of a single mobilisation treatment on pain at various spinal levels in those with and without spinal pain conditions (Table 2.2). However, to date, no study has investigated the immediate hypoalgesic (pain relieving) effects of mobilisation treatment in LBP patients. As most of the studies so far have been conducted on asymptomatic participants, an experimental pain measure, such as the pressure pain threshold (PPT), has been used to determine whether or not hypoalgesia has occurred. PPT is defined as the minimal amount of pressure that a person perceives as painful (Chesterton et al., 2007). PPT is a valid, reliable and widely used measure of the pain modulating system following different interventions in the research and clinical setting (Persson et al., 2004; Walton et al., 2014). There are reports on hypoalgesia following cervical mobilisation (Vicenzino, 1995; Vicenzino et al., 1996 and 1998; Sterling et al., 2001; La Touche et al., 2013), thoracic mobilisation (Fryer et al., 2004), and lumbar mobilisation (Krouwel et al., 2010; Willett et al., 2010; Pentelka et al., 2012). However, conflicting results have been reported by four studies (Soon et al., 2010; Sterling et al., 2010; Salom-Moreno et al., 2014; Snodgrass et al., 2014): one study included symptomatic participants who had whiplash for at least three months (Sterling et al., 2010); two studies included patients with chronic neck pain (Salom-Moreno et al., 2014; Snodgrass et al., 2014); and the fourth study included asymptomatic participants (Soon et al., 2010). Sterling et al. (2010) suggested that these contradictory results might be related to the different musculoskeletal conditions that were studied. Another possible reason is the variation in the duration of symptoms between study participants. Moreover, the degree of chronicity of the

symptoms may also affect the hypoalgesic response. However, no studies have investigated the lasting effects of a single mobilisation treatment on PPT.

A number of studies have measured PPT at specific locations in order to determine the extent of the hypoalgesic effects (local, segmental or systemic), to gain insight into the potential hypoalgesic mechanisms of mobilisation (Krouwel et al., 2010; Willett et al., 2010; Pentelka et al., 2012). A study by Willett et al. (2010) used a repeated-measures design to examine the immediate effects of different mobilisation rates on the 5th lumbar vertebrae (2 Hz, 1 Hz and 0 Hz). The results did not show any significant difference in PPT measures between the different treatments (Table 2.2). However, the PPT values increased following mobilisation at each site of measurement: L5 paravertebral muscles, L5 dermatome, L2 dermatome, and 1st interossei. There are some methodological limitations to this study: the subjects were not blinded to the intervention conditions, and a carry-over effect is possible as the difference in the duration between the three conditions was not clear. However, the widespread changes reported in this study in addition to the local changes may indicate the involvement of both spinal and central modulation of pain after mobilisation.

Another study by Krouwel et al. (2010) compared the hypoalgesic effects of quasi-static-, small- and large-amplitude lumbar mobilisation (posterior-anterior L3 mobilisation at a rate of 1.5 Hz for three sets of sixty seconds) with a repeated-measures design (Table 2.2). The findings failed to report any significant difference in PPT values between the three amplitudes ($p = 0.864$); this could mean that the hypoalgesic effect is not influenced by the amplitude of mobilisation. However, there were widespread changes in PPT values over the sites of the measurements (the L3 paravertebral muscles, the L3 dermatome, the S1 dermatome and the deltoid) that were significantly improved compared to the baseline measurements regardless of amplitude ($p = 0.013$). However, it was not mentioned whether the mobilisation was applied into the level of joint resistance or outside the level. Furthermore, no power calculation was used to justify the number of participants, which may have led to a type-II error. These results were contradictory to a proposed theory of Maitland et al. (2001) and Zusman (1986), who claimed that larger amplitude mobilisation is

superior to smaller amplitude mobilisation with regard to reducing pain. As a result of these contradictory findings, researchers are of the opinion that a greater difference might be observed between mobilisation amplitudes if a symptomatic population is used.

Table 2.2. The effect of passive spinal mobilisations on PPT

Reference	Design	Subjects	Technique	Reliability of the PPT device	PPT
Vicenzino et al., 1995	Within-subjects placebo controlled crossover trail	24 asymptomatic Mean age 19.8	Grade III Lateral glide to C5/6 (3x30s)	None reported	Significant main effect of condition (p<.005) No effect size reported
Sterling et al., 2001	Within-subjects placebo controlled crossover trail	30 subjects (16 female and 14 male) with a mean age of 35.77 years, with mid or lower cervical pain lasting longer than 3 months and a dysfunction at C5/6	Grade III unilateral PA to C5/6 on symptomatic side (3x30s)	PPT left C5/6 ICC 0.91. SEM 1.62 PPT right C5/6 ICC 0.92. SEM 1.41	Sig main effect of condition (p<0.01) Mean increase in mobilisation group 22.5 (SD 2.4)%
Fryer et al., 2004	RCT	96 asymptomatic volunteers, aged 19-34 years	1. Treatment (group 1): thoracic HVLA either for upper, mid or lower levels based on tender vertebra.	PPT T4 ICC 0.93 PPT T6 ICC 0.90	A significant improvement in PPT measurement for mobilisation (P<0.01) and manipulation group (P=0.04), and a non-significant

			2. Treatment (group 2): seated extension mobilisation of either upper, middle or lower thoracic spine based on identification of the most tender thoracic vertebra. 3. Placebo: laser acupuncture with a laser pointer.		improvement shown in the sham group (P=0.88). PPT in the mobilisation group increased by 28.42 kPa (d=0.72) compared to 11.88 kPa (d=0.32) for the manipulation group. Furthermore, a statistical difference was found between the mobilisation and laser group (P=0.01), whereas no significant difference was found between mobilisation and manipulation (P=0.20) or between laser and manipulation groups (P=0.67).
Thomson et al., 2009	RCT	50 asymptomatic subjects with a mean age of 27 years	1. Treatment (group 1): a single HVLA thrust to the identified lumbar segment. 2. Treatment (group 2): lumbar mobilisation into right rotation x30s 3. Placebo: laser acupuncture with a laser pointer.	ICC 0.78	Neither lumbar HVLA nor mobilisation had a significant effect on PPT (P=0.584). Only lumbar mobilisation appeared to have a greater mean increase in PPT and effect size (d=0.78) than the control group (d=0.36).

Willett et al., 2010	Within same-subjects repeated measures	30 asymptomatic Mean age 30 years	Large amplitude (200N), grade III, central PA mobilisations performed to L5 (3x60s), the rate of the mobilisations varied at each experimental session (quasi-static pressure,1 Hz, or 2 Hz).	PPT (L5, L2, 1st interossei) ICC 0.89-0.96 SEM 0.17-0.25	Significant main effect of mobilisation regardless of the rate of mobilisation (P<0.01), average percentage change: L5 paravertebral muscles 19.15% L5 dermatome 17.33% L2 dermatome 14.96% 1st interossei 10.89%
Krouwel et al., 2010	Within same-subject repeated measures	30 asymptomatic Mean age 26 years	All subjects completed three experimental conditions on three separate occasions. 1- quasi-static (maintained at 200 N). 2-small amplitude of oscillations (150N-200N) 3- large amplitude of oscillations (forces between 50 and 200 N) Each condition involved a central PA L3 (3x60sx1.5 Hz)	PPT (L3, S1, mid deltoid) ICC 0.84-0.94 SEM 0.16-0.18	Significant main effect of mobilisation regardless of the amplitude (P<0.05), average percentage change (SD): L3 paravertebral muscles 16.26(1.78)% L3 dermatome 12.84(4.60)% S1 dermatome 11.46(6.37)% Deltoid 16.45(4.22)%
Sterling et al., 2010	Parallel group: mobilisations or control (manual contact)	39 whiplash associated disorder (grade II) 18-65 years	Lateral glide C5/6 (3x60s)	None reported	No significant difference between mobilisation and control group (p=0.49) Percentage change: C6 24.1% (7.3)

		Duration of symptoms greater than 3 months			Median nerve 11.3 %(4.7) Tibialis anterior 7.8 %(4.8)
Soon et al., 2010	Within-subjects placebo controlled crossover trail	24 asymptomatic Mean age 37 years	Grade III unilateral PA left C5/6 (3x60s)	PPT (left C5/6) ICC 0.96	No significant effect (p=0.846)
Pentelka et al., 2012	Within subjects repeated measures	19 asymptomatic Mean age 31.9 years	1. Treatment (group 1): (5x 30s) PA mobilisations to L4. 2. Treatment (gtoup 2): (5x 60s) PA mobilisations to L4.	PPT (L4, S1, deltoid) ICC 0.78-0.86	Significant main effect of mobilisation regardless of the duration (p<0.01). Mean percentage change (60 seconds) (actual change $Kg/cm^{2)}$ L4 paravertebral muscles 56% (2.8), L4 dermatome 41% (1.4), S1 dermatome 41% (1.5), Deltoid 46%(1.6)
La Touche et al., 2012	RCT	32 patients with cervico-craniofacial pain of myofascial origin	1. Treatment: AP upper cervical mobilisation (3x120sx0.5Hz). 2. Sham group: manual contact	None	Significant difference in the percentage changes in PPT in the left and right cervical points for the treatment group (p<0.001).
Salom-Moreno et al., 2014	RCT	52 patients with bilateral chronic mechanical neck pain	1. Treatment (group 1):T3-T6 HVLA thrust manipulation	None	No statistically significant interaction for PPT at any location. Both groups experienced similar PPT

			2. Treatment (group 2): grade III to IV central PA T3-T6 mobilisation		increases after the intervention at all locations ($p<0.01$)
Snodgrass et al., 2014	RCT	64 patients with chronic, nonspecific neck pain (aged 18-55years)	1. Treatment (group 1): a single cervical PA mobilisation with a 30-N mean peak force (3x30s) 2. Treatment (group 2): a single cervical PA mobilisation with a 90-N mean peak force (3x30s) 3. Placebo: received detuned-laser treatment.	ICC 0.93-0.96	The time-by-group interaction for summed PPT was not significant for all groups ($F=1.41$, $P=0.242$).

Abbreviations: RCT: randomized controlled trial; kPa: kilopascals; ICC: intraclass correlation coefficient; SD: standard deviation; SEM: standard error of measurement; s: seconds; C6: the 6th cervical vertebrae; C5/6: facet joint between the fifth and the sixt^{h} cervical vertebrae; L4: 4th lumbar vertebrae; L5: 5th lumbar vertebrae;T3: 3rd thoracic vertebrae; T6: sixth thoracic vertebrae; T4: 4th thoracic vertebrae; III: grade three; IV: grade four; AP: anterior-to-posterior pressure; PA: posteroanterior accessory mobilisation; PPT: pressure pain threshold; HVLA: high velocity low amplitude.

2.9. Changes in sympathetic measures following spinal mobilisation

Based on the hypothesis of Wright and Vicenzino (1995) that SMT affects multiple systems, several studies have examined the effect of spinal mobilisation on the SNS. A number of studies have investigated the effect of different forms of spinal mobilisation by measuring outcomes related to the SNS such as vasomotor, cutaneous and sudomotor responses (McGuiness et al., 1997; Vicenzino et al., 1999; Souvlis et al., 2000). Most of these studies have examined the immediate effects of a single mobilisation treatment on SNS at various spinal levels in participants with and without mechanical spinal pain conditions (Table 2.3). However, to date, no study has investigated the SNS responses to spinal mobilisation in patients with LBP. Skin conductance (SC) (which is also known as sweat response, skin resistance [SR], electrodermal activity [EDA], and galvanic skin response [GSR]) has been utilised as a measure of sympathetic activity over the last 25 years in spinal mobilisation research (Balconi, 2010). It represents a measurement of spontaneous change in the electrical resistance of the toes and fingers, where the glabrous area of the skin is present (Balconi, 2010). A sympathoexcitatory effect results in the activation of synapses in the smooth muscles of vessels via adrenaline release, which leads to vasoconstriction (Storm et al., 2000). Furthermore, other sympathetic measures have been reported in related studies, including heart rate (HR), respiratory rate (RR), blood pressure (BP), thermal pain threshold (TPT) and skin temperature (ST).

A number of studies have reported significant measures of sympathoexcitation, primarily SC, following cervical mobilisation (Peterson et al., 1993; Chiu and Wright et al., 1996; McGuiness et al., 1997; Vicenzino et al., 1998; Sterling et al., 2001; La Touche et al., 2012), thoracic mobilisation (Cleland et al., 2004; Jowsey and Perry, 2010) and lumbar mobilisation (Perry and Green, 2008; Piekarz and Perry, 2016). However, contradictory results have been reported by Chiu and Wright (1998), who found no significant sympathetic change in skin conductance or skin temperature following cervical mobilisation. The authors attributed this to the slow rate of mobilisation and the small sample size of the study (n = 16). On the other hand, a RCT study conducted by Yung et al. (2014) showed significant sympathoinhibitory responses in terms of HR and systolic BP in a mobilisation group (AP pressure to

the right C6 costal process) that was not reported in a placebo group; however, this difference was not found to be significant. The authors reported several limitations: an important limitation was that they mobilised the right side of the costal vertebra C6, and thus, collateral circulation to the left may have affected any true cardiovascular response. Moreover, this study utilised asymptomatic young individuals (aged 24.7 ± 1.9), and therefore, the findings may not be generalisable to older populations with neck pain.

One of the first studies in this field (neurophysiological mechanisms related to manual therapy) was by Peterson et al. (1993), who utilised a within-subjects crossover controlled trial to investigate the influence of cervical mobilisation on SNS activity while recording SC and ST of the upper limbs in asymptomatic participants. In the treatment group, a 50%–60% increase in SC was recorded, in comparison to a 30% increase recorded in the placebo condition (manual contact without any movement). They suggested that the oscillatory component of the mobilisation technique was the reason behind the neurophysiological effect. However, measurement error related to the equipment (the Biopac System) was not reported, and no attempt was made to validate the placebo condition. Thus, it is difficult to ascertain the true effect of the mobilisation, considering the variations in the equipment measurements.

In 1996, Chiu and Wright, by measuring SC of the upper limb, compared the effects of two different frequencies (2 Hz and 0.5 Hz) of cervical mobilisation techniques in asymptomatic participants utilizing a repeated measures design. Their results showed a 50%–60% increase in SC from the baseline and a significant difference in favour of the 2-Hz frequency (two oscillations per second). They suggested that the movement component of mobilisation is important with regard to the neurophysiological effects, as mobilising at a faster oscillatory rate increased the SNS effects. However, a placebo condition was not used in the study, which made it difficult to determine the effect of factors other than mobilisation factors, including psychological factors (such as expectation, anxiety belief and depression), on SC. Moreover, only male volunteers were included, which affected the generalisability of the study findings. Furthermore, no power calculation was used to justify the number

of participants, and the process of randomisation between experimental conditions (2 Hz, 0.5 Hz and control) and allocation was not explained. All these shortcomings limit the applicability of the study findings.

Recently a number of randomised control trials (RCTs) have been conducted on the SNS effects of spinal mobilisations (Perry and Green, 2008; Jowsey and Perry, 2010; La Touche et al., 2012; Yung et al., 2014; Piekarz and Perry, 2016), of which only two studies measured the peripheral sympathetic responses of the lower limbs (Perry and Green, 2008; Piekarz and Perry, 2016). In one such RCT, Perry and Green (2008) reported that spinal mobilisation may influence the nervous system both at the spinal and supraspinal level. This study investigated the effects of unilaterally applied oscillatory lumbar mobilisation (grade III PA to left L4/5 for three sets of sixty seconds) compared to placebo mobilisations and a no treatment control group, on SC measured at both the left and right toes (Table 2.3). Although the researchers performed a power calculation and used a proper randomisation and allocation protocol and a double-blinded design, only male participants were included, which limits the generalisability of the findings to a larger clinical population. The results showed a statistically significant side-specific difference in SC ($p = 0.005$) in the mobilisation group with a percentage change in the order of 13.47% compared to the placebo group (-1.93%) and control group (-0.87%). However, the reliability of the instruments at measuring SC (the Biopac System) was not assessed, which limits the findings.

2.9.1. Salivary measures

There has been rapid progression towards the scientific understanding of different salivary parameters (Nater and Rohleder, 2009). For example, a number of salivary components have been taken into account as meaningful physiological markers apart from hormonal analysis such as cortisol. Saliva is a diagnostic medium that has many advantages over blood and urine, including its non-invasive, safe and pain-free collection method that requires minimal training to undertake (Henderson et al., 2010). Thus, salivary biomarkers might be considered ideal for research studies related to psychology and science (Henderson et al., 2010).

Recently, interest has been growing in salivary alpha-amylase (sAA) as a non-invasive marker for SNS activity, as opposed to cortisol, which is used as a measure of the hypothalamic–pituitary–adrenal (HPA) axis (Bosch et al., 2003). Research on rats showed an increase in sAA secretion after direct sympathetic stimulation (Sayardoust and Ekström, 2003; Proctor and Carpenter, 2007), whereas research on humans showed that sAA is a correlate of SNS activity in human subjects under different stressful conditions, including physical conditions (i.e. exercise, cold and heat) and psychological conditions (Chatterton et al., 1996; Nater et al., 2005; van Stegeren et al., 2006). Research reveals that a concentration of sAA is correlated with the release of norepinephrine into the blood stream (in response to stress), as propranolol (a beta-adrenergic blocker) has the ability to inhibit the response of sAA (Rohleder et al., 2006; van Stegeren et al., 2006). However, only one study has been found that examined the effect of a mobilisation treatment—in the form of a rib raising mobilisation technique—on sAA activity as a measure of sympathetic response (Henderson et al., 2010). This study reported a significant decrease in sAA activity in the treatment group when compared to the placebo. However, since the saliva samples were collected immediately after and 10 minutes after the treatment, an initial proposed sympathoexcitation might have occurred during the procedure.

Table 2.3. Changes in sympathetic measures following spinal mobilisation treatment

Reference	Design	Subjects	Technique	SNS measures	Reliability	Findings
Peterson et al., 1993	Within-subjects Placebo (sham mob), control (no contact). Crossover	16 asymptomatic Aged 18-35 years	Grade III central PA to C5 (3x60s)	SC ST	None reported	SC: significant increase in intervention procedure compared to placebo and control procedures. An increase in the order of 50-60% during intervention steadily decreasing to that of placebo after. Placebo consistently increases in the order of 30% during the intervention and 15-20% after the intervention. ST: significant decrease in intervention procedure compared to control. No significant difference between placebo and intervention procedure.
Chiu and Wright, 1996	Within subjects repeated measures	16 asymptomatic (male volunteers) Mean age 18.5 years	1. Grade III central PA mobilisation to C5 (3x60sx2Hz).	SC ST	None reported	SC: significant increase in 2 Hz group compared to control and 0.5 Hz group. 2 Hz group increased in order of 50-60%.

			2. Grade III central PA mobilisation to C5 (3x60sx0.5Hz). 3. Control (no manual contact).			0.5 Hz group increased in order of 15-20% and control condition increased in order of 14-18%. ST: no significant difference in ST between 3 groups.
McGuiness et al., 1997	Within-subjects Placebo (sham mob), control (no contact) Crossover	23 asymptomatic Aged between 18-29 years	Grade III central PA C5 (3x60s)	BP RR HR	None reported	BP, RR, and HR: significant increase in all outcomes in intervention group compared to control and placebo procedures. RR increased in the intervention group during treatment by 44%, diastolic BP increased by 12.5% and systolic BP increased by 4.5%. HR increased in the order of 10.5%.
Chiu and Wright, 1998	Within-subjects Placebo (4 experimental procedures) Crossover	17 asymptomatic Mean age 20.71 years	Grade III PA mobilisation to the right articular pillar of C5/6 Grade III transverse mobilisation to the left side of C5	SC ST	None reported	SC and ST: no significant difference among the 4 experimental procedures.

Vicenzino et al., 1998	Within-subjects Placebo (sham mob), control (no contact) Crossover	24 asymptomatic Mean age 21 years	Grade III left lateral glide C5 (3x30s)	BP RR HR	None reported	BP, RR and HR: significant increase in all outcomes in intervention group compared to control and placebo procedures. RR increased by 36% during treatment, diastolic and systolic BP increased by 14% and HR increased by 13%.
Sterling et al., 2001	Within-subjects Placebo (sham mob), control (no contact) Crossover	30 subjects (16 female and 14 male) with a mean age of 35.77 years, with mid or lower cervical pain lasting longer than 3 months and a dysfunction at C5/6	Grade III unilateral PA to C5/6 on symptomatic side (3x30s)	SC ST	None reported	SC and ST: significant change in both outcomes in intervention group compared to control and placebo procedures. SC increased by 16%-114% on different measures , ST decrease by 1%-3% on different measures.

Cleland et al., 2004	Within-subjects Placebo (2 experiments) Crossover	15 asymptomatic subjects. Mean age of 29.2 years	Group 1: grade III central PA mobilisation to T12 for 30s by an expert clinician. Group 2: grade III central PA mobilisation to T12 for 30s by a novice clinician.	SC	None reported	SC: by the novice, SC increased by 17.75%, by the expert SC increased by 36.25% during intervention. There was a significant greater change in the mean of SC after mobilisation by the expert clinician ($P < 0.025$) compared to the mean increase in SC after treatment by the novice clinician.
Perry and Green, 2008	RCT	45 asymptomatic males Mean age of 21.5 years	Grade III unilateral PA to left L4/5 facet (3X60s)	SC	None reported	SC: Significant change in SC of the ipsilateral limb during the treatment with unilateral PA oscillatory mobilisation compared with placebo and control ($P=0.005$) groups, this change lasted 5 minutes. SC increased by 13.5 % during intervention (for the mobilisation group) that was greater to the placebo (-1.93%) and control (-0.87%) groups.

Jowsey and Perry, 2010	RCT	36 asymptomatic Mean age of 22.7 years	Treatment: right T4 'screw' mobilisation.	SC	None reported	SC: Significant change in SC from baseline to 5 minutes post intervention in the right hand after a right sided T4 mobilisation compared to placebo intervention (P=0.034). SC in the right hand increased by 16.85% greater than placebo during post intervention period.
La Touche et al., 2012	RCT	32 patients with cervico-craniofacial pain Mean age of 33.19 years	AP upper cervical mobilisation (0.5Hzx3x2minutes)	SC ST RR HR	None reported	SC: significant within session increase by 84%. RR: significant increase within session increase by 10%. HR: significant within session increase by 6%. ST: no change.
Yung et al., 2014	RCT	39 asymptomatic Mean age of 24.7 years	Treatment: AP pressure to the right C6 costal process (1.5Hzx5x10s).	BP HR	None reported	BP and HR: Within-group comparisons indicated statistically significant decrease between baseline and post-AP pressure in HR (AP group) and systolic BP (both groups). There was no statistically significant difference between groups for mean HR, mean systolic BP

						and mean diastolic BP for all time points.
Piekarz and Perry, 2016	RCT	60 asymptomatic male Mean age of 21.53 years	Treatment 1: PA L4 mobilisation (3Hzx3x60s) Treatment 2: PA L4 mobilisation (2Hzx3x60s)	SC	None reported	SC with 3 Hz increased by 20.1%, 12.4% with 2 Hz, -1.3% for placebo and 3.2% for control condition from baseline to intervention period. Only the 3 Hz technique showed a significant increase in SC compared to placebo and control condition.

Abbreviations: RCT: randomised controlled trial; Mob: mobilisation; s: seconds; Hz: hertz; C6: the 6th cervical vertebrae; C5/6: facet joint between the 5th and the 6th cervical vertebrae; L4: 4th lumbar vertebrae; L4/5: facet joint between the 4th and 5th lumbar vertebrae; T3: 3rd thoracic vertebrae; T6: sixth thoracic vertebrae; T4: 4th thoracic vertebrae;T12: 12th thoracic vertebrae; III: grade three; IV: grade four; AP: anterior-to-posterior pressure; PA: posteroanterior accessory mobilisation; SC: skin conductance; ST: skin temperature; BP: blood pressure; HR: heart rate; RR: respiratory rate; HVLA: high velocity low amplitude.

2.10. Concurrent changes in hypoalgesia and SNS responses following spinal mobilisation

Lovick (1991) and Morgan (1991) have suggested that the concurrent hypoalgesic and sympathoexcitation might be produced by stimulation of dorsal (dPAG) in animals. Only two studies have investigated the concurrent effects of spinal mobilisation on hypoalgesia and SNS responses (Sterling et al., 2001; La Touche et al., 2012). Sterling et al. (2001) utilised a repeated-measures design and included patients with chronic cervical pain. Following unilateral cervical mobilisation, there were significant differences in the responses on outcome measures PPT, TPT, SC and ST. Based on their findings, Sterling et al. (2001) concluded that there is some indirect evidence that the dPAG area partially mediates the hypoalgesia resulting from mobilisation, as the concurrent hypoalgesia and sympathoexcitation effects following mobilisation appear to be produced in a parallel manner by this area. La Touche et al. (2012) applied anterior-posterior upper cervical mobilisation in patients with temporomandibular disorders. Their results demonstrated hypoalgesic and sympathoexcitatory effects, which indicated the influence of mobilisation on the CNS. However, PPT was measured only at the cervical and craniofacial levels but not distally to the mobilised level. Moreover, although the anterior-posterior technique was applied, sympathetic measures (SC and ST) were assessed at the right upper limb only. Previous studies that applied the anterior-posterior technique measured SC and ST bilaterally to account for any side differences (Cleland et al., 2004; Piekarz and Perry, 2016).

In summary, there is no evidence to indicate that the immediate hypoalgesic response or SNS effects occur alone or concurrently following passive mobilisation treatment in LBP patients. Furthermore, to date, the dose-dependent effect of mobilisation is unknown, as studies have investigated the hypoalgesic effects and/or SNS responses only after a single session of mobilisation. The overall aim of this thesis was, therefore, to investigate the hypoalgesic and sympathetic effects of passive mobilisation treatment in participants with and without LBP over a course of three sessions of mobilisation. Although the optimal number of sessions of many conservative treatments is unknown, a short course of mobilisation has been recommended for the management of CNSLBP (Airaksinen et al., 2006).

The next chapter will systematically review and evaluate the published RCTs on the hypoalgesic and SNS responses to passive spinal mobilisation along different regions of the spine.

Chapter 3

The sympathetic and hypoalgesic effects of spinal mobilisations: a systematic review

3.1. Introduction

The discovery of the neurophysiological effects of spinal mobilisations is important for clinicians to help them understand the benefits of the spinal mobilisations with making substantial and categorical changes to their perspective (Hegedus et al., 2011). The neurophysiological effectiveness of spinal mobilisation has not been clearly established. Although few systematic reviews regarding this issue have been published (Schmid et al., 2008; Hegedus et al., 2011; Kingston et al., 2014; Voogt et al., 2014), the results of the studies concerning changes in related outcome measures to neurophysiological effects of spinal mobilisation techniques are conflicting. The review by Schmid et al. (2008) comprised of 15 randomised controlled trials (RCTs), investigating the immediate neurophysiological effects of passive accessory cervical joint mobilisation techniques either in asymptomatic subjects or patients with neck pain or upper extremity symptoms. The result suggested that the midbrain is involved in mediating the pain control and autonomic responses of passive cervical mobilisation. Although the overall quality was high, most of the involved trials were conducted by the same group of authors, which potentially affects the evidence. Five of the studies included a symptomatic population, two of which included patients with neurogenic pain and the other two included patients with epicondylalgia, whereas only one of the included studies involved patients with musculoskeletal cervical pain, thus influencing the generalisability of the results to this group of patient.

Hegedus et al. (2011) summarised the results of 10 studies examining the temporal nature of the neurophysiological effects of a single session of spinal mobilisations. Six of the studies were pertinent to the cervical spine, one to the lumbar spine and three to the thoracic spine. The result of this review reported that five minutes or less is the average time of the neurophysiological effects with regard to SNS measures of a single session of spinal mobilisations. Thus, this may cause uncertainty about

any meaningful, lasting effect of a single session of spinal mobilisation. However, the majority of the studies reviewed were rated as having unimportant clinical outcomes and a moderate strength of evidence. Studies were not specific to a population with spinal pain as a population of patients with upper limb symptoms were included; and other forms rather than passive mobilisation were involved. Furthermore, there was an overrepresentation of healthy subjects and an underrepresentation of the lumbar spine as a spinal region.

Voogt et al. (2014) found moderate evidence to suggest that manual therapy increased local pressure pain thresholds in patients with musculoskeletal pain. However, only two of the studies reviewed included mechanical neck pain patients who were treated with manipulation rather than passive mobilisations.

None of the available systematic reviews reviewed the effect of passive spinal mobilisations along the three different regions of the spine with regard to hypoalgesic, and SNS effects (Schmid et al., 2008; Hegedus et al., 2011; Kingston et al., 2014; Voogt et al., 2014). A useful contribution to the literature can therefore be achieved by an updated review that incorporates recent studies. Furthermore, this review will attempt to determine if these neurophysiological effects are influenced by rate, amplitude or duration of mobilisation or if the spinal mobilisation is superior to other forms of therapy regarding the previously mentioned effects.

The aim of this review was to systematically review randomised controlled trials which assess the effectiveness of spinal mobilisations with regard to hypoalgesic and SNS responses in healthy populations or in patients with cervical, thoracic or lumbar pain.

3.2. Methods

Recommendations for conducting reviews from the Centre for Reviews and Dissemination were followed for the methods used to undertake this systematic review (Tacconelli, 2009). In order to ensure a comprehensive and standardised framework for reporting, the Preferred Reporting Items for Systematic Reviews (PRISMA) were followed to report this review (Moher et al., 2009).

3.2.1. Literature search

Electronic databases were searched to identify the maximum number of relevant articles and to minimise selection and publication bias (from database inception to December 2016): Academic OneFile, BioMed Central Journals, CINAHL, SPORTDiscus, MEDLINE (EBSCO), PEDro, Web of Knowledge, SCOPUS, AMED, ScienceDirect, The Cochrane Controlled Trial Register (CENTRAL), Health Technology Assessment, NHS Economic Evaluation, ZETOC, TRIP, Health Services/Technology Assessment Text, National Research Register, Current Controlled Trials website, Science Citation Index and Social Science Citation Index, and OpenGrey.

An adjacency search was also carried out in systematic reviews on SMT using The Cochrane database. A reference list search of all full text articles available online was carried out to identify any supporting literature.

3.2.1.1. Search strategy

Combined with spinal mobilisation/spinal mobilization or manual therapy, the following free text words were used: “neurophysiology”, “neurophysiological effect”, “pain threshold”, “sympathetic effect”, “sympathetic nervous system”.

Table 3.1. Example of a search strategy (ScienceDirect).

ScienceDirect	N of results
Spinal mobilization + sympathetic nervous system	34
Spinal mobilisation + sympathetic nervous system	34
Manual therapy + sympathetic nervous system	178
Spinal mobilization + neurophysiology	22
Spinal mobilisation + neurophysiology	22

Manual therapy + neurophysiology	185
Spinal mobilization + sympathetic effect	0
Spinal mobilisation + sympathetic effect	0
Manual therapy + sympathetic effect	3
Spinal mobilization + pain threshold	49
Spinal mobilisation + pain threshold	49
Manual therapy + pain threshold	120

3.2.2. Eligibility criteria

3.2.2.1. Inclusion

1. Design: Any RCT.
2. Population:

   a) Studies with participants aged 18 years or older as more people experience spinal pain as they grow older (UK BEAM, 2004), including either one or both genders.

   b) Included either healthy participants or patients with non-specific back pain at either cervical, thoracic or lumbar parts of the spine that are not caused by a recognisable known specific pathology (e.g. structural deformity, fracture, osteoporosis, tumor, and infection), inflammatory disorder (e.g. ankylosing spondylitis), cauda equina syndrome or radicular syndrome (UK BEAM, 2004).
3. Intervention:

   a) Studies examined the neurophysiological effects of spinal mobilisation as the main or control treatments were included. All studies must have offered the spinal mobilisation in isolation (without combining it with any other type of physical therapy such as exercises) in at least one group of participants in order to have comparable results post-intervention. However, studies that offered any form of physical therapy interventions other than spinal

mobilisation to some groups of participants (to create a control group) were still included providing that the true intervention group was given spinal mobilisation in isolation. This would minimise bias and make the findings more credible by ensuring that any favourable or unfavourable outcomes, from spinal mobilisation, were attributable to this treatment and could be compared with other treatments.

b) Studies that compared the neurophysiological effects of different rates, sets, duration or amplitudes of spinal mobilisations were also included.

4. Outcome: Studies were included if at least one physiologic outcome measure had been used such as the hypoalgesic effect or/and SNS effects of spinal mobilisation. Some or all of the following outcome measures are expected to be available in the studies included: PPT, TPT, SC, ST, HR, RR, and BP.

3.2.2.2. Exclusion

1. Studies that used spinal mobilisation in combination with other forms of treatment or exercises.
2. Studies that examined mobilisation with movements forms of manual therapy [e.g. the Mulligan sustained apophyseal glide (SNAG) as the focus of this review is the passive spinal mobilisation].
3. Studies with a study population consisting of patients with cervical, thoracic or lumbar pain, which is not mechanical in origin.
4. To ensure accurate and complete interpretation, studies published in languages other than English were excluded.

3.2.3. Selection of studies

All titles were screened by the author to assess for relevance and duplication. The abstracts of relevant titles were evaluated for eligibility. The reviewer retrieved full text articles of every study that met the inclusion criteria. The titles and abstracts of the identified studies were reviewed in order to identify the potential relevance of the studies for the review. Furthermore, the reference lists of all studies retrieved were assessed and a search of relevant studies was performed.

3.2.4. Approach to Methodological Quality Assessment

The eligible articles were evaluated for methodological quality using a criteria list based on the updated method guidelines for systematic reviews in the Cochrane Back Review Group (Appendix 1) (van Tulder et al., 2003). The maximal achievable quality score is 11 and papers that score six or more are considered to have low risk of bias whereas papers that score less than 6 are considered to have a high risk of bias (Verhagen et al., 2001). A second and third reviewer were included in assessment of the quality of the literature.

3.2.5. Data extraction

Data were extracted and summarised (Table 3.2). The following data were extracted from the studies: author, publication year, aim of the study, number of participants, age, gender, duration of complaints, characteristics of the studies, characteristics of the interventions including control intervention, characteristics of the outcome, and finally the results. This data extraction form was designed to provide the key points about each study, which facilitated the comparison process between studies, as well as the synthesis and analysis of the papers.

3.2.6. Data synthesis and analysis

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system was used to assess the overall quality of evidence and to grade the strength of recommendations based on the updated method guidelines for systematic reviews in the Cochrane Back Review Group (van Tulder et al., 2003). The final GRADE score, which indicated either very low, low, moderate or strong quality evidence was calculated (van Tulder et al., 2003).

GRADE requires that after collecting and summarising the evidence, similar evidence in terms of intervention, population, comparator(s) and outcomes need to be grouped together. Then, explicit criteria provided by GRADE was used to rate the quality of evidence that involved study design, risk of bias, indirectness, inconsistency and magnitude of effect. According to the quality of the supporting evidence, recommendations could be characterised as weak or strong. The evidence was summarised in an informative summary of findings tables that

demonstrated the quality of evidence as well as the reasons behind the rate of quality (Guyatt et al., 2011).

3.3. Results

3.3.1. Search strategy

The original search yielded 696 references, of which 679 were excluded after screening the abstracts, as they were considered irrelevant to this review or duplicated. Seventeen were considered relevant references, of which nine were excluded because they did not meet the inclusion criteria. The procedure of study selection is demonstrated in the study flow chart (Figure 3.1). Eight articles (RCTs studies) with a sample size of 492 in total were found to meet the inclusion criteria.

Figure 3.1. Flow chart of systematic review inclusion and exclusion.

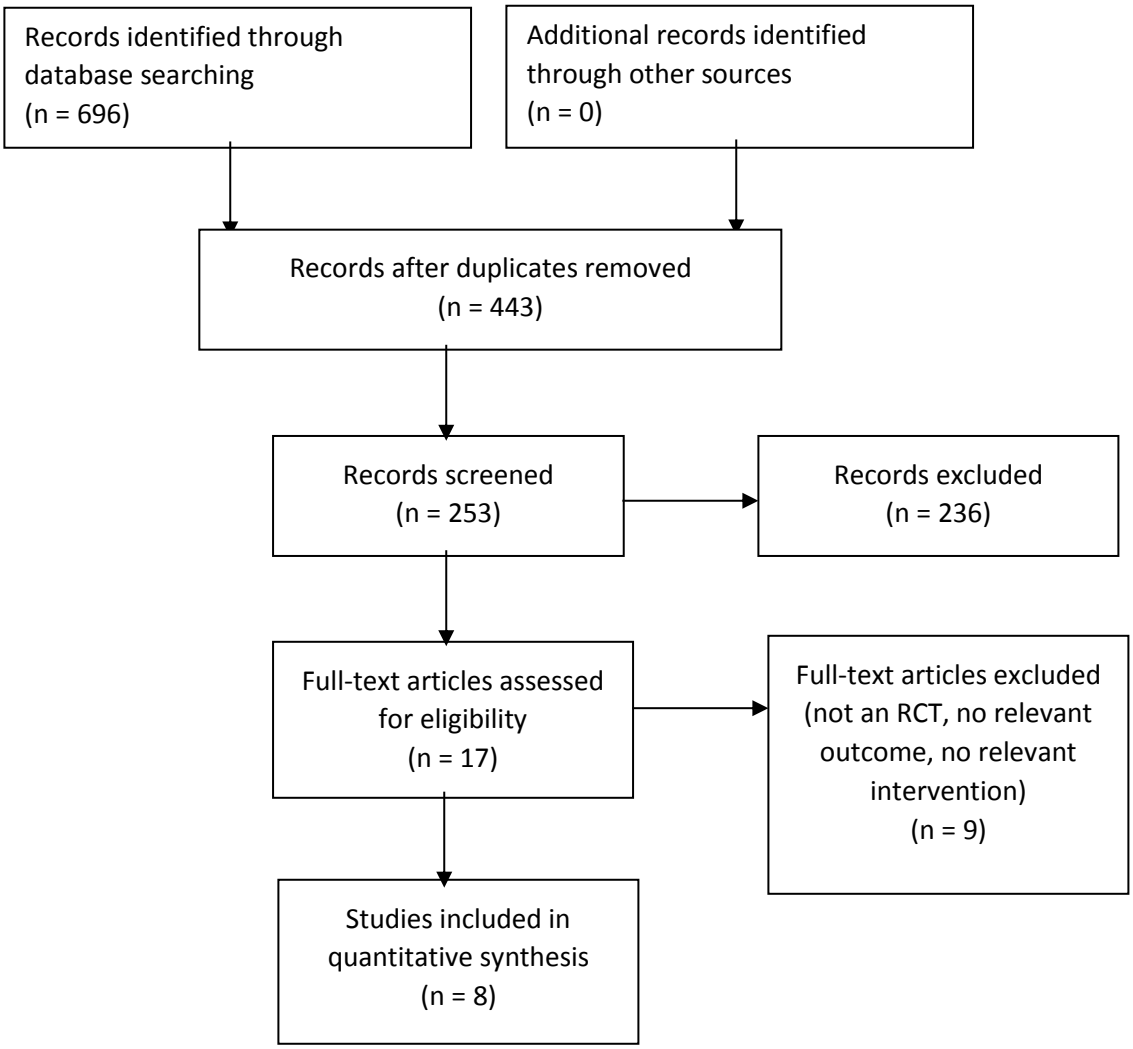


Table 3.2. Data extraction form.

Authors	Aim of the study	Participants	Intervention group(s)	Control group	Outcome measures of interest	Results
Perry and Green (2008)	To examine the hypothesis that specific mechanical mid to end range mobilisation applied to the left L4/5 zygapophysial joint at a rate of 2Hz would produce a significant change in SC during the treatment, which would be greater in the left leg compared to the	45 asymptomatic males, aged 18-25 years.	1. Treatment: grade III unilateral PA to left L4/5 facet. 2. Placebo: light pressure to left L4/5 facet, no oscillation.	Subject laid prone as in other group with no manual contact.	SC	SC: Significant change in SC of the ipsilateral limb during the treatment with unilateral PA oscillatory mobilisation compared with placebo and control (P=0.005) groups. This change lasted 5 minutes. SC increased by 13.5 % during intervention (for the mobilisation group) that was greater to the placebo (-1.93%) and control (-0.87%) groups.

	contralateral one, and greater than that in the placebo and control groups.					
Jowsey and Perry (2010)	To establish whether a T4 PA rotatory mobilisation technique produced any greater responses on the hands' sympathetic activity compared to placebo treatment in an	36 Asymptomatic (23 females and 13 males), aged 18-35 years.	1. Treatment: right T4 'screw' mobilisation. 2. Placebo: T4 pressure without mobilisation.	None	SC	SC: Significant change in SC from baseline to 5 minutes post intervention in the right hand after a right sided T4 mobilisation compared to placebo intervention (P=0.034). SC in the right hand increased by 16.85% greater than placebo during post intervention period.

	asymptomatic population.					
Thomson et al. (2009)	To examine and compare the hypoalgesic effects of mobilisation and manipulation in the lumbar spine in a healthy population.	50 asymptomatic subjects (21 females and 29 males) with a mean age of 27 ± 6 years.	1. Treatment (group 1): a single HVLA thrust to the identified lumbar segment. 2. Treatment (group 2): lumbar mobilisation into right rotation for 30 seconds. 3. Placebo: 30 seconds of laser acupuncture with a laser pointer.	None	PPT	PPT: Neither lumbar HVLA nor mobilisation had a significant effect on PPT (P=0.584). Only lumbar mobilisation appeared to have a greater mean increase in PPT and effect size (d=0.78) than the control group (d=0.36).
Fryer et al. (2004)	To examine and compare the effect of mobilisation	96 asymptomatic volunteers (39 males and 57	1. Treatment (group 1): thoracic HVLA either for upper,	None	PPT	PPT: A significant improvement in PPT measurement for mobilisation (P<0.01) and manipulation group (P=0.04), and a non-significant improvement shown in the sham group (P=0.88). PPT in the mobilisation group increased

	and manipulation of the thoracic spine on PPT in healthy subjects.	females) aged 19-34 years	mid or lower levels based on tender vertebra. 2. Treatment (group 2): seated extension mobilisation of either upper, middle or lower thoracic spine based on identification of the most tender thoracic vertebra. 3. Placebo: 30 seconds of laser acupuncture with a laser pointer.			by 28.42 kPa (d=0.72) compared to 11.88 kPa (d=0.32) for the manipulation group. Furthermore, a statistical difference was found between the mobilisation and laser group (P=0.01), whereas no significant difference was found between mobilisation and manipulation (P=0.20) or between laser and manipulation groups (P=0.67).
Snodgrass et al. (2014)	To determine if force magnitude during	64 patients with chronic, nonspecific neck	1. Treatment (group 1): a single PA mobilisation	None	PPT	PPT: The time-by-group interaction for summed PPT was not significant for all groups (F=1.41, P=0.242).

	posterior-to-anterior mobilisation affects immediate and short-term outcomes in patients with chronic, nonspecific neck pain.	pain (aged 18-55years)	with a 30-N mean peak force. 2. Treatment (group 2): a single PA mobilisation with a 90-N mean peak force. 3. Placebo: received detuned-laser treatment.			
Yung et al. (2014)	To compare the BP and HR response of healthy volunteers to AP pressure applied to the cervical spine versus placebo.	39 asymptomatic subjects (25 females and 14 males) with a mean age of 24.7 ± 1.9 years	1. Treatment: AP pressure to the right C6 costal process. 2. Placebo: light touch applied to the right C6 costal process.	None	BP HR	BP and HR: Within-group comparisons indicated statistically significant decrease between baseline and post-AP pressure in HR (AP group) (-2.8%) and systolic BP (both groups) (-2.4%, -2.6 %). There was no statistically significant difference between groups for mean HR, mean systolic BP and mean diastolic BP for all time points.

Salom-Moreno et al. (2014)	To compare the effects of thoracic thrust manipulation versus thoracic non-thrust mobilisation in patients with bilateral neck pain.	52 patients with bilateral chronic mechanical neck pain with a mean age of 33 years	1. Treatment (group 1):T3-T6 HVLA thrust manipulation 2. Treatment (group 2): grade III to IV central PA T3-T6 mobilisation	None	PPT	No statistically significant interaction for PPT at any location of measurements. Both groups experienced similar PPT increases after the intervention at all locations ($p<0.01$). Within-group and between-group effect sizes were small (SMD < 0.22)
Piekarz and Perry (2016)	To investigate the effects of increasing the oscillation frequency greater than 2 Hz.	60 asymptomatic male Mean age of 21.53 years	Treatment 1: PA L4mobilisation (3Hzx3x60s) Treatment 2: PA L4 mobilisation (2Hzx3x60s) Placebo: same hand position but with a static, non-oscillatory force applied to L4.	Subject laid prone as in other group with no manual contact.	SC	SC with 3 Hz increased by 20.1%, 12.4% with 2 Hz, -1.3% for placebo and 3.2% for control condition from baseline to intervention period. Only the 3 Hz technique showed a significant increase in SC compared to placebo and control condition

Abbreviations: C6: the 6th cervical vertebrae; L4: the 4th lumbar vertebrae; L4/5: facet joint between the 4th and the 5th lumbar vertebrae; T3: the 3rd thoracic vertebrae;T6: the 6th thoracic vertebrae; T4: the 4th thoracic vertebrae; III: grade three; IV: grade four; AP: anterior-to-posterior pressure; PA: posteroanterior accessory mobilisation; PPT: pressure pain threshold; SC: skin conductance; BP: blood pressure; HR: heart rate; HVLA: high velocity low amplitude.

3.3.2. Quality of the trials

Quality scores ranged from 5 to 9 points out of a maximum of 11 points (Table 3.3). The most common problems were failure to blind the clinician and failure to blind the subjects.

Table 3.3. Methodological quality assessment table.

Study	Was the method of randomisation adequate?	Was the treatment allocation concealed?	Were the groups similar at baseline regarding the most important prognostic indicators ?	Was the patient blinded to the intervention?	Was the care provider blinded to the intervention?	Was the outcome assessor blinded to the intervention?	Were co-interventions avoided or similar?	Was the compliance acceptable in all groups?	Was the drop-out-rate described and acceptable?	Was the timing of the outcome assessment on all groups similar?	Did the analysis include an intention-to-treat analysis?	Overall quality score
Jowsey and Perry (2010)	Yes	D/K	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7
Thomson et al. (2009)	D/K	D/K	No	No	No	Yes	Yes	Yes	Yes	Yes	No	5
Fryer et al. (2004)	Yes	D/K	No	No	No	Yes	Yes	Yes	Yes	Yes	No	6
Perry and Green (2008)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8
Snodgrass et al. (2014)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	9
Yung et al. (2014)	No	Yes	No	D/K	No	D/K	Yes	Yes	Yes	Yes	No	5
Salom-Moreno et al. (2014)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	9
Piekarz and Perry (2016)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8

Items could be addressed as Yes, No, Don't Know (D/K).

3.3.3. Study characteristics

3.3.3.1. Intervention

Table 3.4. A list of all the mobilisation techniques used within the studies.

Authors	Interventions
(Perry and Green, 2008)	Unilateral PA grade III oscillatory mobilisations, over the left L4/5 facet, at a rate of 2 Hz for three sets of one minute.
(Jowsey and Perry, 2010)	A right T4 'screw' grade III oscillatory mobilisation for three sets of one minute, at a rate of 0.5 Hz.
(Thomson et al., 2009)	Thirty seconds lumbar mobilisation into right rotation.
(Fryer et al., 2004)	A thirty second seated extension thoracic mobilisations for tender vertebrae.
(Snodgrass et al., 2014)	1- A single PA grade III oscillatory cervical mobilisation with a 30-N mean peak force, at a rate of 1 Hz for three sets of one minute. 2- A single PA grade III oscillatory cervical mobilisation with a 90-N mean peak force, at a rate of 1 Hz for three sets of one minute.
(Yung et al., 2014)	AP pressure to the right C6 costal process at a rate of 1.5 Hz for five sets of 10 seconds.
(Salom-Moreno et al. ,2014)	1. Treatment (group 1):T3-T6 HVLA thrust manipulation. 2. Treatment (group 2): grade III to IV central PA T3-T6 mobilisation.
(Piekarz and Perry, 2016)	1.Treatment (group 1): PA L4 mobilisation (3Hzx3x60s) 2.Treatment (group 2): PA L4 mobilisation (2Hzx3x60s)

Abbreviations: C6: the 6th cervical vertebrae; L4: the 4th lumbar vertebrae; L4/5: facet joint between the 4th and the 5th lumbar vertebrae; T3: the 3rd thoracic vertebrae; T6: the 6th thoracic vertebrae; T4: the 4th thoracic vertebrae; III: grade three; IV: grade four; AP: anterior-to-posterior pressure; PA: posteroanterior accessory mobilisation; HVLA: high velocity low amplitude.

3.3.3.2. Participants

All the studies included both male and female participants, except for two (Perry and Green, 2008; Piekarz and Perry, 2016) that included only male participants. Only two studies used symptomatic subjects, both with chronic nonspecific neck pain (Salom-Moreno et al., 2014; Snodgrass et al., 2014); whereas all other included studies included healthy subjects. In general, the papers included in this review had similar inclusion/exclusion criteria and the subjects involved had similar baseline characteristics that improved the generalisability of the findings.

3.3.3.3. Study outcomes

Table 3.5. The study outcomes (positive and indifferent outcomes).

Outcome Measures		Study Outcomes	N of Studies
Pain related measures	PPT	A statistically significant difference in PPT after mobilisation compared to placebo and/or control.	1
		No statistically significant difference in PPT after mobilisation compared to HVLA, placebo and/or control	3
Sympathetic nervous system indicators	SC	A statistically significant difference in SC after mobilisation compared to placebo and/or control.	3
	BP HR	No statistically significant difference in HR, systolic BP and diastolic BP after mobilisation compared to placebo.	1

PPT: pressure pain threshold
SC: skin conductance
BP: blood pressure
HR: heart rate

3.3.4. GRADE score of overall quality

3.3.4.1. Hypoalgesic Effects of Mobilisation Versus Placebo and Control Groups

One study with low risk of bias (Table 3.3) examined the effect of seated extension, passive thoracic mobilisation on PPT measures and supported its effectiveness in healthy subjects compared to a placebo group (Fryer et al., 2004). One study with high risk of bias (Table 3.3) suggested no significant effect of passive lumbar mobilisation on PPT measures for mobilisation compared to a placebo group (Thomson et al., 2009).

The two trials studying the hypoalgesic effects of passive spinal mobilisation were similar when comparing mobilisation versus no treatment, with healthy subjects and the same outcome measure (PPT) (Fryer et al., 2004; Thomson et al., 2009). Assessment of the overall quality of evidence the final GRADE score (Table 3.6) indicated very low evidence to support the effect of passive spinal mobilisations versus no treatment on PPT measurements in healthy subjects.

Table 3.6. GRADE Evidence profile

intervention	Studies	Type of evidence Score	Quality score	Consistency score	Directness score	Effect size score	Overall quality score
Passive mobilisations vs. no treatment on PPT	Fryer et al., 2004; Thomson et al., 2009	+4	-3[a]	-1[b]	-1[c]	0[d]	-1 (very low quality evidence)
Passive mobilisations vs. placebo on sympathetic outcome measures	Perry and Green, 2008; Jowsey and Perry, 2010; Yung et al., 2014	+4	-3[a]	-1[b]	-1[c]	0[d]	-1 (very low quality evidence)
Passive mobilisations vs. HVLA thrust on PPT	Fryer et al., 2004; Salom-Moreno et al. ,2014;Thomson et al., 2009	+4	-3[a]	-1[b]	-1[c]	0[d]	-1 (very low quality evidence)

PPT: pressure pain threshold

HVLA: high velocity low amplitude thrust

[a] Problem with more than three elements of quality (Unclear allocation concealment in all studies, different baseline characteristics in all studies, care providers were not blinded in all studies, patients blinded in only one study).

[b] Lack of agreement between studies.

[c] Recruitment issues decreasing generalisability.

[d] Not all effect sizes >2 or <0.5 and significant.

3.3.4.2. Sympathetic Nervous System Effects of Mobilisation Versus Placebo and Control Groups

One study with a low risk of bias (Table 3.3) compared the effect of passive thoracic mobilisation techniques (grade III oscillatory mobilisation for three sets of one minute, at a rate of 0.5 Hz) on the SC measures in healthy subjects to placebo and control groups and suggested a significant sympathoexcitatory response (Jowsey and Perry, 2010). Another study with a low risk of bias (Table 3.3) examined the effect of lumbar mobilisation (unilateral PA grade III oscillatory mobilisations, over the left L4/5 facet, at a rate of 2 Hz for three sets of one minute) on the SC measures in healthy subjects compared to placebo and control groups and supported its

sympathoexcitatory response (Perry and Green, 2008). On the other hand, a third study with low risk of bias examined the effect of AP gentle pressure to the right C6 costal process at a rate of 1.5 Hz for five sets of 10 seconds on the HR and BP measures in healthy subjects compared to the placebo group and found within-group (mobilisation) sympathoinhipatory response (decreased HR and systolic BP) (Yung et al., 2014). However, this response was not significant in comparison with placebo group.

The SNS effects of passive spinal mobilisation were similar when comparing mobilisation versus placebo, on healthy subjects and using the sympathetic outcome measures (Perry and Green, 2008; Jowsey and Perry, 2010; Yung et al., 2014). Assessment of the overall quality of evidence using the GRADE system indicated very low evidence to support the effect of passive spinal mobilisations versus placebo on SNS measurements in healthy subjects (Table 3.6).

3.3.4.3. Mobilisation Versus Manipulation

Three studies compared the effect of mobilisation with HVLA thrust on PPT measures in healthy subjects (Fryer et al., 2004; Salom-Moreno et al., 2014; Thomson et al., 2009). Their findings suggested no statistically significant difference in PPT after mobilisation compared to HVLA.

Based on the assessment of the overall quality of evidence the final GRADE score indicated very low quality evidence to support the effect of passive spinal mobilisations versus HVLA thrust on PPT measurements in healthy subjects (Table 3.6).

3.3.4.4. Additional information yielded from individual studies

One study (Snodgrass et al., 2014) compared the effects of different force magnitudes of mobilisation on PPT in chronic non-specific neck pain patients. These authors found that a higher force magnitude of mobilisation (90-N mean peak force) did not lead to a significant increase in PPT compared to a lower force magnitude (30-N mean peak force). Moreover, no significant differences in PPT were found between these groups of patients and the placebo group.

Another study by (Piekarz and Perry, 2016) compared the effects of different rates (3Hz and 2Hz) of mobilisations on SC compared to placebo and control. These authors found that only the 3 Hz technique showed a significant increase in SC compared to placebo and control condition.

3.4. Discussion

The objective of this chapter was to systematically review randomised controlled trials that have assessed the effect of spinal mobilisations on hypoalgesic and SNS responses in healthy populations or in patients with cervical, thoracic or lumbar pain.

The implication for investigations of neurophysiological effects of spinal mobilisations is that if spinal mobilisation produces hypoalgesia and sympathoexcitation; the dPAG of the midbrain is stimulated (Vicenzino et al., 1998). Therefore, if spinal mobilisation stimulates dPAG, then perhaps it may cause pain relief. Thus, studies on neurophysiological effects are important to drive the focus away from the biomechanical model toward a more global model, which covers spinal, peripheral and supraspinal neurophysiological effects (Bialosky et al., 2009; Schmid et al., 2008).

Overall, this review found very low quality of evidence for the use of spinal mobilisations which affect the pain and the SNS. Two studies in this review established a statistically significant change in skin conductance, consistent with sympathetic excitation, which was observed following one application of spinal mobilisations and lasted for five minutes. Only one study, out of four examining the hypoalgesic effects in this review, showed a statistically significant change in PPT following spinal mobilisations (a thirty second seated extension thoracic mobilisations for tender vertebrae) compared to the sham group. Although the results should be interpreted with caution, they support the theory that spinal mobilisations trigger activation of sweat gland mechanisms (Bialosky et al., 2009; Chu et al., 2014).

3.5. Clinical relevance of these findings

In humans, the dPAG is responsible for mediating sympathetic activation and concurrent hypoalgesia (Evan, 2002). It is speculated that dPAG mechanisms

(supraspinal mechanisms) can be activated by stimulation of the receptors of the structures of a spinal segment during mobilisations (Pickar, 2002). Results from the studies in this review have consistently demonstrated increases in skin conductance, with inconsistent results regarding PPT, blood pressure and heart rate, which is inconsistent with the mediated effects of the dPAG.

Dishman and Bulbulian (2000) speculated that spinal reflex pathways might be stimulated by the application of oscillation through spinal mobilisations. Four studies out of eight in this review applied oscillatory mobilisation techniques. Only two of the studies provide some support to this hypothesis; they reported significant sympathetic changes after mobilisations (Perry and Green, 2008; Jowsey and Perry, 2010). The assumption that the oscillatory component is responsible for the sympathetic response after spinal mobilisations is questionable.

Evan (2002) hypothesised that sympathetic activation after spinal mobilisations may result from stimulation of the sympathetic chain and related ganglia at any level of the spine. Two studies in this review provide some support for this hypothesis; they reported side specific sympathetic responses (Perry and Green, 2008; Jowsey and Perry, 2010). However, one study in this review, by Yung et al. (2014), did not report changes in blood pressure and heart rate post AP pressure applied to the right side of C6, where the middle and inferior cervical ganglia project their postganglionic axons to the heart.

3.6. Limitations of the review

Only papers published in English language were involved, which may lead to a publication, cultural or/and language bias. It was not possible to include two reviewers through the process of evaluation of eligibility of studies and data extraction in order to ensure reproducible judgements and minimise selection bias as recommended by the Cochrane Collaboration (Higgins and Deeks, 2008). However, the author had help developing the search strategy from an information resources specialist. In addition, a second and third reviewer were included in assessment of the quality of the literature. Moreover, due to the nature of this review the reviewer was not blinded to publication information of the paper such as authors,

institution, journal name and direction and magnitude of the findings as recommended by Montori et al. (2003).

3.7. Conclusion

This chapter has presented a systematic review of randomised controlled trials which assessed the effectiveness of spinal mobilisations on hypoalgesic and SNS responses in healthy populations or in patients with cervical, thoracic or lumbar pain. This review demonstrates that there is very low evidence to support the effect of passive spinal mobilisations versus no treatment or placebo on PPT and SNS measurements in healthy subjects or those with chronic neck pain. There is very low quality evidence to suggest that passive spinal mobilisation is superior to HVLA thrust regarding hypoalgesia in healthy subjects. To date there have been no studies on the PPT and SNS effects of spinal mobilisation in those with LBP. Studies investigating neurophysiological effects of passive spinal mobilisations in a symptomatic LBP population are necessary. The overall aim of this thesis was therefore to investigate the hypoalgesic and sympathetic effects of passive mobilisation treatment in those with LBP. The following chapter considers the measurement of these variables.

Chapter 4

Methods of measuring sympathetic nervous system and hypoalgesic responses

4.1. Introduction

Recent physiotherapy research has focused on the dynamic continuum concept of the nervous system that includes spinal and supra-spinal responses to physiological and mechanical stimuli. This research measures SNS responses as a quantification of the proposed neurophysiological mechanism. This chapter will consider the methods of measuring sympathetic nervous system responses and the mobilisation technique that were used within the context of this thesis. In addition, consideration is given to the use of pressure algometry to measure PPT and Numerical Pain Rating Scale (NPRS) as one of the patient-reported measures that clinicians often use to measure pain intensity in a clinical setting (Valente et al., 2011).

The previously reported outcome measures from the literature (skin conductance, skin temperature, blood pressure, heart rate, respiratory rate, salivary alpha-amylase, pressure pain threshold and Numerical Pain Rating Scale) (Chapter 2, section 2.8 and 2.9) were used in this thesis as measures of hypoalgesic and sympathetic responses to spinal mobilisation treatment in an asymptomatic population and LBP patients after assessing their reliability within the context of this thesis (Chapter 5). The following section will detail the equipment used in subsequent chapters in this thesis and the specific procedure related to the use of each item.

4.2. Equipment

4.2.1. The e-Health Sensor Shield with Arduino

Physiological recordings of skin conductance, heart rate, respiratory rate and skin temperature were measured by using the e-Health Sensor Shield V2.0 that collected continuous, non-invasive physiologic data through a number of sensors. Cooking Hacks designed the e-Health Sensor Shield for the use of medical researchers. It is usually used alongside Arduino (Figure 4.1), which is an open-source electronics

prototyping platform that can simplify the amount of hardware and software development needed to run a system.

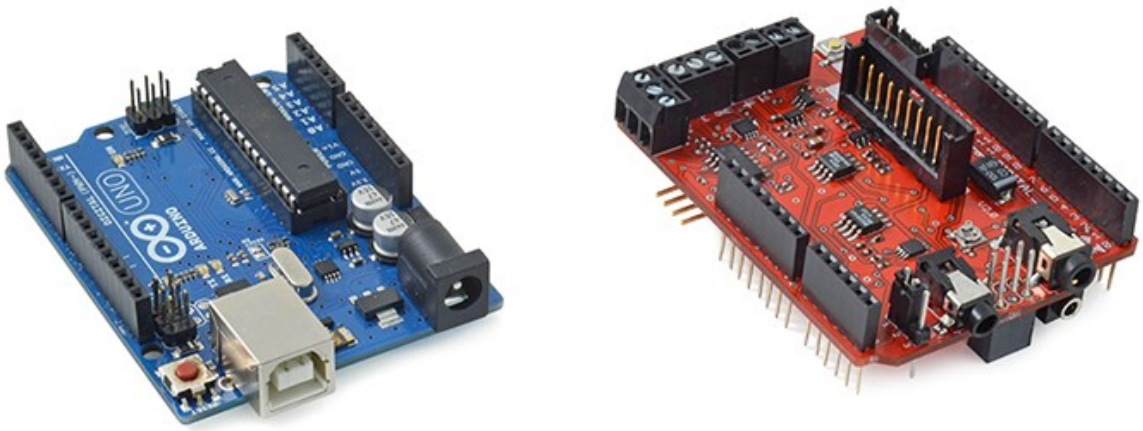


Figure 4.1. Arduino (left) and the e-Health Sensor Shield (right) (Cooking Hacks, 2013).

The e-Health Sensor Shield was stacked on top of Arduino in order to allow the Arduino board to gather information from the different sensors (Figure 4.2). Different biometric sensors can be connected to the e-Health Sensor Shield; however, for the purposes of this thesis, only four sensors were used: airflow, body temperature, galvanic skin response and electrocardiogram (ECG) sensors.

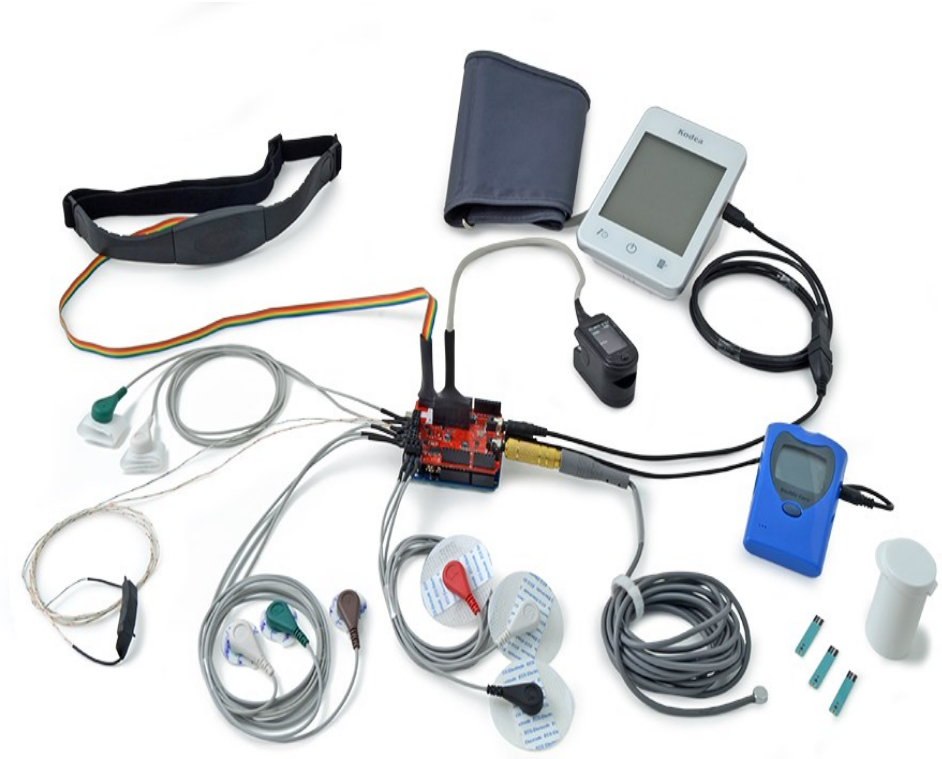


Figure 4.2. The e-Health Sensor Shield with Arduino and related sensors (Cooking Hacks, 2013).

The e-Health Sensor Shield, together with the e-health software coding libraries for the Arduino microcontroller and all the sensors, allows data to be read from each sensor. Information needed to configure the e-Health Shield with Arduino is available on the Labelium and Cooking Hacks' official website: https://www.cooking-hacks.com/documentation/tutorials/ehealth-biometric-sensor-platform-arduino-raspberry-pi-medical. For the purposes of this work, Custom written Labview (version 2013, National Instruments, Texas, USA) was developed to control the e-Health Shield device and enable data acquisition. Two coupled e-health Shields and Arduinos were connected via a USB cable to a personal computer, with the following sensors attached:

1. An airflow (breathing) sensor: composed of a set of two prongs that were placed in the nostrils (Figure 4.3).

Figure 4.3. Airflow sensors (Cooking Hacks, 2013).

2. Two body temperature sensors: placed over the plantar surface of the big toe, bilaterally (Figure 4.4).
3. Two galvanic skin response (GSR – sweat) sensors: placed over the plantar surface of the second and third toes, bilaterally (Figure 4.5). The plantar surface of the second and third toes was selected because it has been reported that it is able to provide clear sympathetic responses from the lower limbs (Elie and Guiheneuc, 1990). Furthermore, the plantar surfaces of the second and third toes were selected because L5 has a coetaneous branch (the medial plantar nerve) that supplies them (Perry and Green, 2008); this permits the peripheral sympathetic response to be measured when mobilisation is later applied (Chapters 6 and 7).

Figure 4.4. Skin temperature sensor (Cooking Hacks, 2013).

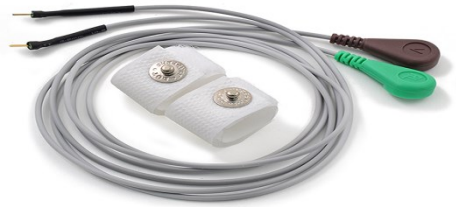
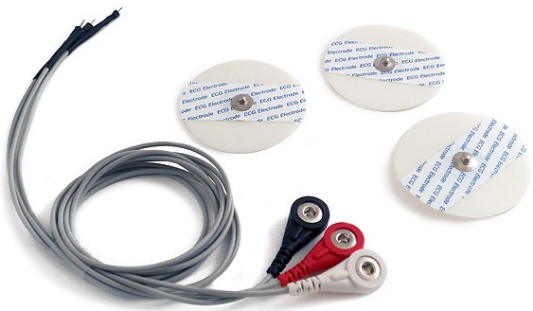


Figure 4.5. Skin conductance sensors (Cooking Hacks, 2013).

4. HR sensors (ECG): connected to the chest. Neutral (White, Figure. 4.6 and 4.7) and positive (Red, Figure. 4.6 and 4.7) sensors were placed parallel to each other (heart level) while negative sensors (Black, Figs. 4.6 and 4.7) were placed below the neutral sensors (Figures 4.6 and 4.7).



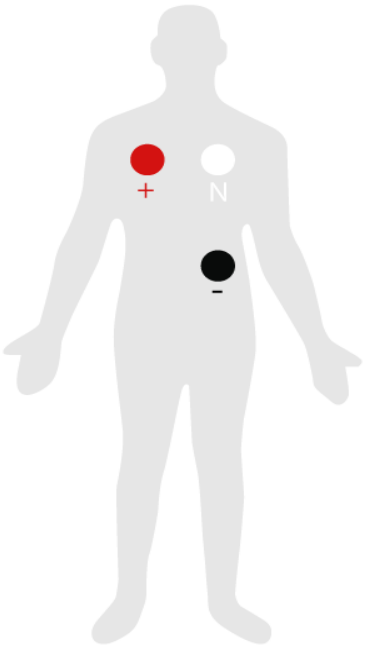


Figure 4.6. Electrocardiogram sensors (Cooking Hacks, 2013); Figure 4.7. Sites of ECG connections (Cooking Hacks, 2013).

In order to measure the skin temperature and skin conductance bilaterally, it was necessary to use a second Arduino and e-Health Sensor Shield, as each device has capability to record from one temperature and one GSR sensor. Data were recorded from all sensors simultaneously using the LabView environment, with signals sampled at 60 Hz. The duration of data acquisition was modified within each of the data collection protocols and will be specifically reported in each of these chapters. Prior to data analysis, the analogue voltage signals collected were transformed into relevant measurement units based on the factory supplied calibration factors.

4.2.2. Blood pressure monitor

Blood pressure was measured by a digital monitor (Kodea KD-202F, Shanghai Kodea Economic & Trade Development Co., Shanghai, China) (Figure 4.8). The cuff was wrapped around the left arm. It measures the pressure of the blood that is sent to the arteries as the blood is pumped out of the contracted heart and into the rest of the body (Jones et al., 2003). The recommendation is to measure blood pressure while the person is relaxed in a seated position (Jones et al., 2003). Two numbers record blood pressure: the first records systolic pressure as the heart beats, while the second records diastolic pressure as the heart muscle relaxes.

Figure 4.8. Blood pressure monitor (Cooking Hacks, 2013).

4.2.3. Wagner algometer

PPT is defined as the point at which a sensation of pressure converts into a sensation of pain, and it has been recognised as a valid and reliable way to quantify pain. As such, it is widely used in clinical and scientific research (Jones et al., 2007; Ylinen et al., 2007; Walton et al., 2014). PPT was measured by using a pressure algometer, which is a mechanical form of pain assessment. Algometry is often used in research to quantify pain; it showed excellent reliability to measure PPT and correlates well with clinical status (Fischer, 1986; Potter et al., 2006). A Wagner algometer (model FDK/FDN, Wagner Instruments) was used in this study. The instrument has a 1-cm rubber footplate and a scale that spans 2 to 20 kg. No calibration was required. The algometer was pressed perpendicularly onto the skin overlaying the test site and participants were instructed to inform the researcher when the algometer's pressure became painful. At that point, a reading was taken and recorded (Figure 4.9).

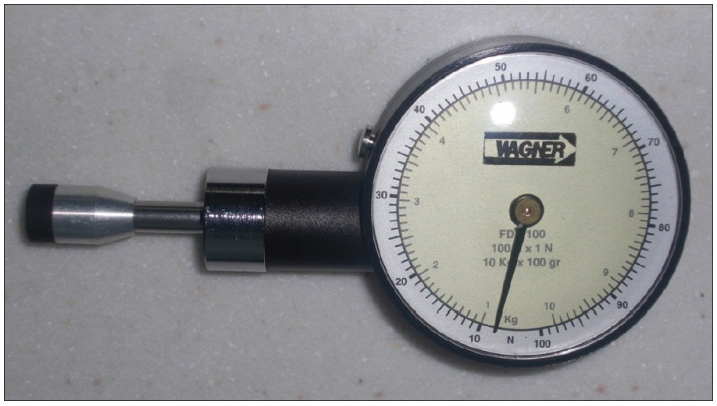


Figure 4.9. Wagner algometer (Buhagiar et al., 2011).

4.2.3.1. Sites of PPT measurement

PPT measures were taken at the following sites:

- Paraspinal muscles at the T12 level (1.5 cm apart from the spinous process on both sides; right and left). These locations were measured because they were at the level of mobilisation (T12) to measure the local hypoalgesic response to mobilisation (Fryer et al., 2004; Thomson et al., 2009; Willett et al., 2010).

- Paraspinal muscles at the L5 level (1.5 cm apart from the spinous process on both sides; right and left). This level was chosen because it has been reported to be the most common site of symptoms within the lumbar region in patients with LBP (Louis, 1981; Butler, 1991; Grieve, 1994).
- The mid-point of the hand web space bilaterally (first dorsal interosseus muscle). The first dorsal interosseus muscle in the hand was selected as it was reported to produce a large amount of normative data that could be compared against PPT values (Vanderween et al., 1996; Chesterton et al., 2003) and could be used to assess whether there was a systemic hypoalgesic effect to the mobilisation treatment applied (Willett et al., 2010).

4.2.4. The Numeric Pain Rating Scale (NPRS)

An 11-point NPRS was used, with 0 being no pain and 10 being most pain imaginable (Figure 4.10). In clinical practice, when assessing changes in a patient's condition within a single session or between treatment sessions, physiotherapists often use this scale and ask their patients to score their pain. It has been reported to be a valid and reliable scale with which to measure pain intensity (Valente et al., 2011). This outcome measure was used only in the last phase of this research, which included LBP patients (Chapter 7).

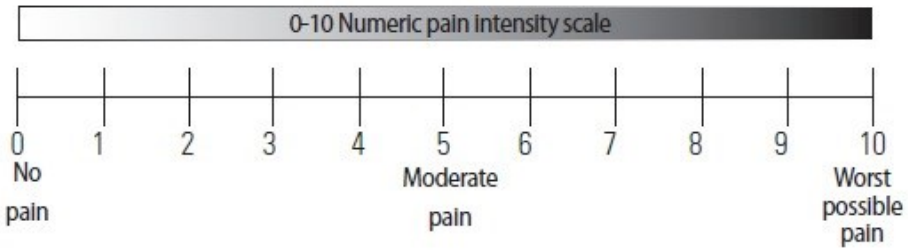


Figure 4.10. Numeric Pain Rating Scale (Dvir, 2015).

4.2.5. Salivary alpha-amylase (sAA)

sAA is a digestive enzyme that separates insoluble starch into dextrin and maltose (Zakowskia and Bruns, 1985). sAA is produced by the salivary glands through the acinar cells and does not diffuse into the saliva from blood (Proctor and Carpenter, 2007). In relation to the total proteins produced by the salivary glands, the percentage of sAA is between 40 and 50% (Zakowski and Bruns, 1985; Makinen, 1989).

In the current thesis, sAA was measured by placing swabs under the participants' tongues; they were asked to give a sign when the swab was full. The swabs were then transferred directly into storage tubes that were labelled with the participants' codes, and then placed into a box of dry ice (Figure 4.11). Then, all samples were centrifuged for 15 minutes at 3000 revolutions per minute at 4°C to pellet the mucins. Then they were transferred to a -80°C freezer for storage for no longer than 6 months. The collection materials for the saliva samples were purchased from the Salimetrics Company (State College, Pennsylvania). All samples were shipped to the Psychology Lab at Anglia Ruskin University where the amylase assays were performed (Appendix 4.1 for a full description of salivary alpha-amylase assay protocol).

Figure 4.11. Saliva swab and storage tube (Salimetrics, 2013).

On the day of testing, the samples were centrifuged to confirm that they had collected the correct volume of saliva (Figure 4.12). However, weighing the tubes before and after sampling can achieve the same aim. For example, if a change of +0.5 g was measured, it was assumed that we had collected 0.5 ml of saliva.

Salimetrics recommends a minimum of 400 ul for duplicate testing of alpha-amylase concentrations (a greater volume is needed for testing using the robot), with volumes of 500 ul or more being preferred. The swabs hold 2 ml of saliva before becoming saturated; however, it was avoided for the swabs becoming fully saturated, as then we had no longer be measuring the correct weight of produced saliva in the time period as it will not be able to go into the swabs. For this reason, in addition to weighing the tube before and after collection, each participant was asked to give a sign when he/she felt that the swab was full, and the amount of time that the swab spent under the tongue was recorded.

Figure 4.12. Centrifuge machine (Biocompare, 2017).

As an alpha-amylase assay is flow-rate dependent, measuring the flow rate of each sample (the flow rate of the saliva into the swab) was necessary in order to correct for the differences that flow rate causes in terms of the concentration of the alpha-amylase in the samples (Nater and Rohleder, 2009).

The collection device (swab and storage tube) was weighed before and after sampling with a decimal balance in order to measure the rate of the saliva flow. In this way, we measured the real physiological difference in response to stimulus (in later studies, spinal mobilisation) rather than an innate difference that is caused by the rate of saliva flow (Nater and Rohleder, 2009). Therefore, this process allowed for the removal of a potential confounder, thereby yielding better results.

4.3. Mobilisation technique

Recent animal studies on rats by Skyba et al. (2003) manipulated the proximal joint (knee joint) to the injured ankle joint (injected with capsaicin) and reported distal hypoalgesic effects that reached the symptomatic area as measured by mechanical withdrawal threshold. These distal pain-relieving effects have been attributed to the involvement of supraspinal mechanisms that activate the descending inhibition of pain, mediated by spinal serotonergic and/or adrenergic receptors that may include the SNS and PAG (Sluka et al., 2006). However, further research is needed to understand the hypoalgesic mechanisms of mobilisations. Furthermore, research on humans reported the wider hypoalgesic effect of mobilisation distal from the targeted areas (Vicenzino et al., 1996; Moss et al., 2007). Moreover, contrasting results were reported by Sterling et al. (2001) and Perry and Green (2008), who found there was a side-specific pain relieving effect after applying unilateral cervical and lumbar mobilisation.

A number of studies have compared the hypoalgesic effects of manual therapy on the thoracic and cervical levels and found similar clinical benefits of hypoalgesia in the symptomatic site (Fernandez et al., 2011; Martinez et al., 2012). PPT was measured in the elbow in patients with epicondylalgia following cervical and thoracic manipulation and similar improvements were found (Fernandez et al., 2011). Another study demonstrated that both thoracic and cervical manipulation produced similar widespread hypoalgesia in patients with chronic neck pain (Martinez et al., 2012). Another three studies compared the widespread hypoalgesic effects of thoracic mobilisation and thoracic manipulation in patients with chronic mechanical neck pain (Cleland et al., 2007; Suvarnnato et al., 2013; Salom et al., 2014). Their results suggested that there was no significant difference between the techniques in terms of PPT values at the cervical level, and that could be explained by the potential central mechanism of pain following manual therapy.

The mobilisation technique chosen for this thesis was applied at the grade III centrally applied posteroanterior (PA) T12 position for three sets of 60 seconds with one-minute rest periods between sets using a pisiform grip (Figure 4.13). The duration of the treatment was five minutes.

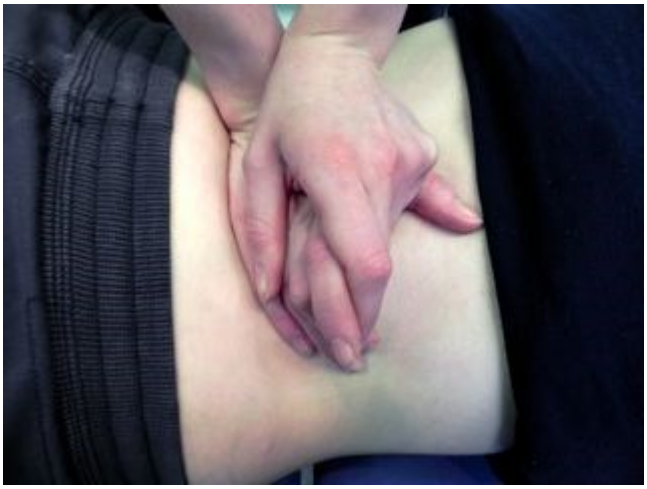


Figure 4.13. Posteroanterior mobilisation with pisiform grip (Physiopedia, 2017).

The components of this technique were selected for the following reasons:
- T12 was selected as the level of mobilisation because of the location of the ganglion of the SNS—they are found to be anterior to the costovertebral joint of the thoracic system. Thus, thoracic mobilisation might stimulate the preganglionic sympathetic cells at the thoracic and lumbar spinal levels either directly or indirectly (Sampath et al., 2015). These stimuli might then travel upwards to be processed at different levels, including the spinal and supraspinal levels. Thus, it was thought that mobilising the thoracic spine might lead to the stimulation of preganglionic sympathetic cells in the thoracolumbar spine, either directly or indirectly. Furthermore, the T12 was chosen because the sympathetic ganglia located between the T10 and L2 vertebrae supply the lower limbs (Grieve, 1994) which allows for the peripheral sympathetic response to mobilisation from the lower limbs (SC, ST from the feet) to be measured.

- The direction of the mobilisation force was selected to be centrally PA. Biomechanically, the T12 only moves in two directions—either extension or flexion—thus, no other directional forces are possible at this spinal level (Maitland et al., 2005).

- The mobilisation was applied for three sets of 60 seconds with one-minute periods of rest between sets. This is consistent with clinical practice (Maitland et al., 2005) and with previous studies examining the sympathetic responses to mobilisation techniques (Sterling et al., 2001; Sterling et al., 2010; Soon et al., 2010; Willett et al., 2010).

- The oscillation frequency was set at 1 Hz (one oscillation per second), which is reported as the most commonly used frequency by physiotherapists in clinical practice (Snodgrass et al., 2006). The treating researcher was able to monitor the mobilisation frequency by using a metronome application on a smartphone that was set to make a sound each second for the duration of the treatment (five minutes). A headset was used so that the sound of the metronome was heard only by the treating researcher and not by the participants or the principal investigator.

- Grade III mobilisation (large-amplitude movement that moves into stiffness or resistance) was used. Prior research reported that this grade might maximise the activation of a descending inhibitory mechanism through the stimulation of mechanoreceptors that might result in pain reduction in areas that are distant to the mobilisation (Vernon et al., 1986; Wright, 1995; Vicenzino et al., 2001; Griensven, 2005). Furthermore, the majority of studies examining the hypoalgesic and sympathetic responses to mobilisation techniques have used large-amplitude (grade III) oscillations (Peterson et al., 1993; Chiu and Wright, 1996, 1998; McGuiness et al., 1997; Sterling et al., 2001; Sterling et al., 2010; Soon et al., 2010; Willett et al., 2010).

In summary, this chapter described the equipment and the specific procedures used to measure the sympathetic and hypoalgesic variables related to this thesis. It has described the rationale for the spinal mobilisation technique to be used. The following chapter assesses the reliability of this equipment in terms of measuring the related variables.

Chapter 5

Within-day test-retest reliability of physiological data recordings

5.1. Introduction

Over the last two decades, there has been an increasing interest in the detection of changes in neurophysiological responses of SNS to manual therapy. Changes are reported for various measurements in the literature including: skin conductance, skin temperature, heart rate, respiratory rate, blood pressure and pressure pain threshold (Sterling et al., 2001; Cleland et al., 2004; Jowsey and Perry, 2010; Krouwel et al., 2010; Willett et al., 2010; Pentelka et al., 2012). The work presented in this chapter was conducted to determine the within-day test-retest reliability (reproducibility) of the measurements described in Chapter 4, that were chosen for this research to assess the hypoalgesic and sympathetic responses following mobilisation treatment. The results of this reliability study underpin later studies presented in this thesis (Chapters 6 and 7) that were conducted to investigate the effects of mobilisation treatment on these variables in asymptomatic and LBP patients.

To the author's knowledge, the reliability of the e-Health Sensor Shield V2.0 and sAA has never been investigated. In addition, this device and associated sensors was specifically purchased and set-up for the experiments. It had not previously been used by any other members of the laboratory or supervisory team. It was therefore important to establish specific test-retest reliability within the context of studies. PPT test-retest reliability has been shown to be excellent (Potter et al., 2006). However, reliability varies according to the PPT sites tested. Moreover, not all sites of measurement of PPT chosen for this thesis have been tested for reliability. Thus, prior to commencing the studies that will be presented later in this thesis, it was necessary to investigate the reliability of all six PPT sites of measurement.

5.1.1. Aims and objectives

The main aim of this study was to evaluate the test re-test reliability (reproducibility) of: i) the e-Health Sensor Shield V2.0 at measuring skin conductance, skin temperature, heart rate and skin temperature; ii) a Wagner algometer at measuring PPT (model FDK/FDN, Wagner Instruments) (at each of six sites); iii) a digital BP

monitor (Kodea KD-202F, Shanghai Kodea Economic & Trade Development Co., Shanghai, China); and iv) measurements of sAA enzyme recorded using sAA assay kit from Salimetrics (State College, Pennsylvania).

Lexell and Downham (2005) defined test-retest reliability as the stability of a measure over time. Reproducibility examines the sensitivity limit of a measure to detect a response change in relation to an intervention (Beckerman et al., 2001). Guyatt et al. (1987) defined the sensitivity to change as the measurement's ability to determine clinical differences over time. These authors describe the responsiveness of a measure between repeated test measurements with regard to the typical difference between subjects. Therefore, these changes and the amount of measurement error should be determined in order to establish the direct influence of any intervention.

The following objectives were determined to achieve the stated aims:

i. The retest correlation co-efficient for each physiological measurement was determined to provide a measure of agreement between sets of measurements.

ii. Standard error of measurement (SEM) and confidence intervals of collected data were calculated to quantify the random differences in the measurement means.

iii. SEM and smallest real difference (SRD) of collected data were calculated to quantify the differences in measurements between applications, in order to assess true changes to the intervention.

5.2. Method

5.2.1. Study design

This was a within-day reliability study.

5.2.2. Ethics approval

This study was approved by the Faculty of Health, Psychology and Social Care Research Ethics Committee (Appendix 5.1).

5.2.3. Participants

Fifteen asymptomatic participants were recruited from among the students at Manchester Metropolitan University by placing a poster advertisement on the Facebook page of the Psychology, Health and Social Care department. Direct generation of interest in the study was achieved by attending lectures and seminars in the department to hand out information sheets with the researcher's contact information. The lectures and seminars provided a setting in which the target population (healthy students) could be found and could be addressed directly as a group, rather than as individuals.

All volunteers who responded were interviewed by telephone to ascertain their appropriateness for the study (Chapter 5, section 5.2.3.1). For those that agreed to participate, an information sheet was provided for their consideration prior to commencement of data collection (Appendix 5.2). The researcher informed the participants of their right to withdraw at any time and they were asked to sign the consent form (Appendix 5.3). A screening assessment was performed on the day of the data collection to confirm that the participant's status had not changed and that they had abstained from exercise and caffeine in the three hours prior to taking the measurements, and that they had refrained from consuming alcohol in the 24 hours prior to taking the measurements.

5.2.3.1. Inclusion and exclusion criteria

Potential participants were required to be healthy individuals aged between 18–55 years, non-smokers, have an adequate understanding of the English language, able to provide informed consent for the study and asymptomatic of spinal pain. The upper limit of 55 years was used in this study in order to reduce the possibility of recruiting individuals with degenerative changes that could potentially affect the outcome measures of the study (Snodgrass et al., 2014). In order to ensure that the extrapolation of the target population's results was uninhibited, both male and female participants were recruited.

Potential participants for this study were excluded if they had a history of back pain in the previous six months, had been diagnosed with a psychiatric or medical disorder that may have influenced their neurophysiological responses (e.g.

rheumatoid arthritis, multiple sclerosis, diabetes and anxiety disorders), had previously had lower extremity or spinal surgery, been pregnant, had a previous history of trauma with related permanent sensation abnormality (dysesthesia), had skin disorders at the location of the electrode placement, were dependent on alcohol, were smokers or were incapable of providing informed consent (e.g. as a result of dementia or limited English language skills) (Perry et al., 2015).

5.2.4. Confidentiality

Each participant was assigned an alphanumeric code upon entry into the study and all study data were labelled using the same code. All information recorded on paper, and any non-computerised data were stored in a locked cabinet in room T0.18 of the John Dalton West building at Manchester Metropolitan University. Computerised data were password protected and accessible only by the named investigators.

5.2.5. Research approach and methods

This study used a same-subject repeated measures design. To determine the within-day reliability, measurements were taken three times for each participant for each physiological measure (Figure 5.1). The within-day reliability was used rather than between days as the aim of the subsequent studies is to compare the within session effect of mobilisation with the effect of subsequent sessions. As a result, each physiological measure (Chapter 6 and 7) was measured before the treatment in each visit to measure the within session effect.

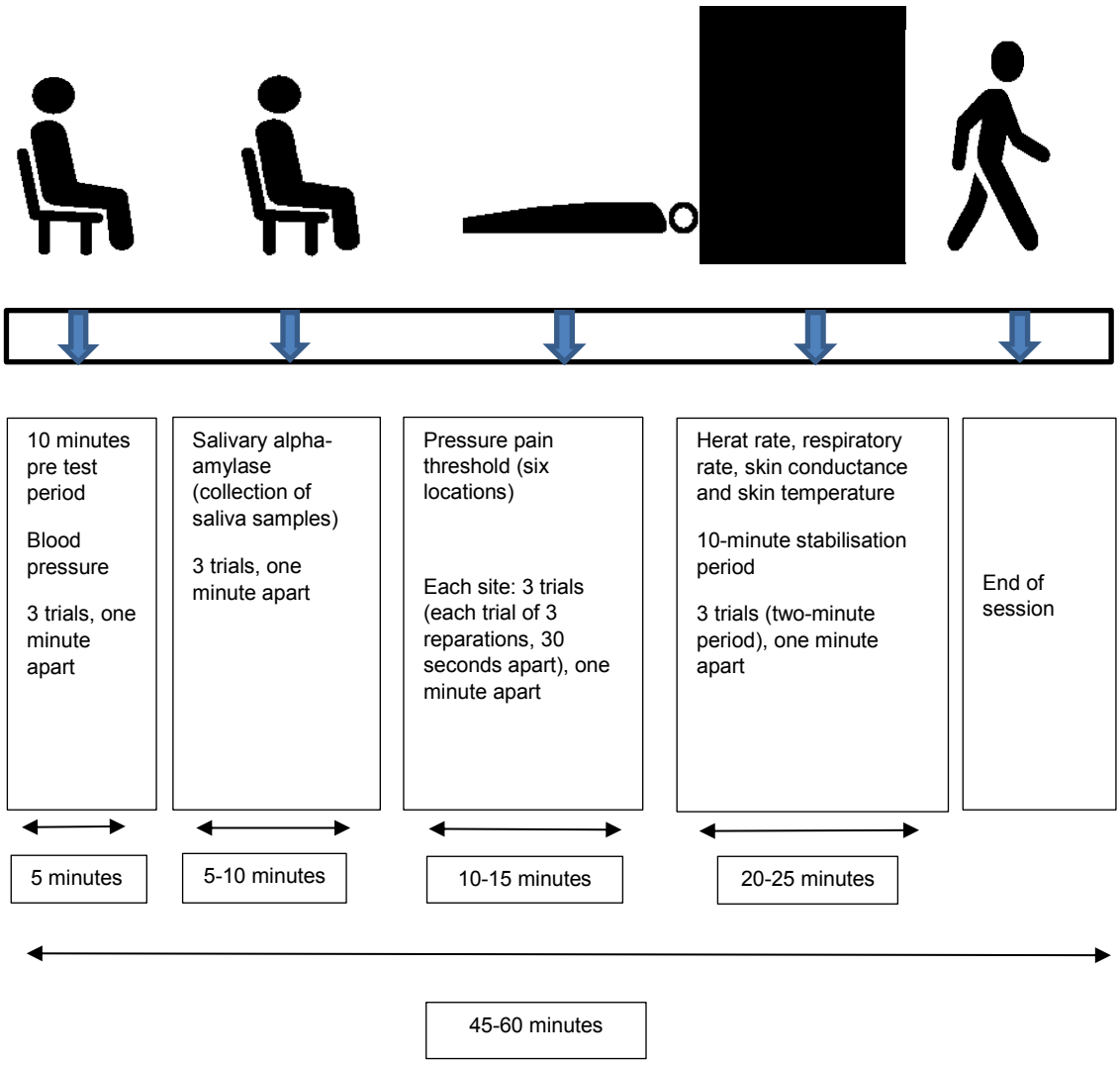


Figure 5.1. An illustration of the study protocol.

5.2.6. Procedure

Participants attended Manchester Metropolitan University on one occasion. Participants were asked to avoid eating, exercising and drinking any caffeinated beverages three hours prior to the meeting, and to refrain from consuming alcohol for 24 hours prior to the meeting, as these are known to be confounding factors that might affect the SNS activity (Wright and Vecenzino, 1995; McGuiness et al., 1997; Katzung, 2001; Yung et al., 2014).

On the day of testing, an oral explanation was given to each participant to familiarise them with the testing and data collection areas. They were given time to reflect on the study information and had the opportunity to ask questions about the study.

Then, they were asked to sign a consent form. The subject's height (m) and weight (kg) was measured using a standard medical scale (Kern, MPE 250K100 HM). All data were collection by the primary investigator in a noise- and temperature-controlled environment (22.2°C).

BP and PPT were recorded and saliva samples were collected at the beginning of the session, followed by the measurements taken by the e-Health Sensor Shield V2.0. The measurements were taken in this order to prevent an earlier measurement from having an effect on a subsequent measurement. Thus, all the measurements that were simultaneously recorded by the e-Health Sensor Shield V2.0 were taken when the participants were in a prone lying position and they were not disturbed.

First, BP was measured using a digital BP monitor (Kodea KD-202F, Shanghai Kodea Economic & Trade Development Co., Shanghai, China) by placing the cuff around the left arm while the participant assumed a relaxed seated position. The BP measurement was taken three times and with one-minute breaks in between. Saliva samples were collected by placing a swab under the participant's tongue. Participants were asked to give a signal when the swab was full (i.e. when saliva was no longer absorbed into the swab and started to pool on the floor of the mouth), and the time the swab spent in the participant's mouth was recorded. The swab was transferred directly to a storage tube that was labelled with the participant's code and then it was placed into a box of dry ice. This saliva collection procedure was repeated three times separated by one-minute breaks. Once the testing for each single participant was complete, the samples were centrifuged and transferred into a freezer where they were stored at -80°C for six months prior to analysis. All samples were shipped to the Psychology Lab at Anglia Ruskin University where the amylase assays were performed (Appendix 4.1 for a full description of salivary alpha-amylase assay protocol).

Later studies in this thesis (Chapters 6 and 7) examine the extent of the hypoalgesic response to mobilisations applied to the asymptomatic thoracic vertebral level (T12); thus, PPT was measured at six sites that were justified in Chapter 4 (section 4.2.3.1).

The sites of PPT measurements were:

- Paraspinal muscles at the T12 level (1.5 cm apart from the spinous process on both sides; right and left).

- Paraspinal muscles at the L5 level (1.5 cm apart from the spinous process on both sides; right and left).

- The mid-point of the web space of both hands (first dorsal interossei).

Participants were required to partially undress their torso; screens were used to protect their dignity at all times. They were instructed to lie in a prone position on an adjustable treatment plinth. The primary investigator located the target spinous process (T12) by palpating the iliac crest and moving medially to the L4/L5 interspace, and then moving to palpate the upwards spinous process one by one until the T12 was located. Then, the primary investigator followed the vertebral attachment of the twelfth rib in order to confirm the identification of the T12 (Cleland et al. 2004). The spinous process of the T12 was marked and marks were made 1.5 cm to the right and left of the T12 spinous process. In addition, marks were made 1.5 cm from the right and left of the L5 spinous process. The mid-point of the hand web space was marked bilaterally as well.

The methodology for the measurement of the PPT was similar to that used in previous studies (Keating et al., 2001; Fryer et al., 2004). Three measurements were taken at each of the six locations separated by thirty seconds, and the set of three measurements was repeated three times, each one was separated by one minute. The algometer was pressed perpendicularly to the marked sites and the participants were instructed to say “now” to the researcher when the algometer’s pressure changed to pain, and a reading was manually recorded. However, prior to testing, a familiarisation PPT was applied on the palmar aspect of the hand to allow participants to experience PPT at that site. Each participant had three PPT readings and the average of each of the three readings was calculated.

Next, the participants were instructed to lie on supine on the same adjustable treatment plinth. The sites of the skin where the e-Health Sensor Shield sensors were applied were first cleaned with isopropyl alcohol to remove any residue on the skin. ECG sensors were connected to the chest and airflow sensors were placed in

the nostrils (Chapter 4, section 4.2.1). The participants were asked to turn over to assume a standardised position (prone with their arms by their sides (palms up) and their legs supported at the knees by a single pillow), which was the same position used in later studies for the mobilisation treatment (Chapter 6 and 7). Body temperature sensors were placed on the plantar surface of the big toe bilaterally, and galvanic skin response (GSR – sweat) sensors were placed on the plantar surface of the second and third toes, bilaterally (Chapter 4, section 4.2.1) (Perry and Green, 2008).

After the application of the electrodes, the participants were instructed not to sneeze, cough, breathe deeply, fall asleep or talk, except to indicate pain or discomfort. They were also asked to avoid interfering with the electrodes.

Similar to previous studies examining SNS responses, each participant had an initial stabilisation period lasting for 10 minutes in order for their body to acclimatise to the environment (Chiu and Wright, 1996; Vicenzino et al., 1995; Cleland et al., 2004; Perry and Green., 2008). Data acquisition (60 Hz sampling frequency) was initiated and measurements were taken continuously over the next two minutes (Perry and Green, 2008). The two-minute measurement period was repeated three times separated by one-minute break in recording. As a result, each patient produced three sets of two-minute data for skin conductance, skin temperature, heart rate and respiratory rate.

Finally, the participants were informed when the testing had ended and the electrodes were removed. The whole session lasted between 45 and 60 minutes. Each participant produced three sets of data for PPT for six different locations, three sets of data for BP, three saliva samples and three sets of data for respiratory rate, heart rate, skin temperature and skin conductance:

- A two-minute period (Trial 1),
- A two-minute period (Trial 2) and
- A two-minute period (Trial 3).

The raw data for heart rate, respiratory rate, skin conductance and skin temperature were processed using custom written Mathematica code (version 10.4, Wolfram Research, Champaign, IL, USA). The completed calculations provided the mean heart rate, respiratory rate, skin conductance and skin temperature per minute throughout the session, and calculated the mean value (integral measurement) of each period of measurement (two-minute period). The integral measurement of each period was used for analysis. Therefore, each participant had three values for the following outcome measures: right skin conductance, left skin conductance, right skin temperature, left skin temperature, heart rate and respiratory rate (Appendix 5.4: Example raw data trace). For pressure pain threshold data, the mean of the three measurements was calculated for each site; thus, every participant had three scores for PPT at each site of measurement. For blood pressure and salivary alpha-amylase, each participant had three values.

5.3. Statistical data analysis

5.3.1. Reliability analysis

For reliability testing, the variance in intra-day measures was calculated separately for each physiological variable (for right and left sides separately where applicable) using the intra-class correlation coefficients (ICC 2, 1; two-way random effect model; interaction absent; absolute agreement definition; single measure); the measurement of each participant was also taken by the same rater (Eliasziw et al., 1994). Eliasziw et al. (1994) recommended that all observations of the analysis should be used to improve precision, including 95% confidence intervals (CI) for the ICC, standard error of measurement (SEM) and minimal detectable change (MDC) ($1.96 \times SEM \times \sqrt{2}$). The ICC and CI represent reliability and assess correlation between test measurements (Fleiss, 1986). The SEM and MDC were calculated as this score of variability is important in order to assess changes to treatment when evaluating pre- and post-treatment measures and is in the unit of measurement of the device (Eliasziw et al., 1994). The SEM is a change that needed to be recorded in order to be 95% confident that none of the results were due to measurement variability (Eliasziw et al., 1994). The MDC represents the smallest change required to ascertain the occurrence of a true change following treatment (Eliasziw et al.,

1994). Descriptive statistics and statistical analyses were performed on all data using Statistical Package for Social Scientists (IBM SPSS Statistics V. 23; IBM Corp., Armonk, NY, USA).

5.3.2 Results

Nine females and six males participated in this within-day reliability study. Participants had an age range of 24.40–48.92 years, and a mean age of 32.9 years (SD 5.86); their mean body mass index (BMI) was 26.35 kg/m^2 (SD 4.63), and they had a BMI range of 20.20–37.30 kg/m^2. No adverse effects were reported by any of the participants upon completion of the study.

5.3.2.1 Reliability of skin conductance measurements

An integral reading was calculated for the three data sets. Each set consisted of two-minute periods of time. Therefore, each participant had three readings for right skin conductance and three readings for left skin conductance. The reliability results for skin conductance are displayed in Table 5.1. Descriptive statistics for all three measurements of right and left skin conductance are displayed in Figure 5.2.

Table 5.1. Within-day reliability of skin conductance measurements (n=15)

	Within-day ICC	Within-day CI	Within-day SEM (v)	Within-day MDC (v)
SC (right side)	0.988	0.971–0.996	± 0.02	0.056
SC (left side)	0.985	0.963–0.994	± 0.02	0.062

Abbreviations: ICC: intraclass correlation coefficient; CI: 95% confidence interval; SEM: standard error of measurement; MDC: minimal detectable change; SC: skin conductance; v: voltage.

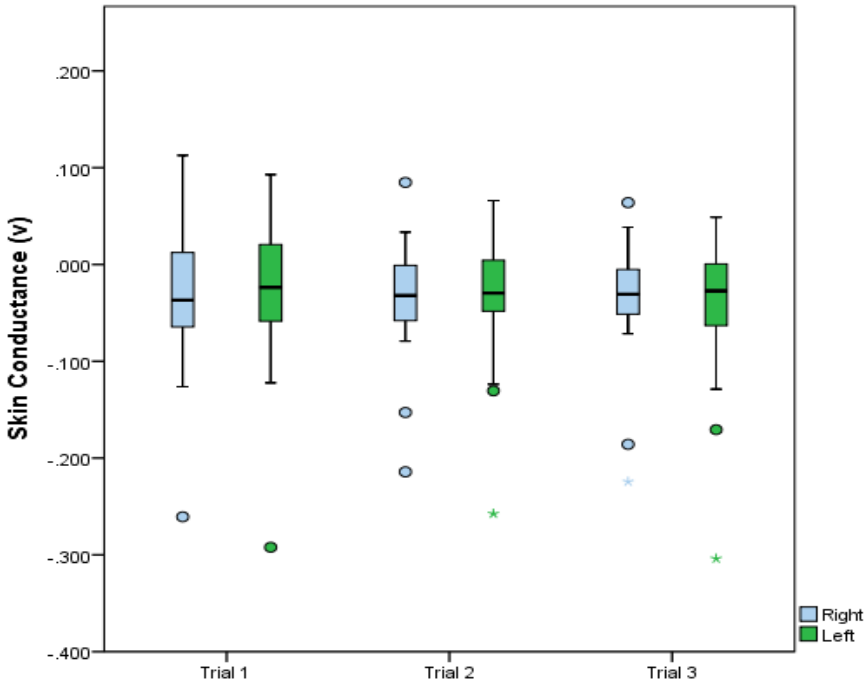


Figure 5.2. Skin conductance measurements for all three trials. The data are medians. Error bars represent non-outlier range (n=15).

5.3.2.2. Reliability of skin temperature measurements

The integral reading was calculated for the three data sets. Each set consisted of two-minute periods. Therefore, each participant had three readings for right skin temperature and three readings for left skin temperature. The reliability results for skin temperature are displayed in Table 5.2. Descriptive statistics for all three measurements of right and left skin temperature are displayed in Figure 5.3.

Table 5.2. Within-day reliability of skin temperature measurements (n=15)

	Within-day ICC	Within-day CI	Within-day SEM (°C)	Within-day MDC (°C)
ST (right side)	0.997	0.993–0.999	± 0.5	1.5
ST (left side)	0.987	0.969–0.995	± 0.59	1.64

Abbreviations: ICC: intraclass correlation coefficient; CI: 95% confidence interval; SEM: standard error of measurement; MDC: minimal detectable change; ST: skin Temperature; °C: Celsius.

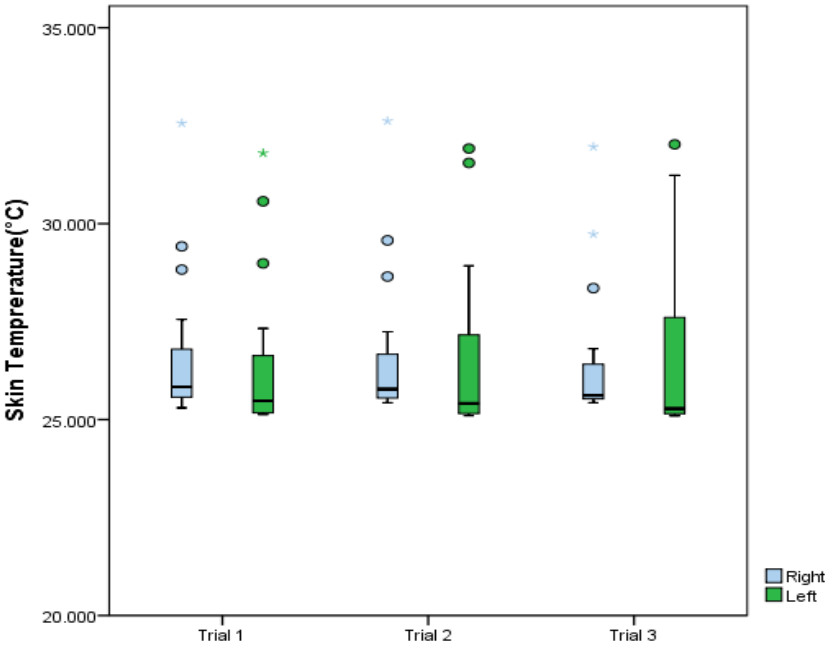


Figure 5.3. Skin temperature measurements for all three trials. The data are medians. Error bars represent non-outlier range (n=15).

5.3.2.3. Results of reliability of respiratory rate measurements

The number of breathing cycles (inhalations and exhalations) per minute was calculated for the three data sets. Each set consisted of a two-minute period of time and the mean of the two-minute rate was calculated. Therefore, each participant had three readings for respiratory rate. The reliability results for respiratory are displayed in Table 5.3. Descriptive statistics for all three measurements of respiratory are displayed in Figure 5.4.

Table 5.3. Within-day reliability of respiratory rate measurements (n=15)

	Within-day ICC	Within-day CI	Within-day SEM (breaths/minute)	Within-day MDC (breaths/minute)
RR	0.889	0.736–0.959	± 0.58	1.59

Abbreviations: ICC: intraclass correlation coefficient; CI: 95% confidence interval; SEM: standard error of measurement; MDC: minimal detectable change; RR: respiratory rate.

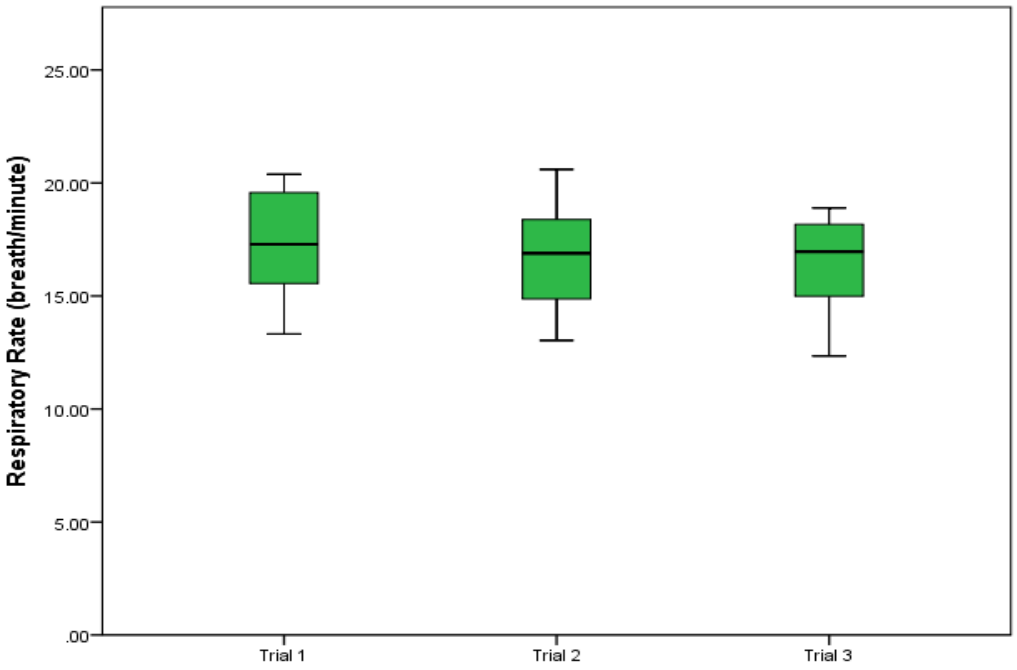


Figure 5.4. Respiratory rate measurements for all three trials. The data are medians. Error bars represent non-outlier range (n=15).

5.3.2.4. Reliability of heart rate measurements

The number of heart beats per minute (heart rate) was calculated for the three data sets. Each set consisted of two-minute period of time and the mean of the rate of the two minutes was calculated. Therefore, each participant had three readings for heart rate. The reliability results for heart rate are displayed in Table 5.4. Descriptive statistics for all three measurements of heart rate are displayed in Figure 5.5.

Table 5.4. Within-day reliability of heart rate measurements (n=15)

	Within-day ICC	Within-day CI	Within-day SEM (beats /minute)	Within-day MDC (beats /minute)
HR	0.86	0.855–0.949	± 1.97	5.45

Abbreviations: ICC: intraclass correlation coefficient; CI: 95% confidence interval; SEM: standard error of measurement; MDC: minimal detectable change; HR: heart rate.

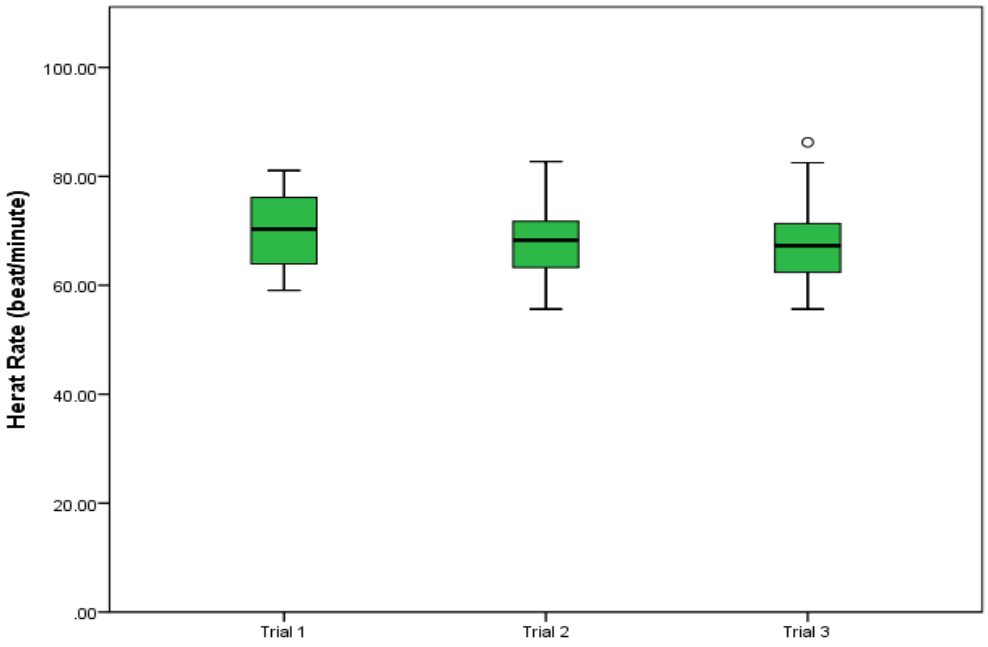


Figure 5.5. Heart rate measurements for all three trials. The data are medians. Error bars represent non-outlier range (n=15).

5.3.2.5. Reliability of blood pressure measurements

Systolic and diastolic BP measurements were recorded three times. Therefore, each participant had three readings for BP. The reliability results for blood pressure are displayed in Table 5.5. Descriptive statistics for all three measurements of systolic BP (SBP) and diastolic BP (DBP) are displayed in Figures 5.6 and 5.7.

Table 5.5. Within-day reliability of blood pressure measurements (n=15)

	Within-day ICC	Within-day CI	Within-day SEM (mmHg)	Within-day MDC (mmHg)
SBP	0.773	0.467–0.917	± 2.65	7.34
DBP	0.535	-0.043–0.826	± 2.4	6.65

Abbreviations: ICC: intraclass correlation coefficient; CI: 95% confidence interval; SEM: standard error of measurement; MDC: minimal detectable change; SBP: systolic blood pressure; DBP: diastolic blood pressure.

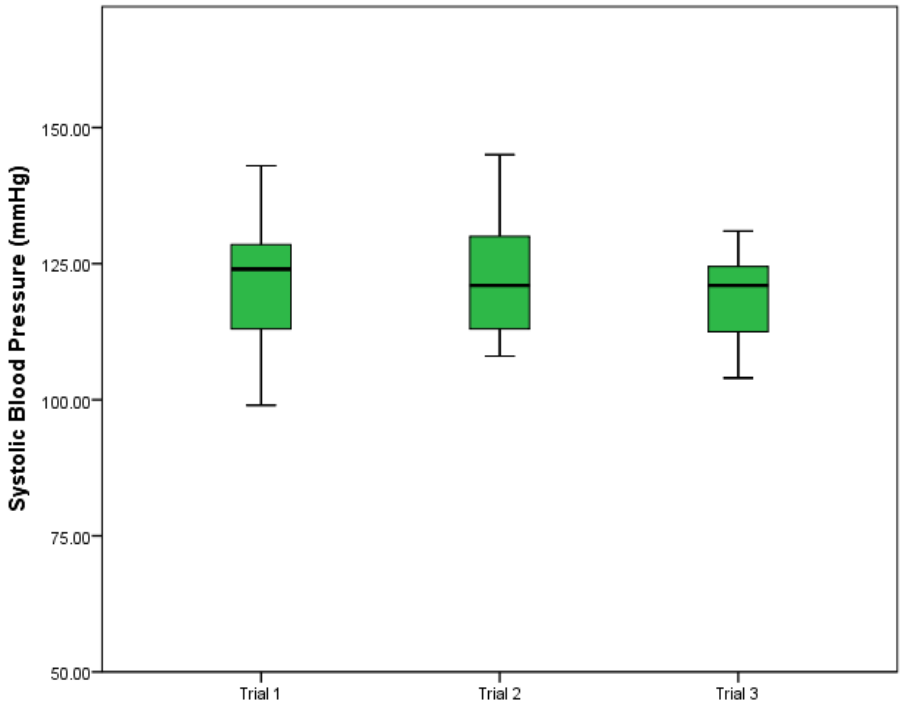


Figure 5.6. Systolic blood pressure measurements for all three trials. The data are medians. Error bars represent non-outlier range (n=15).

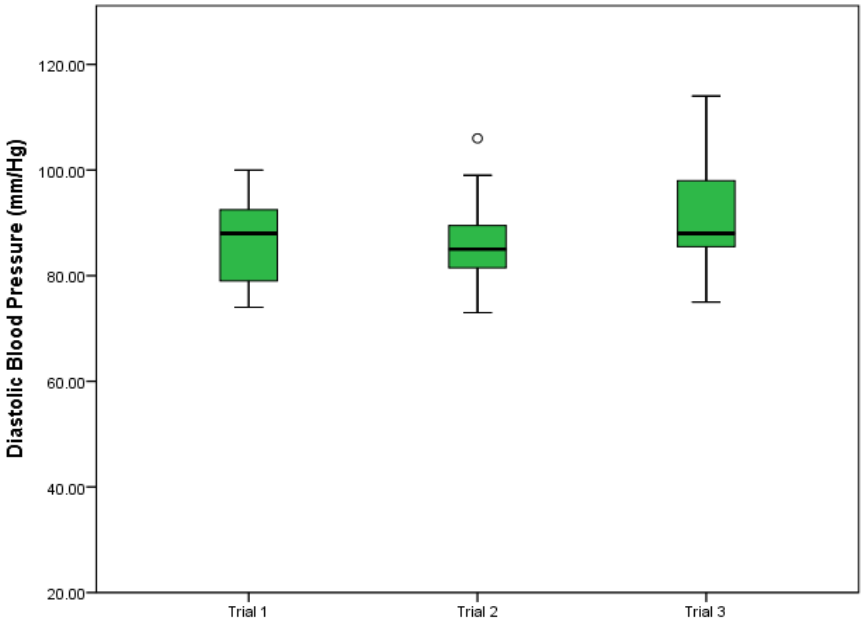


Figure 5.7. Diastolic blood pressure measurements for all three trials. The data are medians. Error bars represent non-outlier range (n=15).

5.3.2.6. Reliability of pressure pain threshold measurements

The mean for the three measurement sets (each set consisted of three measurements) at each location was used for the analysis. Descriptive statistics for all PPT measurements are displayed in Figure 5.8. The reliability results for all PPT data (Table 5.6) at the T12 paravertebral muscles, L5 paravertebral muscles, 1st dorsal interossei muscles were excellent (ICC 0.79–0.97) (Fleiss, 1986).

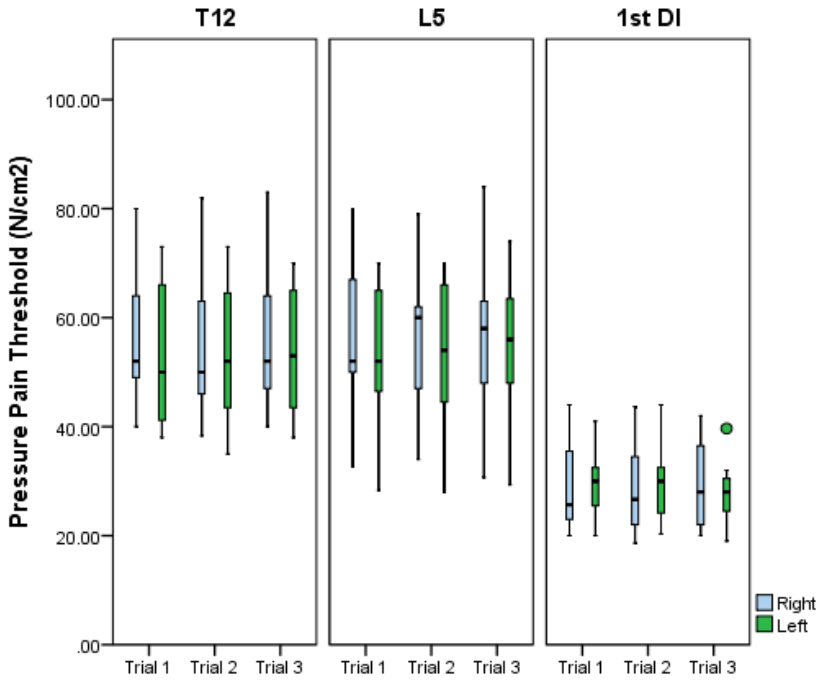


Figure 5.8. PPT measurements for all three trials of paravertebral muscles (T12 and L5) and 1st dorsal interossei muscles. The data are medians. Error bars represent non-outlier range (n=15).

Table 5.6. Within-day reliability of PPT measurements (n=15)

PPT sites	Within-day ICC	Within-day CI	Within-day SEM (N/cm^2)	Within-day MDC (N/cm^2)
$L5_R$	0.964	0.941–0.987	3.617	10.026
$L5_L$	0.94	0.859–0.978	3.297	9.139
$T12_R$	0.904	0.774–0.965	2.874	7.967
$T12_L$	0.971	0.932–0.989	3.487	9.666
$1^{st}\ DI_R$	0.939	0.855–0.978	2.326	6.447
$1^{st}\ DI_L$	0.792	0.513–0.924	1.496	4.147

Abbreviations: ICC: intraclass correlation coefficient; CI: 95% confidence interval; SEM: standard error of measurement; MDC: minimal detectable change. R: right; L: left; L5: 5^{th} lumbar vertebra; T12: 12^{th} thoracic vertebra; 1^{st}DI: first dorsal interossei muscles.

5.3.2.7 Reliability of salivary alpha-amylase measurements

The sAA was measured three times using sAA assay kit from Salimetrics (State College, Pennsylvania). Therefore, each participant had three readings for sAA. The reliability results for salivary alpha-amylase are displayed in Table 5.7. Descriptive statistics for all three measurements are displayed in Figure 5.9.

Table 5.7. Within-day reliability of salivary alpha-amylase measurements (n=15)

	Within-day ICC	Within-day CI	Within-day SEM (U/m)	Within-day MDC (U/m)
sAA	0.709	0.301–0.894	± 8.297	22.99

Abbreviations: ICC: intraclass correlation coefficient; CI: 95% confidence interval; SEM: standard error of measurement; MDC: minimal detectable change; sAA: salivary alpha-amylase; U/m: unit per minute.

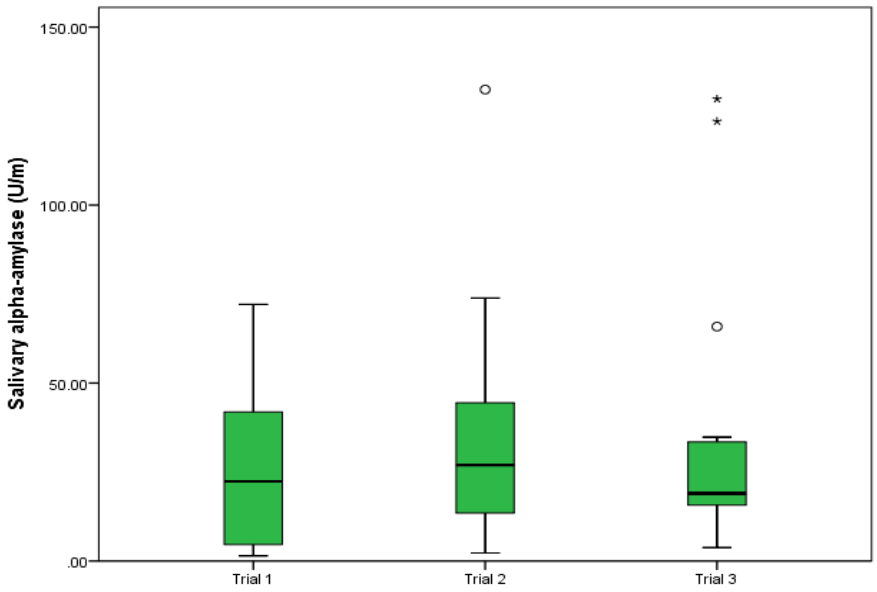


Figure 5.9. Salivary alpha-amylase measurements for all three trials. The data are medians. Error bars represent non-outlier range (n=15).

5.4 Discussion and conclusion

The results of this reliability study demonstrated that the within-day test-retest reliability of skin conductance, skin temperature, heart rate, respiratory rate, systolic blood pressure and PPT measurements were excellent (ICCs of 0.77 to 0.99). On the other hand, the reliability of diastolic blood pressure and salivary alpha-amylase measurements were demonstrated to be fair to good (ICCs of 0.55 and 0.7, respectively). The work also quantified the minimal detectable change for each of the physiological parameters and will therefore inform the interpretation of the results in subsequent chapters.

As this was the first study to assess the reliability of the e-Health Sensor Shield V2.0 for measuring skin conductance, respiratory rate, heart rate and skin temperature and the first study to assess the reliability of measuring the sAA enzyme, comparisons with previous work were difficult.

For blood pressure, the reliability result for systolic blood pressure was excellent (ICC 0.77), whereas, for diastolic blood pressure, reliability was fair to good (ICC 0.55). Although the mercury sphygmomanometer is considered the gold standard for monitoring blood pressure, concerns about the safety of the mercury led to the widespread use of digital blood pressure readers (Skirton et al., 2011). The literature review (Chapter 2, Table 2.2) identified three studies that examined the effect of spinal mobilisation on blood pressure values (McGuiness et al., 1997; Vicenzino et al., 1998 and Yung et al., 2014); these studies used different digital, electronic blood pressure readers. However, reliability results were reported by only one study; they were for systolic and diastolic blood pressure with an ICC of 0.9 and 0.88 (Yung et al., 2014). It has been reported that bias may possibly exist when using electronic devices because they tend to give a high initial reading compared to repeated measurements within a short time frame (Skirton et al., 2011). When ischemia is maintained in the arm distal to the cuff for more than 10 seconds while the cuff is inflated, a change in the blood pressure measurement may occur during repeated measures (Eguchi et al., 2009). Therefore, if ischemia is maintained and the interval time is not adequate for full return of blood flow within the artery, this would explain

the variations, especially in diastolic blood pressure measurements, which lead to lower ICCs than systolic blood pressure.

For the pressure pain threshold, the reliability results for all the PPT data at the T12 paravertebral muscles, L5 paravertebral muscles and 1st dorsal interossei muscles were excellent (ICC 0.79–0.97). PPT at the paravertebral sites at the level of T12 has not been used in previous research thus comparisons were difficult (Chapter 2, Table 2.2). The reliability of PPT at the left paravertebral site at the level of L5 and left 1st dorsal interossei muscles has been tested by Willett et al. (2010), who reported an ICC of 0.94 and 0.93 at these sites compared to 0.94 and 0.79 reported by this reliability study. However, their reliability measure was based on one set of measurements of three repetitions of PPT compared to three sets of measurements (each of three repetitions) used in this study.

Using a convenience sample is considered a limitation in this reliability study, as our participants were asymptomatic volunteers who may not represent a normal patient population. However, it was important to use strict criteria in order to control for any confounding variables that might bias the values measured. Therefore, the advantages of recruiting asymptomatic participants might outweigh the disadvantages as utilising asymptomatic participants allowed for this strict control. Also, a mechanical algometer was used in this study whereby the pressure rate applied by the examiner could not be controlled. An electronic algometer where there is no reliance on the examiner reaction time is considered more accurate (Vaughan et al., 2007).

In summary, the e-Health Sensor Shield, along with other equipment tested, is reliable and suitable for use in the next stage of the research to investigate the effects of mobilisation treatment on these variables in an asymptomatic population and NSCLBP patients. The following chapter assesses the effects of spinal mobilisation on these measurements in an asymptomatic population.

Chapter 6

A single-arm trial investigating the neurophysiological responses of the sympathetic nervous system (SNS) to passive accessory mobilisations in an asymptomatic population

6.1. Introduction

Although spinal mobilisation has been shown to produce hypoalgesic and sympathetic responses, both local and remote, from the treated areas (Krowel et al., 2010; Willett et al., 2010), no studies have established whether these effects occur when mobilising spinal levels that are remote from the treated level. Therefore, the purpose of this preclinical study was to provide empirical evidence of the neurophysiological effects (as measured by SNS activity and PPT) of the thoracic mobilisation technique where the lumbar spine is the targeted level. Another goal was to compare observed SNS and pain responses of the study's participants and to compare and discuss these findings with those of previously conducted studies that used other mobilisation techniques.

6.1.1. Research question

What are the immediate and cumulative effects of thoracic mobilisation treatment on pain and sympathetic measures in an asymptomatic population?

6.1.2. Objectives

- To determine the neurophysiological responses of the SNS to thoracic mobilisations in an asymptomatic population.
- To determine the extent of the hypoalgesic effect (thoracic, lumbar and systemic levels) resulting from thoracic mobilisation in an asymptomatic population.
- To examine the possibility of a dose-dependent effect of thoracic mobilisation on sympathetic and PPT changes in an asymptomatic population.
- To generate data to permit power calculations for the clinical study of NSCLBP patients.

6.2. Method

6.2.1. Study design

This was a single-arm repeated measure design.

6.2.2. Ethics approval

This study was approved by the Faculty of Health, Psychology and Social Care Research Ethics Committee (Appendix 6.1).

6.2.3. Participants

6.2.3.1. Power calculation

Based on an intra-subject standard deviation of .07 from the reliability study (Chapter 5) (Appendix 6.2), a power analysis calculation revealed that 14 participants would enable a difference in skin conductance values (primary outcome measure) from a baseline of 7.5% to be detected at a 5% significance level with 80% power (Rigby and Vail, 1998).

$$n = \frac{2 \times SD^2}{(md)^2} \times 7.8$$

$$n = \frac{2 \times (0.07)^2}{(0.075)^2} \times 7.8 = 14$$

A 7.5% skin conductance value change was selected as it represents a clinically significant difference that has been supported by the results of other studies (Perry and Green, 2008; Perry et al., 2015).

Fourteen participants were recruited from among the students at Manchester Metropolitan University by placing a poster advertisement on the Facebook page of the Psychology, Health and Social Care department. Direct generation of interest in this study was achieved by attending lectures and seminars in the department to hand out information sheets with the researcher's contact information. The lectures and seminars provided a setting in which the target population could be found (Section 6.2.3.2) and could be addressed directly as a group, rather than as individuals.

All volunteers who responded were interviewed by telephone to ascertain their appropriateness for the study. For those that agreed to participate, an information sheet was provided for their consideration prior to commencement of the data collection (Appendix 6.3). The researcher informed the participants of their right to withdraw at any time and they were asked to sign the consent form (Appendix 6.4). A screening assessment was performed on the day of the data collection to confirm that the participant's status had not changed and that they had abstained from exercise and caffeine in the three hours prior to their appointment with the researcher and that they had refrained from consuming alcohol in the 24 hours prior to taking the measurements.

6.2.3.2. Inclusion and exclusion criteria

Potential participants were required to be healthy individuals aged between 18–55 years, non-smokers, have an adequate understanding of the English language, able to provide informed consent for the study and be asymptomatic of spinal pain in the last six months. The upper limit of 55 years was used to reduce the possibility of recruiting individuals with spinal or lower limb degenerative changes that could potentially affect the outcome measures of the study (Snodgrass et al., 2014). In order to ensure that the extrapolation of the target population's results was uninhibited, both male and female participants were recruited.

Potential participants for this study were excluded if they had a history of back pain in the previous six months, had been diagnosed with a psychiatric or medical disorder that may have influenced their neurophysiological responses (e.g. rheumatoid arthritis, multiple sclerosis, diabetes and anxiety disorders), had previously had lower extremity or spinal surgery, been pregnant, had a previous history of trauma with related permanent sensation abnormality (dysaesthesia), had skin disorders at the location of the electrode placement, were dependent on alcohol, were smokers or were incapable of providing informed consent (e.g. as a result of dementia or limited English language skills) (Perry et al., 2015).

Additionally, those with any contraindication, precautions to thoracic mobilisations (Grieve, 1991) were also excluded, which included:

•Bone disease of the spine (osteoporosis, osteopenia)

•Active inflammatory and infective arthritis

•Rheumatoid collagen necrosis of vertebral ligaments

•Signs and symptoms of spinal cord involvement; or involvement of more than one spinal nerve root on one side, or two adjacent roots in one lower limb only

•Cauda equina lesions producing disturbance of bladder and/or bowel function

•Malignancy involving the vertebral column

•The presence of neurological signs

•Spondylolisthesis

•Osteoporosis

•Dizziness

•Congenital generalised hypermobility (Ehlers-Danlos syndrome)

•Advanced spinal or lower limbs degenerative changes

•History of spinal or lower limbs steroid therapy

•Ongoing Anticoagulant therapy

6.2.4. Confidentiality

Each participant was assigned an alphanumeric code upon entry into the study and all study data was labelled using the same code. All information recorded on paper, and any non-computerised data were stored in a locked cabinet in room T0.18 of the John Dalton West building at Manchester Metropolitan University. Computerised data were password protected and accessible only by the named investigators.

6.2.5. Instrumentation and measurements

6.2.5.1. Procedure

Participants presented at Manchester Metropolitan University on three occasions with a minimum interval of two days and a maximum interval of seven days to replicate clinical practice. Participants were asked to avoid eating, exercising and drinking any caffeine products for the three hours prior to the meeting and to refrain from alcohol intake for 24 hours prior to the meeting, as these are known confounding factors that might affect SNS activity (Wright and Vecenzino., 1995; McGuiness et al., 1997; Katzung, 2001).

Visits 1, 2 and 3

On each day of testing, the primary researcher provided a verbal explanation to participants about the testing procedure. They were also asked to sign a consent form. Subject height (m) and weight (kg) were measured using a standard medical scale (Kern, MPE 250K100HM). All data collection was performed in a temperature (22.2°C) - and noise-controlled environment and collected by the primary investigator.

An overview of the study protocol is shown in Figure 6.1. Salivary alpha-amylase, blood pressure were measured at the beginning of the session. Participants were asked to partially undress the top half of the body; screens were used for privacy. They were then instructed to lie face down on an adjustable treatment plinth. The primary investigator introduced the treating researcher (a senior lecturer with experience in manual therapy) who located the target spinous process (T12). The methodology for the PPT measurement was similar to that used in chapter 5 (Section 5.2.6). Then, measurements taken using the e-Health Sensor Shield V2.0 (heart rate, respiratory rate, skin conductance and skin temperature) were continuously recorded before, during and after the mobilisation technique. Similar to previous studies examining SNS responses, the participants had an initial 10-minute stabilisation period so their bodies could adjust to the environment (Vicenzino et al., 1995; Chiu and Wright, 1996; Cleland et al., 2002; Perry and Green, 2008). The sensors were then activated, and measurements were taken over the next two minutes (pretreatment) (Perry and Green, 2008).The treating researcher returned to the testing room to perform the mobilisation technique and was allowed to adjust the plinth height to the appropriate specifications (hips level).

At the exact time the treating researcher started the mobilisation, the primary investigator initiated the data acquisition to record treatment phase measurements. The grade III technique was centrally applied postero-anterior (PA) to T12 for three sets of 60 sec with one-minute rest periods between sets. The treatment lasted for five minutes (Figure 6.2).

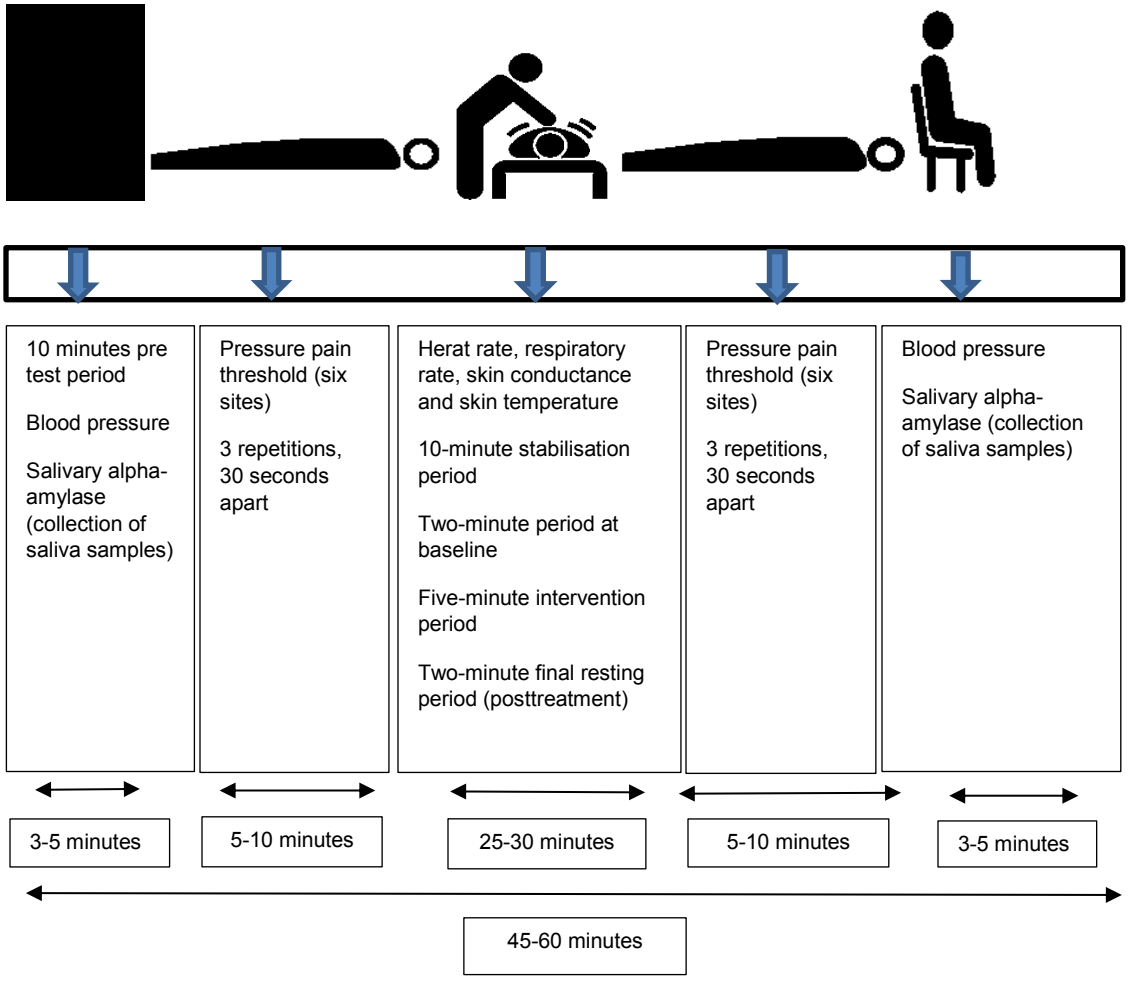


Figure 6.1. An illustration of the study protocol.

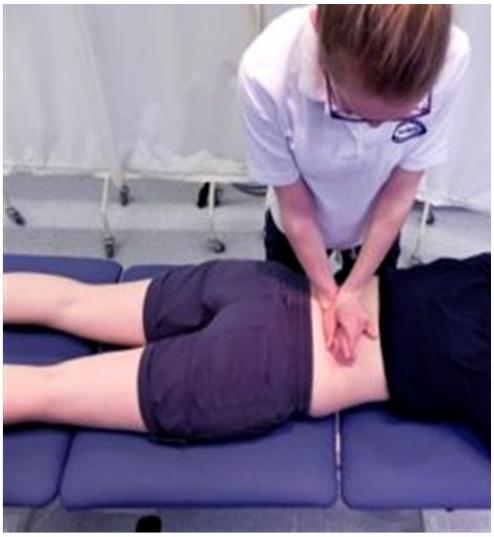


Figure 6.2. Central postero-anterior mobilisation technique (Physiopedia, 2017).

Following the implementation of the mobilisation technique, the primary investigator ended the recording of the treatment phase measurements. At this time, the treating researcher left the treatment room, and the primary investigator began a five minutes time count after the treatment. The posttreatment phase of recording started from the fourth minute of the five-minute period after treatment; it lasted for two minutes to measure the latent SNS responses to mobilisation while the participants were in a prone position.

Next, the participants were informed when the recording of the posttreatment phase ended, and the electrodes were removed.

Each participant produced three sets of data for respiratory rate, heart rate, skin temperature and skin conductance:

- A two-minute period at baseline (pretreatment),
- A five-minute intervention period (treatment) and
- A two-minute final resting period (posttreatment).

The laptop screen was turned in the opposite direction from the plinth where the participant was lying, and the treating researcher stood beside it. Thus, it was ensured that the participant and the treating researcher were blinded to the effect of

the mobilisation, thereby enhancing the internal validity of the study. In addition to this, all the mobilisation treatments were carried out by the same researcher to avoid any individual variations in terms of technique application.

Finally, salivary alpha-amylase, blood pressure and pressure pain threshold were measured at the end of the session (Section 5.2.6). This order was selected in order to avoid any potential effects of one measurement on previous measurements. Each participant produced two sets of data for BP, PPT and sAA: one at the begining of the session and one at the end of the session.

6.2.6. Data analysis

The raw data for heart rate, respiratory rate, skin conductance and skin temperature were processed using custom written Mathematica code (version 10.4, Wolfram Research, Champaign, IL, USA). The software calculated the mean heart rate, respiratory rate, skin conductance and skin temperature of each minute throughout the session and the mean value (integral measurement) of each period (pretreatment, treatment and posttreatment). The pretreatment period consisted of two minutes following a stabilisation period of ten minutes. The treatment period consisted of the five minutes when the mobilisation was performed. The final two minutes of the five minutes posttreatment period were used for analysis. Therefore, for each visit, each participant had three values for the following outcome measures: skin conductance (right and left), skin temperature (right and left), heart rate and respiratory rate. For pressure pain threshold data, the mean of the three measurements was calculated for each site; thus, every participant had two scores for PPT at each site of measurement for each visit. For blood pressure and salivary alpha-amylase, each participant had two scores for each of the three visits.

Descriptive statistics were calculated for all data using the Statistical Package for the Social Sciences (IBM SPSS Statistics V. 23; IBM Corp., Armonk, NY, USA). All data were tested for normality using the Shapiro-Wilk test. The effect of mobilisation was analysed using the two-way repeated measure analysis of variance (ANOVA). For blood pressure, salivary alpha-amylase and pressure pain threshold, the two independent variables were time, which had two levels (before and after

mobilisation), and visit, which had three levels (visit 1, visit 2 and visit 3). For heart rate, respiratory rate, skin conductance and skin temperature, the two independent variables were time, which had three levels (before, during and after mobilisation) and visit, which had three levels (visit 1, visit 2 and visit 3). As ANOVA is considered to be robust to minor deviation from normality (Agresti and Finaly, 2009), it was used when minor deviation from normality was evident. The departure from normality was assessed by histogram and normal Q-Q (quantile-quantile) plot to examine the shape of the distribution (Sabin and Stafford, 1990). Minor departure from normality was due to some minor outlier case in the lower end of the distribution (Sabin and Stafford, 1990). For major normality departure data (where the distribution is skewed), transformation was performed using square root or logarithmic transformation (Sabin and Stafford, 1990). All transformed data were rechecked for normality, and, where the deviations were not resolved, the Friedman test was used (the critical χ^2 (df = 2, p=0.05) = 5.99) or Wilcoxon signed-rank tests (Martin et al., 1993). Wilcoxon signed-rank test conducted where there was two testing points (pre-treatment and post-treatment), and Friedman test was conducted where there was more than two testing points (pretreatment, mobilisation and posttreatment). For multiple testing, a Bonferroni correction was applied, resulting in a critical level set at $\alpha < 0.017$ (0.05/3).

In order to compare our results with previous studies, differences in the mean of all physiological measures before and after mobilisation were presented as percentages of change. The percentage of change for all measures was calculated for the three visits using the following formula:

$$\frac{Measure_{post} - Measure_{pre}}{Measure_{pre}} \times 100 \quad .$$

In addition, the percentage of change for skin conductance, skin temperature, heart rate and respiratory rate, where measures were recorded during intervention, was also calculated using the following formula:

$$\frac{Measure_{during} - Measure_{pre}}{Measure_{pre}} \times 100 \quad .$$

The calculations were repeated for each of the three visits.

6.3. Results

A total of 14 participants (nine females and five males) participated in this study. The mean age of 33.22 years (*SD*= 5.34); the range was 25.48 to 43.76 years. Mean BMI was 26.55 kg/m^2 (*SD*= 5.04), and BMI range was 18.56 to 39.16 kg/m^2. All participants completed the study without reporting any adverse effects. There were no missing data from any visit.

6.3.1. Results of mobilisation treatment on blood pressure

There was a non-significant decrease in systolic blood pressure after mobilisation for the first and second visits compared to the baseline level with mean difference values of -0.07±12.7 mmHg and -0.07±8.5 mmHg (F(1, 13) =0.388, p= 0.544). A non-significant increase was evident in the third visit with a mean difference value of 3.9±13.3 mmHg (Figure 6.3).

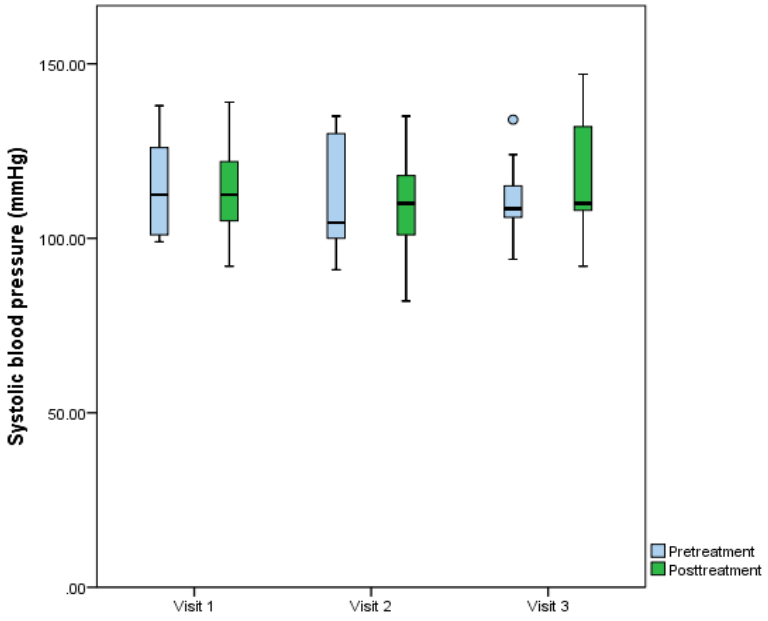


Figure 6.3. Systolic blood pressure response at three visits. The data are medians. Error bars represent non-outlier range (n=14).

There was a non-significant main effect of the visit day on systolic blood pressure, which indicated no difference among the three visits of treatment (F(2, 26) =0.960, p=0.396). The interaction between the time of measurement (before or after

mobilisation) and the visit day (1, 2 or 3) was not significant ($F(2, 26) = 0.591$, $p = 0.561$).

For diastolic blood pressure, there was a significant increase after mobilisation compared to baseline values that was evident in all visits with mean difference values of 8.1±16.3 mmHg, 2.9±10 mmHg and 7.2±14.6 mmHg ($F(1, 13) = 6.349$, $p = 0.026$) (Figure 6.4). There was a non-significant main effect of the visit day on measurements of diastolic blood pressure ($F(2, 26) = 0.099$, $p = 0.906$). However, only changes within the first and third visits (8.07 mmHg, 7.2 mmHg) exceeded the MDC calculated in the reliability study (6.6 mmHg). The interaction between the time of measurement (before or after mobilisation) and the visit day (1, 2 or 3) was not significant ($F(2, 26) = 0.657$, $p = 0.527$). In order to compare the results with previous studies, the percentage of change in systolic BP and diastolic BP for the three visits were calculated and are displayed in Table 6.1.

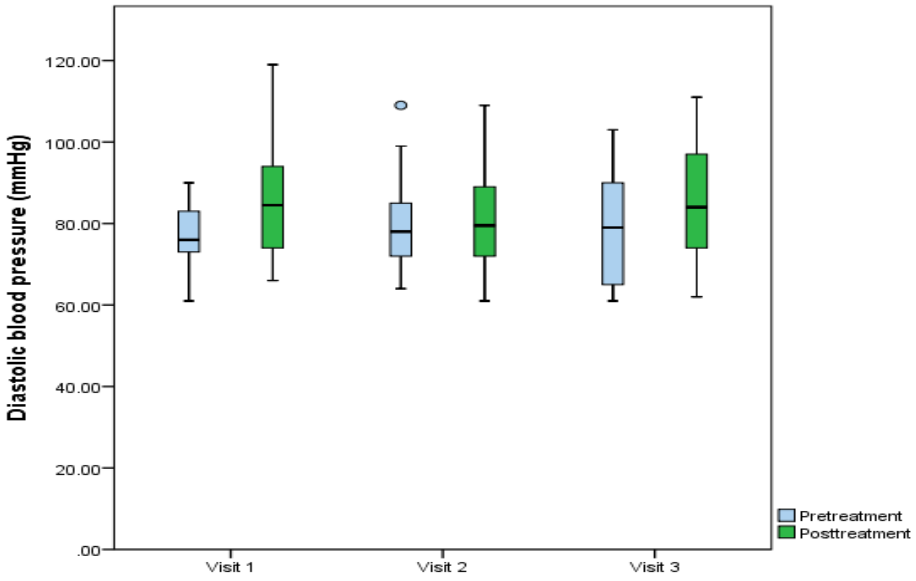


Figure 6.4. Diastolic blood pressure response at three visits. The data are medians. Error bars represent non-outlier range (n=14).

Table 6.1. Percentage (%) change in systolic and diastolic blood pressure at each visit. The data are means ± standard deviation (n=14).

	Visit 1	Visit 2	Visit 3
SPB	0.47±11.6	0.29±7.7	3.64±12
DBP	11.58±24	4.04±13	10.78±18.1

Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure.

6.3.2. Results of mobilisation treatment on heart rate and respiratory rate

For each visit, there was a significant increase in heart rate measurements during mobilisation treatment compared to baseline values with mean difference values of 0.2±8.4 beat/minute, 7.8±10.2 beat/minute and 5.5±7.3 beat/minute (visits 1 to 3, respectively) ($F(2, 26) = 6.459$, $p=0.005$).There was also a significant decrease in heart rate measurements during the final rest period within all visits compared to baseline values with mean difference values of -3.2±10.2 beat/minute, -0.4±11.2 beat/minute and -1.5±9.7 beat/minute (Figure 6.5).

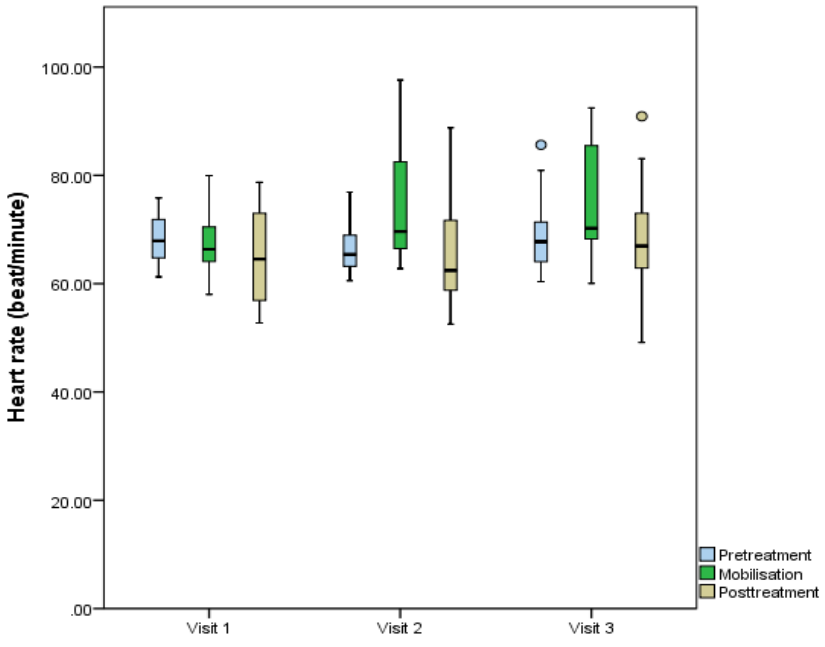


Figure 6.5. Heart rate response at three visits. The data are medians. Error bars represent non-outlier range (n=14).

Bonferroni pairwise comparisons showed that this difference lies between baseline and mobilisation measurements (p=0.047) and between mobilisation and final rest period measurements (p=0.007). However, only the differences that occurred during the treatment period at the second (7.8 beat/minute) and third visits (5.5 beat/minute) exceeded the MDC reported in the reliability study (5.4 beat/minute). There was a non-significant main effect of the visit day on measurements of HR (F(2, 26) =1.145, p=0.334). The interaction between the time of measurement and the visit day (1, 2 or 3) was not significant (F(4, 52) =1.915, p=0.122).

For all visits, there was a significant increase in respiratory rate measurements during mobilisation treatment compared to baseline values with mean difference values of 3.6±4.3 breaths/minute, 6.1±6.8 breaths/minute and 6±4.3 breaths/minute (F(1.305, 16.961) =24.193, p= 0.001). Also, there was a significant decrease in respiratory rate measurements during the final rest period within all visits compared to mobilisation values. The mean difference values of respiratory rate measurements during the final rest period compare to baseline values were -0.04±3.5 breath/minute, 0.3±1.8 breaths/minute and 0.2±4.5 breaths/minute (Figure 6.6).

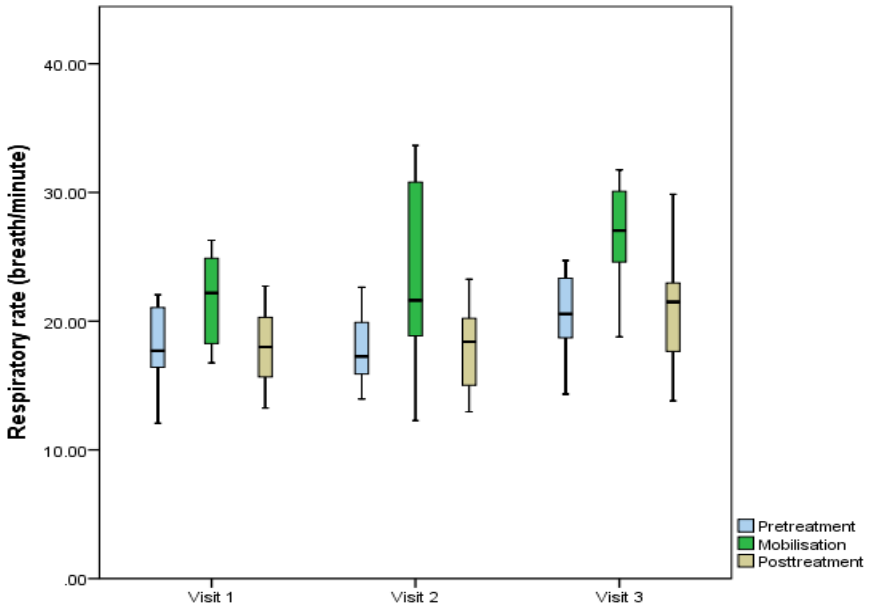


Figure 6.6. Respiratory rate response at three visits. The data are medians. Error bars represent non-outlier range (n=14).

For respiratory rate, there was a significant main effect the visit day on respiratory rate ($F(2, 26) = 13.360$, $p=0.001$). Bonferroni pairwise comparisons showed a significant difference (increase) between baseline and mobilisation measurements ($p=0.000$) and between mobilisation and final rest period measurements (decrease) ($p=0.001$). Only the changes within the mobilisation period in relation to baseline measures within all visits (3.6 breaths/m, 6.1 breaths/m and 6 breaths/m) exceeded the MDC (1.6 breath/minute).

Furthermore, *post hoc* analysis indicated a significant difference between the first and third visits ($p=0.001$) and between the second and third visits ($p=0.003$). The interaction between the time of measurement and the visit day was not significant ($F(4, 52) = 0.959$, $p=0.438$). In order to compare our results with previous studies, differences in the mean of heart rate and respiratory rate measures before and after mobilisation were presented as percentages of change. The percentage of change for the three visits are displayed in Table 6.2.

Table 6.2. Percentage of change (%) in heart rate and respiratory rate at each visit. The data are means ± standard deviation (n=14).

	Visit 1		Visit 2		Visit 3	
	Baseline to treatment	Baseline to final rest period	Baseline to treatment	Baseline to final rest period	Baseline to treatment	Baseline to final rest period
HR	0.74±12.2	-4.2±15.02	11.86±16	-0.20±17.2	8±10.7	-1.84±13.8
RR	23.6±31.03	1.5±19	35.9±42.4	1.63±11	31.58±26.9	1.54±23.04

Abbreviations: HR: heart rate; RR: respiratory rate.

6.3.3. Results of mobilisation treatment on skin conductance and skin temperature

For the three visits, there was a non-significant change in skin conductance level (right side) with a slight decrease during the mobilisation period compared to the baseline level with mean difference values of -0.01±0.08 v, -0.01±0.05 v and -0.04±0.1 v (Figure 6.7). For skin conductance level (left side), the results showed the same trend except for the first visit where there was a slight non-significant increase during the mobilisation period compared to the baseline level with a mean difference value of 0.004±0.06 v. Skin conductance level for both sides tended to

non-significantly increase during the final rest period compared to the treatment period (Figure 6.8) (Table 6.3).

For the three visits, the skin temperature results showed that there was a non-significant change in skin temperature level (both side) with values tending to increase or decrease slightly during the mobilisation period compared to the baseline level with mean difference values ranged between -0.07±0.3°C and 0.03±0.5°C. However, the skin temperature level for both sides tended to return to their baseline values during the final rest period (Figure 6.9 and 6.10) (Table 6.3).

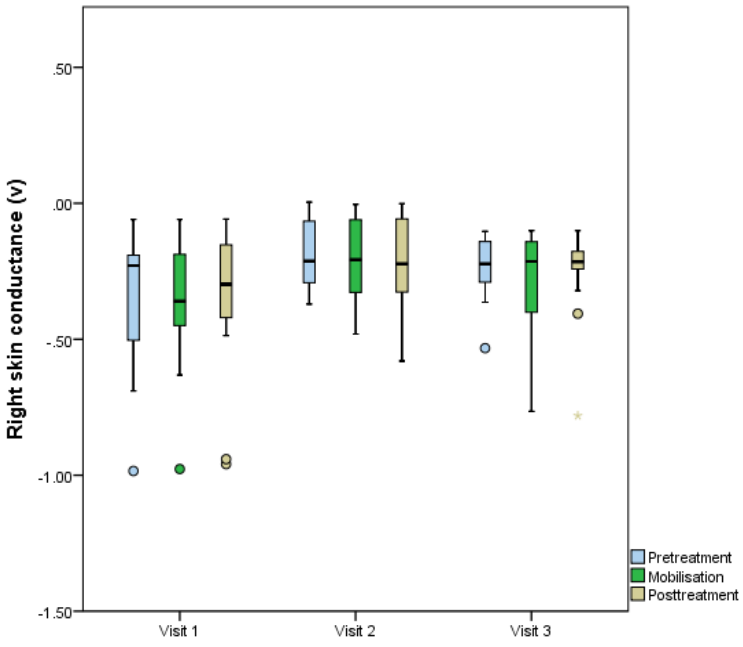


Figure 6.7. Right skin conductance response at three visits. The data are medians. Error bars represent non-outlier range (n=14).

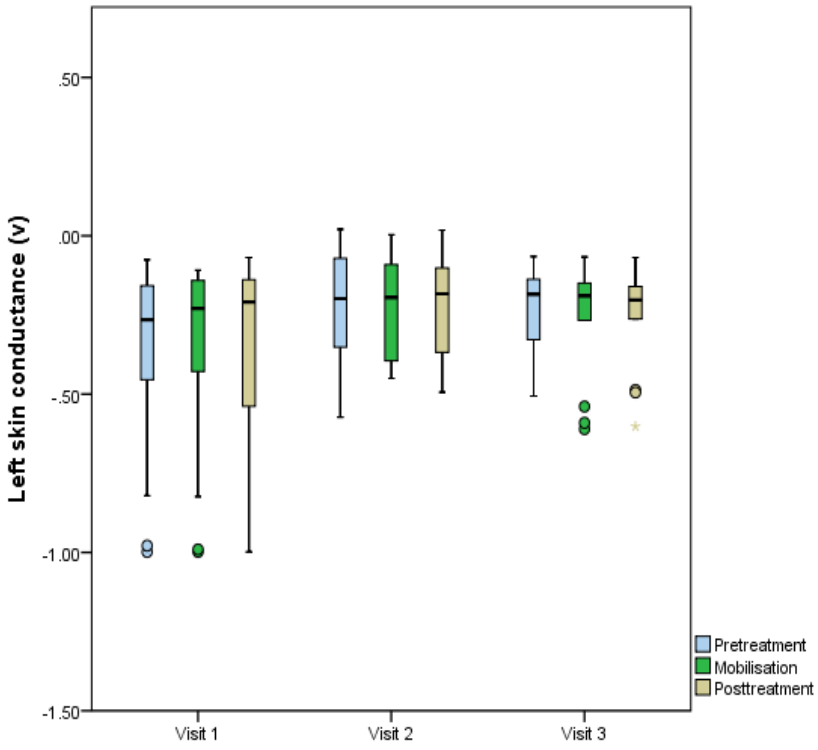


Figure 6.8. Left skin conductance response at three visits. The data are medians. Error bars represent non-outlier range (n=14).

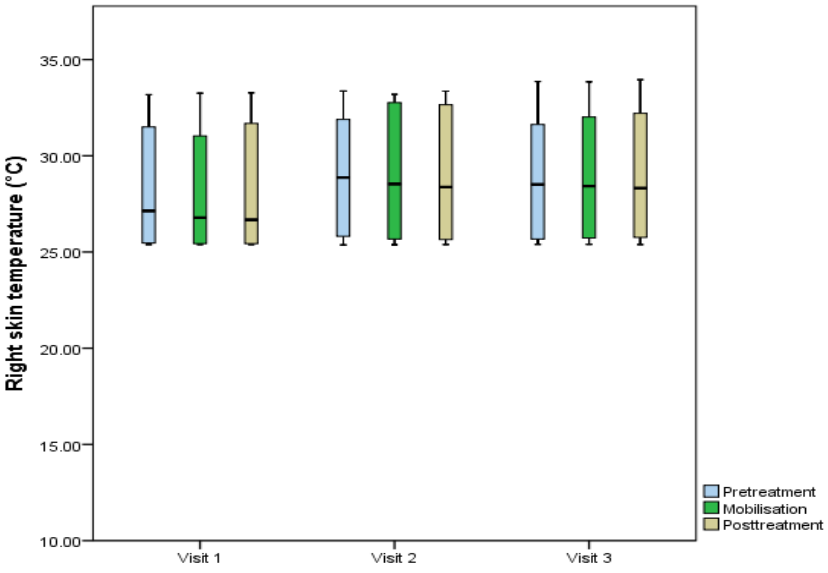


Figure 6.9. Right skin temperature response at three visits. The data are medians. Error bars represent non-outlier range (n=14).

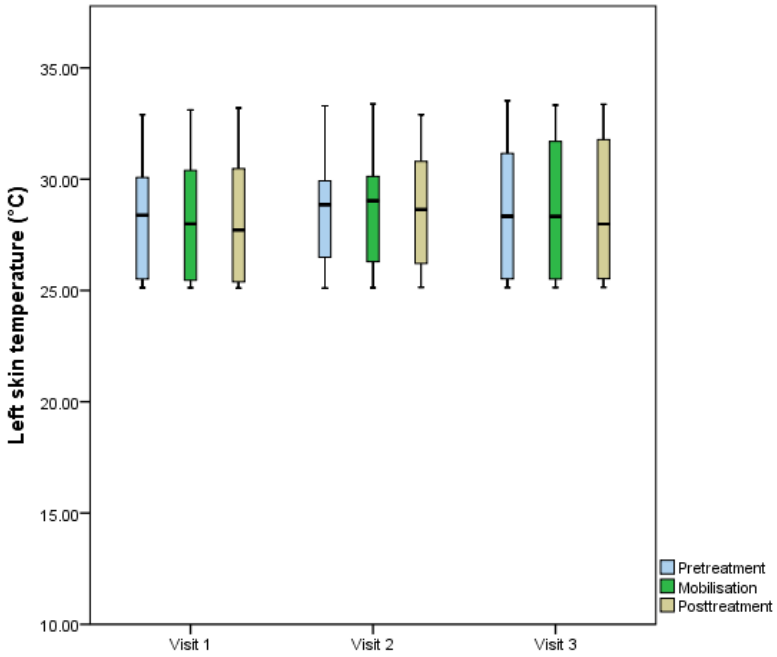


Figure 6.10. Left skin temperature response at three visits. The data are medians. Error bars represent non-outlier range (n=14).

In order to compare the results with previous studies, differences in the mean of skin conductance and skin temperature measures before and after mobilisation were presented as percentages of change. The percentage of change for the three visits are displayed in Table 6.4.

Table 6.3. Results of skin conductance (v) and skin temperature (°C) including mean values before, during and after mobilisation, chi-square and *p* values from the Friedman test. The data are means ± standard deviation (n=14).

	Visit 1					Visit 2					Visit 3				
Outcome measure	PRE	MOB	POST	Chi-square	*p*	PRE	MOB	POST	Chi-square	*p*	PRE	MOB	POST	Chi-square	*p*
RT SC	-.35±.3	-.36±.3	-.35±.3	2.7	.26	-.19±.1	-.21±.2	-.21±.2	.143	.93	-.24±.1	-.28±.2	-.26±.2	.571	.75
LT SC	-.38±.3	-.37±.3	-.35±.3	2.286	.32	-.23±.2	-.23±.2	-.23±.2	1.286	.53	-.22±.1	-.27±.2	-.26±.2	2.714	.26
RT ST	28.4±3.1	28.3±3.2	28.3±3.3	2.714	.26	28.9±3.1	29.01±3.1	28.9±3.1	4.429	.11	28.7±3.1	28.6±3.1	28.6±3.1	3.571	.17
LT ST	28.2±2.7	28.1±2.8	28.2±2.9	.143	.93	28.7±2.6	28.8±2.7	28.7±2.7	2.714	.26	28.6±3	28.7±3.1	28.6±3.1	4.429	.11

Abbreviations: RT SC: right skin conductance; LT SC: left skin conductance; RT ST: right skin temperature; LT ST: left skin temperature.

Table 6.4. Percentage (%) of change in skin conductance and skin temperature (right and left sides) for each visit. The data are means ± standard deviation (n=14).

	Visit 1		Visit 2		Visit 3	
	Baseline to treatment	Baseline to final rest period	Baseline to treatment	Baseline to final rest period	Baseline to treatment	Baseline to final rest period
RT SC	10.04±38.12	-1.2±26.5	-9.51±61.5	0.62±49.8	14.22±38.2	12.05±36.4
LT SC	4.5±32.8	-3±41.7	-2.9±41.5	8.24±33.6	13.75±28.15	18.06±36.14
RT ST	-0.4±1.2	-0.11±1.8	0.1±1.7	0.04±3	-0.23±0.9	-0.2±1.9
LT ST	-0.2±1.2	0.02±1.8	0.3±2.1	-0.13±3.4	0.06±1.8	-0.2±2.5

Abbreviations: RT SC: right skin conductance; LT SC: left skin conductance; RT ST: right skin temperature; LT ST: left skin temperature

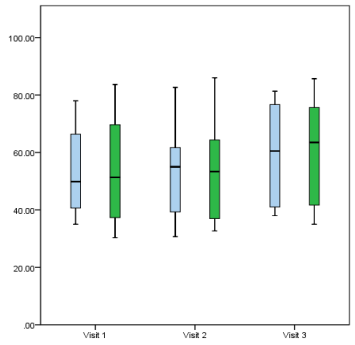
6.3.4. Results of mobilisation on pressure pain thresholds

At all locations of PPT, values after mobilisation exceeded baseline measurements (Figure 6.11). There was a non-significant trend toward an increase in PPT measurements that was evident at all measurement sites within all visits with mean difference values ranged between 0.5±5.2 N/cm^2 and 5.8±9.9 N/cm^2 except at the right 1st dorsal interosseous muscle (F(1,13)= 6.800,p=0.022) with the difference in mean calculated to be 2.33 N/cm^2 and 3.02 N/cm^2 which did not exceed the MDC 5.9 N/cm^2 reported in the reliability study (Table 6.5) (Table 6.6).

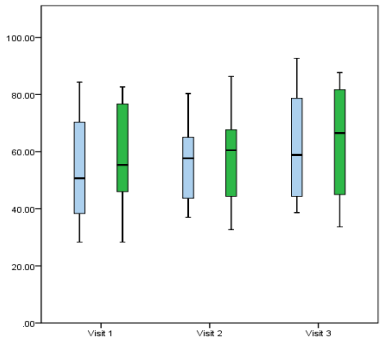
Table 6.5. Mean differences (N/cm^2) in pressure pain threshold for all the sites of measurement at each visit. The data are means ± standard deviation (n=14).

Outcome measure	Visit 1	Visit 2	Visit 3
RT T12	1.5±9.9	1.5±7.3	1.8±9
LT T12	3.8±6.6	3.5±7.8	1.6±11.03
RT L5	1.7±11.4	2.3±7.3	1.2±7.5
LT L5	2.4±10.5	1.3±8.9	5.8±9.9
RT 1stDI	1.7±3.8	1.4±3.4	2.3±3.3
LT 1stDI	0.6±5.2	1.62±4.4	3.02±3.9

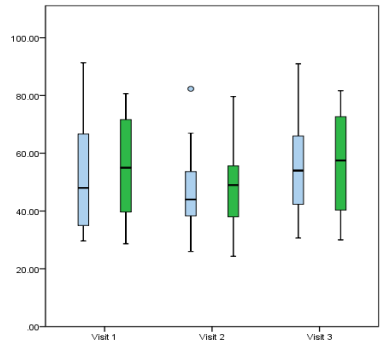
Abbreviations: RTL5: right 5th lumbar para-spinal muscles; LTL5: left 5th lumbar para-spinal muscles; RTT12: right 12th thoracic para-spinal muscles; LTT12: left 12th thoracic para-spinal muscles; RT1STDI: right first dorsal interosseous muscle; LT1STDI: left first dorsal interosseous muscle.



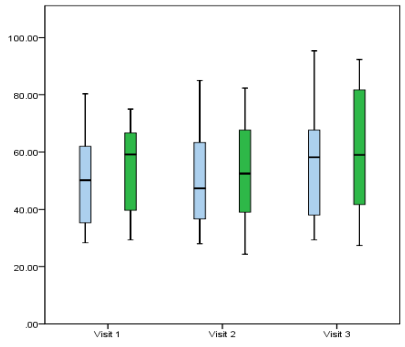
Pressure pain threshold of right thoracic paraspinal muscles (N/cm^2)



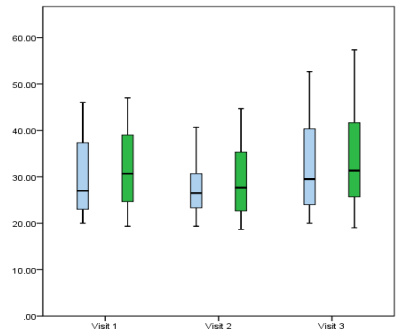
Pressure pain threshold of left thoracic paraspinal muscles (N/cm^2)



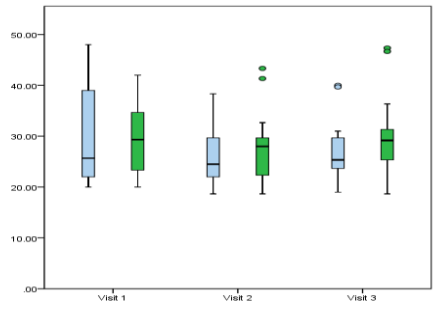
Pressure pain threshold of right lumbar paraspinal muscles (N/cm^2)



Pressure pain threshold of left lumbar paraspinal muscles (N/cm^2)

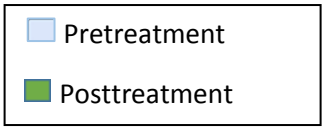


Pressure pain threshold of right 1st dorsl interosseous muscle (N/cm^2)



Pressure pain threshold of left 1st dorsal interosseous muscle (N/cm^2)

Figure 6.11. Pressure pain threshold response of all sites of measurements at three visits. The data are medians. Error bars represent non-outlier range (n=14).



There was a significant main effect of the visit day on PPT at three sites (right L5, left L5 and right T12). Bonferroni pairwise comparisons showed that these differences were between the second and third visits for the right (p=0.01) and left L5 sites (p=0.04) and between the first and third visits (p=0.025) and the second and third visits (p=0.003) for right T12 site. The interaction between the time of measurement and the visit day (1, 2 or 3) was not significant across all the of measurement sites. In order to compare my results with previous studies, differences in the mean of PPT before and after mobilisation were presented as percentages of change (Table 6.7).

Table 6.6. Two-way ANOVA results of pressure pain threshold for all sites of measurements (n=14).

	RT T12	LT T12	RT L5	LT L5	RT 1ST DI	LT 1ST DI
Time	F(1,13)= 0.775, p=0.395	F(1,13) = 3.210, p=0.096	F(1,13)= 1.021, p=0.331	F(1,13)= 2.234, p=0.159	F(1,13)= 6.800, p=0.022*	F(1,13)= 2.651, p =0.127
Visit	F(2,26)= 6.514, p=0.005*	F(2,26) = 3.116, p=0.061	*$F(2,26)=3.813$, p =0.035**	F(2,26)=4.291, p=0.025*	F(2,26)=3.005, p=0.067	F(1.388,18.047)=1.461, p=0.250
Visit * Time	F(1.386,18.022)=0.008, p=0.971	F(2,26) = .376, p=0.690	F(2,26)=0.069, P=0.933	F(2,26)= 1.603, p=0.220	F(2,26)= 0.378, p=0.689	F(1.306,16.975)=2.795, p=0.105

Abbreviations: RTL: right lumbar para-spinal muscles; LTL: left lumbar para-spinal muscles; RTT12: right 12th thoracic para-spinal muscles; LTT12: left 12th thoracic para-spinal muscles; RT1STDI: right first dorsal interosseous muscle; LT1STDI: left first dorsal interosseous muscle.

Table 6.7. Percentage of change (%) in pressure pain threshold for all the sites of measurement at each visit. The data are means ± standard deviation (n=14).

Outcome measure	Visit 1	Visit 2	Visit 3
RT T12	3.1±18.4	2.8±15.1	3.7±17
LT T12	8.1±12.6	6.4±14.7	2.9±18.6
RT L5	5.9±25.9	4.1±15.1	2.9±14.6
LT L5	7.8±25.02	2.6±19.4	10.5±17.9
RT 1stDI	6.3±14.9	4.8±12.1	7.4±12.4
LT 1stDI	4.7±14.9	6.6±15.1	10.8±15.1

Abbreviations: RTL: right lumbar para-spinal muscles; LTL: left lumbar para-spinal muscles; RTT12: right 12th thoracic para-spinal muscles; LTT12: left 12th thoracic para-spinal muscles; RT1STDI: right first dorsal interosseous muscle; LT1STDI: left first dorsal interosseous muscle.

6.3.5. Results of mobilisation on salivary alpha-amylase

The results indicated a significant increase between pre and post mobilisation values within the first visit with a mean difference value of 12.03±20.7 U/m (z= -2.2, p= 0.03). However, this significant change (12.02 U/m) did not exceed the MDC calculated in the reliability study (23 U/m). There was a non-significant decrease within the second and third visits level with mean difference value of -7.9±13.6 U/m and -1.5±19.9 U/m (z= -1.8, p= 0.079; z= -0.22, p =0.83) (Figure 6.12). Differences in the mean of salivary alpha-amylase before and after mobilisation were presented as percentages of change and are displayed in Table 6.8.

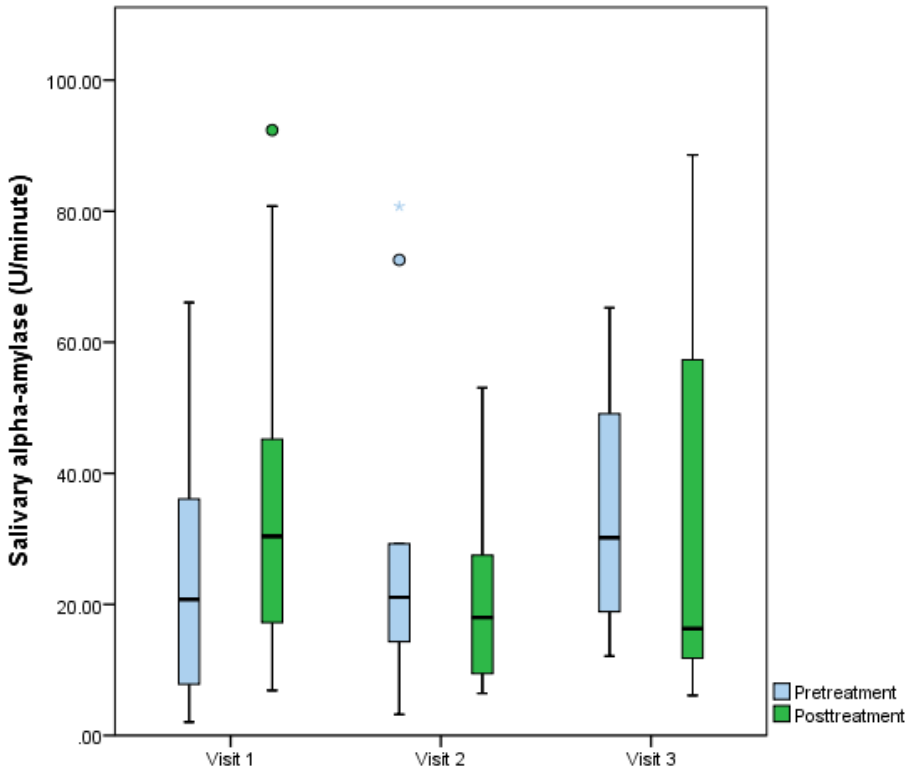


Figure 6.12. Salivary alpha-amylase response at three visits. The data are medians. Error bars represent non-outlier range (n=14).

Table 6.8. Percentage of change (%) in salivary alpha-amylase at each visit. The data are means ± standard deviation (n=14).

	Visit 1	Visit 2	Visit 3
sAA	109.3±126.4	-0.7±54.2	-1.6±60.6

Abbreviation: sAA: salivary alpha-amylase.

6.3.6. Summary of findings

- There was an increase in diastolic blood pressure after mobilisation. However, only differences within the first and third visits for diastolic blood pressure were significant and exceeded the MDC (6.65 mmHg). Differences were not significant between visits.
- There was an increase in heart rate and respiratory rate measurements during mobilisation treatment that decreased during the final rest period measurements within all visits. This increase was significant within all visits for respiratory rate and within the second and third visits for heart rate

measurements that also exceeded the MDC (5.45 beat/minute, 1.59 breath/minute). Differences between visits were significant only between the first and third visits.

- The increase in pressure pain threshold was evident at all measurement sites within all visits. There was a significant difference in PPT measurements at the hand, left lumbar para-spinal muscles (within the third visit) and the left thoracic para-spinal muscles (within the first visit). However, the changes failed to exceed the MDC reported in the reliability study (right hand: 6.4 N/cm^2, left hand: 4.1 N/cm^2, left lumbar: 9.1 N/cm^2; left thoracic: 9.7 N/cm^2).
- There was a non-significant difference in skin conductance and skin temperature measurements within or between the three visits.
- There was an increase in mean salivary alpha-amylase after mobilisation within the first visit, but that decreased within the second and third visits. Although the difference within the first visit was significant, it did not exceed the MDC (22.99 Unit/minute).

6.4. Discussion

6.4.1. The effects of mobilisation treatment on measures of SNS

6.4.1.1. Blood pressure, respiratory rate and heart rate

The results demonstrated an increase in heart rate and respiratory rate measurements during mobilisation treatment that decreased during the final rest period measurements within all visits. This result was significant within all visits for respiratory rate and within the second and third visits for heart rate measurements. All these differences exceeded the MDC reported by the reliability study indicating that the results are clinically significant. There was an increase in diastolic blood pressure after mobilisation, but only differences within the first and third visits were significant.

These results are similar to findings from other studies that reported increased heart rate, respiratory rate and/or blood pressure following cervical mobilisation (Petersen et al., 1993; Vicenzino et al., 1995; Wright, 1995; McGuiness et al., 1997). The authors suggested this was due to the descending pain inhibitory pathways from

dPAG in the midbrain. Another proposal by those authors for the resultant sympathoexcitatory response following mobilisation treatment was direct stimulation to the cervical ganglia and sympathetic fibres as they are located close to the cervical level treated (C5/6). These ganglia connect with organs like the heart through postganglionic fibres. Performing pressure to the neck might cause an increase or decrease to the carotid baroreceptors' function. This can affect heart rate and peripheral vascular resistance (Thoren and Lundin, 1983). However, on both sides of the spine, the sympathetic trunk extends parallel to the spine and might be moved during mobilisation, thus causing stimulation of ganglia along the trunk (Butler 1991).

6.4.1.2. Skin conductance and skin temperature

There was a non-significant difference in skin conductance and skin temperature measurements within or between the three visits. Supporting results have been reported by Chiu and Wright (1998), who found no significant sympathetic change in skin conductance or skin temperature following cervical mobilisation. The authors attributed this to the slow rate of mobilisation and the small sample size of the study (n = 16). On the other hand, a number of studies have reported significant sympathoexcitation in skin conductance and/or skin temperature as evidence of the descending inhibitory mediated response of the dorsal periaqueductal gray (dPAG) following cervical mobilisation (Peterson et al., 1993; Chiu and Wright et al., 1996; Sterling et al., 2001; La Touche et al., 2012), thoracic mobilisation (Cleland et al., 2004; Jowsey and Perry, 2010) and lumbar mobilisation (Perry and Green, 2008; Piekarz and Perry, 2016). The difference in the responses following mobilisation to different levels of the spine might be due to the different peripheral coetaneous innervations or central processing systems for different regions (Perry at al. 2015). However, due to the small sample size in the preclinical study of this thesis (*n*=14), the results should be interpreted with caution.

6.4.1.3. Salivary alpha-amylase

There was an increase in mean sAA after mobilisation within the first visit, but that decreased within the second and third visits. Although the difference within the first visit was significant, it did not exceed the MDC. It was hypothesised that thoracic

manipulative treatment has the ability to modulate the sympathetic activity by activating the thoracic sympathetic chain ganglia that might cause initial sympathetic stimulation that is followed by a prolonged reduction of sympathetic outflow (Wallace et al., 2003). Thus, as samples were collected 10 minutes after the mobilisation, it might be suggested that the initial increase in the sAA within the second and third visits was transient.

6.4.2. The effects of mobilisation treatment on pressure pain threshold

The mechanical PPT of the thoracic level was significantly increased following thoracic mobilisation by 8.1% within the first visit. This local hypoalgesic response to spinal mobilisation might be explained by the local stimulation of the low threshold mechanoreceptors in articular and peri-articular structures following thoracic mobilisation that might inhibit the small diameter, high threshold mechanoreceptors at the level of spine that result in pain modulation in the dorsal horn of the spinal cord (Melzack and Wall, 1965). Zusman (1986) questioned this preferential ability and argued that the proposed hypoalgesic responses of spinal mobilisation might be the result of the suggested ability of the repetitive movement during the application of mobilisation to decrease activity of joint afferents. This might explained other significant increase that was recorded over the lumbar level of 10.5% within the third visit. The pathway emerging from PAG is another possible mechanism as widespread hypoalgesia was demonstrated as occurring away from the treated area distally over the hands of 7.4% and 10.8%.

This widespread effect of thoracic mobilisation on PPT was shown by other investigations that reported a hypoalgesic effect distal to the area of mobilisation and that supported the concept that response to mobilisation is not specific or local to the treatment area (Vicenzino et al., 1996; Moss et al., 2007; Krouwel et al., 2010; Willett et al., 2010; Pentelka et al., 2012). The hypoalgesic response recorded in asymptomatic subjects might suggest the ability of mobilisation to produce hypoalgesia where pain and dysfunction are absent (Willett et al., 2010). However, this significant hypoalgesic response was not evident in all locations at all visits. All statistically significant percentages of change exceeded neither the MDC values

calculated in the reliability study for each measurement site, nor the clinically significant change of 15% reported by Moss et al. (2007).

6.5. Limitations of the study

As a result of being a single-arm study, no control or placebo groups were used which would have been essential to thoroughly investigate the effectiveness of mobilisation treatment. However, previous studies have examined this effect using placebo controlled or controlled studies (Vicenzino et al., 1996; Sterling et al., 2001; Moss et al., 2007). Furthermore, looking at the effectiveness of mobilisation as a treatment form was not the aim of this study. The intra-therapist reliability for performing consistent mobilisation techniques was not tested before conducting this study, and the results of this research are limited to the short-term effects following the application of three mobilisation treatments. Furthermore, as physical assessment was not part of this phase of the study, physiological measurements in normal participants may have been affected if they had an asymptomatic dysfunctional component of their neuro-musculoskeletal system. However, conducting this preclinical study generated data used for the power analysis for the clinical study which minimised the risk of type I and type II errors (the study being underpowered or needing to recruit more samples). The effect of extraneous variables has been reduced by using strict criteria for inclusion and exclusion. In addition, the influence of diurnal variation has been controlled by determining similar appointment times for all visits of each participant.

6.6. Conclusion

The purpose of this preclinical study was to provide empirical evidence of the neurophysiological effects (as measured by SNS activity and PPT) of the thoracic mobilisation technique of the lumbar spine in asymptomatic subjects over a course of three doses. These findings revealed significant sympathoexcitatory effects in terms of blood pressure, heart rate and respiratory rate where there were non-significant results for peripheral sympathetic measures (skin conductance and skin temperature). Significant hypoalgesic effects were evident in some locations, including distal areas, but not at all visits. The next stage of the thesis was therefore to examine the effects of mobilisation treatment on hypoalgesia and sympathetic

activity in patients with nonspecific chronic low back pain over a course of three doses of mobilisation treatment and is detailed in the following Chapter.

Chapter 7

A single-arm clinical trial investigating the neurophysiological responses of the sympathetic nervous system to passive accessory mobilisations in a symptomatic population with nonspecific chronic low back pain

7.1. Introduction

Although clinical research supports the patient-reported benefits of mobilisation treatment in the management of nonspecific chronic low back pain (NSCLBP), the neurophysiological mechanisms behind these effects within patient populations remain unknown (Sparkers, 2005). A number of studies have explored sympathetic responses as a measure of the neurophysiological response of various mobilisation treatment techniques in the cervical, thoracic and lumbar spinal levels, as well as in the upper and lower limbs (Peterson et al., 1993; Vicenzino et al., 1995; Sterling et al., 2001; Perry and Green, 2008; Jowsey and Perry, 2010). The results reported various sympathetic changes among cardiopulmonary, sudomotor and cutaneous vasomotor functions (Peterson et al., 1993; Chiu and Wright, 1996; Vicenzino et al., 1998; Sterling et al., 2001). Their findings reinforce the proposed sympathetic mechanism behind the efficacy of the application of spinal mobilisation techniques. However, among these studies, only a limited number involved a symptomatic population that reported on symptoms only in the cervical and thoracic levels and not in the lumbar level.

As stated in Chapter 3 and summarised in Table 3.3 there have been no clinical studies investigating the neurophysiological responses to spinal mobilisation treatment using a lower back pain (LBP) patient population. Although patient-reported outcome measures can be used by physiotherapists to assess the pain and functional responses of their patients to the prescribed treatment, to date, there is no non-invasive measure available to assess the physiological response. Thus, the aim of this study was to observe, in a clinical population with NSCLBP, the immediate and cumulative neurophysiological responses of the SNS to mobilisation treatment, as it is one of the most commonly utilised physiotherapy treatments in the management of NSCLBP. Another aim was to determine if there is a correlation

between these neurophysiological responses and patient-reported outcome measures.

7.1.1. Research question

What are the immediate and cumulative effects of thoracic mobilisation treatment on hypoalgesic and sympathetic measures in patients with NSCLBP?

7.1.2. Objectives

-To determine the neurophysiological responses of the SNS to thoracic mobilisations in a symptomatic population with NSCLPB.
-To determine the extent of the hypoalgesic effect (thoracic, lumbar and systemic levels) resulting from thoracic mobilisation in a symptomatic population with NSCLPB.
-To examine the possibility of a dose-dependent effect of thoracic mobilisation on sympathetic and PPT changes in a symptomatic population with NSCLPB.
-To establish whether there is a correlation between Numeric Pain Rating Scale (NPRS) changes and PPT changes after thoracic mobilisation in a symptomatic population with NSCLPB.

7.2. Method

7.2.1. Study design

This study utilised a single-arm clinical trial.

7.2.2. Ethics approval

This study was approved by the Faculty of Health, Psychology and Social Care Research Ethics Committee at Manchester Metropolitan University (Appendix 7.1). In addition, as this study was conducted at King Fahad University Hospital (KFUH) in eastern Saudi Arabia, approval was obtained from the research committee of the University of Dammam (Appendix 7.2). The head of the Physical Therapy department at the university hospital also reviewed the protocol and gave signed permission for the research to be conducted within the department on patients referred for LBP physiotherapy treatment (Appendix 7.3).

7.2.3. Participants

7.2.3.1. Sample size calculation

Based on the mean change presented in chapter 6, between visits 1 and 2 (Appendix 7.4) (15% mean change in SC; 21% standard deviation), a sample size calculation revealed that 31 participants would be needed to see a difference in skin conductance values (primary outcome measure) from a baseline of 15%, at the 5% significance level with 80% power (Sim and Wright, 2005). Taking into account a 20% anticipated dropout rate, 37 participants were needed to offset possible loss to follow-up (Sim and Wright, 2005).

7.2.3.2. Patient recruitment

A purposive convenience sample was recruited for this study. Patients with non-specific chronic low back pain (NSCLBP) diagnosed and referred by the orthopaedic physicians to the physical therapy department were screened for eligibility criteria from October 2016 to February 2017 (n = 64). In the current study, NSLBP was defined as lumbar pain with or without referred pain provoked by posture, movement and/or palpation of the lumbar musculature. Inclusion criteria were the following: LBP symptoms of a mechanical, nociceptive nature (NSLBP), a history of NSLBP of insidious onset of more than 12 weeks duration, an age from 18 to 55 years, non-smoker, male or female gender, possession of an adequate understanding of the Arabic language and the ability to provide informed consent for the study. In order to ensure that the results extrapolation to the target population, both male and female were recruited.

Potential participants for this study were excluded (n = 28) if they had undergone physiotherapy treatment within the previous six months. Additionally, participants were excluded if they had been diagnosed with a psychiatric or medical disorder that may have influenced their neurophysiological responses (e.g. rheumatoid arthritis, multiple sclerosis, diabetes and anxiety disorders), had previously had lower extremity or spinal surgery, been pregnant, had a previous history of trauma with related permanent sensation abnormality (dysaesthesia), had skin disorders at the location of the electrode placement, were dependent on alcohol, were smokers or

were incapable of providing informed consent (e.g. as a result of dementia or limited Arabic language skills) (Perry et al., 2015).

Excluded were also those with any contraindication, precautions or red flags to thoracic mobilisations (Grieve, 1991):

•Malignancy involving the vertebral column

•Cauda equina lesions producing disturbance of bladder and/or bowel function

•Signs and symptoms of spinal cord involvement; or involvement of more than one spinal nerve root on one side, or two adjacent roots in one lower limb only

•Rheumatoid collagen necrosis of vertebral ligaments

•Active inflammatory and infective arthritis

•Bone disease of the spine (osteoporosis, osteopenia)

Precautions to thoracic mobilisations (Grieve, 1991):

•The presence of neurological signs

•Osteoporosis

•Spondylolisthesis

•Dizziness

•Congenital generalised hypermobility (Ehlers-Danlos syndrome)

•Advanced spinal or lower limbs degenerative changes

•History of spinal or lower limbs steroid therapy

•Ongoing anticoagulant therapy

Red flags to mobilisations (CSAG, 1994)

- Age of onset <20 or >55 years
- Violent trauma, e.g. fall from a height, road traffic accident

- Constant progressive, non-mechanical pain
- Thoracic pain
- Past medical history of carcinoma
- Systemic steroids
- Drug abuse, HIV
- Systematically unwell
- Weight loss
- Persistent severe restriction of lumbar flexion
- Widespread neurology
- Structural deformity

7.2.4. Confidentiality

Each participant was assigned an alphanumeric code upon entry to the study, and all study data were labelled using the same code. All written information on paper or any non-computerised data was stored in a locked cabinet. All electronic data recorded by the e-Health Sensor Shield for Arduino were anonymised and secured in a locked cabinet within the hospital department. Computerised data were password protected and accessible only to the named investigators.

7.2.5. Research approach and methods

7.2.5.1. Procedure

The majority of the appointments were scheduled at least a month after the referral date. All potential participants were seen by the primary investigator who explained the study and their right to withdraw from it at any time and that this would not deny them the usual physical therapy treatment. In addition to the verbal explanation, participants were given the opportunity to ask questions. Patients who agreed to participate were assessed for their eligibility for inclusion in the study on the same day. In addition, the primary investigator asked for their permission to access their medical record file in order to confirm their eligibility. If they were deemed eligible, they were given a patient information sheet (Appendix 7.5). A cooling off period of 48 hours was allowed between the initial assessment and data collection for participants' consideration of the information provided. If they still wished to

participate a consent form was signed on the day of data collection (Appendix 7.6). Then they were given three appointments with a minimum interval of two days and a maximum interval of seven days.

The initial assessment was the same as the standard physiotherapy examination. The standard subjective assessment was completed, including demographic information (age, gender, occupation and social status), current and past medications and past medical history. In addition, information about their symptoms, including location, distribution, onset, duration, nature of the symptoms, were documented, as well as their functional limitations and pain intensity using the NPRS. Physical examination included lumbar and lumbopelvic examinations, neurological conductance assessment (reflexes, myotomes and dermatomes), neurodynamic assessment (straight leg raise test, femoral nerve test and slump test) and palpation of lumbar segmental motion (Freburger and Riddle, 2001; Maitland et al., 2005; Shacklock, 2005).

All participants signed a consent form prior to data collection. The exact procedure that was used in chapter 6 was also used this chapter. Each participant presented to the Physical Therapy Department at KFUH on three occasions. All participants completed their three visits while they were on the waiting list, thus ensuring that the effect of spinal mobilisation was not mixed with that of other types of treatment during that period. All treatments and data collection were performed in the same area in order to decrease any environmental variance.

Visits 1, 2 and 3

The salivary alpha-amylase, blood pressure and pressure pain threshold were measured at the beginning of session. Then, measurements taken using the e-Health Sensor Shield V2.0 were continuously recorded before, during and after the mobilisation technique. Finally, salivary alpha-amylase, blood pressure and pressure pain threshold were measured at the end of the session. This order was selected to avoid any potential effects from each measurement on the previous measurements.

One more outcome measure which was not used in phase 2 was used in this phase. Participants were asked to verbally rate their pain after PA force applied to their

symptomatic lumbar level on an 11-point Numerical Pain Rating Scale (NPRS) before and after the mobilisation treatment. An overview of the study protocol is shown in Figure 7.1.

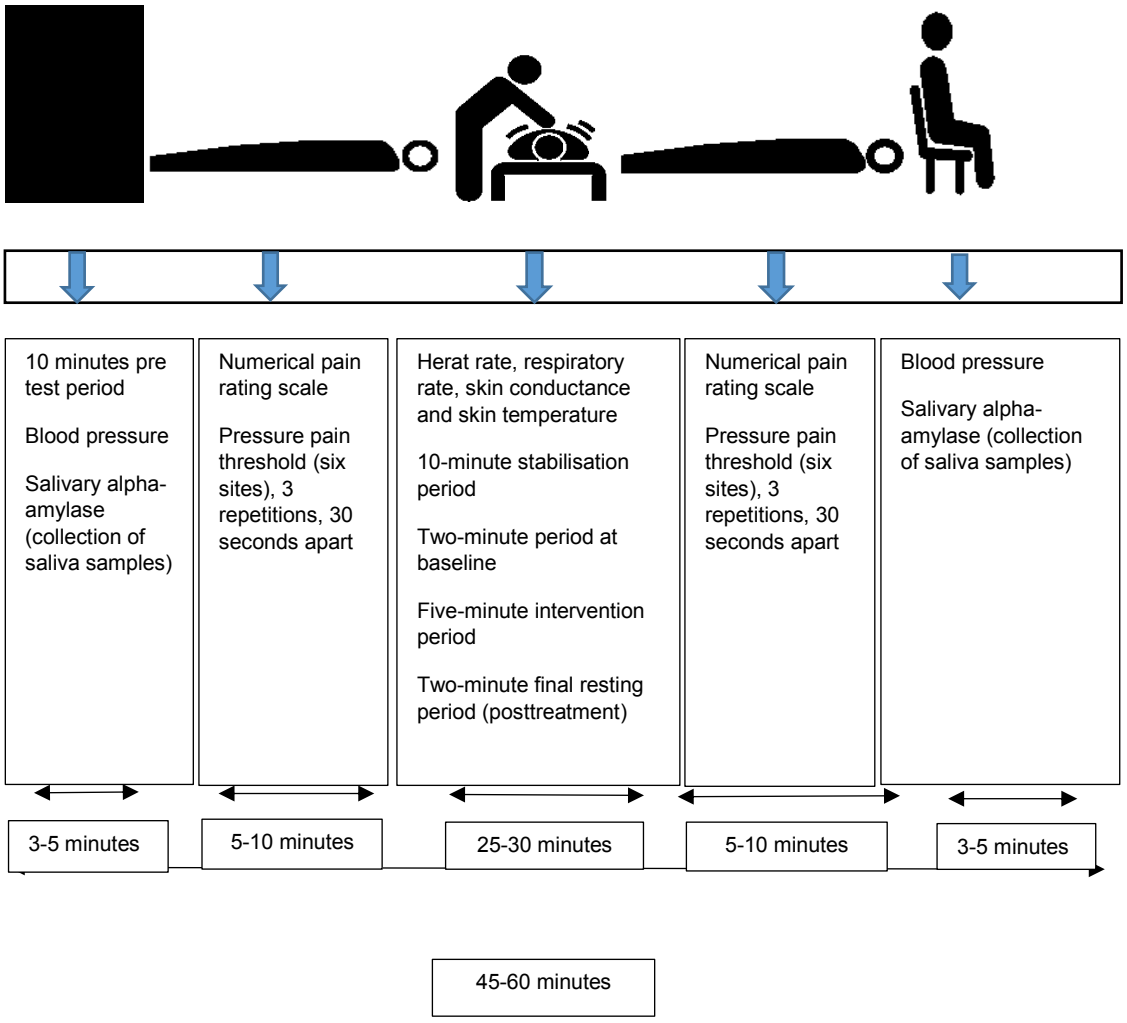


Figure 7.1. An illustration of the study protocol for each of the three visits.

Each participant produced two sets of data for NRPS, blood pressure, pressure pain threshold and salivary alpha-amylase: one at the beginning and end of each session.

Each participant produced three sets of data for respiratory rate, heart rate, skin temperature and skin conductance:

- A two-minute period at baseline (pretreatment),
- A five-minute intervention period (treatment) and
- A two-minute final resting period (post-treatment).

Due to hospital policy, two physiotherapists applied the mobilisation technique. A male therapist applied the treatment for the male patients; a female therapist applied the technique for the female patients. Both physiotherapists had MSc degrees in musculoskeletal physiotherapy and 10 years of experience in manual therapy. However, standardisation of mobilisation technique was attempted to insure that each patient receive the same amount of force. This was done by demonstrating the technique on colleagues, who rated the amount of force they felt on their lumbar area. Several applications were performed until each colleague confirmed that the identical amount of force had been applied.

All the measurements for all patients were taken by the primary investigator. Patients were scheduled at the same diurnal times for the three visits in an attempt to enhance patients' compliance and decrease measurement variations. The analysis of data was conducted when all patients finished all their visits in order to blind the primary researcher to any responses through data collection. All patients received advice to stay active and return to work. At the end of the study, all patients had the opportunity to ask questions about the effects of the mobilisation treatment on their pain and neurophysiological status.

7.2.6. Data analysis

The raw data for heart rate, respiratory rate, skin conductance and skin temperature were processed using custom written Mathematica code (version 10.4, Wolfram Research, Champaign, IL, USA). The software calculated the mean heart rate, respiratory rate, skin conductance and skin temperature of each minute throughout the session and the mean value (integral measurement) of each period (pretreatment, treatment and posttreatment). The pretreatment period consisted of two minutes following a stabilisation period of ten minutes. The treatment period consisted of the five minutes when the mobilisation was performed. The final two

minutes of the five minutes posttreatment period were used for analysis. Therefore, for each visit, each participant had three values for the following outcome measures: skin conductance (right and left), skin temperature (right and left), heart rate and respiratory rate. For pressure pain threshold data, the mean of the three measurements was calculated for each site; thus, every participant had two scores for pressure pain threshold at each site of measurement for each visit. For blood pressure and salivary alpha-amylase, each participant had two scores for each of the three visits.

Descriptive statistics were calculated for all data using the Statistical Package for the Social Sciences (IBM SPSS Statistics V. 23; IBM Corp., Armonk, NY, USA). All data were tested for normality using the Shapiro-Wilk test. The effect of mobilisation was analysed using the two-way repeated measure analysis of variance (ANOVA). For blood pressure, salivary alpha-amylase and pressure pain threshold, the two independent variables were time, which had two levels (before and after mobilisation), and visit, which had three levels (visit 1, visit2 and visit 3). For heart rate, respiratory rate, skin conductance and skin temperature, the two independent variables were time, which had three levels (before, during and after mobilisation) and visit, which had three levels (visit 1, visit 2 and visit 3). As ANOVA is considered to be robust to minor deviation from normality (Agresti and Finaly, 2009), it was used when minor deviation from normality was evident. The departure from normality was assessed by histogram and normal Q-Q (quantile-quantile) plot to examine the shape of the distribution (Sabin and Stafford, 1990). Minor departure from normality was due to some minor outlier case in the lower end of the distribution (Sabin and Stafford, 1990). For major normality departure data (where the distribution is skewed), transformation was performed using square root or logarithmic transformation (Sabin and Stafford, 1990). All transformed data were rechecked for normality, and, where the deviations were not resolved, the Friedman test was used (the critical χ^2 (df = 2, p=0.05) = 5.99) (Martin et al., 1993). Wilcoxon signed-rank test conducted where there was two testing points (pretreatment and posttreatment), and Friedman test was conducted where there was more than two testing points (pretreatment, mobilisation and posttreatment). For multiple testing, a Bonferroni correction applied, resulting in a critical level set at $\alpha < 0.017$ (0.05/3).

In order to compare our results with previous studies, differences in the mean of all physiological measures before and after mobilisation were presented as percentages of change. The percentage of change for all measures was calculated for the three visits using the following formula:

$$\frac{Measure_{post} - Measure_{pre}}{Measure_{pre}} \times 100 \quad .$$

In addition, the percentage of change for skin conductance, skin temperature, heart rate and respiratory rate, where measures were recorded during intervention, was also calculated using the following formula:

$$\frac{Measure_{during} - Measure_{pre}}{Measure_{pre}} \times 100 \quad .$$

The steps were repeated for each of the three visits.

Spearman's correlations were performed to examine the relationship between the percentage of change in PPT at the level of mobilisation and the percentage of change in Numerical Pain Rating Scale (NPRS).

7.3. Results

Thirty six patients with NSCLBP completed all visits. There were no adverse events. The demographic data and details about lumbar symptomatic level and duration of symptoms are displayed in Table 7.1.

Table 7.1. Participants' demographic data and details.

Number of participants	Sex	Age (years)	BMI (kg/m^2)	Duration of symptoms (weeks)	Symptomatic level (number of participants)
N = 36	Female = 22 Male = 14	Mean= 39.3 *SD* = 10.01	Mean = 29.33 *SD*= 5.4	Mean = 56.7 *SD*= 55.4	L5 = 27 L4 = 8 L3 = 1

Abbreviations: BMI: body mass index; SD: standard deviation; L3: 3rd lumbar vertebra; L4: 4th lumbar vertebra; L5: 5th lumbar vertebra.

7.3.1. Results of mobilisation treatment on blood pressure

There was a non-significant decrease in systolic blood pressure after mobilisation for the first visit compared to the baseline level with a mean difference value of -1.6±8.7 mmHg ($F(1, 35) = 0.009$, $p = 0.926$). However, a non-significant increase was evident in the second and third visits with mean difference values of 1.6±11 mmHg and 0.3±10.5 mmHg (Figure 7.2).

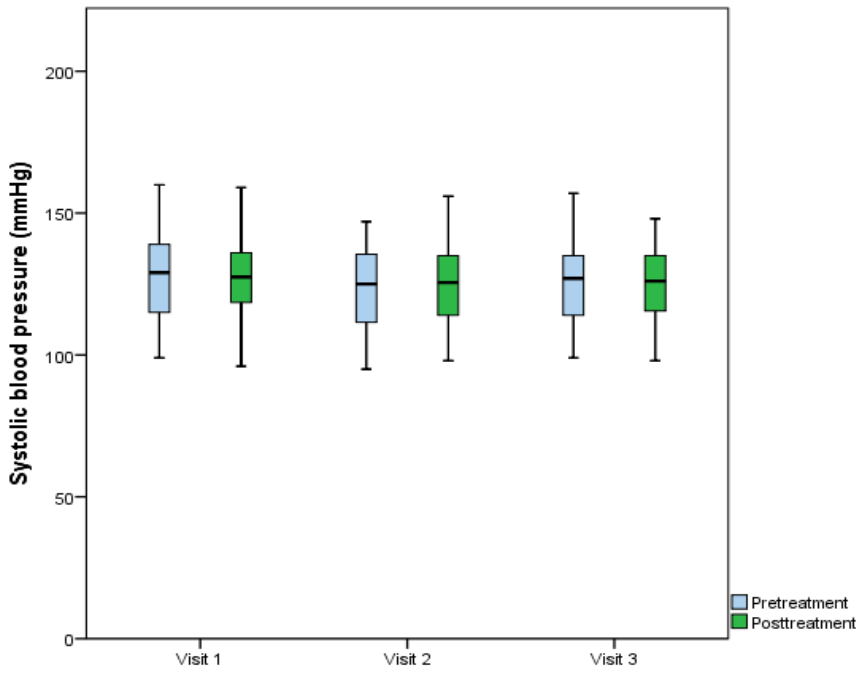


Figure 7.2. Systolic blood pressure response at three visits. The data are medians. Error bars represent non-outlier range (n=36).

There was a significant main effect of the visit day on systolic blood pressure which indicated the difference among the three visits of treatment ($F(2, 70) = 4.529$, $p = 0.014$). Bonferroni pairwise comparisons showed that this difference between the first and second visits was significant ($p = 0.015$). The interaction between the time of measurement (before or after mobilisation) and the visit day (1, 2 or 3) was not significant ($F(2, 70) = 0.939$, $p = 0.396$). For diastolic blood pressure, there was a non-significant increase after mobilisation compared to baseline values that was evident in all visits with mean difference values of 0.2+/-7.6 mmHg, 5±12.3 mmHg

and 1.5±15.4 mmHg ($F(1, 35) = 3.476$, $p = 0.071$; $F(2, 70) = 1.964$, $p = 0.148$) (Figure 7.3). The interaction between the time of measurement (before or after mobilisation) and the visit day (1, 2 or 3) was not significant ($F(2, 70) = 1.478$, $p = 0.235$). However, *t*-tests revealed a significant increase in diastolic blood pressure measurement within the second visit with a mean difference value of 5±12.3 mmHg ($p = 0.02$). In order to compare our results with previous studies, the percentage of change in systolic BP and diastolic BP for the three visits were calculated and are displayed in Table 7.2.

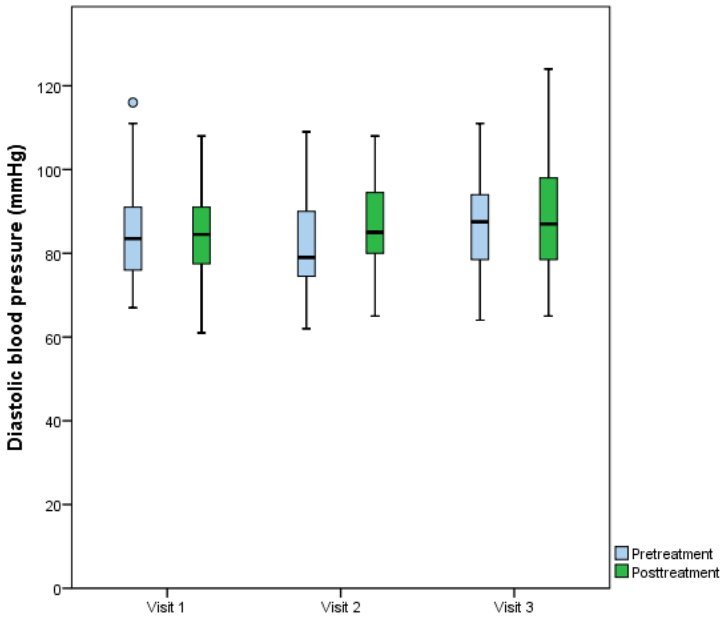


Figure 7.3. Diastolic blood pressure response at three visits. The data are medians. Error bars represent non-outlier range (n=36).

Table 7.2. Percentage (%) of change in systolic blood pressure and diastolic blood pressure at each visit. The data are means ± standard deviation (n=36).

	Visit 1	Visit 2	Visit 3
SPB	-0.9±7.1	1.8±9	0.73±8.7
DBP	0.5±8.8	7.6±16.1	3.02±17.7

Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure.

7.3.2. Results of mobilisation treatment on heart rate and respiratory rate

There was a non-significant decrease in heart rate measurements during mobilisation treatment for the first and second visits compared to the baseline level with mean difference values of -0.9±6.5 beats/minute and -0.6±11 beats/minute ($F(2, 70) = 2.352$, $p = 0.103$). However, a non-significant increase was evident in the third visit with a mean difference value 0.8±7.8 beats/minute (Figure 7.4). Also, there was a non-significant decrease in heart rate measurements during the final rest period within the first and third visits compared to baseline values with mean difference values of -4.3±7.6 beats/minute and -1.6±10.4 beats/minute. However, there was a non-significant increase in heart rate measurements during the final rest period within the second visit compared to baseline values with a mean difference value of 0.5±9.1 beats/minute.

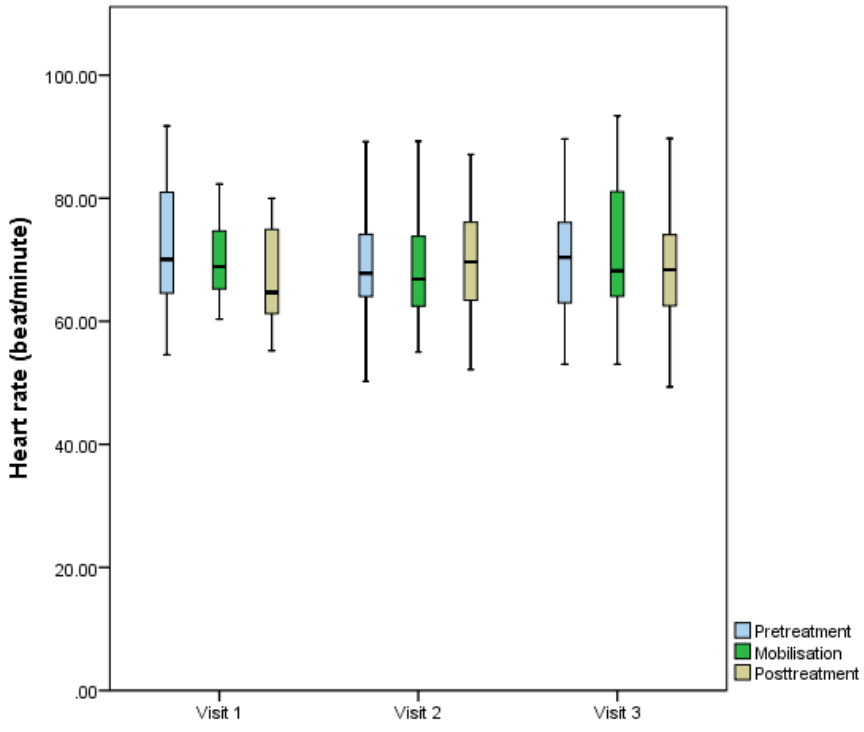


Figure 7.4. Heart rate response at three visits. The data are medians. Error bars represent non-outlier range (n=36).

For all visits, there was a non-significant change in respiratory rate measurements during mobilisation treatment compared to baseline values with mean difference values of 0.4±3.2 breaths/minute, -0.1±2.4 breaths/minute and 0.07±2.3 breaths/minute ($F(2, 70) = 0.923$, $p = 0.402$). Also, there was a non-significant decrease in respiratory rate measurements during the final rest period within all visits compared to mobilisation values. The mean difference values of respiratory rate measurements during the final rest period compare to baseline values were -0.04±4.1 breaths/minute, -0.5±3.7 breaths/minute and -0.5±2.5 breaths/minute (Figure 7.5).

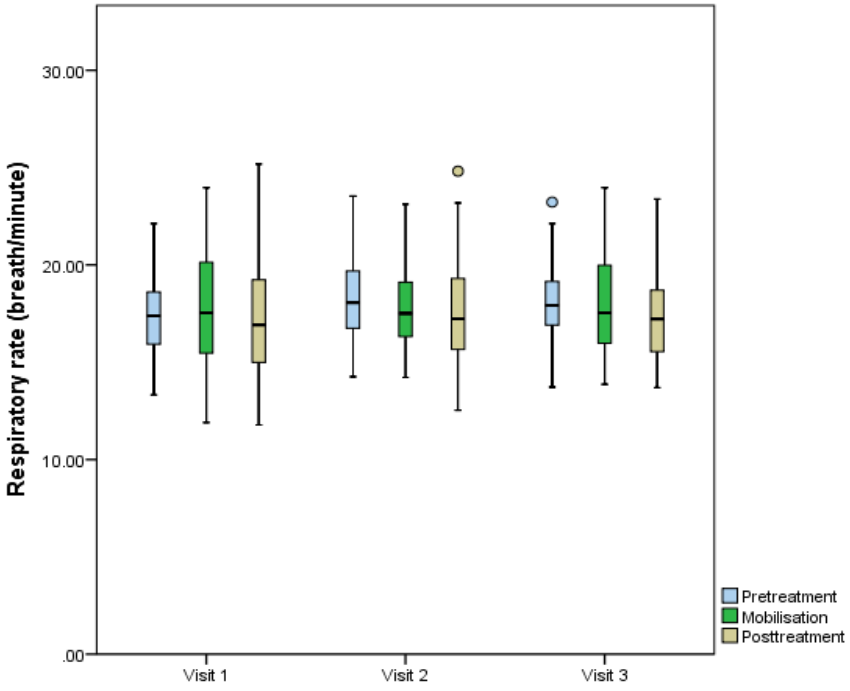


Figure 7.5. Respiratory rate response at three visits. The data are medians. Error bars represent non-outlier range (n=36).

There was a non-significant main effect the visit day on measurements of heart rate ($F(2, 70) = 0.197$, $p = 0.821$). The interaction between the time of measurement (before or after mobilisation) and the visit day (1, 2 or 3) was not significant ($F(4, 140) = 2.048$, $p = 0.091$).

For respiratory rate, there was a non-significant main effect the visit day on measurements of respiratory rate ($F(2, 70) = 0.427$, $p = 0.654$). The interaction between the time of measurement (before or after mobilisation) and the visit day (1, 2 or 3) was not significant ($F(3.094, 108.301) = 0.292$, $p = 0.837$). In order to compare my results with previous studies, differences in the mean of heart rate and respiratory rate measures before and after mobilisation were presented as percentages of change. The percentage of change for the three visits are displayed in Table 7.3.

Table 7.3. Percentage (%) of change in heart rate and respiratory rate at each visit. The data are means ± standard deviation (n=36).

	Visit 1		Visit 2		Visit 3	
	Baseline to treatment	Baseline to final rest period	Baseline to treatment	Baseline to final rest period	Baseline to treatment	Baseline to final rest period
HR	-0.3±9.3	-5.2±10.4	0.5±15.2	1.64±13.8	1.4±11.2	-1.41±14.3
RR	3.7±20	2.2±25.7	0.21±13.6	-1.17±20.6	0.87±13.3	-1.88±13.9

Abbreviations: HR: heart rate; RR: respiratory rate.

7.3.3. Results of mobilisation treatment on skin conductance and skin temperature

At each of the three visits, there was a significant change in right skin conductance level with an observable increase during the mobilisation period (sympathoexcitation) compared to the baseline level with mean difference values ranged between 0.05±0.1v to 0.06±0.1v (Table 7.4) (Figures 7.6 and 7.7). In addition, there was a further significant increase in skin conductance during the final rest period compared to the treatment period (Table 7.4) (Figure 7.8 and 7.9). For skin temperature values, there was a significant decrease during the mobilisation period compared to baseline values that continued to decrease for the final rest period with mean difference values ranged between -0.3±0.5°C to -0.05±0.6°C (Table 7.4).

Table 7.4. Mean differences in skin conductance (v) and skin temperature (°C) for both sites of measurement at each visit. The data are means ± standard deviation (n=36).

	Visit 1		Visit 2		Visit 3	
	Baseline to treatment	Baseline to final rest period	Baseline to treatment	Baseline to final rest period	Baseline to treatment	Baseline to final rest period
SC(RT)	0.05±0.1	0.06±0.1	0.06±0.1	0.06±0.1	0.06±0.1	0.06±0.1
SC(LT)	0.004±0.05	-0.007±0.06	0.009±0.08	0.005±0.08	0.01±0.08	0.001±0.1
ST(RT)	-0.3±0.05	-0.3±0.05	-0.3±0.05	-0.3±0.05	-0.2±0.05	-0.3±0.06
ST(RT)	-0.02±0.05	-0.05±0.06	-0.01±0.5	-0.02±0.8	-0.1±0.4	-0.2±0.6

Abbreviations: SC: skin conductance; ST: skin temperature; RT: right; LT: left.

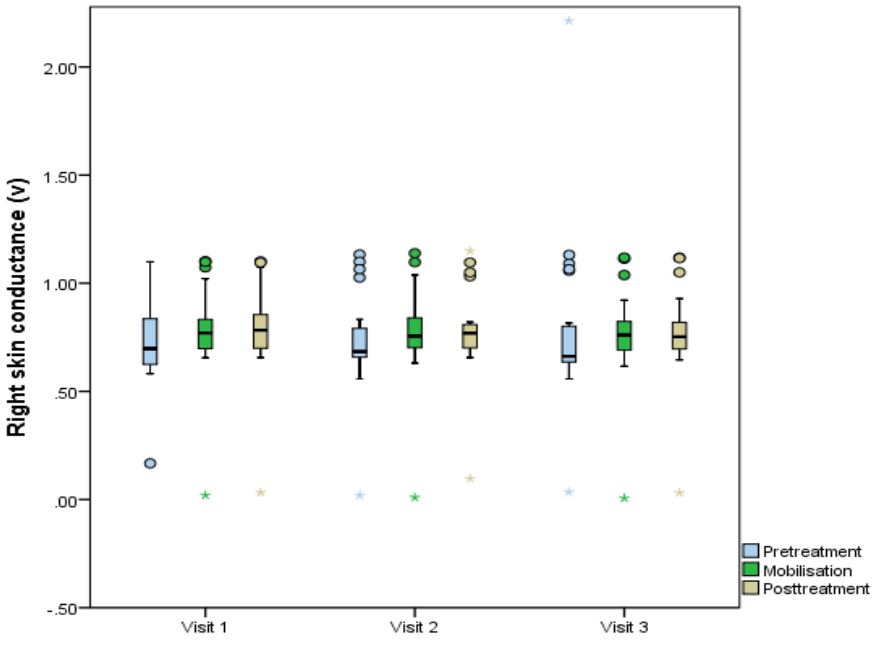


Figure 7.6. Right skin conductance response at three visits. The data are medians. Error bars represent non-outlier range (n=36).

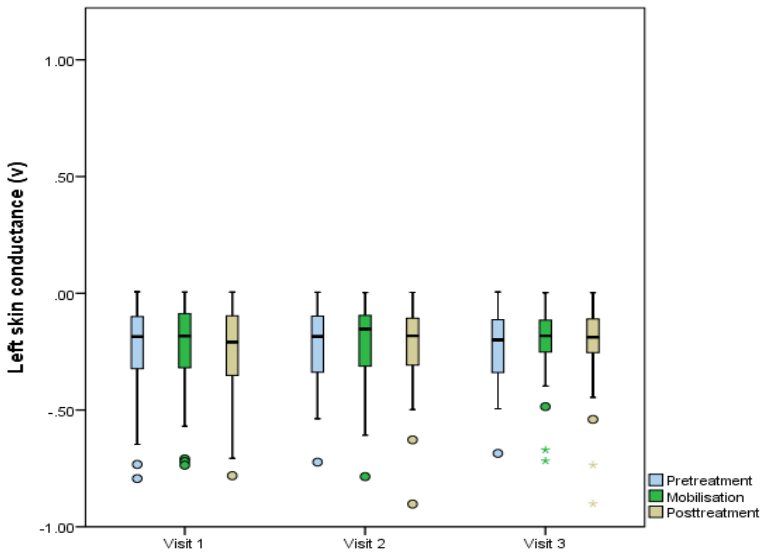


Figure 7.7. Left skin conductance response at three visits. The data are medians. Error bars represent non-outlier range (n=36).

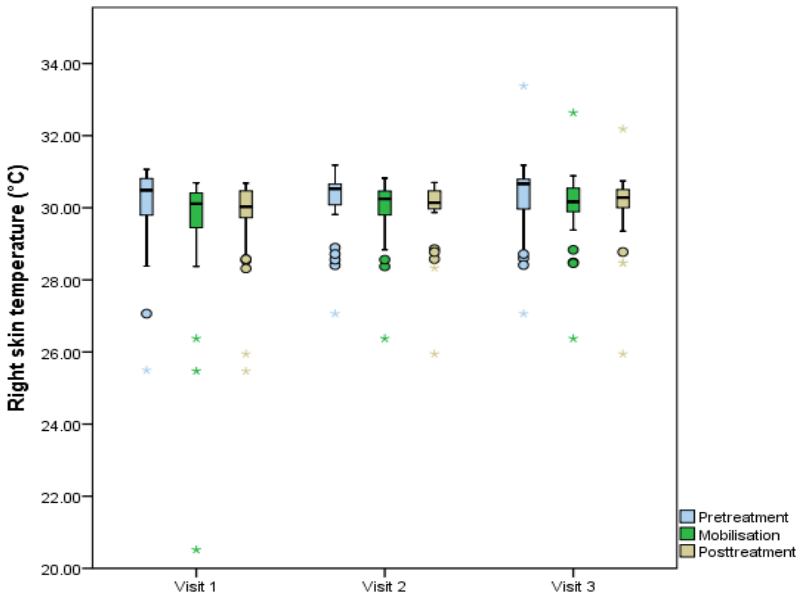


Figure 7.8. Right skin temperature response at three visits. The data are medians. Error bars represent non-outlier range (n=36).

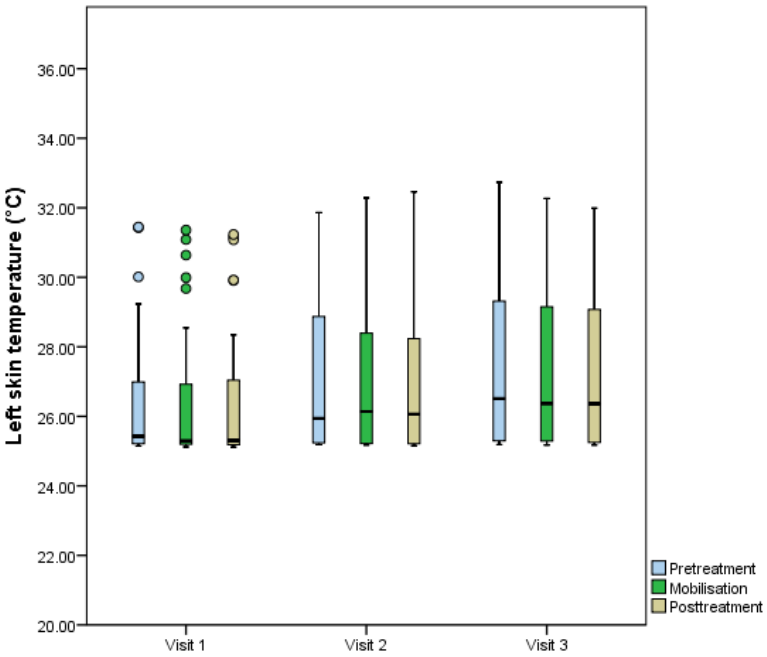


Figure 7.9. Left skin temperature response at three visits. The data are medians. Error bars represent non-outlier range (n=36).

Post hoc analysis using the Wilcoxon signed-rank test was conducted to locate where differences existed between repeated measures (Table 7.5). However, only skin conductance changes among all visits reached the MDC (0.06 v); skin temperature values failed to reach the MDC value (1.5 °C). The percentage of change between skin conductance and skin temperature for the three visits is displayed in Table 7.6.

Table 7.5. Results of skin conductance (v) and skin temperature (°C) including mean values before, during and after mobilisation, chi-square and *p* values from the Friedman test. 1: pre-mobilisation, 2: during mobilisation and 3: post-mobilisation. The data are means ± standard deviation (n=36).

	Visit 1					Visit 2					Visit 3				
Outcome measure	Pre-mobilisation	During-mobilisation	Post-mobilisation	Chi-square	*p*	Pre-mobilisation	During-mobilisation	Post-mobilisation	Chi-square	*p*	Pre-mobilisation	During-mobilisation	Post-mobilisation	Chi-square	*p*
RT SC	0.98±0.9	1.04±0.9	1.04±0.9	12.06	0.00 (1,2) = 0.008 (2,3) = 0.28 (1,3) = 0.004	0.86±0.7	0.92±0.7	0.92±0.7	6.89	0.03 (1,2) = 0.004 (2,3) = 0.91 (1,3) = 0.002	0.83±0.6	0.89±0.6	0.89±0.7	9.17	0.01 (1,2) =0.006 (2,3) = 0.35 (1,3) = 0.004
LT SC	-0.25±0.2	-0.25±0.2	-0.26±0.2	0.056	0.97 (1,2) = 0.65 (2,3) = 0.93 (1,3) = 0.59	-0.23±0.15	-0.22±0.17	-0.23±0.18	1.03	0.59 (1,2) = 0.768 (2,3) = 0.062 (1,3) = 0.912	-0.23±0.15	-0.22+/-0.16	-0.23±0.18	0.38	0.82 (1,2) = 0.69 (2,3) = 0.25 (1,3) = 0.85
RT ST	29.2±3.8	28.91±3.8	28.88±3.8	11.56	0.00 (1,2) = 0.003 (2,3) = 0.37 (1,3) = .001	29.67±2.8	29.4±2.8	29.41±2.8	7.87	0.02 (1,2) = 0.002 (2,3) = 0.96 (1,3) = 0.002	29.78±2.6	29.53±2.6	29.5±2.7	9.17	0.01 (1,2) = 0.007 (2,3) = 0.39 (1,3) = 0.01
LT ST	26.5±1.8	26.48±1.9	26.45±1.9	27.06	0.000 (1,2) = 0.02 (2,3) = 0.017 (1,3) = 0.009	26.98±2.2	26.97±2.3	26.97±2.2	13.7	0.001 (1,2) = 0.38 (2,3) = 0.213 (1,3) = 0.144	27.44±2.4	27.34±2.3	27.29±2.3	16.32	0.000 (1,2) = 0.05 (2,3) = 0.06 (1,3) = 0.05

Abbreviations: RT SC: right skin conductance; LT SC: left skin conductance; RT ST: right skin temperature; LT ST: left skin temperature.

Table 7.6. Percentage (%) of change in skin conductance and skin temperature (right and left side) at each visit. The data are means ± standard deviation (n=36).

	Visit 1		Visit 2		Visit 3	
	Baseline to treatment	Baseline to final rest period	Baseline to treatment	Baseline to final rest period	Baseline to treatment	Baseline to final rest period
RT SC	6.16±21.5	6.91±20.4	7.23±17.5	18.99±66.8	5.98±20.9	8.41±14.9
LT SC	6.51±38.9	14.1±50.7	-2.3±28.3	2.4±31.4	4.36±56.8	7.55±65.02
RT ST	-0.72±1.2	-0.82±1.3	-0.69±1.3	-0.68±1.2	-0.63±1.4	-0.73±1.5
LT ST	-0.09±1.7	-0.21±2.1	-0.02±2	0.003±3.04	-0.35±1.6	-0.51±2.1

Abbreviations: RT SC: right skin conductance; LT SC: left skin conductance; RT ST: right skin temperature; LT ST: left skin temperature.

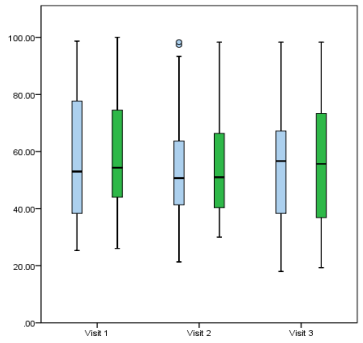
7.3.4. Results of mobilisation on pressure pain threshold

There was a non-significant decrease in PPT measurements that was evident at all measurement sites (except right thoracic paraspinal muscles) within the first visit with mean difference values ranged between -0.3±5.5 N/cm^2 and -3.5±10.6 N/cm^2 (Table 7.7). Also, there was a non-significant increase in PPT measurements that was evident at all measurement sites within the second (except left lumbar paraspinal muscles) and third visits with mean difference values ranged between 0.1±8.8 N/cm^2 and 4.2±10.1 N/cm^2 (Table 7.7) (Figure 7.10). However, the *t*-test revealed significant differences in the PPT measurements at the thoracic para-spinal level within the third visit (p =0.028, p = 0.017) with mean difference values of 3.1 N/cm^2 and 4.23 N/cm^2 and a significant difference at the right hand site within the second visit (p = 0.03) with a mean difference of 1.9 N/cm^2. These changes failed to exceed the MDC reported in the reliability study (8.3 N/cm^2, 8.9 N/cm^{2}and 5.9 N/cm^2) (Table 7.8).

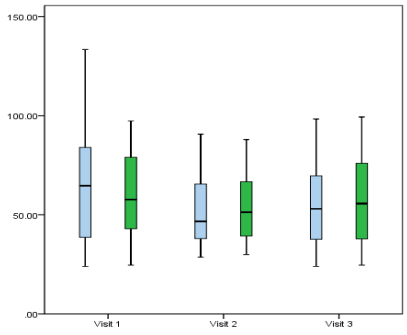
Table 7.7. Mean differences (N/cm^2) in pressure pain threshold for all the sites of measurement at each visit. The data are means ± standard deviation (n=36).

Outcome measure	Visit 1	Visit 2	Visit 3
RT T12	0.17±14.2	0.75±10.5	3.1±8.1
LT T12	-1.44±16.6	1.74±9.3	4.23±10.1
RT L	-3.5±10.6	0.11±8.8	1.7±9.9
LT L	-2.1±11.2	-0.6±9.8	0.91±10.1
RT 1stDI	-0.27±5.8	1.87±5.05	1.96±4.6
LT 1stDI	-0.41±5.4	1.3±4.3	1.04±4.2

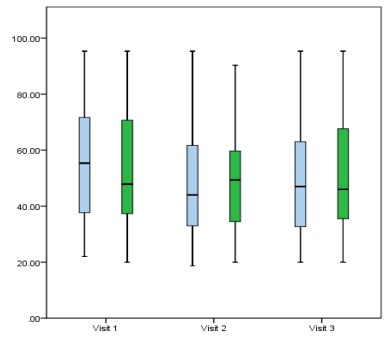
Abbreviations: RTL: right lumbar para-spinal muscles; LTL: left lumbar para-spinal muscles; RTT12: right 12th thoracic para-spinal muscles; LTT12: left 12th thoracic para-spinal muscles; RT1STDI: right first dorsal interosseous muscle; LT1STDI: left first dorsal interosseous muscle.



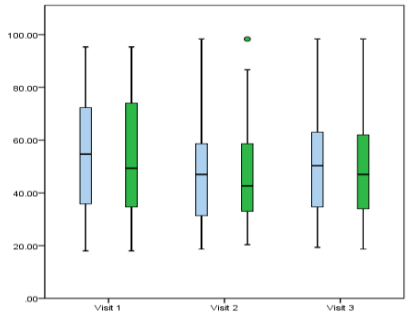
Pressure pain threshold of right thoracic paraspinal muscles (N/cm^2)



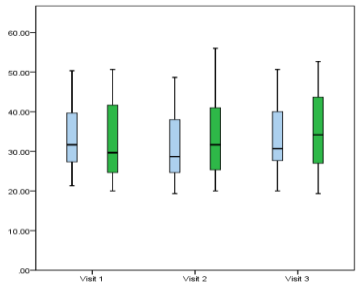
Pressure pain threshold of left thoracic paraspinal muscles (N/cm^2)



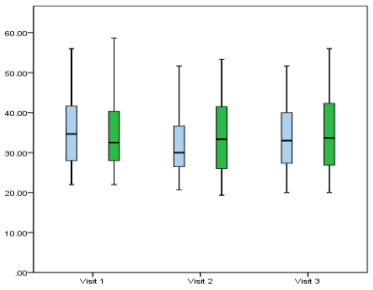
Pressure pain threshold of right lumbar paraspinal muscles (N/cm^2)



Pressure pain threshold of left lumbar paraspinal muscles (N/cm^2)



Pressure pain threshold of right 1st dorsal interosseous muscle (N/cm^2)



Pressure pain threshold of left 1st dorsal interosseous muscle (N/cm^2)

Figure 7.10. Pressure pain threshold response at three visits. The data are medians. Error bars represent non-outlier range (n=36).

There was a significant main effect of the visit day on PPT at three sites (right lumbar paraspinal muscles, left lumbar paraspinal muscles and left paraspinal muscles at the 12th thoracic level). Bonferroni pairwise comparisons showed that these differences were between the first and second visits for the three sites (p = 0.006; p = 0.005; p = 0.002). The interaction between the time of measurement and the visit day (1, 2 or 3) was not significant across the measurement sites except for the right lumbar para-spinal muscles and the right first dorsal interosseous (F(2,70) = 7.552, p = 0.001; F(2,70) = 4.402, p = 0.016). In order to compare my results with previous studies, differences in the mean of PPT before and after mobilisation were presented as a percentage of change (Table 7.9).

Table 7.8. Two-way ANOVA results of pressure pain threshold for all measurement sites.

	RTL	LTL	RTT12	LTT12	RT1STDI	LT1STDI
Time	F(1,35) = 0.155, p = 0.696	F(1,35) = 0.159, p = 0.693	F(1,35) = 1.011, p = 0.322	F(1,35) = 0.987, p = 0.327	F(1,35) = 2.816, p = 0.102	F(1,35) = 1.587, p = 0.216
Visit	F(1.519,53.159) = 6.127,p = 0.008, (1,2)p = 0.006*	F(1.699,59.472) = 5.700,p = 0.008, (1,2)p = 0.005*	F(1.685,58.972) = 1.606, p = 0.212	F(1.670,58.434) = 7.740,p = 0.002, (1,2)p = 0.002*	F(1.593,55.771) =1.110,p = 0.325	F(2,70) = 2.229, p = 0.115
Visit * Time	F(2,70) = 7.552, p = 0.001	F(2,70) = 1.564, p = 0.217	F(2,70) = 0.925, p = 0.401	F(1.612,56.430) = 2.712,p = 0.086	F(2,70) = 4.402, p = 0.016	F(2,70) = 1.527, p = 0.224

Abbreviations: RTL: right lumbar para-spinal muscles; LTL: left lumbar para-spinal muscles; RTT12: right 12th thoracic para-spinal muscles; LTT12: left 12th thoracic para-spinal muscles; RT1STDI: right first dorsal interosseous muscle; LT1STDI: left first dorsal interosseous muscle.

Table 7.9. Percentage of change (%) in pressure pain threshold for all the sites of measurement at each visit. The data are means ± standard deviation (n=36).

Outcome measure	Visit 1	Visit 2	Visit 3
RT T12	6.3±38.8	4.9±22.7	5.8±14.9
LT T12	3.3±26.9	5.5±19.1	7.6±18.7
RT L	-4.3±18.2	4.7±16.9	5.5±18.9
LT L	-2.9±18.8	2.4±20.1	2.9±18.4
RT 1stDI	-0.2±17.6	6.7±18.9	5.6±14.5
LT 1stDI	0.04±14.9	4.01±13.4	2.6±11.9

Abbreviations: RTL: right lumbar para-spinal muscles; LTL: left lumbar para-spinal muscles; RTT12: right 12th thoracic para-spinal muscles; LTT12: left 12th thoracic para-spinal muscles; RT1STDI: right first dorsal interosseous muscle; LT1STDI: left first dorsal interosseous muscle.

7.3.5. Results of mobilisation on salivary alpha-amylase

For the first and second visits, there was a non-significant increase in mean salivary alpha-amylase after mobilisation compared to the baseline level with mean difference values of 3.9±25.4 U/m and 19.3±62.7 U/m (z =-1.28, p =0.198; z =-1.57, p =0.116).. However, for the third visit; the results showed that there was a non-significant decrease in mean salivary alpha-amylase after mobilisation compared to the baseline level with a mean difference value of -2.7±60.7 U/m (z =-0.786, p = 0.432) (Figure 7.11). Differences in the mean of salivary alpha-amylase before and after mobilisation were presented as percentages of change and are displayed in Table 7.10.

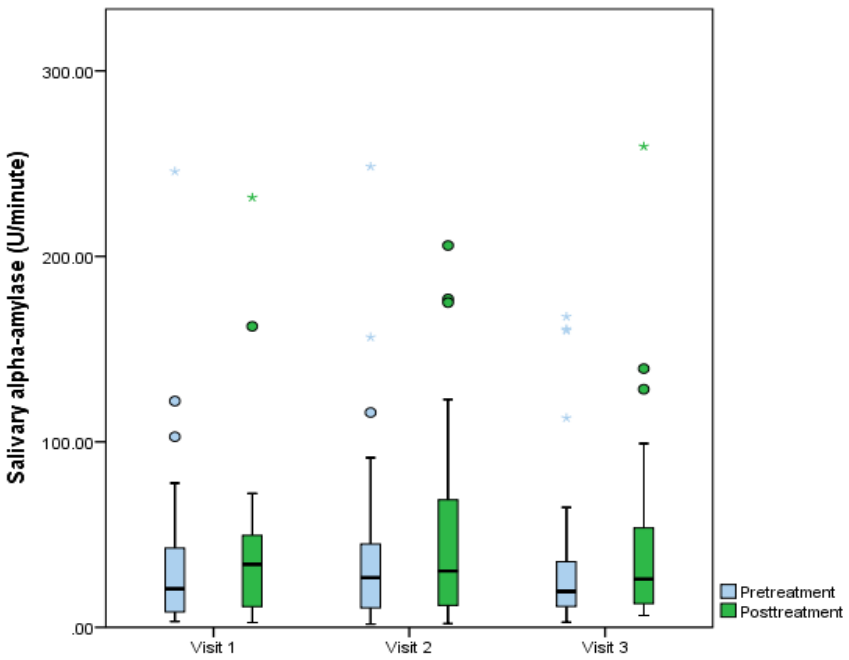


Figure 7.11. Salivary alpha-amylase response at three visits. The data are medians. Error bars represent non-outlier range (n=36).

Table 7.10. Percentage of change (%) in salivary alpha-amylase at each visit. The data are means ±standard deviation (n=36).

	Visit 1	Visit 2	Visit 3
sAA	98.9±249	68.5±145.4	79.4±201.2

Abbreviation: sAA: salivary alpha-amylase.

7.3.6. Results of mobilisation on the Numerical Pain Rating Scale

At each of the three visits, there was a significant change in the NPRS level with an observable decrease after mobilisation compared to the baseline level with mean difference values of -2±1.4, -1.5±1.7 and -1.03±1 ($F(1, 35) = 66.218$, $p = 0.001$) (Figure 7.12).

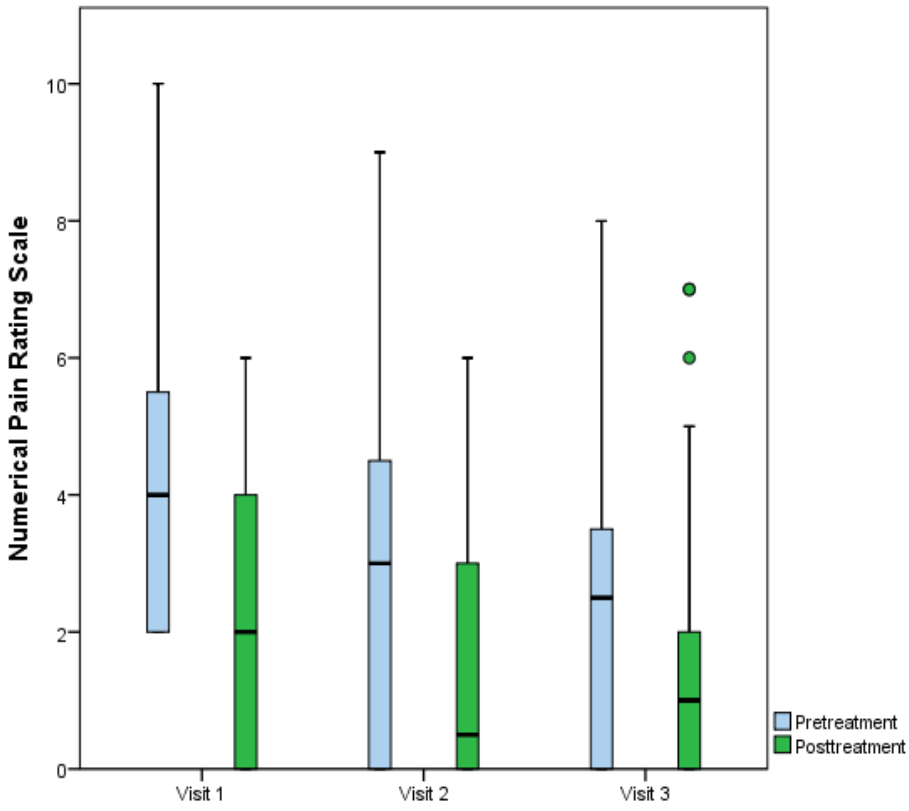


Figure 7.12. Numerical Pain Rating Scale response at three visits. The data are medians. Error bars represent non-outlier range (n=36).

The two-way ANOVA (sphericity assumed) indicated a significant main effect of the visit day on measurements of NPRS ($F(1, 35) = 66.218$, $p = 0.001$; $F(2, 70) = 7.315$, $p = 0.001$). The interaction between the time of measurement (before or after mobilisation) and the visit day (1, 2 or 3) was significant ($F(2,70) = 8.719$, $p = 0.001$). Bonferroni pairwise comparisons showed that this difference was $p = 0.014$ between the first and second visits, and that it was $p = 0.009$ between the first and third visits.

7.3.7. The relationship between change in NPRS and change in PPT

Spearman's correlations were performed to examine the relationship between the percentage of change in PPT at the level of mobilisation and the percentage of change in NPRS for the three visits. There was no association between the change in PPT and the change in NPRS in all visits (visit 1: $p = 0.930$, $r = -0.015$; visit 2: $p = 0.248$, $r = -0.197$; visit 3: $p = 0.107$, $r = 0.273$).

7.3.8. Summary of findings

- There was an increase in systolic blood pressure and diastolic blood pressure after mobilisation. Only the change in diastolic blood pressure within the second visit reached a level of significance that did not exceed that of the MDC (6.65mmHg).
- There was a slight change in heart rate and respiratory rate measurements during mobilisation treatment and the final rest period compared to the pretreatment measurements. However, only the change in heart rate during the final rest period compared to the baseline measurement within the first visit was significant, but it did not exceed the MDC (5.45beat/minute).
- The increase in pressure pain threshold was evident in the second and third visits, but not in the first visit; the most significant increase occurred only at the level of mobilisation in the third visit. In addition, the increase in the right hand PPT within the second visit reached a significant level. However, these significant changes did not reach the MDC values (right hand: 6.4N/cm^2, right thoracic: 7.9N/cm^2; left thoracic: 9.7N/cm^2).
- There was an increase in the right skin conductance during mobilisation treatment compared to the pretreatment measurement that continued to increase during the final rest period, was significant within all visits and reached the MDC (0.056v).
- There was a decrease in the right and left skin temperature measurements during mobilisation treatment compared to the pretreatment that continued to decrease during the final rest period measurements and was significant within all visits, but did not reach the MDC value (right skin temperature:1.5°C, left skin temperature: 1.6°C) reported in the reliability study.
- There was a significant decrease in the Numerical Pain Rating Scale measurement within all visits.
- There was a non-significant difference between before and after mobilisation values of salivary alpha-amylase within all visits. However, there was an increase in the mean value after mobilisation within the first and second visits, but it decreased within the third visit.

- There was no association between the change in NPRS and the change in PPT in all visits.

7.4. Discussion

7.4.1. The effects of mobilisation treatment on measures of SNS

7.4.1.1. Blood pressure, respiratory rate and heart rate

The results of this study demonstrated that application of a posteroanterior grade III mobilisation technique centrally to T12 in patients with nonspecific chronic low back pain produced increases in systolic and diastolic blood pressure. The increase in heart rate and respiratory rate during mobilisation period was not evident in all visits. However, the decrease in heart rate and respiratory rate measurements during the final resting period compared to the measurements during mobilisation period was evident in most of the visits with significant results reported within the first visit.

These results suggested that thoracic mobilisation alerts the sympathetic nervous system in patients with nonspecific chronic low back pain. A possible explanation for the sympathetic activation following mobilisation treatment is the descending pain inhibitory pathways from dPAG in the midbrain as similar respiratory and cardiovascular results have been reported following dPAG stimulation in rats (Lovick, 1991; McGuiness et al., 1997). It has been suggested that blood pressure could be determined by the peripheral vascular resistance that has been found to be controlled by the lateral region within the PAG, suggesting a somatotopic component within the PAG (Carrive and Bandler, 1991). Another explanation might be the stimulation of ganglia along the trunk resulting from the movement of the sympathetic truck during the mobilisation irrespective of the level of mobilisation (Butler 1991). Furthermore, performing pressure to the back might stimulate the baroreceptors (sensitive mechanoreceptors) within the spinal tissue that might have the ability to produce similar cardiovascular changes by their afferent inputs that stimulate PAG activity (Rea and Eckberg, 1987).

7.4.1.2. Skin conductance and skin temperature

My findings suggested that thoracic mobilisation stimulates the sympathetic nervous system, resulting in a peripheral vasoconstrictive effect evidenced by an increase in skin conductance and a decrease in skin temperature in patients with nonspecific chronic low back pain. A number of studies have reported similar results with significant sympathoexcitation in skin conductance and/or skin temperature as evidence of the descending inhibitory mediated response of the dorsal periaqueductal gray (dPAG) following cervical mobilisation (Peterson et al., 1993; Chiu and Wright et al., 1996; Sterling et al., 2001; La Touche et al., 2012), thoracic mobilisation (Cleland et al., 2004; Jowsey and Perry, 2010) and lumbar mobilisation (Perry and Green, 2008; Piekarz and Perry, 2016).

The present study demonstrated unilateral effects in terms of significant changes in skin conductance in the right lower limb. The direct stimulation of the sympathetic fibres resulting from the close anatomical location between thoracic vertebrae and ganglia leading to a simple spinal reflex responsible for the SNS activity might explain the unilateral response (Slater, 2002). Furthermore, this unilateral response might be explained by the specific mediation within the global PAG that need further understanding to explain the different sympathetic responses seen in manual therapy studies (Mouton et al., 1997). A side-specific response has been reported by Perry and Green (2008) who recorded an increase in skin conductance in the lower limbs that was specific to the side of treatment**,** following unilateral lumbar mobilisation in asymptomatic population.

7.4.1.3. Salivary alpha-amylase

The results showed that there was a non-significant difference between before and after mobilisation values of sAA within all visits. As it was not feasible to collect the saliva samples during the course of the procedure, samples were collected 10 minutes after the mobilisation. Therefore, it may be that any initial increase in the sAA was transient and therefore not detected using the protocol employed here. Further work should consider taking salivary samples at an early time point to determine if an initial transient change does occur.

7.4.2. The effects of mobilisation treatment on pain measures

The hypoalgesic response to mobilisation was manifested by changes in the Numerical Pain Rating Scale and pressure pain threshold. A significant trend of decreased NPRS measures was observed in NSCLBP patients within all visits that may suggest that this mobilisation technique was an adequate stimulus to decrease pain scores. The mechanical PPT of the thoracic level was significantly increased following thoracic mobilisation in the order of 5.77% and 7.63% within the third visit of NSCLBP patients. This local hypoalgesic response to spinal mobilisation might be explained by the local inhibitory cord reflex that represents the gate control mechanism suggested by Melzack and Wall (1965). However, Zusman (1986) argued that the proposed hypoalgesic responses of spinal mobilisation might be the result of the suggested ability of the repetitive movement during the application of mobilisation to decrease activity of joint afferents.

Other significant increases were recorded in the order of 6.65% distally over the right hand within the second visit in patients with NSCLBP. The pathway emerging from PAG is a possible mechanism for the widespread hypoalgesia that was demonstrated as occurring away from the treated area. However, all significant percentages of change did not exceed the 15% reported by Moss et al. (2007) that represents a clinically significant change or the MDC values calculated in the reliability study for each measurement site.

7.4.3. The relationship between change in NPRS and change in PPT

There was no association between PPT values and NPRS reported by patients at all visits. This negative correlation has been reported in the literature by Sterling et al. (2001) whose study examined this correlation between PPT and the Visual Analogue Scale (VAS) in patients with neck pain. These findings may suggest that different aspects of pain experience are measured by PPT (neurophysiological outcome) and NPRS (patient reported outcome) may be mediated by various hypoalgesic mechanisms. This may explain the observed change in pain intensity in all visits but not in pressure pain threshold. However, as the application of spinal mobilisation consists of pressure force, pressure pain threshold may not be a

meaningful measure of patient's pain response which also consist of applied pressure force (Snodgrass et al., 2014).

7.5. Limitations of the study

As a single-arm design was used where no placebo controlled group was used in this study that would have been essential to investigate the effectiveness of mobilisation treatment. However, previous studies have examined this effect using placebo controlled or controlled studies (Vicenzino et al., 1996; Sterling et al., 2001; Moss et al., 2007). Furthermore, looking at the effectiveness of mobilisation as a treatment form was not the aim of this thesis. Although the use of a control group is simple and cheap, the specific effect of mobilisation treatment cannot be distinguished from the placebo effects (Vickers and de Craen, 2000). The use of a placebo group allows for the separation of the specific effects of mobilisation treatment from the nonspecific effects (Hancock et al., 2006). As the underlying mechanisms behind the effectiveness of mobilisation treatment are yet to be established, the developing of a placebo that contains the non-specific component but not the specific component is difficult (Bogduk and Mercer, 2004). Hancock et al. (2006) asked 25 experts in the field of manual therapy to rate the appropriateness of ten different placebo techniques. Their findings suggested a very low agreement level between experts due to different beliefs about the active components of manual therapy.

Although the natural resolution of symptoms cannot be ruled out from the results of this study, it was an uncommon aspect of this study that the immediate intervention effects were investigated in LBP patient with symptoms of a chronic nature.

Due to the hospital policy, two clinicians performed the technique where a male physiotherapist performed the technique on male patients and a female physiotherapist performed it on female patients. The intra-therapist reliability for performing consistent mobilisation technique was not tested before conducting this study. Thus, there might be a degree of variation between applicants. However, all mobilisation techniques were performed in a predetermined, standardised manner as stated in section 7.2.5.1. Furthermore, the effect of the extraneous variables was

reduced by using strict inclusion and exclusion criteria and similar appointment times for all visits for treatment in an attempt to control the influence of diurnal variation.

The results of this research are limited to the short-term effects following the application of three doses of mobilisation treatment, whereas in clinical practice, the number of treatment sessions may vary according to the patient's condition. In this study, the long-term effects following mobilisation were not investigated, which would have enhanced the clinical relevance of the results. Empirical evidence suggests that 24-48 hours following intervention some patients experience improvement as the initial soreness decreases. Thus, research should consider looking at the longer-term effects of mobilisation. However, the number of treatment sessions was standardised for both asymptomatic and patient participants in the preclinical and clinical studies for this thesis, and the analysis of the data was postponed until the completion of all the visits of each participant.

It has been suggested that emotion centres (e.g. dorso-lateral prefrontal cortex) and PAG can be stimulated as a result of event anticipation resulting in modulation of pain perception within the brain stem (Wager et al., 2004). Thus, instigation of mobilisation treatment as an event might have the ability to initiate central processing and related clinical benefits. Although the present study attempted to control the possible confounding variables influencing the sympathetic activity, determining the potential effect of intervention expectation on sympathetic function was not possible (Bialosky et al., 2008).

Although the external validity of this study was enhanced because trained physiotherapists treated the NSCLBP patients within a clinical setting, it was limited to the NSCLBP patients as a result of the use of the convenience sample of NSCLBP patients. The results of this study might have been different if tailored mobilisation techniques had been applied to the patients based on the assessment of their spinal stiffness and pain as routinely performed by clinicians. Finally, the results of this clinical study evaluated the effects of only one treatment technique. Further studies are required to investigate the influence of other mobilisation techniques in normal patient populations and, more importantly, in populations where a pragmatic choice of technique and direction of mobilisation are considered.

7.6. Conclusion

The clinical study examined the effects of mobilisation treatment on hypoalgesia and sympathetic activity in patients with NSCLBP over a course of three doses of mobilisation treatment in a clinical setting. Results showed significant peripheral detectable sympathoexcitatory effects in the lower limbs in terms of increased skin conductance and decreased skin temperature following thoracic mobilisation that were not detected in asymptomatic participants. These peripheral sympathetic responses occurred concurrently with hypoalgesic effects in terms of a significant increase in pressure pain threshold values and a significant decrease in NPRS measures. However, the significant pressure pain threshold values were not evident in all locations, and there was no association between changes in pressure pain threshold and changes in NPRS.

Chapter 8

Discussion and conclusion

The following section discusses all the previous chapters and identifies the gaps revealed by the literature review in order to place the results chapters of this thesis (Chapters 5, 6 and 7) within the current context of the area of research related to hypoalgesia and the sympathetic effects of spinal mobilisation as a management of CLBP.

Currently, the dynamic continuum concept of the neuro-musculoskeletal system and its responding ability to various stimuli (mechanical, chemical, thermal, nociceptive and cognitive) at different levels, including the peripheral, spinal and supra-spinal levels, is well recognized. However, the ability of researchers and clinicians to quantify and qualify the proposed mechanisms of intervention action programmes are yet to be developed. Although the use of standard LBP patient-reported outcome measures might help clinicians to clinically assess the pain and functional status of their patients, these measures suffer from a degree of subjectivity. Therefore, a number of authors have called for more objective change indicators that are not influenced by the psychological or cognitive status of the patient (Perry et al., 2015).

A recognized concept within the manual therapy field is that hypoalgesia is related to sympathoexcitation; this leads researchers to measure the sympathetic responses as an immediate physiological measure following manual interventions. However, most of the available research in this area has measured these responses from the upper extremities, and limited research has been conducted on specific patient populations. Although different tools have been used to quantify these various physiological responses, their measurement stability and variability have not been established by the published research.

The first study for this thesis was conducted to determine the test-retest reliability (reproducibility) of the e-Health Sensor Shield V2.0 at measuring skin conductance, respiratory rate, heart rate and skin temperature. In addition, the study attempted to determine the reliability of a Wagner algometer in measuring PPTs, the reliability of a digital blood pressure monitor and the reliability of measuring the sAA enzyme,

which is linked to arousal of the SNS. This was necessary to establish the reliability of this equipment before using it in preclinical and clinical studies, as well as in future clinical research. The findings of this reliability study indicated that the test-retest reliability within a day of skin conductance, respiratory rate, heart rate and skin temperature, systolic blood pressure and PPT measurements was excellent (ICCs of 0.77 to 0.99). On the other hand, the reliability of diastolic blood pressure and sAA measurements was demonstrated to be fair to good (ICCs of 0.55 and 0.7, respectively). Therefore, this equipment was considered reliable and suitable for measures for the next stage of the research to investigate the effects of mobilisation treatment on these variables in an asymptomatic population and in lower back pain patients.

Further analysis of the data from the reliability study was conducted to calculate the MDC for all measures that are independent of any measurement error and could be considered as real change ascribable to the treatment. However, the values for MDC might not necessarily represent the patient-perceived measure of the minimal clinical importance difference; thus, further research is warranted in this area utilising a patient population. To the author's knowledge this is the first study to measure the normative values of skin conductance, respiratory rate, heart rate and skin temperature (e-Health Sensor Shield V2.0), blood pressure (digital monitor), PPT (Wangar algometer) and sAA in a laboratory environment. These results should aid further research in determining whether such intervention causes any real change apart from measurement error.

The use of spinal mobilisations has been recommended by the NICE Guidelines for the management of LBP (2009) and the Chartered Society of Physiotherapy (CSP) (2006). However, there is lack of research in the literature regarding the sympathetic responses as a result of these techniques within a LBP population. Therefore, a preclinical study was designed and conducted to provide normative values for sympathetic measures as a result of these techniques. This was followed by a clinical study investigating these responses to mobilisation that included patients with LBP. Thus, the overall aim of this thesis was to investigate the hypoalgesic and

sympathetic effects of passive thoracic mobilisation treatment in those with and without LBP.

8.1. The effects of mobilisation treatment on pain measures

In the clinical study, the hypoalgesic response to mobilisation was manifested by changes in the NPRS and PPT. A significant decrease in NPRS measures was observed in LBP patients within all visits. This suggests that this mobilisation technique was an adequate stimulus to decrease pain scores. The mechanical PPT of the thoracic level was significantly increased by 8.1% following thoracic mobilisation within the first visit of asymptomatic subjects, and by 5.77% and 7.63% at the thoracic level within the third visit of LBP patients. Other significant increases were recorded over the lumbar level of 10.5% and 7.4%, 10.8% distally over the hands within the third visit in asymptomatic subjects and by 6.65% distally over the right hand within the second visit in patients with LBP. The hypoalgesic response recorded in asymptomatic subjects suggests that the mobilisation technique can produce hypoalgesia where pain and dysfunction are absent (Willett et al., 2010). However, this significant hypoalgesic response was not evident in all locations at all visits for both studies. This might be due to the sample size being too small to detect changes in some PPT as estimation was only based on skin conductance data. All significant percentages of change did not exceed the MDC values of 15% reported by Moss et al. (2007) which indicates that although statistically significant, these changes were not clinically significant.

Furthermore, in the clinical study, the PPT measurements following the first session demonstrated decreasing values in contrast to the second and third visits. It has been established that a treatment reaction, in terms of the worsening of the symptoms or the emergence of new symptoms as minor adverse reactions, following manual therapy is common during the first 24 hour (Thiel et al., 2007). As a result, this may explain the slight decrease in PPT measurements following the first mobilisation treatment. Other studies examined the effect of different lumbar mobilisation doses on the PPT of asymptomatic subjects and found a significant increase with both doses at all measurement locations (Krouwel et al., 2010; Willett et al., 2010; Pentelka et al., 2012). However, the positive treatment effect seen in

those studies may have been enhanced by the expectations of the participants (asymptomatic physiotherapy students).

The local hypoalgesic effect was evident in a number of visits for both asymptomatic and symptomatic subjects in this study. This local hypoalgesic response to spinal mobilisation might be explained by the local inhibitory cord reflex that represents the gate control mechanism suggested by Melzack and Wall (1965). The stimulation of the low threshold mechanoreceptors in articular and peri-articular structures following spinal mobilisation might inhibit the small diameter, high threshold mechanoreceptors at the level of spine that result in pain modulation in the dorsal horn of the spinal cord. However, this preferential ability of the spinal mobilisation toward stimulation of the low threshold mechanoreceptors apart from high threshold neurons has been questioned (Zusman, 1986). Zusman (1986) argued that the proposed hypoalgesic responses of spinal mobilisation might be the result of the suggested ability of the repetitive movement during the application of mobilisation to decrease activity of joint afferents by inhibiting reflex muscle contraction and reducing intra-articular pressure. Furthermore, this spinal movement created through the mobilisation may lead to a hypoalgesic effect at more than one level of the spine, which may explain the segmental hypoalgesic response reported at the lumbar level in asymptomatic participants. These local and segmental mechanisms were supported by functional magnetic resonance imaging (MRI) that was used in an animal study conducted by Malisza et al. (2003) which demonstrated decreased activity of pain in specific areas at the spinal cord following mobilisation in rats.

In addition to the previously mentioned local mechanisms, the pathway emerging from PAG is another possible mechanism because this study demonstrated widespread hypoalgesia occurring away from the treated area. This widespread effect of thoracic mobilisation on PPT that was demonstrated in some visits of the asymptomatic and LBP patients was shown by other investigations that reported a hypoalgesic effect distal to the area of mobilisation and that supported the concept that response to mobilisation is not specific or local to the treatment area (Vicenzino et al., 1996; Moss et al., 2007; Krouwel et al., 2010; Willett et al., 2010; Pentelka et al., 2012). This effect may be indicative of mobilisation's ability to initiate the neural

response from higher structures in the CNS that result in the therapeutic effect being seen. It has been suggested that the remote hypoalgesic effect from the treated area may indicate the stimulation of the descending inhibitory pathways following mobilisation (Moss et al., 2007). However, this widespread hypoalgesic effect was not evident in a significant number of studies.

However, various studies have demonstrated that, due to the lower density of mechanoreceptors in the thoracic and lumbar spine compared to the cervical spine level, PPT values were found to increase in the caudal direction (Keating et al., 2001; Potter et al., 2006). This could explain the greater percentage of change in PPT following cervical mobilisation as the gate mechanism relies on large diameter neurons to inhibit the small neurons responsible for nociceptive signals. A decreased receptive field of mechanoreceptors in the thoracic and lumbar spine would decrease the gate control ability to create a greater hypoalgesic effect and may explain the small percentage of change reported by the current study compared to other studies. In the literature, the increase in the percentage of change in PPT ranged from 12.69% to 26% following cervical mobilisation, both local and remote from where the mobilisation was applied (Vicenzino et al., 1996; Wright and Vicenzino, 1998: Sterling et al., 2001). An increase in the order of 26% at the elbow was recorded by Vicenzino et al. (1996) following cervical mobilisation in tennis elbow patients, compared to another study with a similar methodology but which included asymptomatic participants and recorded a change of 23.5% (Vicenzino et al., 1995). Therefore, the inherent variations among sites might explain the differences in the response range. However, most of those studies were conducted by the same group of researchers and used the same crossover design. Participants' gender might be another possible reason behind the higher percentages in previous studies. In the clinical study 61% of the patients were female, who have been shown to have lower values of pressure pain threshold compared to males (Riley et al., 1998).

Furthermore, Fryer et al. (2004) suggested that the large variation between studies assessing pain with an algometer might be explained by the subjective experience that varies in terms of perception from one to another person. However, a previous study investigating the effect of mobilisation reported the percentages of change in

the absence of true difference values and used these percentages for analysis, which might have affected their conclusions (Bonate, 2000). Another possible reason for the differences in the percentage of change of PPT reported by the current clinical study and previous studies might be the differences in the duration of the symptoms experienced by the participants. A mean value of six to eight months has been reported as the duration of symptoms in previous studies (Vicenzino et al., 1996; Wright and Vicenzino, 1998: Sterling et al., 2001), whereas a longer duration was reported by the current study (a mean value of 56 weeks). Although the inclusion of symptoms with longer durations might reflect clinical populations, it may lead to variations among multiple factors, including processing of pain, functional levels and pain beliefs.

8.2. The relationship between PPT and NPRS

There was no association between PPT values and NPRS reported by patients at all visits. Although the differences in PPT suggest the activation of the hypoalgesic mechanism, pain measures as reported by patients using the NPRS are more clinically relevant. These findings may suggest that hypoalgesia measured by PPT and NPRS may be mediated by various hypoalgesic mechanisms. This has been reported in patients with neck pain by Sterling et al. (2001) whose study examined this correlation between PPT and the Visual Analogue Scale. However, the PPT is largely used as a pain measure both for patients and for the asymptomatic population; thus, further research is warranted in this area to examine the correlation between different patient-reported measures and PPT.

8.3. The effects of mobilisation treatment on measures of SNS

8.3.1. Skin conductance and skin temperature

The findings obtained for indicators of SNS activity suggest that thoracic mobilisation stimulates the SNS, resulting in a peripheral vasoconstrictive effect evidenced by an increase in skin conductance and a decrease in skin temperature within all sessions in patients with LBP, with no significant changes reported by asymptomatic participants. There was an increase in the right skin conductance during mobilisation treatment compared to the pretreatment measurement that continued to increase

during the final rest period, which was significant within all visits and also reached the MDC. Furthermore, there was a significant decrease within all visits in the right and left skin temperature measurements during mobilisation treatment compared to baseline that continued to decrease during the final rest period measurements, but did not reach the MDC value reported in the reliability study. However, thermal asymmetry between lower limbs was evident in the baseline measurements of LBP patients but not in asymptomatic participants. The baseline measurements of skin temperature in LBP patients ranged from 29.2 ± 3.8°C to 29.8 ± 2.6°C for the right lower limb and from 26.5 ± 1.8°C to 27.4 ± 2.4°C for the left lower limb. This asymmetry might be explained by the potential root lesions of L5 and S1 that are common in patients with LBP and represented on the plantar area. Peripheral circulatory changes that are more distinct distally or the abnormal distribution of weight in those patients might influence the plantar temperature (Zaproudina et al., 2006). Muscle function disturbances might cause this change in the above skin temperature as the active muscle produces energy as heat (Takahashi et al., 1994). The symptomatic participants in our study suffered from LBP without radicular referred leg pain due to disc prolapse or possible vascular diseases; thus, more significant findings of skin temperature might be seen in patients with radiculopathies after spine operation. The skin temperature was measured noninvasively in this study; thus, it might be possible to use skin temperature as objective indicator to follow the sympathetic disturbances by evaluating the vasomotor activity of the sympathetic nerve fibres in musculoskeletal disorders.

Our results support findings by other similar studies demonstrating an increased sympathetic activity response to SMT (Peterson et al., 1993; Vicenzino et al., 1996; Vicenzino et al., 1998; Cleland et al., 2004; Perry and Green, 2008; Jowsey and Perry, 2010; Piekarz and Perry, 2016). Our findings show that peripheral sympathetic changes in the lower limb can be measured following thoracic mobilisation not only in a laboratory setting but also in a clinical environment and in patient populations. In the right lower limb, the mean percentage change in skin conductance values ranged from 5.98% to 18.99%**,** which reached significance at all visits in the clinical study. Several studies have demonstrated the bilateral sympatoexcitatory response following mobilisation as evidence of the descending

inhibitory mediated response of the dorsal periaqueductal gray (dPAG) (Slater and Wright, 1995; Sterling et al., 2001). The present study demonstrated specific side effects in terms of significant changes in skin conductance in the right lower limb in LBP patients. Considering previous studies that applied thoracic mobilisation techniques, it was noted that the magnitude of bilateral sympathetic responses was usually different between sides and that might this be explained by the specific mediation within the global PAG. The PAG consists of highly specialised functional regions and subregions. Medullary control nuclei are responsible for the modulation of dPAG regions in animals leading to unilateral and bilateral projections (Mouton et al., 1997). Further understanding of the mediation by the specific central structures may help to explain the different sympathetic responses seen in manual therapy studies. Somatospecific representation of the dPAG, rather than general representation, could be another supra-spinal explanation for the unilateral response. A side-specific response has been reported by Perry and Green (2008) who recorded an increase in skin conductance in the lower limbs that was specific to the side of treatment, following unilateral lumbar mobilisation. It is also possible that the unilateral response was due to the direct stimulation of the sympathetic fibres resulting from the close anatomical location between thoracic vertebrae and ganglia leading to a simple spinal reflex responsible for the SNS activity (Slater, 2002).

Findings from the clinical study support the results of previous studies that have noted similar effects in skin conductance after thoracic mobilisation treatment, such as those by Jowsey and Perry (2010) who reported an increase in range from 1.56% to 8.12% in the upper limbs after thoracic mobilisation was applied to T4 in an asymptomatic population. Perry and Green (2008) reported an increase of 13.5% in the lower limbs in asymptomatic participants after lumbar mobilisation. Also, these findings support the results of studies that applied mobilisation to the cervical level and reported significant sympathetic changes in the upper limbs (Petersen et al., 1993; Chiu and Wright, 1996; Sterling et al., 2001). Sterling et al. (2001) reported a 16% increase in skin conductance in the treatment period for the treatment condition. Chiu and Wright (1996) reported that skin conductance increased by 50-60% above baseline values following central PA cervical mobilisation at the rate of 2Hz, which

was consistent with a study by Petersen et al. (1993). The difference in the magnitude of the responses following mobilisation to different levels of the spine might be due to the different peripheral cutaneous innervations or central processing systems for different regions (Perry at al. 2015). This suggests that the mobilisation grade used in this study was not the optimal one for producing the maximal magnitude in sympathetic change. It has been hypothesised that the movement component of mobilisation might be an important factor in maximising the sympathetic response by increasing the mechanical effects on the level mobilised (Piekarz and Perry, 2016). Pickar and Kang (2006) suggested that discharge from the muscle spindle is increased with high velocity loading compared with lower forces. Recent research has shown that skin conductance activity increased more following 2Hz mobilisation frequency compared to lower frequencies (0.5Hz), thus emphasising the role of oscillation in responses to mobilisation treatment (Chiu and Wright, 1996; Perry et al., 2008; Jowsey and Perry, 2010). Vicenzino et al. (1995) also suggested that reaching the maximum sympathetic activity more rapidly due to an increase in synaptic efficiency in the afferent sensory pathways might lead to increased hypoalgesia. Unfortunately, the present study did not measure the time to maximum sympathetic response that would determine if there is a correlation between frequency of mobilisation and faster sympathetic change. However, the results of the current study suggest the use of skin conductance as a proxy measure for the sympathetic function of the postganglionic efferent to quantify the neurophysiological response to different treatments in physiotherapy (Perry and Green, 2008). The findings support the theoretical framework for the choice of thoracic mobilisation in patients with NSCLBP to affect the peripheral sympathetic outflow to the lower limbs and, potentially, the lower limb symptoms common in LPB patients.

A possible explanation for the non-significant results of skin conductance and skin temperature in the asymptomatic population in comparison with the significant results seen in the patient population might be the presence of the enhanced dorsal horn excitability in spinal pain patients (Boal and Gillette, 2004; Bakkum et al., 2007). Taylor and Murphy (2009), using functional MRI, have reported a correlation between lumbar dysfunction and neuroplastic changes to the dorsal horn and central

pain structures in the midbrain, brainstem, amygdala and thalamus, as well as SNS synaptic activity (Nagai et al., 2004). However, this theory needs further investigation to correlate sympathetic responses to treatment with pain and functional disability measures recorded over a full course of treatment and to correlate these findings with functional MRI results. Due to the small sample size in the preclinical study of this thesis (*n*=14), the results should be interpreted with caution.

It has been suggested that emotion centres (e.g. dorso-lateral prefrontal cortex) and PAG can be stimulated as a result of event anticipation resulting in modulation of pain perception within the brain stem (Wager et al., 2004). Thus, instigation of mobilisation treatment as an event might have the ability to initiate central processing and related clinical benefits. Although the present study attempted to control the possible confounding variables influencing sympathetic activity, determining the potential effect of intervention expectation on sympathetic function was not possible (Bialosky et al., 2008).

8.3.2. Blood pressure, respiratory rate and heart rate

LBP patients demonstrated higher baseline measurements among three visits in terms of heart rate, which ranged from 68.9 ± 9.2 to 71.3 ± 9.8 beats/min compared to 66.55 ± 4.6 to 69.6 ± 7.7 beats/min in asymptomatic participants. The baseline systolic and diastolic blood pressure measurements were also higher in the LBP patients, and ranged from 122.5 ± 14.3 to 127.9 ± 14.9 mmHg and 81.9 ± 12 to 86.6 ± 11.6 mmHg, respectively. Asymptomatic participants had lower systolic and diastolic blood pressure ranging from 110.7 ± 14.9 to 114.1 ± 12.9 mmHg and 77 ± 8.2 to 80.2 ± 12.4 mmHg, respectively, from three visits. Similar results have been reported by Shankar et al. (2011), who showed higher basal ranges of systolic and diastolic blood pressure in a group of chronic low back patients compared to a control group. This might be explained by increased sympathetic cardiovascular activity in the pain group compared to the control group. Furthermore, other studies have reported similar higher sympathetic tone in other pain patients (e.g. myofascial and arthritis pain) and suggested a sympathetic dominance in these patients (Collin et al., 1982; Perry et al., 1989).

Our results demonstrated that, for an asymptomatic population, there was a statistically significant increase within all visits in heart rate and respiratory measurements during mobilisation treatment that decreased during the final rest period measurements. This was significant within all visits for respiratory rate and within the second and third visits for heart rate measurements. All these changes exceeded the MDC reported by the reliability study indicating that the results had clinical as well as statistical significance. There was an increase in systolic blood pressure and diastolic blood pressure after mobilisation, but only the differences within the first and third visits were significant. For LBP patients in the clinical study, there was an increase in systolic blood pressure and diastolic blood pressure after mobilisation. Only changes in diastolic blood pressure within the second visit reached statistical significance, but none were clinically significant. Furthermore, there was a slight increase in heart rate and respiratory rate measurements during mobilisation treatment that decreased during the final rest period compared to the pretreatment measurements. However, only changes in heart rate during the final rest period, compared to the baseline measurement within the first visit, were significant, but they did not reach clinical significance as determined by the MDC in the reliability study (chapter 5).

These results are similar to findings from other studies that reported increased heart rate, respiratory rate and blood pressure following central PA cervical mobilisation (McGuiness et al., 1997). McGuiness et al. (1997) reported a significant increase in respiratory rate in the order of 44% during the mobilisation period and in heart rate in the order of 10.5%, while systolic blood pressure increased by 12.5% and diastolic blood pressure increased by 4.5%. The authors suggested this was due to the descending pain inhibitory pathways from dPAG in the midbrain. Another proposal by those authors for the resultant sympathoexcitatory response following mobilisation treatment was direct stimulation to the cervical ganglia and sympathetic fibres as they are located close to the cervical level treated (C5/6). These ganglia connect with organs like the heart through fibres. Performing pressure to the neck might cause an increase or decrease to the carotid baroreceptors' function. This can affect heart rate and peripheral vascular resistance (Thoren and Lundin, 1983). However, on both sides of the spine, the sympathetic trunk extends parallel to the

spine and might be moved during mobilisation, thus causing stimulation of ganglia along the trunk (Butler 1991).

Similar respiratory and cardiovascular results have been reported following dPAG stimulation in rats (Lovick, 1991). The agreement between results of animal studies with this study and other similar human studies may support the involvement of the descending pain inhibitory system emerging from the dPAG as a possible mechanism behind the effectiveness of manual therapy (Petersen et al., 1993; Vicenzino et al., 1995; Wright, 1995). Studies of both unilateral and central PA cervical mobilisation have reported an increase in blood pressure and a decrease in skin temperature distally at the hand, which suggests peripheral vasoconstriction (Petersen et al., 1993; Vicenzino et al., 1995; Wright, 1995). It has been suggested that arterial blood pressure could be determined by the peripheral vascular resistance that has been found to be controlled by the lateral region within the PAG, suggesting a somatotopic component within the PAG (Carrive and Bandler, 1991). The pre-motor neurons that control cardiac, respiratory, vasomotor and sudomotor functions have been shown to emerge from regions within the brainstem and located caudal to the PAG (McAllen et al., 1995; Shafton and McAllen, 2013). Therefore, the concurrent hypoalgesia with the various sympathetic functions seen following mobilisation might point to the implication of a supramedullary integratory centre (the PAG) (Vicenzino et al., 1998).

Furthermore, central to the hypothesis that spinal mobilisation may stimulate the pain inhibitory pathways emerging from the PAG is the ability of this technique to stimulate receptors located within the spinal tissue (joint, capsule, connective tissue, tendons and ligaments) that may directly or indirectly activate mechanisms originating from the PAG. In addition to these receptors, baroreceptors are found within the vascular tree that may have the ability to cause cardiovascular changes similar to the changes seen in this study (Rea and Eckberg, 1987). As a result, the PAG activity might be activated by afferent input from receptors located within the musculoskeletal and cardiovascular systems (Yezierski, 1991).

On the other hand, these findings were in contrast to the results from a study conducted by Yung et al. (2014) who reported a significant drop in heart rate values

in an AP cervical mobilisation group compared to a placebo group in a pain-free population. In addition, the results demonstrated a drop in systolic blood pressure in both mobilisation and placebo groups. However, these changes did not reach the MDC or cause any pulselessness, and the change in systolic blood pressure did not reach close to 50 mmHg. The authors explained this sympatho-inhibitory effect, as opposed to other similar studies of different mechanisms, as the result of various techniques of manual therapy. This study performed unilateral AP pressure to the right side that might lead to left side circulation which, in turn, may prevent any true cardiovascular response. Other contrasting results were reported by studies investigating the effects of manipulation on blood pressure, and they demonstrate a sympatho-inhibitory response in terms of decreased blood pressure (McKnight and DeBoer, 1988; Yates et al., 1988). However, this form of manual therapy is different from mobilisation in terms of speed and duration of treatment and might be expected to exert different responses in SNS functions.

8.3.3. Salivary alpha-amylase

sAA was used in this study as a noninvasive biomarker to investigate the sympathetic response after thoracic mobilisation. For asymptomatic participants, there was an increase in mean sAA after mobilisation within the first visit and a decrease within the second and second visits. Although the difference within the first visit was significant, it did not exceed the MDC. For LBP patients, there was a non-significant difference between before and after mobilisation values of sAA within all visits. As it was not feasible to collect the saliva samples during the course of the procedure, samples were collected 10 min after the mobilisation. This may be explained by the likely transience in the initial increase in the sAA.

It was hypothesised that manipulative treatment like the rib raising technique has the ability to modulate the sympathetic activity by activating the thoracic sympathetic chain ganglia that might cause initial sympathetic stimulation that is followed by a prolonged reduction of sympathetic outflow (Wallace et al., 2003). Henderson et al. (2010) tested this hypothesis using a saliva biomarker by collecting saliva immediately and at 10 min following rib raising, and they found a significant decrease in sAA in the treatment group compared to the placebo group. However, the saliva

samples were collected differently in this study by using the passive drool method and not by means of an oral swab. Furthermore, it was not stated whether the salivary flow rate was considered to correct the alpha-amylase assay results.

8.4. Recommendations for future work

The following is a detailed synopsis of the important areas for future research that were highlighted by the results of this study:

- The preclinical and clinical study for this thesis explored the immediate hypoalgesic and sympathetic effects following mobilisation treatment. Further work could explore longer-term follow-up (24, 48 or 72 hours) after a single dose of treatment.

- No association was found between the values of PPT and NPRS in patients with LBP. The clinical relevance of the change in PPT values needs to be examined in future research with the incorporation of different, related measures of pain.

- For experimental purposes, all patients in the clinical study were treated using a pre-determined mobilisation technique. However, in clinical practice, the choice of treatment depends on the findings of physiotherapy assessment when the patient responds to a trial intervention dose. It might be of interest to exclude the immediate responders to a trial dose from further research and examine the response over a course of intervention.

- There may be the potential to integrate spinal mobilisation with strategies such as pharmacology, graded movement and patient education, as these strategies are known to affect the process of CNS. Therefore, RCTs are warranted for symptomatic subjects with pain and impaired function in order to produce a more advanced paradigm, which contributes to beneficial clinical guidelines for patients.

- RCTs are needed on symptomatic subjects to examine the neurophysiological effects of spinal mobilisation techniques of different rates, amplitudes and duration of sets, as well as in comparison with other forms of

treatment. The exploration of the extent of hypoalgesia over time might be necessary to ascertain the duration of the treatment effect. Skyba et al. (2003) demonstrated that 45 min was the lasting effect of mechanical hypoalgesia following lower limb mobilisation.

- The exploration of patients' expectations and beliefs was not part of the initial assessment in the clinical study. In addition, there was limited communication with the participants throughout the studies, and this might have influenced the response to mobilisation. Further research should examine whether the clinical effect of mobilisation could be influenced by the level of communication with participants.

- It has been suggested that emotion centres (e.g. dorso-lateral prefrontal cortex) and the PAG can be stimulated as a result of event anticipation resulting in modulation of pain perception within the brain stem (Wager et al., 2004). Thus, instigation of mobilisation treatment as an event might have the ability to initiate central processing and related clinical benefits. Although the present study attempted to control the possible confounding variables influencing sympathetic activity, determining the potential effect of intervention expectation on sympathetic function was not possible (Bialosky et al., 2008). Further studies are recommended to investigate the relationship between the magnitude of hypoalgesia and sympathetic activity following mobilisation and the expectations of patients. Furthermore, focus groups or interviews could be used to explore the experiences of patients who receive mobilisation.

- Taylor and Murphy (2009) have reported (using functional MRI) a correlation between lumbar dysfunction and neuroplastic changes to the dorsal horn and central pain structures (midbrain, brainstem, amygdala and thalamus), as well as SNS synaptic activity (Nagai et al., 2004). However, this theory needs further investigation to correlate sympathetic responses to mobilisation treatment with pain and functional disability measures throughout a full course of treatment and to correlate these findings directly with functional MRI results.

8.5. Original contribution to knowledge

- The reliability study in this thesis was the first to assess the reliability in a laboratory sitting of the e-Health Sensor Shield V2.0 at measuring skin conductance, respiratory rate, heart rate and skin temperature. Furthermore, it was the first to assess the reliability of measuring the sAA enzyme, which is linked to arousal of the SNS. Although the reliability of PPT measures has been tested previously, the sites used for measurements in this study have not been previously tested for reliability.
- The clinical study was the first to investigate the sympathetic effects of mobilisation treatment in NSCLBP patients. These results inform the current evidence and help clinicians in the decision-making process.
- This is the first study to highlight the potential influence of thoracic mobilisation on salivary biomarker indicators as a sympathetic measure.
- This is the first study to assess the extent of hypoalgesic effects in the lumbar area following thoracic mobilisation in an asymptomatic population.
- This is the first study to examine the extent of the hypoalgesic effects over the lumbar and distal areas following thoracic mobilisation in LBP patients.
- This is the first study to examine the dose-dependent effect of mobilisation on sympathetic activity.
- The clinical study found a dissociation between PPT values and NPRS measures that was reported by patients with LBP. This calls into question other studies that have reported PPT in isolation as it could be suggested that a change in this measure may not reflect a change in patient-reported measures of pain.
- The clinical study suggests that various hypoalgesic mechanisms may be responsible for changes seen in PPT and NPRS.

8.6. Conclusions

The aim of this series of investigations was to advance the knowledge surrounding the mechanisms behind the clinical benefits of mobilisation treatment in patients with CLBP. The results of this reliability study demonstrated that the test-retest within a day reliability of skin conductance, respiratory rate, heart rate and skin temperature,

SBP and PPT measurements were excellent the reliability of DBP and sAA measurements was fair to good respectively. The preclinical study findings in asymptomatic subjects revealed significant sympathoexitatory effects in terms of BP, HR and RR where there were insignificant results with regard to peripheral sympathetic measures (SC and ST). Significant hypoalgesic effects were evident in some locations, including distal areas, but not at all visits.

The clinical study in patients with NSCLBP showed significant peripheral detectable sympathoexcitatory effects in the lower limbs in terms of increased SC and decreased ST following thoracic mobilisation that were not detected in asymptomatic participants. These peripheral sympathetic responses occurred concurrently with significant hypoalgesic effects with an increase in PPT values and a significant decrease in NPRS. However, the statistical significant PPT values were not evident in all locations and these changes were not clinically significant. There was no association between changes in PPT and changes in NPRS.

Results suggest that peripheral sympathetic measures might be used as a noninvasive indicator of neurophysiological changes present with lumbar conditions. These changes might include adaptive neuroplasticity, as well as dorsal horn and central processing.

Although the design of the study does not infer results regarding cause and effect, it presents new information that informs future research in the area of the mechanism of action of manual therapy and management strategies for LBP.

Conferences contributions

A poster has been presented at the 8th MMU Postgraduate Research Conference, 5th Nov 2015

A poster has been presented at the 9th Saudi Students Conference in Birmingham, UK, 13th – 14th Feb 2016.

A poster has been presented at MMU Faculty HPSC Faculty Research In High Summer Conference, 4th – 5th July 2017.

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Appendices

Appendix 3.1. Criteria list for the methodological quality assessment (adapted from van Tulder et al., 2003)

A/ Was the method of randomization adequate? Yes/No/Don't know

B/ Was the treatment allocation concealed? Yes/No/Don't know

C/ Were the groups similar at baseline regarding the most important prognostic indicators? Yes/No/Don't know

D/ Was the patient blinded to the intervention? Yes/No/Don't know

E/ Was the care provider blinded to the intervention? Yes/No/Don't know

F/ Was the outcome assessor blinded to the intervention? Yes/No/Don't know

G/ Were co-interventions avoided or similar? Yes/No/Don't know

H/ Was the compliance acceptable in all groups? Yes/No/Don't know

I/ Was the drop-out rate described and acceptable? Yes/No/Don't know

J/ Was the timing of the outcome assessment in all groups similar? Yes/No/Don't know

K/ Did the analysis include an intention-to-treat analysis? Yes/No/Don't know

Appendix 4.1. Salivary alpha-amylase assay protocol

Step 1: Read and prepare reagents according to the Reagent Preparation section before beginning assay. Determine your plate layout

Step 2: Keep the desired number of strips in the strip holder and place the remaining strips back in the bag.

Step 3: Set your plate reader to incubate at 37ºC, and to read in center measurement kinetic mode initially at one minute, then again two minutes later. Choose the 405 nm filter with no reference filter. For plate readers without these options, incubation can take place in a plate incubator/rotator with manual movement of the plate into and out of the plate reader for the 1 minute and 3 minute readings. Kit validation was performed under these conditions.

Step 4: Heat the α-Amylase Substrate to 37ºC in the trough provided. (For ease of use we recommend using a **preheated** 37ºC microtiter plate incubator.) Be sure the α-Amylase Substrate has reached 37ºC before use. A minimum warm up time of 20 minutes, from room temperature, in a preheated microtiter plate incubator is recommended. (If using any other incubator it can take an hour or more to reach 37ºC.) Keep trough covered to prevent evaporation.

Step 5: Saliva samples are to be diluted with the α-Amylase Diluent provided. Prepare a 1:10 dilution of the saliva by pipetting 10 µL of saliva into 90 µL α-Amylase Diluent. Mix well. Further dilute by pipetting 10 µL of the 1:10 dilution into 190 µL α-Amylase Diluent (1:20). Final dilution is 1:200. The remainder of the 1:10 dilution may be set aside in case a different final dilution is necessary.

Step 6: Add 8 µL of controls and/or diluted saliva samples to individual wells.

Step 7: Add 320 µL of the preheated (37ºC) α-Amylase Substrate to each well simultaneously using a multichannel pipette. Discard pipette tips to avoid reagent contamination. **Do not return any of the α-Amylase Substrate left in the tips to the bulk tray once you have dispensed it into the wells. This could contaminate the bulk tray contents and affect any subsequent testing.** Any well containing bubbles at the time of reading must be repeated.

Step 8: If reading kinetically in a programmable 37ºC plate reader, immediately place plate in reader and start reader. **Wells are very full. Program plate reader to mix slowly or liquid could spill into the plate reader.**

Otherwise, follow these steps:

 Start timer **immediately** and mix (500-600 RPM) at 37ºC.

 Transfer plate to reader in time to read the Optical Density (OD) at **exactly** 1 minute, and then return to mixing at 37ºC. **Save** 1 minute OD readings.

 Transfer plate again and read the OD at **exactly** 3 minutes. **Save** 3 minute OD readings.

Calibration

This procedure is standardized using the millimolar absorptivity of 2-chloro-p-nitrophenol under the test conditions described.

Quality Control

The Salimetrics' High and Low α-Amylase Controls should be run at least once on each day of testing. The control ranges established at Salimetrics are to be used as a guide. Each laboratory should establish its own range. Variations between laboratories may be caused by differences in techniques and instrumentation.

Appendix 5.1. Manchester Metropolitan University Ethics Approval for reliability study

MANCHESTER METROPOLITAN UNIVERSITY
FACULTY OF HEALTH, PSYCHOLOGY AND SOCIAL CARE

M E M O R A N D U M

FACULTY ACADEMIC ETHICS COMMITTEE

Manchester Metropolitan University

To: Wafa Hashim

From: Prof Carol Haigh

Date: 05/08/2015

Subject: Ethics Application 1303

Title: **The sympathetic nervous system effects of spinal mobilisations in those with and without chronic low back pain (CLBP)**

Thank you for your application for ethical approval.

The Faculty Academic Ethics Committee review process has recommended approval of your ethics application. This approval is granted for 42 months for full-time students or staff and 60 months for part-time students. Extensions to the approval period can be requested.

If your research changes you might need to seek ethical approval for the amendments. Please request an amendment form.

We wish you every success with your project.

Prof Carol Haigh and Prof Jois Stansfield
Chair and Deputy Chair
Faculty Academic Ethics Committee

Appendix 5. 2. Participant Information Sheet (reliability study)

Participant Information Sheet

Study Title: The reliability of The e-Health Sensor Shield V2.0, Wagner algometer and salivary alpha amylase measurements in asymptomatic population.

The Principal Investigator:

Mrs. Wafa AL Muslem, PhD student, Health Psychology and Social Care department, Manchester Metropolitan University.

wafa_hashim@hotmail.com

wafa-hashem.a.al-muslem@stu.mmu.ac.uk

00447874107120

The Director of Studies:

Dr. Peter Goodwin, Health Psychology and Social Care department, Manchester Metropolitan University

P.Goodwin@mmu.ac.uk

01612472941

I would like to invite you to take part in a research study. This study has been reviewed by the Faculty Ethics Committee. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Ask questions if anything you read is not clear or would like more information. Take time to decide whether or not to take part.

What is the purpose of the study?

You are invited to participate in this study that aims to determine the reliability of The e-Health Sensor Shield V2.0 at measuring blood pressure, respiratory rate, heart rate, skin temperature and sweat levels responses. Also, to determine the reliability of a Wagner algometer at measuring pressure tolerance and the reliability of

measuring alpha amylase from your saliva. This data can then be used to determine if this equipment are reliable and stable measuring tools for future use in hospitals with patients with low back pain undergoing physiotherapeutic treatment.

Who can take part?

We are looking for healthy individuals aged 18-55 years, male and female gender, who able to provide informed consent for the study and asymptomatic of spinal pain.

Do I have to take part?

It is up to you to decide. We will describe the study and go through the information sheet. We will then ask you to sign a consent form to show you agreed to take part. You are free to withdraw at any time, without giving a reason.

What will happen to me if I take part?

If you are prepared to be involved in the study you will be required to attend the Jon Dalton Building on one occasion. The visit will consist of a brief, 5 minutes, interview to determine your suitability for inclusion to the study. You will be asked about your current and past health, any current medications any conditions that may affect the results of the study. The principal investigator will invite you to discuss any aspects of the study. Following that, if you wish to take part in the study, you will be asked to sign the consent form. It is important that prior to your visits, you try not exercise or eat any food for 3 hours or have any drinks that contain caffeine (tea, coffee, coca cola) and refrain from alcohol for up to 24 hours. This is essential as the measurements will be affected by food and certain drinks.

What will I have to do?

First, we will measure your blood pressure using the sphygmomanometer (3 times with one minute rest). After that in order to measure the level of alpha-amylase, you will be asked to express saliva directly into cryotubes through a small straw (3 times with one minute rest). Then, we will measure the pressure tolerance over your lower back, The Wagner algometer will be pressed perpendicularly and you will be instructed to inform the researcher when the algometer's pressure changes to pain and a reading will be recorded (3 times with one minute rest).

You will then be required to lie on your front, on a treatment coach. In order to measure your heart rate, skin temperature, respiratory rate and sweat levels responses, it is necessary to place small electrodes on your body. Airflow (breathing) will be measured by a set of two prongs, which are placed in the nostrils. Heart rate sensors will be connected to your back. Body temperature sensor will be placed over the planter surface of the big toe. Sweat level sensors will be placed over the planter surface of the second and third toes. The sites of the skin where the electrodes will be applied will be cleaned first with isopropyl alcohol to remove any unwanted skin residue. You will be instructed not to deep breath, cough, fall asleep, sneeze, interfere with the electrodes or talk except to indicate pain or discomfort. To allow your body to acclimate to the environment, you will have an initial 10-minute

stabilisation period, and then we will begin to take recordings from the applied sensors over the next eight minutes.

The whole session should not take more than 45 minutes and you will be informed when the period of the test has ended.

Expenses and payments?

Reasonable expenses will be made to volunteers for taking part in the study.

What are the possible disadvantages and risks of taking part?

It is not anticipated that you will experience any abnormal responses from any of the measurement procedures. However, if you experience any undue discomfort, the test will be terminated immediately upon your request.

What are the possible benefits of taking part?

You will not get benefits of taking part but the information we get from the study will help to improve the treatment of people with low back pain.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the primary researcher who will do the best to answer your questions (00447874107120). If you remain unhappy and wish to complain formally you can do this through contacting the primary supervisor,

Dr Peter Goodwin

Manchester Metropolitan University

Birley Building

Birley Fields Campus

53 Bonsall Street

Manchester

M15 6GX

Tel: 01612472941

Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the university will have your name and address removed so that you cannot be recognised. However, your involvement in the study may be revealed as others may see you entering or leaving the testing rooms.

What will happen if I don't carry on with the study?

If you withdraw from the study all the information and data collected from you, to date, will be kept and used for study purposes.

What will happen to the results of the research study?

Before presenting or publishing any data from this study, data will be anonymised.

Who is organising or sponsoring the research?

This study is organised by Manchester Metropolitan University and sponsored by Saudi Cultural Bureau.

Thank you for taking the time to read the information and if you want any more information please do not hesitate to contact the primary researcher (00447874107120).

Appendix 5.3. Consent form (reliability study)

Participant Name: Date of Birth:

Contact Telephone Number:

Study 1- CONSENT FORM

Title of Project: **The reliability of The e-Health Sensor Shield V2.0, Wagner algometer and salivary alpha amylase measurements in asymptomatic population.**

Name of Researcher: **Mrs. Wafa AL Muslem, PhD student, Health Psychology and Social Care department, Manchester Metropolitan University.**

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated **[23rd July 2015]** version **[1.0]** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent.	Date	Signature

Appendix 5. 4: Example raw data trace

Right skin conductance	Right skin temperature	Left skin conductance	Left skin temperature	ECG	AirFlow
0.351562	2.651367	0.327148	2.700195	1.821289	0.03418
0.361328	2.651367	0.341797	2.700195	1.660156	0.029297
0.366211	2.65625	0.341797	2.695312	1.665039	0.029297
0.356445	2.651367	0.322266	2.700195	1.782227	0.024414
0.356445	2.65625	0.341797	2.700195	1.601562	0.019531
0.341797	2.651367	0.351562	2.705078	1.806641	0.019531
0.361328	2.69043	0.34668	2.700195	1.713867	0.014648
0.336914	2.65625	0.341797	2.700195	1.660156	0.019531
0.356445	2.651367	0.322266	2.700195	1.826172	0.019531
0.361328	2.65625	0.341797	2.695312	1.655273	0.009766
0.341797	2.651367	0.327148	2.700195	1.782227	0.014648
0.361328	2.65625	0.327148	2.705078	1.772461	0.014648
0.34668	2.651367	0.341797	2.695312	1.645508	0.014648
0.34668	2.651367	0.327148	2.700195	1.831055	0.004883
0.361328	2.65625	0.366211	2.700195	1.635742	0.014648
0.327148	2.65625	0.34668	2.69043	1.68457	0.009766
0.356445	2.65625	0.322266	2.705078	1.772461	0.009766
0.34668	2.65625	0.375977	2.700195	1.577148	0.009766
0.351562	2.65625	0.327148	2.700195	1.762695	0.014648
0.375977	2.651367	0.332031	2.700195	1.674805	0.004883
0.332031	2.651367	0.336914	2.700195	1.625977	0.009766
0.375977	2.65625	0.322266	2.700195	1.826172	0.004883
0.361328	2.651367	0.341797	2.700195	1.748047	0.009766
0.336914	2.65625	0.327148	2.700195	2.314453	0.014648
0.375977	2.651367	0.356445	2.700195	2.856445	0.009766
0.34668	2.680664	0.341797	2.700195	2.055664	0.009766
0.356445	2.651367	0.361328	2.700195	1.621094	0.009766
0.361328	2.651367	0.327148	2.695312	1.464844	0.009766
0.327148	2.651367	0.34668	2.700195	1.538086	0.024414
0.366211	2.651367	0.327148	2.700195	1.640625	0.014648
0.351562	2.680664	0.341797	2.700195	1.484375	0.019531
0.34668	2.651367	0.327148	2.695312	1.694336	0.009766
0.361328	2.661133	0.341797	2.695312	1.59668	0.004883
0.361328	2.651367	0.336914	2.700195	1.586914	0.009766
0.361328	2.651367	0.317383	2.729492	1.777344	0.004883
0.366211	2.651367	0.351562	2.695312	1.625977	0.009766
0.336914	2.666016	0.361328	2.700195	1.757812	0.004883
0.361328	2.651367	0.34668	2.700195	1.757812	0.009766
0.390625	2.65625	0.341797	2.700195	1.669922	0.004883
0.356445	2.651367	0.322266	2.700195	1.875	0.004883
0.361328	2.651367	0.34668	2.700195	1.723633	0.009766

0.336914	2.651367	0.327148	2.700195	1.811523	0.009766
0.361328	2.651367	0.322266	2.700195	1.850586	0.004883
0.351562	2.65625	0.341797	2.700195	1.699219	0.004883
0.351562	2.65625	0.327148	2.700195	1.889648	0.009766

Appendix 6.1. Manchester Metropolitan University Ethics Approval for pre-clinical study

MANCHESTER METROPOLITAN UNIVERSITY
FACULTY OF HEALTH, PSYCHOLOGY AND SOCIAL CARE

M E M O R A N D U M

FACULTY ACADEMIC ETHICS COMMITTEE

Manchester Metropolitan University

To: Wafa Al Muslem

From: Prof Carol Haigh

Date: 25/07/2016

Subject: Ethics Application 1303

Title: The sympathetic nervous system effects of spinal mobilisations in those with and without chronic low back pain (CLBP)

Thank you for your application for an amendment to your original ethical approval.

The Faculty Academic Ethics Committee review process has recommended approval of your amendment. This approval is granted for 42 months for full-time students or staff and 60 months for part-time students. Extensions to the approval period can be requested.

If your research changes you might need to seek ethical approval for the amendments. Please request an amendment form.

We wish you every success with your project.

Prof Carol Haigh and Prof Jois Stansfield
Chair and Deputy Chair
Faculty Academic Ethics Committee

Appendix 6.2. Calculation of intra-subject standard deviation from the reliability study

skin conductance (trail 1)	skin conductance (trail 2)	skin conductance (trail 3)
-0.053320004	-0.04467281	-0.061967198
0.022751527	0.019996803	0.018878187
0.00751345	0.007868697	0.008086099
0.024250668	-0.032585701	-0.039228955
-0.276431412	-0.235845303	-0.264078196
-0.019269237	-0.02222825	-0.026558853
-0.106401395	-0.101486957	-0.100205643
-0.049508947	-0.03983114	-0.036051579
-0.035504336	-0.030830301	-0.030207694
-0.036498445	-0.025306178	-0.023510817
0.102822581	0.07544566	0.056400969
0.011356714	-0.004344958	-0.01280232
-0.064255445	-0.061551413	-0.039649785
-0.112785453	-0.14168008	-0.17820623
0.041968811	0.033646869	0.040139802
Mean trial 1= -0.036220728 Standard deviation= 0.08	Mean trial 2= -0.040227004 Standard deviation= 0.07	Mean trial 3= -0.045930814 Standard deviation= 0.07

Pooled standard deviation= 0.073

Appendix 6.3. Participant Information Sheet (pre-clinical study)

Participant Information Sheet

Study Title: The neurophysiological responses of sympathetic nervous system to passive accessory mobilisations in asymptomatic population.

The Principal Investigator:

Mrs. Wafa AL Muslem, PhD student, Health Psychology and Social Care department, Manchester Metropolitan University.

wafa_hashim@hotmail.com

wafa-hashem.a.al-muslem@stu.mmu.ac.uk

00447874107120

The Director of Studies:

Dr. Peter Goodwin, Health Psychology and Social Care department, Manchester Metropolitan University

P.Goodwin@mmu.ac.uk

01612472941

I would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Ask questions if anything you read is not clear or would like more information. Take time to decide whether or not to take part.

What is the purpose of the study?

You are invited to participate in this study that aims to determine the nervous system responses of gentle pressure to the spine, by a physiotherapist, in a pain free population.

Who can take part?

We are looking for healthy individuals aged 18-55 years, male and female gender, who able to provide informed consent for the study and asymptomatic of spinal pain.

Do I have to take part?

It is up to you to decide. We will describe the study and go through the information sheet. You can take this information away with you to discuss with your friends and family. If you decide to take part we will ask you to sign a consent form to show you agreed to take part. You are free to withdraw at any time, without giving a reason.

What will happen to me if I take part?

If you are prepared to be involved in the study you will be required to attend room

T0.18 of the John Dalton West building, (Manchester Metropolitan University, Chester Street, Manchester, M1 5GD) on three occasions.

We will determine your suitability for inclusion to the study. You will be asked about your current and past health, any current medications any conditions that may affect the results of the study.

It is important that prior to your visit, you try not exercise or eat any food for 3 hours or have any drinks that contain caffeine (tea, coffee, coca cola) and refrain from alcohol for up to 24 hours. This is essential as the measurements will be affected by food and certain drinks.

What will I have to do?

Visit 1, 2 and 3

You will be required to partially undress your top half. We will have blankets and screens to protect your dignity at all times.

First, we will measure your blood pressure which requires wearing a cuff round your arm which will be pumped up. After that in order to measure the levels of an enzyme which is linked to arousal of the sympathetic nervous system (alpha amylase) we would like to collect a sample of your saliva. To do this we will put a swab under your tongue and you will be asked to give a sign when the swab is full. Then, we will measure the pressure tolerance over your lower back, The Wagner algometer will be pressed perpendicularly and you will be instructed to inform the researcher when the algometer's pressure changes to pain and a reading will be recorded.

You will then be required to lie on your front, on a treatment couch. In order to measure your heart rate, skin temperature, respiratory rate and sweat levels responses, it is necessary to place small electrodes on your body.

Airflow (breathing) will be measured by a set of two prongs, which are placed in the nostrils. Heart rate sensors will be connected to your chest. Body temperature sensor will be placed over the planter surface of the big toe. Sweat level sensors will be placed over the planter surface of the second and third toes.

The sites of the skin where the electrodes will be applied will be cleaned using an antiseptic swab (isopropyl alcohol) to remove any unwanted skin residue. To allow your body to acclimatise to the environment, you will have an initial 10-minute stabilisation period, and then we will begin to take recordings from the applied sensors over the next two minutes.

Directly after that, a physiotherapist will apply gentle pressure (treatment) to one area in the middle of your spine; this will be interspersed with rest periods. Recordings will be taken from the applied sensors throughout this intervention. This treatment will last for 5 minutes.

Following the treatment you will be asked to remain still for a further 10 minutes. During this period the researcher will remain in the room and will inform you when the period of the test has ended.

After that we will measure the pressure tolerance over your lower back, The Wagner algometer will be pressed perpendicularly and you will be instructed to inform the researcher when the algometer's pressure changes to pain and a reading will be recorded.

Finally, we will measure your blood pressure using the sphygmomanometer. Then, in order to measure the level of alpha-amylase, we will put a swab under your tongue and you will be asked to give a sign when the swab is full. The whole session should not take more than 45-60 minutes and you will be informed when the period of the test has ended.

Expenses and payments?

Reasonable expenses will be made to volunteers for taking part in the study.

What are the possible disadvantages and risks of taking part?

It is not anticipated that you will experience any abnormal from any of the measurement procedures or the treatment technique. The technique is designed for treatment of patients with stiff and restricted joints. It is not physically demanding and so should not cause any undue tiredness. However, there is a chance that participant may experience discomfort in the lower back the day after the treatment. This should disappear within 24 hours. If you experience any undue discomfort during the test, it will be terminated immediately upon your request.

What are the possible benefits of taking part?

You will not get benefits of taking part but the information we get from the study will help to improve the treatment of people with low back pain.

What if there is a problem?

If you have any concerns about any aspect of this study, you should ask to speak to the primary researcher who will do the best to answer your questions (00447874 107

120). If you remain unhappy and wish to complain formally you can do this through contacting the primary supervisor,

Dr Peter Goodwin

Manchester Metropolitan University

Birley Building

Birley Fields Campus

53 Bonsall Street

Manchester

M15 6GX

Tel: 01612472941

Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the university will have your name and address removed so that you cannot be recognised. However, your involvement in the study may be revealed as others may see you entering or leaving the testing rooms.

What will happen if I don't carry on with the study?

If you withdraw from the study all the information and data collected from you, to date, will be destroyed and your name removed from all the study files.

What will happen to the results of the research study?

Before presenting or publishing any data from this study, data will be anonymised.

Who is organising or sponsoring the research?

This study is organised by Manchester Metropolitan University and sponsored by Saudi Cultural Bureau.

Thank you for taking the time to read the information and if you want any more information please do not hesitate to contact the primary researcher (00447874107120).

Appendix 6.4. Consent form (pre-clinical study)

Participant Name: Date of Birth:

Contact Telephone Number:

Study 2- CONSENT FORM

Title of Project: **The neurophysiological responses of sympathetic nervous system to passive accessory mobilisations in asymptomatic population.**

Name of Researcher: **Mrs. Wafa AL Muslem, PhD student, Health Psychology and Social Care department, Manchester Metropolitan University.**

Please initial all boxes

4. I confirm that I have read and understand the information sheet dated **[23rd March 2016]** version **[1.0]** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

5. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person	Date	Signature taking consent.

Appendix 7.1. Manchester Metropolitan University Ethics Approval for clinical study

MANCHESTER METROPOLITAN UNIVERSITY
FACULTY OF HEALTH, PSYCHOLOGY AND SOCIAL CARE

M E M O R A N D U M

FACULTY ACADEMIC ETHICS COMMITTEE

Manchester Metropolitan University

To: Wafa Al Muslem

From: Prof Carol Haigh

Date: 09/09/2016

Subject: Ethics Application 1303

Title: The sympathetic nervous system effects of spinal mobilisations in those with and without chronic low back pain (CLBP)

Thank you for your application for an amendment to your original ethical approval.

The Faculty Academic Ethics Committee review process has recommended approval of your amendment. This approval is granted for 42 months for full-time students or staff and 60 months for part-time students. Extensions to the approval period can be requested.

If your research changes you might need to seek ethical approval for the amendments. Please request an amendment form.

We wish you every success with your project.

Prof Carol Haigh and Prof Jois Stansfield
Chair and Deputy Chair
Faculty Academic Ethics Committee

Appendix 7.2. University of Dammam Ethics Approval for clinical study

Kingdom of Saudi Arabia
Ministry of Higher Education
University of Dammam
Office of the Vice President for
Research & Higher Studies

جامعة الدمام
UNIVERSITY OF DAMMAM

المملكة العربية السعودية
وزارة التعليم العالي
جامعة الدمام
وكالة الجامعة للدراسات
العليا و البحث العلمي

اللجنة الدائمة لأخلاقيات البحث على المخلوقات الحية
Institutional Review Board

IRB Number	IRB –PGS-2016-03-138		أيرب-بجس-١٣٨-٠٣-٢٠١٦
Project Title	The sympathetic nervous system effects of spinal mobilization in those with and without low back pain		
Principal Investigator	Wafa Hashem Almuslem		
Supervisor	Dr. Ali Muteb Alshami		
College / Center	Applied Medical Sciences	**Department**	Physical Therapy
Approval Date	2/10/2016		

The application was reviewed and approved at the University of Dammam IRB meeting on Sunday, October 2, 2016.

Approval is given for six months from the date of approval. Projects, which have not commenced within three months of the original approval, must be re-submitted to the University Institutional Review Board (IRB) Committee. If you are unable to complete your research within the validation period, you will be required to request an extension from the IRB Committee.

On completion of the research, the Principal Investigator is required to advise the Institutional Review Board if any changes are made to the protocol, a revised protocol must be submitted to the Institutional Review Board for reconsideration.

Approval is given on the understanding that the "Guidelines for Ethical Research Practice" are adhered to. Where required, a signed written consent form must be obtained from each participant in the study group.

Vice President for Higher Studies & Scientific Research
Chairman of the Institutional Review Board

Professor Abdulsalam Al-Sulaiman

Stamp
جامعة الدمام
UNIVERSITY OF DAMMAM
وكيل الجامعة للدراسات العليا والبحث العلمي
Vice Presidents of Postgraduate & Scientific Research

cc. - Dean
Deanship of Scientific Research
- Director General
King Fahd Hospital of the University
- Director
Center for Research and Medical Consultations
- Supervisor General for Quality and Safety
King Fahd Hospital of the University
- Director
Monitoring Office for Research and Research Ethics
- Director
Pharmacy @ KFHU

Appendix 7.3. Letter from head of physiotherapy department

MINISTRY OF EDUCATION
UNIVERSITY OF DAMMAM
KING FAHD HOSPITAL OF THE UNIVERSITY
AL KOBAR

وزارة التعليم
جامعة الدمام
مستشفى الملك فهد الجامعي
بالخبر

جامعة الدمام
UNIVERSITY OF DAMMAM
(٠٤٣)

Dear Mrs. Wafa Hashem AL Muslem,

This letter is a response to your request for conducting a research study to fulfill your PhD degree in the physiotherapy department at King Fahd Hospital of the University. The title of your study is "The sympathetic nervous system effects of spinal mobilisation in those with and without LBP", as you have provided us.

After studying your request, I am pleased to inform you that the physiotherapy department at King Fahd Hospital of the University, the University of Dammam has accepted your request. However to commence your study's data collection you need to provide the department with an Ethical approval from the University of Dammam Research Ethics on Living Creatures.

Best of wishes,

د. سعد محمد السعدي
Dr. Saad M. Al Saadi
Director Department of Physiotherapy
Pg. 651049 pager 1312

Dr. Saad M Alsaadi (PhD, PT)

Director, Physiotherapy Department

King Fahd Hospital of the University

The University of Dammam

PO Box 40035, Khobar 31952

email: ssaadi@uod.edu.sa

Appendix 7.4. Skin conductance mean difference from pre-clinical study

Skin conductance (visit 1)	Skin conductance (Visit 2)	Mean difference
-0.1389	-0.3703	-0.2314
-0.2666	-0.2276	0.039
-0.84415	0.0122	0.85635
-0.34705	-0.17315	0.1739
-0.34495	-0.34645	-0.0015
-0.66245	-0.472	0.19045
-0.9814	-0.31605	0.66535
-0.17435	-0.1821	-0.00775
-0.2178	-0.09585	0.12195
-0.1985	-0.0403	0.1582
-0.10845	-0.08975	0.0187
-0.4856	-0.31785	0.16775
-0.20675	-0.0424	0.16435
-0.12055	-0.27365	-0.1531
-0.2678	-0.40165	-0.13385
-0.2293	-0.20855	0.02075
-0.81485	-0.00045	0.8144
-0.271	-0.1895	0.0815
-0.42745	-0.4654	-0.03795
-0.64875	-0.3931	0.25565
-0.98375	-0.37505	0.6087
-0.1635	-0.22455	-0.06105
-0.11245	-0.0964	0.01605
-0.2996	-0.07155	0.22805
-0.1093	-0.0892	0.0201
-0.4387	-0.30845	0.13025
-0.2591	-0.0108	0.2483
-0.1337	-0.2204	-0.0867
-0.201	-0.3716	-0.1706
-0.2094	-0.1876	0.0218
-0.97845	0.00835	0.9868
-0.26205	-0.2083	0.05375
-0.51275	-0.5369	-0.02415
-0.5435	-0.3473	0.1962
-0.9695	-0.3915	0.578
-0.16025	-0.1958	-0.03555
-0.0773	-0.07495	0.00235
-0.11305	-0.07965	0.0334
-0.10685	-0.08425	0.0226
-0.3924	-0.29695	0.09545
-0.27255	-0.0389	0.23365
-0.1393	-0.31075	-0.17145

Mean difference = 0.244144969048

Pooled standard deviation= 0.212648

$n = \frac{2 \times SD^2}{(md)^2} \times 7.8$ (Rigby and Vail, 1998)

$n = \frac{2 \times (0.21)^2}{(0.14)^2} \times 7.8$

$n = 31.2$

Dropout rate= 31.2x20/100=6.2

$n =$37

Appendix 7.5. Participant Information Sheet (clinical study)

INFORMED CONSENT STATEMENT For children/minors participating in this study, the term "*You*" addresses both the participant and the parents or legally authorized representative to consent.	**بيان الموافقة المسبقة المتبصرة** **للأطفال والقاصرين المشاركين في هذه الدراسة، فإن مصطلح "أنت"** **يخاطب كل من المشاركين والوالدين أو من ينوب عنه قانونياً.**
PROJECT TITLE : ***The sympathetic nervous system effects of spinal mobilisations in those with and without low back pain (LBP)*** **Name of the Investigator/s--- Wafa Hashem AL Muslem / Dr Peter Goodwin / Dr Emma Hodson-Tole /Mrs. Jackie Hindle** **In collaboration with (*if applicable*):----------** ***(Names)*:----------** ***(Affiliation)* :----------** 1.You are being asked to participate in our study of Title – **The sympathetic nervous system effects of spinal mobilisations in those with and without low back pain (LBP)** for the period/duration of **45 minutes/3 visits** You were particularly selected to participate in this study because **you have been diagnosed with Low Back Pain**. For the specific duration because **we aim to determine the sympathetic nervous system responses to gentle pressure over the spine**. For research purpose, the procedures to be followed are: **– regular physical therapy assessment to assess your suitability for the treatment**. **– you will be required to partially undress your top half. We will have blankets and screens to protect your dignity at all times**. **– we will measure your blood pressure** **– we will measure the levels of an enzyme which is linked to arousal of the sympathetic nervous system (alpha amylase) by collecting a sample of your saliva**. **– we will measure the pressure tolerance over your lower back, The Wagner algometer will be pressed perpendicularly and you will be instructed to inform the researcher when the algometer's pressure changes to pain and a reading will be recorded**.	**عنوان المشروع:تأثير العالج اليدوي للعمود الفقري على الجهاز العصبي السيمباثاوي لمرضى الام اسفل الظهر** أسماء الباحثين: **وفاء المسلم** بالتعاون مع (*إن وجد*): ---------- **(*الأسماء*):----------** **الجهة الأكاديمية): ----------** 1. نحن نطلب منك أن تشارك في دراستنا بعنوان : **تأثير العالج اليدوي للعمود الفقري على الجهاز العصبي السيمباثاوي لمرضى الام اسفل الظهر** المدة /الفترة: 45 دقيقة لمدة ثلاث جلسات تم اختيارك شخصياً لتشارك في هذه الدراسة لأنك :تعاني من ألم في منطقة أسفل الظهر في الفترة المحددة [لمعرفة تأثير العلاح اليدوي للظهر على الجهاز العصبي السيمباثاوي] ونحن نبحث في هذا الموضوع من أجل زيادة فهمنا عن الأهداف من خلال التالي : -سيقوم المعالج الفيزيائي (الباحث) بتقييم حالتك لمعرفة مدى ملائمتك للدخول ضمن عينة البحث. -بداية,سيقوم المعالج بقياس ضغط الدم ثم سيتم اخذ عينة لعاب لاستخدامها لاحقا لتحليل انزيم يفرز بواسطة الجهاز العصبي السيمباثاوي. -سيطلب منك الاستلقاء على السرير و سيتم قياس مدى احتمالك للضغط في نقاط معينة في منطقة الظهر. - سيتم وضع أجهزة استشعار (أقطاب) على منطقة الصدر لعمل تخطيط للقلب. واقطاب بجانب فتحات الانف لقياس معدل التنفس وأقطاب على أصابع القدمين لقياس درجة حرارة الجسم. - بعد مضي عشر دقائق ,سيقدم لك المعالج الفيزيائي العلاج اليدوي لمنطقة الظهر عن طريق الضغط على ثلاث فترات بقوة متوسطة يتخللها وقت خالي من الضغط, ستكون مدة العلاج اليدوي خمس دقائق. خلال ذلك ستقوم الاقطاب بأخذ القياسات بصورة مستمرة. بعد عشر دقائق من الانتهاء من العلاج,سيقيس لك المعالج ضغط الدم مرة أخرى وكذلك ستؤخذ عينة لعاب ثانية. - المدة الزمنية للجلسة لن تتجاوز 45 دقيقة, وسيقوم المعالج باخبارك فور الانتهاء من القياسات.

يرجى ملاحظة أن مشاركتك في هذه الدراسة البحثية تعتبر تطوعية وقبل الموافقة على أن تكون جزءا من هذه الدراسة يرجى قراءة و / أو الاستماع إلى المعلومات التالية بعناية ، لا تتردد في طرح الأسئلة إذا كان هناك شيء لم تفهمه.

2. إذا قمت بالمشاركة في هذه الدراسة فقد يطلب منك التبرع بعينة [لعاب] والتي سيتم إرسالها [إن وجدت] لتحليلها. عينتك ستكون مشفرة والباحثين لا يستطيعون الوصول إلى معلوماتك الشخصية وبياناتك السريرية.

بالإضافة إلى ذلك فإن الباحث سيحصل على البيانات السريرية من سجلك الطبي في المستشفى.

3. تم تصميم هذه الدراسة لاحتمالية الفائدة لك وللمرضى المشابهين لحالتك. وكما أن نتائج الدراسة يحتمل استخدامها مستقبلاً في علاجات بطرق بديلة [لمرضى الام اسفل الظهر] التي يمكن أن تكون ذات فائدة.
4. إن جميع المعلومات التي تم الحصول عليها من السجلات الخاصة بك أثناء الدراسة سرية وستتم حماية خصوصيتك في جميع الأوقات ولن يتم التعرف عليك شخصيًا بأي شكل من الأشكال كنتيجة لمشاركتك في هذه الدراسة . ومع ذلك فإن البيانات التي تم جمعها يمكن أن تستخدم كجزء من المنشورات البحثية والأوراق المرتبطة بـ [العلاج اليدوي للعمود الفقري لمرضى الام اسفل الظهر].
5. في حالة أي أذى أو أمراض غير متوقعة خلال هذه الدراسة فإن التعويض الطبي الضروري سيدفع حسب الأنظمة في المستشفى.
6. مشاركتك في هذه الدراسة تطوعية تمامًا ولك أن ترفض المشاركة في هذا البحث وهذا الرفض ليس له أي عواقب سلبية بالنسبة لك إذا كنت بدأت المشاركة في البحث
7. يمكنك التوقف عن المشاركة في أي وقت و لأي سبب من الأسباب ومن دون أي عواقب.
8. خذ الحرية ولا تتردد في طرح أي سؤال عن أي شيء يبدو غير واضح لك ولك أن تنظر بعناية لهذه الدراسة البحث ونموذج الموافقة قبل التوقيع.
9. بعد مشاركتك ، و في حالة لديك أي استفسار على البحث أو طلب إيضاح لأي موضوع فيمكنك التواصل مع (وفاء المسلم.) في أي وقت على الجوال رقم (0509999707.) أو البريد الإلكتروني (.. walmusallam@uod.edu.sa .)،

هذا بالإضافة إلى أنه سيتم إبلاغك بأية معلومات تؤثر على مشاركتك أثناء تنفيذ البحث

10. يوقع الباحث الرئيس على نموذج الموافقة بعد التبصير ، و نسخة من النموذج الموقع تعطى للمشارك .نسخة موقعة من الموافقة قبل التبصير يجب الاحتفاظ بها في ملف الباحث

You will then be required to lie on your front, on a treatment couch. In order to measure your heart rate, skin temperature, respiratory rate and sweat levels responses, it is necessary to place small electrodes on your body.

Airflow (breathing) will be measured by a set of two prongs, which are placed in the nostrils. Heart rate sensors will be connected to your back. Body temperature sensor will be placed over the planter surface of the big toe. Sweat level sensors will be placed over the planter surface of the second and third toes.

The sites of the skin where the electrodes will be applied will be cleaned using an antiseptic swab (isopropyl alcohol) to remove any unwanted skin residue. To allow your body to acclimatise to the environment, you will have an initial 10-minute stabilisation period, and then we will begin to take recordings from the applied sensors over the next two minutes.

- Directly after that, a physiotherapist will apply gentle pressure (treatment) to one area in the middle of your spine; this will be interspersed with rest periods. Recordings will be taken from the applied sensors throughout this intervention. This treatment will last for 5 minutes.

Following the treatment you will be asked to remain still for a further 10 minutes. During this period the researcher will remain in the room and will inform you when the period of the test has ended.

After that we will measure your blood pressure using the sphygmomanometer. Then, in order to measure the level of alpha-amylase, you will be asked to express saliva directly into cryotubes through a small straw. Finally, we will measure the pressure tolerance over your lower back, The Wagner algometer will be pressed perpendicularly and you will be instructed to inform the researcher when the algometer's pressure changes to pain and a reading will be recorded. The

whole session should not take more than 45 **minutes and you will be informed when the period of the test has ended**. We are investigating this topic in order to further our understandings of the objectives of our work that is **to investigate one of the proposed underlying mechanisms behind the effectiveness of manual therapy in low back pain patients** Your participation in the research study is voluntary. Before agreeing to be a part of this study please, read and/or listen to the following information carefully. Feel free to ask questions if you have any ambiguities. 2. If you participate in this study, you may be asked to donate a sample of [**saliva**] which will be sent to [if applicable] for analysis. Your sample will be coded however; investigators at [analysis center] will not have any access to your personal information and clinical data. 3. In addition, the investigator will acquire clinical data from your medical record at the hospital. 4. Risks are limited to the usual discomfort of donating specific samples. 5. This study designed might benefit you and other similar patients, besides", however, there is a possibility that the results of the study may contribute to future alternative treatments and procedures of **spinal manual therapy** that might also be beneficial. 6. Any and all information obtained from your medical records during the study will be confidential. Your privacy will be protected at all times. You will not be identified individually in any way as a result of your participation in this research. The data collected however, may be used as part of publications and papers related to **low back pain**.	الرئيس وملف اللجنة الدائمة لأخلاقيات البحث على المخلوقات الحيَّة وملف السجل الطبي للمريض.

7. "In case of any unexpected injury or illness during this study, the compensation or the necessary medical treatment will be given as per the rules and regulations of the hospital" 8. Your participation in this study is entirely voluntary. You have rights to discontinue or refuse to participate even after initiation of study at any time for any reason. Such refusal will not have any negative consequences for you. 9. Please feel free to talk to the researcher and ask questions. You may also want to talk to your family, friends, or your personal doctor or other health care provider about joining this study. If you decide that you would like to participate in the study, you will be asked to sign this form and you will be given a copy of the signed form to keep. 10. After your participation, in case you have any questions and/or concerns about research, want clarification or report any matter related to your participation in the research you may contact **Wafa Hashem AL Muslem** any time on the number**0509999707**or via email **walmusallam@uod.edu.sa** 11. In addition, if any new information is learnt, at any time during the research, which might affect your participation in the study, you shall be informed. 12. Principal Investigator of the study will also sign the copy of Informed consent and the signed copy of the Informed Consent will be handed over to the Study Participant. Also, Signed copy of informed consent has to be kept in the PI file, SCRELC file, and patient's medical record file.	

Appendix 7.6. Consent form (clinical study)

I have read or listened to the above information and I have decided that I will participate in the project as described above. The researcher has explained me about the study, other beneficial treatments or procedures available and also clarified my doubts. I also understand what will be expected of me. I now understand that the purpose of the study is to further help the understanding of manual therapy as treatment for low back pain patients. **If I do not participate, there will be no penalty or loss of rights. I can stop participating at any time, even after I have started.**	**لقد قرأت أو استمعت إلى المعلومات المذكورة أعلاه وعليه فقد قررت أنني سوف أشارك في المشروع المذكور. وأوضح الباحث الدراسة بالنسبة لي وأجاب على أسئلتي. وأنا واعٍ تمامًا بما سيطلب مني. وأنا على يقين أن الغرض من هذه الدراسة هو تعزيز فهم [وإذا لم أشارك فلن تكون هناك عقوبة أو فقدان للحقوق ويمكنني التوقف عن المشاركة في أي وقت حتى بعد أن أكون قد بدأت فعليًا بالمشاركة.**
I agree to participate in the study and for my samples to be kept and used for future research on low back pain. **My signature below also indicates that I have received a copy of this English consent form together with an official translation of this document in Arabic.**	**أوافق على المشاركة في هذه الدراسة ولا مانع من أن تحفظ عيناتي وتستخدم للبحث في المستقبل على [.** **يشير توقيعي أدناه أيضا بأنني تلقيت نسخة من نموذج الموافقة باللغة العربية إلى جانب ترجمة رسمية لهذه الوثيقة باللغة الانجليزية.**
Participant's signature …….. **Principal Investigator signature** …… **Witness – I** …….. **Witness –II** …….	**توقيع المشارك** ……