

**DOCTOR OF PHILOSOPHY**

**The neurophysiological effects of physiotherapy (spinal manual and manipulative therapies) on patients with low back pain**

Perry, Joanna

*Award date:*  
2013

*Awarding institution:*  
Coventry University

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# **The Neurophysiological Effects of Guideline- Endorsed Physiotherapy on Patients with Acute and Sub-Acute Low Back Pain**

**By**

**Joanna Perry**

**April 2013**



**A thesis re-submitted in partial fulfilment of Coventry University's  
requirements for the Degree of Doctor of Philosophy for PhD**

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## Acknowledgements

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This program of study would not have been completed without the direct and indirect help of many individuals.

Foremost, I would like to give my very special thanks to Ann Green who, more than anyone else has been with me throughout this entire process providing her unerring (and enduring) support, encouragement and guidance, not to mention the sometimes required (and proverbial) “poking finger” to facilitate me to “keep going”.

Very special thanks also to my supervisor Professor Paul Watson who has provided invaluable advice, counsel and critique and in doing so facilitated me to develop my thought processes and “think out of the box”. Thanks also to Professor Sally Singh, for her input and expertise in assisting the finalisation of the IRAS and R&D ethics process and for providing objectivity and clarity in times of cognitive blur!

I would also like to extend my thanks to Dr Tim Sparks for his methodical and rigorous checking of the clinical statistical analyses.

I would also like to take the time to thank my closest friends and colleagues who have helped me through the programme of studies with their advice, suggestions, support and with welcome diversions, namely; Richard, Paul and Stephen, Julian, Keith, Kim, Gerard and Caroline (and Blue the Cocker Spaniel who had to endure many walks during my “thinking” phases!). Additionally, I would also like to say a thank you to my MSc students for sharing my passion for this area of work; Marie, Pete, Stella, Ram, Vasilis and Amit.

Grateful acknowledgement is also made to all the ‘asymptomatic healthy volunteers’ of Coventry University and to the administrative staff, therapists and, importantly, the patients at the University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary site, for their consent and participation in this programme of study.

Special thanks also to Professor Karen Harrison, for her support throughout this process academically, fiscally and administratively (and that includes ALL the paperwork you’ve had to sign along the way!).

Importantly, I would like to thank the MACP and the CSP for their support in sponsoring the dissemination of the clinical elements of this research and, in particular, the external examiners (Professor Ann Moore and Dr Christopher McCarthy) for giving me the opportunity to revisit this work in the light of their invaluable input. This has truly enhanced my understanding of the PhD process and advanced my perspective on the features of my research.

Finally, I would like to devote this work to my parents, who have always provided a loving environment with unconditional encouragement and support throughout my life, allowing me the luxury to undertake this marvellous career and engage in all the challenges of my studies. I hope this will make you proud of YOUR achievements..... Thank you. X

JP (April 2013)

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## **List of thesis publications, conference papers, posters & awards**

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### **Peer Reviewed Journals**

**Perry J, Singh S, Watson PW, Green A (2011)** A preliminary investigation into the magnitude of effect of lumbar extension exercises and a segmental rotatory manipulation on sympathetic nervous system activity. *Manual Therapy* 16; 190-195.

### **Conference Presentations and Posters**

**Perry J, Singh S, Watson P.J., Green A (2008)** The neurophysiological effects of two spinal therapy techniques. Society for Back Pain Research. Special Poster and Oral Presentation. Keele University November 2008

**Perry J, Singh S, Watson P.J., Green A (2011)** The neurophysiological effects of two spinal therapy techniques. World Congress of Physical Therapy. Special Poster presentation. Amsterdam. June 2011.

**Perry J, Singh S, Watson P.J., Green A (2012)** The neurophysiological effects of physiotherapy on patients with low back pain. Platform Presentation. International Federation of Orthopaedic and Physical Manipulative Therapists (IFOMPT). Quebec City, Canada. November 2012.

### **Awards and Bursaries**

**Perry J, Singh S, Watson P.J., Green A (2012)** The neurophysiological effects of physiotherapy on patients with low back pain. MACP Elsevier Presentation Award; November, 2012.

**Perry J, Singh S, Watson P.J., Green A (2012)** The neurophysiological effects of physiotherapy on patients with low back pain. CSP Educational Bursary Award; December, 2012.

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## List of Abbreviations

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ACC	= Anterior Cingulate Cortex
aLBP	= Acute Low Back Pain
ANOVA	= analysis of variance
ANS	= autonomic nervous system
BP	= Blood Pressure
CES	= Cauda Equina Syndrome
CBPT	= Classification-Based Physical Therapy
CCRCT	= Cochrane Central Register of Controlled Trials
CI	= confidence interval
cLBP	= Chronic Low Back Pain
cm	= centimetre
CNS	= central nervous system
CPG	= Clinical Practice Guideline
CPR	= Clinical Prediction Rules
CPT	= Central Processing Time
CRPS	= Chronic Regional Pain Syndrome
CSAG	= Clinical Standards Advisory Group
CSP	= Chartered Society of Physiotherapy
CT	= Computer tomography
DC	= discharge
DCP	= data capture point
Df	= degrees of freedom
DH	= Dorsal Horn
dPAG	= dorsal Periaqueductal Gray

DPIS	= Descending pain inhibitory system
DV	= dependent variable
EDA	= Electrodermal Activity
EEG	= Electroencephalography
EIL	= extension in lying
EMS	= Electrical Muscle Stimulation
EMG	= Electromyography
EOP	= Eye Opening Penalty response
F	= female
FABQ	= Fear and avoidance beliefs questionnaire
FEV <sub>1</sub>	= Forced Expiratory Volume in 1 second
fMRI	= Functional magnetic resonance imaging
GP	= General Practitioner
GL	= Grey Literature
GRC	= Grey Rami Communicantes
GSR	= Galvanic Skin Response
H reflex	= Hoffmann Reflex
HADQ	= Health anxiety and depression questionnaire
H <sub>0</sub>	= null hypothesis
HVLAT	= high velocity low amplitude thrust
Hz	= Hertz
ICC	= Intra-class correlation coefficient
ICIDH-2	= International classification of functioning, disability and health report
Inception	= initial appointment & treatment episode
IV	= independent variable
L4 / L5	= the 4 <sup>th</sup> and/or the 5 <sup>th</sup> lumbar vertebral segment

LBP	= Low back pain
LOA	= Limits Of Agreement
LRI NHS Trust	= Leicester Royal Infirmary NHS Trust
Lsp F	= lumbar spine flexion
Lsp E	= lumbar spine extension
Lsp LF	= lumbar spine lateral flexion
M	= male
MACP	= Musculoskeletal Association of Chartered Physiotherapists
MCC	= Mid-Cingulate Cortex
MCID	= Minimal Clinically Important Difference
MDC	= Minimum Detectable Change
MDC <sup>90</sup>	= Minimal Detectable Change at the 90% Confidence Level
MeSH	= Medical Subject Heading
MID	= minimum important difference
µm	= micrometre
µMho, Micro Mho, Ohm or Ω	= electrical SC activity level/resistance measurement
mPFC	= Medial Prefrontal Cortex
MRI	= Magnetic resonance imaging
MT	= Manual Therapy
MWM	= mobilisation with movement
n	= number
N/A	= Not Available
NC	= neural conductivity
ND	= neurodynamics
NHS	= national health service
NICE	= national institute for clinical excellence



NLM	= National Library of Medicine
NPRS	= Narrative Pain Rating Scale
NRS	= Numerical Rating Scale
NSAID	= Non-Steroidal Anti-inflammatory Drug
NSLBP	= Non-Specific Low Back Pain (used synonymously with LBP)
ODI	= Oswestry Disability Index
ODQ	= Oswestry Disability Questionnaire
ODS	= Oswestry Disability Scale
OFC	= Orbitofrontal Cortex
OM	= outcome measure
OMPSQ	= Örebro musculoskeletal pain screening questionnaire
p	= (statistical) probability value
PA	= Postero-Anterior
PAG	= Periaqueductal Grey/Midbrain
PASW	= predictive analysis software (otherwise known as SPSS – see below)
PC	= Percentage Change
PCP	= Primary Care Practitioners
PFGF	= Pain Free Grip Force
PHG	= Parahippocampal Gyrus
PPIVM	= Passive Physiological Intervertebral Movement
PPT	= Pressure pain threshold (mechanical or thermal)
PNS	= Parasympathetic Nervous System
PROM	= patient reported outcome measure
QTFC	= Quebec task force classification
RCT	= Randomised Clinical Trial or Randomised Controlled Trial

RMDQ	= Roland-Morris Disability Questionnaire
RMS	= Roland-Morris Scale
ROC curve	= receiver operator characteristics curve
ROM	= Range of Motion
RR	= Respiratory Rate
S2	= Sacral segment (number 2)
SC	= skin conductance
SCB	= significant clinical benefit
SCR	= skin conductance response (percentage change)
SD	= standard deviation
SE	= standard error
SEM	= Standard Error of Measurement
Sensitivity (with optional 95% Confidence Interval)	= Probability that a test result will be positive when the disease is present (true positive rate).
Specificity (with optional 95% Confidence Interval)	= Probability that a test result will be negative when the disease is not present (true negative rate).
SM	= Spinal Manipulation
SMT	= Spinal Manipulative Therapy
SMWLM	= spinal mobilisation with leg movement
SNAG	= sustained natural apophyseal glide
SNS	= sympathetic nervous system
SPSS	= Statistical Package for Social Sciences
SRD	= smallest real difference
ST	= Skin Temperature
STarTBack	=
STT	= Spino-Thalamic Tract
TBC	= Treatment Based Classification

Therapist = the term used in the clinical study to depict the PhD candidate conducted the patient treatments

TOP = Canadian TOP programme

TPT = Thermal Pain Threshold

Type I error = erroneously rejecting the null hypothesis

Type II error = erroneously failing to reject the null hypothesis

UHL = University Hospitals of Leicester

UK = United Kingdom

UKBEAM = United Kingdom Back pain Exercise and Manipulation study

ULNPT 2b = upper limb neural provocation test, with radial nerve bias

USS = Ultra-Sound Scan

UTA = Unable To Attend

VAS = Visual Analogue Scale

vPAG = Ventral peri-aqueductal grey matter

WDR = Wide Dynamic Range

WHO = World Health Organisation

WRC = White Rami Communicantes

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## Abstract

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Low Back Pain (LBP) is a condition that most people experience at least once in their lifetime and for which many will seek physiotherapeutic intervention. Recently published and internationally recognised clinical guidelines for the management of LBP recommend the use of spinal manual and manipulative therapy techniques alongside exercise, advice, education and pharmaceutical therapies, particularly in the early stages. Other areas of development in the last decade include classification systems, clinical prediction rules (CPR's), patient-reported outcome measures (PROMS's) and minimum clinically important difference (MCID) thresholds. Additionally, sympathetic nervous system (SNS) measures of treatment responses are now recognised as providing quantifiable indicators of peripheral, spinal and central effects of manual therapy interventions although research in the lumbar spine is very limited with none providing data on a patient population.

The aims of the study were; to determine the reliability and stability of the Biopac System in recording skin conductance (SC) activity levels and calculate the smallest real difference (SRD) statistic; to generate data on the magnitude of SC response to two commonly utilised treatments for LBP; and to observe the changes in a clinical population receiving guideline-endorsed physiotherapy treatment for the management of acute and sub-acute LBP. Furthermore, clinical data analysis sought to identify correlations of SC measures to PROM's and evaluate the feasibility of using SC responses as a predictive tool for therapeutic outcome.

The ability of the Biopac System to reliably record SNS activity was established by using SC measurements with 12 participants on two occasions, one-week apart. Data was recorded within a natural, non-laboratory setting. Results established that SC measurements could be reliably recorded between data sessions with a measurement variability of; ICC=0.99 ( $p<0.005$ ) with an SRD value of 0.315  $\mu\text{mho's}$  (4.633%). In conclusion, any SC change above the SRD could be regarded as an SNS change that is independent of any measurement error or variability thus representing a real change ascribable to the intervention under investigation.

The pre-clinical investigation compared the magnitude of SC response (SCR) of two, independently administered, specific MT techniques, applied, after randomisation, to the Lumbar 4/5 segment of 50 asymptomatic healthy volunteers. Treatments included; a rotatory lumbar manipulation technique or a repeated McKenzie extension in lying exercise. Findings revealed that both techniques produced statistically significant changes in SNS activity in the lower limbs ( $>$  SRD) with manipulative technique SCR's (76%) that were twice the size of the McKenzie repeated extension in lying exercise (EIL) technique (35.7%) ( $p=0.0005$ ). Only the manipulation technique had a lasting effect that was carried into the final rest period ( $p=0.012$ ) but the SNS response was not a side-specific phenomenon ( $p= 0.76$ ).

The final clinical study recruited 60 acute and sub-acute LBP patients (symptoms of up to 12 weeks duration) who received guideline-recommended physiotherapy treatment within

a hospital-based musculoskeletal out-patient physiotherapy department. SCRs were recorded throughout all treatment episodes with standardised, validated PROM's used for comparison of status at inception, mid-point and at discharge. Functional impairment was determined using the Oswestry Disability Index (ODI) and the Roland Morris Disability Questionnaire (RMDQ) with pain intensity evaluated with the Narrative Pain Rating Score (NPRS).

A preliminary comparison, between the asymptomatic population and a random selection from the patient population, revealed that patients had treatment SCR's that were significantly greater (three-fold) than those of the asymptomatic groups (manipulation,  $p=0.003$ ; EIL exercises  $p=0.001$ ).

Analysis of the patient data indicated that pre-treatment/baseline SC activity levels in the inception data capture point were lower than at discharge (18  $\mu$ Mho's;  $p<0.0005$ ) but, conversely, that treatment SC levels were initially high, but diminished in magnitude by discharge (230 to 172  $\mu$ Mho's;  $p<0.0005$ ) representing a SCR reduction of 125%. Correlational analyses of change scores of maximum SCR's to PROM's, from inception to discharge suggested weak positive correlations of SCR treatment responses to functional disability score improvements ( $\rho=0.278$ ) and pain intensity reductions ( $\rho=0.229$ ) that were significant for function ( $p=0.033$ ) but not significant for pain ( $p=0.080$ ). The final analyses indicated that there were trends in the magnitude of response to specific elements of treatment with manipulation having the largest SCR (266%). Further evaluative analysis of SC readings as a predictor, at inception, of functional outcome, at discharge indicated that a critical/cut-off value of 195% may indicate those patients least and most likely to respond positively to MT treatment. Preliminary logistic regression analysis indicated that the 195% SCR value was excellent at identifying poor responders but less successful at identifying good responders, functionally, to treatment. Nonetheless, SCR was a better predictor of outcome than duration of symptoms and patient age. Characteristically, patients achieving the 195% value were most likely to have higher functional disability and pain intensity scores at inception but by discharge had required fewer treatments, had greater overall functional improvement and lower pain intensities than those not achieving this threshold.

In conclusion, SC activity levels and SCR's may be a reliable, stable, alternative and objective measure of LBP patients' SNS status and changes that occur as a result of symptom abatement throughout a course of physiotherapy treatment. SC readings may (indirectly) reflect the state of dorsal horn (DH) sensitisation and of the central nervous system (CNS) processing system and its facilitatory capacity to activate the descending pain inhibitory system (DPIS). Further research, in patient populations (including chronic LBP patients), is recommended to verify these findings and validate the 195% SCR cut-off point. Definitive RCT's are indicated to further the understanding of guideline-endorsed physiotherapy treatment (a complex intervention –MRC, 2000) and to determine whether the SNS activity measurements can be used to help classify, predict, and ultimately, direct the care of patients with LBP.

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# **1. Introduction**

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## **1.1 The global impact of low back pain (LBP) and its management**

Low back pain (LBP) is a costly and disabling disorder with a great impact on individual patients, society and health care providers (Waddell, 1996) and a “burden in Western Countries” (Pransky et al., 2011). Low back pain is one of the main causes of absence from work in the UK and in 2004/5 an estimated 4.5 million working days were lost through musculoskeletal disorders that mainly affected the back (Health and Safety Executive, 2005) and is one of the single most referred conditions to physiotherapy departments. The economic impact of LBP was estimated, in the UK (1998), to possibly exceed £10 billion (Maniadakis and Gray, 2000).

## **1.2. Physiotherapeutic management of low back pain**

A number of studies have endorsed the use of physiotherapy in the management of LBP with some providing focussed advocacy for exercise therapies (Richardson and Jull, 1995; Hides, Jull and Richardson, 2001; Hayden et al., 2005; Cairns, Foster and Wright, 2006; CSP, 2006 pt 1; Mayer, Mooney and Dagenais, 2008; NICE, 2009) and others supporting the use of manual therapies (Clinical Standards Advisory Group 1994; Royal College of General Practitioners, 1997 & 1999; UK BEAM trial Team 2004; and the Chartered Society of Physiotherapy Guidelines Pt 2, 2006). Most Systematic Reviews of LBP management (CSP, 2006; Ernst and Canter, 2006; Murphy, van Teijlingen and Gobbi, 2006; Brontfort et al., 2008; Haldeman and Dagenais, 2008; Dagenais et al., 2010) have emphasised the need for primary research that investigates effective treatment options for LBP which is also an important consideration for the patient, the treating clinician and for health care policy makers. Furthermore, there has been a call to look at treatment effects beyond asymptomatic healthy norms and a drive

to integrate the theory of the findings from these healthy populations into the clinical environment with patients receiving complex therapeutic LBP interventions. Whilst the development of patient-reported outcome measures (PROM's) have provided some insight into clinically observed patient experiences of therapy (Khorsan et al., 2008), these have traditionally been criticised, by the scientific community, as being “soft”, subjective measures thereby setting the challenge for the development of objective, “gold-standard” measures of change in patient populations (Lawrence et al., 2008 and Goertz et al., 2012). Despite this, there remains a paucity of research evidence that supports, empirically, what patients and clinicians experience regarding the symptoms of LBP and the benefits of therapy.

### **1.3. Low back pain classification**

Attempts have been made, within the last two decades, to classify LBP in order to assist clinicians and researchers with decision making processes and issues of heterogeneity of patient populations. The most commonly utilised and publicised classification system in (physiotherapy) LBP literature is the binary differentiation method of “specific LBP” or “non specific LBP” (NSLBP) with further delineation into acute (up to 6 weeks symptom duration), sub-acute (4-12 weeks duration) and chronic (greater than 12 weeks) LBP. This “system” forms the basis of the decision making process often called “diagnostic triage” whereby symptoms are ultimately determined to be specific (with a known patho-anatomical causative factor e.g. malignancy, infection, disc prolapse, fracture, ankylosing spondylitis or other systemic inflammatory disorders) or non-specific (defined as tension, soreness and/or stiffness in the lower back region for which it is not possible to identify a specific cause – NICE, 2009). In 1987, Spitzer et al., introduced the Quebec Task Force activity-related classification system which recognises the multi-

dimensionality of LBP and provides a system by which published research populations can be compared.

#### **1.4. Measuring the effectiveness of treatment strategies**

Despite both clinical research and anecdotal evidence supporting patient-reported benefits of physiotherapy treatment (van Tulder, Koes and Bouter, 1997; Foster et al., 1999; Sparkes, 2005), the biological/ neurophysiological mechanisms underlying the effects of treatment modalities, particularly within patient populations, remain unknown. Although this does not negate the clinical effects of physiotherapy, it hinders acceptance by the wider scientific and health care communities and impedes the development of rational strategies for improving the delivery and the accuracy of provision of therapeutic strategies and has implications for effective resource management. It is recognised (Pengel et al., 2003) that most patients' symptoms improve within the first month from inception although it is also recognised that up to 84% have continued pain and recurrent episodes requiring further intervention, usually in the form of manual and exercise therapies, which has become a key feature of the CSP (2006 pts 1 and 2) and NICE Guidelines (2009) for the management of LBP. In the Clinical Standards Advisory Group (1994) guidelines, manipulation was recommended where symptoms lasted for "more than a few days" and for patients who needed additional help with pain relief or who were failing to return to normal activities. A number of studies (Hadler, Curtis and Gillings, 1987; Goodsell, Lee and Latimer, 2000; UK BEAM, 2004; Konstantinou et al., 2007) have demonstrated clear patient-reported benefits from manual and manipulative techniques with an ever-increasing body of clinical evidence now supporting the use of spinal manual and manipulative therapies in the treatment of LBP (Dagenais et al., 2010). Despite this, debate remains within the literature regarding the magnitude of response, the mechanism of effect and the clinical



significance of observed treatment effects (Potter et al., 2005). Nonetheless, the outcomes reported in studies to date are indirect, proxy measures of patient-reported (subjective) benefits and are worthy of further substantiation with empirical, neurophysiological data comparisons although this has yet to be conducted (with the Biopac System for skin conductance (SC) data acquisition and management) on a patient population receiving guideline-endorsed physiotherapy treatment.

### **1.5. Manual Therapy (MT) and the quantification of treatment responses**

The recent publication of Guidelines for the management of LBP recommend the use of manual therapy (MT) (particularly manipulative techniques), advice to stay active and return to work, self-management strategies, use of non-steroidal anti-inflammatory medications (NSAID's) and analgesics, exercise and acupuncture in the acute and sub-acute stages of the condition (up to 12 weeks symptom duration), (CSP, 2006; van Tulder et al., 2006; Savigny et al., 2009; Chou et al., 2009 and NICE, 2009). These Guidelines are supported by a number of studies that demonstrated clear patient-reported MT benefits (Goodsell et al., 2000; Konstantinou et al., 2007; Bialosky et al., 2009b). However, there continues to be debate, within the literature, regarding the magnitude and the clinical significance of observed treatment effects (Potter et al., 2005; Theodore, 2010) and, indeed, the existence of "acute" LBP within the population where Hesbaek et al., (2003) argue that LBP was, in fact, a chronic, recurrent condition presenting with periodic attacks and temporary remissions, an opinion that was supported by Loeser and Melzack (1999, p.1609) in their concluding statement that;

*"It is not the duration of pain that distinguishes acute from chronic pain but, more importantly, the inability of the body to restore its physiological functions to normal homeostatic levels."*

The dilemma facing the clinician, in determining the therapeutic, and indeed the physiological effects of MT interventions in the lumbar spine, within a patient population has been the difficulty in accurately, quantitatively and non-invasively measuring the proposed effects, in an objective and quantifiable way, a complicated therapeutic interaction incorporating multiple (guideline endorsed) treatment strategies. Indeed, MT is a common treatment option for pain (Nahin et al., 2009) and has been shown to be effective for some individuals with musculoskeletal LBP (Childs et al., 2004). However despite its recognised clinical effectiveness, the mechanisms by which MT results in reductions in pain intensity and functional disability remain largely unknown. A number of researchers have considered the potential role of MT on pain processing (Vernon, 2000; Pickar, 2002 and Bialosky et al., 2009) with a recent systematic review and meta-analysis (Coronardo et al., 2012) demonstrating a link between SMT and immediate increases in mechanical pressure pain thresholds (PPT). Furthermore, several researchers have explored the neurophysiological basis of specific MT techniques in the cervical spine (Sterling et al., 2001; Moulson and Watson, 2006) and upper limbs (Vicenzino et al., 2001 and Paungmali et al., 2003), utilising the SNS as a measure of neurophysiological response, namely, skin conductance (SC) in the periphery. However, there is only a limited research base studying SNS (SC) changes occurring in the lumbar spine and lower limbs (Perry and Green, 2008, Moutzouri, Perry and Billis, 2012; Tsirakis and Perry 2010; Perry et al., 2011; Rao and Perry, 2011) and none of which were conducted in a patient population receiving guideline-recommended treatment within a pragmatic yet controlled hospital environment. Specific sudomotor SNS changes have been reported with lumbar MT treatments on normal healthy populations with Perry and Green (2008) reporting statistically significant SNS changes in the order of 13.5% ( $p=0.005$ ) on the side of treatment in their treatment group that

received unilateral grade III postero-anterior mobilizations (at a rate of 2Hz) and Perry et al. (2011) indicating that manipulative techniques have a greater magnitude of skin conductance response (SCR) than McKenzie repeated extensions in lying exercises (76.3% and 35.7% respectively). Perry and Green (2008) were the first to demonstrate a significant side specific effect compared to the untreated side, to placebo and control conditions ( $p=0.002$ ) with Perry et al. (2011) being the first to quantify the magnitude of effect of two commonly utilized physiotherapeutic interventions. Moutzouri, Perry and Billis (2012) and Rao and Perry (2011) explored the effects of a centrally applied mobilisation with movement (MWM sustained natural apophyseal glide - SNAG) performed on the L4 motion segment during lumbar flexion and extension, revealing a percentage increase in SNS activity in lower limbs in the order of 11% and 21% respectively. This response was double that of the placebo conditions and statistically significant compared to the control group ( $p=0.05$  and  $p=0.01$  respectively) with Rao and Perry (2011) revealing that 10 repetitions resulted in a significantly greater SCR than the 6 repetitions performed in the study by Moutzouri, Perry and Billis (2012). Tsirakis and Perry (2010) also investigated the effects of a unilaterally applied modified Spinal Mobilization with Leg Movement (SMWLM) technique described by Mulligan (2004: p.77) on SNS changes in the lower limbs. These authors revealed that the SMWLM technique resulted in a statistically significant increase in a percentage change in SNS activity in the order of 30.6% ( $p= 0.049$ ) within the treatment side. Again, participants were healthy asymptomatic volunteers and not patients with symptomatic LBP. Furthermore, treatments were conducted, in isolation to any other therapeutic intervention, within a controlled, non-clinical environment thereby questioning the external validity of these findings to “normal” clinical practice.

Neurophysiological (SNS) effects following MT have revealed, in humans, that MT produces an immediate hypoalgesic (Wright and Vicenzino, 1995; Vicenzino et al. 1995 and 2001; Paungmali et al. 2003; Solly, 2004; Zusman, 2004; Bialosky et al. 2008 and 2009b) and sympathoexcitatory effect (Paungmali et al., 2003; Perry and Green, 2008; Perry et al. 2011; Moutzouri, Perry and Billis, 2012) that are specific to mechanical (Vicenzino et al., 1995 and 1996; Sterling et al. 2001) and thermal nociception (Bialosky et al. 2008 and 2009b). These findings have led to the concept that MT exerts its initial effects by activating specific pathways from the peri-aqueductal gray (PAG) region of the brain (Reynolds 1969; Morgan, 1991 in Potter, McCarney and Oldhand, 2005; Lanotte et al. 2005; Bialosky et al., 2009a) and also by the spinal cord and central pain modulatory circuits and inhibition of the dorsal horn (Price et al. 2002). These mechanisms can be influenced differently by different types of manual techniques including oscillatory (Chiu and Wright, 1996; Perry and Green, 2008; Jowsey and Perry 2010) and non-oscillatory techniques (Paungmali et al. 2003; Moulson and Watson, 2006; Moutzouri, Perry and Billis, 2012; Tsirakis and Perry, 2010; Perry et al., 2011; Rao and Perry, 2011). These results reinforce the concept that the administration of spinal MT can result in recordable SNS responses.

## **1.6. The structure of the thesis**

The aims of this programme of studies fell into 3 distinct areas (chapters 3, 4 and 5) and were developed to add to the body of knowledge required to further understand the mechanisms of action of guideline-endorsed physiotherapy treatment (advice, MT and exercise) on LBP patient outcomes. The working hypotheses included:

- 1) That the Biopac data acquisition system is a reliable and stable method of recording SC activity levels in a non-laboratory environment (chapter 3);

- 2) That the magnitude of observable SNS responses differ according to the nature of the MT stimulus provided (chapter 4 and 5);
- 3) That differences can be observed in SC activity levels and responses within- and between-populations (healthy normals and symptomatic LBP patients) according to the underlying state of the neurophysiological system (i.e. pain intensity, functional disability levels) (chapters 4 and 5);
- 4) That relationships may exist between changes in SCR (to treatment) and patient-reported outcome measures (PROM's) of pain intensity and functional disability;
- 5) That SC measures might possess an ability (at inception) to predict a positive functional outcome at discharge (chapter 5).

Thus, Volume I of this thesis includes the literature review (chapter 2) summarising the current understanding of the epidemiology, prognosis and current guidelines for the comprehensive management of LBP. This is followed by a review of the literature regarding clinical prediction rules and of the outcome measures selected for the clinical study (Oswestry Disability Index; Roland Morris Disability Questionnaire and the Narrative Pain Rating Scale). The main focus of the literature review includes the current understanding of (and the professional knowledge-gaps in) the neurophysiological processes occurring following the onset of LBP and the proposed mechanism of action of selected (guideline-endorsed) manual therapy treatments. Chapter 3 presents the reliability study of the Biopac equipment in measuring SNS (SC) measurement variability within a non-laboratory setting. This is followed by a study investigating the magnitude of effect of two commonly used and currently unexplored treatments, McKenzie repeated extension in lying (EIL) exercise and the rotator lumbar manipulation techniques, on asymptomatic healthy volunteers (chapter 4). Chapter 5

presents the final (main) clinical study involving patients, with the final chapter (6 in volume II) drawing the findings of chapters 3, 4 and 5 together, identifying key limitations and proposing future avenues of research whilst recognising the place for this research within a developing, conceptual model of the effects of physiotherapy in the management of LBP.

Volume II of this thesis comprises of the clinical discussion of chapter 5 and the final discussion of the thesis findings, the limitations of the study and future research recommendations. The conclusions to the study (chapter 7), the reference list (chapter 8) and the Appendices can also be found in volume II.

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## **2. Literature Review**

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This section introduces the reader to the current understanding of the epidemiology and prognosis of LBP. It details the existing classification systems currently utilized within clinical environments and the validity and reliability of patient-reported outcome measures (PROM's) used in the hospital setting for the final clinical study. Current practice guidelines for the management of LBP are reviewed and the development and validity of clinical prediction rules for patients with LBP. The current concepts underpinning the measurement of neurophysiological responses and the interpretation of these measures is then explored followed by a review of the research examining the phenomenon of pain perception and pain processing mechanisms. Finally, a review of the current literature underpinning the concepts behind the neurophysiological mechanisms of action of spinal manual therapies are presented.

### **2.1 The Epidemiology and Prognosis of Low Back Pain**

Low Back Pain (LBP) has been well documented to be an extremely common health problem both in the United Kingdom (UK) and internationally (Andersson, 1998; Lidgren 2003; Rapoport et al. 2004 and Dionne, Dunn and Croft, 2006). In the UK, Maniadakis and Gray (2000) estimated that LBP accounted for over £10 billion in direct and indirect expenditure. Epidemiological studies of LBP have challenges similar to clinical studies regarding the heterogeneity of the populations of studies available for comparison and pooling of data.

Prevalence data and reports on LBP have been collated and reported for numerous decades. Current reports of the prevalence of LBP within the adult general

population of the United Kingdom (UK) have reported the point prevalence to be 18% (Harkess et al., 2005), one-month prevalence 39% (Croft et al., 1995) and one-year prevalence 36.1% (Demyttenaere et al., 2007) although there is a lack of clarity regarding the chosen definition of LBP used. This obstacle provided the impetus for Dionne et al. (2008) to utilise a Delphi process to reach an international agreement for a definition for LBP

*'Pain between the inferior margin of the 12<sup>th</sup> rib and the inferior gluteal folds that is bad enough to limit usual activities or change the daily routine for more than 1 day. This pain can be with or without pain going down the leg. This pain does not include pain from feverish illness or menstruation.'*

Harkess et al. (2005) also identified that the prevalence of LBP had increased more than two-fold between 1950 and 1995 in the northwest region of England from 6.3% to 16.3% in males and from 8.6% to 17.3% in females (age standardized rates).

In the paper by Hoy et al., (2010) a comprehensive summary of the epidemiology literature on LBP was provided. The authors estimated the 1 year incidence of the first-ever episode of LBP ranged from 6.3% (Biering-Sorensen, 1982) to 15.4% (Croft et al., 1999), while estimates of the 1 year incidence of any episode (i.e. first-ever or recurrent) ranged from 1.5% (Al-Awadhi et al., 2005) to 36% (Croft et al., 1999). Within the context of health care and clinic-based studies, episode remission at 1 year ranges from 54% (Schlottz-Christensen et al., 1999), to 90% (Van den Hoogen et al., 1997) although there is a lack of clarity, within the literature, between the incidences of symptom recurrence within this time period. While these findings would seem positive, the natural history of LBP has long been observed to be extremely variable, lasting for a few days to more than a year (Roland, 1983).



Indeed, Hestbaek, Leboeuf-Yde and Manniche (2003) argued that as many as 50% of people with activity-limiting LBP within a general population (i.e. not those receiving workers compensation) will go on to have recurrent episodes within the first year (60% by 2 years and 70% by 5 years) and they highlighted the view of Dunn, Jordan and Croft (2006) that LBP is a chronic, recurrent condition and therefore the categorisation of LBP into acute (up to 6 weeks duration), sub-acute (6-12 weeks duration) and chronic (from 3 month onward duration) is obsolete. Cassidy et al. (2005) found that the rate of recurrence increased with age and Hoy et al. (2010) concluded that true remission is rare, a fact supported by Hush et al. (2009) in their focus group study that revealed that symptom attenuation, functional ability and quality of life are all factors considered by patients under the construct of “recovery” however, these elements are also recognised to be poorly quantified by currently utilised PROM’s and fail to adequately capture the true experiences of patients with LBP (Hush et al., 2010).

Regarding the duration of symptoms, Von Korff et al. (1993) found that at the 1 year follow-up period the median number of LBP pain days in patients who’s LBP lasted less than 3 months was 15.5 days and for patients whose pain lasted between 3 to 6 months the median duration was 128.5 days. Van de Hoogen et al. (1998) found the median episode of pain from inception to remission to be 42 days with Henschke et al., (2009) reporting duration of symptoms to be 58 days (53 to 63 days) with only 71.8% of his population being pain free by 1 year and 72.5% having restoration of function. In contrast, Hancock et al. (2009) found the median number of days to recovery to range between 6-22 days however, their population were acute LBP patients and the sub-group reported (17.9% of the total sample population) only

represented the predicted 'quick recoverers' so their results should be interpreted with caution.

Studies that attempt to attribute causative factors to the occurrence of LBP have suggested anatomical structures such as bones, discs, joints, ligaments, muscles, neural structure, viscera and blood vessels (Deyo et al., 2001). In reality, only 5-15% cases can be attributed to a specific cause such as an osteoporotic fracture, neoplasm or infection (Hollingworth et al., 2002 and Woolf and Pfleger, 2003). The remaining 85% to 95% are generally classified as 'non-specific LBP' as there is no identifiable, specific cause for their symptoms. Epidemiological studies have attempted to infer causation by the examination of factors that may have relationships or predispose populations to the condition (Beaglehole, Bonita and Kjellstrom, 1993), however, due to the methodological and clinical heterogeneity in studies investigating causation, Hoy et al., (2010) concluded that it was not possible at this point in time to relate causation to causality but a number of risk factors that could influence the onset and course of LBP were identified. Age was found to be a common risk factor with the incidence of getting LBP being highest in the third decade (Kopec, Sayre and Esdaile, 2004; Straker et al., 2011) with prevalence increasing to the age of 65 years (Lawrence et al., (1998). Kopec, Sayre and Esdaile (2004) found no gender differences in prevalence of LBP, however the systematic review of Hoy et al. (2010) revealed a mean and median prevalence of LBP that was higher in women. Dionne et al., (2001) discovered that low educational status was associated with an increase in prevalence of LBP and this study also revealed that this association is a strong predictor of episode duration and poor outcome, a finding that contradicts those of Croft and Rigby (1994) who revealed an inverse relationship between social status and LBP occurrence. Body weight was found to be a weak

risk factor by Leboeuf-Yde (2000) although Battie et al. (1995) found that heredity played a major role in lumbar disc degeneration. However, the study by Nachemson (1999) demonstrated that there was no correlation between evidence of radiographic disc disease and symptom reproduction.

Within the last decade there has been a deluge of studies exploring the psychosocial factors associated with LBP including stress, anxiety, depression and adverse pain behaviours and that psychosocial factors are significantly associated with the transition of LBP from acute to chronic status (Pincus et al., 2002) with job dissatisfaction being particularly noted (van Tulder, Koes and Bombardier, 2002).

In conclusion, epidemiological studies measuring the prevalence of LBP have demonstrated a two-fold increase in the last 50 years (Harkess et al., 2005) however, the frequency of LBP in the last decade has shown little change (Rossignol, Rozenberg and Leclerc, 2009). The course of LBP in the general population is not considered to be transient or self-limiting, it is now considered to be a chronic condition that presents with periodic attacks and temporary remission (Hesbaek et al., 2003). Although causative factors for NSLBP have yet to be identified, a number of epidemiological risk factors have been suggested and include age, gender, educational status, heredity and psychosocial factors including job dissatisfaction (Hoy et al., 2010). Prognostically, limited methodological quality of primary and review literature means that there remains uncertainty about the reliability of conclusions that can be drawn (Hayden et al. 2009) however baseline factors consistently reported to be associated with poor outcomes for acute and sub-acute LBP include; higher levels of functional disability, higher intensities of pain, the presence of leg pain, duration of symptoms, older age, poor general health, increased psychosocial stress, demanding work relations and compensation issues

(Hayden et al., 2009) and supported by the review of Chou and Shekelle (2010). Indeed, Henschke et al., (2009) reported that acute LBP patients that present with these prognostic factors had unfavourable outcomes including slower recovery and restoration of function with a third of the sample reporting continued symptoms at the 1 year review. Kent and Keating (2008) suggested that the validity of prognostic factors are enhanced when associated with valid and reliable PROM's (i.e. Oswestry Disability Index, Numeric Pain Rating Scale, etc) and studies in the last couple of decades have increasingly been utilising these to quantify their treatment effects and make associations to predictive and prognostic factors.

## **2.2. Classification Systems, Guidelines and Clinical Prediction Rules**

### **2.2.1. Classification Systems**

The development of classification systems in the field of LBP have been of interest to clinicians and researchers for the last 50 years and are considered by many to hold a particularly important role in the advancement of practice through the stratification of pathological, pathomechanical and psychosocial findings into categories that subsequently – through a process of further abstraction and subsequent analysis – allow for the formulation of generalisations that ultimately are designed to benefit patient care and reduce costs. Indeed, the “creation of order from chaos” (Chapman, 2009) by the application of systematic analysis and knowledge synthesis together with the implementation of structural concepts is one of the eminent achievements that have come to define human civilization and, indeed the research process.

For a classification system to be clinically useful, O’Sullivan, in 2005, argued that it should be based on identification of the underlying mechanism/s that drive the

disorder, in order to provide guidance for targeted interventions which, in turn, should predict the outcome of the condition. Therefore, a review of the current situation regarding classification systems is presented followed by consideration of developed guidelines for the management of LBP and the role of clinical prediction tools in assessing treatment outcomes.

The most commonly utilised and publicised classification system in (physiotherapy) LBP literature is the binary differentiation method of “specific LBP” or “non specific LBP” (NSLBP) that forms the basis of decision making process often called “diagnostic triage” whereby the patients symptoms are determined to be specific (with a known patho-anatomical causative factor e.g. malignancy, infection, fracture, ankylosing spondylitis or other systemic inflammatory disorders) or non-specific (defined as tension, soreness and/or stiffness in the lower back region for which it isn’t possible to identify a specific cause – NICE, 2009).

Beyond this binary system, criteria to classify LBP can be defined as belonging to specific theoretical constructs/categories (e.g. diagnosis of disc prolapse with radiculopathy) or dimensions (i.e. patho-anatomical) of the domain being classified (Deyo et al., 1994) and a number of categorical constructs and emergent dimensions and domains have been developed in the last 30 years (Table 1). In 1987 the Quebec Task Force on Spinal Disorders (Spitzer, Leblanc and Dupuis, 1987) developed an activity-related classification system (QTFC) for the differentiation of spinal disorders that was validated for clinical and research stratification (Atlas et al., 1996). This classification system is reproduced in Table 2. Despite its validation for use, and its apparent ease of application (by clearly identifying the stage of the disorder – acute, sub-acute or chronic -, the patho-anatomical diagnosis +/- red flags, signs and symptoms and work status) it is often regarded as lacking the

specificity required for use with NSLBP where most patients who require non-surgical intervention fall, however, it is multidimensional in nature and is capable of facilitating comparative analyses for use within systematic literature-based reviews. Since 1987, the QTFC system has largely been superseded by the biopsychosocial classification system, also a multidimensional classification system (table 1).

**Table 1: Mechanism Based Classification System for LBP (adapted from O'Sullivan (2005))**

<b>Dimension</b>	<b>Category</b>	<b>Approach</b>	<b>Key Proponents</b>	<b>Outcome Measure</b>
Uni-dimensional	Patho-anatomical	Radiological diagnosis Facet joint & Disc degeneration, tears and prolapse Spondylolisthesis, foraminal & spinal stenosis	Bernard and Kirkaldy-Willis, (1987) Nachemson (1999)	X-ray, CT & MRI scans Diagnostic injections
	Signs & Symptoms	Area & nature of pain  Impairments in segmental movement & function  Symptom provocation tests	Delitto et al., (1995) McGill (2004) McKenzie (1981 & 2000) Sahrmann (2001) Maitland (1986) Bogduk (2004)	VAS for pain/symptoms, Pain Drawings Function (e.g. walking distance), Range of motion Biofeedback Diagnostic blocks
	Prognosis	Based on future outcome of patient	Engel, von Korff & Katon (1996), Dionne et al. (1997) Linton & Hallden (1998)	Örebro Musculoskeletal Pain Screening Questionnaire (OMPSQ)
	Patho-mechanical	Levels of physical activity/inactivity  Loading postures & repetitive movements  Exposure to whole body vibration Ergonomic & environmental factors	Newcomer & Sinaki (1996) Pope & Hansen (1992) Adams et al. (1999) Nachemson (1999) McGill (2004) Abenhaim et al. (2000)	Anthropometry Work station & work posture assessment (OWAS)
	Neuro-physiological	Peripheral, spinal cord and central pain mechanisms  Complex biochemical & neuro-modulation changes at spinal cord and cortical levels	Flor and Turk (1984) Moseley (2003) Wright & Zusman (2004) Wand & O'Connell (2008) Vicenzino et al. (1998)	Anaesthetic Injections Functional MRI Proxy measures of SNS function EEG & EMG
	Psychosocial	Descending cortical Pain modulation Cortical and cognitive up-regulation and attention	Linton (2000) Zusman (2002) Moseley et al. (2007)	Fear-Avoidance questionnaire (FABQ) Health Anxiety and Depression questionnaire
Multi-dimensional	Stage, patho-anatomical, signs & symptoms, psychosocial (biopsychosocial)	Quebec Task Force Classification (QTFC) Based on stage of disorder (acute, sub-acute or chronic), patho-anatomical diagnosis (+/- 'red' flags), signs & symptoms, 'yellow' flags & work status	Spitzer, Leblanc and Dupuis (1987) Linton & Hallden (1998)	QTFC questionnaire Örebro Musculoskeletal Pain Screening Questionnaire (OMPSQ)
	Motor control & movement impairment	Chronic pain disorders, patho-anatomical diagnosis (tissue injury, pain, motor response), patho-mechanical impairment, neurophysiological changes (sympathetically maintained & centrally mediated pain), mal-adaptive coping strategies, fear & avoidance beliefs	O'Sullivan (2005) Childs et al. (2004) Richardson & Jull (1995), Sahrmann (2001)	OMPSQ

**Table 2:** The Activity-Related Quebec Task Force Classification System for Spinal Disorders

Classification	Symptoms	Duration of Symptoms	Working Status at time of evaluation		
1	Pain without radiation	a = < 7 days b = 7 days to 7 weeks c = > 7 weeks	W = Working I = Idle		
2	Pain + radiation to extremity (proximally)				
3	Pain + radiation to extremity (distally)				
4	Pain + radiation to extremity (neurologic signs)				
5	Presumptive spinal nerve compression on X-ray (instability or fracture)				
6	Spinal nerve root compression confirmed by myelography, CT or MRI scan				
7	Spinal stenosis				
8	Postsurgical status			1-6 months after intervention	
9	Postsurgical status 9.1. Asymptomatic 9.2. Symptomatic			> 6 months after intervention	
10	Chronic pain syndrome				W = Working I = Idle
11	Other diagnoses				

(Adapted from Spitzer, Leblanc and Dupuis, 1987)

The classification of LBP has been proposed as a research (and clinical) priority (Ford et al., 2007) due to the possible confounding effects of sample heterogeneity on effect sizes for outcome studies investigating treatment efficacy however, considerable variability exists in the literature on the classification of LBP (Petersen, 1999; Riddle, 1998; Ford et al., 2007). Published classification systems vary in their purpose and in their selection of dimensions, categories and criteria. Furthermore, Ford et al., (2007) identified that this variability is also inherent in the recommended methodology for developing and validating LBP classification systems (Fairbank and Pynsent, 1992; Deyo et al., 1994 and Bogduk, 1997).

Current approaches or models used for the diagnosis and classification of LBP are largely uni-dimensional however, in the last decade there has been greater acceptance of the multi-dimensionality of LBP (and in particular chronic LBP) and newer models are



now being introduced in classification systems to explicate the historical difficulties of identifying and recruiting homogeneous subgroups for research trials and avoid the problems of sample heterogeneity that have hampered research and limited assimilation of findings into evidence-based practice (Fritz and George, 2000).

Previously displayed within the text of Table 1 (modified from O’Sullivan, 2005) summarises the key approaches used to classify LBP patients’. The limitations of all classification systems, and particularly the uni-dimensional categories, are that no single system has sufficient evidence to support clinical and research use (Ford et al., 2007). The traditional medical (and physiotherapeutic) approach to diagnosis of LBP has been from a patho-anatomical perspective (Nachemson, 1999) with a systematically investigative process of hypothetico-deductive reasoning (and radiographic “evidence”) that leads the clinician to a potential source of the symptoms (e.g. joint degeneration, disc prolapse with or without associated nerve pain) and therein guides management. However, as Nachemson (1999) conceded, many ‘abnormal’ (radiographic) findings are also commonly observed in pain-free populations and patho-anatomical findings correlate poorly with levels of pain and disability therefore limiting the universal applicability of this system, particularly with chronic LBP.

The signs and symptoms classification was originally advocated in the 1980’s by McKenzie (1981 and 2000) and Maitland (1986). This classification system sought to detail the patients area, behaviour and nature of pain, to determine impairments in spinal movement and function, palpate changes in segmental mobility (hyper and hypomobility), as well as recording pain responses to mechanical stress (provocation testing) and the effects of repetitive movement on pain behaviour (peripheralisation and centralisation). Evidence for the efficacy of this classification approach for the management of LBP remains limited (Maher, Latimer and Refshauge, 1999; Bogduk,

2004) although Elvey and O'Sullivan (2004) contended that this may well be due to limitations in published research designs and a lack of appreciation of the biopsychosocial (multi-dimensional) nature of chronic sub-groups of LBP populations.

Prognostic classification systems are based on the future outcomes of the patient (Engel, von Korff and Katon, 1996; Dionne et al., 1997) but have limited use for the selection of treatment of management options. Dankaerts et al., (2006) argued that a poor prognosis might occur simply because an appropriate treatment that might otherwise have addressed the cause has not been applied (e.g. the lack of availability of a qualified manipulative therapists or an acupuncturist).

Patho-mechanical classification system (also known as the mechanical loading model – O'Sullivan, 2005) is associated with mechanical factors that are reported to be associated with the initial development of LBP and are frequently reported to contribute to the recurrence and exacerbation of LBP. Factors within this dimension include; sustained and loaded postures and movements, exposure to whole body vibration, repetitive loading tasks as well as sudden and repeated spinal loading associated with sports or manual work (Adams et al., 1999; Nachemson, 1999; McGill, 2004). McGill (2004) also identified the additional influence of ergonomic and environmental factors (e.g. seating and work place design) as well as anthropometric considerations that might cause ongoing peripheral nociceptor sensitization. See figure 1 for more details of O'Sullivan's model.

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Since the 1980's there has been a growing interest within the physiotherapy literature of the involvement of the nervous system in pain disorders with a growing body of knowledge that documents the complex biochemical and neuro-modulation changes that occur in the periphery, the autonomic nervous system as well as at spinal cord and cortical levels (Flor and Turk, 1984; Flor et al., 1997; Vicenzino et al., 1995 and 2001; Moseley, 2003; Wright and Zusman, 2004; Bialosky et al., 2008 and 2009). This has resulted in the 'neuro-physiological' classification system that asserts that pain can be generated and maintained at a peripheral level, as well as centrally at both spinal cord and cortical levels. Central sensitisation of pain can occur secondary to sustained peripheral nociceptive input resulting in changes at spinal cord and cortical levels (Zusman, 2002; Wand and O'Connell, 2008).

Recent advancements in the understanding of the changes that can occur within the nervous system and associated cortical 'adaptations' have resulted in the development of psychological, social and cognitive approaches to the management of LBP patients (Linton, 2000; Zusman, 2002; Woby et al., 2004). Mal-adaptive coping strategies (Linton, 2000), social and work factors can all reinforce psychological factors that can increase the central drive of pain and whilst the debate continues as to whether these factors are a predisposition or a result of a pain disorder there is evidence that cognitive behavioural interventions are effective in reducing disability within sub-groups of chronic LBP populations (Woby et al., 2004, Moseley, 2007, O'Sullivan et al., 2012).

Multi-dimensional classification systems of LBP have been advocated by a number of authors (Elvey and O'Sullivan, 2004; McCarthy et al., 2004; O'Sullivan, 2005; Dankaerts et al., 2006 and Ford et al., 2007). O'Sullivan (2005) stated that the role of the treating clinician is to consider all dimensions of the disorder based on an interview, thorough physical examination combined with a review of any medical and radiological tests as

well as appropriately selected (reliable and valid) screening questionnaires in order to determine the dominance and relationship of factors with the purpose of guiding management and predicting prognosis (Elvey and O'Sullivan, 2004).

It would seem that the requirements of an appropriate classification system is that it should have a comprehensive set of dimensions that adequately describe the complex nature of LBP however, these rudiments are not currently being met within the literature and no single classification system has sufficient evidence to support clinical and research use (Petersen, 1999; Riddle, 1998; Nachemson, Gunnar and Andersson, 1982; Ford et al., 2007). O'Sullivan (2005) proposed a mechanism based classification system derived from a biopsychosocial perspective for use with chronic LBP patients (see figure 1 for details) that acknowledges the multi-dimensionality and diversity of presentation within this population. O'Sullivan's (2005) model proposed three broad sub-groups of patients within his classification system;

- 1) *Adaptive movement and/or motor impairment disorders (with the presence of an underlying pathological process e.g. disc prolapse, stenosis with associated radicular pain +/- neurological deficit, spondylolithesis) that are driven by patho-anatomical processes and responsive to specifically targeted management,*
- 2) *Mal-adaptive movement impairment disorder where the dominant drive of the pain is from the forebrain and is secondary to psychosocial factors it is therefore inconsistent and non-mechanical (results in disordered movement and motor control impairments),*
- 3) *Mal-adaptive movement or motor impairment disorders with associated faulty coping strategies result in abnormal tissue loading (associated with either excessive or reduced segmental spinal stability).*

O'Sullivan's (2005) classification system has received some positive reviews with a number of researchers providing nascent evidence of its reliability (Dankaerts et al., 2006 and 2007; Fersum et al., 2009).

Whilst research into the classification of chronic LBP provides its own challenges, a number of researchers have argued that these classification systems lack construct validity within the acute and sub-acute patient populations (Paatelma, Karvonen and Heinonen, 2009). Paatelma, Karvonen and Heinonen (2009) conducted a pilot study to investigate the reliability of a treatment based classification (TBC) system (that classified patients in accordance with a patho-anatomical/patho-physiological/tissue origin classification system) on patients with LBP. Whilst they found the TBC system reliable within acute and sub-acute patients, they suggested that the complexity of chronic LBP patients (with higher levels of distress and disability) resulted in a lack of effectiveness in improving important outcomes.

Wand and O'Connell (2008) suggested that the disappointing results, of clinical research into sub-grouping of NSLBP, requires an alternative perspective regarding classification systems and management strategies. They contested that patients whose condition is considered chronic will exhibit different signs, symptoms and behaviours to those whose condition is sub-acute or acute, and that different mechanisms may be occurring in the acute and sub-acute populations because mal-adaptive individualisation of response to the underlying problem/condition (as seen in chronic LBP patients) has yet to materialize at a conscious or sub-conscious/cortical level. Furthermore, Wand and O'Connell (2008) observed that the research into the sub-grouping of acute LBP patients allowed the successful prediction of outcomes to manipulation (Flynn et al., 2002; Childs et al., 2004) and stability training (Hicks et al., 2005; Fritz, Whitman and Childs, 2005), a phenomenon that has yet to prove successful within a chronic LBP patient population. Wand and O'Connell (2008) implied that with prolonged exposure to LBP, there may be a transition period (from acute to chronic – possibly within the 'sub-acute' period) whereby the patho-mechanical, patho-anatomical and signs/symptoms

clustering of an acute LBP presentation may be superseded by cortical reorganisation, motor control changes and dorsolateral prefrontal cortex degeneration. They speculated that the reason for the relative lack of success of sub-classification systems, treatment outcomes and clinical prediction rules in chronic LBP patients may reflect a therapeutic void in appropriate 'brain-training' and normalisation of neurological processing.

In summary, within the literature there remains controversy within the field of classification systems for LBP patients. Whilst some authors advocate their use within acute and sub-acute sub-groups of patients, there is greater diversity of opinion regarding their use within a chronic LBP patient population, indeed, a number of authors suggest that this group should be further divided into smaller factions and classified within a biopsychosocial or cortical-reorganisation model. One area of agreement is that classification systems have an important role in the advancement and the reporting of clinical practice and research, in the provision of guidance for targeted interventions and the prediction of therapeutic outcome. Within the final clinical study of this thesis, the QTFC system was utilised for comparative purposes (classification levels 1-4) and due to its ease of application within the clinical setting, its accepted multidimensionality and its recognised validation within published research forums.

### **2.2.2. Clinical Guidelines**

Clinical guidelines have been defined as “systematically developed statements to assist practitioners and patients decisions about appropriate health care for specific clinical circumstances” (Field and Lohr, 1990: 38). The main aim of clinical guidelines is to “improve the quality of care received by patients” (Woolf, 1999) and attempt to utilize an evidence-informed strategy, together with professional consensus, in order to inform clinical reasoning for assessment and treatment.

Care for LBP is fragmented with patients seeking care from GP’s, other primary and secondary care settings, pharmacists, independent allied healthcare practitioners or not at all. Differences in the training, education and scope of practice of these providers have lead to the heterogeneity observed in the management of LBP (Koes et al., 2001; Haldeman and Dagenais, 2008). In an ideal world, all providers involved in managing LBP should be guided by the methodologically best available scientific evidence in order to minimize the ineffectiveness, cost and potential harm of procedures. Clinical guidelines endeavour to locate, evaluate, synthesize and summarise the evidence thus making the practice of evidence-based practice accessible to all.

Clinical guidelines have a number of advantages; they can identify which interventions are unsupported by clinical research and, therefore, may be dangerous, or at best, ineffective for the patient; they also are able to clarify those interventions that have a research base to support their effectiveness thereby “reducing morbidity and mortality and improving quality of life” (Woolf, 1999). However, methods for developing guidelines are not yet standardized, which may impact the perceived validity of the recommendations. Koes et al., (2001), van Tulder et al., (2004) and Arnau et al., (2006) reported that although guideline recommendations were similar, discrepancies were



noted regarding the use of medication, spinal manipulation therapy (SMT), exercise and patient education.

Woolf (1999) advised that guidelines may be harmful to both patients and health care professionals as research and evidence can often be lacking, misleading or misinterpreted and therefore, compromise the quality of care received. Indeed, Woolf (1999) warns that guidelines have the potential to take away a healthcare professionals ability to be an autonomous practitioner by providing limited recommendations for treatment and devalue the clinically reasoned decision making processes required for individually tailored treatment prescription.

Internationally, a number of clinical practice guidelines related to the specific assessment and management of LBP have been published since the turn of the millennium and although the methods for conducting the process have varied, most have been considered to be of high methodological quality (despite some relying heavily on systematic reviews for quality assessments, with the potential of bias in the overstatement of objectivity of this process), have consisted of multidisciplinary professionals and had similar recommendations (Dagenais, Tricco and Haldeman, 2010). Pillastrini et al.'s (2011) international review of guidelines for LBP management recognised the high quality of both of the UK guideline publications (CSP 2006 and NICE, 2009) ranking them in the top three guidelines alongside the Canadian TOP program (TOP, 2009). Pillastrini et al., (2011) indicated that the average quality of the guidelines studied in their review had improved in the last 10 years and are increasingly aligned in their provision of therapeutic recommendations, however, their review was focused on chronic LBP and within primary care and may lack external validity to the management of acute and sub-acute LBP and to the secondary care environment.

Of the reviews considered within the current literature review, six guidelines discussed the management of acute LBP, six discussed Chronic LBP management and six considered LBP with substantial neurological involvement. At all stages, advice to stay active, education and SMT were recommended with different pharmaceutical recommendations at each stage.

Currently, national (UK) guidelines recommend an initial triage to facilitate effective diagnosis and management of the patients' condition (NICE, 2009). This process allows the clinician to differentiate between spinal pathology (and 'red flag' presentations), nerve root pain and specific or non-specific low back pain (NSLBP) in the "early treatment and management of persistent or recurrent LBP". The NICE guidelines (2009) define "persistent or recurrent NSLBP" as pain that has "lasted for more than 6 weeks, but for less than 12 months". The principles of management within the NICE guidelines (2009) care pathway fall into 4 key areas; 1) diagnostic triage and review, 2) promotion of self management (advice and education on the nature of NSLBP, encourage normal activities, exercise and return to work), 3) prescription of appropriate drug treatment for pain management (first-line treatment is paracetamol, which if unsuccessful may include a progressive cascade to NSAID's or weak opioids, tricyclic antidepressants and finally strong opioids), 4) specific treatments lasting up to 12 weeks (a structured exercise programme of up to 8 sessions, or up to 9 sessions of manual therapy including spinal manipulation, or up to 10 sessions of acupuncture needling). In the event of a poor outcome or unsatisfactory improvement then the pathway guides the clinician to consider a combined physical and psychological treatment programme (up to 8 weeks of 100 hours of cognitive behavioural therapy and exercise). In the event of the pain lasting more than 1 year then an orthopaedic surgical opinion may be sought. The NICE guidelines (2009) are the only ones that suggest specific parameters for some of the

recommended interventions for chronic LBP, although, the evidence upon which these were made is unclear. However, Dagenais, Tricco and Haldeman (2010) applauded this strategy and advised the adoption of parameter setting to facilitate the modification of the clinical approach and/or patient expectations when measurable outcomes fail to improve. A key issue with the current guidelines, which is becoming increasingly recognised, is the apparent delay in the publication of treatment guidelines (in particular the use of manipulation techniques) and their actualisation into current practice. Although it is recognised that the publication of the NICE guidelines (2009) is a recent event, it is well-known that manipulative treatment for the management of LBP among physiotherapists is limited with Foster et al., (1999) indicating that only a 3% of her therapists reported using manipulative techniques, with Jackson (2001) and Gracey et al., (2002) recording only a 5% usage. Clearly, these surveys were conducted over a decade ago and more up-to-date information might provide better insight into clinical practice, however, the lack of empirical evidence into its direct relationship to PROM's inhibits clinical decision-making.

Despite the strong recommendation that clinicians evaluate the severity of symptoms and functional limitations of patients, it was apparent that none of the papers offered guidance on choices of specific outcome measures that might accomplish this purpose. Ostelo and de Vet (2005) outlined clinically important and validated instruments to assess pain (e.g. Visual Analogue Scale, or the Numeric Pain Rating Scale) and there are numerous other instruments available to measure physical function or disability specific to LBP (e.g. the Oswestry Disability Index and the Roland Morris Disability Questionnaire) some of which have been successfully translated and validated within other cultures and have the benefit of having the Minimum Clinically Important Difference (MCID) established for LBP which have been reported to correspond to

improvements (on the instruments scale) of between 25-50%. Despite this wealth of 'evidence', PROM's do not feature in the current guidelines and individual practitioners, practices and departments are left to decide on the outcome measures appropriate for their own patients. Whilst this may have some benefit in a world of diversity/heterogeneity, it may be considered to be an impediment for ongoing clinical research.

### **2.2.3. Clinical Prediction Rules**

Clinical prediction rules (CPR's) are research-based tools that quantify the contributions of relevant patient characteristics to provide statistical/numeric indices that assist clinicians in identifying the combinations of clinical examination findings that can predict a condition or outcome (Fritz et al., 2003; Fritz, 2009; Cook, 2008).

Falk and Fahey (2009) summarise the key elements of CPR's as follows:

*“Clinical prediction rules quantify the contribution of symptoms, clinical signs, and available diagnostic tests, and stratify patients according to the probability of having a target disorder. The outcome of interest can be diverse and be anywhere along the diagnostic, prognostic, and therapeutic spectrum”.*

CPR's have been used to describe the likelihood of the presence or absence of a condition (e.g. the presence of red flags in LBP patients), assist in determining patient prognosis (e.g.. Return to work, full recovery or development of chronic disability), and help the classification of patients for treatment either according to guidelines (e.g. acute, sub-acute or chronic NSLBP/urgent or routine) or according to treatment-based classification systems (e.g. McKenzie classification – McKenzie, 1981; or the movement-impairment classification system – O'Sullivan, 2005).

Paatelma et al., (2009) examined Inter-tester reliability in classifying sub-acute low-back-pain patients, comparing specialist and non-specialist examiners. They observed that;

*“Although a number of LBP classification systems have been proposed, what is still unclear is which clinical tests between assessing clinicians are sufficiently reliable to allow subgroup categorization. The reliability and validity of the overall classification systems has been tested and has been reported as moderate or good”.*

As to the reliability of tests used for placing presentations of low-back pain, into separate groupings, the evidence is variable. Paatelma et al., (2009) summarised the current evidence base as follows;

- 1) Discogenic and sacroiliac joint pain = fair to good,
- 2) Segmental dysfunction/facet pain = poor,
- 3) Clinical lumbar instability = poor to good; and
- 4) Clinical central or lateral stenosis = no reliable clinical tests.

CPR's are an attempt to move away from intuitive guessing about which patient has a particular diagnosis and which will respond to a specific intervention by replacing this with an evidence-informed “list” of characteristics that, through an algorithmic process, result in treatment selection or outcome prognosis. However, successful diagnosis and subsequent sub-grouping of patients by CPR's are subject to biases that affect their validity and application in clinical practice especially within complex situations (Fahey and Van der Lei, 2008; p. 213-236; Reilly and Evans, 2006). Flynn et al., (2002) utilised this heuristic reasoning approach by selecting only 5 criteria for a spinal manipulation CPR in NSLBP patients. Their 5 criteria included; duration of current episode (less than

16 days), extent of symptoms (not distal to the knee), Fear Avoidance Behaviour questionnaire (FABQ) score (of less than 19 points), segmental mobility testing (identifying 1 or more hypo-mobile lumbar segments) and hip range of motion (a loss of more than 35° of internal rotation in one or both hips). Flynn et al., (2002) predicted that patients who had at least 4 out of the 5 CPR's could successfully be predicted to achieve at least 50% improvement in disability (as measured by the Oswestry Disability Index) within 1 week with a maximum of 2 manipulative interventions with a positive likelihood ratio of 24.4. Interestingly, the FABQ has been criticised as lacking credibility within an acute population with symptoms of less than 16 days duration (Williams, 2006) and has reported ceiling effects (Kovac et al., 2006) and the minimum clinically important difference (MCID) level has yet to be identified, although it has been identified as possessing moderate correlates ( $\rho=0.52$ ) with the RMDQ (Williams, 2006).

Childs et al., (2004) conducted a validation study of this CPR and achieved an odds ratio of 60.8 indicating that patients that are positive on the 'rule' and received manipulation had a 92% chance of a successful outcome, with an associated number needed to treat for benefit at 4 weeks of 1.9. These (and other studies by the same authors) are the only published reports of CPR's for NSLBP that correspond to a level II clinical prediction rule as described by McGinn et al., (2002).

Underwood et al., (2007) conducted a secondary data analysis of the UKBEAM (2004) dataset to discover if baseline characteristics of patients could predict response to treatment. They discovered that age, work status, 'pain and disability', 'quality of life' and 'beliefs' at baseline could predict overall outcome however they could not predict response to treatment allocation leading Sweetman (2008) to contest that Underwood et al., (2007) may have had more success if they had selected physical examination characteristics for baseline levels. Burton et al., (2004) were able to predict outcomes in

chronic LBP patients receiving osteopathic manipulation. Similar to the findings of Von Korff et al., (1993) and Thomas et al., (1999), they discovered that patients with a history of back pain (at baseline and prior to treatment) in excess of 3 weeks were more likely to have recurrent pain at 1 and 4 year follow ups (55% compared to 14% with acute LBP). The same was true for patients presenting with leg pain, and high fear-avoidance beliefs and the presence of depressive symptoms. Contrary to Sweetmans' comments, Burton et al., (2004) also revealed that 'standard clinical examination data' were unhelpful in the prediction of recurrence or long-term disability.

Hancock et al., (2009) focused on the predictive capacity of a CPR on acute LBP patients. The primary aim of the study was to develop a CPR to allow clinicians to identify the recovery rates of acute LBP patients. They revealed that 3 prognostic factors (baseline pain, duration of current episode and number of previous episodes) were able to differentiate between quick (baseline pain  $\leq 7/10$ ; duration  $\leq 5$  days; previous episodes  $\leq 1$ ) and slow recoverers. Patients fitting the "quick" recovery CPR were 3.5 times more likely to be recovered at any point than patients without the CPR characteristics. A limitation of this study was the small number of patients that were finally analysed within the different strata of the CPR (42 out of the total population of 239 = 17.5%) which might inherently bias any CPR identified.

CPR studies have been frequently criticised within the physiotherapy literature for demonstrating poor methodological quality. Typical areas of concern include a lack of blinding of outcome assessors or treating therapists, a lack of homogeneity within sample populations, small sample sizes, an insufficient follow-up period and, a lack of an assessment of potential psychosocial prognostic factors (Beneciuk, Bishop and George, 2009). The lack of further validation of CPR's within similar and different LBP populations is also a major limitation in the use of CPR's for the variety of clinical

settings that therapists are employed. Kent and Keating (2008) conducted a systematic review investigating the prognostic factors for a predictive rule for poor outcome in patients with recent-onset NSLBP. Their findings were inconclusive due to poor, diverse and disparate methodological quality in the literature reviewed and they recommended strategies for future prognostic research in order to rectify this problem within future reviews. More recently, the development (Hill et al., 2008 and Hay et al., 2008) and subsequent validation (Hill et al., 2010), in the primary care setting, of the STarTBack screening tool for the sub-grouping of people with LBP, has received acclaim. The tool provides a means of identifying prognostic factors indicating an increased risk of poor outcome thereby allowing subsequent treatment to be targeted towards factors that are modifiable (Jones et al., 2006; Koes and van Tulder 2006 and Hilfiker et al., 2007). Fritz, Beneciuk and George (2011) attempted to assess the use of the tool, within a number of American physical therapy clinics, as a means of describing patterns of change in clinical outcomes of a case series of 214 LBP patients. Outcome measures included the 0-10 point narrative pain rating score (NPRS) and the Oswestry Disability Index (ODI) with low, medium and high risk categories identified using the STarTBack tool. Although the authors found conflicting results to those of Hill et al., (2008 and 2010) and Hay et al., (2008) regarding sub-group classification and outcome, Fritz, Beneciuk and George (2011) did agree that the STaRTBack Tool may, when combined with their own CRP, provide important prognostic information for physical therapists, however, they conceded that further research is required to ascertain its use in providing guidance for appropriate treatment selection particularly as the majority of patients tend to fall into the medium risk category.

Fritz (2009) cautioned that while useful as part of decision making, CPR's should not replace clinical judgement – and should be seen as complementary to that process –



which needs to involve experience, clinical opinion, and intuition as well as research evidence. CPR's use quantitative methods to build upon the body of literature and expert opinion and can provide quick and inexpensive estimates of probability. Clinical prediction rules can be of great value to assist clinical decision making but should not be used indiscriminately (Fritz, 2009). Falk and Fahey (2009) advised that the development of valid clinical prediction rules should be a goal of physiotherapy research. Furthermore, specific areas in need of attention include deriving and validating CPR's to identify patients for treatments that are likely to result in substantially different outcomes in heterogeneous groups of patients (CSP, 2002). Within the field of physiotherapy and NSLBP, the majority of CPR-related research has focused on prediction of treatment response and, as Fritz (2009) argued, this is the best context in which to develop CPR's where the nature of the condition (NSLBP) is heterogeneous, with several viable yet discrete treatment approaches which result in complexities in the process of clinical decision making especially when the presumption that sub-groups within the population exist. Fritz (2009) claimed that CPR's within this context have the potential to improve the efficiency and effectiveness of clinical care, however, for true objectivity, in the absence of bias, the subjective nature of currently utilised PROM's should be recognised.

### **2.3. Outcome Measures and measures of clinical and statistical benefits**

According to Copay et al., (2010) health-related quality of life measures are the primary assessment tools for spinal treatments because they have established validity and reliability (McDowell and Newell, 1996) however, outcome scores do not always translate into meaningful clinical changes or benefits in patients lives or 'recovery' (Hush et al., 2010) and are not always transferrable from one population to another. Nevertheless, patient-reported outcome measures (PROM's) are widely used and accepted both clinically and academically as key tools for measurement of patient responses to treatment.

The term minimal important clinical difference (MCID) was first described by Jaeschke et al., (1989) who argued that although statistically significant changes often occurred in instruments measuring change after intervention, in some cases the significant change reported lacked clinical significance. Thus, their operational definition of a MCID was forged;

*“... The smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management.”*

Jaeschke et al.'s, (1989) definition involved two constructs; 1) a minimal amount of patient reported change and 2) something significant enough to change patient management. At the heart of this measure is the patients' perception of what is meaningful change to them.

Since Jaescheke et al.'s, (1989) development of the MCID a number of measures have been identified that mimic MCID's, notably the MID (minimally important difference), MCD (minimal clinical difference), or the MCSD (minimal clinically

significant difference). Although similar sounding, these terms vary in meaning and typically involve change values beyond the variations of the instrument. At present, there is no standard as to how to calculate MCID's, and this has resulted in a lack of clarity concerning the true interpretation of clinical, patient change. This is confounded by the fact that PROM's are, essentially, subjective in nature and can vary according to the health and patho-anatomical presentation of the patient (e.g. LBP with and without radiating symptoms or neurological dysfunction, or age, socioeconomic status and duration of symptoms). Cook (2008) supported Norman, Stratford, and Regehr's (1997) argument, making a case for the development of CPR's by suggesting that whilst MCID's and PROM's are a valuable tool for assessing patients perceptions of the benefits of therapy, more objective measures should be nurtured to "define a new line of inquiry... where attributes of patients that are related to the likelihood of responding positively are prognostically stratified into responsive and stable groups".

Measurement of the effect of physiotherapy (and MT techniques) on the SNS (and in particular, SC changes, could provide an important, objective measure of "effect" beyond the constraints of PROM's. However, meaningful representation of effect or "benefit" requires that, in the first instance, an assessment, statistically, of the reliability (and stability) of the measurement is performed. For this, a number of methods (calculations) can be utilised. Classically, the intraclass correlation coefficient (ICC), standard error of measurement (SEM) and the smallest real difference (SRD) are used to establish the variability, repeatability and the stability of a measure (discussed further in chapter 3) although these calculations only provide a statistical construct of significant effect rather than clinical measures of perceived improvement.

The restoration of 'normal' function and relief of pain and symptoms are key outcomes for physiotherapy and rehabilitation. Traditionally, subjective patient-reported outcome

measures (PROM's) have been utilised to assess function and monitor changes over time. The World Health Organisation's (WHO) International Classification of Functioning, Disability and Health [ICIDH-2] report defines 'activity limitations' as

*“difficulties an individual may have in executing activities” (ICIDH-2, 2000).*

Symptoms and impairments such as reduced range of movement and a restricted straight-leg raise are observable by therapists however, direct observation of activity levels and limitation is less practical and is better assessed by PROM's as these can more accurately gauge the impact of LBP and symptoms on functional daily activities.

Validated, standardised patient-reported questionnaires are a convenient method of collecting and synthesising large amounts of information on activity limitations (Delitto, 1994; Beattie and Maher, 1997) although until the study by Davidson and Keating (2002) few had been conducted specifically on physiotherapy patient populations. Nonetheless, since the late 1990's and the advent and incorporation of evidence-based practice (Sackett et al., 1996), both primary and secondary care physiotherapy departments have incorporated validated PROM's as a means of documenting and auditing patients responses to treatment and have become everyday tools for monitoring patient treatment responses. Within the Hospital setting of the current clinical study (University Hospitals of Leicester NHS Trust – Leicester Royal Infirmary Site), both the Oswestry Disability Index (ODI) and the Roland Morris Disability Questionnaire (RMDQ) are utilized with LBP patients (at inception and discharge) alongside the verbal/narrative pain rating scale (NPRS) which is used within and between all patient treatments. The NPRS is used to establish changes in symptoms (pain intensity) during and between treatment episodes and the ODI and RMDQ are used to assess functional limitation. Additionally, the ODI has been used to assess

outcomes to specific treatments in the CPR developed by Fritz et al. (2002) and Childs et al., (2004) with the establishment of a change score, at discharge, of 50% (or more) indicating a positive outcome. Consequently, these PROM's were the secondary outcome measures for the clinical study (skin conductance activity levels and responses being the primary OM's).

Allocating a search strategy incorporating the key terms for ODI, RMDQ and NPRS, the following 'hits' in the published literature (up to October 2011) were identified; the ODI (more than 735 titles); pain rating scales (VAS – in excess of 1075 titles; NPRS – in excess of 1025 titles) and the RMDQ (more than 335 titles). These three PROM's were the most widely used further supporting their selection within the clinical study, with documented evidence of reliability and validity. Since this literature search, Goertz et al., (2012) have published a systematic study specifically focusing on PROM's for HVLAT for LBP, namely VAS, NPRS, RMDQ and ODI. Goertz et al., (2012) concluded that heterogeneity and inconsistencies in reporting restricted their ability to report definitive findings, however they did concur with Hush et al., (2010) and Pransky et al., (2011) that assessment of the functional capacity of patients may be of greater clinical value than assessing reported pain levels, but that new measures of outcome are warranted for future clinical trials.

### **2.3.1. The Oswestry Disability Index (ODI)**

The Oswestry Disability Index (ODI) is a condition/disease specific (LBP) patient reported outcome measure that was first developed in 1976 and originally published in 1980 by Fairbank et al., and has been widely used within healthcare. Individual items on the index were selected based on the experience of the scale's developers and were pilot tested in a sample of 25 patients. The questionnaire requires only 5 minutes

to complete and 1 minute to score and consists of 10 items addressing different aspects of function. Each item is scored from 0 to 5, with higher values representing greater disability (giving a potential total score of  $10 \times 5 = 50$ ). The total score is divided by the highest possible score (accounting for questions that are purposely omitted by the patient; e.g. 'sex life') and multiplied by 100 to produce a percentage score (0-100%).

Various versions and modifications have been made to the original ODI (Version 1.0) which was modified by Baker et al., (1989) who removed references to medication from the 'pain' and 'sleeping' items, thereby improving the relevance of these items to people not taking medication (ODI Version 2.0). Fairbank and Pynsent (2000) further modified the 'travel' section to produce Version 2.1. Other modifications have occurred by various spine societies and Hudson-Cook et al., (1989) replaced 'sex life' with a new item called 'changing degree of pain' however, this version and other modifications have been highly criticised as they are considered to be conceptually different from the other items.

Davidson (2007) conducted a Rasch analysis of three versions of the ODI. Their findings suggested that the original (version 1.0) and second version (Version 2.0) provided adequate to good construct validity but a third version described by Hudson-Cook et al. (1989) was found to have inferior construct validity. The original Version 1.0 was the ODI utilized in the clinical research of this thesis.

High test-retest reliability coefficients have been reported for the ODI (Versions 1.0 and 2.0) with Fairbank et al. (1980) reporting a value of  $r=0.99$  over 24 hours, and Baker, Pynsent and Fairbank (1989, p. 174-186) finding a value of  $r=0.83$  (Versions

1.0 and 2.0) for the same-day test-retest. Kopec et al. (1995) reported the absolute ICC=0.94.

Validity is the ability of the questionnaire to measure what it is designed to measure (Huck, 2007; p. 75-76). Clinically therefore, it must accurately measure the persons disability and participation in day-to-day activities due to LBP. The effect size measures the practical significance associated with the strength between two variables (<0.2 = small effect size, 0.5 moderate, >0.8 large effect size). Childs and Piva (2005) reported the effect sizes ranging from 1.97 at 1 week to 2.53 at 4 weeks. Fritz and Irrgang (2001) found the the effect size in their study to be 1.12 while Müller et al. (2004) reported floor effects but no known ceiling effects on ODI (version 2.0). Fairbank and Pynsent (2000) revealed that the ODI (Version 1.0) correlated with the RMDQ (n=500, r=0.77) and Roland and Fairbank (2000) revealed 'moderate validity' with VAS (p=0.62) for ODI (version 2.0) with an effect size of 0.8.

A number of authors have recorded responsiveness of the ODI however there seems to be little overall consensus regarding the Minimal Clinically Important Difference (MCID) levels reported. Jaeschke et al., (1989) was the first to define the concept of MCID as 'the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in patient's management'. In their review, MCID represents the smallest difference in the score of an outcome measure that a patient perceives as important. (Jaeschke et al., 1989; Stratford et al., 1998; Finch et al., 2002:271).

Beurskens, de Vet and Köke (1996) were the first to report a MCID for ODI of 4-10 points (NSLBP patients) findings that mirrored those of Resnik and Dobrykowski

(2005). Similar results, but a small band-width, were published by Fritz and Irrgang (2001) with a MCID of 4-6 points (acute LBP patients) and by Childs and Piva (2005) who's MCID=9. Davidson and Keating (2001) reported much higher levels with a MCID of 10.5-15 with Muller et al., (2004) reporting a MCID of 16 (version 2.0). More recently, Goertz et al., (2012), in their systematic review of PROM's in HVLAT treatment for LBP reported within-group MCID's of 6-10% with ranges in scores, for a manipulation only treatment group, in the order of 5-20%. Interestingly, for groups that received a combination of manipulation plus "other therapies" the range was much higher (5-35.6%) indicating the need to consider utilising different levels of MCID's for complex/multiple treatments approaches.

Dwokin et al.'s, (2005) consensus based decision suggested a 30% reduction from baseline to define the MCID of self-reported back pain measures. Ostelo et al., (2008) proposed that the MCID level of improvement for the ODI should also correspond to a 30% improvement (for example, a patient assessed at baseline with an ODI=20 points or 40% functional disability, would need to improve by 6 points to achieve a minimum improvement in function of 30%) however, these authors did not differentiate between single treatment and multiple treatment responses.

Fritz et al., (2009) looked beyond MCID and argued that for conditions such as LBP that have a 'favourable' short-term prognosis the minimum amount of change in a quality of life measure that is either detectable or important may not be sufficiently stringent to measure treatment "success" within a simple/binary construct. Indeed, a threshold MCID for ODI of 6 may be too easily achieved to be useful for distinguishing effectiveness of treatment from the natural tendency towards improvement. Fritz et al., (2009) argued using a threshold criterion of at least 50% improvement on the ODI to define success and they validated this threshold on a clinical LBP population of 243



subject, finding this threshold to have high sensitivity (0.84; 95% CI: 0.79, 0.88) and specificity (0.89; 95% CI: 0.85, 0.93). Bearing all these considerations in mind, it was decided that for the clinical study, an ODI change score (from initial assessment to final discharge) of greater than 50% would be the target MCID.

### **2.3.3. The Roland Morris Disability Questionnaire (RMDQ)**

The RMDQ (also known as the St Thomas' disability questionnaire) is another widely used patient-administered outcome measure of LBP and disability that was developed in 1983. It was originally derived from 24 of the 136 items Sickness Impact Profile (SIP), a generic health measure initially intended for a variety of chronic diseases, with the term 'because of my back pain' added to each item to make it LBP-specific (Gilson et al., 1975 and Bergner et al., 1981). The 24 dichotomous items (questions) describe possible activity restrictions in the present tense caused by back pain and requiring a "yes" or "no" response about activities of daily living. By summing the "yes" answers (1 point each), the range of scores are from 0 (no impairment/disability) to 24 (severe impairment/maximum disability).

The RMDQ primarily measures pain intensity and physical disabilities. There are a number of adapted versions from short form versions (RM-12 and RM-18; Atlas et al., 2003 and Stratford and Binkley, 1997) to a modified version that measures functional limitation over the last 4 weeks rather than just on the day administered (Underwood, Barnett and Vickers, 1999). Within the musculoskeletal literature, more than 300 citations of the use of RMDQ were identified. A number of studies have established the scales' validity (Roland and Morris, 1983) with an internal consistency measure of 0.87 reported by Stratford and Binkley (2000) establishing the scales' construct validity. Reliability has been widely reported with ICC's ranging from 0.79 (Stratford

and Binkley, 2000) to 0.96 (Underwood, Barnett and Vickers, 1999). Sensitivity was reported to be 72% with specificity/responsiveness 82% (Stratford et al., 1998).

Beurskens, de Vet and Koke, (1996) recorded responsiveness at 5 weeks with ROC = 0.93 advising that the RMDQ demonstrated best discrimination between improved and non-improved patients within their cohort study of NSLBP patients. Psychometrically, the RMDQ has been determined to be the most sensitive and appropriate for patients with 'mild to moderate disability' while the ODI is most effective for 'persistent severe disability' (Roland and Fairbank, 2000; and Davies and Nitz, 2009).

Davidson and Keating (2002) compared 5 low back disability questionnaires for their reliability and responsiveness. In contrast to previously reported studies, these authors found the ICC to be markedly lower =0.53 (95%; CI=0.29-0.71). The MCID previously reported by Stratford et al. (1996a and b) of 4-5 points was considered to be too low and the authors suggested (from their data) the MCID for the RMDQ should be set at 8.6-9.5 points and concluded that the RMDQ should not be recommended for use as a measure of functional outcome in a general clinical population as it lacked sufficient reliability and scale width for clinical application. However, it is worthy of note that Davison and Keating (2002) only had very small sample sizes (n=16 and n=47) and it would only take a few patients with unusual variability in scores to skew the reliability data a fact that the authors refer to in a small number of subjects who demonstrated "considerable variability" in RMDQ scores despite reporting 'no change' in their condition. Riddle and Stratford (2002) further opposed Davidson and Keatings' claim contending that the overwhelming majority of evidence supports the use of the RMDQ scale, a stance supported by Deyo, Battié and Beurskens (1998), Bombardier (2000), Kopec (2000) and Davies and Nitz (2009). Goertz et al.'s, (2012) systematic review of PROM's in LBP patients receiving HVLTAT summarised that the within-group MCID for

HVLAT treatments was found to be 2.0-3.5 (range 1.0-22.7) and for treatment involving HVLAT plus “other therapies” the range was (2.5-18.4). Whilst they acknowledged the RMDQ is widely utilised, they also mirrored the findings of Roland and Fairbank (2000) and Davies and Nitz (2009) that its use, particularly in chronic LBP patients (with persistent disability) may result in inconsistencies in interpretation due to the large variability in the range scores highlighted by their review.

Nonetheless, the original 24-Item RMDQ has received the most use and praise within the literature and has been described as providing satisfactory measurement properties for NSLBP patients and resulted in it being recommended by an international group of experts (Bombardier, 2000) for studies into NSLBP.

### **2.3.3. The Narrative Pain Rating Scale (NPRS)**

Despite the fact that pain is often considered to be a measurable physiological event, it is inherently a subjective and personal experience that can range in intensity from slight to agonizing. Pain is often considered to be one of the primary reasons for patients to seek health care advice and for clinicians it is considered a significant outcome measure however, Khorsan et al., (2008) suggested that it should be considered a single component of multiple domains in clinical trials, a sentiment shared by Turk and Dworkin (2004).

Pain rating scales provide a patient-centred, quick and simple way for patients to rate pain intensity and for therapists to observe temporal changes within and between treatment sessions. Typical scales use a written or verbal numeric (e.g., 0-10) or visual (image/100mm line) descriptors to quantify pain between the two extremes. All scales are anchored at each end with a qualifying statement, that is, “0 = No Pain and 10 = the worst pain imaginable” and the patient is asked to select the number that best

represents their intensity of pain. Unlike the VAS, which takes time to complete and analyse but has unlimited possible responses along the line, the NPRS utilises whole numbers and takes seconds to 'administer', is easily translated, inexpensive and capable of being administered over the telephone. Despite these clinical benefits, Flaherty (1996) contended that pain rating scales lack sensitivity and oversimplify the patients' experience of pain by converting pain into a single dimension (intensity).

The validity of NPRS's were originally determined by Downie et al., (1971) and NPRS validity was further established by Bijur, Latimer and Gallagher (2003). Jensen and McFarland (1993) supported these findings and also found the scale to be reliable within subjects. Bolton and Wilkinson (1998) reviewed the scales use amongst chiropractic patients and found it to be clinically responsive and Spadoni et al., (2003) reported an estimate of minimal detectable change at the 90% confidence level ( $MDC_{90}$ ) to be approximately 3-points (27% change) for patients with musculoskeletal problems. More recently, Childs, Piva and Fritz (2005) developed this work by characterising the scales responsiveness within a LBP patient population. In their findings, Childs, Piva and Fritz (2005) declared their confidence that a 2-point (20%) change on the scale represents clinically meaningful change that exceeds the bounds of measurement error for LBP patients. Goertz et al., (2012) in their systematic review of PROM's for HVLAT in LBP trials reported a slightly higher level indicating that for patients receiving this treatment, the within-group MCID for manipulation was 2.5 (range 1.0-2.5) they also compared manipulation NPRS MCID's to literature comparing manipulation plus "other therapies" and documented a within-group MCID range to be higher (2.0-3.3) indicating that studies utilising more than just manipulation as the treatment modality would need to consider the higher MCID level in their analysis of response to treatment.

#### **2.3.4. Minimum clinically important difference (MCID) and the Response-shift Phenomenon**

Controversy exists over what constitutes a 'minimum clinically important difference' (MCID) in terms of PROM's. The various authors have not been able to agree even on the terminology, and some use the term Minimal Important Difference (MID) to represent the concept of 'MCID' (Beaton 2003). Norman, Sloan and Wyrwich (2003) suggest that 0.5 value (50% change) may be considered a universal standard as it is consistently achieved when MCID is divided by standard deviation. However, the issues of measurement of change strongly indicate that the concept of meaningfulness is context-based (Bombardier, Hayden and Beaton 2001). What represents a MCID of an outcome measure can be affected by a number of factors such as whether change between or within individuals is measured, between groups or individuals, and what approach is used to measure change (Bombardier, Hayden and Beaton 2001, Beaton 2003). For instance, Stratford et al., (1998) found that the baseline RMDQ scores can have an effect on the magnitude of responsiveness statistic estimated for patients with low back pain (<6 weeks) i.e., higher baseline RMDQ scores necessitated that a greater amount of change was needed to be considered clinically important change (see table 3; Stratford et al., 1998). However, the results could be influenced by recall bias, and gender can also influence the patient's response to a self-report questionnaire (De Souza et al., 1996, Norman, Stratford and Regehr 1997).

**Table 3: Minimum Clinically Important Difference for Roland-Morris Disability Questionnaire Scores**

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Adapted from Cairns (2002)

Goertz et al., (2012) reported within- and between-group differences, for groups receiving manipulation and manipulation plus “other therapies” that cast doubt on the consistency of PROM’s and of MCID’s with heterogenous populations.

Ceiling and floor effects have also been observed in RMDQ and ODI outcome measures. When compared to ODI scores, a greater proportion of patients scores fall into the top half of the RMDQ score (Kopec et al., 1995). Stratford et al., (1996) found that the MCID for RMDQ ranged between 4-20 points in a 24 item scale. This indicates that RMDQ may not detect improvements in patients with scores less than 4 and deterioration in patients with scores greater than 20. Hence, it is recommended that ODI may be a better choice in populations with higher disability levels, while RMDQ may be more suitable for the general population where the majority may not have higher levels of disability (Bombardier 2000). Furthermore, Gatchel and Mayer (2010) suggest that the recommended 30% improvement in the ODI may not be a valid index and that a 50% improvement, relative to baseline, should be set to identify the MCID in future studies. Theodore (2010) also suggested that an appropriate anchor should not be a subjective assessment but rather an objective external criterion/marker. Glassman and Carreon (2010) contended that this is not currently possible and

proposed that return to work and work retention are the only plausible external criterion for defining MCID although, the National Institutes of Health-funded PROMIS initiative (Gershon et al., 2010) is endeavouring to foster the creation of new measures of both pain and physical functioning. This is particularly relevant as Pransky et al., (2011) suggests that assessment of functional limitations in patients may have greater clinical value than assessing reports of pain intensity.

Schwartz and Finkelstein (2009) have highlighted the fact that patient “response-shift phenomena” can likely significantly affect the measurement properties of a standard PROM from pre-treatment to post-treatment and may account for inconsistencies in patient-reported outcomes after spinal treatments. Response shift bias refers to an error associated with PROM’s which is a threat to the validity of the results (Brown and Burrows 1992: p.13). In simple terms, the changes after treatment intervention lead to a change in participant’s perception of the initial level of functioning, called response-shift bias (Howard 1980: p.94). The concept of functional status is based on patient perceptions of their health status, and could be different for each individual, as some individuals make more demands on themselves than others (Beurskens, De Vet and Koke 1996). Thus, a change in individual’s perceptions after treatment may have influenced their responses to post-treatment PROM’s such as RMDQ and ODI. Schwartz and Finkelstein (2009) suggest that the duration of symptoms may be a factor in the phenomenon as it can influence the mechanism of coping as the patient adapts to their disability. These authors suggest that the affects of the response shift phenomenon may be more relevant when the completed treatment effect is partial rather than total (e.g. in LBP with associated leg pain where outcomes are less favourable) and may account for under-emphasis of the full measurement of treatment outcomes. They advise that consideration of this possible

source of bias will enhance the meaningfulness and interpretability of clinical research data and limit the obfuscation of differences between treatments (Schwartz and Finkelstein, 2009).

### **2.3.5. Summary**

Health-related quality of life measures are important and widely utilised assessment tools for spinal treatments because of their established validity and reliability, however, it is recognised that some outcome scores (e.g. the NPRS) do not always translate into meaningful changes in patients lives and changes in patients perception of their condition, over time, and can result in interventions being universally rejected or to response-shift bias adding to the complexity of interpretation of change. Clearly, a more objective measure of patients' status (i.e. SC activity levels) at inception, and the extent and nature of change (percentage change in SC response), over time, that is not biased by subjective elements and diverse patient-coping mechanisms, could be a useful adjunct to patient assessment and to therapeutic management.

MCID's have been recognised as important benchmarks for improvement in individual patients however, there is little consensus within the literature regarding appropriate targets for LBP patients. For patients undergoing physiotherapy interventions reported targets for the NPRS have been set at 2-3 points on an 11 point scale (Childs, Piva and Fritz, 2005; Farrar et al., 2010 and Goertz et al., 2012); ODI has been suggested to be set at 10.5-15 points out of a possible total of 50 (Davidson and Keating, 2002) or a percentage improvement in score of 50% or more (Fritz et al. 2009) with RMDQ set between 3-13 points (Cairns, 2002). More recently the emphasis has turned towards levels of Significant Clinical Benefit (SCB) rather



than the minimum change indicated by the MCID scores with change levels for NPRS quoted as 2.5 points (Spandoni et al., 2003, Stratford, 2001; Goertz et al. 2012); 19 points for ODI (Davidson and Keating, 2002) and 8.7 for RMDQ (Ostelo et al., 2004) however, these are more reflective of a group mean rather than individual change scores which are considered to be more representative of clinical effect.

Lastly, the reliability of SC measurements (utilising the Biopac data acquisition system) have not been reported. Furthermore, observational data on different populations (healthy normals and symptomatic patients) is lacking, particularly in the lumbar region. Finally, relationships between SCR's and PROM changes following a course of physiotherapeutic intervention are unknown thereby highlighting a knowledge gap in this area of research.

## **2.4. The autonomic nervous system, neurophysiological measurements and pain processing**

The following sub-chapters review the anatomy of the autonomic nervous system (ANS and its divisions) and discuss how ANS responses are currently measured. It continues with an exploration of the mechanism of control of blood vessels and the sudomotor system with a focus on the sympathetic nervous system (SNS) and its cortical, spinal and peripheral connections. Finally, a review of the current concepts that underpin the theories of pain processing are discussed before the following section that explores the effects of manual therapies on SNS activity and SCR's.

### **2.4.1. Anatomical Divisions of the Autonomic Nervous System**

The last two decades have provided some promising insight into the potential capacity of elements of the autonomic nervous system (ANS) to provide an objective measure of

physiological change occurring during complex therapeutic interventions. The following section aims to introduce the reader to the key elements of the ANS and how changes in this system can be captured and linked to current knowledge and concepts underpinning the mechanisms of action of manual therapies.

The ANS controls the internal environment of the body and supplies viscera, glands, smooth muscle and cardiac muscle. It is divided, topographically and anatomically, into two complementary parts – the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). See figure 2 (overleaf). The ANS regulates the internal state of the body and acts, either catabolically (SNS – expending energy; increasing heart rate and shunting blood centrally from the periphery), or anabolically (PNS – conserving energy; slowing heart rate and absorbing nutrition) (Goldberg, 2010, p54-55). These two ‘systems’ leave the central nervous system (CNS) at different sites and usually have opposing effects on the structures they supply through endings that are mainly adrenergic or cholinergic. Within the nervous system, both the somatic and autonomic nervous system function as one unit, with interaction between both systems. Notably, their functioning can be influenced by each other (Benarroch, 2006) with several areas of interaction between the somatic and ANS being purported in the periphery, DH of the spinal cord, brainstem, and forebrain (Zusman 2002).

Like the somatic nervous system, the ANS has afferent, connector and efferent neurones. The afferent impulses originate in the visceral receptors to the CNS. The efferent pathways comprise of pre- and post-ganglionic neurones which form the ganglia which sit outside of the CNS and antero-lateral to the vertebral bodies of the spine from T2 to L4.

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**Figure 2:** A diagram of the efferent paths of the ANS. The parasympathetic pathways are represented by blue and the sympathetic by red lines; the interrupted red lines indicate postganglionic rami to the cranial and spinal nerves.

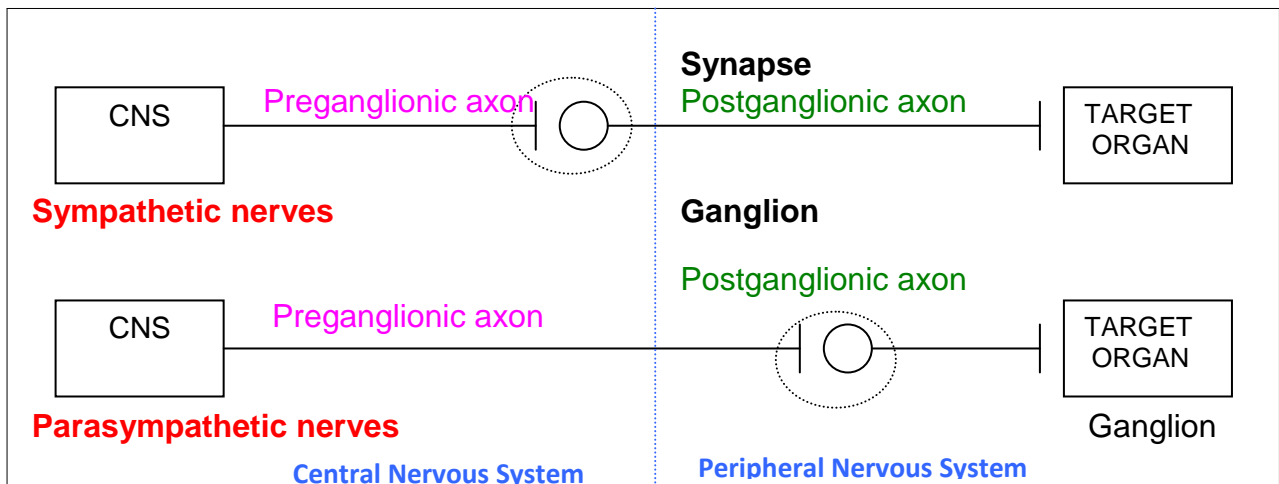
Taken from Williams et al., (1989; p.1154)

Topographically, the PNS and SNS's differ with respect to their connections to the central nervous system. Parasympathetic nerves emerge from the central nervous system in selected cranial (III, VII, IX and X) and sacral (S2 to S4) spinal nerves. Sympathetic axons emerge from the spinal cord in the T1 to L2 spinal nerves. Accordingly, parasympathetic nerves are described as having a craniosacral outflow and sympathetic nerves as having a thoracolumbar outflow.

The SNS is the larger part of the ANS being widely distributed throughout the body. Its function is to prepare the body for an emergency and redistributed the blood to the core and muscles (brain and heart) and from the periphery (skin causing it to sweat) and the gastro-intestinal tract (arresting digestion) (Snell, 2010; p.397). The SNS consists of the efferent nerve fibre pathways (SNS outflow) from the spinal cord, two ganglionated sympathetic trunks, branches, plexuses and regional ganglia.

Anatomically, unlike somatic motor pathways, which have no synapses once leaving the CNS, autonomic motor pathways show synapses within autonomic ganglia, which are aggregates of cell bodies outside the CNS. Thus, an autonomic pathway involves two neurons in series. Axons conveying information from the CNS to such ganglia are called preganglionic axons, and the neurons that form the ganglia and whose axons lead from them to the peripheral target organs are called postganglionic axons (Figure 3).

**Figure 3:** The anatomical similarities and differences between the sympathetic and parasympathetic nervous systems



(Where CNS = central nervous system)

The anatomical difference between the sympathetic and parasympathetic nervous systems is that parasympathetic ganglia lie close to the target organ, while sympathetic ganglia lie some distance away. Consequently, postganglionic parasympathetic fibres may be short, and postganglionic sympathetic fibres are relatively longer. The different locations of ganglia should also be noted, i.e. in the sympathetic division, ganglia lie close to the spinal cord and consist of two chains (sympathetic trunks) (Figure 4)

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(Taken from Palastanga et al., 1994; p.871 with permission)

In contrast, ganglia of the parasympathetic branch lie within or near to the visceral organ that they supply. The SNS, which is the larger division of the ANS, has a much more widespread distribution than the parasympathetic system as it innervates the sweat glands of the skin, the muscles of piloerection, and the muscular walls of many blood vessels. Since sweat gland activity is controlled solely by sympathetic nerve activity, this measurement has been considered as an ideal way to monitor the

autonomic nervous system. Fowles (1974 and 1986) and Venables and Christie (1980) first documented the use of SC (otherwise known as electrodermal activity/response – EDA/R; Galvanic skin response – GSR or skin potential response - SPR) as a means of quantifying and monitoring SNS activity levels and responses to stimuli. Cholinergic stimulation of cutaneous blood vessels in the epidermis, via fibres from the sympathetic nervous system, constitutes the major influence on the production of sweat by these eccrine glands. Thus, it is recognised that the measurement of sweat responses, to therapy, are a valid choice for direct measures of SNS and superior to measures of HR and BP that can be influenced by both the PNS and the SNS thereby making direct changes in SNS activity levels, in accordance to therapy, more complicated. Indeed, Bialosky et al., (2009) have presented a model which identifies several pathways within the peripheral and central nervous system that could explain the effects of manipulation. Within this model, it was suggested that the effects of manipulation either could influence or be influenced by the autonomic nervous system. During a state of central sensitization, there is a corresponding over-activity in the lateral gray matter and an expected increase in sympathetic activity will be present (Sato, 1979 and 1997).

The cell bodies of preganglionic sympathetic neurons are located in the lateral horns of the grey matter in the T1 to L2 segments of the spinal cord. Their axons leave the spinal cord in the ventral roots of the spinal nerves at these same levels. After traversing the spinal nerve, preganglionic sympathetic neurons enter the ventral ramus of the spinal nerve, and just beyond the intervertebral foramen form the white rami communicantes (WRC) (Figure 5).

**Figure 5:** The course of the preganglionic sympathetic axons.  
(Taken from Palastanga et al., 1994; p.873)

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On entering the sympathetic trunk, preganglionic sympathetic neurons terminate or assume an upward or downward course within the trunk. Preganglionic neurons from the WRC, derived from lower thoracic and lumbar WRC tend to pass downwards to lower lumbar and sacral levels within the trunk, before terminating. When they terminate, preganglionic sympathetic neurons do so by synapsing with the cell bodies of postganglionic sympathetic neurons located in the sympathetic ganglia. The axons of the postganglionic sympathetic neurons then leave the sympathetic trunk, or pass upward or downwards within it before leaving.

Of interest in the present series of studies, unlike the WRC (which only exist between T1 and L2 levels), grey rami communicantes (GRC) leave the sympathetic



trunk at all levels, so that every ventral ramus receives a GRC, and importantly for the segmental levels of L3 to S1 only GRC are evident. This is of significance when considering the lumbar plexus, as Williams and Warwick (1980) observed that, occasionally, an interruption of preganglionic fibres occurs in ganglia situated proximal to the sympathetic trunks; these are known as 'intermediate ganglia' and are most numerous on the GRC in the cervical and, more importantly here, the lumbar regions. Harris and Wagnon (1988) described these cervical and lumbar regions as being non-sympathetic, and attribute this fact to their conflicting observations between the sympathetic thoracic region and non-sympathetic cervical and lower lumbar regions.

Once they join the ventral ramus, some of the postganglionic sympathetic neurons assume a short recurrent course to enter the dorsal ramus of the spinal nerve, but the majority pass distally within the ventral ramus. The postganglionic neurons use the course of the dorsal rami and ventral rami to reach their destinations which are principally the blood vessels in the tissues supplied by these rami. These include the blood vessels in any of the muscles or joints supplied by the rami, and any blood vessels in the skin, in the case of those nerves with cutaneous branches. In addition, some postganglionic sympathetic neurons follow the course of cutaneous branches of the somatic nerves to reach sweat glands in the skin and muscles of piloerection. Table 4 summarises the key anatomical, physiological and pharmacological characteristics of the SNS and PNS and Table 5 details the effects that these systems have on some of the key target organs and the current means of recording these effects.

**Table 4: Comparison of the anatomical, physiological and pharmacological characteristics of the two divisions of the ANS.**

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Adapted from Snell (2010, p406)

**Table 5: The effects of ANS on organs of the body & means of detecting response**  
(see Glossary of terms for details of measurement definitions)

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Adapted from Snell (2010, p 407)

#### **2.4.2. Control of Blood Vessels, the Sudomotor System and SNS Activity**

With few exceptions, there is no significant parasympathetic innervation of blood vessels. Indeed, a rich supply of sympathetic postganglionic nerve fibres regulate vasomotor and sudomotor activity making electrodermal measures of sweat activity a valid measure of stimulus response for the SNS.

The efferent postganglionic fibres that pass in the GRC to the spinal nerve supply vasoconstrictor fibres to the blood vessels, secretomotor fibres to the sweat glands and motor fibres to the muscles of piloerection in the areas supplied by the corresponding spinal nerve. Thus most, if not all, peripheral branches derived from the spinal nerves contain postganglionic sympathetic fibres. However, considerable uncertainties exist regarding the sympathetic supply to the lower limb (Williams and Warwick, 1980).

The pelvic section of the sympathetic trunk comprises four or five sacral ganglia and is continuous, proximally, with the lumbar plexus. As mentioned earlier, only GRC pass from the ganglia to the sacral and coccygeal spinal nerves, i.e. no WRC pass to this part of the sympathetic trunk.

Vascular branches from the pelvic sympathetic plexus pass postganglionic fibres to the roots of the sacral plexus, particularly those forming the tibial nerve, to be conveyed to the popliteal artery and its branches in the leg and foot. The preganglionic fibres concerned with supplying the lower limb are derived from the lower three thoracic and upper two or three lumbar segments of the spinal cord, via the white rami which can pass either to the lumbar or, via synapses in the upper two or three sacral ganglia, where postganglionic axons pass to the tibial nerve and its subsequent connections to the lower leg.

Cutaneous fascicles of human peripheral nerves convey post-ganglionic sympathetic axons destined to the blood vessels, sweat glands and hairs. The fibres are involved in thermoregulation, so the skin and core temperatures determine the relative levels of sympathetic activity directed to each set of end-organs (Macefield and Wallin, 1996). Spontaneous and elicited/evoked changes in skin conductance (SC) have been suggested as a measure of neurophysiologic arousal followed by activity in the SNS (Wallin, 1981 and Storm et al., 2000). Storm et al., (2000) concur that SC measurement changes may provide a valid and objective method for evaluating a persons' state of arousal and help detect covert changes that may ordinarily escape subjective evaluation or direct observation. Moreover, these variables have been used to evaluate the reaction to pain and CNS processing dysfunctions (Gutrecht, 1994).

Figure 6: The cerebral origins of the skin conductance response

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Adapted from Patterson, Ungerleider and Bandettini (2002)

The neuroanatomical substrates of neurophysiologic SC activity arousal in humans are not fully understood but it is assumed that it is linked to increased sympathetic activity (Tranel and Damasio, 1994). Tranel and Damasio (1994) found that the brain-stem reticular substance, hypothalamus, premotor cortex, amygdala, hippocampus and the sympathetic preganglions were all actively involved areas in increasing SNS activity (figure 6). Two different types of post-ganglionic sympathetic efferent nerve fibres in the skin have been described; noradrenaline synapses in smooth muscles in the vessels, and fibres with acetylcholine that innervate the sweat glands. SNS activation of palmar and plantar sweat glands, result in increased sweat production that is measurable with SC. The high density of sweat glands in these areas makes this means of measurement highly responsive (Storm et al., 2000). Lim et al., (2003) investigated the sudomotor nerve conduction velocities and central processing times (CPT) of SC responses in the hands and the feet of 30 healthy adults. Their results found that SC amplitudes were greater in the fingers compared to the toes (onset times to electrical stimulation; 1.6 seconds and 2.38 seconds respectively) and they determined that this was due to the higher density (24-30%) of sweat glands in the hands compared to the toes and the fact that the neural outflow volley to the feet has greater dispersal due to increased distance travelled. Central processing times (CPT) for fingers and toes were calculated to be between 141 and 194 ms respectively. Lim et al., (2003) concluded that the comparability of the finger/toe CPT's were that the SC responses in the lower limb had been compensated by faster neural conduction along the small myelinated autonomic efferent fibres in the spinal cord between T6 and L2. These findings were contrary to those of Bach et al., (2010) who found no difference in the test variance between hands and feet and their standard response times but agreed that response times

were 1.3 seconds and that response times in excess of 10 seconds represented CNS processing prior to response. Overall, both Bach et al., (2010) and Lim et al., (2003) recommended that SCR's are a potential tool for ANS assessment within clinical practice and are stable for detection of SNS changes secondary to evoked stimulation. Furthermore, Hengedus et al., (2011), advised that although the evidence is limited in the use of SCR's in patient populations, and particularly in the lumbar region, future studies should now be focused on responses of patients to interventions and correlates to functional limitation and symptom intensity changes.

Electrophysiological experiments have shown that, under normal conditions, human peripheral nociceptive fibres, A $\delta$  axons (Elam and Macefield, 2004) and C axons (Elam et al., 1999), are not directly activated by SNS activity, findings that are supported by the pharmacological studies by Zahn et al., (2004) and clinical research investigating SNS arousal in chronic regional pain syndrome (CRPS) patients (Baron et al., 2002). It is therefore widely accepted that the SNS does not activate nociceptors in the sensory nervous system under normal conditions however, there remains a lack of clarity regarding the behaviour and the role of the SNS in symptomatic/patient populations.

#### **2.4.3. Central Connections of the Autonomic Nervous System (ANS)**

The last two decades have seen the advancement of functional brain imaging with concomitant developments in the knowledge of cerebral brain processing. Despite this there remains a lack of clarity in understanding of brain activity in relation to the regulation of pain-related physiological responses.

Beyond the peripheral nociceptor and dorsal horn, nociceptive information ascends to the thalamus in the contra-lateral spinothalamic tract (STT) and to the medulla and

brainstem via the spino-reticular and spino-mesencephalic tracts. Dostrovsky and Craig (2006, p. 187-203) identified that these tracts serve different purposes related to both their lamina origin in the dorsal horn and their final central destination. Tracey and Mantyh (2007) advised that these spinal projections to the brainstem are important for integrating nociceptive information with autonomic processes and for the conveyance of nociceptive information to the forebrain after brainstem processing thereby influencing the interpretation of pain experiences and perception. Although the thalamus plays a central role as a critical relay site for nociceptive information, its connections spinally and supra-spinally are still debated in terms of processing in humans particularly chronic pain, however in 1981, LeBars et al., described experiments on rats and identified that distal noxious thermal conditioning stimulation was able to induce strong inhibition of A-alpha and C-fibre responses which were diminished by the injection of naloxone. These findings were further developed in 1990 by DeBroucker et al., who revealed, in a case controlled series of 3 human participants, that noxious, but non-painful, stimulation was able to trigger the distant/diffuse noxious inhibitory control (DNIC) system in patients with thalamic lesions which, these authors considered, excluded the possibility that masking of pain, by a second, distal, painful focus could be solely due to attentional processes, furthermore, they concluded that lemniscal and spino-thalamic pathways could not be involved in triggering DNIC systems thereby indicating that the brainstem and the spino-reticular tracts must represent key neuronal links. This is a construct that has, more recently, been supported within a review conducted by Yarnitsky (2010) who renamed the process previously known as DNIC as Conditioned Pain Modulation (CPM) and found that in patients with chronic pain syndromes (e.g. fibromyalgia, tension-type headache, idiopathic pain syndrome and irritable bowel syndrome)

there was evidence that pain inhibited pain, particularly with respect to the inducement of distal pain to inhibit proximal pain. These findings support the developing concept that a central neuroplastic mechanism exists, particularly in chronic pain states. Indeed, Apkarian et al., (2004), utilising magnetic resonance imaging (MRI) scanning on chronic LBP patients, found that this group of patients had 5-11% less neocortical gray matter volume than healthy control subjects and that the reduction in gray matter volume was correlated to the chronicity/duration of their pain symptoms. Apkarian et al., (2004) suggested that the observed thalamic and prefrontal cortex atrophy may be an adaptive change to the hyper-toxicity of neuro-transmitters leading to long-term neural plasticity. They also suggested there may be an initial hyper-perfusion of these regions in the first 3-12 months of LBP but as the pain continues, hypo-perfusion occurs causing the resultant atrophy at the 24-36 month period and that this may be the reason why patients become less responsive to therapeutic interventions as their LBP becomes chronic and is reflected in the transition from thalamic processing (in acute pain) to thalamo-cortical processing in the chronic stages (Moseley, 2007). Ruscheweyh et al., (2011) countered these findings in a study performed on patients with chronic pain, controls and past-pain patients. Whilst these authors agree that there was evidence of gray matter degeneration similar to the findings of Apkarian et al., (2004), Ruscheweyh et al., (2011) found no correlation between the extent/volume of degeneration and the duration of symptoms, furthermore, they also revealed that these degenerative changes were reversible after 10-12 months cessation of pain. Tracey and Mantyh (2007) suggested that severe chronic pain could be considered a neurodegenerative disorder that particularly affects the prefrontal cortex with consequential negative effects on the descending inhibitory system which, if unarrested may contribute to



the chronic pain state supporting Hurwitz’s (2011) commentary that more focus should be placed on the early resolution of pain in the acute pain state to prevent chronicity in LBP.

Piché, Arsenault and Rainville (2010) investigated the cerebral correlates of pain-ratings, motor responses and skin conductance evoked by noxious electrical stimulation utilising data acquisition by the Biopac system (SC & EMG in the lower limbs) and functional-MRI (fMRI) brain imaging equipment of 11 healthy volunteers. In their covariance analysis they revealed that brain regions activated during pain were also involved in sensorimotor and SNS physiological regulatory responses (see table 6 below for a summary of the regions identified) which support the research conclusions of Rhudy, MacCabe and Williams (2007) that noxious stimuli evoke a robust SC response that is driven (rather than precipitated by) low-level neural processes but is sensitive to the psychological context.

Table 6. A summary of the responses of brain activity regions during pain, motor system & SNS activity, primary associated response and clinical interpretation.

	<b>Brain activity regions</b>	<b>Clinical Interpretation</b>
Pain sensitivity	ACC Bilateral PHG  mPFC/OFC	Suggests an important contribution of higher-order brain processes to individual differences in pain sensitivity.  Subjective emotional & cognitive correlates with decision-making, reward-prediction, expectation and actualisation
Motor evoked activity	ACC OFC	Corresponds with the role of these areas in goal-oriented cognitive/ behavioural processes
SNS reactivity	PAG ACC MCC OFC	Negative correlation between SNS reactivity and brain activity.

**Key:** ACC = Anterior Cingulate Cortex; PHG = Parahippocampal Gyrus; mPFC = Medial Prefrontal Cortex; OFC = Orbitofrontal Cortex; PAG = Periaqueductal Grey/Midbrain MCC = Midcingulate Cortex.

Tracey et al., (2002) specifically monitored PAG activity in their experiment assessing the influence of attention and distraction on pain perception. They found significant increases in activity within the PAG in subjects who were distracted compared to when they paid attention to their pain, with concomitant changes in pain ratings that suggested a varying capacity to engage the descending inhibitory system. Wagner et al., (2004) extended these observations to consider the influence of expectations on brain region activity. They found that there was stronger prefrontal cortex activation during anticipation of pain and that this correlated with greater placebo-induced pain relief and increased PAG activation particularly during anticipation of an 'event' and that this was related to activity in the dorso-lateral prefrontal cortex. Furthermore, responses in Primates have revealed that OFC and PFC activity levels are correlated to reward prediction, reward expectation and reward actualisation/ detection and that these are linked to motivation and goal-directed behavioural processing and decision-making (Rolls and Grabenhorst, 2008). These results support the concept that prefrontal mechanisms can trigger dopamine and opioid release within the brainstem during expectancy and can thereby influence the descending pain modulation system with subsequent modulation of pain perception and processing (Leknes and Tracy, 2008). Lidstone, de la Fuente-Fernandez and Stoessle (2005) revealed that the placebo response is partly mediated by the activation of reward-circuitry and that meso-corticolimbic dopamine release plays a central role and is highly linked to expectancy. They found that expectation of a clinical improvement was a form of expectancy of reward resulting in striatal dopamine release and placebo analgesia via the endogenous opioid systems. Placebo activated cortical areas that are known to respond to reward expectation

include the OFC, dorso-lateral PFC and the ACG (Schultz, Dayan and Montague, 1997; Mayberg et al., 2002 and Petrovic et al., 2002).

Contrary to the above findings, Piché, Arsenault and Rainville (2010) found that their subjects displayed individual differences in pain perception, motor reactivity and SNS activity which reflected individual differences in brain activity (e.g. subjects that displayed high ANS reactivity were inversely active – less active – in the PAG region of the brain). They also identified an inverse relationship between motor responses and SNS activity and subjects who had less OFC activity had higher ANS activity. From this, Piché and colleagues were able to identify brain sub-systems (particularly within OFC processing for pain) that suggest that psychological factors related to pain may inversely influence ANS and motor reactivities and that negative emotional states that result in activation of the ACC (Devinsky, Morrell and Vogt, 1995; Vogt, 2005), amygdala and the PAG (Devinsky, Morrell and Vogt, 1995) may exert ongoing regulatory feedback through the descending pathways affecting spinal nociceptive processes. In contrast, the body of works by Critchley and colleagues (Critchley et al., 2000 Critchley, 2005) found that in acute pain states, the activity in the Insula/inferior frontal gyrus covaried with SC amplitudes and reflected the ongoing regulation of SNS responses associated with pain arousal.

In conclusion, research supports the use of SC responses as a measure of SNS/ANS reactivity to stimulation and that there are fMRI links to brain activity and SC responses particularly in acute pain states, the picture is more cloudy as acute pain states become more chronic/affective whereby individual differences in pain sensitivity reflect the variability in the supra-spinal elaboration of afferent information and the neuro-plasticity and adaptive changes that are occurring in the thalamo-cortical and pre-frontal cortices of the brain.

#### 2.4.4. Determinants of peripheral sympathetic nervous system activity

Quantification of ANS responses have been performed by a variety of proxy measurements which are summarised in table 7.

Table 7: Current, published literature reporting treatment effects on SC responses

Region	Specific Joint treated	Authors	Technique utilised	Outcome measured
Peripheral	Shoulder	Simon, Vicenzino & Wright 1997	GHJ AP Gd III	↑ SC, ↓ ST
	Elbow	Paungmali et al., 2003	MWM elbow jt	↑ SC,
		Vicenzino, Collins & Wright 2004	Neuro Mob	↑SC,PPT & PFGF
	Wrist & Hand			
	Hip			
	Knee			
Ankle & Foot				
Spinal	Cervical	Petersen, Vicenzino & Wright 1993	C5/6 PA Gd III	↑ SC
		Vicenzino et al. 1994	C5 Lat Glide	↑ SC, ↓ ST
		Vicenzino et al. 1995	C5 Lat Glide	↑ SC, ≈ ST
		Chiu & Wright 1996	C5 PA diff rates	↑ SC ≈ ST
		Vicenzino, Collins & Wright 1996	Lat Glide C5	↑ SC, no change ST
		Vicenzino et al., 1998	Lat Glide C5/6	↑ SC, no change ST
		Sterling & Watson 2001	Uni-lat PA C5	↑ SC, ↓EMG, ↓pain
		Moulson & Watson 2006	MWM Rotation	↑ SC ≈ ST
	Slater, Vicenzino & Wright 1994	Uni-lat PA T6	↑ SC (bilateral)	
	Thoracic	Jowsey & Perry 2010	Rotatory Mob	↑ SC, no change ST
		Colloca et al., 2000 & Colloca et al., 2003	Intra-operative manip	↑ SC (Bilateral)
	Lumbar	Perry & Green 2008	Unilat PA L4/5	↑ SC (Ipsilateral)
		Perry et al., 2011	EIL & Manip	↑ SC
		Moutzouri, Perry & Billis	MWM L4	↑ SC (bilateral)

Skin conductance responses (SCR's) have been identified in the literature to be the more stable proxy measure of SNS activity in the limbs (as compared to skin temperature changes) and rely on the detection of a peak/maximum response or computing the mean response over an anticipated time window relative to baseline (Bach et al., 2010). SC responses can loosely be grouped into; spontaneous (Bach et al., 2010), anticipatory (Patterson et al., 2002) or evoked/reactive (Patterson et al., 2002; Donaldson et al., 2003). Many authors have identified SC responses to a variety

of stimuli; heat pain (Bach et al., 2010; Loggia et al., 2011); anger (Janssen et al., 2004); empathy (sambo et al., 2010); deep and superficial pain (Burton et al., 2008 and 2009), mechanical pain (Breimhorst et al., 2011), electrical pain (Macefield et al., 2002, 2003 and 2010; Donaldson et al., 2003; Breimhorst et al., 2011) and psychological anxiety (Donaldson et al., 2003). Within the physiotherapy literature, maximum SCR's have been utilised to monitor the SNS response to a variety of treatment modalities, both peripherally and spinally. These are summarised in table 7.

### **2.5. Pain perception and nociceptive processing**

The physiological basis of nociception, particularly the mechanisms of signalling and modulation of nociceptive stimuli is covered in this section.

Pain is one of the main reasons that patients seek musculoskeletal out-patient physiotherapy intervention for LBP. Peripheral nociceptors are specialist neural tissues that are sensitive to noxious change occurring within their receptive field. Given the presence of 'adequate stimulus' (potential or actual tissue damage, for example, with facet joint and associated ligamentous and capsular injury or disc degeneration) their thresholds are met and a signal is transmitted to the associated neurone. Torebjörk and Ochoa (1980) determined that there were two types of afferent nociceptor fibres; A $\delta$  and C fibres with different characteristic features (see table 8).

**Table 8:** Properties of nociceptors (A $\delta$  and C) & mechanoreceptors (A $\beta$  & C-tactile)

Properties	High-Threshold Mechanical nociceptors	Polymodal Nociceptor	Mechanoreceptor	
Axon type	A $\delta$	C	A $\beta$	C-Tactile Afferents
Myelination	Yes	No	Yes	No
Fibre diameter	3 $\mu$ m	0.5 $\mu$ m	8 $\mu$ m	
Conduction speed	15 m/s	1 m/s	50 m/s	0.6 to 1.3 m/s <sup>-1</sup>
Stimulus	Pressure	Pressure Pinch Thermal Chemical (K <sup>+</sup> ions, serotonin, acetylcholine & Histamine)	Cutaneous touch Pressure	Slowly moving light touch (3cms <sup>-1</sup> ) Innocuous cooling
Sensation	Fast pain Well localized Sharp Pricking	Slow pain Diffuse Dull Aching Burning	Tickle/itch Vibration Discriminatory touch Proprioception	<b>Sub-conscious</b> "social/affective touch"* SNS skin response Pleasure Interoception Diminish nociceptor signalling in lamina II of dorsal horn

Adapted from Strong et al., (2002, p.15-16) and \*Olausson et al., (2008 & 2010)

Somatosensory nociceptors can be divided into 2 distinct types; mechanical nociceptors and polymodal nociceptors. Mechanical nociceptors have characteristically high thresholds and respond specifically and in a slowly-adapting way, to strong mechanical stimuli but not to heat, cold or chemical irritants. Their receptive fields are distinctive and their neural units myelinated with conduction speeds of 5-25 metres per second and densely distributed over the skin. Polymodal nociceptors also respond to strong mechanical stimuli, but unlike mechanical nociceptors are sensitive to noxious heat, strong skin cooling and to chemical irritants (Meyer et al., 1994. p.13-44). A mechanical stimulus may be generated; cutaneously, by stroking (massage) manoeuvres; arthrogenerally, by joint mobilisations, mobilisations with movement techniques and manipulation (to name a few); myogenically by specific soft tissue techniques, exercise, muscle release techniques, massage and deep transverse friction manoeuvres; and

neurodynamic techniques (e.g., sliding and gliding techniques). Although a number of high quality articles have discussed the outcomes of these techniques on observable patient outcomes (e.g. range of movement and pain intensity levels) few have conducted research on the SNS responses to mechanical treatment techniques.

Relating to the haptic sense, Olausson and colleagues (2008 and 2010) have recently published their findings regarding the existence of unmyelinated tactile C-fibre mechanoreceptive afferents that are responsive to stimulation from pleasant touch rather than noxious stimulation. Olausson and colleagues (2008 and 2010) claimed to have identified these nerve units in humans within non-glabrous, hairy skin that respond “vigorously” to slow and light stroking usually performed with a soft object. Olausson et al., (2002) identified, through fMRI, that the signals generated by stimulation of C-tactile afferents project via lamina I & II of the spinothalamic tract to the posterior lobule of the insular cortex and to the posterior ventral medial nucleus but, unlike A-Beta fibres, not to the ventral posterior lateral nucleus of the thalamus and from there to the somatosensory areas 1 and 2 of the cortex. Morrison, Löken and Olausson (2010) suggest that C-tactile afferents have more in common anatomically with interoceptive and visceral systems – relevant to a broad set of bodily feelings like pain, itch and hunger – than to exteroceptive afferent systems processing tactile and nociceptive stimuli. Morrison, Löken and Olausson (2010) went on to claim that activation of C-tactile afferent brain projections is associated with somatic and multimodal responses which may reflect cortical processing of affective touch that they termed “social touch” thereby supporting Craigs’ (2008) proposal that the posterior and anterior insular regions integrate emotionally salient inputs between the limbic regions (ACC and OFC) with pluripotent effects on homeostatic regulation on motivational conditioning (reward-related) and social

conditioning. The role of C-tactile afferents in homeostatic function was further defined by Olausson et al., (2008) in an experiment involving subjects who specifically lacked A-beta afferents. They found that activation of C-tactile afferents on the forearm were able to produce (excitatory) sympathetic skin responses (detected in the palm of the hand) although it is worthy of note that this study only had 2 subjects and responses were not consistent between subjects. The findings of these authors are worthy of note given the social, professional context of the “therapeutic encounter” within which patients are consensually touched and receive motivational input and reward from the treatment episode (Bialosky et al., 2008).

Within the classical framework of neural anatomy, it is accepted that as primary afferent fibres in peripheral nerves travel proximally, they group together to form spinal nerves with ventral and dorsal roots prior to entering the spinal cord and dividing into short ascending and descending branches that run longitudinally in the dorsolateral fasciculus Lissauer. Within several segments they leave the tract to synapse on neurones in the dorsal horn. The dorsal horn is the first site for integration and processing of incoming sensory information and is divided into different laminae with distinct functions and chemical profiles (Willis and Coggeshall, 1991). Figure 7 depicts the laminae divisions and their synapsing afferents.



Figure 7: the terminations of afferent fibres in the dorsal horn.

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Taken from Bandler and Shipley (1994)

Lamina I (the marginal Zone) is an important nociceptor relay site with high densities of projection neurones identified that function to process nociceptor information and in may be influenced by non-nociceptive mechanical stimulation generated by manual therapy interventions (Pickar, 2002; Dishman and Bulbulian, 2000 and Zusman, 2004 and 2010). There are nociceptive-specific neurons that are elicited solely by nociceptors, and wide dynamic range neurons (also in lamina V and, in the cervical and lumbar regions only, lamina VI), which respond to both nociceptive and mechanoreceptive input (Strong et al., 2002).

Afferent fibres of all distal origins establish a matrix of connections with the dorsal horn neurons, exerting a homeostatic changing pattern of excitatory and inhibitory inputs that determine the firing of the dorsal horn projection neurons and of interneurons that mediate spinal reflex responses. In health these neurons are

segregated however, Woolf, Shortland and Coggeshall (1992) identified that peripheral nerve injury can trigger sprouting of afferents into Lamina II with resultant adaptation of function and threshold levels of the afferent fibres to this lamina.

Second-order neurones arise from different regions of the dorsal horn, cross the midline and ascend the spinal column to the brain stem and thalamus in the antero-lateral column. They synapse in a number of brainstem nuclei (including the periaqueductal grey region/PAG) and in several thalamic nuclei. The PAG surrounds the cerebral aqueduct of the midbrain and can be divided, anatomically, into 4 distinct regions; medial, dorsal, dorso-lateral and ventro-lateral, each with a high degree of functional specificity (Henderson, Keay and Bandler, 1998). These columnar longitudinal projections from the PAG permit connections with all levels of the nervous system and plays an important role in integrating functions critical to survival (fight or flight) through its influence on the nociceptive, autonomic and motor systems (Behbehani, 1995 and Morgan et al., 1998). Functions controlled by the PAG include pain facilitation, analgesia as well as fear and anxiety (Behbehani, 1995). Pain modulation can be demonstrated from stimulation of various regions of the PAG however, stimulation of the dorsolateral and ventrolateral subregions produces different autonomic and motor system responses (Lovick, 1991 and Morgan, 1991). Fields and Basbaum (1994; p.243-257) reported that stimulation of the PAG or the nucleus raphe magnus inhibits spinothalamic tract cell transmission and has been proposed as a possible mechanism of action of manual and manipulative therapies (Zusman 1986, 2004 and 2010; Pickar 2002 and Bialosky et al. 2009). Olsson et al., (2008 and 2010) add that C-tactile afferent stimulation (light stroking or “social touch”), may also play a part in inhibiting noxious transmissions by providing a blockade in laminae I and II of the dorsal horn and that cortically, stimulation of these fibres are

processed interoceptively (by the posterior insular cortex) resulting in SNS, emotional and motivational changes rather than motor responses.

Injury of any source results in marked up-regulation of nociceptive system function (Boal and Gillette, 2004) and, consequentially, enormous neuroplasticity and change in many aspects of central nervous system function (Woolf 1994 and 2011, Bakkum 2007) . Up-regulation of nociceptive system function has effects on somatomotor and somatosympathetic function (Storm et al., 2000) and whilst this system is normally quiescent, regular strong, intense, potentially damaging stimuli triggers pain perception, a cascade of interactions between these systems and, ultimately, a hyperalgesic state that is characterized by a diminished threshold for noxious stimulation and, through the process of neuroplasticity, altered response thresholds for other forms of stimuli (Moseley et al., 2006 and Wand and O'Connell, 2008) . As indicated, along with somatosympathetic activity alterations, an emergent model was proposed by Sterling et al., (2001) who advocate, alongside sympathetic changes, pain also influences concurrent alterations on patterns of neuromuscular activation and control. Sterling et al., (2001) suggest that the presence of pain leads to inhibition or delayed activation of local (to the source of pain) deep muscles or muscle groups (e.g. Multifidus) that perform key synergistic functions thus limiting unwanted motion with resultant alterations in the patterns of motor activity and recruitment during functional activity. This concept is supported by the research of Hides, Richardson and Jull (1996) and Hodges and Richardson (1996) and while the changes in the control of these muscle may be initiated by pain and/or tissue injury, they are often sustained beyond the acute pain phase (Hides, Richardson and Jull, 1996), and may contribute, unless arrested, to chronicity (Hides, Jull and Richardson, 2001 and Wand and O'Connell, 2008).

Primary (peripheral) sensitization is characterised by nociceptive system activity with a concomitant up-regulatory response following tissue injury. This is a complex sensitization process whose different forms of sensitisation may develop depending on the nature of the injury or disease. Activation of nociceptors, sensitisation of currently responsive nociceptors, recruitment of mechanically insensitive or silent nociceptors, and phenotype conversion of non-nociceptive afferents, represent four major mechanisms whereby temporal and spatial summation of nociceptive afferent inputs to the central nervous system may occur following tissue injury (Johnson 1997). Acting in concert, these mechanisms can contribute to substantial up-regulation of peripheral nociceptive system function. Ultimately, this may be interpreted as pain at higher levels within the CNS leading to neuroplastic changes and central sensitization (Woolf, 1994 and 2011). Central sensitisation may be considered to be a possible link between the presence of pain, the sensory-motor system and the autonomic nervous system (Wand and O'connell, 2008 and Bialosky et al., 2011)

Central sensitization describes the changes occurring at a cellular level to support the process of neuronal plasticity that occurs in the nociceptive system neurones in the spinal cord and in the supraspinal centres because of excitation of nociceptive pathways (Woolf, 1994 and 2011). Central sensitization contributes to a number of aspects of neuroplasticity, including increased excitability of a wide dynamic range (WDR) cells (Woolf, 1989), increased receptor field size (Cook et al., 1987) and changes in somatic withdrawal reflexes (Woolf, 1984) and, more recently, wider appreciation of the role of changes occurring at cellular (Chacur et al., 2009) and at genetic levels (Chiang et al., 2010) with, ultimately, clinical manifestations occurring

secondary to neuroanatomical reorganisation in the dorsal horn neurons (Flor et al., 1997 and Flor, 2003).

Peripheral and central sensitization have been implicated in changes in autonomic function and research over the last two decades has begun to reveal that a link may exist between the experience of pain and alterations in sympathetic activity, and suggesting that sympathetic outflow may influence (or maintain) afferent activity in nociceptive neurons (Campbell et al., 1992 p.121-149; Koltzenburg, 1992 p.213-243; Janig and Koltzenburg 1992; Devor, 1995, Sato, 1997; Benarroch, 2001; Zusman, 2002 and Lim et al., 2003). The potential role of the SNS and postganglionic noradrenergic neurons in complex regional pain syndromes remains controversial, and little consideration has been given to the role of these mechanisms in less severe musculoskeletal disorders, including LBP. However, alterations in SNS function have been recorded, and abnormalities of somatosympathetic reflex responses demonstrated in patients with frozen shoulder (Mani et al., 1989) and patients with tennis elbow (Smith et al., 1994 and Thomas et al., 1992) as well as neck pain (Sterling et al., 2001).

More recently, functional brain imaging (fMRI) studies have provided evidence of the close association between areas of the nervous system responding to pain (e.g. the thalamus and the anterior cingulate, anterior insular, somatosensory and premotor cortices) and areas controlling autonomic and motor function and emotional state (Porro and Cavazzuti, 1996). Lovick (1991) and Chudler and Dong (1995) revealed that both the basal ganglia and the PAG region receive nociceptive inputs as well as coordinating important aspects of movement and motor control.

The afferent nociceptive pathways and central mechanisms of processing and modulation provide a complex means of indicating to an organism the potential for injury and are systems that can be countered by other associated networks. In 1969 Reynolds published a seminal study investigating the descending pain inhibitory system (DPIS) and highlighting the importance of the PAG in the control of nociception. Reynolds (1969), Cannon and Liebeskind (1987) and Jones (1992), revealed that stimulation of discrete brain regions produced profound endogenous analgesia in animals. Furthermore, these authors identified two distinct forms of analgesia with associated behavioural, physiological and pharmacological correlates. Bandler and Shipley (1994) found that both the dorsolateral and ventrolateral columns appear to be important for modulating pain perception. Figure 8 provides an illustration of these pathways.

The characteristics of each PAG region are summarised in Table 9 overleaf. Essentially, the dorsolateral column of the PAG region has characteristic analgesia associated with fight/flight behaviour, aversive reactions (Besson, Fardin and Oliveras, 1991; Fanselow, 1991, and Morgan, 1991) and sympathoexcitation (Lovick, 1991 and Lovick and Li, 1989). Pharmacological studies indicate that dorsolateral PAG analgesia is non-opioid as it is not blocked by naloxone administration (Cannon et al., 1982) and does not exhibit tolerance (Morgan and Liebeskind, 1987), also its onset is generally rapid, within 20 minutes (Takeshige et al., 1992). Projections from the dorsolateral PAG utilize noradrenaline as a neurotransmitter and this noradrenergic system has a key role in mediating morphine analgesia in relation to mechanical nociceptive stimuli by inhibiting the release of substance P at spinal cord level (Kuraishi, 1990 and Kuraishi et al., 1983 and 1991).

**Figure 8: The lateral and ventrolateral columns within the periaqueductal grey region.**(Injection of excitatory amino acids within each of these columns elicits opposing response characteristics as indicated.)

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Taken from Bandler and Shipley (1994)

**Table 9: A comparison between the dorsolateral and the ventrolateral PAG and its characteristics.**

	<b>PAG Region</b>	
	<b>Dorsolateral</b>	<b>Ventrolateral</b>
Characteristic behaviour	Fight or flight Aversion	Immobility Freezing Recuperation
SNS response	Sympathoexcitation	Sympathoinhibition
analgesic response to naloxone	Not blocked	Not blocked
Stimulation tolerance	Non exhibited	Exhibited
Onset time	Rapid (3-20 mins)	20-40 minutes
Transmitter	Noradrenaline	Serotonin (5-hydroxytryptamine)
Stimulant	Mechanical Nociception	Thermal nociception
Primary Actions	At Spinal cord level Inhibits release of Substance P	Inhibits release of somatostatin

The ventrolateral column of the PAG region has characteristic analgesia associated with immobility (Morgan, 1991) or 'freezing' (Fanselow, 1991), recuperative behaviour and sympathoinhibition (Lovick, 1991). The analgesic effect is blocked by the administration of naloxone in the dorsal raphe nucleus (Cannon et al., 1982) and is tolerant to repeated stimulation (Morgan and Liebeskind, 1987) and described as an opioid form of analgesia, requiring a longer period of peripheral, thermal stimulation (Takeshige et al., 1992). Projections from the ventrolateral PAG, via the nucleus raphe magnus, use serotonin (5-hydroxytryptamine) as a neurotransmitter and is specific to morphine analgesia directed towards thermal nociceptive stimuli (Kuraishi et al., 1983) by inhibiting the release of somatostatin (Kuraishi, 1990).

### **2.5.1. Summary**

Research over the last two decades has indicated that mechanisms exist to sensitize nociceptors, to recruit previously inactive nociceptors and to utilize afferent inputs via myelinated neurons to contribute to nociception. These mechanisms contribute to substantial spatial and temporal summation of nociceptive inputs. Central mechanisms are important in neuroplastic adaptations seen in continued pain states and there is a movement away from a peripheralist view of pain to a much more integrated understanding that recognises the highly diverse, interactive, emotive, motivational, genetic and cellular components of the nociceptive processing system.



## **2.6. The proposed mechanisms of action of spinal manual therapy**

Having reviewed the key components within the nociceptive processing system, this section reviews the literature supporting the proposed mechanical, physiological and neurophysiological mechanisms of action of spinal manual therapy and explores the use of skin conductance activity levels and maximum SC responses as outcome measures to analyze the effects of different physiotherapeutic approaches to musculoskeletal pain with a focus on the critical evaluation of previous literature on the neurophysiological effects of MT techniques. Details of the literature search strategy are provided in appendix II.

### **2.6.1. Review of the literature on the origins, definitions and evidence of effects of spinal manipulative therapy (SMT) techniques**

Spinal Manipulative Therapy (SMT) is one of the oldest forms of healing art practised as far back as 2500 years ago (Hooper 2005:746). Hippocrates, the father of modern medicine, had utilised spinal manipulation for treating various conditions such as scoliosis , and even designed a table for manipulation which remained in use for more than 2000 years (Hooper 2005:746). In the early part of nineteenth century, spinal manipulation was largely viewed with suspicion due to increasing concern about its safety in patients with tuberculosis (Hooper 2005:746). In the present era, SMT is used widely by chiropractors, osteopaths and physiotherapists for relieving pain for various musculoskeletal disorders such as non-specific low back pain, mechanical neck pain, and certain types of headaches (Bronfort, Haas and Evans 2005) and has become one of the most studied treatment options for LBP (Mierau 2000:208). For example, there were only nine studies in the Ottenbacher and DiFabio (1985) review but the review by Van Tulder, Koes and Bouter (1997) had 25 studies in it (Bronfort, Haas and Evans 2005:150). However, large scale surveys in

UK found that only 3-9% of physiotherapists use manipulation clinically, in contrast to 59% use of joint mobilization (Foster et al., 1999, Jackson, 2001 and Gracey, McDonough and Baxter, 2002). This is, in part, due to the fact that the exact mechanisms through which SMT relieves pain have not been clearly established (Pickar, 2002) and the concerns about the safety of SMT (Ernst and Canter 2006) render it less 'acceptable' (for clinical applicability/use) in the eyes of the scientific and clinical communities.

In general, the recommendations for the management of acute LBP are similar among the clinical guidelines of various countries (Koes et al. 2001 and Pillastrini et al., 2011). Most, but not all, of the countries recommend spinal manipulation for the treatment of acute LBP patients without nerve root problems or serious spinal pathology. However, the Dutch, Australian and Israeli guidelines do not recommend the use of spinal manipulation for acute LBP patients (Koes et al., 2001). This discrepancy in the recommendation of clinical guidelines concerning the SMT for acute LBP patients among the different countries may be due to different interpretations of the available evidence, as recommendations are based not only on research evidence but also on consensus as well (Koes et al., 201, Pillastrini et al., 2011). Despite a growing number of studies reporting on clinical effectiveness of SMT in patients with acute LBP, the uncertainty surrounding the precise mechanisms by which SMT relieves symptoms (pain and functional impairment) provides a background for academic and clinical debate within an acute LBP patient setting.

There is a plethora of manual techniques such as joint mobilizations, passive joint stretching, and muscle energy techniques used under the umbrella term SMT (Hooper 2005:747). The complex issue of terminology in defining SMT was

considered by American Academy of Orthopaedic Manual Physical Therapists who defined SMT based on six characteristics, namely: Rate of force application, Location in range of available movement, Direction of force, Target of force, Relative structural movement and patient position (Mintken et al., 2008). Evans and Lucas (2010) in their reappraisal of manipulation, devised a model to identify specific 'action' features (of the practitioner) and specific 'response' features (on the part of the recipient). This model is presented in Figure 9.

**Figure 9: The relationship of the features of manipulation, compared with other manual therapy interventions**

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(Taken from Evans & Lucas, 2010)

However, for the purposes of this thesis SMT is used to denote a high-velocity low-amplitude thrust (HVLAT) delivered to a joint (i.e., Lumbar segment facet joints) in a

specific direction (Bergmann, 2005:756). In other words, Spinal manipulation is defined as a 'small-amplitude rapid [thrust] movement, not necessarily performed at the limit of a range of movement, which the patient cannot prevent taking place' (Maitland et al., 2005: xvi) and involving joint gapping in a starting position that involves a combination of 3 physiological movements that are in a coupled manner and designed to produce an audible "pop"/gapping of the joint surfaces. In this thesis, "Spinal Manipulation", "Spinal Manipulative Therapy" (SMT), "Rotatory Lumbar Manipulation" and "High-Velocity Low-Amplitude Thrust" (HVLAT) are used synonymously.

SMT was originally, thought to have some local mechanical effects. For example, SMT helped release trapped synovial meniscoids in zygapophyseal joints of the spine, change the thixotropic property of synovial fluid, help reduce a subluxed disc material and break joint adhesions (Greenman 2003:108). However, there is no evidence to support these assertions.

SMT essentially delivers a mechanical input to the tissues of the spine (Pickar, 2002). SMT is often, but not always, associated with a cracking or popping sound called cavitation (Conway et al., 1993). In other words, cavitation is the 'formation of gaseous bubbles within the synovial fluid of the joint, as a result of a distraction that causes a local reduction in pressure' (Potter, McCarthy and Oldham, 2005). Brodeur (1995) proposed that the sound associated with the cavitation is generated by elastic recoil of the synovial capsule as it is released from the capsule/synovial fluid interface and the review paper by Evans (2002) concluded that cavitation should not be an absolute requirement for the mechanical effects to occur but agreed that it may be a reliable indicator of successful joint gapping. Although Protopas and Cymet (2002) concluded from, their review paper, that the articular release is a physiological event

that may or may not be audible and that not all noise coming from a joint signifies an articular release, moreover, due to the paucity of evidence, they were unable to state whether or not cavitation occurred in the absence of an audible crack. Cramer et al. (2000) found MRI evidence to support the hypothesis that spinal manipulation (lumbar side-posture spinal manipulation) leads to joint gapping (1.2 mm) in spinal zygapophysial joint. However, authors acknowledged the small sample size (n= 16) of their study and recommended that a larger clinical trial needed to be carried out to further define these results. This cavitation is associated with 5-10 degrees increase in joint Range of Motion (ROM) (Sandoz, 1976). However, association does not mean causation; and it is debatable whether the increase in range of motion is the result of cavitation (Beffa and Mathews, 2004) indeed, there is now growing evidence indicating that the achievement of an audible “crack” does not influence neurophysiological response (SNS activity changes) nor does it influence hypoalgesia (Sillevis and Cleland, 2011). The conventional belief asserts that when SMT is applied to a particular joint, cavitation occurs in that particular joint. In other words, anatomical location of cavitation is directly related to the selected technique. In contrast, Beffa and Mathews (2004) analysed the cavitation sounds from thirty asymptomatic adults obtained by applying SMT for two different regions of the body (Lumbar and Sacro-iliac joint). The results indicated that there was no correlation between the anatomical location of cavitation sounds and the adjustment technique selected. Some authors argued that the sound of cavitation is a sign that the procedure has been performed correctly and thus will have the desired therapeutic effect (Lewit 1978:466). However, the evidence is contrary to the established convention. Flynn, Childs and Fritz (2006) in a pragmatic study (n=70), found that there was no correlation between the presence of lumbar cavitation and improved

outcomes in terms of pain intensity, range of motion and functional disability levels (Oswestry Disability Score) in patients with non-radicular LBP. Similarly, a prospective cohort study (n=78) of patients with mechanical neck pain found that there was no correlation between the number of audible pops (i.e., cavitation) heard during thoracic SM and clinically meaningful improvement in pain, range of motion and disability, although Bereznick et al., (2008) did demonstrate (in a case-study, cohort design) that responses to a side posture lumbar manipulation (that produced and audible crack) did demonstrate a “refractory period” of 40-95 minutes however, the study had only 3 asymptomatic subjects and lacked clinical application. In summary, there is some evidence to suggest that cavitation is required during SMT to achieve the required joint capsule and musculo-reflexogenic effects and that therapist's can accurately detect a cavitation. However, there is less certainty regarding the segmental level that underwent the cavitation particularly when based on the sound and that the sound of an audible release does not necessarily indicate that the appropriate reflexes were stimulated. Furthermore, there is a lack of research that explores whether or not cavitation is always audible, leading Bakker et al., (2004) to suggest that the therapeutic benefits reported with SMT and the audible release may not be physiological in nature but rather psychological with the joint “crack” having a powerful placebo effect on both the patient and the practitioner.

One of the theoretical rationales for the mechanisms underlying the effects of SMT is that the mechanical thrust leads to alteration in the sensory signal from paraspinal tissues resulting in the improvement of physiological function (Pickar, 2002). Ianuzzi and Khalsa (2005) investigated this issue based on the hypothesis that SMT may alter the inflow of sensory information from mechanoreceptors in the facet joint capsules which may explain the neurophysiological effects of SMT. In the human

lumbar spine, the displacement rate produced due to physiological rotations gave rise to concomitant increases in the magnitude of facet joint capsule strain. But, unique patterns of facet joint capsule strains were also recorded in response to the high loading rates of simulated spinal mobilisations. Ianuzzi and Khalsa (2005) inferred that this unique mechanical input may have resulted in a novel pattern of mechanoreceptor firing and subsequently, a novel input to the central nervous system. The high variability, the small sample size and the use of cadaveric specimens limits the generalisability of the results of Ianuzzi and Khalsa (2005) study.

A musculo-reflexogenic mechanism has also been proposed for the attenuation of pain following SMT. SMT elicits an inhibitory stretch reflex response generated from the capsules of the zygapophysial joints (Indahl et al., 1997). The distension of a porcine zygapophysial joint by injecting saline resulted in decreased motor unit action potentials of paraspinal muscles (Indahl et al., 1997). This phenomenon wherein SMT is followed by brief reflex relaxation of paraspinal muscles was investigated by Dishman and Bulbulian (2000). The effect of spinal manipulation and mobilization on the amplitude of tibial nerve H reflex from gastrocnemius muscle was recorded before and after the manual techniques in asymptomatic subjects. The authors concluded that manual techniques lead to short-term inhibitory effects on the motor system. However, the results did not discriminate between the effects of the manipulation and the mobilization techniques. Also, the experimental procedure involved changing the subject's position between mobilisation and the H-reflex measurements. This change in positions could have affected the results of the study, as it is known that H-reflex response is sensitive to movement (Meier-Ewert, 1973 and Hayes and Sullivan, 1976). Hence, it is difficult to attribute the results to

manipulation alone although Suter, McMorland and Herzog (2005) attempted to rectify this potential dilemma by investigating the effect of SMT on H-reflex in healthy subjects without changing position finding no significant changes in H-reflex amplitude in their healthy subjects in response to Sacro-iliac manipulation. Thus, the authors inferred that the attenuation observed in H-reflex in healthy subjects is attributable to movement artefacts and not to the effect of manipulation. Interestingly, in the second part of this experimental study (Suter, McMorland and Herzog 2005), the authors found that the H-reflex amplitude was decreased in low back pain patients who received sacro-iliac manipulation, even when the patients were treated and tested in the same position. Thus, there is some evidence to support the view that SMT leads to motor neuron attenuation. More importantly, the clinical consequence of motor neuron attenuation has yet to be fully established (Dishman and Bulbulian 2000). Possibly, the inhibition of motor neuron excitability, following SMT, could disrupt the 'pain-spasm-pain cycle' which might be present in low back pain patients. Although, it should be noted that this concept of 'Pain-Spasm-Pain Cycle' is controversial and not clearly established (Roland 1986) and this transient inhibition of motor neuron excitability can possibly be due to the phenomenon of 'post-activation depression/inhibition' (Dishman, Cunningham and Burke, 2002).

Herzog, Scheele and Conway (1999) investigated the segmental effect of SMT by applying SMT to cervical, thoracic, lumbar and sacro-iliac joint and measuring EMG readings of various limb and back muscles. The results indicated that different SMT to different regions elicited distinct EMG responses. Hence, the authors argued against the general effects of SMT. However, there was overlap of muscle responses when SMT was applied to different regions of the body. For example, cervical SMT affected thoracic muscles, thoracic SMT affected cervical and shoulder



muscle and lumbar SMT affected thoracic muscles. Thus, SMT does produce distinct responses when applied to each region of body but the responses do overlap and do not correspond to a particular segment as previously believed. In conclusion, the premise that segmental effects are based on the convergence of paraspinal tissues on motor neuron pool of cervical and lumbar region is not strongly supported by the evidence.

#### 2.6.2. The proposed neurophysiological mechanisms of action of spinal manipulative therapy

Pickar (2002), Zusman (2004 and 2010) and George et al., (2003 and 2006) argued that explanations for the pain relieving/hypoalgesic outcomes observed after SMT cannot be entirely attributed to biomechanical effects occurring in the target tissues. Bialosky et al., (2008 and 2009) supported this opinion, stating that studies which support the biomechanical effects of manual therapy were merely based on quantification of movements within the joints (Gal et al., 1997 and Colloca et al., 2006) and not on long term positional changes within the structures as advocated by Mulligan (2004) with the use of MWM techniques (Tullberg et al., 1998 and Hsieh et al., 2002). Furthermore, Bialosky et al., (2009) highlight that the effects of manipulative therapy applied on a joint will not be limited to that joint alone, as the forces generated by the technique tend to dissipate over a larger area, affecting the surrounding muscles, nerves and fascia (Herzog, Kats and Symons, 2001 and Ross, Bereznick and McGill, 2004). Indeed, Kent et al., (2005) and Cleland et al., (2006) argued that the choice of technique does not seem to influence the outcome as much as identifying an individual likely to respond, and signs and symptom responses don't necessarily correlate to the region of application (Cleland et al., 2005 and 2007) suggesting that mechanisms other than biomechanical alterations are associated with the changes observed in patients (and asymptomatic individuals)

following administration of treatment interventions. The current literature therefore supports, in part, a neurophysiological mechanism as one of the underlying process for the outcomes observed with SMT (Pickar 2002, George et al., 2006, Moseley, 2007, Bialosky et al., 2009 and Zusman 2004 and 2010). It is also recognized that motivation, emotion, genetic factors and expectation also contribute to the overall response (Bialosky et al., 2008).

On application of SMT, joint mechanoreceptors and muscle proprioceptors are stimulated and bombard the spinal (dorsal horn) and supra-spinal centers (periaqueductal region/PAG in the midbrain) with afferent sensory input (Pickar and Wheeler, 2001; Pickar, 2002, Wilson 2001 and Zusman, 2004). Evidence of the influence of SMT on these centers was provided by Malisza et al., (2003), who performed knee joint mobilizations, following capsaicin injection in rats, demonstrating decreases in the activation of areas pertaining to pain generation in the brain and the dorsal horn (DH) of spinal cord. Peripherally, musculoskeletal injury induces an inflammatory response which induces the body's natural healing processes, reduces the thresholds of nociceptive receptors and influences pain processing which can be influenced with observed effects on blood and serum cytokines levels. Indeed, a number of researchers have explored these peripheral mechanisms of pain modulation notably Teodorczyk-Injeyan, Injeyan and Ruegg (2006) who found, in asymptomatic individuals, that spinal manipulation was able to reduce levels of inflammatory cytokines but not those of Substance P and, more recently, Teodorczyk-Injeyan et al., (2010) found that SMT can influence interleukin-2-regulated responses in LBP patients. Interleukin-2 is a key immunoregulatory hormone which has been found to be immunosuppressed in LBP patients, the authors suggest that the systemic consequences of SMT may encompass a

“priming” effect on the immune system (via stimulation of systemic somatoautonomic reflexes) with resultant restoration of interleukin-2 levels in the blood. Degenhardt et al., (2007) revealed changes of blood levels of b-endorphin, anandamide, N-palmitoylethanolamide, serotonin and endogenous cannabinoids following SMT and Padayachy et al., (2010) found that SMT had an immediate effect on serum cortisol levels in patients with mechanical LBP. Recent insights have demonstrated a central role for dopaminergic neurotransmission in modulating pain perception and natural analgesia in supraspinal regions including the key pain processing regions of the brain, notably, the basal ganglia, insula, thalamus and peri-aqueductal gray regions (Wood, 2008 and Gabriela et al., 2011). Dopamine’s primary role involves pleasure and motivation and increases in levels of dopamine are correlated to “risk-taking”, insomnia, exercise and ‘reward’. Skinner et al., (2011) found that painful stimuli classified as “physically or emotionally distressing” resulted in increased dopamine release and brain activity that were correlated with anti-nociception. Clearly this is an area of research that requires consideration when constructing management strategies in patients with sleep deprivation and high levels of anxiety. This, and the immune and hormonal influences of SMT, are in the very embryonic stages of investigation and not within the scope of this thesis however, it is noted that ANS stimulation has wide-reaching, systemic effects beyond those reported immediately after instigation.

There is growing evidence to suggest that SMT may exert an effect on the spinal cord, and in particular the dorsal horn (DH). Boal and Gillette (2004) looked at a LBP population and reported (both in vivo and in vitro) evidence identifying long-term potentiation in DH nociceptive neurons and concomitant DH and central nervous system neuroplastic changes occurring following the onset of LBP. They went on to

reveal that these LBP patients, who underwent SMT, incurred neuroplastic changes in their DH and the authors suggested that HVLAT provides “an intense somatosensory afferent barrage” to the nervous system that facilitates the activity of the small mechanosensitive afferents (A $\delta$  fibers) and suppressing central and spinal hyperexcitability generated by C-fibre stimulation. Pickar and Wheeler (2001) agreed with this premise by proposing that joint based therapies “bombard the central nervous system with sensory input from muscle and proprioceptors”. Bakkum (2007), undertaking research on rats, also found that the presence of a hypomobile lumbar spinal segment caused activity dependent neuroplasticity in the dorsal horn with resultant mal-adaptive central changes. Malisza et al., (2003), also experimenting on rats, quantified observed DH responses by fMRI during light touch, noting a trend towards a decrease in DH activation following ‘therapy’. Other authors have associated the effects of MT with hypoalgesia (Vicenzino et al., 2001; Mohammadian et al., 2004; George et al., 2006), muscle activity changes (Herzog et al., 1999 and Sterling et al., 2001) and spinal reflex excitability changes (Bulbulian et al., 2002; Dishman and Burke, 2003) which Bialosky et al., (2009) speculated may indirectly implicate a spinal cord mediated effect. Bialosky et al’s., (2009) proposed pathway (spinal and supra-spinal) model is reproduced in figure 10 overleaf.

Supraspinally, as indicated in an earlier sub-chapter, there are a number of structures implicated as being instrumental in the pain experience. Specifically, structures such as the anterior cingular cortex (ACC), amygdale, rostral ventromedial medulla (RVM) and the periaqueductal gray (PAG) regions (Vogt et al., 1996; Derbyshire et al., 1997; Peyron et al., 2000; Moulton et al., 2005; Guo et al., 2006; Bee and Dickenson, 2007; Oshiro et al., 2007; Staud et al., 2007). Bialosky et al., (2009) also classified placebo and psychological responses to MT within the

supraspinal mechanism of action arguing that such factors are related to the descending pain inhibitory system (DPIS) with associated changes in the opioid system (Sauro and Greenberg, 2005), in dopamine production (Fuente-Fernandez et al., 2006), and in the central nervous system (Petrovic et al., 2002; Wager et al., 2004; Matre et al., 2006) although these observations were not in studies exploring MT and therefore may be open to debate.

**Figure 10: Bialosky et al's (2009) proposed pathway of spinal & supra spinal mediated effects of manual therapy.** (Bold arrows indicate suggested mechanisms)

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### 2.6.3. Skin conductance as a measure of sympathetic nervous system activity

Skin conductance (also known as: galvanic skin response - GSR; Electrodermal activity - EDA; sweat response; skin resistance - SR) has been described as a measurement of spontaneous alterations in the electrical potential or electrical resistance of the glabrous areas of the skin on the toes and feet (Balconi 2010: p.36, Bryant and Oliver, 2009: p.194). An increase in the SNS activity leads to release of noradrenaline (which activates synapses in smooth muscles in the vessels) leading to vasoconstriction, and fibres with acetylcholine that innervate the sweat glands (Venables and Christie 1973; Storm et al., 2000) and has been utilised in SMT research for the last 25 years.

The earliest recorded investigations into the SNS effects of MT were fraught with methodological issues concerning poor experimental variable control and low sample sizes (e.g.. Harris and Wagnon, 1987; Ellestad et al., 1988). In 1993, Petersen et al., identified the need for methodologically superior studies into the role of the SNS in the manual and manipulative therapies and published a repeated measures, double-blind, placebo-controlled trial on 16 asymptomatic, physiotherapeutically naïve males who received a cervical mobilisation whilst having the skin temperature changes (ST) and SCR recorded in their upper limbs. Their results revealed a 50-60% increase, from baseline levels, in SC for the treatment group compared to a 30% increase for the placebo condition. Petersen et al., (1993) suggested that the manual contact aspect of SMT had a substantial (30%) placebo effect, nevertheless, they suggested that it was the movement/oscillatory component that maximised the neurophysiological effect (50-60%). These researchers did not report any attempt to establish the measurement error of their equipment (not Biopac) nor did they attempt to validate their placebo technique therefore it is difficult to ascertain the true effect of

the SMT technique above that of the equipments measurement variability, a common problem within most of the published reports in the 1990's and addressed, in this thesis in the reliability study of chapter 3.

Chiu and Wright (1996) sought to establish the maximal neurophysiological effects of two different rates of application of a commonly used SMT technique performed in the cervical spine. The authors compared the effects of a fast (2Hz) and slow (0.5Hz) rate of cervical SMT on SC in the upper limbs of asymptomatic participants utilizing a repeated measures design. The researchers defined SMT performed at the rate of 2Hz as 2 oscillations per second, and 0.5Hz as 1 oscillation per 2 seconds and recruited 16 healthy, male volunteers (age: 18-25 years), which made generalizing the findings of this study difficult to a general population. Furthermore, no power calculation was performed to justify the sample size. Treatment conditions (2Hz, 0.5Hz and control) were order-randomized over 3 consecutive days however, the process of randomization and allocation was not stated. Both the treatments involved application of 1 minute x 3 sets of grade III, postero-anterior mobilizations performed centrally on C5 vertebrae, at different rates. To blind the researcher and participants, the recording equipment was situated in an adjacent room and whilst this reduces the possibility of assessor bias, it was, however, unclear if an independent assessor was employed to measure the outcomes. It was also unclear if participants had knowledge about the purpose of study, or about the treatment interventions applied. The results of recorded SCR's determined a significant difference between SMT (2Hz) and SMT (0.5Hz) ( $p=0.0022$ ), and between SMT (2Hz) and control conditions ( $p=0.0008$ ), during treatment, favouring mobilizations performed at 2Hz.

Additionally, the SMT (2Hz) condition demonstrated a sympathoexcitatory response, with a magnitude of effect of 50-60% from baseline SC values, reflecting those of



Petersen et al., (1993). SNS changes in the 0.5 Hz technique demonstrated an increase of 15-20% with an increase in the order of 14-18% for the control condition. The outcomes of Chiu and Wrights' (1996) investigation established that mobilizations performed at a faster oscillation rate produced an increase in sympathetic activity, over mobilizations of slower oscillation rate, suggesting that the movement component of SMT may be an important factor to gain maximum neurophysiological output. However, in the absence of a placebo condition, the effects of factors other than SMT (such as psychological factors) on SC output could not be determined. Non-significant ST changes were recorded and because no placebo condition was instigated and the study was conducted on a small sample population of asymptomatic health volunteers, interpretation to a patient group is limited.

The results of the work of Chiu and Wright (1996) are in direct contrast to the study by Willett, Hebron and Krouwel (2010) who also investigated the immediate effects of different rates of SMT (2Hz, 1Hz and 0Hz) performed on the lumbar spine. Their measures of hypoalgesia included PPT but not SNS, utilizing a repeated measures design. Recruiting 30 healthy volunteers (age: 18-57 years), participants were randomized by an electronic randomizer into conditions involving different rates of lumbar mobilization, which were carried out on 3 separate occasions. However, it was unclear about the duration of time gap given between the three conditions which may have generated carry-over effects. The treatment technique engaged 1 minute x 3 sets of grade III, large amplitude, postero-anterior mobilizations applied centrally on the L5 vertebrae. PPT measures were recorded using a pressure algometer, at 4 different sites: paraspinal muscles adjacent to L5 vertebrae; signature zone of L2 dermatome; signature zone of L5 dermatome; 1<sup>st</sup> dorsal interossei. However, it was

unclear if an independent researcher was employed to record PPT measurements. The results did not demonstrate any significant difference in PPT measures between the different rates of lumbar SMT ( $p=0.26$ ), indicating that alterations in the rates of SMT did not influence the amount of hypoalgesia produced. However, within each of the individual rates of SMT technique, a difference between before and after treatment was noticed for PPT values, at all 4 measurement sites. These results may be due to methodological issues with population bias (the participants were not naïve to the treatment conditions) with a resultant type II error (failure to reject the null hypothesis when, in fact, the alternate hypothesis is supported), or simply because of the difference between cervical and lumbar regional responses to SMT. Use of SNS measures may have provided the link needed for further extrapolation of findings.

In a similar study by these authors, Krouwel, Hebron and Willett (2010) conducted an investigation to compare the effects of large, small and quasi-static amplitudes (depth) of lumbar SMT on hypoalgesic outcomes of PPT, utilizing a repeated measures design. Similar to the researchers' previous study, this study also recruited 30 healthy volunteers (mean age: 26.43 years) again, without performing a power calculation. Participants were randomized into conditions involving different amplitudes/depths of lumbar mobilization, which was carried out on 3 separate occasions, this time, with a gap of 48 hours between each. All treatments were conducted at a rate/frequency of 1.5 Hz. PPT measures were recorded, again using a pressure algometer, but at 4 different sites: paraspinal muscles, adjacent to L3; region above patella; 5<sup>th</sup> metatarsal; mid deltoid. However, similar to researcher's previous study, it was unclear if an independent researcher was employed to record PPT measurements and not all participants were physiotherapeutically naïve

therefore unblinded. The results did not reveal any significant difference in PPT measures between the different amplitudes of lumbar SMT ( $p=0.864$ ), indicating that alterations in amplitudes of SMT did not influence the amount of hypoalgesia produced however, it was unclear if the SMT's were into or out of the point of joint resistance and, to date, the clinical significance of changes in PPT's within a symptomatic patient population have yet to be established. This was in contrast to Maitland et al., (2001) who claimed that mobilizations with larger amplitude were superior to smaller amplitudes at reducing pain levels in patients. The researchers therefore suggested that the difference between SMT amplitudes might be larger if the study were to be conducted on a symptomatic, segmentally hypomobile population.

Vicenzino et al., (1994) investigated sudomotor changes in their repeated measures, double blind, placebo-controlled trial again using ( $n=34$ ) normal, asymptomatic, naïve subjects. Uniquely, these researchers utilised a peripheral/dermatomal region (C6) to detect sudomotor changes from a unilaterally conducted treatment technique (C5/6 left lateral glide) and finding that SC was significantly different in the treatment group (up to 33% increase compared to placebo (7%) and control (4%) groups). Notably, Vicenzino et al., (1994) performed measurements bilaterally and discovered a general SNS response rather than a response that was specific to an intended unilateral target area. They concluded that this represented a complex supra-spinal reflex rather than the result of the traditionally conceptualised simple spinal reflex and in doing so provided the groundwork for almost two decades of investigation into the effects of SMT on neurophysiological responses, with the resultant call, by a number of authors (George et al., 2007, Moseley et al., 2007, Bialosky et al., 2009 and Hengedus et al., 2011 to name a few) for a paradigm shift in how health

professional assess and manage patients with pain and functional impairment following musculoskeletal injury.

Slater et al., (1994) revealed opposing results to those of Vicenzino et al., (1994). Slater et al., (1994) found that a unilaterally applied T6 postero-anterior accessory mobilisation to the costovertebral joint (Maitland et al., 2005; p311) combined with a sympathetic slump (Butler, 1991; p.142) produced a 300% change in SC values for the treatment condition (a 50% increase above placebo), which was greater in the right upper limb compared to the left. This study by Slater et al., (1994) was not without its flaws in that although the authors used a placebo treatment, it was considered that the results obtained from placebo and experimental conditions might have simply been a response to orthostatic adjustment. Furthermore, they also failed to establish the stability of their SNS measurement within and between participants. The results of Slater et al., (1994) appeared to be in conflict with those of Vicenzino et al., (1994), in that their results supported the argument that SNS activity changes are not simply a generalised response, but can be biased to an anatomical region, a finding that was supported by Perry and Green (2008) who conducted a “high quality” (Hengedus et al., 2011) randomized control trial investigating the outcomes of an unilaterally applied oscillatory lumbar mobilization technique on SCR in the lower limbs, utilizing an independent group design. The investigation recruited 45 healthy participants, based on a power calculation from data obtained from the study by Vicenzino et al., (1995). Whilst the inclusion of all male, and aged matched population, made the group homogenous and negated the effects that the female hormone (progesterone) may have on sweat levels, it was difficult to generalize the findings of this study to a larger, clinical population. Nonetheless, the investigation followed stringent methodological criteria. The participants were randomized using a

concealed third party allocation into groups: SMT, placebo and control. Participants were blinded to their allocation to groups. Also, the post trial questionnaire confirmed that participants could not distinguish between treatment and placebo interventions ( $p=0.388$ ), however, they could comprehend when they received the control intervention. The researcher and the subjects were blinded to the outcomes by utilising an independent assessor, unaware of the treatment allocation and screening the equipment from the treatment area. The SMT intervention, a unilateral grade III oscillatory mobilization (at a rate of 2Hz), was applied to the Left L4/5 zygapophyseal joint (3x1 minute applications over a 5 minute period). The results indicated a statistically significant side specific difference in SCR in the SMT group (sympathoexcitatory SCR of 13.47%) that was greater to the placebo (-1.93%) and control (-0.87%) groups, for the treatment period ( $p<0.005$ ), adding to the developing construct that SMT in the lumbar spine may have both a spinal (dorsal horn) and a supraspinal (dPAG) influence. This experiment was performed in a laboratory controlled environment on asymptomatic participants and although Biopac equipment was used and the researcher established their own reliability (in pre-trial pilot studies) at performing the grade and the rate of the technique, the equipments' measurement variability/stability was not assessed.

These studies did not attempt to demonstrate any analgesic effect of the technique however, the work of Vicenzino et al., (1995 and 1998b) and Sterling et al., (2001) provide some support for the theory that SMT produces mechanical hypoalgesia. Vicenzino et al., (1995) demonstrated that a left lateral glide to the cervical spine produces a significant increase in SC values ( $>150\%$  compared to baseline) and in pressure pain thresholds (PPT) in the order of 123% above baseline for normal subjects (125% and 107% for SC and PPT respectively for placebo condition).

George et al., (2006) suggested that pain relief after SMT could be due a number of possible mechanisms involving spinal and descending inhibitory pathways. In an experimental study, asymptomatic subjects (n=40) were randomised to ride a stationary bike, perform lumbar extension exercises or receive spinal manipulation. The subjects underwent thermal pain sensitivity testing pre and post-treatment. George et al., (2006) found evidence to support the view that local dorsal horn mediated inhibition of C-fibre input was a potential hypoalgesic mechanism for SMT in healthy subjects and corroborate the view that SMT may have both segmental effects as well as global ones. Thus, SMT may invoke the pain gate mechanism at the spinal cord level resulting in hypoalgesia.

Most authors and clinicians now recognise that pain relief, due to SMT, involves a number of complex interactions including spinal and central neural pathways, endocrine responses with contributory elements from motivational, reward and expectation factors. Song et al., (2006) found that (activator-assisted) SMT delivered to male rats lead to reduction in pain and hyperalgesia caused due to intervertebral foramen inflammation. In a study by Skyba et al., (2003), SMT led to a significant decrease in experimentally induced pain in rats, even after the administration of naloxone (blocks opioid receptors) and bicuculline (blocks GABA receptors). From this result, the authors inferred that pain relief results from descending inhibitory mechanisms mediated through serotonin, dopamine and noradrenaline. However, these results were based on animal models which limits the generalisability of these studies to human (and patient) populations. Mohammadian et al., (2004) investigated the hypoalgesic effects of SMT in experimentally induced pain and inflammation in asymptomatic, healthy subjects. The authors found that administration of SMT lead to a significant reduction in experimentally induced allodynia and hyperalgesia. The

authors inferred that pain relief was due to a centrally-mediated mechanism as there was no appreciable increase in local blood flow. However, the authors did not explain the exact mechanism through which the conceptualised central-inhibition could have occurred.

Unfortunately, much of the published research exploring the effects of manipulative therapy on the SNS has focused upon outcome measures occurring within the upper quadrant, on asymptomatic healthy volunteers and on animals. Few studies have explored the responses of SMT on symptomatic individuals, and, none have been performed on symptomatic patients with low back pain. The following discussion looks at the limited literature on patient populations.

Vicenzino et al., (1998), in a repeated measures design study, performed 30 seconds x 3 sets of cervical SMT (grade III oscillatory, lateral glide) technique on C5/6, on patients with contra-lateral side lateral epicondylalgia. Along with statistically significant changes for SC and PPT measures for the treatment condition (different from placebo and control groups), the study also reported that an increase in SC was strongly correlated with an increase in PPT outcomes supporting the theory that SMT induced hypoalgesia, distal to the location of treatment, was due to an increase in the SNS activity and not local elbow myogenic changes.

The concurrent effects of cervical SMT on pain, sympathetic nervous system and motor activity were investigated by Sterling, Jull and Wright (2001). The study recruited 31 symptomatic participants (mean age: 35.77 years; SD: 14.92 years) with a history of chronic (>3months) lower cervical pain. The inclusion criteria were reinforced by involving a physiotherapist to diagnose if symptoms of cervical pain originated from the C5/6 segment. However, no power calculation was evident. A

repeated measures design was implemented, involving three conditions: SMT, placebo and control. Although, the participants were randomized, by drawing lots, to determine the order of the conditions received, on the 3 separate days, the method of allocation was not mentioned. The SMT technique involved 3 sets of 1 minute grade III postero-anterior mobilizations applied unilaterally to the symptomatic articular pillar of C5/6. However, the frequency at which mobilizations were performed was not defined. Various outcome measures were employed: Pain levels were evaluated using pressure pain threshold (PPT), thermal pain threshold (TPT), and a visual analogue scale (VAS), before and after the intervention; SCR's and ST changes were continuously recorded throughout the treatment technique to measure the sympathetic nervous system response; Motor activity was measured, by asking patients to perform a cranio-cervical flexion test before and after treatment, while EMG was recorded from superficial neck muscles. An independent assessor was employed to measure the outcomes, in order to blind the researcher to the results. Although, being a repeated measures design, the post trial questionnaire revealed that merely 3 out of 30 participants could identify the treatment accurately, indicating that participants were blinded effectively. The results showed a significant difference between SMT and placebo, and between SMT and control for the values of SCR's, towards the SMT group ( $p < 0.05$ ), during the treatment. SMT demonstrated a sympathoexcitatory response of SCR's, with a magnitude of effect of 16%. Unfortunately, SCR's were not recorded post treatment. As a result, the longitudinal effects of cervical SMT could not be analyzed. In contrast, no changes between groups were observed for ST change values. The PPT measures revealed a significant difference between SMT and placebo, and between SMT and control, demonstrating a hypoalgesic effect post treatment, on the side specific to treatment.



The magnitude of effect for changes in pain threshold (PPT) post treatment was 22.5%. Similar outcomes were observed with EMG results for superficial neck muscles, during a cranio-cervical flexion test, performed after the treatment. A significant difference was noticed, for EMG values, between SMT and placebo, and between SMT and control. In contrast, the VAS measures of pain intensity, post treatment, did not exhibit any significant differences between SMT and placebo. The overall results supported that SMT-induced hypoalgesia was due to an increase in the sympathetic nervous system activity.

There exists a counter-view that the effect of SMT is through placebo analgesia. Bialosky et al., (2008) investigated the effect of participant-expectation in the relief of pain associated with SMT. In this study, a symptomatic patient population was selected and participants (n=60) were randomly assigned to receive positive, negative or neutral expectation instructions regarding the effects of SMT on pain perception. All patients underwent quantitative testing before and after SMT. The results indicated that a significant correlation was present in pain perception of patients who had received a negative instruction and significant hyperalgesia. Bialosky et al., (2008) concluded that patient expectation (of a negative response) does influence pain perception (accentuates) but that positive expectations do not. Again, an important consideration, within a typical complex therapeutic encounter, between therapist and patient within a clinical setting.

In conclusion, there is some evidence to suggest that SMT has mechanical, musculo-reflexogenic, neurophysiologic and placebo effects. However, the overall strength of evidence supporting SMT is weak and few studies have been conducted on a symptomatic patient population with none on patients with LBP.

#### 2.6.4. Review of the literature on the evidence of neurophysiological effects of the Mulligan 'mobilisation with movement' (MWM) technique

The Mulligan concept, initially established by Brian Mulligan in the 1970's (Exelby 1995), has become an essential component of spinal MT involving the simultaneous application of an accessory joint glide and an active physiological movement to restore normal motion within a joint, therefore termed Mobilizations With Movement (MWM) (Mulligan Concept, 2011). An accessory glide is described as a translation or sliding movement performed by application of an external force on a joint (Maitland 2001: 221). Whereas, a physiological movement of a joint is identified as normal movement of a body segment in any given direction (Petty and Moore 2001: 46). The MWM technique, when applied on the spine, is also called Sustained Natural Apophyseal Glide (SNAG) since it engages a sustained accessory glide to the vertebral joint, in combination with an active physiological spinal movement, performed by the patient (Exelby 2001; Mulligan 2004: 44). A large survey conducted by Konstantinou et al., (2002), which had a response rate of over 2300 questionnaires, revealed that more than one in three chartered physiotherapists in Britain utilized SNAGs as part of their intervention for patients with LBP being a popular treatment of choice as it produced instant pain relief followed by an increase in spinal range of motion (Wilson 2001; Exelby 2002). Moreover, MWM's can allow for the treatment to be performed in weight bearing positions (Mulligan 2004: 44), and into the direction of symptom reproduction (Exelby 2002), making it feasible to instantaneously monitor outcomes. The effectiveness of Mulligan techniques has been linked to conflicting hypotheses (Hing 2009). Initially, it was believed that SNAG's corrected minor positional faults or mal-tracking problems in zygapophyseal joints (Mulligan 2004: 17; Exelby 1995). This biomechanical effect was thought to

restore the previously reduced accessory glides in joints, resulting in relief of symptoms (Exelby 2002). However, Hearn and Rivett (2002) dispute that since SNAGs were performed in an upright position, compressive forces acting on the joints due to gravity or due to stabilization provided by the surrounding musculature, increased the resistance in joints, and decreasing the amount of accessory glides possible. Recent research has therefore postulated the possibility of a neurophysiological mechanism, to be the basis of effectiveness of Mulligan SNAGs (Moulson and Watson 2006; Moutzouri, Perry and Billis 2012), similar to various SMT techniques. Furthermore, Vicenzino, Paungmali and Teys (2007) speculated that the almost instantaneous effects of SNAGs were unlikely to be because of activation of the descending pain inhibitory system (DPIS), and were more likely to be as a result of biomechanical effects. Krouwel, Hebron and Willet (2010) argued that this theory was based on subjective and physiological reasoning, and was not supported with any evidence. Nonetheless, on analysis of the studies on the neurophysiological effects of SNAG's by Moulson and Watson (2006), it is evident that although the technique demonstrated a sympathoexcitatory effect, there was no significant difference between treatment and placebo conditions during the intervention. However, the number of repetitions of SNAGs performed was fewer than that advocated by Mulligan (Hing, Bigelow and Bremner 2007) with Moulson and Watson (2006) suggesting that if a higher dosage of SNAGs had been applied, a larger difference between the SNAGs and placebo groups may have been observed. In general, the dosage of Mulligan techniques has been ill defined in the literature, and in particular, the number of repetitions performed has varied between different research articles (Hing, Bigelow and Bremner 2007). According to Vicenzino and Cleland (2007), in clinical practice, Mulligan techniques are most commonly

prescribed in sets of 6 to 10 repetitions although, there has been no published research that has investigated the optimal dosage of Mulligan techniques required to be performed in treatment sessions. A Rao and Perry (2011) attempted to answer this research question and, utilising 90 asymptomatic, healthy participants in a randomised controlled trial, revealed that although both 6 and 10 repetitions of a flexion SNAG centrally applied to L4 spinous process did produce statistically significant sympathoexcitatory responses (compared to the control group), the skin conductance responses for the 10 repetition participants were significantly greater than the 6 repetitions group (mean SCR change for 10 reps 20.5% and for 6 reps 14.5%,  $p < 0.005$ ) suggesting that 10 repetitions of the MWM had a greater magnitude of effect on SNS activity outcomes compared to the 6 repetition choice. Thus, the understanding of the neurophysiological mechanism as a source of the perceived effectiveness of Mulligan techniques remains inadequate. Moreover, the majority of the research on the Mulligan concept has been limited to peripheral MWMs with studies on the neurophysiological effects of MWM's on lumbar spine very rare indeed. The following discussion aims to review the current literature on the effects of MWM's on the SNS.

Moulson and Watson (2006) evaluated the effects of cervical SNAGs on SC and ST measures in both upper limbs, adopting a repeated measures design. The study included 16 asymptomatic participants (age: 18-37 years). However, there was no power calculation performed to justify this selection which might have lead to a type II error in the analysis and inferences of the results (Pinnock, Lin and Smith, 2002: 922). While, the order of participants receiving each of SNAGs, placebo and control conditions was randomized, the authors failed to mention the process of randomization or allocation. SNAGs were applied for 3 repetitions x 1 set on the

C5/6 intervertebral joint, while participants performed simultaneous right cervical rotation. The number of repetitions of SNAGs implemented (3 repetitions) was less than recommended by Mulligan (2004) and Vicenzino and Cleland (2007). Other areas of bias in the study were that the participants dictated the speed and distance/range of cervical right rotation, resulting in a potential lack of control of this extraneous variable. Additionally, it was not evident if data that was provided (of the SCR's and ST recordings) were converted to percentage changes from baseline for during and after treatment periods. As a result, the validity of direct comparison of the measurements to other studies is questionable. The results of the post intervention questionnaire revealed that 13 out of 16 participants were aware of SNAG's being the actual treatment, due to the nature of repeated measures design which may have influenced the results. The results revealed that Mulligan SNAG's demonstrated a sympathoexcitatory response, with a statistically significant increase during treatment ( $p < 0.0005$ ) and after treatment ( $p = 0.001$ ), in comparison with the control condition. However, there was no significant difference detected in SCR's during the treatment period, between SNAG's and placebo conditions ( $p = 0.176$ ), although there was a trend towards an increase in SCR's favouring the SNAG's condition. It was also observed that none of the ST change measures reached statistical significance between conditions.

Moutzouri, Perry and Billis (2012) studied the effects of lumbar SNAG's on SCR's in the feet of 45 asymptomatic participants (age: 18-46 years), utilizing a randomized, independent group design. Similar to Moulson and Watson (2006), there was no power calculation performed which may have lead to a type II error in the interpretation of the results (Pinnock, Lin and Smith, 2002: 922). SNAG's were applied for 6 repetitions x 3 sets on the L4/5 lumbar segment, while participants

performed simultaneous lumbar flexion. In addition to the treatment SNAG, a control (no movement or hands-on procedure) and a placebo condition were utilised with the placebo intervention just requiring participants to perform forward flexion for 6 repetitions x 3 sets without the glide component, which could be speculated to be the physiological component of SNAGs technique, as described by Mulligan (1999). Lumbar flexion from a seated position involved movement of multiple spinal (e.g. thoracic, cervical) and peripheral (e.g. hips, shoulder) joints, unlike in Moulson and Watson's (2006) study, where cervical right rotation could be principally isolated to the cervical spine. Blinding of the subjects was validated by a post-treatment questionnaire and results demonstrated a significant sympathoexcitatory response to the SNAG treatment during the treatment period compared to control for both the left ( $p=0.004$ ) and right ( $p=0.044$ ) lower limbs. However, there was no significant difference between SNAG's and placebo conditions for left ( $p=0.87$ ) and right ( $p=0.84$ ) lower limbs, although there was a trend towards an increase in SCR's favouring the SNAG condition. This was similar to the results of Moulson and Watson (2006), suggesting that SNAG's may not utilize dPAG mediated analgesia to produce its effects. However, this could be due to the fact that fewer repetitions of the technique were performed. This hypothesis might be supported by the small-scale study by Konstantinou et al., (2007) who, using lumbar MWM's as a treatment and a static resting position as placebo, found that although there was a statistically significant improvement in lumbar range of flexion in the MWM group ( $p= 0.005$ ) there was no difference between the groups (nor any reduction in intensity) with respect to pain ( $p=0.800$ ) although it is worthy of note that the true increase in range of flexion was less than  $4^\circ$  highlighting the importance of considering if statistical significance equates to clinical significance. Indeed, Moutzouri, Perry and Billis

(2012) found no difference between their asymptomatic SNAG and placebo groups in lumbar flexion range of motion, suggesting that the proposed biomechanical changes are not translated to asymptomatic volunteers with no functional impairments. Furthermore, Konstantinou et al., (2007) and Moutzouri, Perry and Billis (2012) did not use patient populations nor PPT measures of effect to allow comparison of hypoalgesia and SNS activity responses to treatment.

Experimental studies investigating the effects of MWM's have been conducted on patient populations with lateral epicondylalgia. Paungmali et al., (2003) conducted a repeated measures, placebo controlled study on 24 patients with chronic lateral epicondylalgia (mean age 48.5 years) in order to evaluate whether MWM's at the elbow produced concurrent hypoalgesia and sympathoexcitation. These authors were the first to publish the reliability of their measures of SNS (equipment utilised was a AT64 Skin Conductance Monitor) reporting stable measures (across the pre-treatment period) with a very high ICC (0.88) and a small Standard Error of Measurement (0.011 micro-siemens). The MWM treatment resulted in an initial hypoalgesic effect and concurrent sympathoexcitation with improvements in pain resulting in increased pain-free grip force and pressure pain thresholds. The authors suggested that the MWM treatment technique exerted neurophysiological effects similar to that reported for some spinal manipulations. A year later, Paugmali et al., (2004) published an article reporting the effects of the same lateral glide MWM technique (to 18 patients with lateral epicondylalgia) and measuring changes in pain-free grip strength, PPT, TPT and range of movement at the elbow with an upper limb neural provocation test, with radial nerve bias (ULNPT 2b), after administration of naloxone, saline or control substance by injection. The authors reported that none of the 3 injections achieved statistical significance, suggesting that the initial

hypoalgesic effect observed following the MWM was not antagonized by naloxone, implicating a non-opioid mediated hypoalgesic mechanism of action following the MWM technique.

#### 2.6.5. Summary

Skin conductance responses (SCR's) have been utilized by various researchers to measure the responses, within the sympathetic nervous system, of SMT (Chiu and Wright 1996; Vicenzino et al., 1998; Sterling, Jull and Wright 2001; Moulson and Watson 2006; Moutzouri, Perry and Billis, 2012; Perry and Green, 2008; Jowsey and Perry, 2010; Perry et al., 2011, Rao and Perry, 2011). In addition to skin conductance, some research studies also employed skin temperature (ST) changes measurements for the same purpose (Chiu and Wright 1996; Sterling, Jull and Wright 2001; Moulson and Watson 2006; Jowsey and Perry 2010). Although, Moulson and Watson (2006) suggest that ST changes were superior in comparison to SCR's in terms of its validity and sensitivity to record sympathetic nervous system activity, they failed to fully justify their reasoning for this assertion and most published studies (including their own study) have not established statistically significant response effects with ST measurement. In their recent systematic review of the neurophysiological effects of SMT, Hengedus et al., (2011) support the lack of evidence to support the use of ST changes over SCR's as a measure of SNS activity. As a result, this thesis utilized skin conductance activity levels and maximum SCR's as the primary outcome measures to determine the changes in SNS activity.



## **2.7. Conclusion of the literature review and scope of the thesis**

Epidemiologically, LBP is recognised as a global problem with potentially serious personal, societal, service and economic ramifications that have led to the development of Guidelines for the assessment and management of the condition. However, it is also recognised that the application of guideline-endorsed practice, by the primary target population, can take time to embed especially in the absence of empirical primary research in diverse, heterogeneous patient populations. Nonetheless, risk factors for the development of chronicity in LBP patients have been established (e.g. age, work and educational status) and factors indicating patients who could be at risk of a poor outcome identified (e.g. high levels of functional disability and pain intensity, the duration of symptoms, presence of leg pain, age, stress levels and poor socioeconomic status). The classification of patient sub-groups, that are identifiable as being responsive to therapy, remains controversial, with clinical prediction rules and tools to identify “at risk” patients (STarT-Back Tool, Hill et al., 2008 and 2010) being developed but lacking full validation. Conversely, the development and utilisation of patient reported outcome measures (ODI, RMDQ and the NPRS) are increasingly accepted as being useful adjuncts to clinical assessment of patient status at inception, and as a means of determining the extent of “benefit” from treatment at discharge. Whilst some PROM’s are considered to be reliable and valid within the construct of LBP populations they are not yet universally applied by clinicians and are open to interpretation bias. For this reason, there remains a distinct lack of consensus, within the practice-guideline documents, as to the best tool for the patient and the clinical context within which they present. This fact is confounded by a discernible lack of objectivity in PROM’s with a number of critiques claiming that they fail to capture the patients’ true experience of LBP and are open to mis-interpretation due to the summative nature of comparisons made. However, the last 2 decades has seen the

development of objective measures, including neurophysiological tools to measure changes in patients' sympathetic activity although the development of this area of research has lacked preliminary establishment of the tools (Biopac) reliability (measurement variability, repeatability and stability). Furthermore, there is a paucity of research available that provides normative data from asymptomatic (normal) populations or research that has translated normative findings into patient populations.

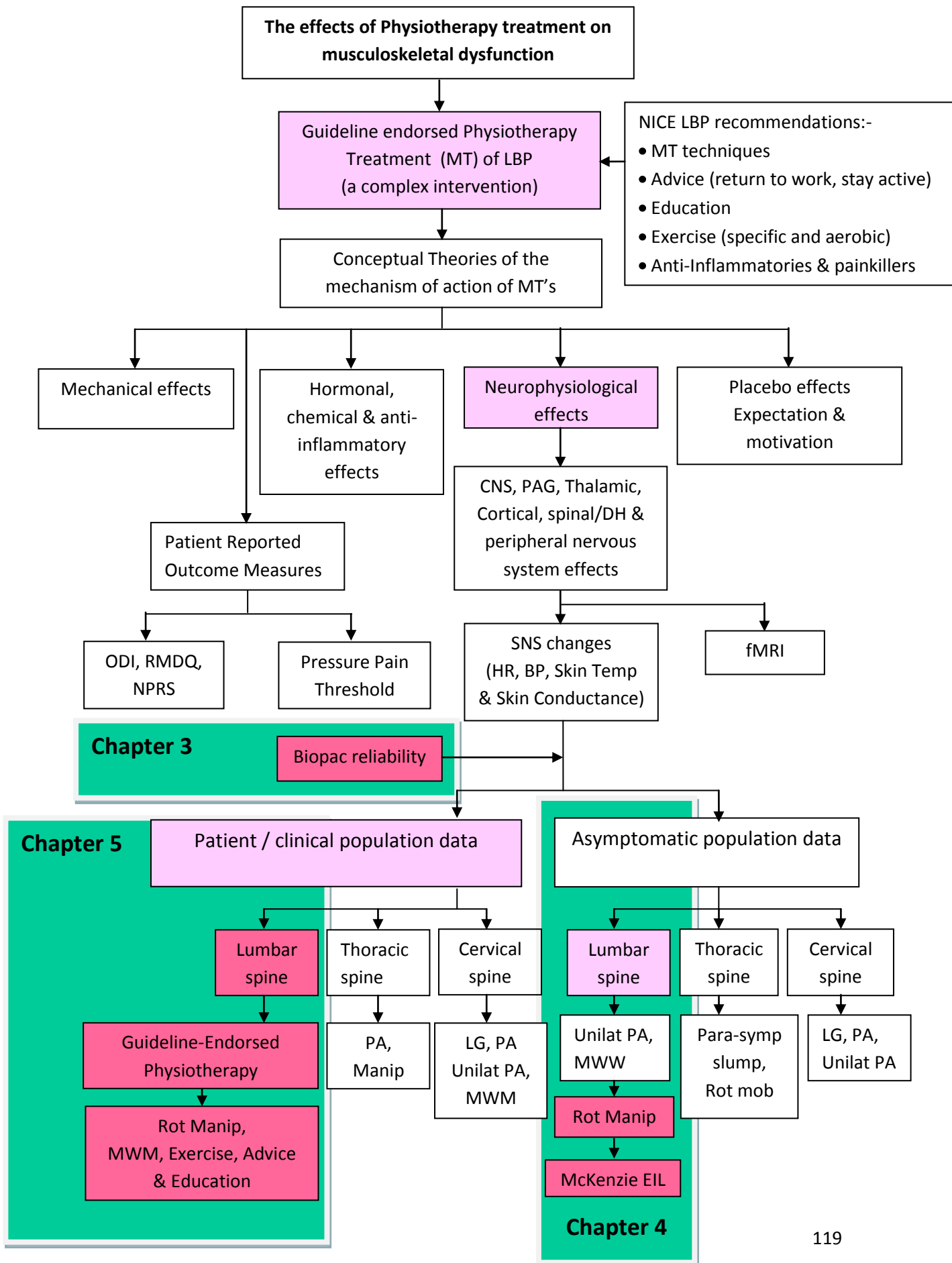
Thus, the key research questions and knowledge gaps that form the basis of this thesis include:-

- Chapter 3 - What is the reliability (retest correlations, measurement stability and variability –SEM and SRD) of the Biopac data acquisition system for SC measurement collection in a non-laboratory environment?
- Chapter 4 - What are the effects of a lumbar rotatory manipulation technique or a repeated McKenzie EIL exercise of SCR's in normal healthy volunteers?
- Chapter 5 - What are the SC activity levels of patients presenting for a course of guideline endorsed physiotherapy management for acute or sub-acute LBP?
- Chapter 5 - How do SCR's to guideline endorsed physiotherapy treatments correlate with currently utilised PROM's of pain intensity (NPRS) and functional disability (ODI and RMDQ) at inception and at discharge from treatment?
- Chapter 5 - What is the feasibility (to inform future clinical RCT studies) of using Biopac to identify any trends in SCR's to treatment thereby suggesting a critical value (cut-off point) to indicate patients, at inception, that might have good functional outcomes, at discharge?

Overall, the researcher has sought to establish the reliability and measurement error of the Biopac measurement system (chapter 3), to generate pre-clinical SC data on the effects of 2 specific (guideline endorsed) treatments for LBP. Furthermore, this data set facilitated the estimation of an appropriate sample size calculation for the final clinical study and for future research in the (natural) clinical environment. The third study comprised of clinical SC observations conducted on the target, patient population with LBP symptoms. Analysis of the data generated from this arm of the study was used to determine normative, patient values (for Biopac SC readings) which were then analysed correlatively, with currently utilised clinical PROM's. Lastly, trend analysis provided information (to inform future research and RCT development) suggesting the feasibility of Biopac as potential tool for use, in future patient-therapy studies.

Figure 11 overleaf illustrates the trail of evidence and the research gaps (in light pink) that informs the next three chapters (green blocks) and the key areas of research within this thesis (dark pink).

**Figure 11:** Flow chart indicating the key research gaps and research areas of this thesis



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### **3. Pilot Study to Determine The Reliability of Biopac Measurements**

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#### **3.1. Introduction.**

The last two of decades have seen an increasing interest in the measurement of sympathetic nervous system (SNS) changes in the detection of response to manual therapies. Notably, changes in skin conductance (SC) have been the most commonly utilised measure and are recognised as being superior to ST, HR and BP recordings. Conceptual theories incorporating the detection of neurophysiological responses (SNS) in the periphery are now emerging and are at the forefront of research into the effects of manual and manipulative therapies. Physiological recordings of SC activity levels and of changes (percentage change) in skin conductance responses (SCR's) are commonly measured using a Biopac GSR100B Electro-dermal Activity Amplifier (MP35; Biopac Systems Inc; Santa Barbara, CA) with silver/silver chloride electrodes applied to the digits of the hands or feet. Paungmali et al., (2003) using, National Instruments software card (6504 Bridge Point Parkway, Austin, Texas) to collect skin conductance readings on an Autogenics AT64 monitor (620 Wheat Lane, Wood Dale, Indiana), found SC measures to be stable, reporting acceptable levels of reliability with a high ICC (0.88) and a small SEM (0.011  $\mu$ siemens), however, these reliability measures were undertaken in a controlled laboratory environment and not in a busy environmentally variable non-laboratory setting that would typify the traditional clinic or hospital treatment area. Thus, Paungmali et al.'s, (2003) findings cannot be considered transferrable to the Biopac equipment nor to a clinical environment. Therefore a reliability study of Biopac SC measures, within a "natural" environmentally variable (with regards to noise, environmental temperature and activity levels) setting was

conducted to determine the reliability, measurement stability and variability of the Biopac equipment within a non-laboratory setting thus ensuring accurate interpretation of SCR change scores for the clinical study.

### **3.2. Aims and Objectives.**

The overarching aim of this pre-clinical pilot study was to assess the test-retest reliability (reproducibility) of the Biopac baseline (pre-treatment) measurements of SC in a normal, asymptomatic population. To achieve this, a number of objectives were set:-

- i. to determine the retest correlation coefficient (ICC, 2,1 model) to facilitate comparison with Paungmali et al's. (2003) findings
- ii. to assess random or systematic changes in the mean SC measurement between two applications (mean differences; SEM; confidence intervals; and Bland and Altman Plots with Limits of Agreement)
- iii. to quantify measurement variability between applications (SEM, SEM%; SRD) in order to determine (for future studies) the minimum effect size for the assessment of treatment response.

Test-retest reliability is an assessment of the stability of a measure over time (Rousson, Gasser and Seifert, 2002; Lexell and Downham, 2005). It determines whether the measure is able to produce reliable results or whether it is significantly influenced by the situation or the state of the subject over time (Rousson, Gasser and Seifert, 2002). Assessing the reliability and sensitivity of a measurement may involve a number of different statistical techniques. These may include evaluating the relationship between two sets of measurement; evaluating the difference between repeated sets of measurements; determining the level of agreement between measures (Bland and Altman, 1986), or assessing the level of inherent variability between repeated measurements. In this study, a combination of these statistical

methods rather than a single statistical test was chosen as it has been generally agreed within the literature, that a set of statistical methods rather than a single statistical test is required for assessing reliability and sensitivity (Lexell and Downham, 2005; Ageberg, Flenhagen and Ljung, 2007).

Without test-retest reliability or reproducibility, it would not be possible to assess the degree to which a measure is sensitive enough to detect a change in participants' responses as a result of targeted interventions (Beckerman et al., 2001).

Responsiveness or sensitivity to change has been defined as the ability of a scale or measurement to detect clinically relevant changes over time (Guyatt, Walter and Norman, 1987). Guyatt and colleagues describe responsiveness in relation to typical variation within-subjects, between repeated test measurements (Guyatt, Walter and Norman, 1987), therefore reproducibility has a direct influence on the responsiveness of a measure. To determine the direct influence of any intervention, it is thus necessary to be aware of these variations and the amount of measurement error contained within the Biopac instrument itself.

### **3.3. Design.**

This investigation was a prospective cohort study utilising a repeated measures design.

### **3.4. Methods.**

#### **3.4.1. Participants.**

The study recruited a convenience sample of 12 healthy, asymptomatic, non-smoking volunteers from the student and staff population at Coventry University (6 women and 6 men, aged 19-53 years; mean 37.4 years, SD = 7.45) by placing an

advertisement on the notice board in the Faculty of Health and Life Sciences Charles Ward Building for a two week period. All volunteers that responded to the advertisement were telephone interviewed (n=19) to ascertain their appropriateness for the study and of the 16 individuals that met the inclusion criteria, 12 could attend on the two individual days of the study. An information leaflet was provided for those that agreed to attend for their consideration prior to commencement of their data collection (appendix III). Three days prior to the day of data collection all 12 of the participants were consented and assessed (by means of a standard physiotherapy subjective and physical examination) to ensure that they met the criteria for the study (see table 10 overleaf). A mixed gender group was utilised, to ensure that extrapolation of the results to the target research population was not inhibited. Ethical approval was obtained from the Coventry University research ethics committee (appendix IV). Once the researcher and the participant were satisfied of their eligibility, the participant was asked to sign the consent form and informed of their right to withdraw at any time (Polit and Hungler, 1995). In accordance with good ethical practice, a cooling-off period of 72 hours was provided between the participant signing the consent form and their first data collection appointment. On each of the two days of data collection an abbreviated screening (re-) assessment was performed to ensure that no changes in their status had occurred and that they had abstained from caffeine, alcohol and exercise in the 3 hours prior to the study.



**Table 10:** Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Male or female gender	History of musculoskeletal symptoms within the last 6 month
Age between 18 and 55 years	Existence of concurrent medical disorders or psychiatric illnesses that may affect neurophysiological readings (e.g. Diabetes, anxiety disorders, Multiple Sclerosis, rheumatoid arthritis)
Posses an adequate understanding of spoken English	Previous history of lumbar spine surgery or lower limb surgery
Asymptomatic	Pregnancy
Able to provide informed consent for the study	Skin disorders at the site of electrode placement (e.g. athletes foot, psoriasis, eczema, verruca)
	Previous history of trauma with resultant persistent dyesthesia (abnormality of sensation which would affect neurophysiological readings)
	Alcohol dependency and smokers (that could affect neurophysiological readings)
	Those participants not willing or able to consent to inclusion

### 3.4.2. Equipment

Physiological recording of SC was measured by a BioPac GSR100B Electro-dermal Activity Amplifier (MP35; BioPac Systems Inc; Santa Barbara, CA), employing a constant voltage technique, sampled absolute direct current SC at the rate of 200 samples per second, and recorded through a BioPac AcqKnowledge computer software package running on an IBM compatible computer with Microsoft Windows installation (Figure 12). The Biopac software programme was installed, under license, on the investigators password protected laptop which was kept in a locked cabinet in a secure room in room CW220 at Coventry University.

**Figure 12:** The Biopac computer set up



**Figure 13:** Electrodes and equipment



A low frequency filter was set at 0.2Hz and a high frequency filter at 500Hz in order to limit any extraneous signal interference (e.g. other electrical devices in close proximity as might occur within a hospital/clinical environment). SC readings were recorded using silver/silver chloride electrodes (Figure 13 above) from the plantar aspect of the second and third toes of both feet simultaneously (12mm electrode gel contact area), using Biopac Systems Gel medium (as recommended by Biopac Systems manufacturer). The selection of electrode placement was determined by consideration of the spinal region most commonly producing symptoms (L4-S1 segments). The L4-5/S1 segments have a cutaneous branch, the medial plantar nerve, which supplies the plantar aspect of the toes under study (Williams et al., 1989).

To facilitate measurement consistency and thereby enhance the reliability of the study, the same diurnal appointment time was repeated for the second attendance of the participant. Reliability was further enhanced by using the same researcher to apply the electrodes and take the recordings. The subjects did not receive any feedback

regarding the outcomes of the recordings, ensuring blinding on the part of the participant.

#### 3.4.3.Procedure:

All participants were asked to refrain from exercising, eating or drinking any caffeine products 3 hours prior to the measurements (on both days).

Participants lay quietly on a plinth, in a standardised position (supine with their arms by their sides and their legs supported at the knees by a single pillow). The participants lay with the lower half of the body unclothed to underwear/shorts. The skin on the toes of each foot was prepared by cleansing of the conductance electrode sites with isopropyl alcohol to remove any unwanted skin residue that might affect the measurements (Petersen et al., 1993; Chiu and Wright 1996 and Perry and Green 2008). The Biopac SC electrodes were then applied to the second and third toes of each foot (Figure 14 overleaf). During the recording period the participants were requested to lay still, try not to deep breathe, cough, sneeze, interfere with the electrodes or fall asleep. All participants were compliant with these instructions. The procedure was repeated on a second occasion (one week between recordings as was considered standard clinical practice for patients undertaking a programme of physiotherapy) so that each participant provided two sets of data for analysis. The diurnal timings of the two measurements were replicated to prevent any external bias between the two recordings. All participants completed both sets of recordings.

**Figure14: Electrode Placement**



Following the protocol employed by Perry and Green (2008), the participants had an initial 10-minute stabilisation period, used to allow the subject's body to acclimatise to the environment. Following this period, recordings of SC were considered settled and stable and a 2-minute period of data acquisition was recorded for statistical comparison. At the end of the data acquisition period the recordings were terminated and the electrodes removed. The internal validity of the data acquisition process was enhanced by blinding both the participants and the researcher to the data being recorded (the data acquisition equipment was placed in a position whereby neither could observe the recordings and were therefore unable to influence the nature of the recordings throughout the procedure). Furthermore, the researcher did not analyse any of the data until the final participants' second data recording session was completed.

#### 3.4.4. Statistical Data Analyses:

Analysis of the SC data obtained involved calculation of the "Integral Measurement" ( $\mu\text{mho's}$ ) for the final two minutes of the 12 minute data collection period for each participant on each attendance (for details of the integral measurements gained from

Biopac software analysis program please refer to appendix V). The Statistical Package for Social Scientists (SPSS v.14) software package was used to calculate the intra-class correlation coefficient (ICC 2,1) and the MedCalc statistical software package was used to calculate the Bland and Altman Limits of Agreement.

To assess the test-retest reliability of the Biopac measures of SC as robustly as possible, the following statistical methods were used:-

i) Retest correlation co-efficient

Assessment of agreement between of the two sets of test results was conducted using the intra-class correlation coefficient (ICC 2,1) and is defined as the between-subject variance divided by the between-subject variance plus the within-subject variance otherwise known as the “relative reliability”. The Pearson’s product moment correlation co-efficient was not chosen as this test is traditionally used to assess the strength and linear association between two different variables/measures rather than assessment of the agreement between two (or more) sets of the same measurement (Bland and Altman 1986 and 1995). Indeed, Shrout and Fleiss (1979; p.420-428) suggest that the ICC (and in particular ‘Model 2,1’ whereby the measurement is carried out on each subject by the same rater) is the more appropriate statistic for measurement of agreement. Fleiss (1986; 2-31) recommends ICC values above 0.75 for excellent reliability and values between 0.4 – 0.75 for fair to good reliability, with values below 0.4 suggestive of poor reliability. However, an ICC only produces a value between 0 and 1 which can be difficult to interpret clinically (Ageberg, Flenhagen and Ljung, 2007) and according to Lexell and Downham (2005) would not be a suitable standalone measure of an instruments’ retest reliability, in this case, the test-retest of

the 2 minutes of data recording following the stabilisation period on the two different attendances of the 12 participants.

i) Assessment of changes in the mean

To assess for any random or systematic change in the results between the two test situations (Lexell and Downham, 2005; Ageberg, Flenhagen and Ljung, 2007; Bland and Altman, 1986) the following indices were recorded: mean difference between the test occasions with the standard error of the mean difference and the 95% confidence intervals (95% CI) and the Bland & Altman plots of the 95% limits of agreement (LOA). These methods can estimate any systematic bias, e.g. if values on the reliability presentation were always greater than those on the initial presentation then the mean difference would always be positive and the reverse would be true if the b=values were smaller, suggesting a systematic shift in measurements between test occasions. If zero is included in the 95% CI, no significant systematic change in the mean is present. The Bland & Altman LOA graphs also allow visual assessment for other systematic biases and magnitude of the inherent variability within the Biopac measure.

iii) Assessment of measurement variability

To quantify the actual size of the variability between the two sets of measurements (or the “within-subject variation”, or “typical variation” Lexell & Downham (2005), the following indices were used: Standard Error of Measurement (SEM) which calculated as the square root of within-subject variance which is the square root of total variance multiplied by 1- ICC); and SEM% which is the calculation of SEM divided by the mean and multiplied by 100. Any change following an intervention that is smaller than the typical variation would need to be interpreted with extreme caution. To evaluate if change scores represent important changes a reference range which takes account of measurement variability can be calculated; the Smallest Real Difference (SRD) which

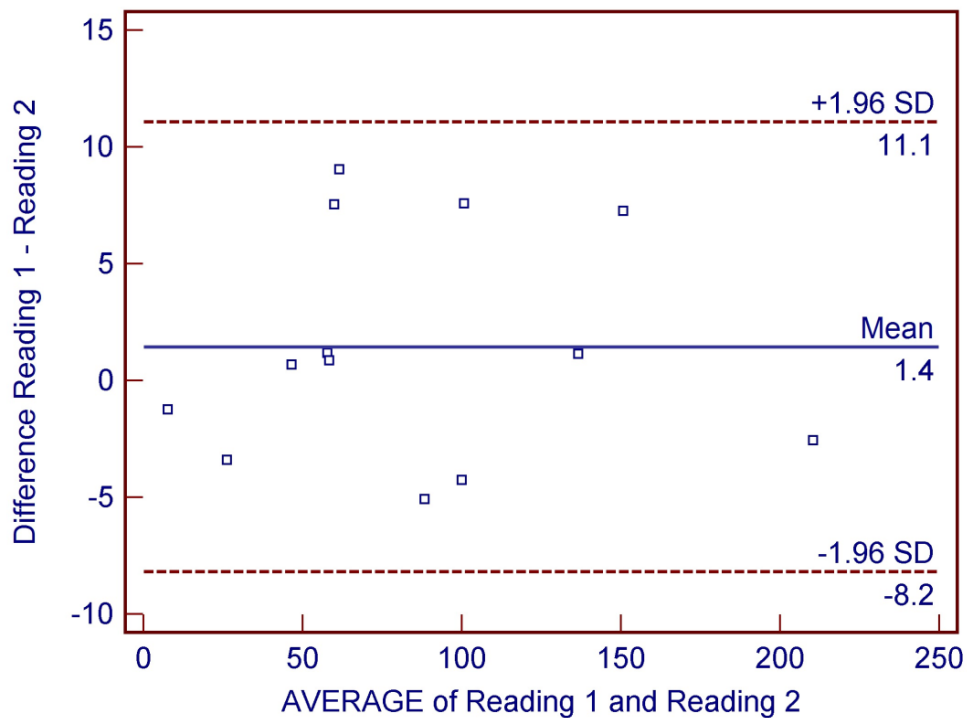
is equal to  $1.96 \times \text{SEM} \times \sqrt{2}$ ; and 95% SRD which equals the mean difference between the two test occasions  $\pm$  SRD. If the difference in score/measurement for a participant following in intervention is outside this reference range then it can be said to represent a “real” change that is likely to be attributable to an intervention and not inherent variability. Therefore, the smaller the reference range, the more sensitive the measure is at detecting “real change” (Lexell and Downham, 2005).

### **3.5. Results.**

Results revealed an ICC=0.997 (2,1; two-way random effect model; Absolute Agreement Definition) that was statistically significant ( $p < 0.0005$ ) and a confidence interval (CI) = 0.996-0.999, suggesting a strong correlation between test scores and representing excellent reliability (Fleiss 1986) that can be considered satisfactory for clinical measurement.

Bland and Altman Limits of Agreement (1986) are illustrated in Figure 15 and confirmed that the bias between the two applications was small (1.4  $\mu\text{mho's}$ ) with the difference lying, in 95% of participants, between 11.1 to -8.2 ( $\pm 21.8$ )  $\mu\text{mho's}$ . Zero is contained within the 95% CI indicating that the small degree of variability observed was negligible and not systematic.

**Figure 15:** Bland Altman Plot illustrating the Limits of Agreement for the two applications of SC Baseline readings.



Calculations of the standard error of measurement (SEM) revealed that to be 95% sure that any SC results are not due to measurement variability a change in the order of +/- 0.1138  $\mu\text{mho's}$  ( $\text{SEM} = \text{SD}\sqrt{1-\text{Cronbach's alpha}}; 2.0782\sqrt{1-0.997}$ ) would need to be recorded which is translated into a percentage error value of 4.632% [ $= (\text{SEM}/\text{mean}) \times 100$ ]. The smallest real difference measurement was calculated to be 0.315  $\mu\text{mho's}$  ( $1.96 \times \text{SEM} \times \sqrt{2}$ ) and represents the minimum difference required to be confident that a real change had occurred.



### 3.6. Discussion of Findings and Limitations of the study

It was the aim of this pilot study to assess the test-retest reliability, measurement variability and calculate the smallest real difference statistic of the Biopac equipment measures of SC in an asymptomatic healthy population. This was necessary in order to establish the reliability of Biopacs' use for research on SNS (SC) responses within a natural (non-laboratory) environment, thereby providing validity for the use of Biopac SC measures in the pre-clinical and, latterly, the patient study as well as for future clinical research. To gain information regarding the degree of test-retest measurement agreement, as well as systematic or random change and variability of the Biopac equipment in a natural environment, different statistical techniques were employed as it has been suggested that no one standalone statistical measure should be deemed sufficient (Bland and Altman, 1986; Ageberg, Flenhagen and Ljung, 2007).

The results showed that the Biopac equipment had acceptable random measurement error and test-retest reliability. There was evidence of minimum measurement variability between applications of the equipment (ICC=0.997;  $p=0.0005$ ; 2:1 two-way random effect model; Absolute Agreement Definition) which is comparable with the findings of Paungmali et al. (2003) who had an ICC of 0.88 for their SC data acquisition unit within a laboratory setting. Bland and Altman Limits of Agreement were conducted to detect any bias between applications and findings revealed only small bias between applications (1.4  $\mu\text{Mho's}$ ) with the difference lying, in 95% of participants, between 11.1 to -8.2 ( $\pm 21.8$ )  $\mu\text{Mho's}$ . This indicates that although it was possible to observe a small degree of variability, this variability was not systematic. As no other published study has conducted this type of analysis, comparisons to laboratory settings was not possible.

Further analysis of the data calculated that the Standard Error of Measurement was 0.1138  $\mu\text{mho's}$ , with a percentage error value of 4.6326% and a Smallest Real Difference of 0.3154  $\mu\text{mho's}$ . The SRD is the smallest measurement change that can be interpreted as a real difference, taking account of the fact that the measurement error makes the observed value of a measure differ from its true value (Beckerman et al., 2001). Although Paungmali et al., (2003) did calculate a SEM in the order of 0.011  $\mu\text{mho's}$  (a value lower than the current study), their measurements were taken in an environmentally controlled laboratory setting which was not transferrable to a clinical hospital setting therefore, this is the first study to provide data for use within a natural, clinical environment. Furthermore, the conversion of the SEM of 0.1138  $\mu\text{Mho's}$  into percentage change in SCR permits application of the measure into SCR (percentage change) within future clinical studies.

It was therefore considered that Biopac SC measurements in the lower limb were reliable for measurements of SNS response within a clinical/non-laboratory setting, with any measurement in excess of 0.3154  $\mu\text{mho's}$  (>4.633% change from baseline to treatment period) being regarded as an SNS change that is independent of any measurement error or variability and ascribable to the intervention under investigation.

The main limitation of the findings was that the study sample was a convenience sample, and the participants were healthy asymptomatic volunteers and therefore may not be representative of a symptomatic patient population. However, it was felt that the advantages of using asymptomatics outweighed the disadvantages as the recruitment of an asymptomatic population (see inclusion/exclusion criteria in Table 10) permitted strict control of any potential confounding variables that might otherwise distort or bias the SC readings (e.g. The effects of medications used for

pain, spasm or anxiety and the effects of symptoms of musculoskeletal, cardiovascular or neurological conditions).

To the authors knowledge this is the first study to conduct these normative values of SC activity levels with the Biopac data acquisition equipment within a natural, non-laboratory environment and to publish the results for future studies (Perry et al., 2011). These findings should help researchers determine whether a change in individuals' readings, are a true change rather than simply measurement error.

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## **4. Magnitude of Effect of Physiotherapy Treatments**

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### **4.1. Introduction**

Dagenais et al's., (2010) systematic review of LBP management supports the recommendations of Ernst and Canter (2006) and Bronfort et al., (2008) who call for primary research on manual and manipulative therapies to determine the effectiveness of the variety of options for the management of LBP. Until recently, determining the nature of neurophysiological responses occurring as a result of specific manual therapies has been a challenge due to the difficulty in accurately, quantitatively and non-invasively measuring the proposed effects on the key target tissues. Several researchers have explored the neurophysiological basis of specific MT techniques in the cervical spine (Sterling et al., 2001; Moulson and Watson, 2006) and upper limbs (Vicenzino et al., 2001 and Paungmali et al. 2003), utilising the SNS (SCR) as a measure of neurophysiological response. However, there is only a limited research base studying the lumbar spine and lower limbs (Perry and Green, 2008, Tsirakis and Perry 2010; Moutzouri, Perry & Billis, 2012).

The purpose of this pre-clinical study was to provide empirical evidence of the neurophysiological effects (as measured by recordings of sympathetic nervous system –SNS- activity) of two commonly advocated specific MT approaches to the management of LBP; repeated McKenzie Extension In Lying Exercise with overpressure (EIL) and a rotatory segmental manipulation (Manip) technique. Key objectives were to compare and contrast observed SNS responses within and between the groups and to discuss these findings with those of other previously conducted studies on other treatments for LBP (i.e. unilateral spinal mobilisations

and mobilisations with movement). Furthermore, the study aimed to contribute to the developing knowledge-base that provides evidence of SNS responses to specific treatments and thereby inform future clinical research and to enhance clinical decision making.

The recent publication of guidelines for the management of LBP, recommended the use of MT and exercise for the condition (CSP, 2006; van Tulder et al., 2006; Savigny et al., 2009 and Chou et al., 2009). These guidelines are supported by a number of studies that demonstrated clear patient-reported benefits (Konstantinou et al., 2007; Goodsell et al., 2000; Bialosky et al., 2009). However, there continues to be debate within the literature regarding the magnitude and the clinical significance of observed treatment effects (Potter et al., 2005; Theodore, 2010) with a lack of data available regarding specific treatment effects.

Specific sudomotor SNS changes (otherwise known as galvanic skin response, or electro-dermal activity – GSR and EDA – and hitherto referred to as skin conductance responses – SCR's) have been reported with lumbar and lower limb MT treatments on normal healthy populations. Perry and Green (2008) reported statistically significant SCR's changes in the order of 13.5% ( $p=0.005$ ) on the side of treatment in their treatment group receiving unilateral grade III Postero-anterior mobilizations (at a rate of 2Hz). This was the first study to demonstrate a significant side specific effect compared to the untreated side, to placebo and control conditions ( $p=0.002$ ). Moutzouri, Perry & Billis (2012) explored the effects of a centrally applied mobilisation with movement (MWM sustained natural apophyseal glide - SNAG) performed on the L4 motion segment revealing a percentage increase in SCR's in the right and left lower limbs in order of 10.6% and 11.2% respectively. This response was double that of the placebo condition and statistically significant

compared to the control group ( $p=0.04$  and  $p=0.0004$  respectively). Tsirakis and Perry (2010) also investigated the effects of a unilaterally applied modified Spinal Mobilization with Leg Movement (SMWLM) technique (Mulligan, 2004:77) on SNS changes in the lower limbs. These authors revealed that the SMWLM technique resulted in a statistically significant increase in a percentage change in SCR's in the order of 30.6% ( $p= 0.049$ ) within the treatment side.

It is now recognised that MT can produce neurophysiological (SNS) effects, in humans, and that SNS responses to MT are linked to immediate hypoalgesia (Wright and Vicenzino, 1995; Vicenzino et al., 1995 and 2001; Paungmali et al., 2003; Solly, 2004; Zusman, 2004; Bialosky et al., 2008 and 2009b) and sympathoexcitation (Paungmali et al., 2003 and Perry and Green, 2008). These SNS responses were found to be specific to mechanical nociception (Vicenzino 1995 and 1996; Sterling et al., 2001) and thermal nociception (Bialosky et al., 2008 and 2009). These findings have led to the concept that MT exerts its initial effects by activating specific pathways from the peri-aqueductal gray (PAG) region of the brain (Potter et al., 2005; Lanotte et al., 2005; Bialosky et al., 2009) and also by the spinal cord and central pain modulatory circuits and inhibition of the dorsal horn (Price et al., 2002). These mechanisms can be influenced differently by different types of manual techniques including oscillatory (Chiu and Wright, 1996; Perry and Green, 2008; Jowsey and Perry 2010) and non-oscillatory techniques (Paungmali et al., 2003; Moulson and Watson, 2006; Tsirakis and Perry, 2010; Moutzouri, Perry and Billis, 2012). However, prior to this study, no published articles have reported recordings of SCR's following lumbar spine rotator manipulation or during repeated McKenzie EIL exercises.

## **4.2. Aims and Objectives**

The aim of this pre-clinical study was to generate data on 2 commonly utilised lumbar treatment techniques and to compare the magnitude of SNS change (SCR) during and between the two treatments.

### Objectives:-

The objectives of this pre-clinical study of the effects of different treatment on SNS responses were as follows:

- 1) to observe the SCR's to a repeated McKenzie Extension In Lying (EIL) treatment technique
- 2) to observe the SCR's to a rotatory grade V segmental (L4/5) lumbar manipulation technique (Manip)
- 3) to calculate any differences in effect between the two techniques
- 4) to compare any effects between the uppermost/"opening" (or gapping – Evans, 2009) side and the underneath/"closing" (or impacting – Evans, 2009) side during the manipulative procedure.
- 5) to generate SCR data to permit a power calculation for the clinical study on LBP patients and for future post-doctoral research.

## **4.3. Null Hypotheses**

The following null hypotheses were tested within this pre-clinical study:-

- H01) There is no significant difference in SCR's as a result of performing 3 sets of 10 McKenzie EIL exercises.
- H02) There is no significant difference in SCR's as a result of performing a rotatory grade V lumbar manipulation to the L4/5 segment.

- H03) There is no significant difference in SCR's between the McKenzie EIL exercise and the manipulation (grade V) technique.
- H04) There is no difference in SCR;s between the uppermost/"opening" (or gapping – Evans, 2009) side and the underneath/"closing" (or impacting – Evans, 2009) side during the manipulative technique..

#### **4.4. Method**

The overarching methodological philosophy of this study was positivistic, that is, seeking falsification of the null hypothesis through the process of hypothetico-deduction. A prospective, quasi-experimental, randomized, independent subjects design was selected to establish a cause-effect relationship. Quasi-experimental designs are appropriate to investigate differences in effect of two interventions (the manipulation [grade V] or McKenzie EIL technique) in the absence of a control group. The reasons for not recruiting a control group in this study were based upon the fact that previously published researchers (and this studies researcher) have conducted a number of other studies where control group data had been gathered. Subsequent comparisons of this data had revealed that all control groups had very similar findings regarding SCR's. The findings of studies where control group data have been reported are summarized in table 11 overleaf.



**Table 11:** Reported data for control groups where SC percentage change values given

Researchers	Treatment Modalities (Design)	Participant numbers & groups	Control Group SNS (SC) % change from baseline during the “intervention period”)	SE	CI
Moutzouri, Perry & Billis (2012)	L4 MWM into flexion <i>(Independent Groups design)</i>	n= 45 15 control 15 placebo 15 Uni PA	-1.01	N/A	N/A
Rao & Perry (2011)	MWM Difference between 6 or 10 reps to L4 segment with flexion <i>(Independent Groups design)</i>	n= 90 30 control 30 (x 6 reps) 30 x (10 reps)	-0.40	+/- 1.11	-2.68 to 1.87
Tsirakis & Perry (2010)	L4/5 SMWLM <i>(Independent Groups design)</i>	n= 45 15 control 15 placebo 15 Uni PA	0.83	+/-1.70	N/A
Perry & Green (2008)	L4/5 uni-lateral PA mobilisation <i>(Independent Groups design)</i>	n= 45 15 control 15 placebo 15 Uni PA	-0.99	+/- 2.41	N/A
Moulson & Watson (2006)	MWM Rotation to C6 <i>(Repeated Measures design)</i>	n= 16 control placebo treatment	-0.044	+/- 0.015	-0.077 to -0.011
Vicenzino et al. (1995)	Unilateral Glide to C5/6 <i>(Repeated Measures design)</i>	n= 24 control placebo treatment	-0.20	N/A	N/A

(Where **Blue** boxes indicate lumbar spine data; **Pink** boxes represent asymptomatic participants and other treatment areas. N/A = Not Available)

Unfortunately, not all published studies reported control group percentage change in the intervention period (Sterling et al., 2001; Vicenzino et al., 1998) however, in those studies that provide this data, a comparison of the results (of the 255 control condition participants) are very similar demonstrating a small amount of variance, both within and between studies, with a combined-data range of -1.01 to 0.83% indicating stability in control readings in the ‘intervention period’ thereby countering the need to recruit a control group for the current study as it was reasoned that the results would not be dissimilar. Furthermore, the percentage change recorded in the control conditions in the above studies is below the bounds identified by the previous reliability study of this thesis (Chapter 3), that identified the SRD value as 4.632%.

#### 4.3.1. Power calculation for sample population

A previous study (Perry and Green, 2008) recorded SCR's in the lower limbs in control, placebo and lumbar spine treatment situations. Using the n-Query advisor software and based upon a pooled standard deviation estimate from placebo and control groups of 9.4%, it was calculated that 50 participants (25 per group) would enable a SCR difference of 7.5% in percentage change from baseline to be detected at the 5% significance level with 80% power. This effect size was selected as has been utilised in a previous paper looking at SNS treatment responses in the lumbar mobilisations (Perry and Green, 2008) and was greater than the SRD established in the pilot study (4.6%).

#### 4.3.2. Participants

The study recruited a convenience sample of 52 healthy, physiotherapeutically naïve, asymptomatic, non-smoking volunteers from the student and staff population at Coventry University (demographic characteristics are detailed in table 12). Of those recruited, 2 were unable to attend on the day of data collection and were therefore omitted from the final data analysis.

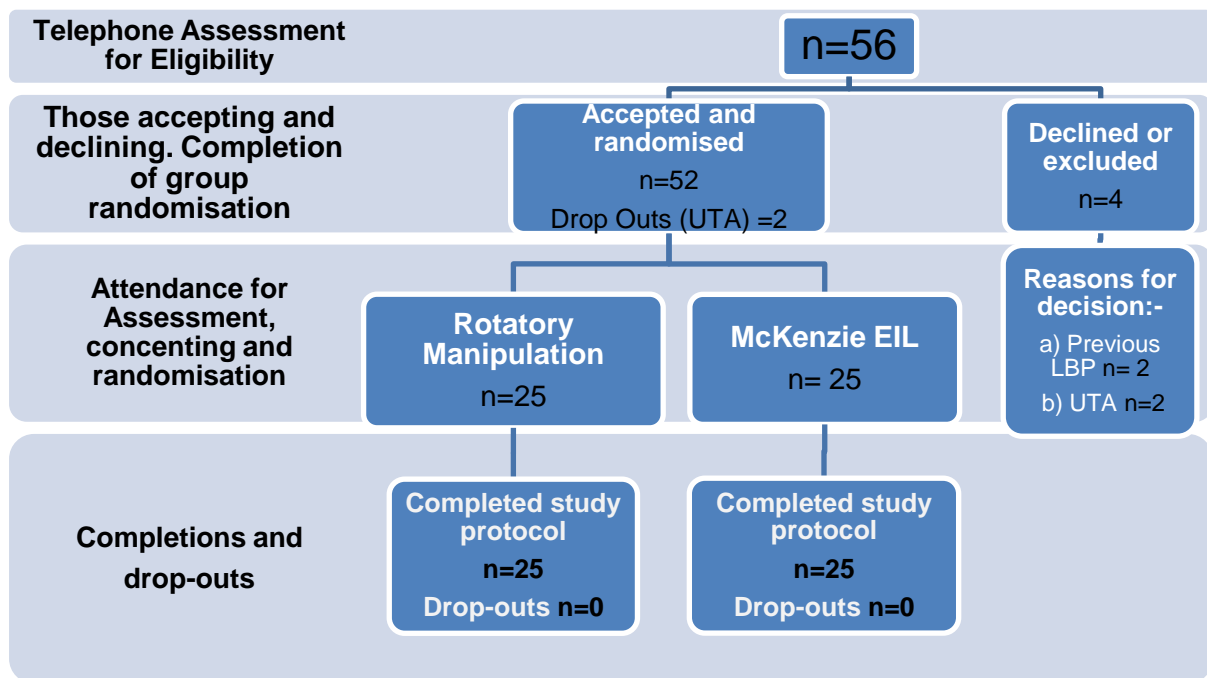
**Table 12: Baseline measures of demographic variables of the two experimental groups**

<b>Demographic Variable</b>	<b>McKenzie EIL</b>	<b>SMT</b>
Gender (n)	25	25
<i>Male</i>	10	11
<i>Female</i>	15	14
Age ( <i>years</i> ) Mean (SD)	37.7 (8.28)	36.9 (8.27)
Height ( <i>cms</i> ) Mean (SD)	176.4 (11.12)	175.8 (10.98)
Weight ( <i>Kgs</i> ) Mean (SD)	70.36 (10.14)	71.10 (11.03)

Recruitment was achieved by visiting the lectures and seminars (where the target population were in attendance), handing out information sheets with the researchers contact details, and inviting students and staff to consider participation in a one-off data acquisition procedure whereby they would undergo one treatment commonly used in the management of lower back symptoms. Participants that contacted the investigator were interviewed for their suitability for the study (by phone) and, if considered suitable, invited to attend for a brief assessment and for consenting to the study (see consort diagram, figure 16 for details of the recruitment process). All volunteers satisfied the criteria set out in previous studies (Moulson and Watson, 2006; Perry and Green, 2008) and documented in table 10 of the previous chapters reliability study. The only difference in the exclusion criteria being that they had no contra-indications to manual therapy treatments as detailed by Maitland et al. (2005). An asymptomatic population was again selected for this pre-clinical study as it was unknown if any responses could be detected in a normal healthy population and it was necessary to limit the potential confounding effects that prescription medications, pain and the existence of co-morbidities might have on the primary outcome measure (SCR). Furthermore, it is recognised that, ethically, it is good clinical practice to establish normative values in an asymptomatic population prior to conducting clinical research on patient populations (DoH Research Governance Framework, 2005).

Prior to acceptance into the study, participants were assessed by the researching therapist (JP) means of a standard physiotherapy subjective and physical examination to ensure that they had no contra-indications to either treatment procedure. A mixed gender group was utilised, to ensure that extrapolation of the results to the target patient population was not inhibited.

**Figure 16:** Consort diagram illustrating the recruitment and randomisation of participants



All volunteers received written information (appendix VI) indicating that they would be given a commonly administered manual therapy treatment technique for ‘back trouble’. Participants were advised that the nature of the treatment would be painless and that they may or may not hear a “click” in their back and that this is normal and they should not be concerned but should they wish to discontinue the treatment at any point they would be allowed to do so without prejudice or coercion. They all indicated that they understood the information provided and gave informed consent prior to the experiment (appendix VI). They were not advised about the specific nature of the measurements being taken (that is, SNS responses), just that the measures were non-invasive, painless and were recording any sweat changes in their feet before, during and after completion of the treatment.

The fifty participants attended, on one occasion, in order to undergo one of the two experimental conditions (the manipulation or the McKenzie EIL technique – see below). The researcher was responsible for conducting the treatments as the final clinical study would involve the researcher providing the treatments to the follow-on clinical/patient population and was considered to be a suitable strategy to reduce any bias that might occur as a result of different therapists utilising different treatment approaches. At the time of the study, the researcher performing the treatments was a senior physiotherapist with 16 years of musculoskeletal clinical experience, she had a Masters degree in Manipulative Therapy (Coventry University, 2001), was a full member of the Musculoskeletal Association of Chartered Physiotherapists (MACP) and had previously held the position of Clinical Team Lead in a musculoskeletal out-patients department of a Leicester city accident and emergency hospital (Band 8a). Currently, the researcher works as an academic within the Faculty of Health and Life Sciences at Coventry University as a senior lecturer in musculoskeletal physiotherapy research, lecturing on both the undergraduate and post-graduate programmes and specialising in spinal musculoskeletal and manual therapy.

Internal validity of the study was enhanced with the incorporation of a number of strategies, namely; by using the same therapist to conduct all treatments thereby minimising variability in the technique, by blinding both the participants and the researcher to the data being acquired during the treatment procedure, and by the utilisation of random allocation of participants to one of the two treatments by using random numbers tables generated by the nQuery software programme. For the participants receiving the manipulation technique, further randomisation of the side of treatment (right or left) was conducted by also employing a random numbers table generated by the nQuery software programme.

Ethical approval for the study was granted from the Coventry University Ethics Committee (appendix IV).

#### 4.3.3. The choice of segmental level for treatment application

The two treatments selected for this study were the rotatory grade V lumbar manipulation technique and the repeated McKenzie EIL exercise which are detailed below. Both techniques were performed by the Researcher and localised to the L4/5 segmental level in order to maximise the focus of the effect. The L4/5 segment was selected as it has been reported to be the most common site of symptoms within the lumbar region (Louis, 1981; Butler, 1991 and Grieve, 1994) and reflected the researcher's clinical experience of patients attending for physiotherapeutic management of LBP. In most instances, the area of symptom provocation is the lower lumbar segmental region (L4/5 and L5/S1 levels) and is frequently accompanied by referred symptoms into the lower limb and foot. This observation is supported by Nathan (1968) who dissected 390 adult cadaveric lumbar sympathetic trunks and discovered that osteophytic encroachments resulted in macroscopic changes in the sympathetic trunks of 78.4% of his subjects. The highest incidence was seen at the L4/5 intervertebral joint and it is speculated (Grieve, 1994) that symptoms of sympathetic trunk compression may be expected to appear in the lower limbs and/or pelvic viscera.

Based on the cadaveric studies of neuraxial motion by Louis (1981), the concept of neural 'tension points' was introduced (Butler, 1991). Butler (1991) has observed three such tension points within the central nervous system, at the C6, T6 and L4 levels. With specific reference to the L4 segment, he argues that the dura mater is firmly attached to the posterior longitudinal ligament, and consequently tethers the

system, limiting movement of the emerging peripheral nerves, therefore generating a vulnerable site within the nervous system at this level. It is this phenomenon and its potential effects on both neural and vascular biomechanics, which he suggests may be, in part, responsible for his clinical observations.

It was therefore, a combination of both personal clinical observation, and the anatomical considerations of cadaveric and clinical studies that led to the decision to focus this element of research on the L4/5 segment.

#### 4.3.4. Treatment Modalities

**i) The Repeated McKenzie EIL exercise technique:** - A localised centrally applied postero-anterior mobilisation technique was statically applied to the spinous process of the L5 segment (with over-pressure) whilst the subject actively performed 3 sets of 10 repetitions of a lumbar extension manoeuvre in prone lying (see figure 17 overleaf) according to the protocol described by McKenzie (2003). There was a one minute rest between each of the three sets (of 10 repetitions). The EIL treatment took no more than 4 minutes to complete.

**Figure 17: The repeated McKenzie EIL exercise (with overpressure) technique**

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The unabridged version of the thesis may be viewed at  
the Lanchester Library, Coventry University.

**ii) Rotatory Manipulation Technique:** - Following the localisation and isolation of the L4/5 mid-range position (between lumbar flexion and extension) with a passive physiological intervertebral movement (PPIVM) technique (Maitland, 2005), a localised segmental rotation technique (high-velocity low amplitude grade V manipulation) was performed to the L4/5 segment (that involved joint gapping in a starting position that included a combination of 3 physiological movements that were in a coupled manner and designed to produce an audible “pop”/gapping of the joint surfaces). Random allocation procedures determined whether the participant received this in either right or left side-lying (computer generated random allocation of left or right side) and the treatment technique was performed according to the detailed protocol described in Maitland et al., (2005), by Herzog (2000) and provided in video CD format within the book by Gibbons and Tehan (2000; see a snap-shot of the technique in figure 18 below). In accordance to the procedure detailed by Gibbons and Tehan (2000), and including the PPIVM technique to isolate the L4/5



segment, the treatment took 2 minutes to complete (the last 50 seconds was the HVLAT manipulation technique).

**Figure 18: The L4/5 rotatory manipulation (HVLAT) technique (initial set-up illustrated)**

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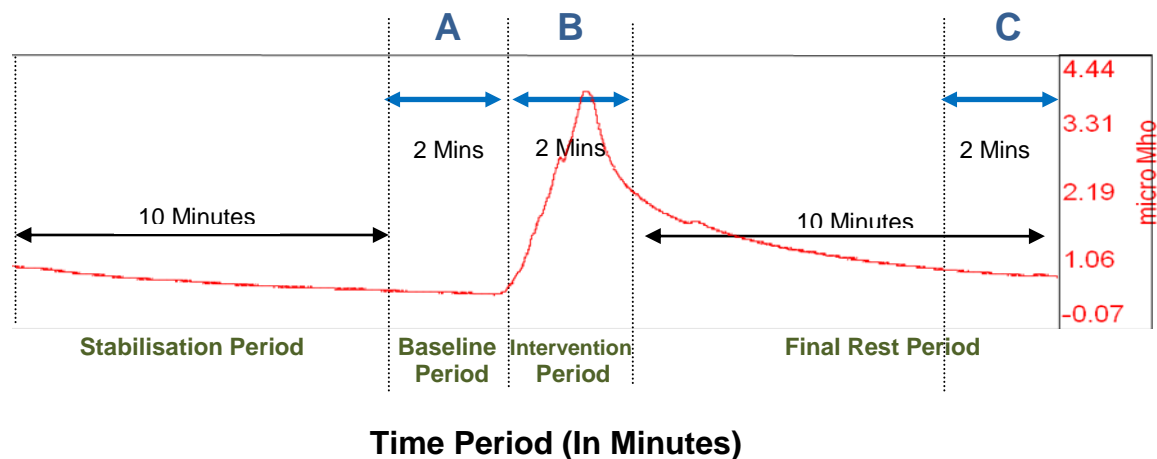
**4.3.5. Sympathetic Nervous System outcome measures (data collection)**

Physiological recording of SC was continuously measured, without interruption, throughout the entire experimental period (pre-treatment, peri-treatment and post-treatment) by a Biopac GSR100B Electro-dermal Activity Amplifier (MP35; Biopac Systems Inc; Santa Barbara, CA), employing a constant voltage technique and sampling the absolute, direct current SC at the rate of 200 samples per second using silver/silver chloride electrodes in exactly the same way as detailed in the pilot study.

Prior to data collection the temperature and humidity of the room were noted in accordance with the protocol set out by Petersen et al., (1993) and Chiu and Wright (1996). The skin was prepared in accordance with the standard protocol for Biopac

measurement (Petersen et al., 1993; Chiu and Wright, 1996 and Perry and Green, 2008) and replicated the set-up procedure detailed in the previous chapter. The SC electrodes were applied, as before, to the second and third toes of each foot as advised by Perry & Green (2008). During the entire experimental procedure participants lay in a comfortable position upon an adjustable treatment plinth. As before, participants were instructed, prior to the commencement of data recording, not to sleep, deep breathe, cough or sneeze, talk, fidget with the sensors, or move unless otherwise instructed to do so by the investigator. Following previously documented protocols (Chiu and Wright, 1996; Perry and Green, 2008), the participants lay quietly for the initial 10 minute period, used to stabilise the SC measures. SC values were continuously recorded throughout the course of the experimental period (pre-treatment, peri-treatment and post-treatment), including the 10 minute final rest period. The whole procedure lasted no more than 24-26 minutes (manip or EIL technique respectively). After all the data was collected and saved, analysis of the output consisted of calculating the “integral” readings for the three data capture points (baseline, intervention and final rest periods). The ‘baseline period’ consisted of the 2 minutes following the 10 minute stabilisation period. The ‘intervention period’ readings were taken as the initial 2 minutes of the treatment period (where either the McKenzie EIL or the Manipulation technique was performed). Following completion of the treatment and during the 10 minutes of rest (in the original starting position) the last 2 minutes of the rest period were used and documented as the ‘final rest period’. Thus, each participant generated 3 readings each representing a 2-minute period in the baseline (illustrated in Figure 19 overlaid by the letter A), intervention (B) and the final rest period (C) allowing comparative analysis.

**Figure 19:** Schematic representation of the timing protocol employed for each participant



By turning the laptop screen away from the treatment area neither the participant nor the principal Investigator was able to receive any feedback regarding SNS activity (see figure 11 in the pilot study), thus ensuring the blinding of the participant and the researcher to the effects of treatment.

#### 4.3.6. Data analysis of skin conductance response (SCR)

Analysis of the SC analysis and the SCR data obtained involved calculation of the “Integral Measurement” ( $\mu\text{Mho's}$ ) for baseline, intervention and final rest periods. Intervention and final rest period values were then converted into percentage change (PC) from baseline using the formula below and further detailed in a previous paper (Perry and Green, 2008).

$$(\% \text{ change}) \text{ SCR} = \frac{(y-x)}{x} \times \frac{100}{1}$$

Where:-  $y$ = new SC reading,  $x$ = original SC reading

The Statistical Package for Social Scientists (SPSS v.15) software was used to calculate descriptive (mean, SD, mean differences, maximum, and minimum values) and inferential statistics (paired and unpaired t-tests) to test the 4 null hypotheses.

## 4.4. Results

### 4.4.1. Environmental conditions

Room temperature was recorded at the beginning and end of each subject's experimental session as per published guidelines (Uematsu et al., 1988) with relative constancy within each session demonstrated (mean 24.7°C, SD 0.275, range 24.2–25.3°C) with a maximum within subject experimental room temperature variation being no more than 0.3°C (mean 0.2°C, SD 0.1°C, range 0.0-0.3°C).

### 4.4.2. Skin Conductance Analysis

Demographic characteristic of the participants are displayed in table 13 below. Both groups were similar in age and the gender distribution.

**Table 13: Demographic characteristics of the two treatment groups (Age and Gender)**

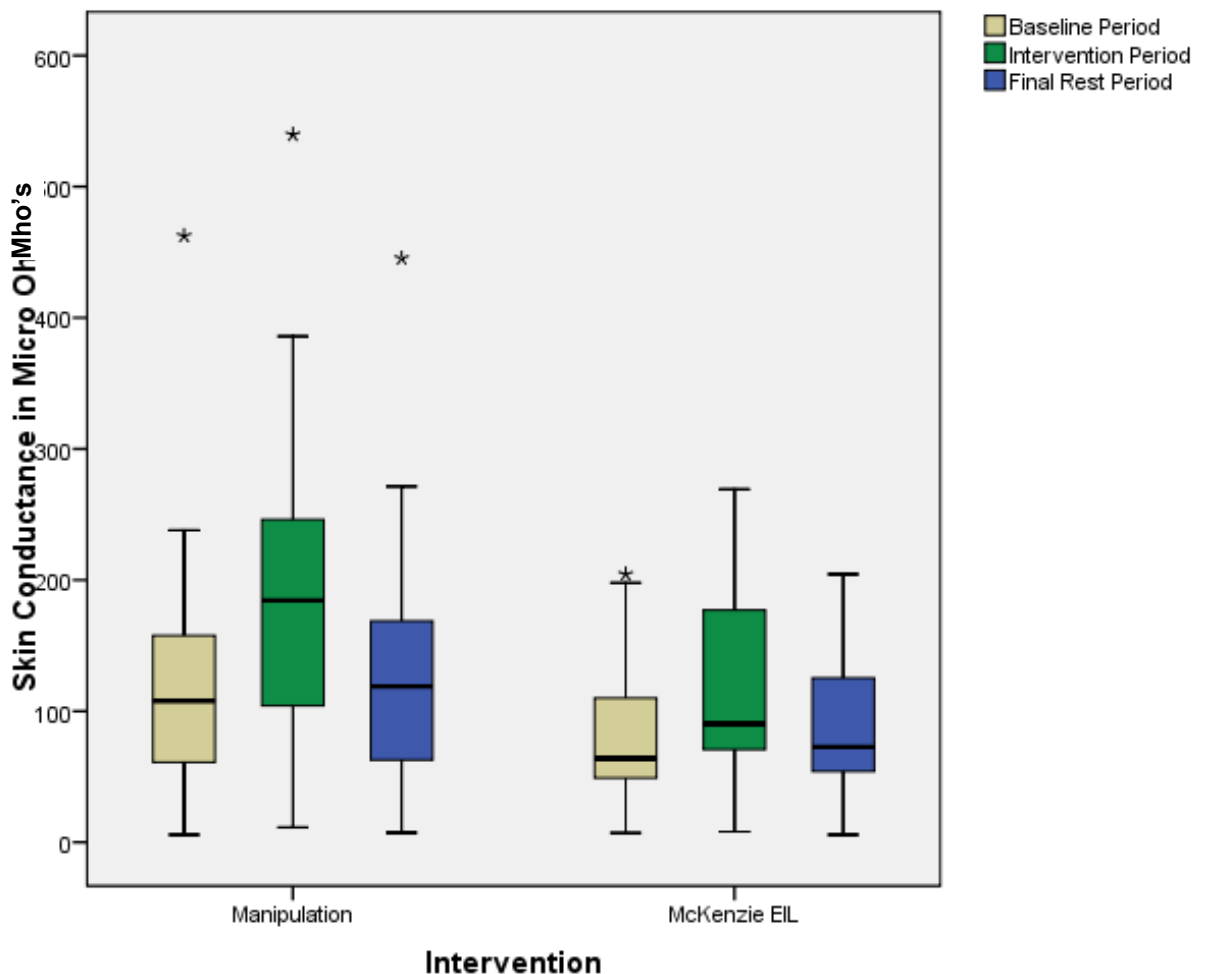
		<b>Manipulation Group</b> (n=25)	<b>McKenzie EIL ex Group</b> (n=25)
<b>Age</b>	Mean	37.8	37.2
	SD	9.2	7.0
	Min	19	21
	Max	50	50
<b>Gender</b>	Males	18	17
	Females (%)	7 (28%)	8 (32%)

Descriptive statistics for the primary outcome measures (SC analysis and SCR's) for the two groups over the three time periods are illustrated in Table 14 and Figure 20 overleaf.

**Table 14:** Illustrating group mean  $\mu\text{Mho's}$  & Percentage Change (PC) readings

Group	Intervention period	Mean ( $\mu\text{Mho's}$ )	Mean difference from baseline ( $\mu\text{Mho's}$ )	SD ( $\mu\text{Mho's}$ )	Mean PC (SD)	Min	Max
Mc-Kenzie EIL (n=25)	Baseline period	84.6		53.4			
	Intervention Period	120.1	35.5	74.5	35.74 (24.02)	-4.1	96.8
	Final Rest Period	88.2	2.6	52.9	2.72 (18.08)	-51.7	38.1
Manip (n=25)	Baseline period	119.0		97.4			
	Intervention Period	193.6	74.6	126.4	76.35 (75.07)	8.8	441.8
	Final Rest Period	128.9	9.9	94.0	12.94 (31.29)	-28.2	187.3

**Figure 20:** Boxplot of changes in SC ( $\mu\text{mho's}$ ) between the baseline, intervention and final rest periods for the 2 groups. (Where \* indicates an extreme case).



There was increased SC activity levels (sympatho-excitation) from baseline to intervention periods for both treatments (McKenzie EIL = 35.5 $\mu$ mho's, 36% change from baseline; manipulation group = 74.6  $\mu$ mho's, 76% change from baseline). Both these results were considerably greater than the SEM (0.1138), percentage error (4.632%) and the SRD (0.315) values (of the previous chapter) indicating that the results were not due to measurement error/ variability. Differences between the intervention and the final-rest periods revealed that for the McKenzie EIL technique there was a return of SC activity levels after cessation of the intervention (2.7% change from baseline). The manipulation group also had a return in activity towards baseline although the activity remained higher than that of the McKenzie EIL treatment (12.9% change).

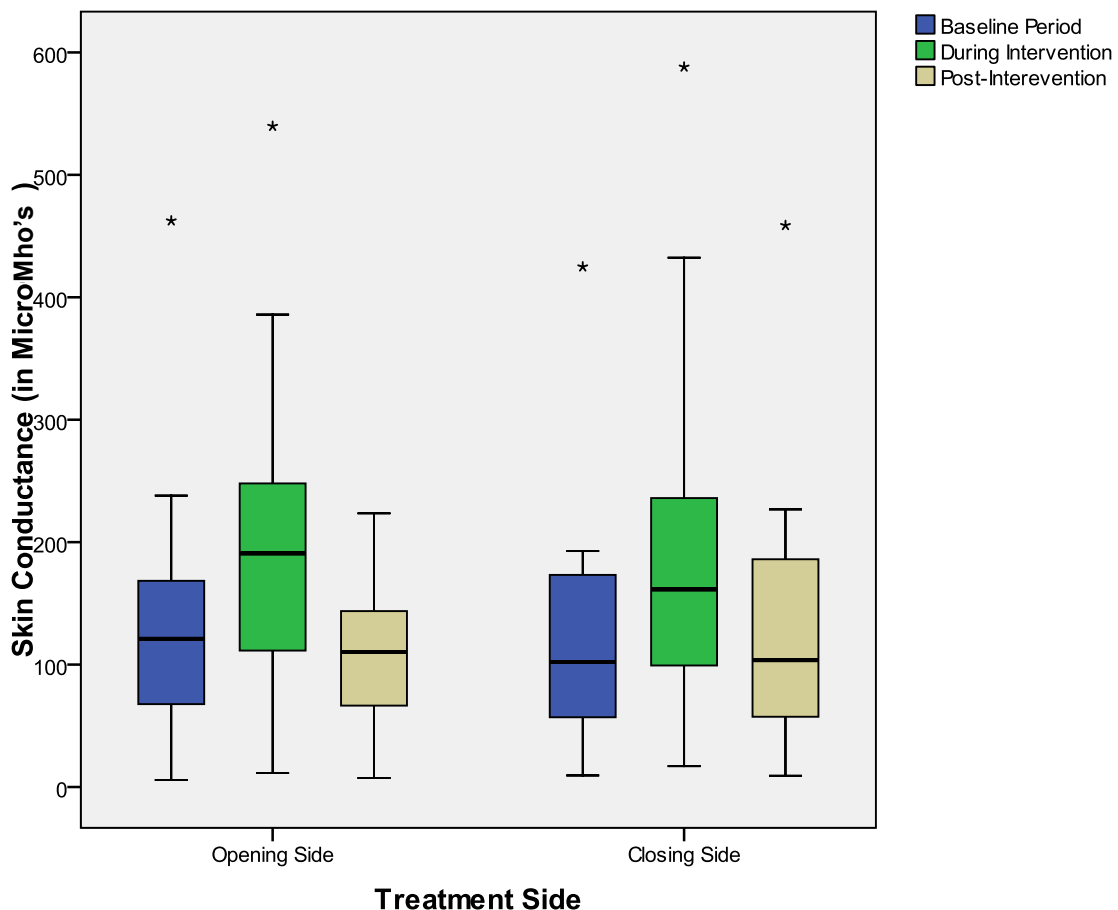
Descriptively, differences in the magnitude of effect between the two groups indicated that the manipulation technique resulted in higher SCR's (76.35%) compared to the EIL exercise (35.74%). Indeed, the difference between the manipulation technique and the EIL exercise was more than twice (in favour of the manipulation technique) with the treatment SCR's, in the final rest period, remaining higher for the manipulation technique (12.94%) than for the EIL exercise (2.72).

Regarding the existence of any side-specific SCR's within the manipulation group only, data is provided in table 15 and figure 21 (overleaf) and suggested that there was little difference between the uppermost (opening) side (79.65%) and the underneath (closing) side (73.06%) during the intervention periods. This was also the case in the final rest periods (15.57% and 10.30% respectively) although the opening side did have higher readings.

**Table 15:** Comparisons between the percentage change (PC) in SC between the opening (uppermost) and closing (underneath) sides in the manipulation group

Manipulation Group (n=25)	Side	Mean difference (μMho's)	Mean Percentage Change (%)	Standard Deviation (PC data)
During Intervention	Opening Side	74.57	79.65	84.90
	Closing Side	75.77	73.06	65.38
Final Rest Period	Opening Side	9.83	15.57	37.98
	Closing Side	11.07	10.30	23.27

**Figure 21:** Boxplot comparing the manipulation group treatment sides (where \* indicates an extreme case)



To test the null hypotheses, inferential statistical analyses were conducted. For H01 and H02 paired t-tests were performed (independently) for each treatment between

the baseline, intervention and the final-rest periods revealing that there was a statistically significant difference in the McKenzie EIL group between the baseline and the intervention period ( $p=0.0005$ ), between the intervention and the final-rest period ( $p=0.0005$ ) but not between the baseline and the final-rest period ( $p=0.173$ ). therefore null hypothesis 1 was rejected as there was evidence to suggest that there was a statistically significant difference in SCR during the intervention period but that SCR was not maintained into the final rest period.

Inferential testing of H02 (with the manipulation group) revealed a statistically significant differences in SCR's between the baseline and the intervention period ( $p=0.0005$ ), between the intervention and the final-rest period ( $p=0.0005$ ) and between the baseline and the final-rest period ( $p=0.001$ ). Therefore null hypothesis 2 was rejected as there was evidence to support a statistically significant difference in SCR's during the intervention period that was maintained into the final rest period.

To test H03, an unpaired/independent t-test was performed between the two groups during the intervention periods and between the final-rest periods to test for any difference in magnitude of SCR's and differences in the longevity of the SCR's between the two techniques. During the intervention period there was a statistically significant difference between the two groups with the manipulation technique having a greater effect in the order of 40.61% ( $p=0.001$ ) clearly exceeding the SEM, percentage error and SRD measurements. During the final-rest period there was also a significant difference between the groups with the manipulation group having a 10.22% greater response overall ( $p=0.048$ ).

Testing of H04 within the manipulation group revealed that there was no statistically significant difference between the sides during ( $p=0.76$ ) or following ( $p=0.557$ )



treatment. Therefore, null hypothesis 4 was not rejected as there was no statistically significant evidence of a difference in SCR's between the opening and the closing sides during or following the manipulation.

Details of the power calculation for the clinical study are provided in the following chapter.

#### **4.5. Discussion and limitations of the findings**

This is the first study to objectively measure the magnitude of effect (on the SNS) of two commonly used treatment techniques to the lumbar spine. Both techniques produced statistically significant changes in SNS activity in the lower limbs (that were greater than the SRD) with the manipulative technique producing twice the size of effect as the McKenzie EIL technique (74.6  $\mu$ mho's or 76.3% increase in activity from baseline  $p= 0.0005$  for manipulation; 35.5  $\mu$ mho's or 35.7% increase,  $p=0.0005$  for the McKenzie EIL exercise group). Only the manipulation technique had a lasting effect that was carried into the final rest period (12.9% increase from baseline  $p=0.012$  manipulation group; 2.7% increase,  $p=0.173$  for McKenzie EIL group).

These findings suggest that although both techniques are capable of causing statistically significant changes in SNS activity, the manipulation technique was able to cause twice the magnitude of response (when compared to McKenzie EIL) and has an effect that continues into the final rest period. The lasting effects of manipulation were also recorded by Haas et al., (2003) who reported effects (on patient-reported pain and joint stiffness) lasting up to 5 hours post-manipulation in their patients receiving cervical manipulation.

The changes in SNS activity following the two treatments in the current study are comparable to other studies effect with a unilateral PA mobilisation to the lumbar spine resulting in a 13.3% increase in activity (Perry and Green, 2008), a centrally applied MWM to L4 resulting in a 10.2-11.6% increase in activity (Moutzouri, Perry and Billis (2012) and a SMWLM resulting in a 30.6% increase in SNS activity in the treated leg (Tsirakis and Perry, 2010). In terms of the observed efficacy of SCR's in asymptomatic participants, it would appear that manipulation achieves the greatest increase in SCR (76%), followed by McKenzie EIL exercises (36%), SMWLM technique (30%), unilateral facet joint mobilisation (13%) and MWM into lumbar flexion (10-11%). Certainly, future research now has a quantifiable platform from which to launch a raft of further enquiry with respect to these, and indeed, other treatments. However, this data may not be transferrable to a patient population with LBP and further research exploring the neurophysiological status and SCR's to treatments is warranted to verify the findings for clinical application.

A possible explanation for the findings of this study may be the differences in the physical nature of the treatment. Although both treatments involved physical contact between the therapist and the participants lumbar region, the manipulative technique was a passive procedure (on the part of the participant) with the position of the heart remaining relatively static rather than the McKenzie EIL technique whereby the participant actively moves the torso thus causing relative vertical movement of the heart. Slater et al., (1995) considered this a possible explanation for the findings of their study, arguing that orthostatic changes may be responsible for changes in SNS activity. If this were the case in the present study then the McKenzie EIL technique would be most likely to cause BP changes and a greater SNS change due to the effort exerted, by the participant, and the changes in the head-body relationship

during treatment compared to the manipulation technique. Another explanation may be the differences in the length of time each of the two techniques was performed (McKenzie EIL = 3 repetitions of 10 McKenzie EIL exercises with a one minute rest between repetitions versus one manipulation lasting approximately 50 seconds). If this difference were to be a governing factor in the magnitude of effect of the techniques then it would make intuitive sense that the more protracted, and participant active, technique (McKenzie EIL) would have the greatest magnitude of effect however this was not the case implying that it was not necessarily the time taken to complete the treatment that was the governing factor here. Finally, one other element that may have resulted in the differences in response, between treatments, may have been the extent of physical contact between the therapist and the participant. The manipulative technique requires the therapist to have a greater degree of close physical contact with the participant (arms, thighs and trunk) in order to achieve the required body-part leverage necessary to achieve a successful, localised thrust manoeuvre, whereas the EIL technique requires only localised segmental hand contact, at the 5<sup>th</sup> lumbar spinous process, during the technique. It is possible that this component of touch may have been an important element. Although no previous studies have reported the effects of touch on SCR's and SC activity levels, Olausson et al., (2008 and 2010) reported that light stroking touch stimulated C-tactile mechanoreceptors which were linked to cortical processing systems and to SNS excitability. Sefton et al., (2011) reported reductions in  $\alpha$ -motorneurone pool excitability and EMG amplitudes with an increase in cervical spine range of motion following a neck massage in 16 chronic neck pain patients. Although Sefton et al.'s, 2011 study was a randomised cross-over placebo-controlled trial, the use of a repeated measures design and a limited sample size may indicate

that the results should be interpreted with caution. Furthermore, it may be argued that the haptic sense received during manipulation is dissimilar to the light stroking touch found, by Olausson et al., (2008), to induce SNS excitation.

Many authors allude to the immediacy of effect of manipulative responses with the mechanism of action being ascribed to modulation of dorsal horn excitability (Boal and Gillette, 2004; Bialosky et al., 2009). Bialosky and his team conducted research on both normal healthy volunteers (Bialosky et al., 2008) and patients with symptomatic LBP (Bialosky et al., 2009) revealing that the lumbar manipulative technique produced significantly greater hypoalgesia than McKenzie EIL or stationary bicycling. Bialosky et al., (2008 & 2009) hypothesized that manipulative techniques inhibit pain at the dorsal horn of the spinal cord through alterations of neuroplastic changes consistent with central sensitization (Boal and Gillette 2004). They suggest that manipulation may provide a novel stimulus that acts as a counter-irritant to C fibre-mediated pain. Wright and Vicenzino (1995), Vicenzino et al., (1996 & 1998) and Sterling et al., (2001) observed that spinal MT's were also associated with SC changes and hypoalgesia in symptomatic participants (Kuraishi et al., 1983; Vicenzino et al., 1998; Sterling et al., 2001) leading to the concept that the dPAG region of the mid-brain may have a role in facilitating the descending pain inhibitory system and therefore an associated reduction in perceived pain. If this concept is extrapolated to the current study then it is plausible to expect a greater response to the manipulative technique rather than the McKenzie EIL technique although it is noted that the participants of the current study were asymptomatic and pain-free and therefore it was deemed necessary to repeat the study on a symptomatic LBP population in order to determine any anti-nociceptive effects. Although it is worthy of note that Bialosky et al., (2008 and 2009) found no differences, between a

normal/experimental population and a symptomatic/patient population, in the degree of hypoalgesia following lumbar spinal manipulation indicating that results on healthy normals may reflect patient responses.

Further sub-group analysis of the manipulation group revealed that the SNS response was not a side-specific phenomenon, that is, that there was no significant difference in the magnitude of the effect between the uppermost/opening and the underneath/closing side ( $p= 0.76$ ). From a clinical perspective, most therapists reason that placing the symptomatic side uppermost will theoretically 'open' or 'gap' the dysfunctional intervertebral foramen with the rotatory manipulative technique and hypothetically 'release' impinged structures and augment healing through restoration of movement (through joint cavitation) and improved local motor control of the dysfunctional segment (Bialosky et al., 2009 and Herzog, 2010). Contrary to the findings of Perry and Green (2008), who observed a side-specific response to a unilaterally applied technique, the manipulative technique in the current study was not side-specific, that is, the rotatory manipulation technique was tensioning both facet joints of the selected segment rather than having a specific effect on the uppermost facet joint therefore accounting for the bilateral effect noted. An alternative explanation might be that the effect was not at a spinal segmental level, but was at a central/cortical level (Bialosky et al., 2009). The findings of Lovick (1991), Wright (1995), Zusman (2004) and Bialosky et al., (2009) might support a more global, central response to a segmentally applied technique. The findings of the current study suggest that the manipulation technique may be conducted on either side and still generate the same SNS response, although the author acknowledges that these results should be interpreted with caution until a larger ( $n=25$  in this study which is small) or a patient population have been sampled and

the variability (spread/SD) within the data reduced. Furthermore, the author acknowledges the argument that the use of t-tests in these analyses may have resulted in the risk of a type I error (rejection of the null hypothesis when in fact the null hypothesis is true), however, reanalysis, using an ANOVA statistical approach, confirmed the original results.

At the time of conducting, and reporting (Perry et al., 2011) these preliminary pre-clinical findings, it was not known how these responses might translate to a symptomatic population and were considered a limitation to this study. Indeed, it is proposed that future research be conducted on a symptomatic patient population to investigate how spinal treatments might influence SNS activity levels and whether there is any correlation in SNS findings and patient-reported levels of pain/symptoms and functional disability (through validated questionnaires). O'Leary et al., (2007) conducted a study on patients with neck pain revealing that specific upper cervical spine (for C2/3 dysfunction) exercises resulted in immediate hypoalgesia but changes in peripheral SNS activity (C6/7 distribution) were negligible. Whilst the authors agree that different physiotherapeutic treatments may result in different physiological effects with different endogenous pain control mechanisms it is worthy of note that electrode placement may have been a factor in O'Leary et al's., study.

In conclusion, this pre-clinical study demonstrated that both the McKenzie EIL exercise and the rotator manipulation techniques can affect an immediate and statistically significant change in SNS activity (sympathoexcitation) and that the magnitude of activity for the manipulation technique was double that of the McKenzie EIL procedure. Also, only the manipulation technique had a prolonged effect on SNS activity levels into the final rest period. The study also revealed that there was no

side specific effect with the manipulation treatment. Putting together the results of the reliability study of chapter 3 and the current study, it would appear that both the manipulation technique and the McKenzie EIL exercise are viable treatment options (along with MWM and facet joint oscillatory mobilisation techniques – Moutzouri, Perry and Billis, 2012 and Perry and Green, 2008) for the lumbar spine as indicated by SCR's over and above those that can be explained by measurement variability (SRD) and these results complement those of other researchers indicating that both mobilisation techniques (Perry and Green, 2008) and MWM's (Moutzouri, Perry and Billis, 2012) performed to the lumbar spine can result in skin conductance responses that are recordable within the toes of normal healthy human volunteers.

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## **5. Clinical Study**

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### **5.1. Title**

#### **“A Longitudinal, Pragmatic, Observational Study Of The Sympathetic Nervous System Responses to Guideline-Endorsed Physiotherapy on Acute & Sub-Acute LBP Patients”**

A pragmatic, longitudinal observational study designed to explore the responses (as recorded by Biopac SC activity levels and SCR's) of LBP patients (of 12 weeks duration) to guideline-endorsed physiotherapy treatment and to determine the correlation of SCR's to currently utilised, clinically applied, PROM's with a preliminary evaluation of the utility of the Biopac system at predicting (at inception to a course of treatment) patients functional outcome at discharge.

### **5.2. Summary of the background to the study**

Despite a decade of published guidance supporting the use of physiotherapy in the rehabilitation of LBP patients, there continues to be a paucity of empirical knowledge to support evidence-informed clinical decisions, guide patient choice and advise policy makers. Questions exist about; the presenting neurophysiological status of patients attending clinics with LBP and the changes that occur, within and between, treatments that use guideline-endorsed physiotherapeutic strategies; about the comparability of findings between patients and asymptomatic healthy volunteers from previously published studies; and the presence and strength of any correlations between patients' neurophysiological responses to treatment and currently utilised patient-reported measures of clinical change/improvement (pain intensity [NPRS] and functional disability [ODI and/or RMDQ]). Furthermore, there is currently no data available to clinicians regarding the nature of any trends in the neurophysiological



SCR's recorded during guideline-endorsed physiotherapy management. Lastly, there is a no information currently available that has explored the feasibility of using the Biopac system (SCR's) for determining, in the initial assessment, the predictive capacity for a positive outcome (currently recognised as being an improvement in ODI score of >50%), at discharge.

### **5.3. Introduction:**

A number of studies and clinical Guidelines have endorsed the use of physiotherapy in the management of acute and sub-acute LBP. It is widely recognised that systematic reviews of LBP management (CSP Guidelines 2006; Ernst and Canter, 2006; Murphy, van Teijlingen and Gobbi, 2006; Haldeman and Dagenais, 2008; Bronfort et al., 2008) emphasise the need for studies that investigate the effects of the various treatment options recommended with LBP patient populations rather than normal healthy volunteers. These are important considerations for the treating clinician, for patients and for health care policy makers. Despite both clinical research and anecdotal evidence supporting patient-reported benefits of physiotherapy treatment (van Tulder, Koes and Boulter, 1997; Foster et al., 1999; Sparkes, 2005), the biological/ neurophysiological mechanisms underlying the effects of treatment modalities, particularly within patient populations, remain unknown and there are currently no published studies, using LBP patient populations, exploring the neurophysiological responses to guideline-endorsed physiotherapy management. Although this does not negate the clinical effects of physiotherapy, it hinders acceptance by the wider scientific and Health Care communities and impedes the development of rational strategies for improving the delivery and the accuracy of provision of therapy and has implications for effective resource management. It is recognised (Pengel et al., 2003) that most patients'

symptoms improve within the first month from inception however up to 84% have continued pain and recurrent episodes requiring further intervention, usually in the form of manual or exercise therapies, which has become a key feature of the guidelines for the management of LBP. In the Clinical Standards Advisory Group (1994) guidelines, manipulation was recommended where symptoms lasted for more than a few days and for patients who needed additional help with pain relief or who were failing to return to normal activities. These proposals have some support from the CSP guidelines (2006 pt 2) and the NICE guidelines (2009) and a number of studies (Hadler, Curtis and Gillings, 1987; Goodsell, Lee and Latimer, 2000; UK BEAM, 2004 and Konstantinou et al., 2007) who have demonstrated clear patient-reported benefits from manual and manipulative techniques. Despite this, there is debate within the literature regarding the magnitude and the clinical significance of observed treatment effects (Potter et al., 2005). Nonetheless, currently the outcomes reported in clinical studies are indirect, subjective measures of patient-reported benefits and are worthy of further substantiation with empirical, neurophysiological data comparisons.

Although the clinician can currently assess the responses and effects of the treatment/s that they have prescribed utilising PROM's of functionality and pain intensities, to date, there is no means of determining (or measuring) the physiological effects of the array of therapies (especially the MT's) that they have at their disposal, nor can they accurately, quantitatively and non-invasively measure the proposed effects on the key target tissues. Currently used PROM's are considered valuable and valid measures, at discharge, of comparing the extent of changes that the patients report in their functional capacity and their pain experience, however they provide no predictive capacity, at inception, to the patients' outcome at discharge.

Several researchers (Petersen, Vicenzino and Wright, 1993; Vicenzino, Collins and Wright, 1994 & 1996; Slater and Wright, 1995; Vicenzino et al., 1995; Wright and Vicenzino, 1995; Chiu and Wright, 1996; Vicenzino et al., 1998 & 2001; Sterling, Jull and Wright, 2001; Paungmali et al., 2003; Moulson and Watson, 2006 and Jowsey and Perry, 2010) have explored the neurophysiological basis of specific physiotherapeutic techniques in the cervico-thoracic spine and upper limbs, utilising the sympathetic nervous system (SNS) as a measure of neurophysiological response. However, there is only a small number of published studies investigating the lumbar spine and lower limbs (Perry and Green, 2008; Perry et al., 2010 and Moutzouri, Perry and Billis, 2012), indeed, studies involving symptomatic patient populations are very limited, with small sample sizes (Slater and Wright, 1995; Vicenzino, Collins and Wright, 1996; Sterling, Jull and Wright, 2001; Vicenzino et al., 2001; Paungmali et al., 2003) and only report on symptoms in the cervico-thoracic spine and upper limbs and not in the lumbar spine and lower limbs. Specific SNS changes have been reported with cervical spine and with upper limb MT's, namely; sudomotor function (Petersen, Vicenzino and Wright, 1993; Vicenzino, Collins and Wright, 1994; Chiu and Wright, 1996; Sterling, Jull and Wright, 2001) cutaneous vasomotor changes (Petersen, Vicenzino and Wright, 1993) and cardiac and respiratory functions (Vicenzino et al., 1998). These results provide reinforcement of the concept that the administration of spinal techniques can result in a SNS and an associated analgesic response and is worthy of extrapolation within a LBP patient population. Further re-enforcement for neurophysiological change measures within LBP patient research came from the review, by Wand and O'Connell (2008) who challenged the concept of the existence of clinical sub-groups of LBP patient populations and proposed a model that purported that persistent back pain may be a problem of cortical reorganisation and degeneration. Whilst Wand and O'Connell's

(2008) model was based on evidence within the literature that consisted of chronic, persistent LBP rather than acute and sub-acute LBP patients, the authors do acknowledge that sensitization of the nociceptive system and enhanced synaptic efficiency of nociceptive networks is not unique to chronic pain groups (>12 weeks duration), indeed, they recognise that the proposed changes in the periphery, the spinal cord (Thompson 2005; p. 379-397 and Apkarian and Scholz 2006) and the brain (Flor 2003) may start within the initial few weeks of symptom onset (Giesecke et al., 2004). Furthermore, Wand and O'Connell (2008) challenged researchers to develop clinical strategies that are targeted at normalising neurological processing, however, they do not suggest how these neurophysiological (and cortical) changes and responses might be pragmatically measured within clinical settings.

Although early indicators demonstrate the validity and stability of neurophysiological measurements (SNS and in particular SC activity changes and SCR's) of the responses observed with specific treatments, no work has recruited a LBP patient population or attempted to correlate observed SCR's to other validated patient-reported measures of pain - NPRS (Childs, Piva & Fritz, 2005) and function - Roland-Morris Disability Questionnaire-RMDQ and the Oswestry Disability Index-ODI (Roland and Fairbank, 2000; Schiphorst Preuper et al., 2007). These PROM's are recognised as being helpful as general indicators of improvements in symptoms and function (see chapter 2.3), but lack the objectivity that neurophysiological measurements may provide.

## **5.4. Aims, objectives and hypotheses**

### **5.4.1. Aims of the study**

The aim of this clinical study was to observe and record the currently unknown neurophysiological status (SNS) of patients presenting for physiotherapy with acute and

sub-acute LBP (of up to 12 weeks duration) and observe any SNS changes (through SC activity response recordings) occurring as a result of receiving guideline-endorsed physiotherapy treatment (a complex healthcare intervention) at three data capture points during their entire programme of care (at inception, at mid-point and at discharge). Furthermore, the study aimed to compare within- and between-treatment skin conductance activity levels and skin conductance responses (SCR) with currently used (within the University Hospitals of Leicester NHS Trust) PROM's of pain intensity (NPRS) and functional impairment (ODI and RMDQ) and to attempt to evaluate the utility of Biopac readings of SCRs as a possible predictor, at inception, of patients' outcome at discharge (50% improvement in ODI score from inception to discharge – Flynn et al., 2002 and Childs et al., 2004)

#### 5.4.2. Objectives

The objectives of the clinical study were as follows:

- i) To observe and analyse levels of neurophysiological activity and changes occurring during and after physiotherapy treatment within patients with LBP.
- ii) To understand the relationships between maximum SCR's to treatment and currently used PROM's that measure changes in pain intensity (NPRS) and functional disability (ODI and RMDQ).
- iii) To evaluate the utility of SCR's as a predictive tool, at inception, as an indicator of patient-reported functional outcome at discharge.

#### 5.4.3. Research Questions and Hypotheses for the Clinical Study

In order to evaluate the utility of the Biopac SNS activity data acquisition system as a quantitative measure of neuro-physiological response to physiotherapy treatment of acute and sub-acute LBP patients, it was necessary to record SC levels of activity within

and throughout the entire treatment programme. In order to manage the vast amount of data generated 3 key data capture points were identified (inception, mid-point and at discharge) for comparison. Details of the measurements taken are provided in the following chapters.

### **Research Question One**

“What are the SC activity levels of patients presenting for guideline-endorsed physiotherapy management of acute or sub-acute LBP, and do these SC activity levels change within and between episodes of treatment at inception, mid-point and at discharge?”

#### Null Hypothesis One (H0-1a)

*“There will be no differences in SC activity levels in (acute & sub-acute) LBP patients within individual physiotherapy treatment sessions.”*

#### Null Hypothesis One (H0-1b)

*“There will be no differences in SC activity levels in (acute & sub-acute) LBP patients between individual physiotherapy treatment sessions.”*

### **Research Question Two**

“How do maximum SCR's to treatment correlate with other currently utilized, patient-reported indicators of pain intensity and of functional disability at the commencement and the termination of the programme of care?”

#### Null Hypothesis Two (H0-2)

*“There will be no correlation between SCR's (during treatment) and reported levels of pain intensity (NPRS) and functional disability (ODI) at (and between) inception and discharge.”*

### **Research Question 3**

“Is it possible to utilize Biopac SC measurements to identify any trends in SCR’s to elements of treatment and as a potential indicator, at inception, of outcome of patients function at discharge?”

#### Null Hypothesis 3 (H0-3)

*“There will be no relationship between SCR’s following guideline endorsed physiotherapy treatment at inception and a positive ODI change score greater than 50% at discharge”*

## **5.5. Methodology, Patient Recruitment and Ethical considerations and clearance**

### 5.5.1. Methodological Approach and the Research Design

Altman (1991; p.75) acknowledges that research design is arguably the most important aspect of the statistical contribution to medicine. Using Altmans (1991; p75-99) classifications of research designs the most appropriate approach to answering the research objectives within a clinical population was to utilise a prospective, longitudinal, observational design. Altman (1991;p.75-76) advises that observational studies require the researcher to collect data on the attributes or measurements of interest, but does not directly influence or manipulate events/variables. This can often be the requirements of clinical studies that seek to observe, within a natural (hospital) environment, the influence of a ‘factor’ (in this case guideline-endorsed physiotherapy treatment) upon a vulnerable (patient) population where ethical approval for otherwise “untraditional” management strategies would be difficult to secure, in particular, interventions that might deny patients the full scope of therapeutic care in the absence of unequivocal evidence to support one approach above another . The attributes of interest in this arm of the

Thesis were SCR's to treatment, reports, from the patient, of their pain intensity (NPRS) and reports of their functional limitations (ODI and RMDQ) at inception, at mid-point and at discharge from the programme of care. The duration of LBP symptoms (in weeks), although not the primary or secondary variable of interest, was considered a covarible for the final analysis as it is recognised as an important factor that can potentially influence outcome at discharge. The primary SNS measurements being observed were the SC activity levels and the maximum SCR's (% change) that occurred within and between treatment episodes and within (SC activity levels & SCR's) and between (SCR's) individuals. The prospective and longitudinal components of the study were the extent of changes that occurred, over time, in NPRS, ODI, RMDQ and SNS measurements at the three data collection points (inception, mid-point and at discharge).

Observational studies are best used to study factors (or exposures) which cannot be controlled by the researchers. In the current study, it would not be possible to randomize individuals to have or not to have LBP. Nevertheless, as stated by Gray-Donals and Kramer (1988; cited by Altman, 1991;p.91), 'the goal of an observational study should be to arrive at the same conclusions that *would* have been obtained by an experimental trial'. As this was a prospective longitudinal study looking at changes that occurred over the course of a programme of physiotherapy treatments, a cohort study of a group of LBP patients was recruited. Altman (1991;p.96) explained that the benefits of prospective studies are that because of the nature and quality of the data recording undertaken, control can be carefully achieved thus ensuring internal (and also external) validity. However, it is acknowledged that prospective, longitudinal cohort studies are not without limitations. The most common (to cohort and other studies) is the selection of participants for the study.



This is particularly so for follow-up studies performed within a clinical setting where finding and recruiting participants who meet the strict inclusion and exclusion criteria (controlled for in order to minimise extraneous variables and strengthen the studies internal validity) can be a lengthy and time-consuming process. In order to minimise this component, it was decided that a Hospital (with an Emergency Department and a number of Out-Patient Consultant-led Musculoskeletal clinics) local to the researcher with a large number of acute and sub-acute referrals would provide the required sample population. Additionally, and pragmatically, a hospital where the researcher had previously worked (for 7 years) within the clinical setting and was familiar with the nature of the referrals, the referring practitioners, the department and the IT procedures and the administrative and clinical staff would provide a smoother transition into the practical research environment.

Altman (1991; p.97-98) also advised that another difficulty specifically encountered in cohort studies is that some participants will fail to attend for follow-up for the length of the study (i.e. they move to other areas or lose interest in gaining treatment). The longer the study, the more participants are likely to be lost to follow-up thereby weakening any analysis and inferences that may be made thus resulting in bias. In order to minimise the effects of loss to follow-up a full and detailed explanation of the study (and its requirements) was provided to each potential participant in addition to ensuring that timings of treatment follow-ups were discussed and negotiated with the patient encouraging engagement in their own recovery goals and treatment plans. Treatment programmes were designed to be completed within a 6 week period thus limiting the potential influence of external events (e.g. changes in job) or habits (e.g. taking up a new hobby/sport) and limiting the effects of natural regression to the mean, a potential factor that might influence lengthier studies performed within an

acute or sub-acute population. By not using a postal questionnaires but ensuring completion of questionnaires (PROM's - ODI and RMDQ) on attendance, the issues of non-response/return was eliminated. Finally, the conduction of a power calculation to determine the optimum population sample size (including loss to follow-up) was conducted to limit bias, ensure ethical practice (by not over- or under-recruiting patients) and strengthen the internal validity of the study.

#### 5.5.2. Power Calculation to determine the optimum Sample Size

As this was both an observational and a feasibility study of a surrogate objective marker (skin conductance response - SCR) for change in symptoms reported by patients complaining of a multidimensional disease (NSLBP), a power calculation was not strictly necessary. However, to meet the requirements of the Ethics Committee, a sample size was calculated using data gathered from the preliminary study (Chapter 3, Table 14 and Perry and Green 2010) in order to strengthen the internal validity of the clinical study and ensure that ethically speaking no patients had to receive research procedures (measures of SCR's) that they were not ordinarily required to do so.

The number of participants required to calculate a statistically significant difference ( $p < 0.05$ ) at 80% power with an effect size of 0.38 (35% mean percentage change in SCR as a meaningful SCR difference from baseline for the treatment condition; standard deviation 92%) was 57 patient participants (Sim and Wright, 2005). Anticipating a drop-out rate of 20% (12-13 patients) it was determined that 70 patient's would be required to account for possible loss to follow-up (Kirby, Gebiski and Keech, 2002).

### 5.5.3. Ethical Approval Process

This clinical study formed the final part of a PhD at Coventry University and was therefore peer reviewed by the Faculty (of Health & Life Sciences) Ethics Committee, the Coventry University Ethics Committee (Registry & Applied Research Dept), the NHS Research Ethics Committee (NREC) and the University Hospitals of Leicester (UHL NHS Trust) Research and Development Office (details of the submissions and approval letters are provided in appendix VII). The programme of study was supervised by a Director of Studies (Ann Green) and a Professorial Team based at both Coventry University (Professor Sally Singh) and within UHL NHS Trust (Professor Paul Watson). The Musculoskeletal Manager at the University Hospitals of Leicester NHS Trust (Mr Barry Savage) also reviewed the protocol and gave signed permission for the study to be completed within the Unit and on patients referred to the service for physiotherapy treatment of LBP.

### 5.5.4. Patient recruitment

A purposive, convenience sample was recruited for this study. All patients referred for treatment of LBP (as a primary complaint) to the Physiotherapy Department at the University Hospitals of Leicester NHS Trust (Leicester Royal Infirmary Site) that met the inclusion criteria for the research were considered for participation into the study (see Table16).

**Table16: Inclusion and exclusion criteria**

Inclusion Criteria	Exclusion Criteria
<p>Patients with an acute presentation of non-specific LBP ≤ 12 weeks duration</p> <p>Male and female gender</p> <p>Age between 18 and 55 years</p> <p>Possesses an adequate understanding of spoken English</p> <p>Verbal Pain Rating Score of ≥ 2/10</p> <p>ODI baseline score of ≥ 14%</p> <p>RMDQ Baseline score of ≥ 4/21</p> <p>Mechanical provocation of symptoms/pain: postures, movement and activities</p>	<p>Sick-listed for more than 12 weeks</p> <p>Chronic exacerbation of LBP</p> <p>Existence of concurrent medical disorders or psychiatric illnesses that may affect neurophysiological readings (e.g. Diabetes, anxiety disorders, Multiple Sclerosis, rheumatoid arthritis)</p> <p>Patients with previous lumbar spine surgery or lower limb surgery</p> <p>Pregnancy</p> <p>Skin disorders at the site of electrode placement (e.g. athlete's foot, psoriasis, eczema, verruca)</p> <p>Previous history of trauma with resultant persistent dyesthesia (chronic abnormality of sensation which would affect neurophysiological readings)</p> <p>Alcohol dependency and smokers (that could affect neurophysiological readings)</p> <p>Those with precautions and contra-indications to physiotherapy treatment (including exercise classes)</p> <p>Those participants not willing or able to consent to inclusion</p>

Initially, the Therapist (that is, the researcher JP) reviewed all the paper/electronic referrals to the department and excluded all unsuitable participants according to the information provided by the referrer. All potential participants (n=159) were then contacted by the bookings clerk (by telephone) and permission to be contacted by the Therapist obtained. If the participant refused (or was uncontactable by telephone) at this stage they were given an appointment (in the usual way or, in the absence of a contactable number, by postal appointment) with another therapist

within the department. If the patient granted permission to be contacted by the Therapist (JP) then the Therapist (JP) contacted the participant (n=84) and, subject to the criteria being met for inclusion, the Therapist assessed the participants willingness to take part in the study, explained the nature of the study and provided an appointment for assessment and for the patient to sign the informed consent documentation (n=70). In addition to a verbal explanation of the study, participants were also sent an information leaflet (see appendix VIII) explaining the nature of the study with a written confirmation of their appointment details. This allowed the participant adequate time for consideration of the information provided and a cooling off period of at least 48 hours prior to assessment and recruitment. The formal face-to-face recruitment, question and answer session and consent signing session took place in a private clinical room within the physiotherapy department. All clinical assessments, treatments and data collection procedures were undertaken within the clinical treatment area and always within the same cubicle with the same set up for each session in order to minimise any environmental variance between sessions.

#### 5.5.5. History and physical examination

Patient recruitment, assessment and treatment took place between July 2009 and May 2011. For all participants, the initial “consenting interview” allowed them to receive appropriate information to questions that they had about the study and its implications and also gave the participant the opportunity to discuss any elements of the study not clear from the information sheet in the invitation pack sent out with the appointment. The initial “consenting-interview” and subjective assessment interview also allowed the researcher and the patient to determine their suitability for the study and if both were in agreement to continue, the participants were asked to sign the carbonated informed consent form (see appendix VIII) for the study (n=60), the

consent form was carbonated so that the top copy could be retained by the participant, a copy could be placed in the patients medical notes and a copy placed within the On-Site research file. Also at this time, a letter was sent to the referring clinician to advise them of their patients' inclusion into the study (appendix IX).

At the initial assessment the patients completed a standard physiotherapy examination (maximum 45 minutes). The usual subjective assessment was completed (i.e. demographic information including, age and gender; social details and occupation (including working status; sick leave, restricted duties/phased return, normal work duties, does not work). All responses were documented as well as past-medical and drug histories. The patients' report of the duration and onset of the symptoms, the location, behaviour and nature of the symptoms were also recorded. Self-reported measures of pain/symptoms and functional limitations and SMART (specific, measurable, achievable, realistic and timed) goals were discussed and recorded. Finally, pain intensity (NPRS) and the two functional PROMS (ODI and RMDQ) were completed. This was performed prior to commencement of the physical examination (in accordance to the Trusts policy). Physical examination (see appendix X for a summary of patient findings) measures included lumbar active range of motion (Waddell et al., 1992), lumbopelvic assessment (Freburger and Riddle, 2001), neurological examination (of conductance [reflexes, myotomes and dermatomes +/- the Babinski test] and dynamics [straight leg raise test or femoral nerve neurodynamic test +/- the slump test] – Shacklock, 2005) and palpation of lumbar segmental motion (Maitland et al., 2005 and Petty 2011).

All participants included in the study were assessed to have a mechanical, nociceptive (+/- peripherally evoked neurogenic symptoms) presentation with restriction of one or more lumbopelvic movements and one or more hypomobile lumbar segments on palpation. On completion of the interview and physical examination, commencement of

the non-invasive recordings of their SC activity levels was undertaken. These were performed whilst the patient relaxed in a comfortable position on the treatment plinth (maximum 10 minutes). Physiological recordings of SC were continuously measured, without interruption, throughout the entire treatment period (up to 45 minutes depending on the nature of the program of treatment provided) by a Biopac GSR100B Electro-dermal Activity Amplifier (MP35; Biopac Systems Inc; Santa Barbara, CA), employing a constant voltage technique and sampling the absolute, direct current SC at the rate of 200 samples per second. Participants were informed (prior to attending their appointments) that they were required to avoid certain behaviours such as consuming stimulants (e.g. drinks with caffeine and nicotine products – Thomas, 2002), to avoid heavy exercise for about four hours prior to the appointment (Koltyn, 2000) and alcohol (Vicenzino et al., 1995) and to not eat within the hour of attending for treatment (Chiu and Wright, 1996). These factors are known to influence SNS measurements if not adhered to therefore participant compliance with these prohibitions was monitored by way of a series of screening questions prior to each session. All participants were adherent to the protocol. In accordance with the previous two studies, care was taken not to allow the patients to fall asleep, cough, sneeze, deep breath, or talk during baseline measurement recording.

All examinations were conducted by the Therapist (JP) who also discussed the findings and treatment options with the participant. All treatments were prescribed in accordance with the guideline-endorsed recommendations and administered by the Therapist. The participants' right to withdraw at any stage was observed throughout their treatments.

All patient data was anonymised and only minimal data kept on record (ID number, age, gender, symptom type, onset, behaviour and distribution, NPRS, ODI and

RMDQ Scores and dates of attendance). This data was kept in a study file that was locked and kept secure within the Hospital Department. All electronic (SNS) data recorded from the Biopac equipment was anonymised and stored in an encrypted computer file stored in the same locked cabinet.

#### 5.5.6. Patient information and consenting procedures and details of the treating therapist.

Informed consent of the participant was ensured in a number of ways; by provision of an information sheet (appendix VIII) explaining the nature of the study, any potential risks, benefits and burdens to taking part as well as their role within the study at least 48 hours prior to initial assessment as well as written consent (see appendix VIII); by reviewing the nature and purpose of the study at the initial assessment and allowing the participant the opportunity to ask questions about the study and their role within it; by reminding the participants that they may withdraw from the study at any time and without prejudice to ongoing physiotherapy treatment.

The Therapist is an experienced musculoskeletal physiotherapist (24 years) and a member of the Chartered Society of Physiotherapy (CSP), the Health Care Professions Council (HCPC) and the Musculoskeletal Association of Chartered Physiotherapists (MACP). For pragmatic reasons, the Therapist recruited, consented, assessed and treated the participants. In order to limit bias that might occur in the recruitment, assessment and treatment process it was decided that a single therapist be used rather than multiple therapists. Furthermore, because there was only one Biopac system available, it was not possible to undertake multiple/simultaneous treatments nor was it practicable to train the staff to set up the equipment and record readings on the password protected laptop that had the Biopac analysis software installed. Additionally, the nature of electronic appointment



times and booking system within the department did not permit the clinical staff to extend assessment and treatment times by the additional 20 minutes required to collect the baseline and final rest period SC activity levels so, for pragmatic reasons, the Therapist booked and conducted all data collection requirements. An additional advantage with this approach is that it was also possible to provide treatment times that better suited the patients and have appointment times, each week, that were at the same diurnal times thereby limiting measurement variations and enhancing patient compliance and reducing drop-out rates. Whilst all data collection was performed by the Therapist, the Therapist remained blind to the responses occurring during data collection. The data analysis was only conducted after all participants had finished the study thereby minimising any bias to the analysis procedure and ensuring ethical practice was adhered to. Additionally, the Therapist had also undertaken two nationally recognised GCP (Good Clinical Practice) courses at the Leicester General Hospital and had received GCP certification for training in ethical consent taking for researchers (see Appendix XI – Good Clinical Practice Certificates) and was considered to have a good understanding of the ethical principles underpinning informed consent within a patient population. This study did not involve vulnerable subjects and excluded participants who were unable to represent their own interests and therefore the study did not pose a risk to this population.

#### 5.5.7. Potential risks, burdens and benefits to patients

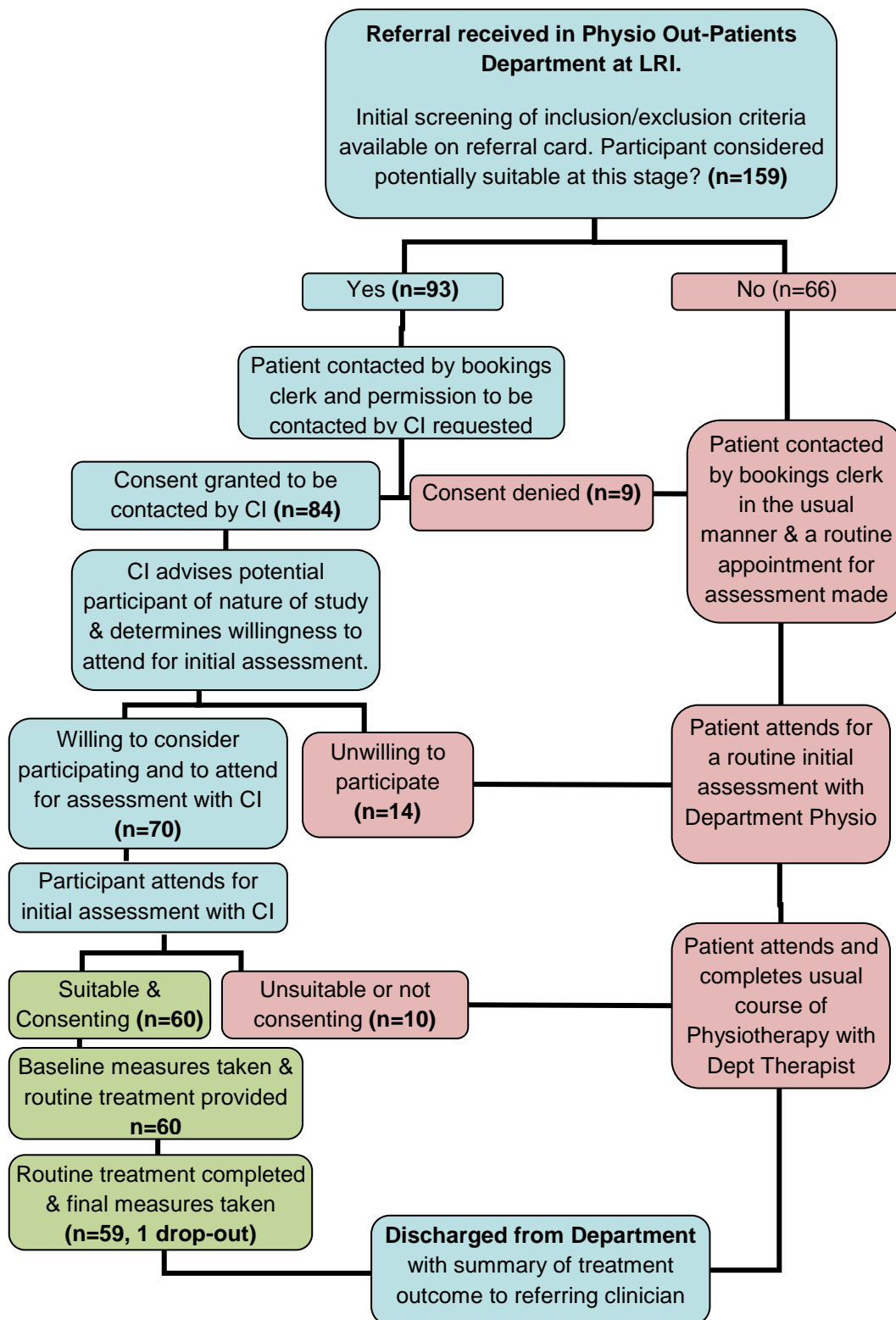
No serious ethical issues were anticipated or encountered as a result of this study as patient's treatment and management choices did not differ to 'normal' treatment as a result of taking part in the study. The only burden to the patient was the additional 10-15 minutes required (to their treatment time) in order to gather the required

neurophysiological data for the study. The neurophysiological measurements taken did not cause any change in symptoms nor was there any risk of it causing psychological distress to participants as the electrodes comprised of non-invasive surface sensors that were secured with a Velcro strap to the glabrous (hairless) skin over the second and third toes of each foot. Participants did not experience any discomfort from any of the measurement procedures nor the treatments undertaken, except for very minimal discomfort as a result of some of the manual treatments employed (e.g. exercise or joint mobilisations). Testing would have been terminated immediately upon the participants request or if they had expressed any undue discomfort, fatigue or if any abnormal responses to the treatment/s had occurred. This did not happen and all data was recorded according to the protocol described.

Participants who consented to take part in the study did not benefit directly from inclusion in the study but they understood that their inclusion could enhance clinical understanding of the place of physiotherapy treatment in the management of low back pain and participants also had the opportunity to learn about the effects of their treatment programme on their functional, neurophysiological and pain status at the end of the study.

Figure 22 illustrates the recruitment processes undertaken by the administrative staff and the Therapist (CI).

**Figure 22:** A flow chart depicting the patient recruitment procedures



## 5.6. Assessment and Treatment Protocols

### 5.6.1. Initial assessment (inception)

Following the initial assessment and consenting procedures, and in accordance with current departmental policies, patients had the opportunity to discuss the findings of their assessment and the proposed, guideline-endorsed treatment options, which, although tailored to the patients specific requirements, consisted of techniques to address the primary and secondary physical dysfunctions found on the assessment. The choice of technique, and its application, was determined according to the severity, irritability and the nature (SIN) of the presentation. Regarding the nature of the condition, a structural (patho-anatomical) hypothesis was generated to assist the reasoning for treatment selection (i.e. arthrogenic/facet joint; discogenic; neurogenic; myogenic and combinations thereof). A summary of the primary complaints of the patients attending for initial assessment is provided in Table 17 below.

**Table 17:** Summary of patient examination findings: primary & secondary complaints

Primary Physical Complaint	Total Number of Patients	Two or more Secondary Physical complaints
Localised lumbar facet joint dysfunction	31	35
Discogenic dysfunction	24	33
Neurodynamic dysfunction	5	26
Limited internal Hip ROM > 35°	0	5
Functional Core Instability/Muscle Weakness	0	48
Global/Aeorobic weakness	0	6
<b>Total</b>	<b>60</b>	<b>153</b>

Treatments were prescribed according to the assessed primary complaint and consisted of combinations of techniques designed to improve the mobility of hypomobile segments (including joint mobilisation techniques – accessory and physiological; the rotatory

manipulation technique [as per chapter 5]; a MWM technique and/or the repeated McKenzie EIL technique [seen earlier] or soft-tissue techniques [including trigger-point release, Swedish Massage or neurodynamic techniques – sliding or gliding techniques]), local and/or global exercise techniques to strengthen core musculature and enhance aerobic fitness (NICE, 2009). In addition to specific manual and exercise techniques, advice and education regarding the nature of LBP, and on pacing of activities, of return to work and to hobbies were also provided.

Treatment began on their initial attendance. SC electrodes were attached to the toes in accordance to the protocol, outlined in the previous chapters, and left in place throughout the entire treatment time and for the 10 minutes post-treatment rest period. An attempt was made to schedule each subsequent visit at similar times of the day as the initial assessment in order to control the influence of any diurnal variation on the SCR. On each visit, patients had their NPRS, SC activity levels and SCR's recorded whilst undergoing the physiotherapy treatments as per the assessment findings and by the guideline-endorsed treatment recommendations with appropriate modifications to the programme made in accordance to the progression of their condition (follow-up sessions took no more than 40 minutes). It was considered important that treatments were guideline-endorsed and tailored to the presenting needs of the patient on each of their visits utilising manual therapy techniques (see below) over electrotherapy techniques as the NICE (2009) and CSP (2006) guidelines for the treatment of LBP, in this patient subgroup, do not endorse electrotherapy modalities (e.g. Interferential therapy- IFT, Transcutaneous Electrical Nerve Stimulation - TENS, Ultrasound - US etc).

The manual techniques employed consisted of segmental facet joint mobilisations (Perry and Green, 2008), the lumbar rotatory (HVLAT) manipulative technique (chapter 5 and Perry et al, 2011), the repeated McKenzie EIL technique (Chapter 5 and Perry et al.,

2011), the MWM flexion/extension technique (3 sets of 10 repetitions, Moutzouri, Perry and Billis, 2012) and Swedish massage and trigger-point release (for 15 minutes) to the thoraco-lumbar region. Treatments were all performed by the Therapist and given in accordance to the decisions made on the day between the therapist and the patient. Not all treatments were required and classifications of the treatments offered are provided in table 18 below, with their intended purpose and desired outcome suggested.

**Table 18:** Classifications of the manual therapy (MT) techniques used on patients.

MT technique	Definition	Desired Outcomes
<b>Joint biased</b> <ul style="list-style-type: none"> <li>• i) Manipulation</li> <li>• ii) Mobilization</li> </ul>	Passive movement of a joint beyond the normal range of motion  Passive movement of a joint within its normal range of motion	Improved range of motion  Decrease muscle spasm  Decreased pain
<b>Soft tissue biased</b> <ul style="list-style-type: none"> <li>• i) Swedish massage</li> <li>ii) Deep tissue massage               <ul style="list-style-type: none"> <li>• iii) Trigger point</li> </ul> </li> </ul>	Stroking and kneading of the skin and underlying soft tissue  Deep stroking and pressure across the muscles and soft tissue  Deep pressure to areas of local tenderness	Improve circulation Decrease muscle spasm Relaxation Re-align soft tissue Break adhesions Increase range of motion Release muscle spasm Remove cellular exudates
<b>Nerve biased</b> <ul style="list-style-type: none"> <li>• i) Neural dynamics</li> </ul>	Passive, combined movement of the spine and extremities, within their normal range of motion, in ways to elongate or tension specific nerves.	Improve range of motion Decrease pain
<b>Combined Joint &amp; Soft Tissue</b> <ul style="list-style-type: none"> <li>i) MWM (NAGS &amp; SNAGS)</li> <li>ii) McKenzie EIL (with overpressure)</li> </ul>	Glide techniques to the spine, performed whilst the patient actively moves Sustained passive movement of a segment whilst the patient uses arms to achieve lumbar extension.	Improved range of motion Improved motor control of movement Decrease pain Restore disc alignment

Adapted from Bialosky et al. (2009) to provide a classification of the MT techniques utilised in the clinical study along with specific examples of each.

In essence, patients presenting with a hypomobile segment/s received the manipulative, MWM and/or McKenzie EIL techniques as a primary management strategy, massage and/or myofascial trigger point release techniques were provided, as needed, for management of any soft-tissue/myogenic symptoms either in

combination with the above techniques or not. As indicated above, all patients received standard, guideline-endorsed advice and education to keep active and return to work in addition to a standardised exercise program to strengthen the core, maintain spinal and lower limb range and flexibility and to improve cardiovascular fitness.

For the MWM treatment, the technique described by Mulligan (2004, p.44) was used (see figure 24 below). A Mulligan belt was placed on the anterior waist of the patient, below the anterior superior iliac spines (Mulligan 2004: 44) with the belt hanging open on the posterior aspect. When necessary, a towel was inserted between the belt and the patients' waist to avoid any undue pressure caused by the technique.

**Figure 23: The MWM (SNAG) technique for lumbar flexion**

This item has been removed for data protection reasons. The unabridged version of the thesis may be viewed at the Lanchester Library, Coventry University.

In order to conduct the treatment the therapist stood posterior to the patient and put on the Mulligan belt below her own waist, applying a tension. Meanwhile, the patient was requested to remain stationary. The belt was useful in providing a counterforce

for the application of the technique, and stabilising the patients position during the active lumbar flexion movement. Finally, the MWM (Sustained Natural Apophyseal Glide – SNAG – technique) was applied for 3 sets of 10 repetitions.

SNAGs involved the application of a sustained accessory glide on the lumbar spine, along with the patient performing lumbar flexion (Exelby 2001; Mulligan 2004: 44).

The direction of flexion was selected, as restriction of flexion range of movement was a common presentation in patients with LBP, in clinical practice (Sullivan, Shoaf and Riddle, 2000) and was also the case with the patients within this study (with any extension deficit being addressed by the McKenzie EIL technique). Considering individual variances, patients were requested to utilise their full, available, pain-free lumbar flexion range while performing forward flexion. The glide was applied with either the thumb pads of both hands, or the ulnar border of the therapists right hand while the left hand was placed on the treatment table for support (Mulligan 2004: 44).

The researcher stood posteriorly in a long-standing stride, close to the treatment table. The glide was applied centrally at the lowest point of the (superior) spinous process of the segment that was assessed to be hypomobile (Mulligan, 2004; p.15), and was not released until the desired number of repetitions of the SNAG (10 repetitions) had been performed. A central technique was employed since Konstantinou et al. (2002) reported that centrally applied SNAG's were most commonly utilized in clinical practice. The amount of force applied with the active movement was that determined, by the therapist, to be required to overcome joint resistance but remain pain free. Wilson (2001) recommends that application of force can vary from minimal to vigorous depending on whether treating pain or resistance.



### 5.6.2. Mid-point and discharge assessment and treatment

During the subjective element of each/all reassessment/s, repeat ODI and RMDQ questionnaires were completed by the patient as well as an evaluation and documentation of the patients presenting NPRS status. After completion of the programme of treatment (i.e. following discharge from therapy) a retrospective calculation of the mid-point of the programme of care was established. For example, if the patient attended for 5 treatments, then the median treatment episode (number 3) was identified as the mid-point data capture point. In cases where the mid-point fell between sessions (i.e. total number of treatments = 6) then the mean treatment episode was selected (i.e. 3<sup>rd</sup> treatment episode). As with the initial treatment episode, patients completed the questionnaires prior to commencement of SC data collection and their subsequent treatment session. The 'half-way' point data was completed by 59 participants (one drop-out was incurred due to geographical relocation with their work). By conducting this mid-way assessment it was hoped that a comprehensive picture of the changes in SC activity levels and SCR's would be gained.

As with the protocol employed in all the previous treatment episodes (and according to Departmental policy), the patients final attendance for treatment (n=59) consisted of reassessment of clinical findings (e.g. lumbar ROM, neural conductivity and neurodynamic measurements, segmental mobility assessment and hip ROM), documentation of current pain intensities (NPRS) and functional disability levels (ODI & RMDQ). These were conducted prior to the recordings of SC activity levels and SCR's. Details of the participants scores at discharge are provided in appendix X with data summarising the SC activity levels (at baseline, during treatment and in the final rest periods) and SCR's detailed for each participant, in appendix XII. Most

programmes of treatment took between 3-5 treatments (maximum number 8) and were in accordance with the normal Trust protocol. Patients were discharged once their reported intensity of pain was intermittent and  $\leq 1$  on NPRS, they had restoration of full, pain-free range of lumbar motion or it was discontinued at the patients request as they had achieved their own personal goals (e.g. return to work).

For all patients in the study, their referring physician was advised of their patients' completion of the study and the outcome of treatment at discharge.

### **5.7. Data collection and analysis procedures**

Of the 60 patients recruited at inception, 59 completed the study (see consort diagram, figure 25) and their data was analysed using the SPSS (Statistical Package for Social Scientists version 17) and latterly the PASW (Predictive Analysis Software) statistical package (version 20). Additionally, MedCalc (version 11.6.1.0 medcalc software company, Belgium) was used for the ROC Curve analyses.

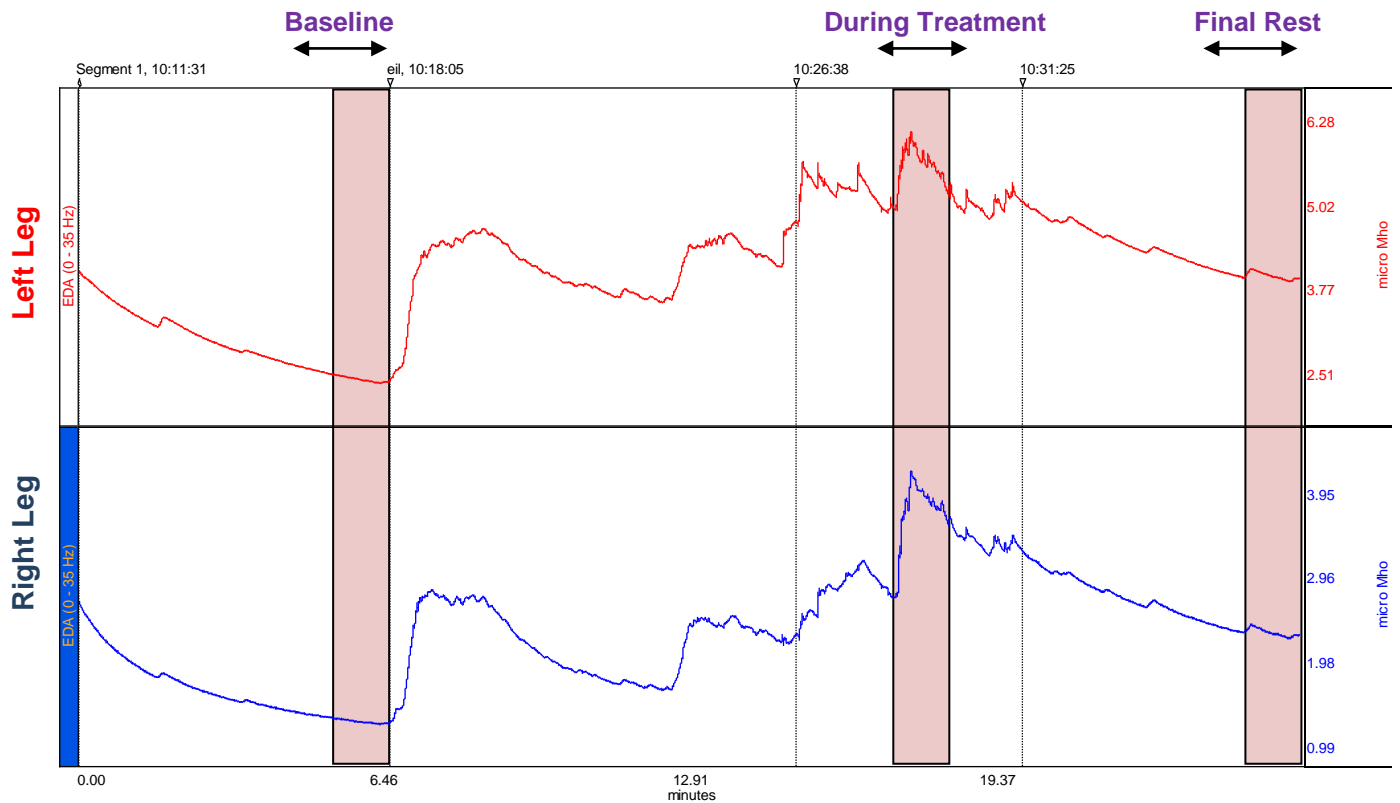
The indicator of SNS response that was used in this study, as in the previous study and those of other researchers (Vicenzino et al., 1998; Paungmali et al., 2003; Perry and Green, 2008, Perry et al., 2010), was the integral value (see appendix V) of the skin conductance (SC) measures. This is calculated, at source within the Biopac software, and was the primary outcome measure in the study. Skin conductance is classified as continuous data at ratio level and is measured in microMho's ( $\mu\text{Mho}$  or  $\mu\Omega$ ). For each of the episodes of care that participants attended, three SC activity level measurements were collected from the continuous SC readings obtained; Baseline, During Treatment and Final Rest periods. For the baseline measurement, the final 1 minute of the 10 minute pre-treatment rest period was observed and

recorded. For the “During Treatment” period, the maximum response was located (both visually and by employing the time-to maximum [t-max] feature on the Biopac screen) and a 1 minute period of time, that captured the maximum response, was also recorded (as well as documenting, retrospectively) the nature of the treatment being undertaken at that point in time (additional data analysis methods utilised in the patient & asymptomatic group comparisons are detailed in Appendix XIII). For the “Final Rest “ period, the last 1 minute of their 10 minute post-treatment rest period was recorded. A typical data chart from the Biopac unit is displayed in Figure 24 overleaf displaying data gathered from a participant during the initial episode of treatment (at inception).

Readings were obtained, simultaneously, from both the right and the left limbs for all 3 periods within each of the treatment episodes at each data capture point (inception, mid-point and discharge). For each data capture point within (baseline, during treatment and final rest period) and between (inception, mid-point and discharge) each episode of treatment, the results from both limbs were pooled using the following calculation:-

$$\text{Pooled SC Activity Level} = \frac{\text{Left leg SC Activity level} + \text{Right leg SC Activity level}}{2}$$

**Figure 24:** Schemata of Biopac Data recording from a participant indicating the 1 minute data capture points within a single episode of care (baseline, during treatment and final rest periods – in pink).



This raw data was defined “SC Activity level”. In some instances it was necessary to normalise the baseline for between-participant comparisons. In this case the calculation depicted in chapter 4 (sub chapter 4.3.6. page 150) was utilised to determine the percentage change of SC activity levels between two time periods. This data was termed the skin conductance response (SCR) and was expressed as a percentage (%) i.e. the percentage change in SC activity from one point in time (e.g. Baseline) to the new point in time (e.g. during treatment). Therefore the maximum effect indicator could be expressed as either the SC activity level or as SCR (% change) depending upon whether the focus of the question was within- or between-participant or event.

Of the secondary outcome measures (ODI, RMDQ and NPRS), ODI is a 0-100% scale with an absolute zero value and was therefore considered (and has previously, be considered in published articles) to be of ratio level therefore permitting a parametric analytical approach (presuming that all assumptions, for parametric testing, are met). RMDQ is measured on a 0-24 item scale and, for the requirements of statistical analysis, was considered (and has previously been treated in published papers as), ordinal level data and therefore subject to non-parametric statistical analytical approaches. Regarding the NPRS, the decision was made to consider this 0-10 scale as ordinal level data. Whilst some authors consider pain to be of interval/ratio level data, it was decided that this would only be true for within-participant comparisons but not between-participant comparisons (one patients' pain may not necessarily equate to, or with, another individual). Also the narrow breadth of the measure meant that detailed comparative analyses may lead to type I (erroneous rejection of the null hypothesis) or Type II errors (erroneous failure to reject the null hypothesis) (Chou and Pong cited in Lu and Fang, 2003;p.446). In order to permit comparison for (some) correlation analyses ODI and NPRS change scores (e.g. change in score for ODI or NPRS from baseline to discharge) were converted into percentage change from the original value utilising the calculation detailed above for SCR. This also permitted comparisons of data to other published papers that have documented change scores for these measures (e.g. Childs et al, 2004).

Descriptive analysis of all data (including age, gender, symptom duration and number of treatments to discharge) was conducted using calculations of frequency, central tendency (number, sum, mean or median difference, with data on minimum, maximum and range), standard deviation, standardised error and confidence

intervals and displayed using tables and charts (simple and clustered box-plots, line graphs of means and simple or matrix scatter graphs) to highlight any differences, relationships or trends in observations. Prior to inferential testing of hypotheses 1a, 1b and 2, data distributions were checked for normality (Skewness & Kurtosis) furthermore, all statistical analyses were independently checked and verified by Dr Tim Sparkes (statistician in the Mathematics and Statistics Department at Coventry University).

In order to test the null hypotheses, inferential statistical analyses, exploring the differences and the distribution of variables were performed and included: (independent and paired) 2-way ANOVA; Pearsons Correlation (SCR and ODI data) or Spearman rank correlation co-efficient (RMDQ where used and NPRS data) with predictive values being calculated with ROC curves (receiver operator characteristics curves) and direct logistic regression analyses with the final models including significant variables. Where necessary, detailed considerations and justifications for specific tests have been included within the results sections for clarity. All  $p$  values were two-sided tests, and the significance level, for all analyses, was set at 5% ( $p < 0.05$ ).

## **5.8. Results of the clinical study.**

This section details the descriptive and inferential statistical analyses performed on the clinical data collected on patients referred to the University Hospitals of Leicester NHS Trust (UHL NHS Trust) from local Primary Care Trusts (PCT's) and Hospital Consultants. The primary outcome variables included Skin Conductance (SC) activity levels and SC responses (SCR's - %). The secondary OM's included the Narrative Pain Rating Scale (NPRS), the Oswestry Disability Index (ODI) and the Roland Morris Disability Questionnaire (RMDQ).

### **5.8.1. Summary of preliminary comparisons of patient and normal participants**

Prior to the main analysis of the patient data, a between-group comparison was conducted to determine the homogeneity of a random selection (using a random numbers table generated by n-query software package) from a sample of the patient/clinical participants (n=50) to a previously published (Perry et al., 2011) 'normal' asymptomatic (experimental) population (n=50, detailed in the previous chapter). This was conducted in order to determine if the baseline data from the two populations were homogenous thereby endorsing the validity of the planned statistical analysis conducted on the findings of the patient population. Details of the sampling procedures and the analyses are provided in appendix XIII. Results indicated homogeneity of baseline findings between the normal healthy participants and the symptomatic patient population. Further analysis, conducted to investigate any differences in SCRs between the patient and the asymptomatic groups revealed that the patient groups responded with significantly greater magnitude of effect (over two-fold) to both treatments (manipulation technique SCR's > 200%, McKenzie EIL exercises SCR's >104%) than the asymptomatic population (manipulation SCR's >76%, McKenzie EIL exercises SCR's >35%) and, similar to the pre-clinical findings

on the asymptomatic population (chapter 4, Perry et al., 2011) that the manipulation treatment provided the greatest magnitude of response (almost two-fold) when compared to the McKenzie intervention; where “group” (patients versus normal’s) was the factor,  $F=9.618$ ,  $p=0.003$  and where the treatment intervention (manipulation versus EIL) was the factor,  $F=12.410$ ,  $p=0.001$ . These results indicated that although there was comparative homogeneity of the groups (at baseline) with comparable, sympathoexcitatory responses (and magnitudes of response within each group) to the two treatments, the patient group had significantly greater overall responses to therapeutic interventions than the asymptomatic groups.

### **5.8.2. Main Analysis of Patient data**

The following, main, analyses featured the observations taken, with the Biopac system, of SC activity levels (raw data at baseline, during treatment and in the final rest periods) and maximum treatment responses (SCRs – percentage change values) for the patient group only. The first analysis details the Biopac readings obtained, longitudinally, detailing within- and between- session analyses, at the three key data capture points (inception, mid-point and at discharge) and identifying the patients’ SC activity levels at baseline, during treatment and in the final rest periods.

Further analysis of the results of the Biopac system, with a LBP patient population, examined any correlations between SCR’s and the secondary outcome measures, namely, the standardized patient-reported outcome measures (NPRS, ODI and RMDQ). The final analysis, explored and analysed the emergent trends in the data and evaluated the feasibility of using the Biopac system (SCR’s), at initial assessment, as a non-subjective (empirical), quantitative tool for outcome prediction at discharge.



### 5.8.3. Characteristics of the patient group at initial appointment (inception)

#### 5.8.3.1. Demographic and anthropometric data analysis

The Consort Diagram (figure 25) details the recruitment of participants into the patient study. Of the 84 patients who were telephone-contacted, 70 agreed to attend for initial assessment. Of the 70 who attended the department for interview to consider the study, 60 consented to take part or met the inclusion criteria and were eligible for entry into the study. These 60 consented participants went on to receive the standard physiotherapy assessment (detailed earlier). Of the 60 who entered the study, 59 completed all elements of the study and formed the basis of the completed analysis (one drop-out was recorded who moved geographical locations, during their treatment, due to work).

**Figure 25:** A Consort Diagram Illustrating the recruitment of patients

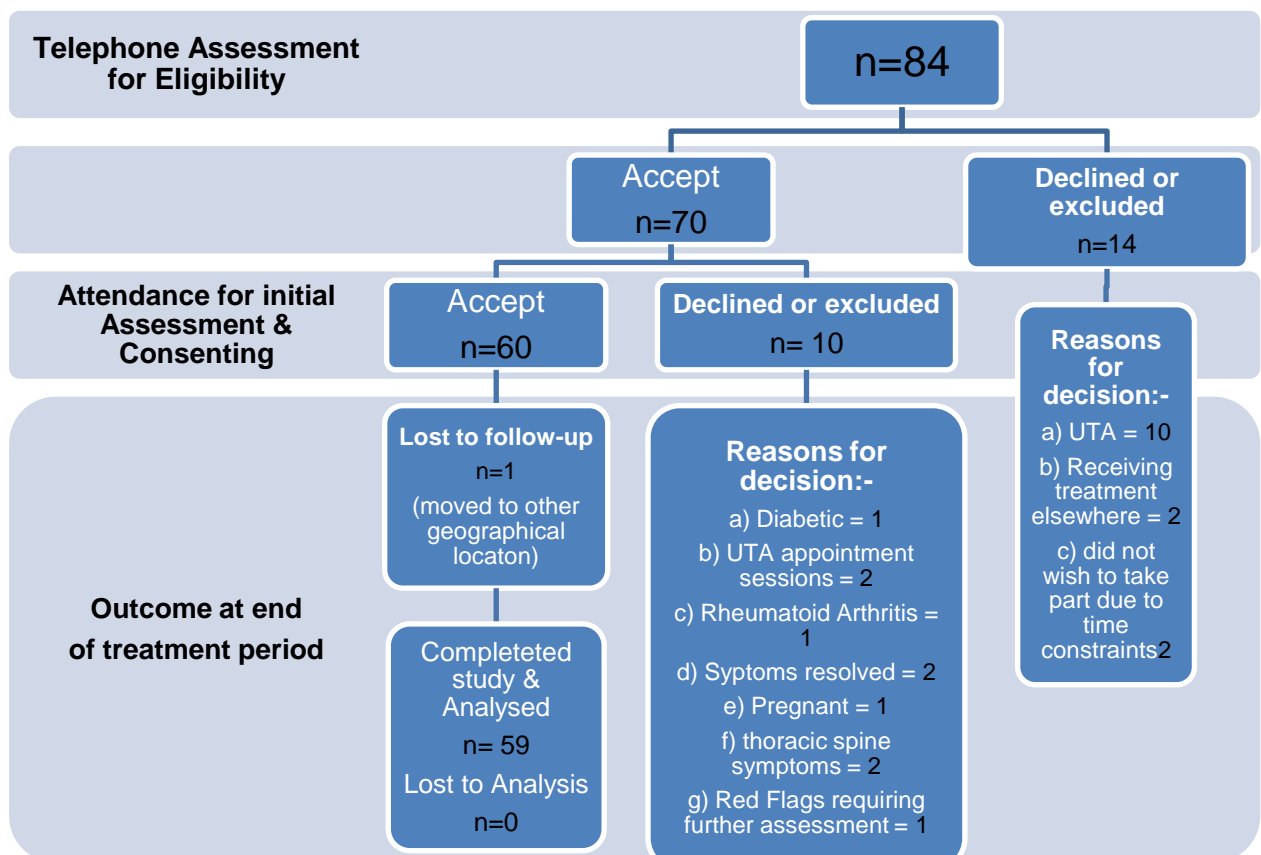


Table 19 details the demographic characteristics of the patient group with Table 20 provide a summary of the key examination findings (details for each individual participant [age, gender, Quebec Task Force Classification, work status, ODI, RMDQ, NPRS scores and primary physical findings] are provided in Appendix X). Appendix XII provides details of the SC readings for baseline, treatment and final rest periods for the three data capture points (inception, mid-point and discharge). Sixty patients were assessed at inception with 59 patients completing their course of treatment and providing data (at mid-point and discharge) for all within- and between-session analyses. Table 19 summarises the key findings at inception. The mean age was 39 years with 25 males and 35 females. The mean symptom duration at assessment was 7 weeks. For the primary outcome measure of maximum SCR the mean change of 219.4% was recorded. For the secondary outcome measures, functional disability and pain intensity levels mean ODI's were 43%, with RMDQ's being 12 (out of a possible score of 24; median= 11) with pain intensity means (NRPS) recorded as 7.5 (out of 10; median = 8). Lastly, 25/60 (42%) were unable to work due to their symptoms with 77% (46/60) having symptoms radiating into the lower limb. Lumbar flexion ROM was restricted for 87% of the participants with 58% presenting with limitation of lumbar extension and 70% with restricted side flexion. Despite 43% of participants having limitation in neurodynamic mobility tests, only 8% had positive neurological (conduction) findings. All patients had one or more hypomobile lumbar segments on palpation.

**Table 19:** Summary of the key patient OM data at inception

n= 60			Mean (SD)	Minimum	Maximum	Standard error
Age (yrs)			<b>39.75</b> (8.32)	21	54	1.07
Symptom Duration (Weeks)			<b>7.03</b> (3.62)	1	12	0.47
Primary OM		<b>Max SCR (%)</b>	<b>219.4</b> (153.09)	80.0	811	19.76
Secondary OM	Functional Disability	<b>ODI</b>	<b>42.93</b> (17.82)	16	86	2.30
		<b>RMDQ</b>	<b>12.68</b> (4.70)	4	22	0.64
	Pain Intensity	<b>NPRS</b>	<b>7.50</b> (1.36)	3	10	0.17

**Table 20:** A summary of the key clinical findings at inception

	Work Status		Pain/symptom radiation				Positive restriction				
	Working	Unable to work	No radiation	Radiation to knee	Radiation to foot	Radiation + neuro	Lsp F	Lsp E	Lsp SF	Hip IR	ND
<b>n</b>	35	25	14	22	19	5	52	35	42	9	26
<b>%</b>	58	42	23	37	32	8	87	58	70	15	43

5.8.3.2. Research question 1 (H0-1a &b) Observed SC Readings within and between treatment sessions

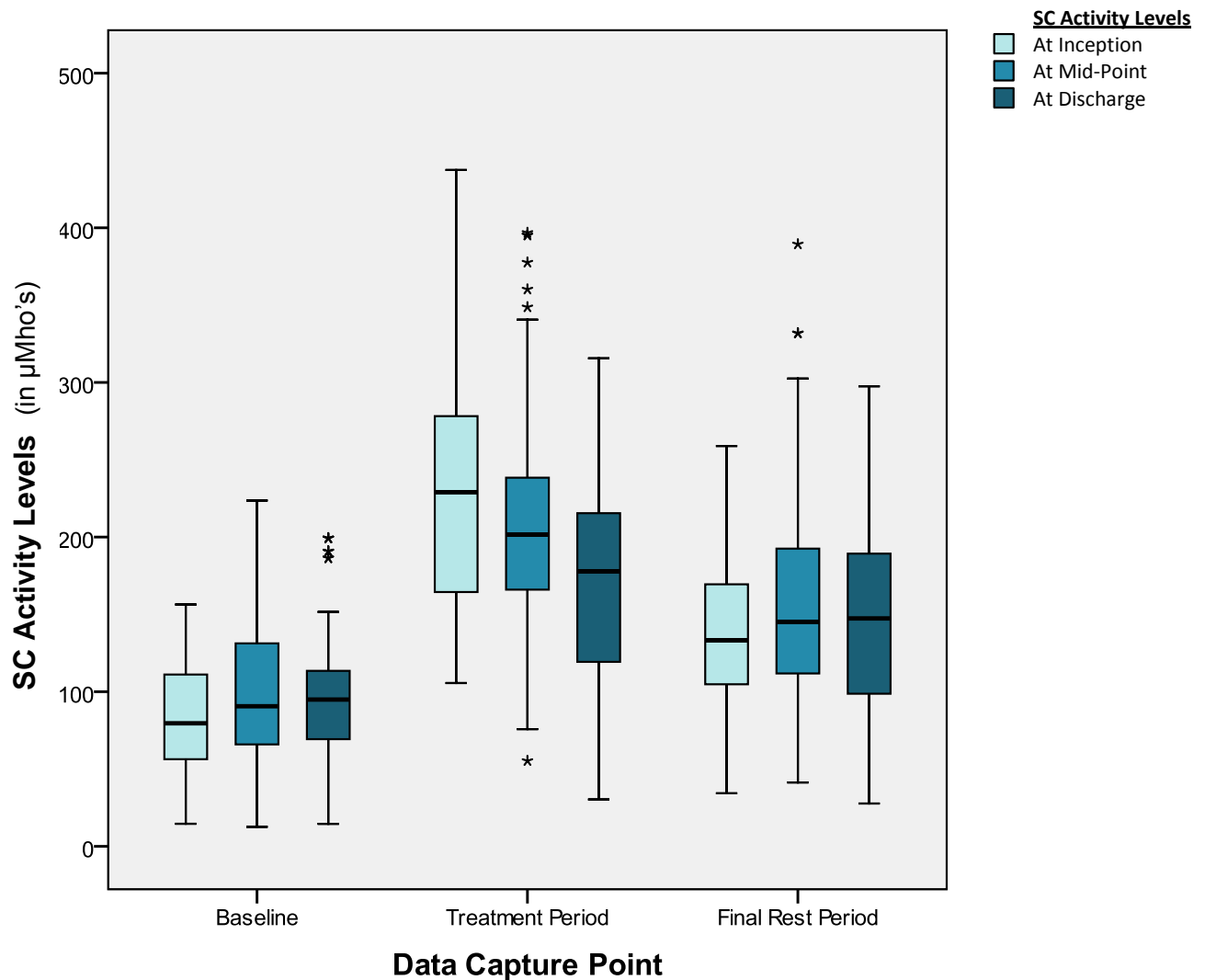
Table 21 summarizes the SC activity levels recorded within the treatment episodes (baseline, during treatment and in the final rest period) and between each of the three data capture points (inception, mid-point and discharge).

**Table 21:** Illustrating the characteristics and the SC activity levels (In  $\mu\text{mho's}$ ) and percentage change (PC) from baseline levels within and between treatments

SC activity levels (in $\mu\text{mho's}$ ) SCR (% change from baseline)	Inception (n=60)	Mid Point (n=59)	Discharge (n=59)
<b>Baseline Period</b>			
Mean	82	98	100
SD	34.1	47.9	49.2
Range	15 to 156	13 to 224	15 to 199
CI 95%	73 to 91	85 to 110	87 to 113
<b>Treatment Period</b>			
Mean (& PC from Baseline %)	230 (219%)	217 (160%)	172 (94%)
SD	85.0	83.2	66.4
Range	106 to 437	55 to 397	30 to 316
CI 95%	208 to 253	195 to 238	154 to 178
<b>Final Rest Period</b>			
Mean (& PC from Baseline %)	140 (86%)	162 (79%)	144 (55%)
SD	54.9	78.3	70.4
Range	34 to 259	41 to 389	28 to 297
CI 95%	125 to 154	142 to 182	125 to 162

Descriptive analyses (of H01) included means, standard deviations, range and confidence interval analyses. Findings revealed that within each of the episodes of treatment (baseline, during treatment and final rest) there was a change in SC activity levels with an observable increase in levels (sympathoexcitation) in the “during treatment” period (from the “baseline” period) that was maintained (but not fully sustained) into the final rest period. This was the case at each of the three data capture points; inception, mid-point and discharge. Furthermore, whilst baseline SC activity levels across the three data capture points increased (from inception to mid-point and to discharge), this was not the case for the ‘during treatment’ SC activity levels whose responses, although still sympathoexcitatory, diminished as the programme of therapy progressed to discharge (also indicated with comparisons between the SCR data). The final rest period SC activity levels were observed to remain relatively consistent from inception to mid-point and on to discharge. These trends are illustrated in figure 26 and later in Figure 27.

**Figure 26:** Boxplot illustrating the change in SC levels (in Micro Mho's) at the three data capture points (Inception, Mid-Point and Discharge) within each episode of treatment (Baseline, Treatment and Final Rest Periods).(where \* indicates an extreme case).



A summary of the inferential statistical analyses of null hypotheses 1 a and b (H01 a and b) are presented in tables 22 and 23 respectively.

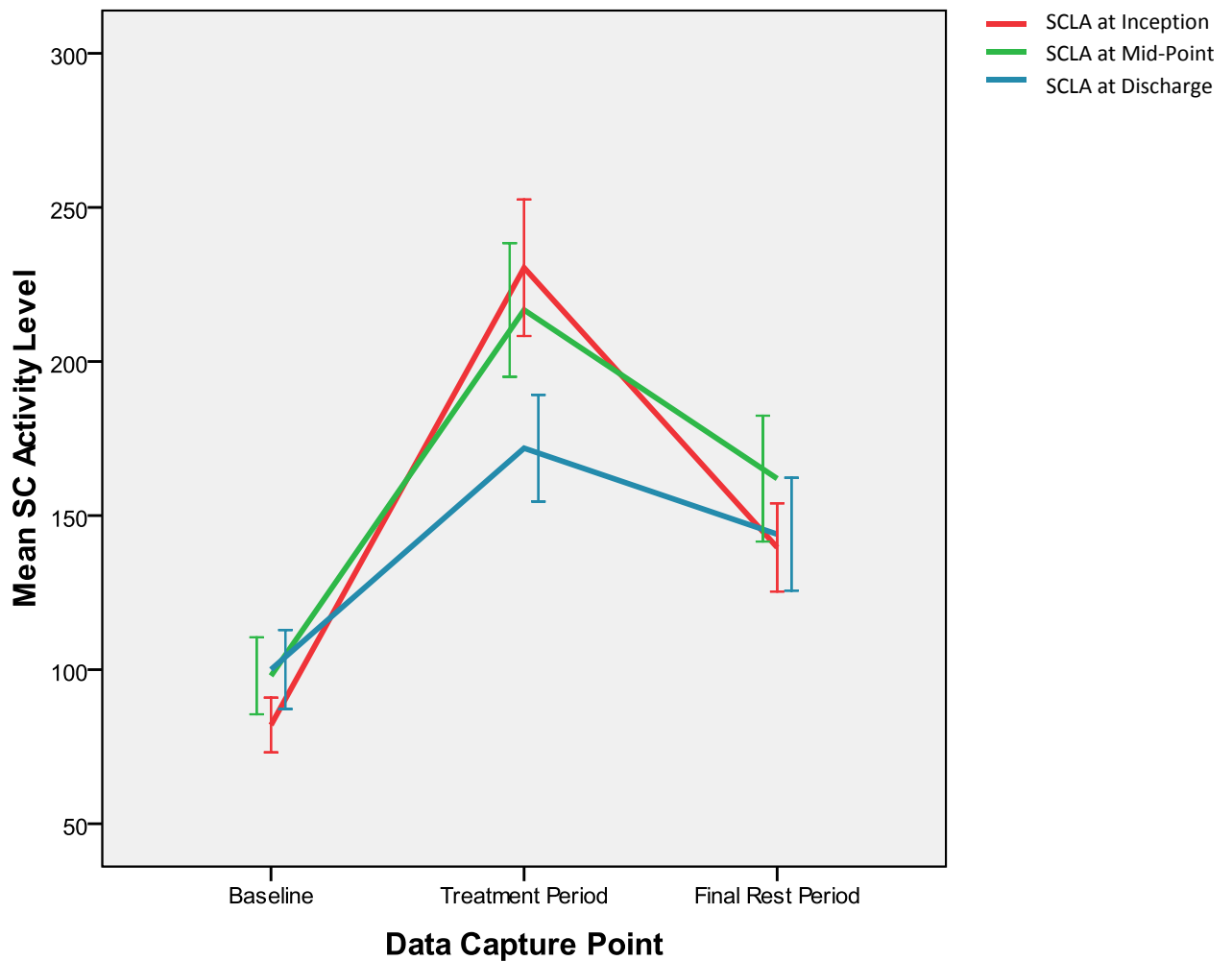
**Table 22:** Two-way Uni-variate ANOVA of SC activity levels (Baseline, Treatment and Final Periods) between participants & treatment time periods at the three data capture points

2-way ANOVA (Factors:- Participant & Treatment time period)	Mean SC activity level (in $\mu\text{mho's}$ )	Df	F value	<i>p</i> value
Inception	150.8 (CI 144 to 158)	59	3.162	<b>&lt;0.0005</b>
Midpoint	158.9 (CI 154 to 164)	58	10.978	<b>&lt;0.0005</b>
Discharge	138.6 (CI 134 to 143)	58	9.740	<b>&lt;0.0005</b>

For H01a (no differences in SC activity levels within individual treatment sessions and between participants) a uni-variate 2-way ANOVA (general linear model) was used with the SC activity levels (in micro-mho's) as the dependent variable and the two factors being; the participant and the treatment time period (baseline, treatment and final rest periods). This analysis indicated that within each individual participant there were statistically significant differences in SC activity levels between the different phases of the treatment episode (baseline, treatment and final rest period) and that these differences were significant at each data capture point (inception, mid-point and at discharge). Furthermore, post hoc analysis using Tukeys HSD (honestly significant difference) revealed that the differences were significant ( $p < 0.0005$ ) between all three treatment periods (see appendix XIV for further details) indicating that between baseline and final rest, treatment and final rest, and baseline and final rest periods there was a significant change in SC activity levels at each of the data capture points throughout the programme of care. Consequently, Null hypothesis H01a was rejected as there is evidence to suggest that a difference in SC activity levels exists within individual physiotherapy treatment sessions in an acute and sub-acute LBP population.

To test null hypothesis H01b (no difference in SC activity levels between data capture points – inception, mid-point and discharge – within the baseline, treatment and final rest periods), a uni-variate 2-way ANOVA (general linear model) was used with the SC activity levels (at baseline, during treatment and in the final rest period) as the dependent variable and the two factors being; the participant and the data capture point (inception, mid-point and discharge). A summary of the findings are presented in figure 27 and tables 23 and 24.

**Figure 27:** Line graph charting the SC activity levels (means) within each treatment session at the three different data capture points (inception, mid-point and discharge) (with Error Bars: 95% CI's).



**Table 23:** Two-way Uni-variate ANOVA of SC activity levels between participants and the three data capture points (inception, mid-point and discharge) at the three treatment time periods (Baseline, Treatment and Final Periods)

2-way ANOVA (Factors:- Participant & Data Capture Point)	Mean SC activity level (in µMho's)	Df	F value	p value
Baseline Periods (mean)	93 (CI 89 to 97)	2	7.503	<b>0.001 *</b>
Treatment Periods (mean)	207 (CI 198 to 216)	2	14.722	<b>&lt;0.0005 *</b>
Final Rest periods (mean)	148 (CI 141 to 155)	2	3.980	<b>0.021 *</b>

(where \* indicates a statistically significant)

**Table 24:** Post Hoc analysis using Tukeys HSD analysis

	Inception to Mid-point	Inception to Discharge	Mid-Point to Discharge
Baseline	<b>0.005 *</b>	<b>0.001 *</b>	0.915
Treatment Period	0.430	<b>&lt;0.0005 *</b>	<b>&lt;0.0005</b>
Final Rest Period	<b>0.022 *</b>	0.857	0.085

(where \* indicates a statistical significance)

The results of this analysis indicate that between each data capture point there was a statistically significant difference in SC activity levels through the different phases of the treatment session (baseline, treatment and final rest period) and between participants. The post-hoc analyses (using Tukeys HSD – table 24) highlight that between each of the baseline periods there was a rise in SC activity levels from inception to mid-point (18% increase) but this rise, although maintained, did not increase, to the point of statistical significance, from mid-point to discharge (a further increase of only 4% i.e. the SC activity level was maintained from treatment to final rest periods). For the ‘during treatment periods’ the most significant change occurred in the latter part of the programme of therapy (mid-point to discharge) where the SC activity levels diminished (25% reduction by discharge on top of the 6% reduction from inception to mid-point) that is also highlighted by the reduction in the magnitude of SCR’s from baseline to during treatment). Within the final rest phases, the most significant change (decreased SC activity level) occurred in the earlier treatment sessions (inception to mid-point) and beyond that the activity levels stabilized with no statistically significant activity level changes.

Overall, interpretation of these results would indicate that patients receiving physiotherapy management, for an acute and sub-acute LBP population, can be observed to have lower levels of SC activity at the commencement of therapy and that these levels increase as they progress, through the programme of care, to discharge. Furthermore, patients have higher magnitudes of SC level change to treatment at the



inception of their programme of care. But, as the programme of care continues towards discharge, SC activity levels diminish. Final rest period SC activity levels initially rise but soon stabilize. Consequently, Null hypothesis H01b was rejected as evidence exists to suggest that there is a difference in SC activity levels in LBP patients between data capture points as they progress through their programme of therapy.

#### 5.8.3.3. Research question 2 - Comparisons between skin conductance responses (SCR's) and patient-reported outcome measures (H0-2)

In order to determine if maximum neurophysiological responses (SCR's) to treatment are associated with other currently utilized, patient-reported indicators of pain intensity or functional disability, correlative analyses were conducted to test the null hypothesis (H0-2) *“There will be no correlation between SCR's (during treatment) and reported levels of pain intensity (NPRS) or functional disability (ODI or RMDQ) from inception to discharge”*. The correlation coefficient  $r$  measures the degree of 'straight-line' (linear) association between variables thereby providing a value from -1.0 to +1.0 (Altman, 1991; p.278). The validity of correlation coefficient calculations (and their associated hypothesis tests) requires that the variables display a 'normal distribution' which, according to Altman (1991), is best checked by examining means, standard deviations and ranges (Altman, 1991;p.123-124) and, visually, with a scatter diagram of the data (Altman 1991;p. 279). In the absence of a normal distribution, or, when categorical/ordinal level/ranked data (e.g. NPRS) is utilized then the non-parametric equivalent (Spearman's rho correlation) may be utilized. Table 25 summarises the key descriptive findings from the primary and all secondary OM's at the three data capture points (inception, mid-point and discharge).

**Table 25: Summary statistics for the outcome measures at the three data capture points.**  
(Published and achieved MCID levels are provided where known).

	Inception (n=60)	Mid-point (n=59)	Discharge (n=59)	MCID level	
				Published	Achieved
<b>SCR (% change)</b>	<b>217.3 (#)</b>	<b>160.1</b>	<b>94.0</b>		
SD	153.6	154.2	95.1	Value not established	Value not established
Range	80 - 812	11 - 1001	7 - 693		
95% CI	177 to 257	120 to 200	69 to 119		
<b>NPRS (0-10)</b>	<b>7.49</b>	<b>2.73</b>	<b>0.27</b>	<b>2.5</b>	<b>7.22 *</b>
SD	1.4	1.5	0.4	-	1.5
Range	3 - 10	0 - 6	0 - 1	-	3 - 10
95% CI	7 to 8	2 to 3	0.2 to 0.4	-	7 to 8
<b>ODI (%)</b>	<b>42.41</b>	<b>15.59</b>	<b>7.83</b>	<b>50</b> (MCID = 19)	<b>78.7*</b> (34.5)
SD	17.5	6.3	8.1	-	23.3
Range	16 - 86	4 - 34	0 - 30		21-100
95% CI	38 to 47	14 to 17	6 to 10		29 to 39
<b>RMDQ (0-24)</b>	<b>12.68</b>	<b>5.30</b>	<b>1.61</b>	<b>8.7</b>	<b>10.36*</b>
SD	4.7	3.3	2.1	-	4.9
Range	4-21	0-13	0-8	-	2-22
95% CI	11 to 14	4 to 6	1 to 2	-	9 to 12

\* indicates that this value reached a statistically significant difference of  $p < 0.0005$

NB. (#) = the SCR's from previous to current subsections are slightly different as the previous analysis was to 1 decimal point and this analysis to 2 decimal points

Prior to the main correlational analysis it was necessary to explore the relationship between the two functional disability PROM's (ODI and RMDQ) because Altman (1991; p.282-283) advises that even when the assumptions for correlation are not violated, misuse of correlation (and the subsequent mis-interpretation of results) can occur when two methods are used to calculate the same quantity (Altman, 1991; p.284), in the case of this study, this would occur when including both "functional disability" scales (ODI and RMDQ). A Spearman's rho correlation (for RMDQ, ordinal level data) was therefore performed prior to the main correlational analyses (see appendix XV - ODI and RMDQ analyses) and, as might be anticipated, this analysis revealed the existence of a strong positive, linear, statistically significant correlation between the ODI and the RMDQ disability scales ( $r=0.645$ ;  $p=0.0005$ ). Consequently, it was decided that the use of both scales in further analyses could potentially bias the results and their subsequent interpretation. Therefore, the decision was made to only report and utilise (for

comparison purposes) just the one scale in the final analyses. The ODI scale was selected by virtue of the fact that the ODI scoring system has the added quality of providing a predictive element to the success, at discharge, of outcome to treatment (Flynn et al., 2002 and Childs et al., 2004) although it was acknowledged that the RMDQ may be more sensitive to this acute/sub-acute population (Goertz et al., 2012).

### Main Correlation analyses

In order to conduct a thorough analysis of any relationships between the primary and the two secondary OM's an analysis of relationships between SCR, ODI and NPRS was performed, for all three data capture points independently (inception, mid-point and at discharge) as Altman (1991; p.283-284) advises that repeated measures may provide "spurious" correlations. Details of this set of preliminary analyses are provided in Appendix XVI with assessments of the assumptions of normality also included.

Overall, findings indicated that throughout all data capture points (inception, mid-point and discharge) there were moderate (Cohen, 1988) positive correlations between the two secondary OM's of functional disability (ODI) and pain intensity (NPRS) ( $r=0.525$ ;  $r=0.454$ ;  $r=0.543$  for inception, mid-point and discharge respectively) that reached the statistically significant level ( $p < 0.0005$  for all points) indicating that levels of reported functional disability were consistently, moderately and positively correlated with reported pain levels (i.e., high levels of reported pain intensity correlated with high levels of reported functional disability). Regarding SCR and ODI there was a strong positive, statistically significant correlation at inception ( $r=0.821$ ;  $p<0.0005$ ) indicating that at inception, high SCR's to treatment are correlated to high levels of reported functional disability). Interestingly, this was not the case at mid-point ( $r= 0.139$ ;  $p=0.293$ ) or discharge ( $r= -0.106$ ;  $p=0.426$ ). This phenomenon was also observed for

SCR and NPRS (although the extent of the relationship was not as strong) where, at inception, there was a moderate positive statistically significant correlation ( $r=0.459$ ;  $p<0.0005$ ) suggesting that at the commencement of the programme of treatment there was a relationship between high SCR's to treatment and to high levels of reported pain intensity. As with ODI and SCR, this correlation was not maintained (nor statistically significant) at mid-point ( $r= -0.163$ ;  $p=0.217$ ) or at discharge ( $r= -0.159$ ;  $p=0.229$ ) however, it was noted that the level of change in the NPRS OM, from mid-point to discharge, was so small (0-1) that it was likely that the assumptions associated with this type of statistical analysis were at risk of being violated and, therefore, results should be interpreted with caution.

Ultimately, preliminary trends in the data analysis of correlation would indicate that at inception, SCR has a stronger positive relationship to functional disability levels (ODI scores) than to levels of pain intensity (NPRS reports) but that this relationship does not appear to be consistent throughout the programme of care to discharge and may be a product of sampling violations (i.e. it was not a random sample).

#### Correlations between levels of change in skin conductance responses (SCR's) from inception to discharge

Having explored the strength and nature and the significance of correlations at the three different data capture points and found that there were trends in changes between the primary OM (SCR) and the secondary OM's (ODI and NPRS) particularly at inception, it was necessary to explore the nature and magnitude of changes occurring between the two definitive data capture points, from inception to discharge, in order to determine whether SCR's might be considered a feasible objective measure of neurophysiological status, in LBP patients, and a tangible measure of physiological change over time that might be reflective of functional

disability and pain intensity levels. The mid-point data capture point was not utilised in this analysis as prior studies exploring changes in the key PROM's at mid-point were not available for data comparison. Furthermore, it was acknowledged that unlike inception, the mid-point and discharge data capture points were not fixed points for each patient and therefore it may be considered to possess the potential for statistical bias.

In order to compare changes between individuals, data for all OM's were converted into percentage change measures; for SC activity levels, these were the SCR's ('baseline' to 'during treatment' period from inception to discharge), for ODI and for NPRS these were the calculations of percentage change in scores from inception to discharge. Descriptive statistical analyses are detailed in table 26 with further analyses of skewness and kurtosis provided at the end of appendix XVI).

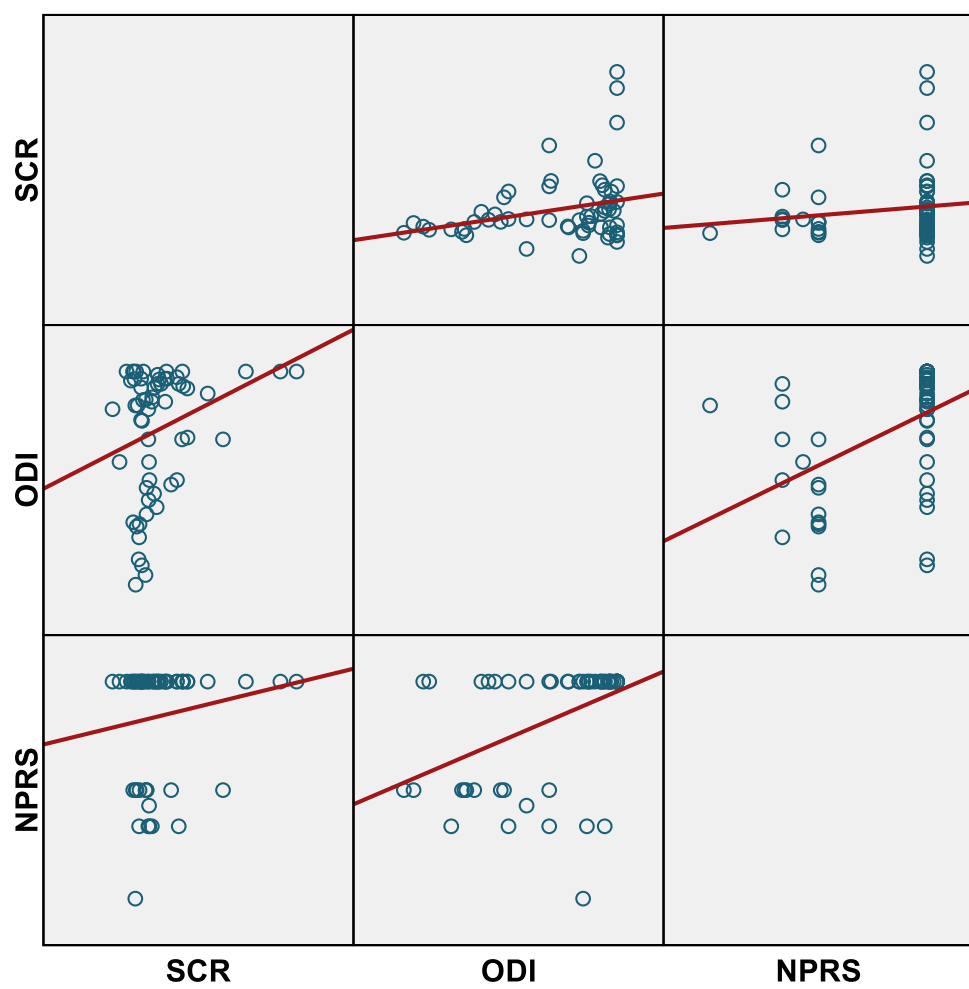
**Table 26: Descriptive statistics of percentage change measures for skin conductance response (SCR), narrative pain rating score (NPRS) and Oswestry disability index (ODI) from Inception to Discharge**

<b>Percentage Change from Inception to Discharge</b>	<b>Mean</b>	<b>Std. Deviation</b>	<b>N</b>
SCR (baseline to treatment)	-123.3	110.14	59
NPRS	-96.0	6.81	59
ODI	-78.7	23.27	59

The results indicate that descriptively there was a drop, from inception to discharge in all three OM's with SCR's reducing by 123% with corresponding reductions in pain intensity (NRPS) by 96% and reported functional disability (ODI score) by almost 79%. Therefore, descriptively speaking, it would appear that patients, at discharge, were reporting reductions in pain intensity and improvements in functional ability with corresponding reductions in the recorded maximum SCR's to the treatments provided.

Further, descriptive and inferential statistical analyses were conducted to identify the direction, strength and statistical significance of any relationships between the all OM variables. Scatterplots and both Pearson’s Correlation coefficients (for SCR and ODI) and Spearman’s rho correlation coefficients (for NPRS data comparisons) were utilised to investigate the relationships between percentage change measurements from inception to discharge for the three OM’s (SCR, ODI and NPRS). The findings are summarised in the matrix scatter graph (figure 28) and in table 27 overleaf.

**Figure 28:** A matrix scatter-plot illustrating the interaction between the three OM’s measured in percentage change from inception to discharge (with the best fit line provided in red)



**Table 27:** Inferential statistical analysis (using Pearson's Correlation and Spearman Rho Correlation Coefficients) of relationships between percentage change measurements from inception to discharge for the three OM's (SCR, ODI and NPRS) (significant correlations are highlighted in **bold** and in pink boxes)

		SCR	ODI	NPRS
<b>SCR</b>	Pearson Correlation	1	0.278 <sup>*</sup>	0.141
	Sig. (2-tailed)	-	<b>0.033</b>	0.286
	N	59	59	59
<b>ODI</b>	Pearson Correlation	0.278 <sup>*</sup>	1	0.457 <sup>*</sup>
	Sig. (2-tailed)	<b>0.033</b>	-	<b>&lt;0.0005</b>
	N	59	59	59
<b>NPRS</b>	Spearman's rho Correlation	0.229	0.509 <sup>*</sup>	1
	Sig. (2-tailed)	0.080	<b>&lt;0.0005</b>	-
	N	59	59	59

\* = Correlation is significant at the 0.05 level (2-tailed).

As can be seen from Table 27 above, the results were similar for both Pearsons and Spearman's rho calculations with respect to comparisons of NPRS and the other OM's. The decision to utilise Spearman's rho correlations for NPRS was made in view of the 'rank' nature of this OM which is better suited to Spearman's rho investigations as the assumptions (Altman, 1991; p.285) for the use of this test are less stringent than those of the parametric equivalent (Pearsons Correlation).

Results regarding the relationships between the primary OM (SCR) and the two secondary OM's (ODI & NRPS) revealed that there was a weak ( $r= 0.278$ ;  $p=0.033$ ), but statistically significant, positive correlation between changes in SCR's and ODI scores indicated that as functional disability mean changes diminished (from inception to discharge) so did the mean difference in the maximum SCR to the treatment. There was, also a weak positive correlation between mean differences in SCR and median differences in NPRS (Spearman's rho) from inception to discharge, however, this weak positive relationship did not reach a statistically significant level ( $r= 0.229$ ;  $p=0.080$ ). Not unsurprisingly, there was a moderate, statistically significant correlation

(Spearman's rho) in the differences between the two secondary OM's of ODI and NRPS ( $r= 0.509$ ;  $p < 0.0005$ ) indicating that as functional disability levels diminished so did pain intensity. A similar comparison was performed for the RMDQ scale and details provided in appendix XVI with the assessments of normality for this data.

Regarding null hypothesis two (H0-2) - *"There will be no correlation between SCR's (during treatment) and reported levels of pain intensity (NPRS) or functional disability (ODI) at, or between, inception and discharge"*, the null hypothesis was rejected as there was evidence, at inception, of a moderate-strong relationship between SCR's and functional disability (ODI scores) and a moderate relationship between SCR and pain intensity levels (NPRS), and that by discharge, percentage changes in SCR (reductions in SC responses) were correlated to improvements in reported function (ODI) (from inception to discharge). However, it was not possible to demonstrate a statistically significant relationship between changes in SCR and pain intensity improvements from inception to discharge. Interpretation of the results of these analyses should be considered with caution due to the non-random sampling of the patients and the potential for spurious correlational effects involving repeated measures over time (Altman, 1991; p. 282-283).

#### **5.8.3.4. Research Question 3**

##### **Identification of trends in SCR to treatment**

In order to evaluate the utility of Biopac SC measurements (during treatment) as a potential indicator, at inception, of final, functional outcomes at discharge, the maximum SCR's to treatments were identified by visual inspection using markers that indicated treatment-type that were documented following the completion of each treatment episode and by reference to patient treatment notes. Furthermore, trend analyses, of the nature of the treatment being undertaken at the time of the maximum SCR reading,



were examined. The findings are summarised below and in appendices XXIII and XIX. For the 60 participants initially taking part in the study at inception, 59 attended at mid-point and again at discharge thereby providing  $60 + (2 \times 59) = 178$  potential data collection points for recordings of the maximum SCR to treatment. Of these, 176 were identified as being recorded in three key treatment areas; 1) Rotatory lumbar manipulation (HVLAT), 2) Repeated McKenzie Extension in Lying exercises and, 3) mobilisations with movement with just 2 treatments being classified as “other” (specific soft tissue techniques). Details of the SCR data on the three key treatment types identified at the three data capture points (inception, mid-point and discharge) are summarised in table 28 and illustrated in figure 29.

**Table 28:** Details of the key treatments providing maximum SCR's for trend analysis

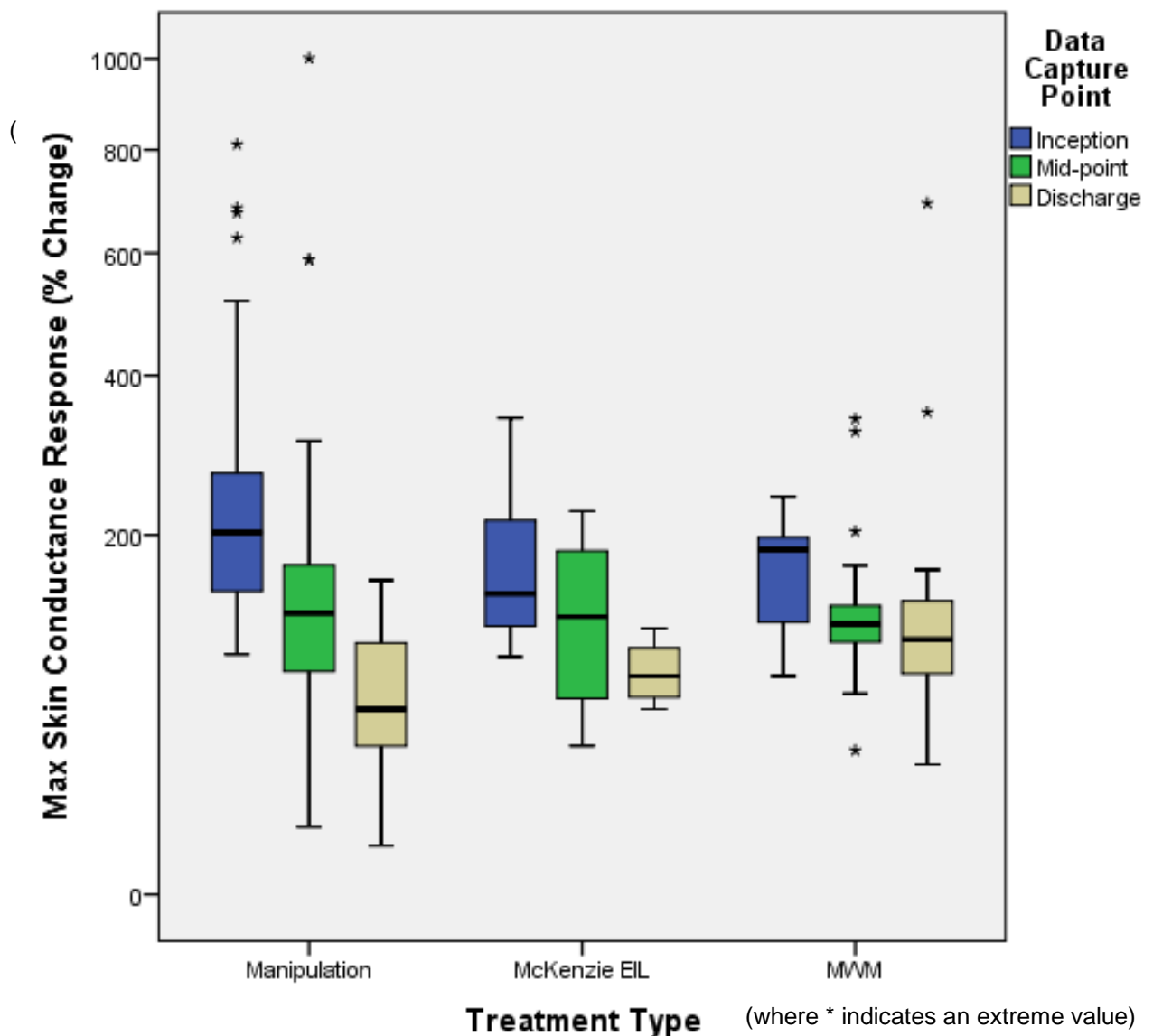
Maximum SCR	Manipulation (n=103)	McKenzie EIL (n=24)	MWM (n=49)	Total (n=176)	Significance	
					F value	p value
<b>Inception</b> n mean SCR (%) SD	31(52%)	14 (23%)	15 (25%)	60	-	-
	<b>266.7</b>	<b>172.3</b>	<b>165.4</b>	<b>219.4*</b>	3.316	<b>0.043</b>
	192.9	80.7	52.0	153.1	-	-
Mean ODI % (SD)	47.65 (20.37)	39.64 (16.57)	36.27 (9.32)	47.65 (17.82)	2.492	0.092
Mean NPRS (SD)	7.55 (1.41)	7.29 (1.64)	7.60 (0.99)	7.50 (1.36)	0.228	0.797
<b>Mid-point</b> n mean SCR (%) SD	32 (56%)	6 (10%)	19 (33%)	57	-	-
	<b>181.6</b>	<b>128.0</b>	<b>139.3</b>	<b>161.9</b>	0.465	0.708
	198.2	72.1	75.3	156.7	-	-
Mean ODI % (SD)	15.62 (6.71)	19.33 (6.77)	14.00 (5.45)	15.59 (6.34)	1.308	0.281
Mean NPRS (SD)	2.78 (1.39)	2.33 (1.86)	2.84 (1.54)	2.73 (1.45)	0.336	0.799
<b>Discharge</b> n SCR (%) SD	40 (68%)	4 (7%)	15 (25%)	59	-	-
	<b>72.1</b>	<b>83.7</b>	<b>155.1</b>	<b>94.0*</b>	4.720	<b>0.013</b>
	39.6	23.3	166.0	95.1	-	-
Mean ODI % (SD)	6.80 (7.06)	17.0 (1.16)	8.13 (10.34)	7.83 (8.12)	3.091	0.053
Mean NPRS (SD)	0.25 (0.44)	0.75 (0.50)	0.20 (0.41)	0.27 (0.45)	2.658	0.079

(significant differences between treatment types at the  $p < 0.05$  level indicated by a \* and highlighted in red)

Overall, the rotatory lumbar manipulative technique (HVLAT) was the most frequently recorded maximum SCR of all the techniques performed (n=103, 58%) at all 3 data capture points, followed by MWM's (n=49; 28%) and McKenzie EIL exercises (n=24; 14%). Regarding the magnitude of response at inception and mid-point, the lumbar

manipulative technique resulted in the highest sympathoexcitatory response (266.7% and 181% response respectively) however, by discharge the patients SCR's to this technique had diminished (by 114.6% inception to discharge) with the largest magnitude of response, at discharge, being recorded with the MWM technique (155.1%) despite the fact that manipulation was still the most utilised procedure at discharge. This observation can also be seen in figure 29.

**Figure 29:** Box-plot illustrating the max SCR's of the key treatment techniques at the three data capture points



Normality of secondary OM's for between-treatment (type) ODI ( $p=0.092$ ) and NPRS

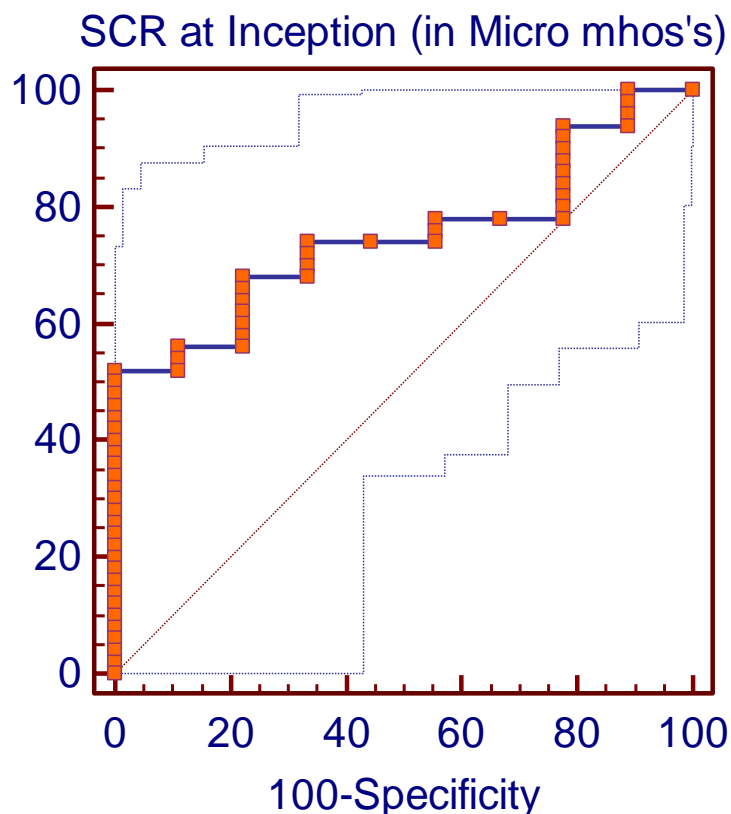
( $p=0.797$ ) measures at inception was established (table 28 above) prior to inferential statistical comparison (using one-way ANOVA - i.e. no difference between ODI and NPRS between treatments at all 3 data capture points). Results suggested that the difference in the recorded maximum SCR's at inception (and also at discharge) may be due to the nature of the treatments undertaken (inception;  $p =0.043$  for spinal manipulation and at discharge;  $p=0.013$  for MWM's). However, it is emphasised that these results are only a preliminary trend analysis and that findings should be interpreted with caution as violations to the assumptions of these tests must be acknowledged (non-random selection, the potential for underpowered sample sizes and lack of homogeneity in the numbers of participants in the different treatment types and small deviations in skewness and kurtosis – appendix XVI) and hypothesis testing is inappropriate as a true 'cause-effect' relationship is not verifiable at this stage.

#### Magnitude of SCR at inception as a predictor to a positive functional outcome (change in ODI of >50%) at discharge

The correlation analyses of research question 2 provided information describing the nature, strength and significance of relationships between the primary and the secondary OM's however, this type of analysis is unable to predict the value of one (known) variable in an individual (e.g. functionality – an improvement in function at discharge as measured by a change in ODI score > 50%) when the value of only one variable (SCR to treatment at inception) is known (Altman, 1991; p.277). In order to explore the viability of using the Biopac System, within a clinical environment for future research into treatment effects, it was of interest to investigate the potential for the Biopac System to predict at inception (using SCR's to treatment), either a positive (> 50% improvement in ODI) or a negative (< 50% improvement in ODI) functional outcome at discharge using a recognized PROM with a known, validated, measure of

change (Childs et al., 2004). To achieve this, determination of a “cut-off” point is recommended (Altman, 1991; p.417-419) whereby “successful” outcome (in this case “ODI discharge improvement >50%”) can be predicted from the magnitude of maximum SCR to treatment at inception. Altman (1991; p418) recommends a graphical approach whereby sensitivity is plotted against 1-specificity for each cut-off. By joining up these points, the resultant curve (ROC curve – receiver operating characteristics curve) is generated and the best cut-off point can then be calculated (a value that maximizes the sum of the sensitivity and specificity). Medcalc software (version 12.3.0.0) was utilized to perform the analysis and the ROC curve displayed in figure 30 below.

**Figure 30:** ROC Curve of max SCR’s to treatment (all) at inception & ODI change scores (%)



From this small sample of data, early indications suggested patients with a maximum SCR critical value >195% (cut-off point) at inception are most likely ( $z=3.564$ ;

$p=0.0004$ ) to achieve a positive outcome at discharge (ODI change  $>50\%$ ), (sensitivity  $52\%$ ,  $95\%$  CI=  $37.4$  to  $66.3$ ; specificity  $100\%$ ,  $95\%$  CI=  $66.4$  to  $100$ ) although it is acknowledged that this type of analysis does not establish cause-effect and further study is required to verify and validate this preliminary finding and to determine any link between specific treatments and ultimate clinical outcome. Further details of the analysis are provided in Appendix XVII.

Using the inception SCR  $195\%$  criterion as a cut-off threshold, comparative analyses of the study population identifies that  $46\%$  ( $n=27$ ) of the patients (who had readings in excess of  $195\%$  SCR to treatment) achieved an ODI change score in excess of  $50\%$  at discharge. The details of the differences between the participants achieving the  $195\%$  SCR cut-off threshold (and those below this limit) are summarised in table 29. Overall, the characteristics of patients, who were most likely to get a positive outcome at discharge (according to the ODI change score of  $>50\%$ ) appear to have received their initial treatment at an earlier point in time following onset of symptoms ( $5.7$  weeks compared to  $8.1$  weeks;  $p=0.011$ ), had higher functional disability levels at inception (ODI  $55\%$  compared to  $31.5\%$ ;  $p < 0.0005$ : RMDQ scores  $15.2$  compared to  $9.5$ ;  $p < 0.0005$ ) and higher pain intensities (NPRS  $8$  compared to  $7$ ;  $p=0.004$ ). Conversely they required fewer treatments (mean  $4.1$  compared to  $6.4$ ,  $p < 0.0005$ ) and were more likely to achieve a significant clinical benefit (SCB) level in their RMDQ change scores ( $13.5$  compared to  $7.6$ ;  $p < 0.0005$ ) and reduction of pain (NPRS reduction of  $7.8$  compared to  $6.7$ ;  $p=0.003$ ).

**Table 29: Comparisons of participants achieving and not achieving the 195% SCR threshold value (including comparisons to the MCID levels for OM's)**

Category	All Subjects	SCR Threshold Level measurement		Sig. (p value)
		Less than 195%	More than 195%	
<b>Number</b>	59	32	27	-
<b>Age</b>	39.7	39.5	40.0	0.798
<b>Gender (%Female)</b>	59%	59%	59%	1.000
<b>Symptom Duration (wks)</b>	7.0	8.1	5.7	<b>0.011*</b>
<b>Number of Treatments</b>	5.4	6.4	4.1	<b>&lt;0.0005*</b>
<b>ODI Baseline score</b>	42.4%	31.5%	55.3%	<b>&lt;0.0005*</b>
Mean ODI score change Base to DC	-78.7%	-74%	-85%	0.077
% achieving MCID ODI Change > 50% at DC	85%	41%	44%	0.057 <sup>A</sup>
<b>RMDQ Baseline score</b>	12.1	9.5	15.2	<b>&lt;0.0005*</b>
Mean RMDQ score change base to DC	10.4	7.6	13.5	<b>&lt;0.0005*</b>
% patients achieving MCID > 8.7 at DC	63%	24%	39%	<b>0.003*</b>
<b>NPRS Baseline Score</b>	7.5	7.0	8.0	<b>0.004*</b>
Mean NPRS score change base to DC	7.2	6.7	7.8	<b>0.003*</b>
% patients achieving MCID > 2.5 at DC	100%	100%	100%	1.000
<b>SCR reading (%SC Change)</b>				
Initial appointment	219.4	132.9	318.2	<b>&lt;0.0005*</b>
Mid-Point	160.1	126.5	200.0	0.067
Discharge	94.0	67.2	125.7	<b>&lt;0.017*</b>

**Key:** SCR=Skin Conductance Response; wks=weeks; DC=Discharge; Sig=significance value;

\* = statistically significant

A = the assumption of 'minimum expected frequency' value violated for the Chi Squared test

These findings were supported by a preliminary regression analysis that assessed the predictive capacity of the new/unknown variable (SCR) against the previously known and validated outcome predictor (ODI improvement score > 50% at discharge – Flynn et al., 2002 and Childs et al., 2004). According to the advice of Altman (1991; p.320-321 and 351-358), direct logistic regression analysis was conducted and the results of this analysis are provided in Appendix XVIII indicating that SCR has the potential to be a stronger predictor of ODI improvement >50% (inception to discharge) greater than duration of symptoms and of age. However, it is acknowledged that these findings require validation within a larger sample population and should therefore be interpreted with caution.

#### **5.8.4. Summary of the results.**

The preliminary comparative analyses involving the 2 populations of this research thesis (asymptomatic volunteers in chapter 4 and the group of patients with LBP) determined that SCR's in both populations were similar regarding their sympathoexcitatory nature as well as with respect to the differences in the magnitude of response between the two treatment techniques (the lumbar rotatory manipulation technique and the repeated McKenzie EIL exercise). However, regarding the extent of SCR's between the two populations, interesting differences revealed that the patients experienced SCR's that were more than twice that of the asymptomatic groups for both the rotatory manipulation technique and the repeated McKenzie EIL exercise.

The LBP patient data analysis provided evidence to support that SC activity levels could be observed to change within-treatment sessions (with recordable sympathoexcitatory SCR's to guideline-endorsed treatment approaches) and between-treatment episodes with observed increases in SC activity levels and diminution of SCR's (to treatment) from inception to discharge. Further correlational analyses of SCR and PROM data (ODI and NPRS) suggested that correlations exist. Furthermore, correlations in the differences in SCR's, ODI and NPRS change scores, from inception to discharge indicated that SCR's were better correlated to measures of functional ability than to pain intensity reports. Lastly, preliminary trend analyses indicated that three key elements of the multi-faceted guideline-endorsed physiotherapy approach were observed to have maximum SCR's within treatment periods and at the different data capture points of therapy. Although numbers for analysis were acknowledged to be limited (making hypothesis testing inappropriate), the treatment elements that were identified included; lumbar manipulation, McKenzie

EIL exercise and MWM's. Lastly, the provision of guideline-endorsed physiotherapy, to acute and sub-acute LBP patients', was found to achieve positive clinical outcomes, at discharge, as measured by improvements in excess of the published minimally clinically important difference (MCID) and the significant clinical benefit (SCB) levels of validated PROM's. Furthermore, using the previously validated improvement threshold score in ODI (of > 50%), results indicated that it may be feasible to consider utilizing a SCR critical value of 195% (recorded at inception during treatment) as a possible predictor of a positive functional outcome at discharge as it is a stronger predictor (of outcome) than duration of symptoms and age (commonly recognized predictive factors), although future corroboration and verification of this phenomenon is highly recommended.



## **5.9. Discussion of Clinical Results, recommendations for future research and study limitations.**

The following section focuses on a discussion of the results from the LBP patient study, notably; the observed changes (within and between treatment episodes) in SC activity levels and SCR's during physiotherapy treatments for LBP, on correlations between SC measures and PROM's and, finally, it included an evaluation regarding the potential of SC measures as a predictor (at inception) for a positive functional outcome at discharge. Comparisons between the asymptomatic and the patient populations are presented in the final discussion.

Unlike other clinically-based studies, in the current study there was a very low drop-out rate of participants. Indeed, of the 70 who agreed to attend for initial interview to consider participation, 60 were eligible for the study (85%) and only 1 patient dropped-out after commencement of data collection and treatment (due to geographical relocation with work) representing a final drop-out rate of <2%. This is considered a strength of the study as intention to treat and imputation statistical analyses were not necessary which might have biased the following discussion.

### 5.9.1. Comparisons between the current patient population and other published research

Epidemiological and PROM (ODI, RMDQ and NPRS) comparisons between the current clinical studies patient population with other published research indicated that the patient group of the current study bore strong resemblances to the baselines of the populations of other, published studies. Studies reviewing the clinical course of acute LBP (Grotle et al., 2005) and those investigating the effects of physiotherapy and MT's on symptomatic populations of LBP patients were visually compared (Childs et al., 2004; Konstantinou et al., 2007; Owens et al., 2007; Juni et al., 2009; Thomas et al. 2009; Fritz et al., 2010; Brontford et al., 2011). Demographically, similarities were

observed in age (39.7yrs for the current study; Grotle et al., 2005 = 38.9; Konstantinou et al., 2007 = 38.3; Owens et al., 2007 = 40 and Fritz et al., 2010 = 37.2). Inception PROM comparisons identified similarities in the mean scores of the ODI, with the current study = 42.9 and Fritz, Delitto and Erhard (2003) = 42.8, Childs et al., (2004) = 41.2, Thomas et al., (2009) = 39.5 and Fritz et al., (2010) recording a mean population score of = 41.7. Davidson and Keating (2005) classified scores within this banding as 'moderate disability'. RMDQ scores for the current study were 12.7 with Grotle et al., (2005) recording scores of = 9.0, Konstantinou et al., (2007) = 11.4 and Juni et al., (2009) = 12.8. For NPRS, the mean for the current study was 7.5 with Grotle et al., (2005) = 6, Konstantinou et al., (2007) = 7 and Juni et al., (2009) = 6.8.

Grotle et al., (2005) advised that the natural (untreated) clinical course of recovery, in acute LBP patients (0-20 days duration), is typified by an improvement in pain, at 12 weeks, of 58%. In the current study the reported reduction in pain, at discharge, was 96%. Whilst this time point may not be strictly analogous with Grotle et al.'s (2005) it is worthy of note that the current studies population had a greater mean improvement, above Grotle et al.'s scores, in the order of 42% which is almost double the improvement seen as a result of the natural (untreated) course of healing. Indeed, the overall improvement, at discharge in NPRS was more than 7 which is in excess of the published MCID (of 2.5). Regarding the functional disability scores, Grotle et al. (2005) advised that the natural (untreated) course of acute LBP would result in an improvement, in RMDQ scores, in the order of 68% (for the 3 months data collection point) whereas the current study reported an improvement in RMDQ scores, at discharge of 87%. Relating this to the MCID, the current study reported an average improvement of 10.36 which is greater than published standards of improvement that patients perceive as beneficial (RMDQ = 8.7). Grotle et al., (2005) did not report ODI

changes during the natural course of LBP resolution, however, other published researchers have reported change scores secondary to their intervention. ODI scores for the current study demonstrated significant improvements in functional ability throughout the programme of treatment (scores were reported as 42.9% at inception reducing to 15.6% at mid-point and then to 7.8% at discharge). These improvements are in excess to those reported by Fritz, Delitto and Erhard (2003) at their 4 week data capture point (21.4% for the SMT group) and at the 1 year follow-up (17.4%) indicating that the guideline-endorsed treatment option was, at least comparable, in ODI outcome, to Fritz, Delitto and Erhard's (2003) intervention and therefore may represent an appropriate choice of management. Regarding the MCID for ODI (19 points or 30-50% in published papers), the current study recorded a mean score improvement of 34.5 points (78.7%) which is a difference that is in excess of those that are perceived, by patients, as representing beneficial improvement further supporting the treatment approaches utilized. Whilst these results (for all PROM's) do not imply causation, the use of guideline-endorsed physiotherapy management approaches (defined by the MRC in 2000 as a complex intervention) are certainly capable of achieving improvements in pain and in function beyond the levels, perceived by patients, as representing beneficial change.

One issue with the use of MCID's and PROM's in evaluating patient responses to treatment was recognised, initially, by Hays and Woolley (2000) and, more recently, by Copay et al., (2007) who found that the baseline severity of symptoms can influence the ultimate outcome of the MCID and that the MCID will vary depending on the variability of the presentation in the population, for example, patients presenting with localised/ simple, non-radiating LBP will have different MCID findings than a patient with LBP with radiculopathy (Lauridsen et al., 2006). Another predicament with the use of PROM is

the reporting of summed average scores. Ringash et al. (2007) reported that the use of a summed average score for a population results in regression to a common mean that can dilute extreme or diverse changes that can occur and can result in clustering of responders “average score” with the potential to weaken or, at worst, distort the nature (and strength) of the distribution of scores thereby causing mis-interpretation.

Conversely, Taylor et al. (1999) argued that ODI changes in scores are able to infer meaning because of the tools well-defined and reported responsiveness. Davidson and Keating (2002) suggested that condition-specific outcome measures are less responsive than their general health counterparts in that they lack other facets associated with disability (emotional, social, and psychological factors). Although Walsh et al. (2003) claimed that the use of condition-specific measures is acceptable in the general population but that supplementation with general health measures such as the Short Form 36 is advisable, especially in multidisciplinary management of LBP. For the current study, the use of inclusion and exclusion criteria, for participant selection, enhanced the homogeneity of the group (and therefore the internal validity), furthermore, the reported inception PROM's for the current population were comparable to other published studies in LBP populations. However, it is acknowledged that the use of patients with and without radicular symptoms may have increased the variability (diversity) in the PROM's reported, a factor that may have been disguised by the use of the summed population average score (Ringash et al., 2007). Future SC measurement studies should consider sub-grouping patients with and without radicular symptoms.

Another issue with the use of PROM's is that they require patients' to understand the context of improvement and are asked to report on changes to a current state of health which requires the individual to make a retrospective judgment. The nature of this

practice has been identified as being subject to recall bias (Norman, Stratford and Regehr, 1997; Beaton, Boers and Wells, 2002; Guyatt et al., 2002) and has been documented as possibly producing the 'response-shift phenomenon' (Schwartz and Finkelstein (2009). In the current study, the use of PROM's at each attendance may have limited the potential effects of recall bias and the response-shift phenomenon, however, a more immediate measure of change, as provided by recordings of SC, might be considered a less subjective, reflective or retrospective indication of change.

#### 5.9.2. Skin conductance values as a measure of within and between treatment change

The results of research question 1 gathered SC information (activity levels and SCR's) on patients presenting with acute and sub-acute LBP (of up to 12 weeks duration) throughout a programme of guideline-endorsed physiotherapy. The study aimed to determine whether, SC levels changed within and between episodes of treatment at inception, through mid-point to discharge. Two components (null-hypotheses) were examined to explore this research question (within-treatment and between-treatment SC activity levels and SCR's). The key findings provided evidence to reject both null hypotheses in favour of the alternate hypotheses that both within- and between-treatment differences in SC activity levels were observable. The results revealed a number of important areas for consideration. Firstly, that between data capture points the baseline (pre-treatment) SC activity levels increased as the course of treatments progressed with levels observed to increase from inception to mid-point (by 19.5%; 16  $\mu$ Mho's), with a total increase, by discharge, of 22% (18  $\mu$ Mho's). These levels were in excess of those that may be attributed to measurement error (> than SRD of 4.6%; 0.3154  $\mu$ Mho's, of chapter 3). These findings were supported by the Post-hoc analyses that indicated that the most significant change (increase) in this baseline

level occurred within the first few treatments (inception to mid-point 19.5%,  $p=0.005$ ) but that the change from mid-point to discharge was not significant and did not rise above the SRD value. This pattern of SC activity level recordings was also reflected (to a lesser extent) in the final rest periods with an increase in SC activity between inception and mid-point of 8.6% ( $p= 0.022$ ).

Secondly, that during the “treatment period” of each episode of care, SC activity levels were observed to increase (from baseline levels) indicating a sympathoexcitatory response to treatment ( $p<0.0005$ ). This was particularly in the initial episode of care with SCR’s of 219% however, it was also observed that the magnitude to this sympathoexcitatory response to MT stimulation diminished significantly ( $p<0.0005$ ) from inception, through mid-point (SCR = 160%) to discharge (SCR’s = 94%). Within the treatment episode, it was also noted that these excitatory, “during treatment” responses were maintained into the final rest period (albeit to a lesser magnitude) at each data capture point indicating that the responses to treatment were not a temporary/transient/phasic phenomenon of the “during treatment” period and that the effects of treatment may possess longevity, lasting beyond the point in time of application. Lastly, observations taken in the final rest period indicated that despite an initial increase in SC activity levels between data collection points (inception to mid-point;  $p=0.022$ ), overall, observations were relatively consistent throughout the programme of care (inception to discharge;  $p=0.857$ ).

Overall, the findings of the data from this element of the current thesis would support the concept that patients (with acute and sub-acute LBP) demonstrate SNS (SC) activity levels and SCR’s suggesting that within- and between-treatment neurological (SNS) responses and adaptations occur within the stimulus-processing mechanisms of

the nervous system.

Woolf (1994 and 2011) conceptualised that stimulation of peripheral nociceptive receptors (e.g. by injury and/or inflammation) results in substantial 'up-regulation' of peripheral nociceptive function and sensitization of the dorsal horn (DH) with Storm et al. (2000) suggesting that this was reflected by altered states of SNS arousal. Boal and Gillette (2004) further substantiated Woolfs' (1994) findings in their study reporting both in-vitro and in-vivo evidence that identified the development of long-term potentiation (enhancement of signal transmission) in nociceptive neurons specifically within the DH of patients with LBP. Boal and Gillette (2004) also discovered that the LBP patients in their study also developed concomitant neuroplastic changes in the DH and the central nervous system. This phenomenon is corroborated by Bakkum (2007) with the findings, in his laboratory-based research, revealing that the presence of experimentally induced hypomobile spinal segments, in rats, caused DH neuroplasticity with resultant mal-adaptive central changes. Bakkum et al., (2007) identified that his rats had increases in DH synaptic density, neuronal plasticity and synaptic hyperactivity that were related to the experimentally induced hypomobile segments, leading them to hypothesise that these changes occurred as a functional spinal physiological response to the diminished mechanical stimulation within the joint receptors.

Considering these elements, within the context of the findings of the current study, it may be suggested that the LBP patients initially presented with inhibited baseline SNS (baseline SC at inception) activity levels which may represent the status of the DH (which would be sensitized and subject to neuroplastic changes [Woolf, 1994 and 2011] , in the acute and sub-acute stages of the condition [Bakkum et al., 2007], due

to the long-term potentiation incurred by the “up-regulated” state of nociceptor activity [Boal and Gillette, 2004] and the potential, reactive “down-regulation”/an altered/diminished arousal state of the SNS system [Storm et al., 2000]).

Subsequently, the observed (high) sympathoexcitatory responses (during the treatment period) to the MT treatment-stimulus (SCR=219% above baseline levels at inception) may be a reflection of the heightened/adapted responses (to specific, segmental stimulation from the MT approaches employed) that could be anticipated within a sensitized and/or neuroplastically adapted DH, central and sympathetic nervous system. Furthermore, Woolfs’ (1994 and 2011) concept is supported when considered in the light of the fact that the normal process of tissue healing (occurring naturally following an injury, e.g. LBP) is typified by restoration of peripheral nociceptor activation thresholds (“down-regulation”) and the associated dorsal horn (DH) desensitization. Within the context of the findings of this thesis, the observed diminution of the “heightened” magnitude of SCR to treatment, supports this ‘tissue healing model’, that is, SCR to MT were initially high (SCR’s 219% at inception) but as healing (“tissue repair”) progressed and symptoms abated, SCR’s diminished (160% at mid-point and 94% at discharge). Indeed, by discharge, SC activity levels were similar to those recorded in the normal healthy/asymptomatic participants (of chapter 4), for example, looking specifically at the data trends of maximum SCR’s to treatments (chapter 5, research question 3), in the case of the rotatory manipulation treatment, SCR’s were initially high at inception (266%) but diminished by mid-point (182%) and further reduced by discharge (72%) achieving levels that were in accordance to the asymptomatic manipulation group of chapter 4 (SCR = 76%). These diminished magnitudes of response to treatment may have occurred either through the course of the conditions natural processes of healing (regression to the mean) or may



indicate the neurophysiological adaptive changes that were occurring with time. Alternatively, it may be speculated that the “treatment” component (e.g. rotatory manipulation) could have been considered a “novel” stimulus that would be expected to give a SNS response and that with repeated (mid-point and discharge) application, the patients either accommodated to or, through the process of cortical re-organisation, the stimulus resulted in the observed reduction in the magnitude of responses. McCabe et al., (2005), Moseley and Gandevia (2005) and Moseley et al., (2006) demonstrated that strangeness, foreignness and peculiarity are features of movement stimulus when there is sensory-motor incongruence within the cortical processing regions of the brain. Fink et al., (1999) correlated such “conflict” with increased activation in the dorsolateral pre-frontal cortex, an area of the brain found to have altered activity and neurodegeneration in (chronic) LBP patients (Apkarian et al., 2004). Clearly, the observational design of this study does not permit cause-effect relationships of this nature to be established, however, it is reasonable to suggest that SCR’s may provide an alternative, empirical, method of quantifying the neurophysiological status and the changes occurring throughout a course of treatment. However, further (future) data collection and verification of these observations is warranted, within patient populations, to authenticate these suppositions.

### 5.9.3. Comparisons between skin conductance measures and patient-reported OM’s

The second research question sought to verify whether or not SC readings correlated with commonly utilized clinical measures of patient status (PROM’s) and changes in status as a result of therapeutic intervention. Results identified the nature and the strength of correlations between the primary OM of SCR’s (percentage change in SC activity level reading from baseline to during treatment) with the secondary PROM’s of functional disability and pain intensity. To the authors’ knowledge, no other published

study has explored any correlations between SC measurements and currently used PROM's within a LBP patient population.

Prior to the main analyses, preliminary data comparison of correlations between (just) the 2 functional disability measures, at inception, revealed a "medium to large" positive correlation (according to the guidelines provided by Cohen, 1988. p.79-83) ( $r=0.645$ ;  $p < 0.0005$ ). This finding compared well to other reported comparisons of ODI and RMDQ within LBP patient populations (at inception). Fairbank and Pynsent (2000) and Davidson and Keating (2002) both reported correlation co-efficients for the two scores in the order of  $r=0.77$ . Accordingly, for further correlative analysis, it was decided that only 1 functional PROM (the ODI) would be used thereby ensuring that any potential interpretation bias was minimised (Altman, 1991; 282-284). Furthermore, the ODI was the functional PROM of choice as change scores of  $> 50\%$  have been recognized as representing acceptable and validated levels of improvement in LBP populations with 'moderate' disability (40-60% on ODI) and has been used, in other studies, to establish criterion validity of other outcome responses to SMT (Fairbank and Pynsent, 2000; Roland and Fairbank, 2000; Childs et al., 2004 and Goertz et al., 2012) and therefore suitable for comparative analysis (Childs et al., 2004 and Davidson and Keating, 2005). The other secondary measure (NPRS) was also found to have a statistically significant medium positive correlation with ODI scores ( $r=0.525$ ;  $p<0.0005$ ) and compared well to other published reports of correlations between ODI and pain intensities (Roland and Fairbank, 2000 ODI and VAS  $r=0.62$ ).

Correlations for the primary OM (SCR) and the secondary PROM's (NPRS and ODI) at inception indicated there were strong positive and statistically significant relationships between SCR's (during treatment), levels of reported functional disability

(SCR and ODI;  $r=0.821$ ,  $p<0.0005$ ) and to reported pain intensity (SCR and NPRS;  $r=0.459$ ,  $p<0.0005$ ) with patients reporting high levels of functional disability and/or pain intensities being more likely to have SCR's to treatment that were of greater magnitude than patient's reporting lower levels of functional disability and or pain intensities. This might imply that SCR's may provide further insight into the patients "experience" of LBP (at inception) and provides some support for Woolf's (1994 and 2011) concept (discussed above) that acute injury (in this case LBP) can result in neural adaptations and resultant modifications to nociceptor and sudomotor activity (function).

Further analyses of the SCR and PROM data were performed in accordance with Altmans' (1991; p.284) recommendations with repeated measures designs. For this analysis, a single correlation, of the mean (SCR and ODI) or median (NPRS) differences was conducted for changes in measures (SCR, ODI and NPRS) taken from inception to discharge. Following on from the previous analyses (at inception), functionally, patients with higher reductions (from inception to discharge) in their magnitude of the SCR's (during treatment) were positively, although weakly, correlated ( $r= 0.278$ ;  $p =0.033$ ) with reductions in ODI score by discharge (i.e. patients with reductions in SCR's had similar reductions in reported disability). Furthermore, patients reporting reductions in NPRS by discharge had moderate to strong correlations between reduced pain intensity reports and reduced functional disability. However, in comparison, SCR's and NPRS correlates were only weakly positively correlated and, moreover, this relationship did not reach statistical significance ( $r= 0.229$ ;  $p =0.080$ ). Indicating that SCR's changes (from inception to discharge) are better correlated to function than to pain but that function and pain are moderately, positively and significantly correlated ( $r=0.509$ ,  $p<0.0005$ ). At this point it is worth

acknowledging that the correlational change scores (for ODI and NPRS) indicated that a large number of the participants had highly favourable improvements in their reported function and reductions in pain intensities, this may have resulted in 'clustering' of OM change scores at one end (the "improved" end) of the spectrum which could result in skewed analyses and mis-interpretation of inferences (Fitzmaurice, Laird and Ware, 2004) because of this, a log transformed analysis of the data was conducted but results were unchanged from those presented. Nonetheless, the results of the correlational analyses should be interpreted with caution in light of the spread/diverse nature of the inception data, the inherent clustering of change scores (high levels of functional ability and pain intensity improvements) and the limited sample size.

Roland and Fairbank (2000) and Davies and Nitz (2009) found that psychometrically, ODI was most effective for persistent severe disability and therefore may not truly capture the functional problems of an acute and sub-acute population despite its widespread utilization in other acute populations (Childs et al., 2004; Flynn, Childs and Fritz, 2006 and Thomas et al., 2009 and Fritz et al., 2010). The ODI, although a highly validated and reliable tool has been found, by Müller and colleagues (2004), to possess floor effects and Bombardier (2000) recommends that ODI is a better choice for populations with higher disability levels whilst RMDQ is more suitable for populations with lower levels of pain intensity and physical disability although independent analysis of SCR and RMDQ change scores (inception to discharge) indicated no correlation between measures at all (appendix XVII,  $r = 0.028$ ,  $p = 0.834$ ) which may be a reflection of the RMDQ's ordinal scale of measurement or that SCR and RMDQ are measuring two different entities. Davison and Keating (2005) considered that the ODI was able to represent different levels of disability in sub-groups of patients (with scores of 0-20% =

no disability; 20-40% = minimal disability; 40-60% = moderate disability; 60-80% = severe disability and 80-100% = “Crippled”). The population in the current study had ODI scores ranging from 18-86% which covers all of the available sub-group ranges and thereby might influence the results of the analyses, by limiting the strength of the relationships observed. Indeed, a number of researchers have excluded participants whose scores were less than 30% on the ODI scale at inception (Flynn, Childs and Fritz, 2006 and Thomson et al., 2009), and this might be a consideration (to enhance homogeneity) for future studies utilizing patient populations and SCR values.

Additionally, minimal values for inclusion criteria for the other PROM's have also been documented, with participant RMDQ scores of less than 4-6 being excluded (Hurley et al., 2004 and Owens et al., 2007 respectively) and NPRS values of less than 4-5 being proscribed in other studies (Schneider et al., 2010 and Santilli et al., 2006 respectively). Whilst in the current study RMDQ ranges were from 4-21, it was also noted that patients' NPRS's ranged from 3-10 which, like the ODI may be considered to be quite wide-ranging and although inclusive/representative of the diverse presentations of symptom intensity within an acute and sub-acute group with LBP, it may also have influenced the strength of any correlations between the OM's, indicating that this might be an area for further, future research.

Ultimately, SCR's, pain intensity and functional disability are only 3 ways of exploring the phenomenon of LBP and may not truly “capture” the full and diverse (qualitative) nature of the experience, indeed, Turk and Dworkin (2004) and Khorsan et al., (2008) warn against the uni-dimensionality of OM's and particularly the NPRS's by emphasizing that they should only be considered along-side other functional, emotional and physiological components (i.e. functional disability measures, ROM and, for this study, SCR's). Overall, it would appear that SCR's following the

administration of guideline-endorsed lumbar physiotherapy treatment, correlate better with function rather than pain intensity, but that function correlates strongly to pain suggesting that rather than SCR being a substitute for functional disability measures or pain intensity changes, it could represent an additional or alternative (objective/empirical) adjunct to the currently utilized, subjective measures employed within clinical (as well as, research) practice.

As alluded to above, these findings support the concept that normal (not maladaptive) neuroplastic changes (occurring secondary to nociceptive stimulation and DH hypersensitivity) result in CNS processing of pain and symptoms in the early stages of symptom onset and that these 'processes' may be detected through changes that occur in the sudomotor system (functional disability levels reported with high ODI scores) and in pain reports (NPRS) and, now, the responses of the sympathetic nervous system to stimulation (maximum SCR's during treatment administration). Additionally, the results provide preliminary support for the concept that manual therapy treatments may result in SCR's that could represent a non-invasive, proxy-indicator of central neurophysiological status, supporting the findings of Vicenzino et al., (2001), Frey Law et al., (2008) and Bialosky et al., (2008 and 2011) who found that pain sensitivity decreases directly in response to manual therapy.

#### 5.9.4. Trend analyses and evaluation of Biopac SC measures as a predictor (at inception) of a positive functional outcome at discharge.

The final observations in this clinical study (research question 3) sought to explore any trends in the nature of the responses observed and to evaluate the feasibility of utilizing the Biopac system as an indicator (at inception) of patients that might be predicted as good responders to treatment by discharge.

Identification of trends in maximum SCR's to treatment indicated that of the 178 SCR's recorded over the 3 data capture points, 103 were identified as responses occurring during a rotatory manipulation, 49 during a lumbar MWM manoeuvre and 24 as a result of repeated McKenzie EIL exercise (2 treatments were identified as soft tissue techniques and because of the low numbers were not included in the analyses). Of these identified treatments, manipulation achieved the greatest SCR at inception and mid-point, but the magnitude of the SCR's tailed-off by discharge (266%, 182% and 72% respectively). The repeated McKenzie EIL exercise had responses, over time, that also indicated a diminishing response (172%, 128% and 84% respectively) with the MWM technique being the most consistent responder, over time, between the three data capture points (165%, 139 % and 155% respectively). Whilst these are only identified trends, it is worthy of note that SCR's can be recorded and, indeed, may differ in the magnitude of the responses observed and may relate to the type of treatment being received. Future studies may find these observations of use in informing the development of appropriately designed and powered patient studies investigating (and quantifying) the magnitude of SCR's and establishing the efficacy of different treatments of LBP. That said, it is important to note that the SCR's used in this trend analysis were independent recordings of maximum treatment responses in the three data capture points and, therefore, do not represent repeated measures of within-patient manipulation, EIL or MWM recordings over time. Furthermore, the SCR values represented the overall maximum response achieved within the entire treatment episode, within each data capture points data recording period. Therefore, it is of note that the influence of other components of treatment, that also occurred within the treatment episode, are not known thereby preventing any causal links between observed responses and the specifics of the

treatments provided. Therefore, further randomized controlled trials are recommended to verify and to validate any cause-effect relationships between the specific treatments identified, in this study (and those of normal, asymptomatic volunteers).

The predictive utility of the Biopac system SCR measures was evaluated by comparing a known clinical predictor (ODI percentage change score >50%), to the new primary OM of maximum SCR to treatment (Altman, 1991; p.277). Using a ROC curve analysis, early indications suggested that patients with a maximum SCR critical value >195% (sensitivity = 52, specificity = 100) at inception were most likely to achieve a positive functional outcome at discharge ( $z=3.564$ ;  $p=0.0004$ ).

Interpretation of these findings would indicate that whilst the ability of the SCR cut-off value of less than 195% is excellent (specificity = 100) at identifying patients who will have a poor discharge outcome with treatment (not achieve the MCID ODI threshold of 50% improvement), it was less able (sensitivity = 52) to identify patients (SCR >195%) who would ultimately report a good functional outcome to treatment (ODI >50%), indicating that a proportion of patients, despite having SCR's below the 195% threshold (implying a less favorable ODI change score at discharge), managed to achieve the MCID improvement threshold of >50% improvement. This may indicate a number of possibilities; that the SCR threshold value of >195% has only limited predictive capacity (by accurately identifying those patients less likely to respond positively to manual therapies); that the ODI functional status indicator and change score MCID>50% has limited transferability as an indicator of neurophysiological responses to MT treatments over time; or that more data is required to verify these findings within LBP sub-populations. Clearly, further research is required to authenticate these findings.



The last analysis conducted in evaluating the predictive capacity of SCR measurements utilised direct logistic regression analyses (Altman, 1991; p.320-358). Results indicated that regardless of the 195% SCR threshold, SCR measures were a strong predictor of good outcome, at discharge, more so than currently recognized predictors of outcome, that is, the duration of symptoms and the patients' age. Indeed, putting all the predictive findings together, it was possible to identify trends, within the patient population that suggested that patients that met the critical value (of >195% SCR) at inception were characteristically those that had commenced treatment within the first 6 weeks of onset of symptoms (the most acute patients), that presented with higher levels of functional disability (ODI 55% for those with SCR's >195% compared to 31.5% for those not meeting the threshold;  $p < 0.0005$ : RMDQ scores 15.2 compared to 9.5;  $p < 0.0005$ ) and higher pain intensities (NPRS 8 compared to 7;  $p=0.004$ ). Interestingly, those patients who achieved this 195% SCR threshold were also observed to require fewer treatments (mean 4.1 compared to 6.4,  $p < 0.0005$ ) and were also more likely to achieve the MCID level (>8.7) in their RMDQ change scores (13.5 compared to 7.6;  $p < 0.0005$ ) and reported greater reductions of pain intensity (NPRS reduction of 7.8 compared to 6.7;  $p=0.003$ ). Consequently, it may be implied that the SCR threshold value may provide an independent indicator of improvement beyond levels of pain intensity, functional disability, duration of symptoms and age and certainly worthy of further, experimental investigation in future studies.

Whilst the critical value/ "cut-off" threshold of 195% lacks validation at this point, it is of interest that the patients not meeting the threshold represented the more sub-acute (> 6 weeks duration of symptoms) patients who, by virtue of the protracted length of their symptoms may have undergone the 'maladaptive' neuroplastic changes in the dorsal

horn and CNS, as described by Woolf (1994 and 2011), and which might be considered to require more than just the mechanical stimulus of SMT to facilitate the magnitude of change -in SCR- (as seen in more acute patients and in the early treatment sessions) and in the central processing system and activation of the DPIS. Indeed, it is not known if the benefits ultimately gained from these patients longer treatment programs (>6 treatments) and protracted interaction with the therapist provided a greater cognitive (frontal cortex) component to their outcome that may indicate a more 'cerebral' element to the therapeutic interaction (Bialosky et al., 2011). Obviously it is beyond the scope of this study to determine this but certainly an area of research that is developing rapidly in the literature and an arm of future studies that might be interesting to explore further, particularly within a more chronic LBP sub-population.

#### 5.9.5. The strengths and the limitations of the clinical study:

The following discussion identifies the strategies utilized to enhance the rigor of the clinical study and some of the limitations of the chosen approach.

#### The studies strengths and elements enhancing the rigor of the investigation.

Key elements employed to enhance the rigor of the study included; 1) the performance of a pre-clinical study to provide data for the power calculation to determine the sample size for the clinical study (thereby ensuring ethical practice by not over-recruiting or underpowering the study and thereby minimizing the risk of type I and type II errors), 2) the utilization of pre-determined, strict inclusion and exclusion criteria (thereby reducing the influences of extraneous variables - that are characteristics of heterogeneous populations - on data analysis), 3) by providing clear information and interview opportunities for participants to discuss the additional requirements (temporal and

procedural) of taking part in the study which enhanced the rigor of the study by limiting the drop-out rate (n=1), 4) screening of the participants (prior to each data collection opportunity) to ensure adherence to the requirements of the study (e.g. refraining from consumption of alcohol, caffeine products, exercise etc for 4 hours prior to data collection), 5) providing similar appointment times for all treatment sessions thereby limiting the effects that diurnal variation may have upon the data recordings, 6) by utilising a standardized (and previously pilot-tested for reliability) set-up for SC data collection (and analysis), 7) using the same therapist to perform all treatments (for the pre-clinical and the clinical studies) in a standardized, predetermined manner (i.e. treatments were performed identically and in accordance with the procedures described in the text of the thesis chapters), 8) by performing the study in a “natural setting” and undertaking guideline-endorsed physiotherapy practices, rather than single treatment modalities within a laboratory setting, thereby enhancing the external validity of the study to clinicians treating patients within Hospital environments and ensuring that all patients received clinically reasoned, evidence-informed treatment procedures thus ensuring that the requirements of the conditions detailed within the ethics committees approval documents were maintained (Coventry University, NREC and the local R&D office), 9) utilizing recognized, reliable and validated (within LBP populations) PROM’s as secondary outcome measures, 10) by ensuring that the data collection times, within the assessment and re-assessment episodes of care, for the primary OM (SC) and the secondary PROM’s (ODI, RMDQ and NPRS) were conducted independently (ie questionnaires were not completed whilst SC data was being gathered) ensured that the requirements (of OM independence in repeated measures designs) for data analysis were adhered to, 11) by taking PROM measures prior to the beginning of each treatment and then, retrospectively, identifying the mid-point of treatment for each

individual, thereby standardising this point for all patients and permitting an additional arm of analysis for trend identification, 12) by determining that statistical data extraction and subsequent analyses were only commenced after all treatments had been completed (for all patients), thereby minimizing any influence that either assessor (and analyser) bias might have, furthermore, all data analyses were independently checked and verified by a statistician, employed within the Coventry University Mathematics and statistics department (Dr Tim Sparks).

#### The studies limitations and proposed considerations for future research.

The results of the present study should be considered in light of several limitations.

Firstly, it is recognised that because of the design of this inquiry, a pragmatic observational study, it was not possible to assign a true cause-effect relationship to the data observations and trends made within this patient population, thereby limiting any inferences that can be made from the statistical analyses conducted. Nevertheless, it is also acknowledged that this is also the first study, of its kind, to record SC measures within a LBP patient population, thereby providing clinical data that might inform future randomised clinical trials (RCT). For the current clinical study, however, weaknesses in the observational nature of the design meant that, no randomisation of patients was performed, no control group was allocated and the independent variables were not 'manipulated', thereby limiting the interpretation of the statistical analyses used (particularly with the parametric statistical tests). Future studies are proposed that utilise elements of variable (independent) manipulation, randomisation (allocation) and control that would permit inference of cause-effect following statistical analysis.

Secondly, the use of a non-probabilistic convenience sample of acute and sub-acute LBP patients could limit the external validity of the study to the broader LBP population,

especially with respect to the more chronic sub-population of LBP patients. As indicated earlier, the use of patients with simple LBP in addition to those with radicular LBP symptoms may have weakened the homogeneity of the group leading to interpretational bias. Thus, future studies with sub-group delineation are recommended to enhance inference.

Thirdly, although the therapist and patient were both blind to the SNS (SC) measures being recorded during all treatments (due to the fact that this was a pragmatic study), the therapist conducting the treatment was also the therapist performing the research which may have the potential to create bias. According to Schutz et al. (1995) the lack of blinding can lead to an exaggerated estimation of treatment effect in the order of 17% (although it is worthy of note that the reported SCR effect sizes within this study were in excess of this amount and all exceed the published MCID's for the PROM's) and all statistical analyses were independently checked and verified by a statistician (Dr Tim Sparks, Department of Mathematics and Statistics, Coventry University).

Fourthly, no attempt was made to influence the order of the treatments delivered to the patients. Although the types of treatment were specifically detailed and consistently performed between patients (by the same therapist, thereby strengthening the internal validity) and are recognised as being 'guideline-endorsed' approaches to LBP management, the order of the prescribed treatments may have influenced the SCR's obtained. Counter-balancing (Newell and Burnard, 2011: p. 172) may have alleviated the effects of potential confounding extraneous variable, however, due to the pragmatic nature of the study this was deemed unrealistic as it would not have reflected current clinical practice. Another solution might have been to have conducted a re-analysis of any order effects on the data however, because of the limited number of participants it was decided

that a more conservative analysis of the data was more realistic although it is acknowledged as being a potential limitation to the interpretation of the analyses presented.

Fifthly, it is recognised that as a pragmatic study, the numbers of treatments given to the patients were not standardized, although the author attempted to limit the bias that this would create by pre-determining the criteria for the points at which patients were discharged (e.g. achievement of the NPRS levels, restored lumbar motion and return to work) and by ensuring that all PROM's were taken at each attendance with identification of the mid-point conducted, retrospectively, in order to limit bias in the data analysis. Despite this, it is acknowledged that the point of discharge may have been different for each patient because the reasons for discontinuing care were left to the discretion of the individual patient and the therapist. There were a variety of reasons for why care was discontinued; most were related to clinical improvement, but three of the patients programmes of care were protracted by scheduling difficulties with their return to work. Because the main aims of the study were to observe SC recordings under routine clinical circumstances, the length of time the patient spent within the clinic was extended (due to the requirements of stabilising the recordings prior to treatment and recording post-treatment responses) and discharge timing lacked strict control. This approach could have potentially caused the Hawthorne effect and influenced the outcome measures obtained. Recommendations for future studies would be to identify and control clear, pre-determined data capture points within a set time period. Based on the recommendations of the NICE (2009) guidelines, a 12 week treatment programme would suffice, however, considering the experience of the current study, and its acute and sub-acute LBP population, 6 weeks to 8 weeks might also be appropriate.

Sixthly, companion psychometric questionnaires (e.g. The Hospital Anxiety Questionnaire, Fear Avoidance and Behaviour Questionnaire or the Short-Form 36 health questionnaire) to determine which specific factors were elevated were not included. Whilst this was not standard practice in the Hospital setting utilised it may be important to examine such information for future research and for research on a more chronic patient population, as has been recommended by Walsh and colleagues (2003).

Seventhly, although strict inclusion and exclusion criteria were adhered to, specific levels of pain intensity (NPRS) and of functional disability (ODI and RMDQ) were not included, which may have subtly influenced the homogeneity of the group for statistical analysis? Whilst it was intended to have a group that was the most representative of acute and sub-acute patients receiving treatment within the clinical setting, it might be of value, in future studies, to exclude patients with pain less than 5/10 (NPRS), an ODI score at inception less than 30% or RMDQ scores of less than 5/24.

Although the feasibility of a the use of SCR measures to detect patients most likely to benefit from early, targeted treatments could not be verified in the context of the present study, the potential for the predictive capacity of this tool is worthy of further investigation. Current patterns of care indicate that most patients experiencing an episode of LBP initially enter the health care system through a primary care setting (Deyo and Phillips, 1996), and many patients are referred from a primary care setting to physiotherapists (Freburger, Carey and Holmes, 2005a). Referral from a primary care setting to physiotherapists adds to the costs of care but may also improve outcomes (Nordeman et al., 2006 and Pinnington, Miller and Stanley, 2004). Data on current practice patterns suggest that the decision to refer a patient with LBP to a

physiotherapist is highly variable across and within geographic regions and is markedly influenced by factors other than the consideration of modifiable prognostic factors (Freburger, Carey and Holmes, 2005b) and, as Childs, Flynn and Wainner, (2012) acknowledge, most referring clinicians are still reluctant to refer to physiotherapy before four weeks from onset of symptoms, despite the evidence that adherence to recommendations results in fewer clinic visits, reduced long-term health care utilisation and greater improvements in disability limitation and pain reduction (Fritz, Cleland and Brennan, 2007). Furthermore, practitioner and practice engagement and enforcement of the clinical guidelines for the management of LBP is not universal nor is it consistently applied although it is recognised, by practitioners, as being essential to ensure the appropriateness of therapeutic input at the optimum point in the patients' symptom episode which has the potential to substantially affect the quality of life, functional disability and the cost-effectiveness of care provided to patients with LBP.

#### **5.10. Conclusion to the clinical study**

To the authors' knowledge, this is the first study to evaluate the effects of physiotherapy treatment on SC activity levels and SCR's within an acute and sub-acute LBP patient population within a clinical environment. The results indicated that patients may have SC activity levels and SC responses (to treatment) that may reflect the existence of an altered/adapted, plastic state of DH sensitisation in response to tissue injury and resultant up-regulation of nociceptor, DH and CNS activity and concomitant down-regulation of the SNS. Over time, SC recordings may be able to monitor these neurophysiological adaptations/changes with identifiable reductions in SCR's to treatment as the programme of therapy progressed towards discharge.

SCR and PROM correlates indicated that SCR's were more strongly correlated with



functional disability PROM's than with pain intensity although there was evidence to support strong correlations between function and pain. Observations indicated that SCRs to treatment diminished in magnitude, from inception to discharge, as functional ability improved and pain reduced. Furthermore, preliminary analyses of positive outcomes from therapy (as measured by an ODI improvement > 50%) indicated that maximum SCR's, during treatment, were stronger predictors of outcome than duration of symptoms and patient age, with patients who achieved the SCR critical value of >195% (with treatment at inception) most likely to require fewer treatments despite having higher initial levels of functional disability and higher intensities of pain at inception. Whilst the SCR critical value of 195% was able to identify poor responders to treatment, the predictive capacity of this 195% threshold level lacked specificity to predict those patients that would respond positively to treatment.

Further research is highly recommended, within a number of areas, to verify and validate these unique observations and findings, and to determine whether SNS (SC) activity and response measurements are of value in clarifying and elucidating the magnitude and efficacy of treatments for LBP and adding to the body of knowledge that is developing within the areas of LBP classification, outcome prediction, and optimum prescription of guideline-endorsed physiotherapy that is considered to be a complex therapeutic intervention in patients with LBP.

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## **6. Final Discussion and Suggestions for Further Work**

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The following discussion draws together all the previous chapters and having identified the knowledge-gaps from the literature review (chapter 2) places the findings of this research thesis (chapters 3, 4 and 5) into the current context of research within the area of the SNS and the effects of physiotherapy and manual therapies. The key findings of the thesis are reviewed within the current and evolving philosophy that underpins the “professional knowledge landscape” of physiotherapy and the manual therapies for the management of acute and sub-acute LBP.

The concept of the neuro-musculoskeletal system as a dynamic continuum that is able to respond and adapt peripherally, spinally and supra-spinally to a variety of thermal, chemical, nociceptive, mechanical, physiological and cognitive stimuli is now well recognised within physiotherapy research. Nonetheless, the mechanisms by which clinicians (and researchers) are able to qualify and quantify the proposed mechanisms of action of the treatment programmes prescribed are still in the developmental phases. The use, clinically, of standardised and LBP specific PROM's is an acknowledged practice that assists the clinician in determining the status of a patient (in terms of pain intensity and functional disability) and the outcomes achieved following therapeutic intervention, furthermore, the identification of levels of MCID places the context of reported change measures within the bounds of acceptable patient-perceived benefits to therapy. Whilst these measures may be applauded for providing some insight into the experience of LBP and the role that therapy plays in affecting change, PROM's are recognised as suffering from a degree of subjectivity, floor and ceiling effects, recall-bias and the response-shift phenomenon causing some authors and critics to call for more objective and immediate indicators of change that is

not subject to patient, cognitive or psychological influence. Measurement of SNS (SC) responses to therapy and the concept that SNS sympathoexcitation is related to hypoalgesia is a recognised phenomenon within the manual therapy research that is able to provide such immediate measurement of “internal”/physiological change however, most of the research into this area is in the upper quadrant and only a handful of studies have been conducted within patient populations. Whilst the Biopac Data Acquisition System is a widely used tool for measuring a variety of physiological responses, there has been no published research that has established the tools reliability, measurement variability and stability in taking SC measurements nor has the smallest real difference (SRD) statistic been calculated that facilitates interpretation of SC findings beyond measures that may be as a result of equipment or procedural/administration error. Furthermore, there was no available data of the equipments reliability within a non-laboratory, clinical environment (i.e. in an environment where heat, humidity and noise is not controlled), information that is essential for use within a clinical application with a patient population.

The findings of chapter 3 indicated that the Biopac Data Acquisition System (for SC measures) had acceptable random measurement error and test-retest reliability for use in a non-laboratory situation. The research in this element of the thesis revealed that there was minimum measurement variability between applications of the equipment (ICC=0.997;  $p<0.0005$ ) and that although it was possible to observe a small degree of variability, this variability was not systematic. Further analysis of the data found that any measurement in excess of the calculated smallest real difference (SRD) of 0.3154  $\mu\text{Mho's}$  (or 4.633%) could be regarded as an SNS (SC activity level) change that is independent of any measurement error or variability and could be considered to represent real change ascribable to the intervention under investigation. Whilst it is

acknowledged that these findings were the first to be published (Perry et al., 2011) on the Biopac System providing statistical levels of SRD for SC activity levels, it is also recognised that statistical measures of SRD do not necessarily translate into patient perceived measures of clinically important difference (MCID) indicating the need for further, patient-focused research in this field.

In 2009, the publication of the NICE Guidelines for the management of LBP (in addition to the CSP, 2006 guidelines) recommended that LBP management and treatment strategies should include (amongst other recommendations) the use of manual and manipulative therapies, particularly in the acute and sub-acute stages of the condition. However, a knowledge gap was recognised, within the literature, indicating a lack of information regarding the SNS (SC) responses, observable in the lower limbs, as a result of lumbar spinal therapies. Indeed, prior to the research presented in this thesis there was only one paper providing insight into the SNS responses occurring with a lumbar treatment technique. Perry and Green (2008) identified that their population of naïve, normal, healthy males experienced sympathoexcitatory, side-specific responses to a uni-laterally applied postero-anterior mobilisation technique to the L4/5 segment. More recently, Perry collaborated with other researchers in publishing a study identifying that a lumbar MWM technique was able to produce bilateral sympathoexcitation in the lower limbs, again in normal healthy volunteers (Moutzouri, Perry and Billis, 2012). However, there was still a knowledge-gap regarding the effects of other, commonly applied, NICE (2009) recommended, lumbar techniques, namely; lumbar rotatory manipulation and McKenzie's repeated EIL technique. Consequently, a pre-clinical study was designed and conducted (chapter 4) to determine normative SCR values as a result of these techniques. Findings revealed that both treatments had

statistically significant sympathoexcitatory responses (that were above the established SRD of 4.3%) and that the manipulation technique had a response (SCR 76%) that was significantly greater (double the magnitude of response) than the McKenzie EIL technique (SCR 35%) and, unlike the Perry and Green (2008) article, that there was no significant side-specific difference in SCR (in the manipulation technique). Again, this study was the first to publish SC findings with lumbar treatment techniques (Perry et al., 2011).

As identified above, one of the strengths of this body of work was the recruitment and recording of SC data, independently, from a patient and an asymptomatic/“normal” population of participants. Uniquely, therefore, this thesis provided an opportunity for comparison between data from an asymptomatic (chapter 4) and a symptomatic group (chapter 5) to determine whether there were any differences, or similarities in SCR’s between the populations. Pre-clinical testing on asymptomatics is acknowledged as a valuable precursor for clinical testing (and ethically recognized as adhering to the protocol of Good Clinical Practice). Results from the analysis indicated that SCR’s behaved similarly for both treatments in both groups. The observed sympatho-excitatory responses (from baseline to during the treatment periods) both reached levels of statistical significance. Importantly, and uniquely to this study, the responses, in the patient groups were found to be significantly (statistically) greater (for both treatment techniques). Overall, the 25 participants retrospectively allocated into the manipulation technique group were recorded to have generated the greatest SCR with this selection of participants from the patient group having almost three times the magnitude of response than that observed in the asymptomatic group participants (SCR’s 200% and 76% respectively) with the McKenzie’s EIL exercise having a similar but reduced magnitude of response (SCR’s 104% and 35% for patients and

asymptomatics respectively). To the authors knowledge these findings have not been reported in previously published papers despite patient populations being investigated (Vicenzino, Collins and Wright, 1996; Sterling et al., 2001, and Paungmali et al., 2003). Indeed, Schmid et al., (2008) conducted a systematic review of 15 papers that explored the evidence for a CNS component in the responses observed with passive mobilizations in the cervical spine. In their pooled data analysis Schmid et al., (2008) reported SCR responses (mean pooled differences between intervention and control measures) of 35.1% (+/- 16.5), however, these results did not distinguish between the data gathered from norms and from patients, indeed, of the studies meeting the quality criteria for the review, only 7 reported SCR findings, and of those, only 2 included patient populations that lacked normative comparisons (Vicenzino et al. 1998 and Sterling et al., 2001) thereby making any comparisons to the current study unconvincing. Nonetheless, the findings of the data from this element of the current thesis would support the concept that patients (with LBP) could be demonstrating SNS responses (SCR's) that indicate an adapted neurological pain processing mechanism.

The findings of the pre-clinical study (chapter 4) were used to inform the sample size calculation for the final, clinical study (chapter 5) in this thesis. Further comparisons of the clinical, patient data and the data from the pre-clinical/normative study revealed that patients initially presented with SC activity levels (e.g. 90  $\mu$ mho's in the manipulation responders) that were lower, in the early stages of LBP presentation, compared to their normal counterparts (119  $\mu$ mho's), although these differences did not achieve a level of statistical significance ( $p=0.07$ ) these findings might hint at the possibility that symptomatic LBP individuals present with SNS-inhibited activity levels and would be an observation worthy of further exploration in future studies. Looking at the patient populations' responses, over time, to treatment also revealed that

manipulation SCR's diminished from the heightened initial responses (i.e. 266% at inception to 182% at mid-point) to levels, at discharge, that corresponded to those observed in the asymptomatic population receiving the manipulation technique (i.e. 72% for patients compared to 76% for asymptomatics). This could be considered to corroborate fit with the models proposed by Woolf (1994 and 2011), Boal and Gillette (2004) and Bakkum et al. (2007) that tissue injury and segmental lumbar hypomobility results in adapted nociceptor and mechanoreceptor DH, CNS and SNS synaptic activity.

Thus, it is feasible, within the construct of the present studies findings, to consider that following the onset of injury, patients experiencing pain (LBP), particularly in the early stages, may present with enhanced/"up-regulated" levels of DH neuronal excitability/sensitisation/potentialiation (Woolf, 1994; Bakkum, 2007; Boal and Gillette, 2004), that may not seemingly be evident in an asymptomatic population.

Furthermore, these proposed 'normal adaptive neuroplastic changes' to the DH and CNS (Boal and Gillette, 2004; Taylor and Murphy, 2010) have, through fMRI investigations, been specifically correlated to pain activated regions in the brain – Thalamus, Amagdala and Brainstem – (Piché, Arsenault and Rainville, 2010; and Nagai et al., 2004) and to the resultant triggering of the PAG, the DPIS and to the associated changes, systemically and peripherally, in SNS activity levels. The greater the magnitude of SCR's in the 'acute' group (with symptom duration less than 6 weeks and associated high pain and functional disability levels) would support this construct but it would be worthwhile for future studies, to seek to verify this hypothesis by correlating these findings directly with fMRI data.

In his review paper, Woolf (2011) highlights' that whilst new research is emerging, regarding the discovery of genetic and environmental contributors to pain plasticity, treatments that produce analgesia by normalizing hyperexcitable central neural activity (ie SMT's) remain at the forefront in symptom management despite the relative paucity of strong evidence that observes these neuro-plastic changes within patient populations. Clearly, this is an area with a considerable knowledge-deficit, for future investigation within patient populations.

Few published studies have been performed on patient populations and none, to the authors' knowledge, have looked at the lumbar spine and lower limbs. Other studies that have recruited patients have explored the thoracic and cervical regions but have reported effects of lesser magnitude (16%, Sterling et al., 2001) for treatments possibly reflecting regional differences in peripheral cutaneous innervation or central processing systems.

Central to the premise that MT stimulates the SNS (and, through central processing systems, indirectly activates a descending pain inhibitory system [DPIS]), is the concept that MT stimulates local receptors which, in turn, are capable of directly or indirectly activating the PAG mechanisms (Zusman, 1986; Wright 1995). This study demonstrated that guideline-endorsed physiotherapy (and in particular MT), resulted in sympathoexcitation, suggesting activation of the dPAG (noradrenalin) and the DPIS (Lovick, 1991) that may also correspond to (either directly or indirectly) restoration of function with further correlations with reductions in pain intensity. The author readily acknowledges that it is not possible, from this study, to directly attribute a cause/effect relationship here and that other factors (such as the psychosocial and emotional constructs of pain processing) could play a significant part in the experience of



patients. Nonetheless, it is worthy of note that each patient in this study underwent a “therapeutic” experience by which they purported significant benefit regarding pain and symptom reduction and improvements in function (mean ODI score reduction of 79%) with 95% of patients having returned to work by discharge. Tracey et al. (2002) found that there was a distinct correlation between the level of engagement of the DPIS, pain reports and levels of ‘distraction’ (including placebo and expectation) and Wagner et al. (2004) found that the PAG and dorso-lateral prefrontal cortex (emotions centre) can be selectively activated during anticipation of an “event”, triggering opioid release within the brain-stem thus modulating pain perception, it is possible that instigation of a MT technique might constitute just such an “event” and be powerful enough to result in the cascade of central processing responses that may be responsible for clinically observed improvements. Future studies are recommended (which may incorporate Biopac EEG with SC) to explore this possible link.

Historically, a number of authors (Wyke and Polacek, 1975; Yeziarski, 1991) argue that local mechano-receptors, located within the musculoskeletal system in joints, capsule, ligaments, connective tissue and tendons may be responsible for local, spinal cord inhibitory reflex. Pickar (1995) demonstrated that manipulation of cat spinal joints stimulated receptors and afferent nerve fibres within the capsule and associated connective tissues of the spinal column. Furthermore, Wyke and Polacek (1975) and Katavich (1998) suggest that stimulation of large diameter, low threshold mechanoreceptors in articular and peri-articular structures by SMT may produce a local spinal cord inhibitory effect and that these effects represent predictions of the ‘Gate Control’ theory (Melzack and Wall, 1996). However, Zusman (1986) has challenged the ability of SMT to preferentially stimulate large diameter joint afferents at the expense of small diameter, high threshold afferents, arguing that the proposed

hypoalgesic effects of SMT include hysteresis, a decrease in joint afferent activity following sustained or repetitive passive movement. More recently, Bialosky et al., (2008) revealed that patient expectations of manipulative techniques directly influenced the magnitude of SNS responses, with other authors describing significant responses, to SMT, recording increased blood levels of inflammatory Cytokines but not of Substance P (Teodorczyk et al., 2006), of restoring levels of Inter-leukin-2 (found to be depleted in LBP patients - Teodorczyk et al., 2010) in addition to increasing levels of b-endorphins and serotonin (Degenhardt et al., 2007). Additionally, Padayachy et al., (2010) found that serum cortisol levels were affected in LBP patients and that patients receiving SMT had increases in the levels of these hormones, a finding that Skinner et al., (2011) also identified with respect to levels of blood dopamine which have been found to be affected in subjects affected by pain, sleep deprivation and anxiety (Skinner et al., 2011).

Ultimately, it is possible that the treatment techniques, used in this study, directly stimulated local sympathetic fibres especially as the ganglia have a close anatomical relationship with the vertebral motion segment (Slater, 2002) and therefore the observed SNS excitatory response may simply be a spinal reflex (Magoun, 1978). Sterling et al. (2001) reported changes in superficial muscle activity following SMT arguing that this may be a response to a locally induced muscle stretch and stimulation of mechanoreceptors with resultant activation of segmental myogenic spinal reflex mechanism, although a number of authors have reported direct causal links between SMT and reflex muscle inhibition (Indahl et al., 1997; Herzog et al., 1999 and 2001; Dishman et al., 2000 and 2002; Colloca et al., 2006 and Zusman 2004). Indeed, it is feasible that the techniques in the current study may have been a SNS response to direct compression of the lumbar tissues overlying the painful segment.

Previous authors (Chiu and Wright, 1996 and Perry and Green 2008) have suggested that the parameters of the MT stimulus are important in determining the magnitude of the SNS activity. These authors theorised that the oscillatory aspect of the treatments they performed may have been responsible for the magnitude of the SNS change observed. Indeed, it has been argued that the lack of significant SCR's previously reported with the non-oscillatory SNAG performed in the study by Moulson and Watson (2006) further supported this argument although the more recent study by Moutzouri, Perry and Billis (2012) did find significant SCR's during their application of MWM's to the lumbar spine thus countering this argument or indicating that the lumbar spine may respond differently to the cervical region with regards to MWM techniques. However, Moutzouri, Perry and Billis's (2012) SCR's in the MWM group were not found to be significantly different to the placebo technique thereby questioning, further, this supposition. The results of the clinical study of this thesis, and the previous preliminary study on a normal population (Perry et al., 2011) neither support nor negate this theory as none of the treatments, that were identified as providing maximum SCR's, were oscillatory techniques. However, the magnitudes of response to the treatments in the currently reported studies were much greater than those found with oscillatory techniques (on normal/ asymptomatic populations) and therefore it may be argued that these results might counter this theory. The findings of the currently reported body of works endorse Bialosky et al.'s (2009) model that considers both spinal cord and supra spinal mediated effects of manual therapy (see figure 31 overleaf) although, it is worthy of note that much of the evidential literature supporting Bialosky et al.'s (2009) model is based on animal experiments and laboratory-controlled experiments on asymptomatic healthy volunteers.

With reference to the concepts within Bialosky et al.'s (2009) model (figure 31 overleaf), it is hoped that some of the findings of this thesis provide some additional information,

filling some of the knowledge gaps and areas lacking evidence of clinical (LBP) application that, until now, have only been established with laboratory studies on asymptomatic humans, animal studies and inferences from cervical spine studies. Analysis and consideration of the clinical data, from the current study, could provide a unique input (indicated by the bold red arrows) to the model by confirming the existence of a measurable effect (clinically, functionally and neurophysiologically) of treatment (SCR changes) that correlate to patient reported changes in pain intensity (NPRS) and functional disability (ODI and RMDQ scores). It is worthy of note that despite the publication of this and other models (e.g. George et al., 2006) and the general acceptance of these constructs within the profession, most of these models remain incomplete and purport a rather biomedical, approach to pain management, that is, that anatomical spinal structures are the source of pain and contribute to long-term potentiation of nociceptors. Indeed, whilst Wand and O'Connell (2008) acknowledge the input that peripheral and spinal receptors have regarding clinical pain manifestations, they also challenge that therapies for LBP (and in particular chronic LBP) should be based around the 'cortical dysfunctional model' presented in their review paper (figure 32 details this model).

Figure 31 : The pathway considering both spinal cord and supra spinal mediated effects of manual therapy. Bold arrows indicate suggested mechanisms. Taken from Bialosky et al. 2009. (Bold red arrow indicate the contribution of this research to the model)

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**Figure 32: Wand and O'Connells (2008) 'cortical dysfunctional model for chronic LBP.**

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Whilst the data generated by the current thesis does not include a chronic LBP population which is the focus of Wand and O'Connell's (2008) review, nor does it provide any corroboration of the cortical dysfunctional elements that they purport, it is not inconceivable that the high pain intensities reported by the clinical population of the current thesis, coupled with the high functional disability levels reported could form part of the constructs within the chronic LBP model, that is; (refer to the coloured numbers in the following text corresponding with those in figure 32); **1** New episode of low back pain results in peripheral nociceptive input (high pain intensity reorts on NPRS); **2** this leads to activation of the central pain neuromatrix with resultant **3** sensory-motor incongruence with back movements and functional activities (high functional disability levels in ODI & RMDQ scores) **4** and motor control changes, increased guarding and co-contraction; **5** where intra-/sub-cortical facilitation / decreased inhibition may represent the heightened SCR's to inception treatment. Clearly, more studies are required to explore these theories and to validate how SC activity levels and SCR's might contribute to this 'cortical dysfunctional model' for chronic LBP populations.

A preliminary evaluation was also conducted with the aim of estimating the predictive utility of the Biopac system SCR measures within a LBP population. Whilst it is acknowledged that this is not the same as calculating the MCID (a patient-perceived standard level of meaningful improvement), it was recognized that the data from this study could provide a unique opportunity to compare the new (SCR) data to a known patient-perceived and validated clinical predictor (ODI percentage change score >50%) of positive therapeutic outcome. Indeed, early indications from the analysis suggested that the critical value of 195% SCR (at inception) was excellent at identifying poor responders to MT treatment (specificity = 100) which could be useful, in the early stages of treatment, at guiding the therapist, and the patient, towards more hands-off, cognitive

approaches, the SCR 195% critical value was less able to detect good responders to treatment (sensitivity = 52) which could imply that the predictive capacity of SCR measures lack true application. Conversely, it was noteworthy that in the clinical study, a large number of the patient participants achieved MCID scores in excess of those reported, in other studies, as representing achievement of patient reported benefits from therapy. Indeed, the mean participant changes in PROM's demonstrated improvements, from inception to discharge, in function, on the ODI scale (an average improved score of 34%, where reported MCID = 19%), on the RMDQ scale (average improvement of 11 points, MCID = 8.7) and pain intensity NPRS (an average reduction of 7.2 points, with MCID = 2.5). Thus, it might be conceivable that this patient population responded to the guide-line endorsed therapeutic intervention in a manner that exceeded the expectations of PROM's within other similar clinical studies. This may have had implications for the correlation and for the predictive capacity analyses. Clearly, further studies are called for to verify and validate these findings. Finally, the last analysis, evaluating the predictive capacity of SCR measurements, indicated that regardless of the 195% SCR threshold, SCR measures were a strong predictor of good outcome, at discharge, more so than currently recognized predictors of outcome, that is, the duration of symptoms and the patients' age. Furthermore, good responders to therapy were characteristically those that had commenced treatment within the first 6 weeks of onset of symptoms (the most acute patients), that presented with higher levels of functional disability and higher pain intensities and were observed to require fewer treatments to achieve symptom abatement. Thus, despite its obvious limitations the SCR threshold value of 195% may provide an alternative and independent indicator of improvement beyond levels of pain intensity, functional disability, duration of symptoms and age and should be considered for further investigation.

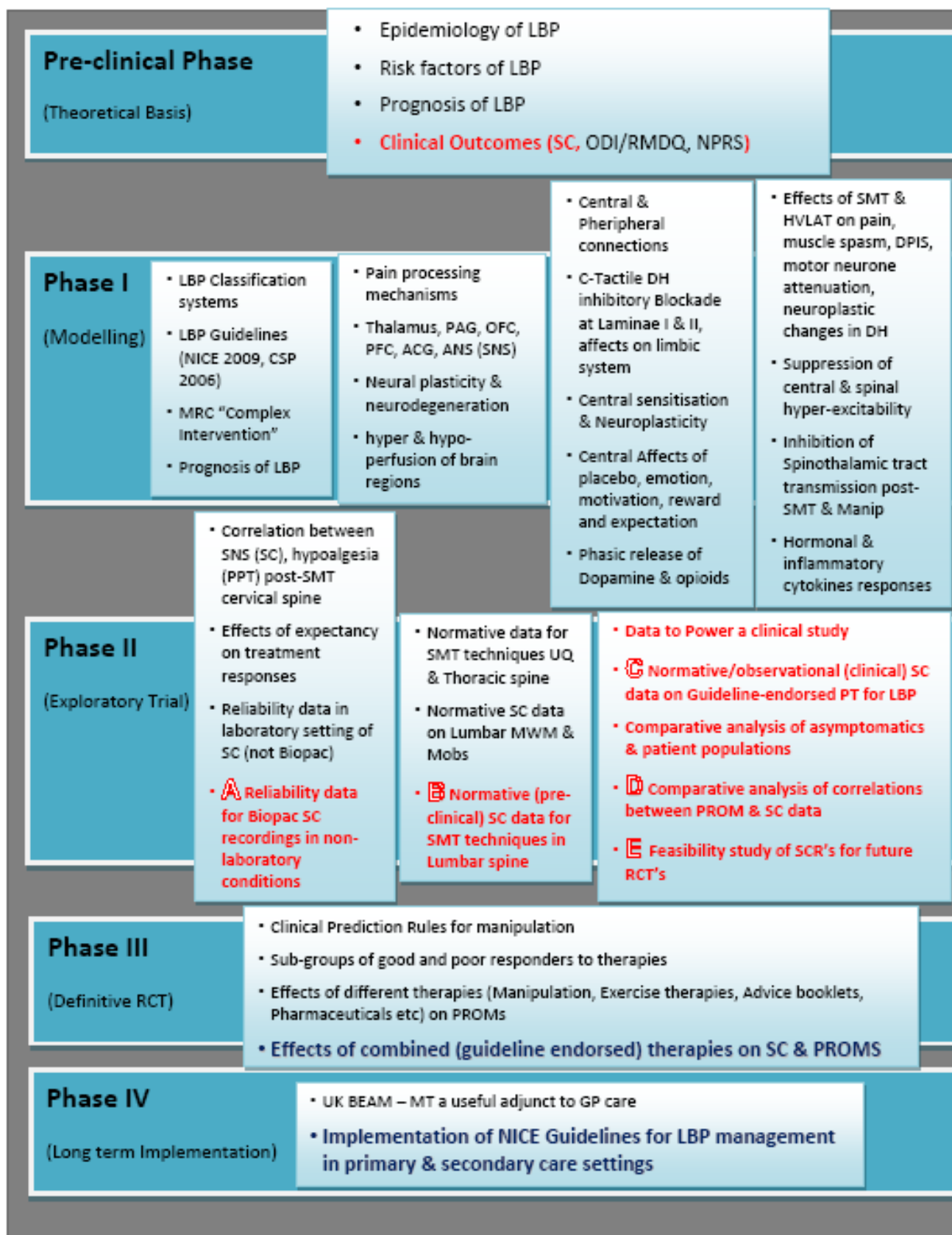


As discussed above, whilst the critical value/ “cut-off” threshold of 195% lacks validation at this point, it is of interest that the patients not meeting the threshold represented the more sub-acute (> 6 weeks duration of symptoms) patients who, by virtue of the protracted length of their symptoms may have undergone the ‘maladaptive’ neuroplastic changes in the dorsal horn and CNS, as described by Woolf (1994 and 2011), and which might be considered to require more than just the mechanical stimulus of SMT to facilitate the magnitude of change -in SCR- (as seen in more acute patients and in the early treatment sessions) and in the central processing system and activation of the DPIS. Indeed, it is not known if the benefits ultimately gained from these patients longer treatment programs (>6 treatments) and protracted interaction with the therapist provided a greater cognitive (frontal cortex) component to their outcome that may indicate a more ‘cerebral’ element to the therapeutic interaction (Bialosky et al., 2011). Obviously it is beyond the scope of this study to determine this but certainly an area of research that is developing rapidly in the literature and an arm of future studies that might be interesting to explore further, particularly within a more chronic LBP sub-population. Unfortunately, it was not within the scope of this research to validate this SCR cut-off threshold further, nonetheless, it is recommended that future clinical trials be conducted to legitimize this threshold parameter within stratified patient populations and to ascertain its validity at predicting overall outcome to manual, exercise and indeed cognitive therapies within different (primary and secondary) health care settings.

Regarding the nature of the “therapeutic” encounter that the patients in this study received, the Medical Research Council (MRC, 2000 and Craig, Dieppe and Macintyre, 2008) might define the combined, pragmatic and clinically representative approach of advice/education, exercise and manual therapy techniques as a “complex intervention”. Within the context of researching the phenomenon of “complex interventions”, the

research within the current thesis may be considered to fall into phase II of the MRC's framework by providing, on the back of a broad theoretical understandings of MT interventions, an 'exploratory' insight into a number of areas that could be used to inform definitive RCTs (phase III) and long-term implementation studies and clinical guidelines/recommendations (phase IV). How the current thesis fits into this framework is illustrated in figure 33 overleaf. Within the illustration, the 5 key findings of the thesis are depicted by the letters **A****B****C****D****E** where; **A** = the Biopac reliability study (chapter 3), **B** = the normative (pre-clinical) SC data for two commonly used lumbar treatment techniques, **C** = observational (clinical) SC data on Guideline-endorsed physiotherapy for acute and sub-acute LBP; and the comparative, preliminary, analysis of asymptomatics & patient populations, **D** = the correlative analysis of clinical PROM's and SC data, and **E** = the preliminary feasibility study of SCR's for predicting clinical outcome at discharge.

**Figure 33:** A representation of the place of the thesis findings within the MRC framework for Complex Interventions (2000) the letters ABCDE refer to research questions addressed within the thesis, Bold blue lettering indicates areas for future research



The publication of the national guidelines (CSP, 2006 and NICE, 2009) for the management of LBP clearly recommend the use of manual and manipulative therapies, presenting moderate to strong evidence of its effectiveness, particularly in an acute patient population. Indeed, Sizer (2008), in his invited commentary on 'spinal manipulative therapy for acute low back pain', argues that SMT should not be considered 2<sup>nd</sup> line treatment after GP care (advice on staying active and drug management) on the contrary, he cautions that SMT should be considered a non-pharmaceutical 1<sup>st</sup> line care approach serving as a healthy alternative to the contemporary primary care practice model. However, Sizer (2008) does caution that biopsychosocial considerations should also be included when evaluating the influence of SMT treatment selection on outcomes, particularly with the more chronic patient populations. To the authors' knowledge, this study is the first to provide empirical, clinically relevant, evidence supporting the early use and the resultant positive outcomes of lumbar manual and manipulative treatments (in addition to advice, education and exercise) in an acute NSLBP population, supporting the published guidelines as well as clinicians anecdotal arguments for the integral use of MT treatment approaches within a comprehensive (guideline-recommended) patient care package. It would be of interest to consider a sub-group of chronic patients in future studies as it remains unknown what their SCR status, at inception, may be and how this might differ in terms of responses to treatment and to final outcome measurements, indeed, if the findings of the current study are extrapolated, beyond the 12 week symptom duration criteria, it may be anticipated that a more chronic LBP population would have a poorer SNS response to MT treatment approaches, and require more extensive treatment programs, including alternative, cognitive behavioural approaches to activate the central pain processing areas within the cortex and ultimately the DPIS (Oosterwijck et al., 2011). Indeed, the work of a number of authors have demonstrated

that the presence of chronic pain, including back pain, is associated with decreased thalamic grey matter density (Apkarian et al., 2004 and Ruscheweyh et al., 2011) and that the provision of an appropriate “stimulus” has the effect of “rebooting the system” (Apkarian et al., 2005) and facilitating an adaptive change that aligns the patient back to normal parameters. Indeed, Apkarian et al. (2005) found that with the abolishment of pain there was observable (MRI and voxel-based analyses) restoration of regional grey matter densities in LBP patients (Ruscheweyh et al. 2011). Moreover, Moseley (2008) advises that the presence of pain and the phenomenon of cortical reorganization are related and speculates that the effects of physiotherapy interventions/treatments on ‘body and motor maps’ requires the patient to carefully attend to and discriminate the location, quality and intensity of the therapeutic stimulus (i.e. an externally, mechanically and proprioceptively induced stimulant e.g. a manipulative procedure) facilitates normalization of the internal ‘maps’.

In contrast to this theory, Bialosky et al.’s (2008) study revealed that normal (asymptomatic) subjects with negatively incited expectations, for SMT-induced hypoalgesia, experienced significant increases in pain perception following the procedure, suggesting the role of recipient expectation on the effects of SMT, and importantly, the role of the therapist in the competent assessment of patients’ attitudes and the matching of patient choice and expectations to the optimum treatment approach. The elements of cortical reorganization, placebo and expectation formed a part of Moseley’s (2007 and 2008) work and Bialosky et al.’s 2009 ‘comprehensive model’ are worthy of consideration however they are beyond the scope of this studies data analysis although their importance is acknowledged.

Finally, the concept that neurophysiological (SC) activity levels and changes occurring in the lumbar region can be credibly and reliability monitored (with the Biopac system) and

potentially modulated with guideline-endorsed physiotherapy and MT treatment. This research provides observational evidence to support early active physiotherapeutic intervention that is seen to restore function and a pain-free status. The findings of this study corroborate the advice provided in a number of key guideline texts that endorse the use of manual and manipulative techniques in the acute and sub-acute stages of symptom onset. Furthermore, whilst this programme of research is not definitive, it does provide clinicians, patients, GP's/referrers and managers supplementary evidence to support the early referral of LBP patients to appropriately qualified practitioners for consideration and application of guideline-recommended physiotherapy and MT treatment (CSP, 2006 part 2; Mercer et al., 2006; Fritz, Cleland and Brennan, 2007 and Childs, Flynn and Wainner, 2012).

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## **7. Conclusion**

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The processes of evidence informed practice and clinical research are inherently interwoven. This multi-level, integrated and often cyclic process starts with clinical observations and the generation of research questions. Through the conduct of research, the development and testing of theoretical concepts and the systematic collection and analysis of data, the findings may be disseminated back into the therapeutic encounter between the therapist and patient. In the execution of this mission and with the explicit, judicious and conscientious (Sackett et al., 1996) application of findings into clinical decision making, ultimately, it is hoped that patients, clinicians and managers achieve furtherment of knowledge and understanding. Thus, the administration of optimum, research-informed, clinically effective treatments that meet the patient's expectations, manage symptoms and provide appropriate education and advice in a timely manner.

### **Contributions to Knowledge**

The aim of this series of studies was to contribute to the professional-knowledge surrounding the observable effects of physiotherapy (and particularly spinal manual and manipulative therapies) on patients presenting with LBP in a clinical environment. Chapter 2 identified the key knowledge-gaps in the LBP arena, recognising that although epidemiological risk factors, classification models, clinical prediction rules and OM's exist, none truly capture the diverse nature of the patient experience of LBP and none provide an objective marker for research comparisons. Furthermore, the current research in the area of SNS status and treatment responses to therapies was severely lacking in the lumbar region and lower limbs. Thus, the initial aim (chapter 3) was to establish the reliability and measurement stability of Biopac SC readings within

a natural (non-laboratory). This reliability study was paramount to the following chapters (4 and 5) of the thesis where knowledge-gaps in the effects of commonly used manual therapy treatments were investigated, initially in a pre-clinical, normal population and, latterly, and pragmatically, within an acute and sub-acute LBP patient population receiving guide-line endorsed physiotherapy treatment.

The pre-clinical investigation (chapter 4) established normative values for SC responses to two, independently applied, specific MT techniques, applied to the lumbar region. Findings from this study revealed that both treatment techniques produced statistically significant sympathoexcitatory changes that were detectable in the lower limbs (and were greater than the SRD established in the reliability study). Moreover, the rotatory manipulative technique produced twice the size of SCR as the McKenzie EIL technique, and contrary to other research, was not side-specific, with only the manipulation technique having a lasting effect into the final rest period.

The preliminary data comparisons of the pre-clinical asymptomatic participants with data extracted from observations from the patient participants challenged the assumption that normative and patient population studies were analogous. Results suggested that patients with acute or sub-acute LBP were significantly more (SC) responsive to treatment (at inception) than their normative counterparts. Whilst it was acknowledged that this may, in part be due to the “composite” nature of the patient treatment experience, it was noted that future studies were necessary to enhance understanding within this remit.

The main analyses of the patient observations suggested that initially, patients attended with inhibited baseline SNS levels of activity and these levels were observed to increase as they completed their programme of therapy. Additionally, SCR's were greatest at inception but as therapy progressed towards discharge, the magnitude of SCR to



treatment diminished to levels that corresponded to SCR's found in asymptomatic norms. Analyses of the existence of correlations between SCR and currently used PROMs, indicated that SCR's were positively and statistically correlated to functional disability more than to pain intensity. Due to the strength of the correlations it was hypothesised that SCR's might constitute an objective, alternative, and complementary measure of patient outcome within a clinical or research setting. Furthermore, a preliminary exploration of the utility of inception SCR measures at predicting functional outcomes at discharge (employing a validated ODI improvement score in excess of 50%) indicated that a (SCR) treatment response threshold of 195%, whilst excellent at identifying poor responders to MT treatment, was less accurate at identifying good responders, to manual and manipulative therapies.

Clearly, the observational design of the clinical study was not able to infer any cause-effect results, however, it does provide some interesting and new information that contributes, in phases one and two of the MRC's framework for 'complex intervention' research that could inform future, definitive, phase 3 clinical randomised controlled trials into LBP management strategies.

The findings of the clinical study indicated that patients have SCR's to treatment that are significantly greater than those seen in asymptomatic healthy volunteers, and that SCR's to treatment may reflect the DH sensitisation in the early stages of symptom onset indicated by higher treatment-SCR's that also correlate to higher levels of functional disability, to high levels of pain intensity and to short symptom duration. Patients with higher treatment SCR's treated in the early stages of symptoms required fewer treatments to achieve symptom and pain resolution and achieved positive functional outcomes so that by discharge treatment SCR's were significantly reduced, pain had

abated and there was a positive change in functional disability (as represented by an improvement score on ODI in excess of 50%).

A key, but preliminary, suggestion from the findings of this study was that SCR's might be a non-invasive indicator of neuroplastic adaptations, DH and CNS processing that occur as a result of lumbar injury.

It is believed that the findings of this study adds to the body of knowledge required to further understand the mechanisms of action of manual therapies, in particular manipulation and MWM's, and prompt further research within patient populations.

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**Appendix I – Copies of Published Articles, Awards and Conference and Poster Presentations**

**Peer Reviewed Journal Publications from this PhD**

**Perry J**, Singh S, Watson PW, Green A (2011) A preliminary investigation into the magnitude of effect of lumbar extension exercises and a segmental rotatory manipulation on sympathetic nervous system activity. *Manual Therapy* 16; 190-195.

**Conference Presentations and Awards from this PhD**

**Perry J**, Singh S, Watson P.J., Green A (2008) The neurophysiological effects of two spinal therapy techniques. Society for Back Pain Research. Special Poster and Oral Presentation. Keele University November 2008

**Perry J**, Singh S, Watson P.J., Green A (2011) The neurophysiological effects of two spinal therapy techniques. World Congress of Physical Therapy. Special Poster presentation. Amsterdam. June 2011.

**Perry J**, Singh S, Watson P.J., Green A (2012) The neurophysiological effects of physiotherapy on patients with low back pain. Platform Presentation. International Federation of Orthopaedic and Physical Manipulative Therapists (IFOMPT). Quebec City, Canada. November 2012.

**Perry J**, Singh S, Watson P.J., Green A (2011) The neurophysiological effects of physiotherapy on patients with low back pain. MACP Elsevier Presentation Award. November 2012.

**Perry J**, Singh S, Watson P.J., Green A (2011) The neurophysiological effects of physiotherapy on patients with low back pain. CSP educational Bursary Award. December 2012.



Original article

## A preliminary investigation into the magnitude of effect of lumbar extension exercises and a segmental rotatory manipulation on sympathetic nervous system activity

Jo Perry<sup>a,\*</sup>, Ann Green<sup>a</sup>, Sally Singh<sup>a</sup>, Paul Watson<sup>b</sup>

<sup>a</sup> Coventry University, Faculty of Health and Life Sciences, Department of Physiotherapy, Priory Street, Coventry CV1 5FB, UK

<sup>b</sup> Department of Anaesthesia, University of Leicester, University Road, Leicester, UK

### ARTICLE INFO

**Article history:**

Received 22 April 2010

Received in revised form

17 October 2010

Accepted 25 October 2010

**Keywords:**

Manipulation

McKenzie exercise

Physiotherapy

Sympathetic nervous system

### ABSTRACT

Two commonly utilised manual therapy techniques; McKenzie's lumbar extension exercises (EE); and segmental rotational grade V manipulation were investigated to determine their magnitude of neuro-physiological effect. Proxy measures of sympathetic nervous system (SNS) activity (skin conductance) were utilised to ascertain neurophysiological response. This study determined the neurological effects of these two treatment techniques in addition to establishing the Biopac System as a reliable measure of neurophysiological changes.

A quasi-experimental, independent group's design was utilised, with random allocation of 50 normal, healthy participants into a manipulation or an EE group. Neurophysiological measurements of skin conductance were taken in the lower limbs before, during and after the administration of the techniques. Results were converted into percentage change calculations for the intervention and the post-intervention periods.

Both treatments increased SNS activity during the intervention period, 63% for the manipulation group ( $p = 0.0005$ ) and 42% for EE group ( $p = 0.0005$ ) with the manipulative technique having significantly greater effect ( $p = 0.012$ ). Further analysis of the manipulation group found no difference between the 'opening' and the 'closing' side of the technique ( $p = 0.76$ ). Biopac System is a reliable method for measuring SNS activity with minimum measurement variability.

Preliminary evidence now exists supporting the neurophysiological effects of two lumbar techniques.

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# A Preliminary Investigation Into The Magnitude of Effect Of Two Commonly Used Lumbar Treatment Techniques On The Sympathetic Nervous System



J. Perry<sup>1</sup>, S. Singh<sup>1</sup>, P.J Watson<sup>2</sup>, A. Green<sup>1</sup>

<sup>1</sup>Dept of Physiotherapy, Coventry University; <sup>2</sup>University Hospitals of Leicester NHS Trust, Department of Anaesthesiology

## Background

- > 58.9% of UK Physiotherapists utilise spinal joint techniques or McKenzie's extension in Lying (EIL) as preferred treatments for LBP +/- leg pain (Foster et al, 1999)
- > However, there is no consensus regarding the efficacy of the choices of treatment.
- > Changes in SNS activity levels following spinal manual therapy have been linked to hypoalgesia & pain modulation in the cervical spine & upper limbs (Petersen et al, 1993; Vicenzino et al, 1994 & 1998; Slater et al, 1994; Sterling et al, 2001).
- > Preliminary work on the lumbar spine has indicated similar links (Perry & Green, 2009).

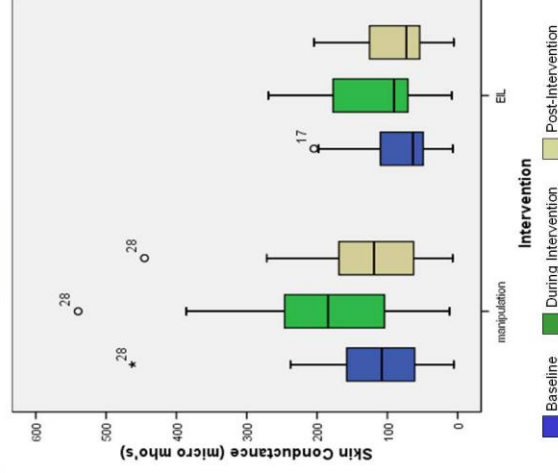
## Methodology

- > A single-blinded, quasi-experimental, independent group's design.
- > Random allocation of 50 normal, healthy participants (25 per group) into either the lumbar manipulation or an EIL group.
- > Biopac® non-invasive neurophysiological measurements of skin conductance (SC) recorded proxy-measures of SNS activity in both lower limbs (2<sup>nd</sup> & 3<sup>rd</sup> toes).
- > Readings were taken before, during & after the administration of the techniques.
- > Results were calculated using Area Under the Curve & converted into percentage change for the intervention & the post-intervention periods.
- > Null hypotheses were tested using both within- & between-groups t-tests with the level of significance set at  $p < 0.05$ .

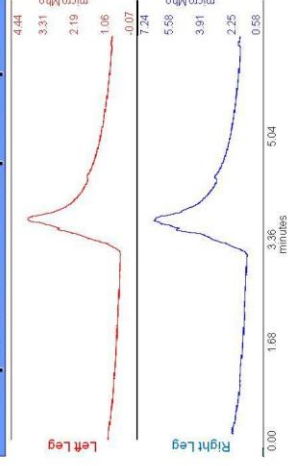
**Figure 1:**  
Experimental Set-up



**Figure 2:**  
Boxplot of SC measures for 3 periods of both groups



**Figure 3:**  
Biopac readout of Manip technique



## Results

- > See Figure 2 for details of effects
- > Both treatments increased SNS activity, from baseline levels, during the intervention period.
- > The EIL technique increased SNS activity by 42% from baseline levels ( $p=0.0005$ ).
- > The manipulation technique increased SNS activity by 76% from baseline ( $p=0.0005$ ).
- > The manipulative technique had a significantly greater effect than the EIL technique ( $p=0.012$ ).
- > For both treatments, only the manipulation technique had an effect that lasted into the post-intervention period ( $p=0.001$ ).
- > Further analysis of the manipulation group found no difference between the 'opening/gapping' side and the 'closing/compression' side of the technique ( $p=0.76$ ).

## Conclusions

- > Both treatment techniques resulted in significant neurophysiological responses.
- > The manipulation technique had a greater effect than the EIL technique.
- > The manipulation technique had an effect that was continued into the post-treatment period.
- > Despite popularly held beliefs regarding the nature of effect of the side being manipulated (opening or closing side) there was no evidence to support that one side was superior to another regarding magnitude of effect.
- > It is postulated that the sympatho-excitatory response was mediated through reflex pathway.
- > Results of this study are consistent with other studies on the cervical spine.

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# **IFOMPT 2012**

*Rendez-vous* of Hands and Minds

September 30th to October 5th, 2012

Québec City, Canada

## ***Certificate of Presentation***

This is to certify that

***Jo Perry***

presented the following title(s) as part of the  
official IFOMPT 2012 Conference program:

***The neurophysiological effects of spinal manipulative therapy on  
patients with acute and sub-acute LBP.***

Elaine Maheu, Conference Co-Chair

Rob Werstine, Conference Co-Chair

The neurophysiological effects of physiotherapy on patients with low back pain (LBP).

Jo Perry.

Senior Lecturer Coventry University. UK.  
MSc, MCSP, mMACP, mHPC, Grad Assoc Phys, PgCertEd.  
[hsx472@coventry.ac.uk](mailto:hsx472@coventry.ac.uk)  
PhD Team: Ann Green, Sally Singh & Paul Watson



## Study Outline

- Clinical element in a PhD programme of study
- Observational
- A pragmatic, non-experimental, prospective cohort design
- Neurophysiological responses (SC activity levels & SCR - % change)
- Acute & Sub-acute NSLBP (of up to 12 weeks duration)
- Guideline-endorsed Physiotherapy (CSP, 2006; NICE, 2009)



## Guideline endorsed recommendations for the management of acute LBP

- Advice to stay active and return to work
- Self-management strategies
- Exercise (aerobic and specific)
- SMT
- NSAID's
- (Acupuncture)

(CSP, 2006; NICE, 2009)



## Background to the study - 1

- Patient-reported outcome measures widely utilised
- PROM's "subjective" in nature
- Currently utilised & validated with LBP:-
  - Oswestry Disability Index (ODI, version 2.1)
  - Roland Morris Disability Questionnaire (RMDQ)
  - Narrative Pain Rating Scale (NPRS)



## Background to the study - 2

- Strong conceptual links between SNS & pain processing
- SC is a quantifiable & reliable measure of response to manual therapies
- Most studies with SNS conducted on asymptomatics
- Patient studies largely on the upper quadrant
- None on patients with acute and sub-acute LBP
- Current knowledge gaps; normals & patients, PROM's & SCR's & patient treatment responses



## Methods - 1

- Ethical approval obtained
- **The research design : observational, non-experimental, prospective, repeated measures cohort study**
- A power calculation advised 57 patients needed (Perry et al. 2011)
- 60 patients were recruited by convenience sampling
- 1 drop-out
- n=59



## Methods – 2 (SNS recordings)

Primary OM - recordings of SC & SCR's:-

- Biopac Data Acquisition system (MP35)
- Non-invasive electrodes attached to 2<sup>nd</sup> & 3<sup>rd</sup> toes both feet
- Continuous recording of SC activity



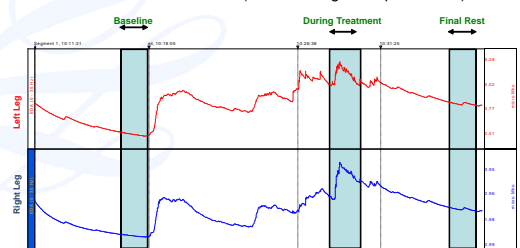
1 minute data capture points provided data for analysis

- baseline
- treatment
- final rest

ALL Recordings for analysis taken: Inception & Discharge.



## Methods – 3 (SC recordings: inception & DC)





## Methods – 4 (Secondary OM's)

- ODI (version 2.1) (Fairbank et al, 1980 & 2000)
  - PROM of functional status/limitations
  - 0 to 100% scale
  - high scores indicate high functional disability
- NPRS (Childs et al, 2005)
  - patient-reported measure of pain intensity
  - 0 to 10 scale (11 points): 0 = "no pain", 10 = "the worst pain imaginable"
  - high scores indicate high pain intensity levels



## RQ - 1

Do patients with acute & sub-acute LBP have the same SCR's as normal healthy volunteers?



## Results – 1 (normals V's patient data)

### Data analysis

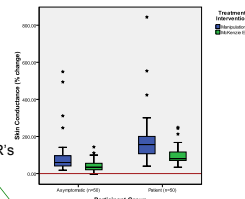
- 2 independent groups
  - 50 asymptomatics (Perry et al 2011)
  - 50 patients (random selection)
- 2 independent treatments
  - 25 Rotatory L4/5 HVLAT Manipulation
  - 25 Repeated (x10) EIL exercise
- Maximum SCR's compared for 2 treatments
- Homogeneity assured (age, gender, height & weight)



## Results 1

(Normals V's Patient data)

- Both groups sympathoexcitatory
- regarding the 2 treatments :-
- within group differences in SCR's (F=9.618; p=0.003)
- between group differences in SCR's (F=12.410; p=0.001) &



Skin Conductance (% Change from Baseline)	Asymptomatic Group n= 50		Clinical / Patient Group n= 50	
	Manipulation (n=25)	McKenzie EIL (n=25)	Manipulation (n=25)	McKenzie EIL (n=25)
n#	25	25	25	25
Mean SCR	76.35	35.74	200.80	104.66
SD	75.07	24.02	176.94	58.45
95% CI	25 to 123	12 to 73	127 to 273	80 to 129
SC activity at baseline	103	102	76	90



## RQ - 1

Do patients with acute & sub-acute LBP have the same SCR's as normal healthy volunteers?

- Both populations sympathoexcitatory
- SCR's for Manipulation greater than EIL exercise

Overall, patient's have a greater magnitude of response



## RQ - 2

What are the SCR's of patients to treatment over time?



## RQ - 2

What are the SCR's of patients to treatment over time?

- Whilst baseline SC levels rose from inception to discharge
- Treatment responses declined (I to DC)



## RQ - 3

How do SCR's to treatment compare with PROM's?

(what are the relationships between PROM's and SCR's to treatment?)

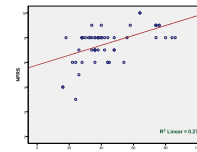


## Results – 3 (patient data – OM correlations)

- Patients with acute or sub-acute NSLBP (<12/52)
- Findings at inception (population means):-
  - ODI Inception = 42% (8% at DC = 78% improvement)
  - NPRS Inception = 7.5 (0.27 at DC)
  - SCR Inception = 219% (94% at DC = 123% reduction)

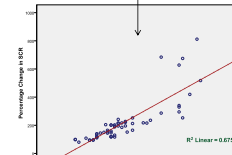
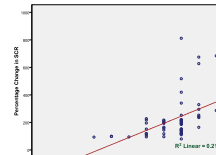


## Results 3 - (Clinical data SCR & PROM correlations)



### Inception

- ODI & NPRS moderately +vely correlated ( $r=0.525$ ;  $p<0.0005$ )
- SCR & NPRS moderately +vely correlated ( $r=0.459$ ;  $p<0.0005$ )
- SCR & ODI strongly +vely correlated ( $r=0.821$ ;  $p<0.0005$ )



## RQ - 3

How do SCR's to treatment compare with PROM's?

(what are the relationships between PROM's and SCR's to treatment?)

- ODI & NPRS - Moderately correlated
- NPRS & SCR - Moderately correlated
- SCR & ODI - Strongly correlated
- SCR better correlated to function than to pain intensity



## RQ – 4 Trends

Are there any observable trends in SCR according to the nature of the treatment that provides the max SC Response?

Is it feasible to utilise SCR's to treatment at inception as an empirical predictor of a positive functional outcome at discharge?

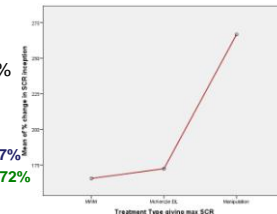


## Results 4 – Observed trends

n=60 (SCR's at inception)

- Overall mean max SCR 219%
- 3 key treatments identified

- n=31 (52%) Manip (HVLAT) SCR 267%
- n=14 (23%) repeated EIL SCR 172%
- n=15 (25%) MWM SCR 165%



## Results 4 – Observed trends

- n=31 (52%) Manip (HVLAT) SCR 267%
- n=14 (23%) repeated EIL SCR 172%
- n=15 (25%) MWM SCR 165%

ANOVA comparisons (& post hoc) analyses:

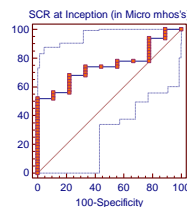
- No differences between treatments groups regarding ODI scores ( $p=0.082$ ) & NPRS levels ( $p=0.797$ )
- Differences between treatment regarding SCR's (0.043) = manipulation treatment



## Results 4a – (trends!)

From this small sample of data:

- Possible trends identified using linear regression and ROC curve analyses
- SCR more powerful than age & symptom duration as a predictor for positive outcome at DC (ODI change score > 50% at discharge)
- Early indications suggest patients with a SCR critical value >195% at inception are most likely to achieve a positive outcome at DC (ODI change >50%) (Sensitivity 52; Specificity 100)
- Further study required to validate this.....



## Key Messages - 1

- SCR's in asymptomatics and patients comparable (sympathoexcitatory)
- However, patient SCR's are greater in magnitude than those in asymptomatic groups (x3 fold)
- Patients have inhibited SC activity levels at inception
- By DC SCR's to treatment diminish
- SCR's, at inception, are strongly correlated with functional disability & moderately correlated with pain intensity
- SCR's may be an indicator of altered DH processing in acute pain states



## Key Messages - 2

- Preliminary observations indicate SCR's differ according to nature of treatment (lumbar rotatory manipulation > repeated EIL ex > MWM)
- Preliminary Regression & ROC curve analyses indicate SCR's (at inception) may have some feasibility in providing an early empirical indicator of functional outcomes at DC
- SCR's may be a useful tool for MT research in patient populations



## Key Messages - 3

- Future studies (including suitably powered RCT's) are recommended for verification and validation of these preliminary findings and to establish the potential of any predictive capacity of SCRs in patient populations

Thank you for your attention.....

Thanks are extended to the patients and staff at the Leicester Royal Infirmary for their assistance in the completion of this study & to Coventry University for support in allowing time to collect, analyse and present this data.





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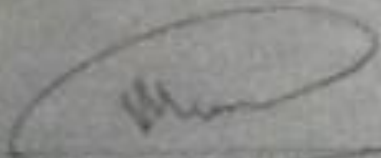
## Certificate of Award

*This is to certify that*

*Joanne Perry*

*has been awarded*

## The MACP Elsevier Presentation Award

  
(Prof. M. J. C. P.)

27<sup>th</sup> October 2017

Date

A professional website recognised by  
THE CHARTERED SOCIETY OF PHYSIOTHERAPY



## **Appendix II - Details of the literature search strategy**

The current research was based on a background of work performed by various researchers. This literature was searched using the EBSCO search engine within the library web-page. The following sources were selected: Academic Search Complete, AMED, CINHAL, Medline, PEDro, PsycINFO, Pubmed, SportsMed, SAGE Journals online and Science Direct databases.

### **The keywords utilized included:**

manipulative therapy, manual therapy, physiotherapy, physical therapy, mobilization, manipulation, Mulligan, SNAG, NAG, MWM, mobilization with movement. These terms were changeably intermeshed with: sympathetic nervous system, autonomic nervous system, neurophysiological, manipulation induced analgesia, analgesia, descending pain inhibitory system, DPIS, skin conductance, SC, SCR, galvanic skin response, GSR, sweat response, skin temperature, Biopac, lumbar, low back, spine and spinal.

In addition, a Zetoc alert was set up to search, on a weekly basis, for all articles with the following subject headings and authors: Manipulation, low back pain, sympathetic nervous system, Vicenzino (Author).

Secondary searches were also performed on key texts.

## **Appendix III - SUBJECT INFORMATION SHEET**

**Title of Project:** The reliability of the Biopac System Skin Conductance Measurements in a natural, non-laboratory setting with asymptomatic healthy volunteers.

**Principal Investigator:** J. Perry MSc, MCSP, MMACP, mHPC, Grad Assoc Phys. PgCert Ed. Senior Lecturer (Physiotherapy) Coventry University. Tel 02476887890.

**Director of Studies:** Mrs. A Green. Associate Head of Physiotherapy, Coventry University.

### **Purpose of Study:**

You are invited to participate in this study that aims to determine the reliability of the Biopac System at measuring resting skin conductance (sweat levels) responses over two time periods. This data can then be used to determine if the Biopac is a reliable and stable measuring tool, outside of the laboratory setting, and for future use in hospitals to measure patients with back trouble.

### **Procedures:**

If you are prepared to be involved in the study you will be required to attend the Charles Ward Building (room CWG01) on two separate occasions (and at the same time of day). The first visit will consist of a brief, 5 minute, interview to determine your suitability for inclusion to the project. This will comprise of a series of questions about your current and past health, any current medications and any conditions which might influence the results of the research (eg skin complaints). At this meeting, you will be invited to discuss any aspects of the study with the Principle Investigator. Following this, should you wish to be included in the study, you will be asked to sign a consent form before starting the measurements. Prior to your visits it is essential that you try not eat any food for 2 hours or have any drinks that contain caffeine (tea, coffee, coca cola etc) or refrain from alcohol for up to 24 hours prior to the study. This is important as food and certain drinks can affect the skins sweat responses.

### **Experimental procedure:**

The experiment will take place in room CWG01. Your skins sweat response will be measured by asking you to lie still, on a treatment couch. You will be asked to remain completely silent throughout the procedure unless you have need to advise the researcher of any change in your condition which requires that you discontinue the test. Additionally, you will be asked not to cough or sneeze throughout the procedure. In order to measure your skin response it is necessary to place small disc/electrodes on the second and third toes of each of your feet. Once you are settled and comfortable, readings will begin. This should not take more than 15 minutes and the researcher will inform you when the period of the test has ended.

### **Risks, discomforts and benefits:**

It is not anticipated that you will experience any discomfort from any of the measurement procedures however, testing will be terminated immediately upon your request, if you experience any undue discomfort. The results obtained from

the study will be very important in helping to determine the reliability of SC measurements and will be used to support further research with patients who have back trouble.

**Confidentiality:**

You will be allocated an identification number which will remain confidential to the principal investigator and the project director. All the data recorded, using only the assigned number for identification, will be stored on a password protected laptop computer that only the principal investigator and the project director can access. Consent forms will be stored in a locked cupboard. The results of the study will be reported but it will not be possible to identify individual subjects. Once the study has been completed, the data will be stored with the project director in a secure place for 7 years, after which time it will be destroyed.

**Request for more information:**

You are encouraged to discuss any concerns regarding the study with the Principal Investigator at any time, and to ask any questions you may have.

**Refusal or withdrawal:**

You may refuse to participate in the study and if you do consent to participate then you will be free to withdraw from the study at any time and without fear of prejudice. If you do decide to withdraw from the study then please contact the Principal Investigator at the earliest opportunity. In the event that you withdraw, all your data will be destroyed.

## CONSENT SHEET

**Title of Project:**

The reliability of the Biopac System Skin Conductance Measurements in a natural non-laboratory setting with asymptomatic healthy volunteers.

**Principal Investigator:**

J. Perry MSc, MCSP, MMACP, mHPC, Grad Assoc Phys. PgCert Ed. Senior Lecturer (Physiotherapy) Coventry University. Tel: 02476887890.

**Project Supervisor:**

Mrs. A Green. Associate Head of Physiotherapy, Coventry University.  
Tel: 02476888883

You are voluntarily making a decision whether or not to participate in this research study. Your signature certifies that you have had sufficient time to consider the information provided and that you have decided to participate, having read and understood the information provided and that you do not have any learning difficulty or medical condition that affects your ability to understand the information nor any decision regarding your participation. Your signature also certifies that you have received enough information about the study had the opportunity to discuss this study with the investigator and that all your questions have been answered to your satisfaction.

I, (the undersigned) \_\_\_\_\_  
*please PRINT*

of \_\_\_\_\_

postcode \_\_\_\_\_

Telephone \_\_\_\_\_

consent to participate in this study and give my permission for any results from this study to be used in any report or research paper, on the understanding that confidentiality will be preserved. I understand that I may withdraw from the study at any time without prejudice. If so, I undertake to contact the Principal Investigator (Tel: 02476887890) at the earliest opportunity.

Signature: \_\_\_\_\_ Date: \_\_\_\_\_  
*Subject*

I have explained the nature of the procedures involved in the study to which the subject has consented to participate and have answered all questions. In my judgement the subject is voluntarily and knowingly giving informed consent and possesses the legal capacity to give informed consent to participate in this research study.

Principal Investigator: \_\_\_\_\_ Date: \_\_\_\_\_

*My signature as witness certifies that the subject signed this consent form in my presence as his voluntary act and deed.*

Witness: \_\_\_\_\_ Date: \_\_\_\_\_



# Appendix IV – Coventry University Ethics Approval for Pre-Clinical Study

**REGISTRY RESEARCH UNIT  
ETHICS REVIEW FEEDBACK FORM**  
(Please return to Registry Research Unit within 10 working days)

Name of applicant and Faculty/School: Jo Perry, HLS

Research project title: A longitudinal investigation into the neurophysiological effects of routine physiotherapy treatment on patients presenting with low back pain of up to 12 weeks duration

Comments by the reviewer

1. Evaluation of the ethics of the proposal:  
*No ethical issues with this research. Ready to go through normal procedure - approval is expected regarding SRS application once we have received responses at all.*

2. Evaluation of the participant information sheet and consent form:  
*Clear, comprehensive & easy to understand. Clearly identifies benefits, risks, procedures and our role in the research process.*

3. Recommendation:  
 (Please indicate as appropriate and advise on any conditions. If there are any conditions, the applicant will be required to resubmit their application and this will be sent to the same reviewer).

Approved - no conditions attached

Conditional upon the following - please use additional sheets if necessary

Rejected for the following reason(s) - please use other side if necessary

Further advice/notes - please use other side if necessary

Name and signature of reviewer: *Nicky Lambert*  
 Date: *10.2.09*

*Approved*  
*12/10/09*  
*to S&S*

**Memorandum**

**Coventry University  
Academic Registry  
Registry Research Unit  
University Applied Research Committee**

To: Ms Jo Perry

From: Laura Noble

Email: [Laura.Noble@coventry.ac.uk](mailto:Laura.Noble@coventry.ac.uk)  
[ethics.uni@coventry.ac.uk](mailto:ethics.uni@coventry.ac.uk)

Tel. No: 024 7688 7011

Delivery Point: JA109

Our Reference:

Date: 12 March 2009

**Application for ethical approval**

Dear Jo,

Thank you for your Ethics application. Your submission has undergone full consideration including final approval by the Chair of the University Applied Research Committee. I have attached, for your records, the final decision recorded.

I am pleased to inform you that you may now forward your application to the appropriate REC. Please note that before you can do so, your IRAS form needs to be locked on-line and subsequently be signed off by your supervisory team and Prof Ian Marshall, Pro-Vice Chancellor (Research). You can make an appointment to see Prof Marshall via his PA, Miss Suky Sanghera, on 024 7688 5294 or via e-mail, [S.Sanghera@coventry.ac.uk](mailto:S.Sanghera@coventry.ac.uk)

Should you have any further queries, please do not hesitate to contact me.

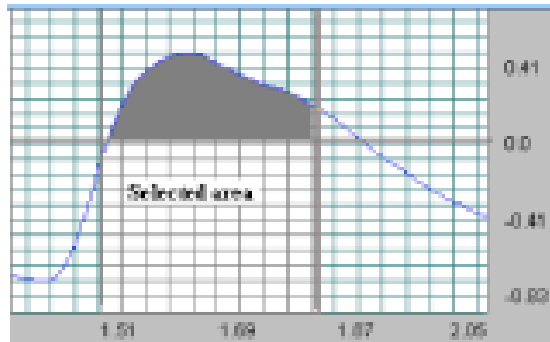
Best wishes,

*L. Noble*

Laura Noble  
Business Partner for Research (HLS)

**Appendix V – An explanation of the ‘integral measure’ form Biopac Pro 3.7 Software.**

The following graph denotes integral calculation graphically:



The area shaded in grey is the result. As described in [section\(.,.\)](#) an integral measure is the running summation of the data between two end points of the selected area on the output graph. It utilizes ‘zero’ as the baseline, which allows negative values if the output waveforms extend below zero. It is conveyed in terms of amplitude units multiplied by horizontal units.

The formula used for integral calculation is as follows:

$$\text{Integral} = \sum_{i=1}^{n-1} [f(x_i) + f(x_{i+1})] * \frac{\Delta x_i}{2}$$

Where:

n – number of samples;

i – index (i = 1..n-1);

$x_i, x_{i+1}$  - values of two neighboring points at horizontal axis ( $x_1$  – the first point,  $x_n$  – the last point);

$f(x_i), f(x_{i+1})$  - values of two neighboring points of a curve (vertical axis);

$\Delta x_i = \frac{\Delta X}{n-1}$  - horizontal sample interval;

$\Delta X = x_n - x_1$  - horizontal distance of increase at horizontal axis.

(Adapted from Biopac Systems Inc 2010).

## **Appendix VI - SUBJECT INFORMATION SHEET** (Pre-clinical study)

**Title of Project:** The effects of a physiotherapeutic treatment technique to the lower back on the immediate sweat response in the feet of normal healthy male volunteers.

**Principal Investigator:** J. Perry MSc, MCSP, MMACP, mHPC, Grad Assoc Phys. PgCert Ed. Senior Lecturer (Physiotherapy) Coventry University. Tel 02476887890.

**Director of Studies:** Mrs. A Green. Associate Head of Physiotherapy, Coventry University.

### **Purpose of Study:**

Patients with back trouble often complain of pains and stiffness and seek physiotherapeutic advice and intervention to hasten recovery and relieve symptoms. Joint mobilisation (spinal manipulative therapy) techniques are popular techniques involved in the treatment of this condition. You are invited to participate in a study which aims to determine the effects of a physiotherapeutic technique applied to the lower back, currently used in clinical practice with patients with back trouble, by investigating the effects of this technique on changes in the skins sweat response in healthy subjects.

### **Procedures:**

If you are prepared to be involved in the study you will be required to attend the Charles Ward Building (room CWG01) on one occasion. The visit will consist of a brief, 10 minute, interview to determine your suitability for inclusion to the project. This will comprise of a series of questions about your current and past health, any current medications and any conditions which might influence the results of the research (eg skin complaints). At this meeting, you will be invited to discuss any aspects of the study with the Principle Investigator. Following this, should you wish to be included in the study, you will be randomly allocated into one of two treatment groups. You will receive either a rotation technique or a back arching technique whist skin electrodes record any changes in your sweat response. Prior to your visit it is essential that you try not eat any food for 2 hours or have any drinks that contain caffeine (tea, coffee, coca cola etc) or refrain from alcohol for up to 24 hours prior to the study.. This is important as food and certain drinks can affect the skins sweat responses.

### **Experimental procedure:**

The experiment will take place in room CWG01. Your skins sweat response will be measured by asking you to lye still, on a treatment couch. You will be asked to remain completely silent throughout the procedure unless you have need to advise the researcher of any change in your condition which requires that you discontinue the test. Additionally, you will be asked not to cough or sneeze throughout the procedure. In order to measure your skin response it is necessary to place a small disc/electrode to the second and third toes of each of your feet. Once you are settled and comfortable, initial baseline measures will be taken (this takes 10 minutes), then you will receive one of two treatments. This will last no longer than 2 minutes. Following the treatment you will be asked to remain still for a further 5

minutes. During this period the researcher will remain in the room and will inform you when the period of the test has ended (total 17 minutes of recording time. The experiment will last no longer than 20 minutes.

All measurements will be recorded by an associated, independent researcher.

**Completion of the experiment:**

Following the experimental procedure, you will be advised which treatment you received and the effects of that treatment on your sweat response. You will then be free to go.

**Risks, discomforts and benefits:**

It is not anticipated that you will experience any discomfort from any of the measurement procedures or the treatment technique, except perhaps for very minimal discomfort in the establishment of your joint's normal level of stiffness. The techniques are designed for treatment of patients with stiff and restricted joints and requires little active participation on the part of participant. It is therefore not physically demanding and so should not cause any undue tiredness. Testing will be terminated immediately upon your request, if you experience any undue discomfort of fatigue or if any abnormal responses to the technique occur. The results obtained from the study will be very important in helping to determine the effectiveness of this technique on the nervous system and will be used to determine choices for treatments on patients suffering with back trouble.

**Confidentiality:**

You will be allocated an identification number which will remain confidential to the principal investigator and the project director. All the data recorded, using only the assigned number for identification, will be stored on a password protected laptop computer that only the principal investigator and the project director can access. Consent forms will be stored in a locked cupboard. The results of the study will be reported but it will not be possible to identify individual subjects. Once the study has been completed, the data will be stored with the project director in a secure place for 7 years, after which time it will be destroyed.

**Request for more information:**

You are encouraged to discuss any concerns regarding the study with the Principal Investigator at any time, and to ask any questions you may have.

**Refusal or withdrawal:**

You may refuse to participate in the study and if you do consent to participate then you will be free to withdraw from the study at any time and without fear of prejudice. If you do decide to withdraw from the study then please contact the Principal Investigator at the earliest opportunity. In the event that you withdraw, all your data will be destroyed.

**CONSENT SHEET** (pre-clinical study)

**Title of Project:**

The effects of a physiotherapeutic treatment technique to the lower back on the immediate sweat response in the feet of normal healthy volunteers.

**Principal Investigator:**

J. Perry MSc, MCSP, MMAPCP, mHPC, Grad Assoc Phys. PgCert Ed. Senior Lecturer (Physiotherapy) Coventry University. Tel: 02476887890.

**Project Supervisor:**

Mrs. A Green. Associate Head of Physiotherapy, Coventry University.  
Tel: 02476888883

You are voluntarily making a decision whether or not to participate in this research study. Your signature certifies that you have had sufficient time to consider the information provided and that you have decided to participate, having read and understood the information provided and that you do not have any learning difficulty or medical condition that affects your ability to understand the information nor any decision regarding your participation. Your signature also certifies that you have received enough information about the study had the opportunity to discuss this study with the investigator and that all your questions have been answered to your satisfaction.

I, (the undersigned) \_\_\_\_\_

*please PRINT*

of \_\_\_\_\_

postcode \_\_\_\_\_

Telephone \_\_\_\_\_

consent to participate in this study and give my permission for any results from this study to be used in any report or research paper, on the understanding that confidentiality will be preserved. I understand that I may withdraw from the study at any time without prejudice. If so, I undertake to contact the Principal Investigator (Tel: 02476887890) at the earliest opportunity.

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

*Subject*

I have explained the nature of the procedures involved in the study to which the subject has consented to participate and have answered all questions. In my judgement the subject is voluntarily and knowingly giving informed consent and possesses the legal capacity to give informed consent to participate in this research study.

Principal Investigator: \_\_\_\_\_ Date: \_\_\_\_\_

*My signature as witness certifies that the subject signed this consent form in my presence as his voluntary act and deed.*

Witness: \_\_\_\_\_ Date: \_\_\_\_\_


**Subject Selection Questionnaire**

<b>Criteria</b>	<b>Quantification Criteria</b>	<b>Actual Value</b>	<b>Criteria met Yes(√)/No(X)</b>
Age	Over 18 years		
Medium height	5ft4 to 6ft (150 – 180 cms)		
Average weight	140 to 200 lbs ( Kgs)		
Consent	form completed	_____	
Naivety	No previous LBP	_____	
	No Previous PT or SMT	_____	
Good General Health	No Neurological disorder/s (MS)	_____	
	No Previous lower limb trauma/injury	_____	
	No DM	_____	
	No Anxiety disorders	_____	
	No Psychiatric disorder	_____	
Medication	None That may influence sympathetic tone	_____	
Nicotine Ingestion	Non-Smoker	_____	
Recent ingestion (within 2 hours)	Caffine	_____	
	Food	_____	
Recent ingestion	Alcohol	_____	
Skin disorder affecting the sites of electrode placement	clear	_____	

To meet criteria for inclusion shaded area needs to answer Yes & clear area No

Participant No.

## Appendix VII – Ethics Committee Approval Documents (Clinical study)

University Hospitals of Leicester   
NHS Trust

DIRECTORATE OF RESEARCH & DEVELOPMENT

Research & Development Office  
Leicester General Hospital  
Gwendolen Road  
Leicester  
LE5 4PW

Director: Professor D Rowbotham

Assistant Director: John Hampton

R&D Manager: Carolyn Maloney

Direct Dial: (0116) 258 8351

Fax No: (0116) 258 4226

08/06/2009

Miss Joanna Perry  
Coventry University  
Faculty of Health & Life Sciences  
Department of Physiotherapy  
Priory Street Rm 205  
Coventry  
CV1 5FB

Dear Miss Joanna Perry

Ref: UHL 10755

Title: A longitudinal investigation into the neurophysiological effects of routine physiotherapy treatment on patients presenting with low back pain of up to 12 weeks duration

Project Status: Project Approved

End Date: 01/05/2012

I am pleased to confirm that with effect from the date of this letter, the above study now has Trust Research & Development permission to commence at University Hospitals of Leicester NHS Trust.

All documents received by this office have been reviewed and form part of the approval. The documents received and approved are as follows:

Document Name	Version Number	Date
Invitation letter	1.0	26.03.09
GP/Referring Clinicians letter	1.0	26.03.09
Questionnaire; The Roland Morris Disability Questionnaire		
Questionnaire; The Oswestry Low Back Pain Score		
Protocol	2	28.04.09
Summary/Synopsis	2	28.04.09
PIS	2	28.04.09
CF	2	28.04.09

*Please be aware that any changes to these documents after approval may constitute an amendment. The process of approval for amendments should be followed. Failure to do so may invalidate the approval of the study at this trust.*

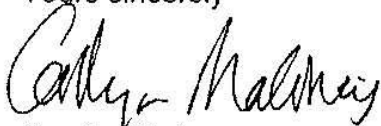
We are aware that undertaking research in the NHS comes with a range of regulatory responsibilities. Attached to this letter is a reminder of your responsibilities during the course of the research. Please ensure that you and the research team are familiar with and understand the roles and responsibilities both collectively and individually.

You are required to submit an annual progress report to the R&D Office and to the Research Ethics Committee. We will remind you when this is due.

The R&D Office is keen to support research, researchers and to facilitate approval. If you have any questions regarding this or other research you wish to undertake in the Trust, please contact this office.

We wish you every success with your research.

Yours sincerely



Carolyn Maloney

**Acting Assistant Director of R&D**

Encs: .Researcher Information Sheet.



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**Leicestershire, Northamptonshire & Rutland Research Ethics Committee 2**

1 Standard Court  
Park Row  
Nottingham  
NG1 6GN

Telephone: 0115 8839428  
Facsimile: 0115 9123300

27 April 2009

Miss Joanna Perry  
Senior Lecturer  
Coventry University  
Priory Street,  
Coventry  
CV1 5FB

Dear Miss Perry

**Full title of study:**            **A longitudinal investigation into the neurophysiological effects of routine physiotherapy treatment on patients presenting with low back pain of up to 12 weeks duration**

**REC reference number:**    **09/H0402/55**

The Research Ethics Committee reviewed the above application at the meeting held on 16 April 2009. Thank you for attending to discuss the study.

**Ethical opinion**

In discussion, the Committee queried the following issues:

- The Committee asked for further explanation of the measurements of conductivity. You explained that the patients will be having their normal physiotherapy treatment and the only difference is that sweat levels will be measured at each visit, to see if it changes as they progress. Currently there is only subjective information on changes in pain levels. Measurements will be taken between the second and third toe as there are nerve links to the vertebrae there. Measurements of sympathetic activity will be taken before, during and after treatment at each visit. You have published a previous study on upper limbs but not lower. This showed that manual physiotherapy had an effect on upper limb conductivity.
- The Committee asked what will happen with the participant's treatment if they withdraw during treatment. You explained that there are eighteen physiotherapists in the Department so they would be seen by a colleague. The Committee suggested that the wording in the information sheet could be made friendlier so patients did not feel they were being discarded if they withdrew. You agreed that you would be happy to do this.
- The Committee noted that the font used on the information sheet was quite small and requested that it was changed to font size 12 or 14.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

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### **Ethical review of research sites**

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

### **Conditions of the favourable opinion**

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

*For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>. Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.*

*Sponsors are not required to notify the Committee of approvals from host organisations.*

1. The sentence 'In the event that you withdraw, during your treatment programme, your case will be passed to another Physiotherapist who will continue your treatment' in the information sheet must be reworded. The Committee requested that the following wording is used instead: 'In the event that you withdraw, during your treatment programme, your care will continue, although you may see a different Physiotherapist. This would not affect the standard of care you receive'.
2. The font size on the information sheet should be increased to size 12 or 14.

Please let me have a copy of the revised documents with updated version number and date and I will acknowledge receipt.

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

### **Approved documents**

The documents reviewed and approved at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering Letter		26 March 2000
Protocol	1	26 March 2009
Investigator CV		
Application	8621/32143/1/851	25 March 2009
NRES Researcher Training Certificate		19 June 2008
Consent Training Certificate		08 August 2008

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Research Guidelines Session Certificate		18 April 2008
Letter of invitation to participant	1.0	26 March 2009
Summary/Synopsis	1	25 March 2009
Investigator CV		
University Ethics Approval		12 March 2009
AHP Training Fellowship Feedback		
GP/Referring Clinicians Letter	1.0	26 March 2009
Participant Consent Form	1.0	26 March 2009
Participant Information Sheet	1.0	26 March 2009
Questionnaire: The Roland Morris Disability Questionnaire		
Questionnaire: The Oswestry Low Back Pain Score		
Compensation Arrangements		09 March 2009
Statistician Comments		26 March 2009

### **Membership of the Committee**

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

### **Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

### **After ethical review**

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review -- guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email [referencegroup@nres.npsa.nhs.uk](mailto:referencegroup@nres.npsa.nhs.uk).

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09/H0402/55

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

**Mr Ken Willis / Miss Jeannie D McKie**  
**Chair / Committee Coordinator**

Email: jeannie.mckie@nottspct.nhs.uk

*Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments  
"After ethical review – guidance for researchers" SL-AR2 for other studies*

*Copy to: Professor Ian Marshall, Coventry University  
R&D office for NHS care organisation at lead site - UHL*

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**Leicestershire, Northamptonshire & Rutland Research Ethics Committee 2**

**Attendance at Committee meeting on 16 April 2009**

**Committee Members:**

<i>Name</i>	<i>Profession</i>	<i>Present</i>	<i>Notes</i>
Mr John Aldridge	Senior Lecturer in Nursing	No	
Dr Timothy Bedford	Consultant Anaesthetist	Yes	
Ms Elaine Blackshaw	Clinical Trial Manager	Yes	
Mr Geoff Dickens	Research Coordinator	Yes	
Dr Susan Dyson	Doctor of Education, Head of Nursing & Midwifery Research	No	
Miss Lorenza Francescut	Research Assistant	No	
Mrs Bessie Hayes	Educational Psychologist (retired)	Yes	Co-opted member
Mrs Sue Maguire	Pharmaceutical Advisor	No	
Dr Roy Matthew	Consultant Oncologist	Yes	
Mr Mike Newman	Consultant Gynaecologist	No	
Dr Susan Price	Consultant in Clinical Genetics	No	
Mr Michael Tawn	Solicitor	No	
Miss Alison Thorpe	Research Technician	Yes	
Dr Graham Warwick	Consultant Nephrologist	No	
Mr Ken Willis	Medical Device Manager	Yes	

**Also in attendance:**

<i>Name</i>	<i>Position (or reason for attending)</i>
Ms Lisa Brooks	Administrative Officer
Miss Jeannie McKie	Committee Coordinator

## **Appendix VIII**

## **PARTICIPANT INFORMATION SHEET**

**Title of Project:** The effects of a course of physiotherapy treatment for back pain on patients' levels of pain, on their return to normal activities and on their sweat levels (in both feet).

**Principal Researching Physiotherapist:** J.Perry MSc, mMACP, mCSP, mHPC, Grad Assoc Phys.  
PgCert.Ed Senior Lecturer in Physiotherapy, Coventry University, Faculty of Health & Life Sciences. Tel 024 7688 7890

**Director of Studies:** Ann Green. Associate Head of Physiotherapy & Dietetics, Coventry University. Tel: 024 7688 8883

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. This leaflet tells you the purpose of this study and what will happen to you if you take part and gives you more detailed information about the conduct of the study. Please do not hesitate to ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

### **What is the purpose of Study?:**

You are invited to participate in a study which aims to determine the effects of physiotherapy techniques, currently used in clinical practice, on skin sweat values, on pain and on day-to-day activity. People with low back pain often complain of muscle and joint pain and stiffness and seek help from physiotherapists to relieve symptoms, hasten recovery and return to work. There are a number of treatment approaches used by physiotherapists that aim to restore function and reduce symptoms but little is known about their effects on the nervous system. By measuring the sweat levels in the feet, it is possible to measure the responses of the nervous system to the treatments given and to record any changes as recovery progresses. The purpose of this study is to record any nervous system changes at each treatment session and determine if these reflect and changes that you report in your symptoms. The study forms part of a Doctorate and is sponsored by Coventry University in partnership with the University Hospitals of Leicester NHS Trust.

### **Why have I been chosen?**

All patients referred to the Leicester Royal Infirmary with lower back pain will be considered for the study. You may be asked to join the study if you have had your symptoms for less than 12 weeks, are between the ages of 18 and 55, you do not suffer with skin complaints affecting your feet, are a non-smoker and are willing to take part in the study which will involve you attending (and completing) a normal course of physiotherapy treatment.

### **Do I have to take part?**

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason and without fear of prejudice. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. It is customary for the Researcher to advise your referring clinician (eg. GP or consultant) of your decision to take part in the study unless you explicitly request that they are not notified. As in all cases, the physiotherapist will also write a discharge report at the end of your course of treatment to advise the Doctor of your progress. If you do decide to withdraw from the study then please contact the Principal Investigator/treating physiotherapist at the earliest opportunity. In the event that you decide not to continue with the study during your treatment program (but wish to continue having treatment), your case will be passed to another Physiotherapist who will continue your treatment.

### **What will happen to me if I take part and what will I have to do?**

If you are prepared to be involved in the study you will be invited to attend the Physiotherapy Department at the Leicester Royal Infirmary NHS Trust for a normal/standard course of Physiotherapy treatment to your lower back (4-8 treatments – once or twice a week - tailored to your needs). The first visit, should you consent to join the program, will consist of an interview and physical assessment where you will be invited to discuss any aspects of the study with the Principle Investigator/Physiotherapist. Also on this occasion, measurements of your sweat levels will be recorded by placing 2 small skin sensors to the 2<sup>nd</sup> & 3<sup>rd</sup> toes of your feet and asking you to lie still for 5-10 minutes. Treatment will be administered in accordance with usual care lasting 20-30 minutes. Further treatment sessions will then be booked in accordance to normal physiotherapy practice for the Trust. Treatments will be conducted as normal, the only difference to your sessions, from that of other patients not in the study, will be the addition of the recordings of your foot sweat levels. Because the readings are very sensitive to sweat changes, it is requested that prior to each visit you do not eat any food for 2 hours or have any drinks that contain caffeine (tea/coffee/Cola) or alcohol and that you refrain from heavy exercise prior to your treatment.

### **Visit 1 Assessment and Initial Baseline Recordings:**

On the first visit a researcher will undertake a standard physiotherapy assessment of your back and evaluate your suitability for the investigation. This will comprise of a series of questions about your current and past

health, any current medications and any conditions that might influence the results of the research (eg skin complaints or prior illnesses). This will be followed by an examination of your spine and your presenting condition as well as the skin on your feet where the sensors will be placed. Next, recordings of your sweat levels will be made and you will be asked to lie absolutely still, in a comfortable position for 5-10 minutes. You will be asked to remain completely silent throughout the procedure unless you have need to advise the researcher of any change in your condition which requires that you discontinue the test. Additionally, you will be asked not to cough or sneeze throughout the recordings as this may disturb the readings. This visit should last no more than 1 hour.

**Visit 2 and Subsequent Treatment Sessions:**

On these visits your skin sweat level will again be recorded in the same way. You will then undertake normal physiotherapy treatment during which your skin sweat levels will be monitored. At the end of each treatment session a final measure will be taken during which time you will be asked to lay still for five minutes. During this period the researcher will remain in the room and will inform you when the period of the test has ended. This visit should last no longer than 45 minutes.

**Final Treatment:**

Following the completion of your course of treatment you will be interviewed and the outcome of treatment determined (ie pain levels, activity levels and return to work status). A final measure of your skin sweat levels will also be recorded. This session should last no more than 45 minutes.

**Risks, discomforts and benefits:**

It is anticipated that you will not experience any discomfort from any of the measurement procedures or the treatments undertaken, except perhaps for very minimal discomfort as a result of the treatments employed. The techniques used are designed for treatment of patients with stiff joints and many are passive techniques on the part of the patient and are therefore not physically demanding and so should not cause any undue tiredness. Testing will be terminated immediately upon your request, if you experience any undue discomfort of fatigue or if any abnormal responses to the technique occur. If you take part in the study you will learn about the place of this technique in the treatment of spine pain. The results obtained from the study will be very important in helping to determine the effectiveness of the techniques on the nervous system and will enhance our understanding of how physiotherapy to the lower back might accelerate healing.

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against The University Hospitals of Leicester NHS Trust, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

**Will my taking part in the study be kept confidential?**

You will be allocated an identification number that will remain confidential to the Principal Investigator and the Director of Studies. All the data recorded, using only the assigned number for identification, will be stored on an encrypted, password-protected computer that is stored in a locked cabinet. Examination and Treatment records will be stored in a locked cupboard and managed according to the Trusts Data Protection Procedures. The results of the study will be reported but it will not be possible to identify individual participants. Once the study has been completed, the data will be stored in accordance with the Trusts Data Protection Policy and with Coventry Universities Data Protection Procedures.

**What if there is a problem?**

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. In the first instance you are encouraged to discuss any concerns regarding the study with the Principal Investigator/treating physiotherapist (Miss Jo Perry 02476887890 or 0116 2585813). Should you have any further concerns you should contact the Director of Studies (Mrs Ann Green 02476888803) or the Supervisors in the Trust (Professor Paul Watson 0116 2584613 or Professor Sally Singh). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

**Reviewers of the Study:**

This study is sponsored by Coventry University and has been reviewed and approved by both the University Ethics Committee and the NHS Research Ethics Committee for Leicestershire.

## CONSENT FORM

### Title of Project:

*The effects of a physiotherapy treatment to the lower back on sweat levels in both feet in patients with back pain.*

Study Number:

Patient Identification Number for this study:

**Principal Investigator:** J.Perry MSc, mMACP, mCSP, mHPC, Grad Assoc Phys. PgCert.Ed Senior Lecturer in Physiotherapy, Coventry University, Faculty of Health & Life Sciences. Tel 024 7688 7890

**Director of Studies:** Ann Green. Associate Head of Physiotherapy & Dietetics, Coventry University. Tel: 024 7688 8883

Please initial box

1. I confirm that I have read and understand the information sheet dated 17<sup>th</sup> December 2008 (version 1.) regarding 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 understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Leicester University, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

4. I agree to my referring medical practitioner (ie GP) being informed of my participation in the study.

5. I agree to take part in the above study.

\_\_\_\_\_  
Name of Patient

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of Person  
taking consent

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature



# THE OSWESTRY LOW BACK PAIN SCORE

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# **ROLAND & MORRIS 24 PAIN QUESTIONS**

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## **Appendix IX – Letter to Referring Clinician**

GP/Referring Clinicians Address

Date Line

Dear (Clinician Name)

**Re- Patients Name; Address; NHS ID No; D.O.B.**

I write to advise that your patient has been invited to take part in a study observing the effects of routine physiotherapy treatment to the lower back on sweat levels in both feet. This is a non-invasive measure of sweat levels, before, during and after physiotherapy treatments and provides a proxy measure of neurophysiological activity which has been correlated to symptoms in neck pain and tennis elbow patients but not yet in a Low Back Pain population. Results of these neurophysiological measures will be compared to standard subjective measures of pain (Narrative Pain Rating Score) and disability (Oswestry Disability Index and Rolland Morris Disability Questionnaire).

The study is being run as a collaboration between Coventry University (Faculty of Health & Life Sciences, Department of Physiotherapy) and The University Hospitals of Leicester NHS Trust at the Leicester Royal Infirmary. Please find enclosed a copy of the participant information sheet. If you have concerns about any part of the study then please do not hesitate to contact us to discuss the matter using the contact details at the end of this letter.

At the end of the program of treatment we will write to advise you, in the usual manner, of the treatment strategies employed and your patients' outcome.

Yours Sincerely,

**Jo Perry** (Chartered Physiotherapists) MSc, mMACP, mCSP, mHPC, Grad Assoc Phys.  
PgCert.Ed.  
Senior Lecturer in Physiotherapy (Coventry University).

**Principal Investigator:** J.Perry MSc, mMACP, mCSP, mHPC, Grad Assoc Phys. PgCert.Ed Senior Lecturer in Physiotherapy, Coventry University, Faculty of Health & Life Sciences. Tel 024 7688 7890. **Director of Studies:** Ann Green. Associate Head of Physiotherapy & Dietetics, Coventry University. Tel: 024 7688 8883.


## Appendix X – Table summarizing patient assessment findings

Participant No.	Gender (M/F)	Age (Yrs)	QTF Classification	Work Status at DC	RMDI (0-24)		NPRS (0-10)		ODI (0-100%)		Key Physical Findings at inception (√ indicates a positive sign)					
					Day 1	DC	Day 1	DC	Day 1	DC	Lsp F	Lsp E	Lsp LF	Hip IR	NC	N D
1	F	49	1 a W	W	10	2	8	0	40	1	√	√	√	-	-	-
2	M	53	3 b I	W	11	8	8	1	28	22	√	-	√	-	√	√
3	F	41	3 c W	W	9	5	6	1	45	18	-	-	√	-	-	-
4	F	38	1 b W	W	10	1	3	0	24	5	√	-	-	-	-	-
5	M	46	3 c W	W	18	3	8	1	80	2	√	√	√	√	-	√
6	F	44	2 c W	W	18	3	7	0	48	20	√	√	√	-	√	√
7	F	45	2 a I	W	7	5	6	1	36	1	√	√	√	-	-	-
8	M	26	2 c W	W	6	2	8	0	38	0	√	-	√	-	-	-
9	F	37	2 c I	I	10	1	6	0	28	4	√	√	√	√	-	-
10	M	33	3 c W	W	4	0	6	0	44	6	√	-	√	-	-	√
11	F	48	3 b W	W	16	2	8	1	48	6	-	-	√	-	-	-
12	F	36	1 b W	W	8	1	7	0	38	1	√	-	-	-	-	-
13	F	46	3 c I	W	5	0	5	0	26	12	√	√	√	-	-	-
14	M	21	1 b W	W	14	0	7	0	36	18	√	-	-	√	-	√
15	M	27	2 c W	W	16	1	9	0	58	0	√	-	√	-	-	-
16	F	27	3 b W	W	19	2	9	0	74	20	√	√	√	-	-	√
17	F	44	2 b I	W	10	0	7	0	36	30	√	√	-	-	-	-
18	M	47	2 c I	W	7	1	8	1	28	16	√	√	√	-	-	√
19	M	36	2 b W	W	6	2	7	0	26	4	√	√	√	-	-	-
20	M	48	2 a I	W	12	0	8	0	40	0	√	√	√	-	-	√
21	F	49	2 b I	I	10	2	8	1	38	4	√	-	√	-	-	√
22	M	54	4 a I	I	11	8	8	1	40	20	√	√	√	-	-	√
23	F	42	3 c I	W	11	4	8	1	28	12	√	-	√	-	-	-
24	F	37	1 s I	W	11	1	6	0	22	5	√	√	√	-	-	-
25	M	44	4 a I	W	16	1	10	0	64	4	-	√	√	√	√	√
26	F	45	2 c W	W	20	3	9	0	74	18	-	√	√	-	-	-
27	M	46	2 c W	W	7	5	8	0	28	0	√	-	-	-	-	-
28	F	30	2 c W	W	9	1	8	0	36	0	√	√	√	-	-	-
29	F	39	3 a I	W	10	1	7	0	36	2	√	√	√	-	-	√
30	F	34	2 b W	W	16	2	7	0	42	2	√	-	-	-	-	-
31	F	47	3 c I	W	14	2	8	1	32	0	√	-	-	-	-	-
32	F	35	3 b W	W	11	1	8	0	38	4	√	-	-	-	-	-
33	F	48	3 b W	W	12	0	8	0	33	0	√	-	√	-	-	√
34	F	30	3 b I	W	16	0	6	1	44	6	√	√	-	-	-	√
35	M	32	3 a I	W	16	1	4	0	16	14	√	√	√	√	-	√
36	F	25	4 c W	W	19	1	9	0	76	18	√	√	√	-	-	-
37	F	43	1 b W	W	12	0	8	0	38	0	√	-	-	-	-	-
38	M	48	2 c I	W	9	0	8	0	28	16	√	-	√	-	-	√
39	M	24	3 b W	W	6	2	6	1	24	2	√	-	√	-	-	√
40	M	49	3 b I	W	12	0	8	0	56	6	√	√	√	-	-	√
41	F	49	3 b W	W	10	1	7	0	36	1	√	-	-	-	-	√
42	M	52	1 b W	W	12	8	8	0	86	1	√	-	√	-	-	√
43	F	43	1 b W	W	12	5	7	1	48	22	-	√	-	-	-	-
44	F	36	4 a I	W	9	1	7	0	34	18	√	√	√	√	√	√
45	M	45	2 a W	W	16	2	6	1	54	5	√	√	√	-	-	-
46	F	42	3 b I	W	9	1	8	0	30	2	√	-	-	-	-	√

Participant No.	Gender (M/F)	Age (Yrs)	QTF Classification	Work Status at DC	RMDQ		NPRS (0-10)		ODI (0-100%)		Key Physical Findings at inception (√ indicates a positive sign)					
					Day 1	DC	Day 1	DC	Day 1	DC	Lsp F	Lsp E	Lsp LF	Hip IR	NC	ND
47	F	47	2 c W	W	16	3	9	0	40	16	√	-	-	-	-	-
48	M	29	1 b W	W	10	1	8	1	18	10	√	√	√	-	-	-
49	M	38	3 b I	W	10	1	8	0	38	1	√	√	√	√	-	√
50	M	33	1 c W	W	14	0	8	0	44	2	-	√	-	-	-	-
51	F	33	2 c W	W	18	0	10	0	64	4	√	-	-	-	-	-
52	F	44	2 b W	W	12	0	9	0	34	1	√	-	√	-	-	-
53	F	29	2 b I	W	10	1	8	0	36	5	√	√	√	-	-	√
54	M	30	1 b W	W	14	0	8	0	34	2	√	√	√	-	-	-
55	F	26	1 c W	W	22	0	8	0	84	1	√	√	√	-	-	-
56	F	41	1 a I	W	22	0	9	0	76	2	-	√	-	√	-	-
57	M	44	2 a W	W	7	0	8	0	42	0	√	√	√	-	-	-
58	M	50	4 b I	W	8	3	4	1	16	2	√	√	√	-	√	√
59	F	40	1 c W	W	18	1	9	0	74	18	-	√	-	-	-	-
60	M	41	2 b I	?	20	?	8	?	74	?	√	√	√	√	-	√

### Key

- QTF = Quebec Task Force Classification
- 1 Pain without radiation
  - 2 Pain with radiation to extremity (proximally)
  - 3 Pain with radiation to extremity (distally)
  - 4 Pain with radiation to extremity (with neurological signs - NC)
  - a < 7 days duration
  - b 7 days to 7 weeks duration
  - c > 7 weeks duration
  - W Working
  - I Idle (off work/sick)
- M = Male
- F = Female
- NPRS = Narrative Pain Rating Scale
- ODI = Oswestry Disability Score
- DC = Discharge
- LspF = Lumbar spine Flexion range of movement
- LspE = Lumbar spine Extension range of movement
- LspLF = Lumbar spine Lateral Flexion range of movement
- HipIR = Hip Internal range of movement
- NC = Neural Conductivity Tests (myotomes, Dermatomes and Reflexes)
- ND = Neurodynamic tests (straight leg raise, passive knee flexion, slump)

University Hospitals of Leicester   
NHS Trust

Directorate of Research & Development

This is to certify that

Jo Perry

Attended the Research Guidelines session  
covering

- ICH-GCP (EU GCP Directive 2005)
- Research Governance Framework (DoH 2005)
- The EU Directive (2001)
- The Medicines for Human Use Regulations (2004)

*It is your responsibility to renew your GCP training annually*

18<sup>th</sup> April 2008

Signed by Clinical Trainer





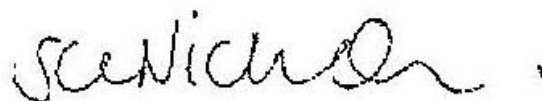
This is to certify that on 8<sup>th</sup> August 2008

**Jo Perry**

Completed consent training:  
Topics covered;

- *Importance of informed consent*
- *The Process*
- *Communicating and application*

Signed:



Clinical Trainer Sarah Nicholson:

## CERTIFICATE OF ATTENDANCE

This is to certify that

**Joanna Perry**

attended

## NRES Researcher Training Day

4 CPD points (non-clinical)  
Royal College of Physicians  
Code: 42589

on Thursday 19 June 2008

*at Marriott Royal Hotel, College Green, Bristol, BS1 5TA*

Signed by



National Research Ethics Service  
4-8 Maple Street, London, W1T 5HD

'Facilitating and promoting ethical research'



**Appendix XII Raw SCR data & Type of treatment that resulted in the maximum SCR**

Patient ID number	SCR at Inception				SCR at Mid-Point				SCR at Discharge			
	Baseline	Treatment	Final Rest	Treatment type	Baseline	Treatment	Final Rest	Treatment type	Baseline	Treatment	Final Rest	Treatment type
1	36.6	114.5	45.1	1	33.2	75.8	43.5	2	14.7	30.3	27.7	2
2	54.8	120.6	150.0	2	52.2	166.7	99.8	1	44.7	77.1	41.2	2
3	91.6	230.5	106.7	1	98.4	230.5	194.4	1	100.0	159.8	156.1	4
4	68.9	133.1	242.3	3	151.1	197.6	192.0	2	107.6	163.1	189.3	1
5	84.2	437.4	87.0	1	76.7	204.4	165.5	1	94.9	180.6	173.2	1
6	73.3	229.1	120.1	1	69.4	165.3	93.5	1	67.5	89.3	114.8	2
7	56.3	123.7	166.7	2	78.2	173.1	129.6	2	70.3	113.3	245.9	1
8	120.5	277.0	129.6	3	62.2	136.7	99.8	1	150.6	211.5	187.3	1
9	129.0	279.2	242.3	3	156.4	259.7	165.1	3	107.6	163.1	189.3	1
10	55.3	181.0	87.0	2	65.9	173.2	139.4	1	116.4	230.5	157.7	1
11	79.3	279.2	75.5	1	76.7	201.7	165.5	1	94.9	180.6	104.9	1
12	56.4	165.2	154.7	2	83.7	228.7	119.8	1	107.6	163.1	189.3	1
13	69.5	135.3	150.8	3	77.3	325.9	131.9	2	67.5	119.3	114.8	2
14	132.9	400.2	231.0	1	133.3	396.8	389.4	1	199.3	315.6	297.5	1
15	77.4	259.7	155.8	2	53.7	220.0	131.5	2	90.9	232.3	121.4	1
16	14.8	107.7	34.3	1	20.2	139.1	67.6	1	14.6	65.4	57.4	2
17	110.6	285.6	179.8	3	72.6	174.6	112.6	1	87.5	187.9	98.7	1
18	102.1	225.8	195.7	3	175.1	194.7	193.1	3	190.8	264.1	237.9	1
19	120.5	236.3	129.6	1	118.6	360.2	186.4	1	151.6	210.6	177.3	1
20	82.1	259.8	195.7	3	145.4	204.5	134.1	1	186.4	220.8	204.3	1
21	36.6	105.6	45.5	2	23.2	55.3	41.3	1	14.7	30.3	27.7	2
22	54.9	162.0	104.7	1	65.9	187.1	139.4	3	68.3	147.5	102.0	2
23	92.7	219.2	104.2	1	70.5	142.5	111.0	1	101.0	187.8	173.1	4
24	156.4	325.9	165.1	2	156.1	340.6	302.5	1	150.6	211.5	187.3	1
25	50.6	396.8	68.2	1	60.4	105.8	79.7	1	70.8	154.2	109.0	1
26	102.9	406.5	170.6	1	104.7	204.4	156.5	1	132.5	257.3	207.9	2
27	58.0	139.1	168.3	1	83.1	157.8	130.9	1	44.7	77.1	41.2	1
28	79.5	174.6	122.6	2	85.0	217.8	235.2	3	80.5	180.5	90.5	1
29	127.5	277.2	242.3	3	129.2	282.7	209.4	1	107.6	263.1	189.3	1
30	57.1	180.9	85.0	1	101.1	170.8	165.5	2	68.3	147.5	102.0	1
31	111.6	279.2	149.1	2	95.6	201.6	174.2	4	94.9	180.6	104.9	1
32	56.4	165.5	109.1	2	65.3	176.3	106.6	2	107.6	263.1	189.3	1
33	77.3	235.3	131.9	3	63.2	128.9	80.0	2	80.5	213.7	147.3	2
34	131.9	389.4	133.3	1	146.1	348.7	202.5	1	199.3	217.2	297.5	1
35	141.7	282.7	258.9	1	145.4	204.5	174.1	3	90.9	132.3	121.4	1
36	20.2	156.5	67.6	1	20.4	139.1	67.2	1	44.3	115.4	57.4	2
37	72.7	220.0	112.6	1	96.2	214.4	162.4	2	113.5	263.1	64.0	1
38	96.0	202.2	198.8	3	162.7	225.3	186.0	1	190.8	264.1	237.9	1
39	120.5	235.1	129.6	1	156.1	340.6	302.5	2	107.6	114.9	189.3	1
40	82.3	259.8	195.7	3	186.1	377.6	302.5	2	186.4	220.8	204.3	1
41	36.6	110.5	45.0	2	38.3	80.5	53.7	1	32.3	60.3	27.7	2
42	24.8	153.2	104.9	1	104.1	144.2	138.1	2	87.5	187.9	98.7	2
43	90.8	240.6	103.8	1	94.4	201.5	112.9	1	102.0	177.8	175.1	1
44	129.2	315.6	209.9	1	123.7	295.2	131.9	2	107.6	193.1	189.3	1
45	60.2	191.1	124.0	1	96.8	192.9	142.3	1	70.8	154.2	109.0	1
46	53.7	131.5	115.4	1	52.7	231.2	145.0	2	56.0	119.3	107.2	2
47	55.8	190.8	168.3	2	90.2	293.9	148.3	3	70.3	113.3	245.9	1
48	113.2	203.8	178.6	2	113.6	235.1	245.2	2	150.6	211.5	187.3	1
49	128.9	279.2	242.3	2	156.1	340.6	302.5	2	107.6	130.5	189.3	1
50	56.3	180.8	88.0	1	98.4	230.5	194.4	1	113.5	230.5	157.7	1
51	69.6	269.1	114.4	1	69.2	153.2	113.4	1	44.7	77.1	41.2	1

Patient ID number	Baseline	Treatment	Final Rest	Treatment type	Baseline	Treatment	Final Rest	Treatment type	Baseline	Treatment	Final Rest	Treatment type
52	100.5	265.7	147.3	3	95.6	201.6	174.2	2	80.5	113.7	119.0	2
53	120.6	297.5	199.3	1	223.7	395.2	331.9	1	199.3	315.6	297.5	1
54	90.9	230.5	121.4	1	67.5	241.7	104.7	1	90.9	132.3	114.8	1
55	14.6	133.1	57.4	1	12.6	139.1	67.6	1	14.6	115.4	57.4	2
56	124.0	437.4	144.5	1	90.7	183.9	124.3	2	68.3	139.4	76.4	1
57	80.3	229.1	144.2	2	119.6	205.9	159.5	1	190.8	264.1	207.9	1
58	82.7	163.7	145.7	1	63.2	128.9	80.0	2	107.6	163.1	64.0	1
59	64.5	277.0	142.7	3	156.1	340.6	302.5	4	186.4	220.8	204.3	3
60	63.4	279.2	131.8	3	-	-	-	-	-	-	-	-

Key to treatment Types:-

1 = Spinal Manipulation

2 = MWM

3 = McKenzie EIL

## **Appendix XIII – Comparisons between the patient & the asymptomatic group**

### Demographic, Anthropometric data and Experimental data extraction

The data from participants recruited into the pre-clinical study (n=50) were compared with a random sample of the patient participants (data was taken from all 3 data capture points where data was available for the treatments under investigation; the total number of manipulation events = 123, the total number of EIL events = 56 – it is of note that in some cases both treatments were conducted within the same treatment episode but only one treatment response was used for the analysis) from the clinical study (n=50). Concealed random selection was achieved by the constructing a random numbers table (in the nQuery software package) and selecting 50 patients (see tables below).

**Table:** The allocation of patient participants from the data pool for manipulation (Manip) and EIL (McKenzie extension in lying exercise) treatment groups (where A = Manipulation only data pool; B = EIL only data pool; and C = Manipulation and EIL data pool)

Participant ID number	Treatment Allocation	SCR group
1	Manip	A
2	EIL	C
3	Manip	C
4	EIL	B
5	EIL	B
6	Manip	A
7	Manip	C
8	EIL	B
9	EIL	B
10	Manip	A
11	Manip	A
12	EIL	C
13	Manip	C
14	Manip	A
15	Manip	A
16	EIL	B
17	EIL	B
18	EIL	C
19	Manip	A
20	EIL	C
21	Manip	A
22	EIL	B
23	EIL	C
24	Manip	A
25	Manip	C

Participant ID number	Treatment Allocation	SCR group
26	EIL	B
27	Manip	C
28	Manip	C
29	Manip	A
30	EIL	B
31	Manip	A
32	EIL	B
33	Manip	A
34	EIL	C
35	Manip	A
36	EIL	B
37	Manip	A
38	EIL	B
39	EIL	B
40	Manip	A
41	EIL	B
42	EIL	B
43	EIL	C
44	Manip	C
45	EIL	B
46	EIL	B
47	Manip	A
48	EIL	C
49	Manip	C
50	Manip	A

Prior to allocating which data was extracted for which patient, each patient was identified as to which treatments had been performed on them (regardless of

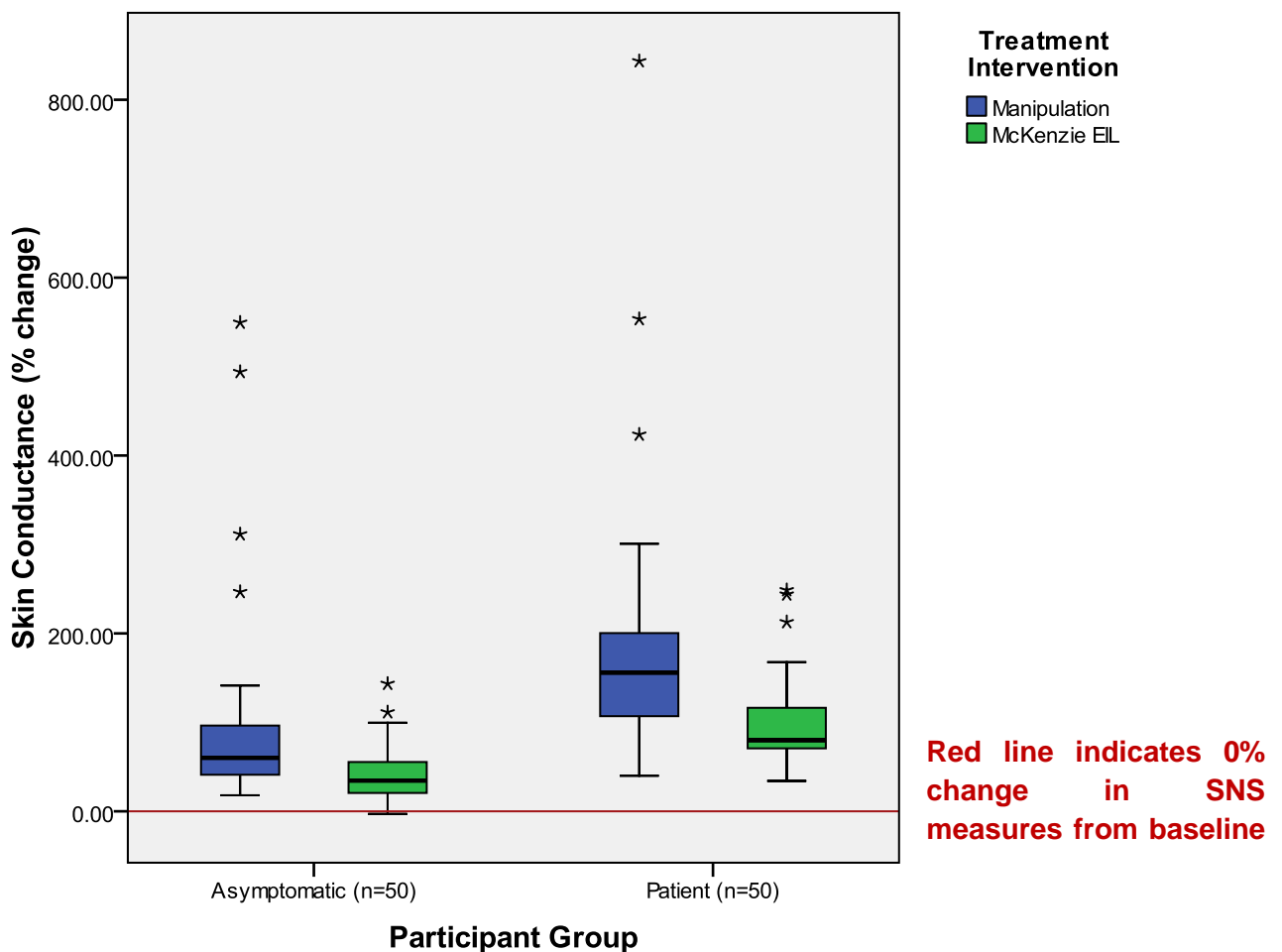
whether it was a maximum effect recording or not), for the manipulation procedure 123 events were identified within the 178 treatments episodes conducted. For the EIL technique, 56 events were recorded. Thirty two patients received both treatments within the same episode of care. Therefore, a data pool consisting of three groups was created for the randomization process (A = manipulation n=91; B = EIL = 24; C = manipulation and EIL = 32) and the data was extracted according to the treatment data required/allocated for that patient number. For both the clinical (patient) and the experimental (asymptomatic) groups, data was extracted that identified the independent participants as having a SCR to either the manipulation technique or the McKenzie EIL technique.

Demographic comparisons (age and gender) were conducted between the two groups to detect any differences in age and gender between the groups. Results demonstrated that there was group homogeneity (ie that there was no statistically significant difference between the patient and the asymptomatic groups) regarding age (t-test:  $t = -0.890$ ;  $p = 0.376$ ) and gender (Mann-Whitney U;  $z = -1.0$ ;  $p = 0.317$ ) where the level of significance was set at 95% ( $p < 0.05$ ). Analysis of recordings of the baseline levels of SC activity between the 2 treatments also revealed no statistically significant differences (level of significance set at 95%,  $p < 0.05$ ) between the patient and the asymptomatic groups (independent t-test;  $t = 1.836$ ;  $p = 0.07$ ). These results indicated that there was evidence to suggest that there were no significant differences (in age, gender and baseline SC levels) between the two groups and satisfied the requirements of equality of group variance permitting further inferential analysis. A summary of the findings are provided in the table and figure overleaf.

Table: The effects of the two treatment techniques on the asymptomatic and the patient groups.

Skin Conductance	Asymptomatic Group n= 50		Clinical / Patient Group n= 50	
	Manipulation (n=25)	McKenzie EIL (n=25)	Manipulation (n=25)	McKenzie EIL (n=25)
n=	25	25	25	25
<b>Mean SCR (%)</b>	<b>76.35</b>	<b>35.74</b>	<b>200.80</b>	<b>104.66</b>
SD	75.07	24.02	176.94	58.45
95% CI	25 to 123	12 to 73	127 to 273	80 to 129
<b>SC activity at baseline</b>	119	85	90	76
<b>SC activity in final rest period</b>	129	88	140	118
<b>Age (in yrs) Mean</b>	37.5		38.8	
SD	(8.24)		(8.41)	
Range	19-50		21-51	
<b>Gender (F/M)</b>	15/35		20/30	
% female	30%		33%	

**Figure:** A clustered boxplot illustrating the magnitude of effect (percentage change from baseline of SC activity) of two different treatment modalities (Spinal Manipulation & McKenzie EIL) between the Asymptomatic and Patient groups. (\* indicates extreme cases)



Descriptive analysis of the comparisons between the treatment responses of the two groups revealed that there was a greater response to both treatments for the patient group compared to the asymptomatic group (pooled analysis of the right and left limbs) in the order of more than double the magnitude of response (see table above) with the manipulation treatment having the greatest magnitude of response (almost twice that of the McKenzie EIL treatment) within both the patient and the asymptomatic groups. A univariate 2-way ANOVA (utilizing a General Linear Model) was used in order to test the null hypothesis that there would be no difference in SCR between the two treatments (manipulation and McKenzie's EIL) and between the two groups (patient and asymptomatic participants). The dependent variable was the maximum SCR during the treatment with the group (patient and asymptomatic participants) being the fixed factor and the intervention (manipulation and McKenzie) being the random factor. Results revealed that there was a statistically significant difference between both factors; Group  $F=9.618$ ,  $p=0.003$  and Intervention  $F=12.410$ ,  $p=0.001$  (level of significance set at 95%,  $p < 0.05$ ).

Therefore, regarding the nature of the effect on SCR, both groups experienced a sympathetic-excitatory response to both treatments. Within and between the groups, there was a significant difference between the SCRs of the two treatments with the manipulation technique having the greatest magnitude of response which was notably highest within the patient participants. Consequently, it was possible to reject the null hypothesis as there is evidence to support the alternative hypothesis that there is a difference within the groups (baseline to treatment) and a difference between the groups regarding the magnitude of SCR between the two treatments although these results should be interpreted with caution as the variance within each of the groups for each of the treatments is high (SD's) which might lead to a type I error (rejection of the null hypothesis when it might actually be true). However, there is a degree of separation between the two groups regarding the 95% CI for the two treatments, that is; for the manipulation technique 95% CI's for asymptomatics and patients were 25 to 123 and 127 to 273 micro Mho's respectively and for the EIL treatment 95% confidence intervals were 12 to 73 and 80 to 129 micro Mho's for the manipulation and EIL treatments respectively, thus providing some support for the rejection of the null hypothesis.



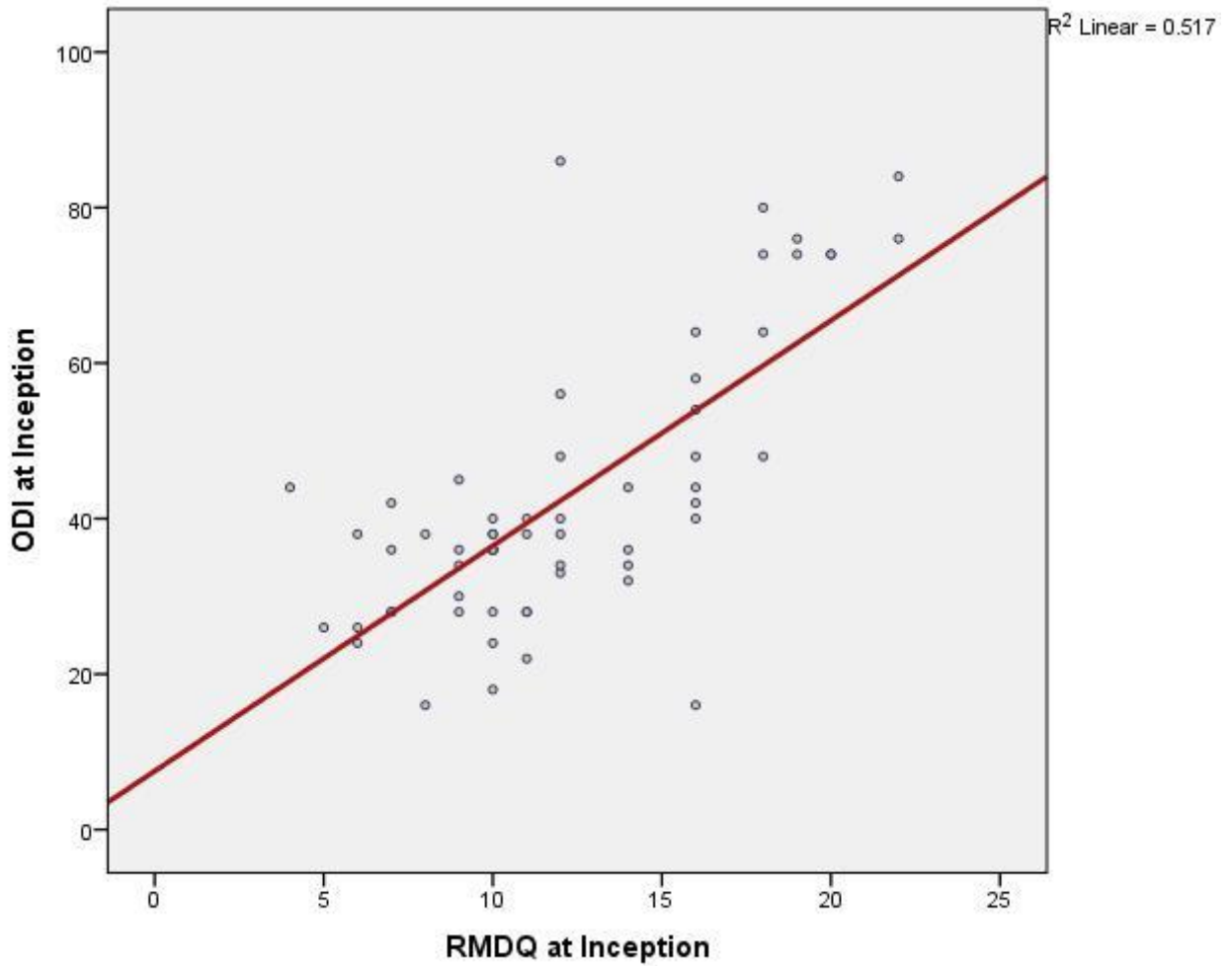
## Appendix XIV: ANOVA comparisons and post-hoc testing for H01

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
SCR at Inception	Baseline	60	81.72	33.86	4.37	72.98	90.47	14.60	156.40
	Treatment Period	60	231.23	84.51	10.91	209.40	253.06	105.60	437.40
	Final Rest Period	60	139.53	54.48	7.03	125.46	153.60	34.30	258.90
	Total	180	150.83	86.72	6.46	138.07	163.58	14.60	437.40
SCR at Mid-Point	Baseline	59	98.00	47.88	6.23	85.52	110.48	12.63	223.65
	Treatment Period	59	216.73	83.22	10.83	195.03	238.41	55.30	396.80
	Final Rest Period	59	161.99	78.34	10.20	141.58	182.41	41.31	389.40
	Total	177	158.91	86.18	6.48	146.12	171.69	12.63	396.80
SCR at Discharge	Baseline	59	100.04	49.18	6.40	87.23	112.86	14.55	199.30
	Treatment Period	59	198.81	69.45	9.04	180.71	216.91	60.30	315.60
	Final Rest Period	59	143.78	70.44	9.17	125.43	162.14	27.70	297.50
	Total	177	147.55	75.26	5.66	136.38	158.71	14.55	315.60

**Table** illustrating the PAWS (SPSS version 17) output for the post-hoc (Tukey HSD) Multiple Comparisons analysis of SC activity levels when compared to data capture point (inception, mid-point and discharge) and treatment period (baseline, treatment and final rest period) \*. The mean difference is significant at the .05 level.

Dependent Variable	Data Capture Point	Data Capture Point	Mean Difference	Std. Error	Sig. (p value)	95% Confidence Interval	
						Lower Bound	Upper Bound
SC at Inception	Baseline Period	Treatment Period	-149.51 <sup>†</sup>	11.18	>0.0005	-176	-123
		Final Rest Period	-57.81 <sup>†</sup>	11.18	>0.0005	-84	-31
	Treatment Period	Baseline Period	149.51 <sup>†</sup>	11.18	>0.0005	123	176
		Final Rest Period	91.70 <sup>†</sup>	11.18	>0.0005	65	118
	Final Rest Period	Baseline Period	57.81 <sup>†</sup>	11.18	>0.0005	31	84
		Treatment Period	-91.70 <sup>*</sup>	11.18	>0.0005	-118	-65
SC at Mid Point	Baseline Period	Treatment Period	-118.72 <sup>†</sup>	13.17	>0.0005	-150	-88
		Final Rest Period	-54.73 <sup>†</sup>	13.17	>0.0005	-95	-33
	Treatment Period	Baseline Period	118.72 <sup>†</sup>	13.17	>0.0005	88	150
		Final Rest Period	54.73 <sup>†</sup>	13.17	>0.0005	24	86
	Final Rest Period	Baseline Period	63.99 <sup>†</sup>	13.17	>0.0005	33	95
		Treatment Period	-54.72 <sup>†</sup>	13.17	>0.0005	-86	-24
SC at Discharge	Baseline Period	Treatment Period	-98.77 <sup>†</sup>	11.74	>0.0005	-126	-71
		Final Rest Period	-43.74 <sup>†</sup>	11.74	=0.001	-71	-16
	Treatment Period	Baseline Period	98.77 <sup>†</sup>	11.74	>0.0005	71	126
		Final Rest Period	55.02 <sup>†</sup>	11.74	>0.0005	27	83
	Final Rest Period	Baseline Period	43.74 <sup>†</sup>	11.74	=0.001	16	71
		Treatment Period	-55.02 <sup>†</sup>	11.74	>0.0005	-83	-27

**Appendix XV: Preliminary analysis of correlations between ODI and RMDQ**



	Mean	Std. Deviation	N
ODI at Inception	42.93	17.821	60
RMDQ at Inception	12.22	4.423	60

Spearman's rho		ODI at Inception	RMDQ at Inception
ODI at Inception	Correlation Coefficient	1.000	0.645**
	Sig. (2-tailed)	.	>0.0005
	n	60	60
RMDQ at Inception	Correlation Coefficient	0.645**	1.000
	Sig. (2-tailed)	>0.0005	.
	n	60	60

\*\* . Correlation is significant at the 0.01 level (2-tailed).

		ODI at Inception	RMDQ at Inception
ODI at Inception	Pearson Correlation	1	.719**
	Sig. (2-tailed)		.000
	N	60	60
RMDQ at Inception	Pearson Correlation	.719**	1
	Sig. (2-tailed)	.000	
	N	60	60

\*\* . Correlation is significant at the 0.01 level (2-tailed).

## Appendix XVI - Preliminary analyses of correlations between OM's (SCR, ODI and NPRS at Inception, at Mid-point and at Discharge.

In order to explore the relationships between the OM's at the 3 data capture points,

3 Null hypotheses were generated:-

### H0a

*“At the initial treatment episode (Inception), there will be no relationship between SCR's (during the treatment period of the session) and levels of functional disability (ODI) and intensity of pain (NPRS) recorded at that time point.”*

### H0b

*“At the mid-point of the treatment programme (Mid-Point), there will be no relationship between SCR's (during the treatment period of the session) and levels of functional disability (ODI) and intensity of pain (NPRS) recorded at that time point.”*

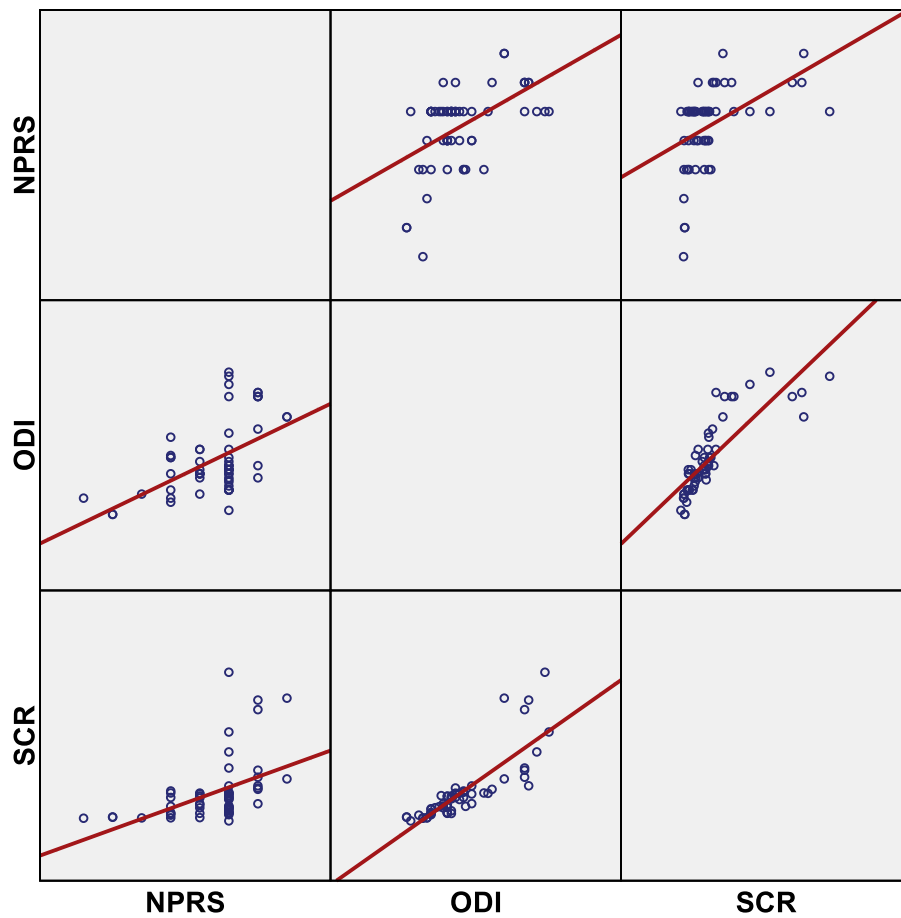
### H0c

*“At the end of treatment programme (Discharge), there will be no relationship between SCR's (during the treatment period of the session) and levels of functional disability (ODI) and intensity of pain (NPRS) recorded at that time point.”*

### OM Correlations at the initial appointment

Preliminary analysis of the relationships between OM's (SCR during treatment, NPRS and ODI) at inception are presented in the following Figure and table.

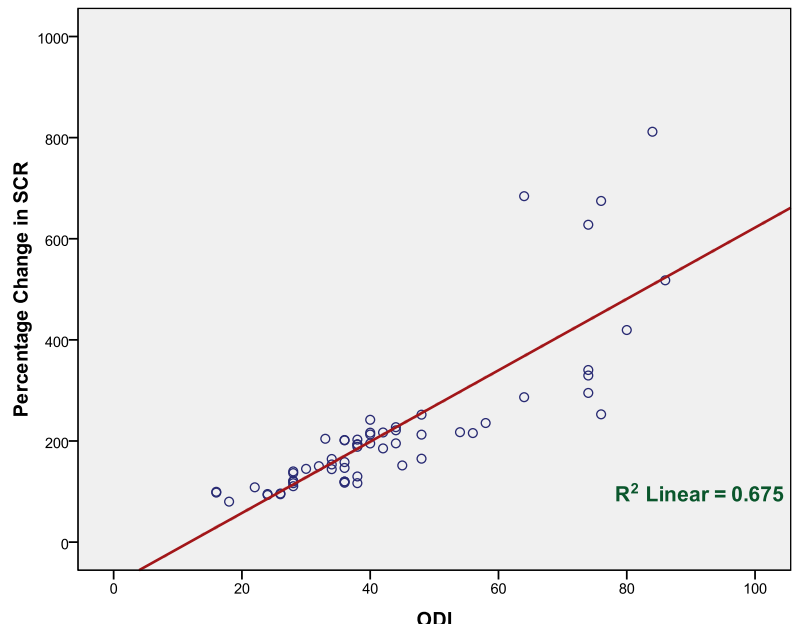
**Figure:** A matrix scatterplot chart illustrating the relationships between the SCR, ODI and NPRS at inception (with the best fit line provided in red)



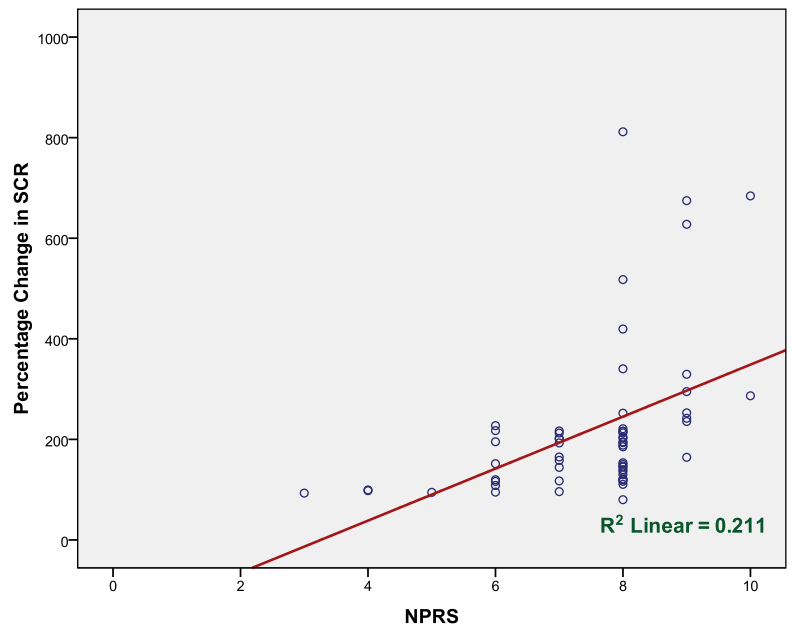
The matrix scatterplot chart above illustrates the inter-relationships between the variables SCR, ODI and NPRS at inception. Individual scatterplots for each relationship are provided below:-

**Individual scatter-plots for comparisons between the primary OM (SCR at inception during the treatment period) and ODI and NPRS at inception.**

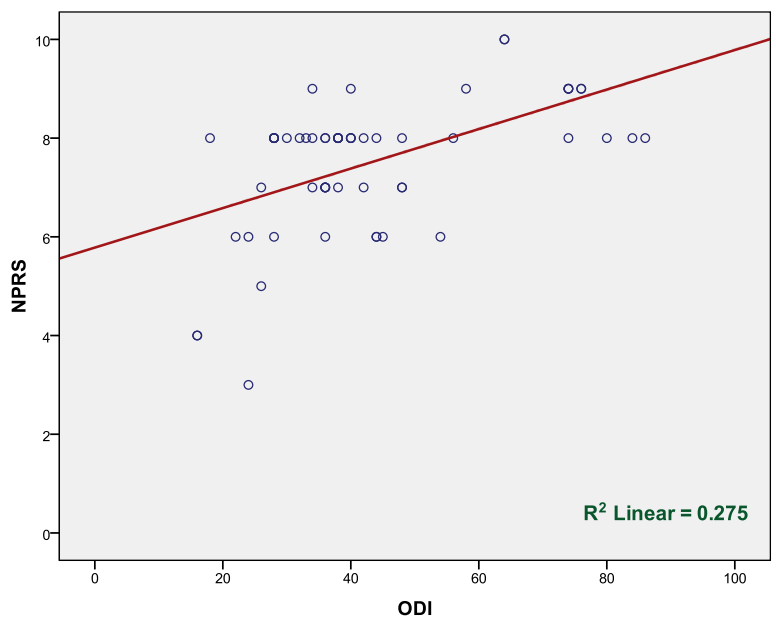
a) SCR and ODI scores at inception



b) SCR and NPRS at inception



c) ODI and NPRS at inception



All relationships can be described as being positive in direction and the extent (rho value) and statistical significance (using Pearson Correlation Coefficient analyses) of the relationships are presented in table i.

**Table:** Pearson Correlation Coefficient results for the OM at Inception

		NPRS at Inception	ODI at Inception	SCR during treatment at Inception
NPRS at Inception	Pearson Correlation	1	0.525**	0.459**
	Sig. (2-tailed)		<0.0005	<0.0005
	N	60	60	60
ODI at Inception	Pearson Correlation	0.525**	1	0.821**
	Sig. (2-tailed)	<0.0005		<0.0005
	N	60	60	60
SCR during treatment at Inception	Pearson Correlation	0.459**	0.821**	1
	Sig. (2-tailed)	<0.0005	<0.0005	
	N	60	60	60

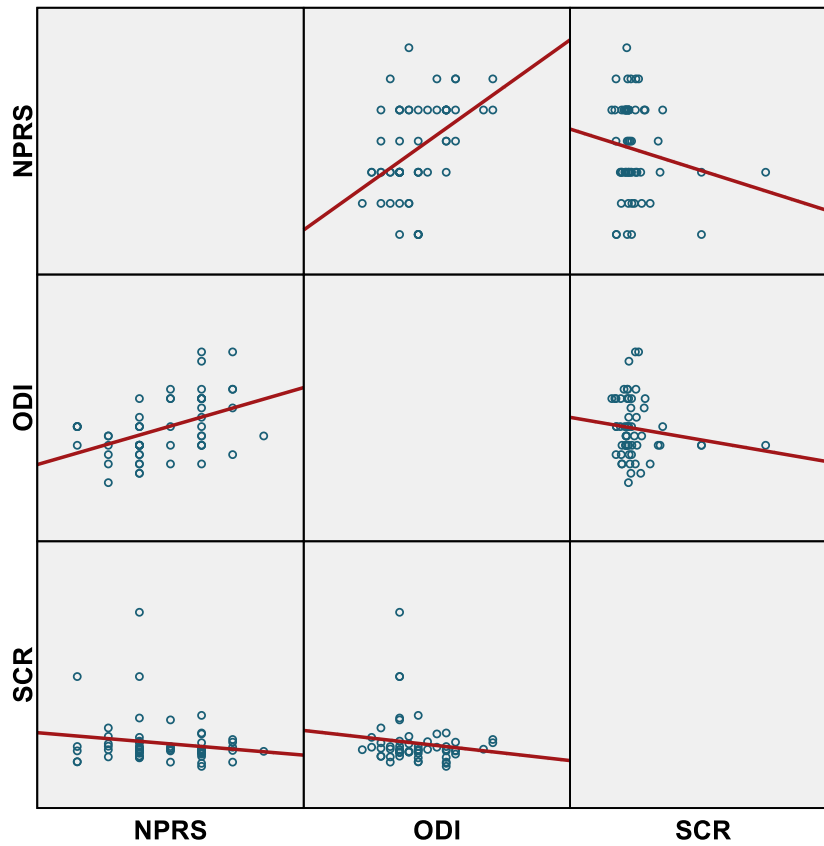
\*\* . Correlation is significant at the 0.01 level (2-tailed).

Analysis of the correlations revealed that both secondary OM's (ODI and NPRS) were positively and significantly correlated to SCRs. For ODI there was a strong (Cohen's guidelines, 1988) positive linear correlation ( $r=0.821$ ;  $p>0.0005$ ) indicating that at inception greater SCR's (during treatment) are positively associated with higher ODI scores (higher reported functional disability). Another finding of this analysis was that there was also a statistically significant, moderate positive correlation between SCR's and NPRS ( $r=0.458$ ;  $p=0.0005$ ) indicating that higher levels of reported pain levels at inception were positively associated with higher SCRs to treatment. Furthermore, there was also a moderate positive correlation between higher levels of patient-reported pain and greater functional disability ( $r=0.525$ ;  $p<0.0005$ ).

#### OM Correlations at Mid-Point

An identical analysis to that described above was conducted for the OM data at midpoint. The matrix scatter plot of the data is provided below.

**Figure:** A matrix scatterplot chart illustrating the relationships between the SCR, ODI and NPRS at Mid-Point (with the best fit line provided in red)

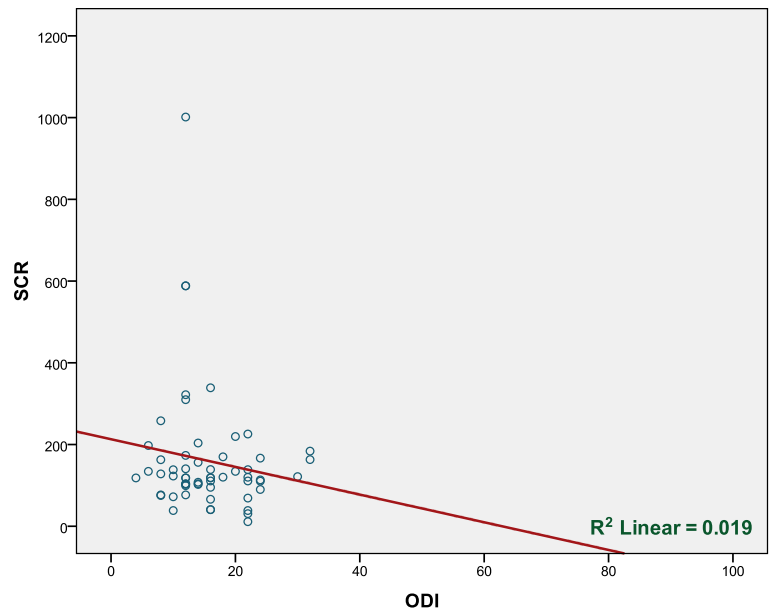


The matrix scatterplot chart above illustrates the inter-relationships between the variables SCR, ODI and NPRS at mid-point. Individual scatterplots for each relationship are provided below:-

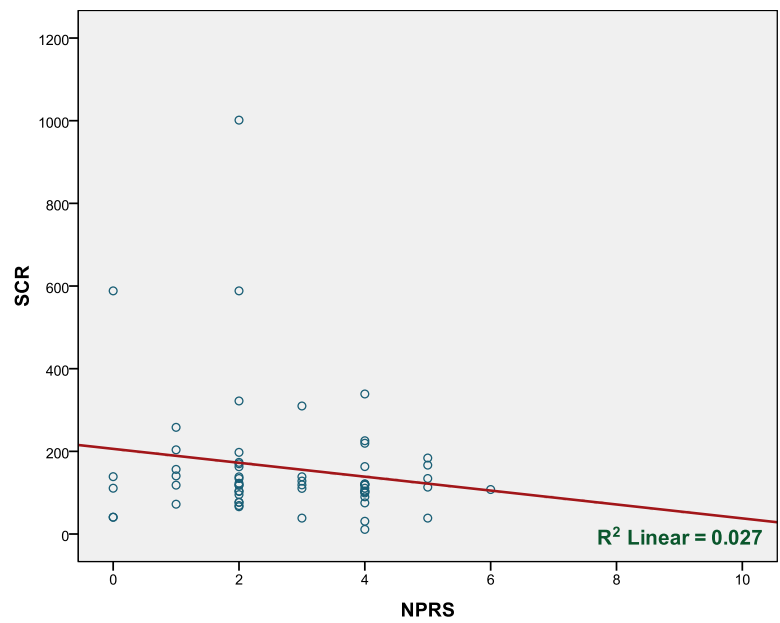


**Individual scatter-plots for comparisons between the primary OM (SCR at inception during the treatment period) and ODI and NPRS at inception.**

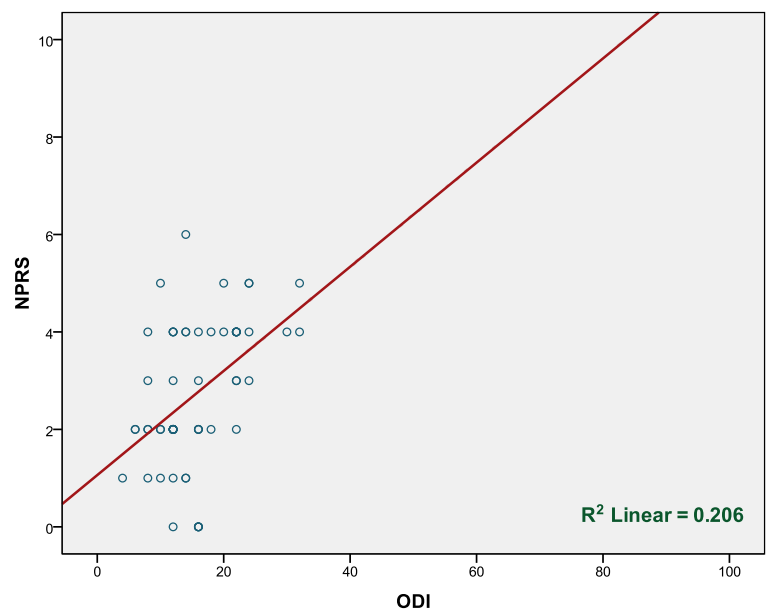
a) SCR and ODI scores at Mid-Point



b) SCR and NPRS at Mid-Point



c) ODI and NPRS at Mid-Point



At mid-point the only statistically significant relationship was between the two secondary OM's (ODI and NPRS) which was a positive correlation ( $r=0.454$ ;  $p<0.0005$ ). All other relationships were weakly negative and failed to reach the level of statistical significance ( $p<0.05$ ). Results are illustrated in the table below.

**Table:** Pearson Correlation Coefficient results for the OM at Mid-Point

		NPRS at Mid-Point	ODI at Mid-Point	SCR during treatment at Mid-Point
NPRS at Mid-Point	Pearson Correlation	1	0.454**	-0.163
	Sig. (2-tailed)		<0.0005	0.217
	N	59	59	59
ODI at Mid-Point	Pearson Correlation	0.454**	1	-0.139
	Sig. (2-tailed)	<0.0005		0.293
	N	59	59	59
SCR during treatment at Mid-Point	Pearson Correlation	-0.163	0.139	1
	Sig. (2-tailed)	=0.217	=0.293	
	N	59	59	59

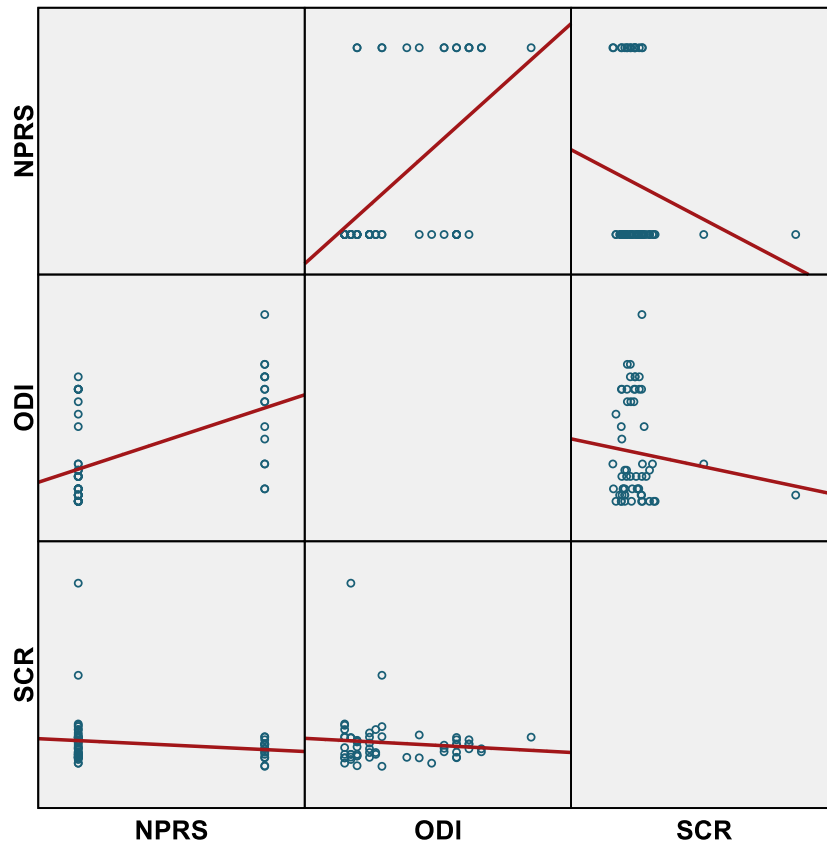
\*\* . Correlation is significant at the 0.01 level (2-tailed).

These results might indicate that at mid-point whilst ODI and NPRS are correlated with changes (reductions) in functional disability reductions corresponding to changes (reductions) in pain, these correlations did not hold true for SCR's to the treatments undertaken.

### OM Correlations at Discharge

Preliminary analysis of the relationships between OM's (SCR during treatment, NPRS and ODI) at discharge are presented in the Figure and table overleaf.

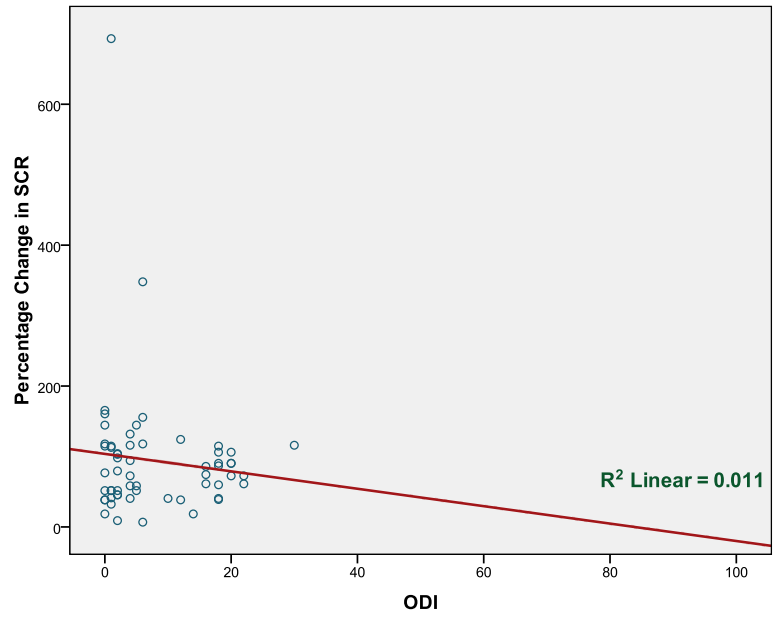
**Figure:** A matrix scatterplot chart illustrating the relationships between the SCR, ODI and NPRS at discharge (with the best fit line provided in red)



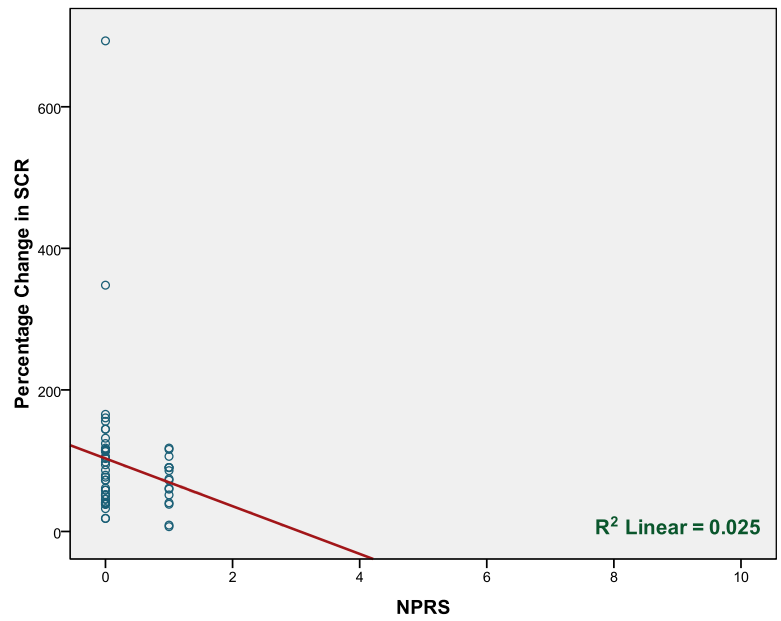
The matrix scatterplot chart above illustrates the inter-relationships between the variables SCR, ODI and NPRS at discharge. Individual scatterplots for each relationship are provided below:-

**Individual scatter-plots for comparisons between the primary OM (SCR at inception during the treatment period) and ODI and NPRS at discharge.**

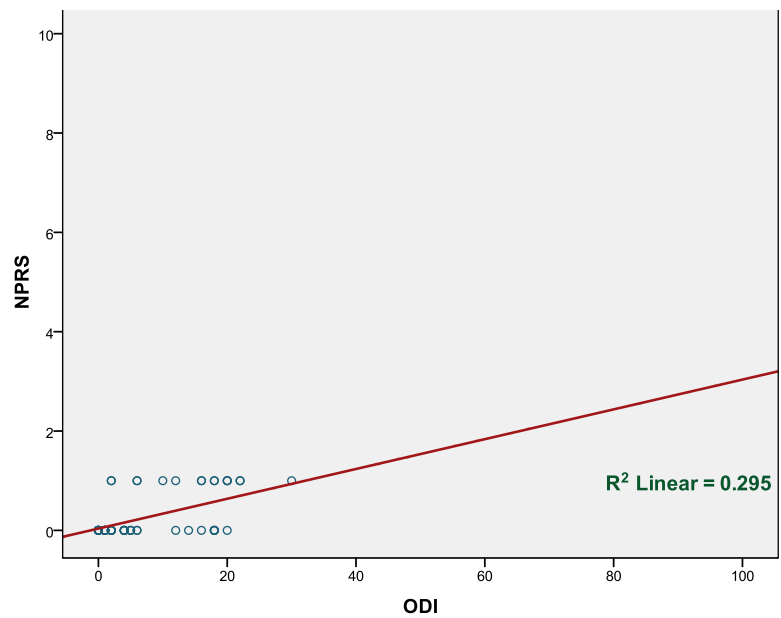
a) SCR and ODI scores at discharge



b) SCR and NPRS at discharge



c) ODI and NPRS at discharge



As with the mid-point results, the results at discharge revealed a moderate, positive relationships between ODI and NPRS ( $r=0.543$ ;  $p<0.0005$ ). All other relationships were weakly negative and failed to reach the level of statistical significance ( $p<0.05$ ). Results are illustrated in the table below.

**Table:** Pearson Correlation Coefficient results for the OM at Inception

		NPRS at discharge	ODI at discharge	SCR during treatment at discharge
NPRS at discharge	Pearson Correlation	1	0.543**	-0.159
	Sig. (2-tailed)		<0.0005	0.229
	N	59	59	59
ODI at discharge	Pearson Correlation	0.543**	1	-0.106
	Sig. (2-tailed)	<0.0005		0.426
	N	59	59	59
SCR during treatment at discharge	Pearson Correlation	-0.159**	-0.106	1
	Sig. (2-tailed)	0.229	0.426	
	N	59	59	59

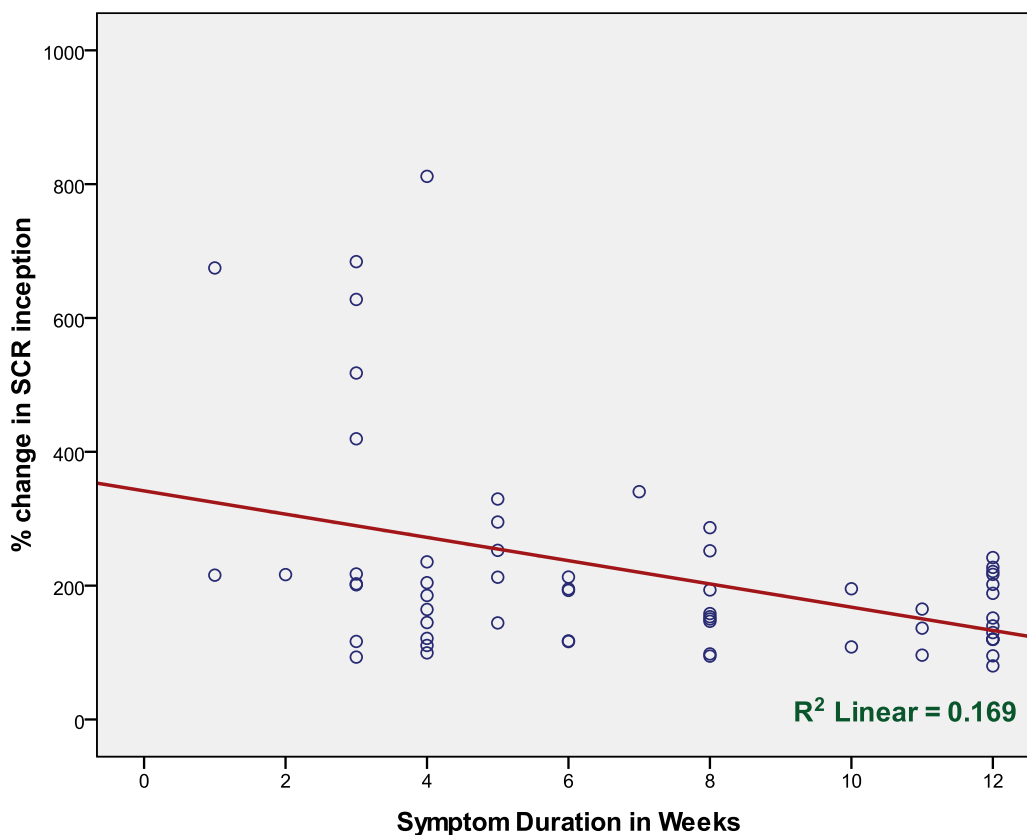
\*\* . Correlation is significant at the 0.01 level (2-tailed).

Again, these results might indicate that at discharge whilst ODI and NPRS are correlated with changes (reductions) in functional disability reductions corresponding to changes (reductions) in pain, these correlations did not hold true for SCR's to the treatments undertaken however, it is worthy of note that the data for NPRS and ODI falls within such low parameters (0-1 and 0-30 respectively) that true comparisons are difficult to make.

#### Duration of symptoms and SCR

Further analysis, using duration of symptoms (at the time of inception) as a factor revealed a moderate negative correlation (according to Cohen's guidelines, 1988) between SCR during treatment and the duration of symptoms prior to initial treatment ( $r= - 0.411$ ,  $p = 0.001$ ) suggesting that SCR's diminished as time to initial appointment was lengthened (see figure 21 overleaf).

**Figure:** Scatterplot illustrating the negative correlation between SCR and Symptom duration



Furthermore, there was also a moderate negative correlation between symptom duration and ODI score ( $r = -0.391$ ,  $p = 0.002$ ) and a weak negative correlation between symptom duration and NPRS however, this failed to reach the significance level ( $r = -0.165$ ,  $p = 0.206$ ). These results suggest that at inception the levels of SCR and ODI scores may be a product of the length of symptoms duration, albeit of only moderate strength. Duration of symptoms is not a statistically significant correlative factor in reported pain levels.

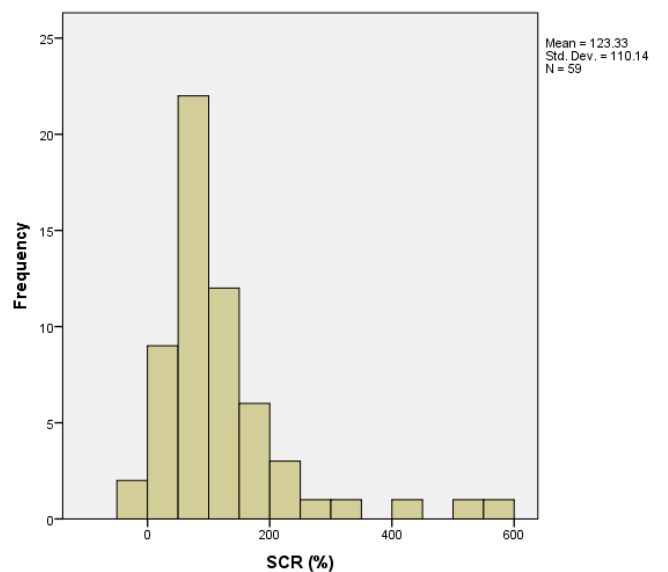
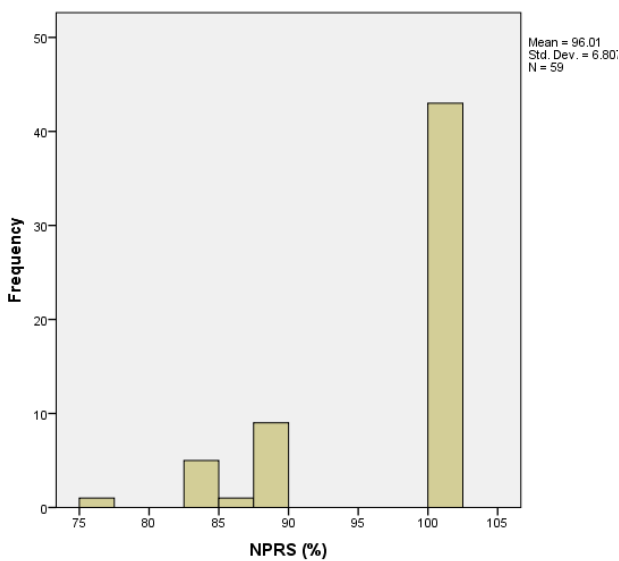
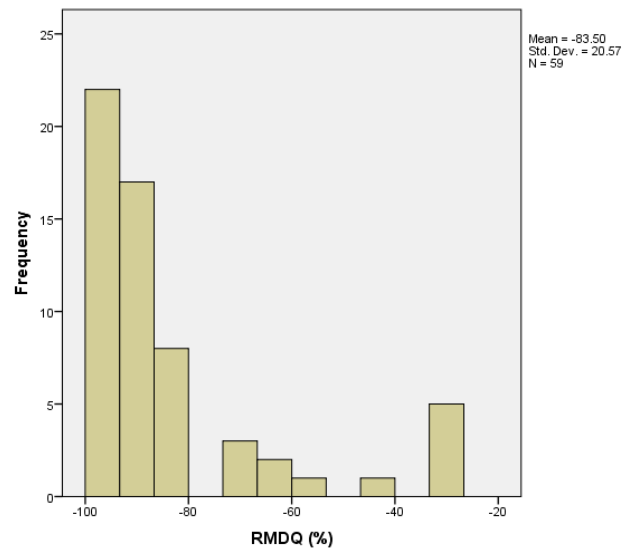
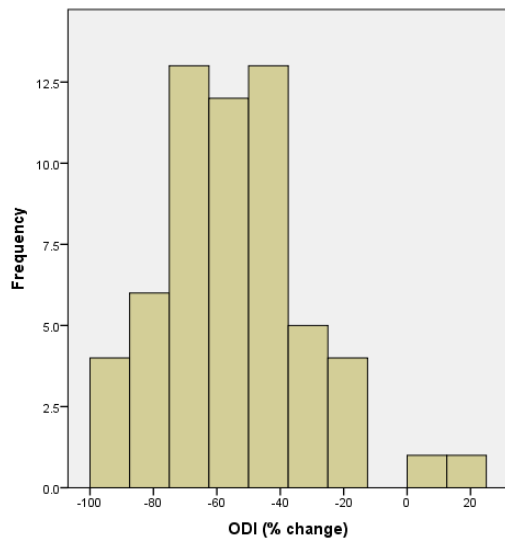
Consequently, Null Hypothesis H02 can be rejected as there is evidence to support a positive linear correlation between the primary OM (SCR) and the secondary patient-reported subjective measures of functional disability (ODI) and

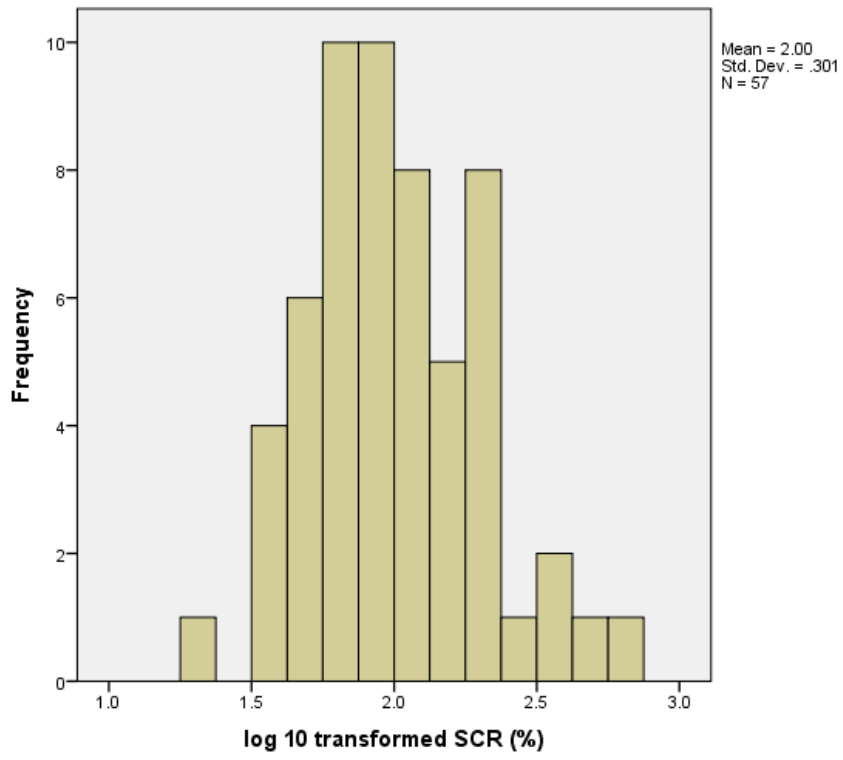
of pain (NPRS). It is also noted that these results may be partially confounded by the duration of symptoms prior to commencement of treatment.

**Skewness & Kurtosis analyses for the inception to discharge percentage change OM's**

Inception to Discharge % change	n	Min	Max	Mean	Std. Deviation	Skewness		Kurtosis	
						Statistic	Std. Error	Statistic	Std. Error
SCR	59	-95.4	23.1	-54.6	23.35	0.785	0.311	1.276	0.613
ODI	59	-100.0	-21.4	-78.7	23.27	0.995	0.311	-0.263	0.613
NPRS	59	-10.0	-3.0	-7.2	1.52	0.813	0.311	0.782	0.613
RMDQ	59	-100.0	-27.3	-83.5	20.57	1.711	0.311	2.093	0.613

**Histograms of OM (percentage change from Inception to discharge**





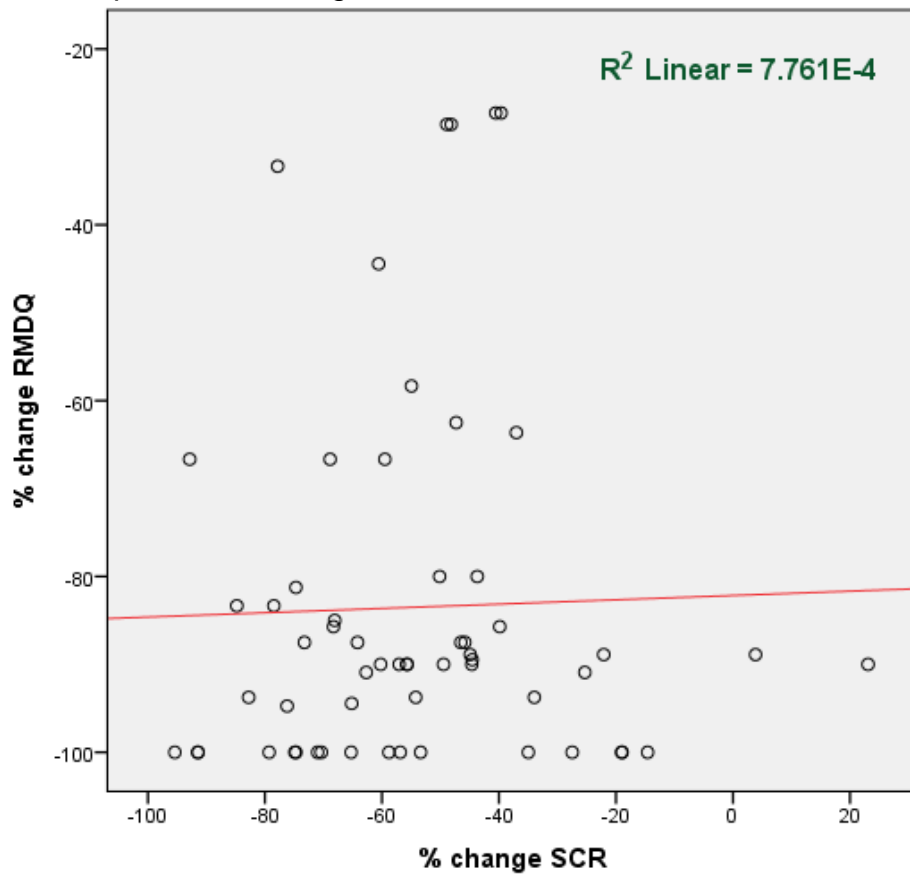


**Appendix XVII: Additional Correlative analysis of SCR and RMDQ changes from inception to discharge**

SCR and RMDQ score changes from inception to discharge were converted into percentage change scores to normalise the data for correlative analysis. Descriptively the change scores are illustrated in the table and the figure below:-

Outcome measure	n	Inception	Discharge	min	max	Percentage change
SCR	59	217.31%	160.13%	-95.40	23.09	-54.57% (+/- 23.35)
RMDQ	59	12.68	1.61	-100	-27.27	-83.50% (+/- 20.57)

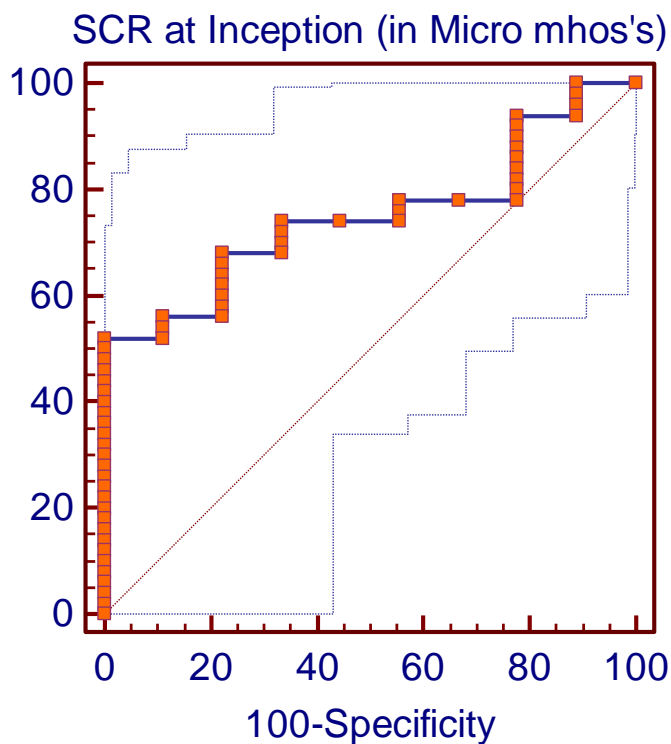
Figure plotting the percentage change readings of RMDQ scores and SCR's from inception to discharge.



Correlative analyses, using the Spearman Rho correlation coefficient inferred that there was not a statistically significant correlation between the two OM's. See table below.

		SCR	RMDQ
Spearman's rho	SCR %change (Inception to DC)	Correlation Coefficient	1.000
		Sig. (2-tailed)	-
		n	59
	RMDQ Change (Inception to DC)	Correlation Coefficient	0.091
		Sig. (2-tailed)	0.492
		n	59

**Appendix XVIII - ROC curve Data Analysis**



Variable	SCR at Inception (% change in SC Activity from baseline to treatment periods)	
Classification variable	ODI (those achieving > or < 50% change from inception to discharge)	
Sample size		59
Positive group :	ODI > 50% = 1	50
Negative group :	ODI < 50% = 0	9
Disease prevalence (%)		unknown

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.749
Standard Error <sup>a</sup>	0.0698
95% Confidence interval <sup>b</sup>	0.619 to 0.853
z statistic	3.564
Significance level P (Area=0.5)	0.0004

<sup>a</sup> DeLong et al., 1988

<sup>b</sup> Binomial exact

Youden index

Youden index J	0.5200
Associated criterion	>195.08

### Criterion values and coordinates of the ROC curve

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI
≥80.04	100.0	92.9 - 100.0	0.00	0.0 - 33.6	1.00	1.0 - 1.0		
>80.04	100.0	92.9 - 100.0	11.11	0.3 - 48.2	1.12	0.9 - 1.4	0.00	
>95.1	94.0	83.5 - 98.7	11.11	0.3 - 48.2	1.06	0.8 - 1.3	0.54	0.06 - 4.6
>96.1	94.0	83.5 - 98.7	22.22	2.8 - 60.0	1.21	0.8 - 1.7	0.27	0.05 - 1.4
>119.62	78.0	64.0 - 88.5	22.22	2.8 - 60.0	1.00	0.7 - 1.5	0.99	0.3 - 3.7
>120.07	78.0	64.0 - 88.5	44.44	13.7 - 78.8	1.40	0.8 - 2.6	0.49	0.2 - 1.2
>129.88	74.0	59.7 - 85.4	44.44	13.7 - 78.8	1.33	0.7 - 2.4	0.59	0.2 - 1.4
>139.83	74.0	59.7 - 85.4	66.67	29.9 - 92.5	2.22	0.9 - 5.7	0.39	0.2 - 0.8
>146.72	68.0	53.3 - 80.5	66.67	29.9 - 92.5	2.04	0.8 - 5.2	0.48	0.3 - 0.9
>150.18	68.0	53.3 - 80.5	77.78	40.0 - 97.2	3.06	0.9 - 10.5	0.41	0.2 - 0.7
>185.31	56.0	41.3 - 70.0	77.78	40.0 - 97.2	2.52	0.7 - 8.8	0.57	0.4 - 0.9
>188.52	56.0	41.3 - 70.0	88.89	51.8 - 99.7	5.04	0.8 - 32.5	0.49	0.3 - 0.7
>193.54	52.0	37.4 - 66.3	88.89	51.8 - 99.7	4.68	0.7 - 30.3	0.54	0.4 - 0.8
<b>&gt;195.08</b>	<b>52.0</b>	<b>37.4 - 66.3</b>	<b>100.00</b>	<b>66.4 - 100</b>			<b>0.48</b>	<b>0.4 - 0.6</b>
>811.64	0.0	0.0 - 7.1	100.00	66.4 - 100			1.00	1.0 - 1.0

The Biopac systems' ability to predict (using maximum SC treatment responses in the initial treatment episode) functional outcome at discharge, utilizing a known, validated predictor (an ODI change score equal to or greater than 50% from inception to discharge; Flynn et al., 2002 and Childs et al., 2004) was unknown as prior to this investigation, no clinical data for this type of analysis was available. Therefore, a preliminary analysis was undertaken to explore the potential.

Altman (1991; p.320-321 and 351-358), advises that in order to conduct a regression analysis to assess the predictive capacity of an unknown variable (SCR) against a known outcome predictor (ODI improvement score > 50% at discharge), direct logistic regression analysis should be performed.

Consequently, the ODI improvement score (0-100%) was transformed into a binary, categorical outcome (achieved or did not achieve ≥50% improvement).

Out of the 59 patients who provided data at both inception and discharge, 50 (84.7%) achieved, at discharge, an overall outcome in ODI change score in excess of 50% improvement. Furthermore, Altman (1991; p284-285) advises

that in cases where natural regression to the mean might be a covariant factor in the findings (eg. age and duration of symptoms prior to commencement of treatment), it is necessary to include these factors within the analysis, and therefore, the model included the main independent variable (SCR at inception) and two covariant factors; age and duration of symptoms.

The full model, containing all predictors, was statistically significant, Chi Squared (3, n=59) = 25.19,  $p < 0.0005$ , indicating that the model was able to distinguish between respondents who reported an improvement > 50% in ODI function and those who did not achieve 50% improvement. The model as a whole explained between 34.7% (Cox & Snell R square) and 60.5% (Nagelkerke R squared) of the variance in ODI change scores and correctly classified 86.4% of cases. As shown in the table below all three of the independent variables made a unique significant contribution to the model (SCR at inception, symptom duration and age). The strongest predictor of reporting an improvement in ODI score >50% was the max treatment SCR at inception, recording an odd ratio of 1.029 ( $p = 0.042$ ).

**Table : Logistic regression predicting likelihood of achieving a 50% improvement in ODI score from inception to discharge**

	B	S.E.	Wald	Df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Max SCR at Inception (%)	.028	.014	4.141	1	.042	1.029	1.001	1.057
Age (years)	-.216	.088	5.997	1	.014	.806	.678	.958
Symptom Duration (weeks)	-.591	.239	6.113	1	.013	.554	.346	.885
Constant	11.745	4.535	6.707	1	.010	126149.776		

## Notes regarding Area under the ROC curve, with standard error and 95% Confidence Interval

This value can be interpreted as follows (Zhou, Abuchowski & McClish, 2002):

- the average value of sensitivity for all possible values of specificity;
- the average value of specificity for all possible values of sensitivity;
- the probability that a randomly selected individual from the positive group has a test result indicating greater suspicion than that for a randomly chosen individual from the negative group.

When the variable under study cannot distinguish between the two groups, i.e. where there is no difference between the two distributions, the area will be equal to 0.5 (the ROC curve will coincide with the diagonal). When there is a perfect separation of the values of the two groups, i.e. there no overlapping of the distributions, the area under the ROC curve equals 1 (the ROC curve will reach the upper left corner of the plot).

The 95% Confidence Interval is the interval in which the true (population) Area under the ROC curve lies with 95% confidence.

The Significance level or P-value is the probability that the observed sample Area under the ROC curve is found when in fact, the true (population) Area under the ROC curve is 0.5 (null hypothesis: Area = 0.5). If P is small ( $P < 0.05$ ) then it can be concluded that the Area under the ROC curve is significantly different from 0.5 and that therefore there is evidence that the test does have an ability to distinguish between the two groups.

## Youden index

The Youden index  $J$  (Youden, 1950) is defined as:

$$J = \max \{ \text{sensitivity}_c + \text{specificity}_c - 1 \} \text{ where } c \text{ ranges over all possible criterion values.}$$

Graphically,  $J$  is the maximum vertical distance between the ROC curve and the diagonal line.

The criterion value corresponding with the Youden index  $J$  is the optimal criterion value only when disease prevalence is 50%, equal weight is given to sensitivity and specificity, and costs of various decisions are ignored.

The next section indicates the different selection criteria or cut-off values with their corresponding sensitivity and specificity of the test, and the positive (+LR) and negative likelihood ratio (-LR).

When a test is used either for the purpose of screening or to exclude a diagnostic possibility, a cut-off value with a high sensitivity may be selected; and when a the test is used to confirm a disease, a higher specificity may be required.

DeLong ER, DeLong DM, Clarke-Pearson DL (1988) Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 44:837-845.

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Zhou XH, Obuchowski NA, McClish DK (2002) *Statistical methods in diagnostic medicine*. Wiley-Interscience.

Zweig MH, Campbell G (1993) Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clinical Chemistry* 39:561-577.

## **Appendix XVIV – The Direct Logistic Regression Analysis of SCR's as a predictor**

The Biopac systems' ability to predict (using maximum SC treatment responses in the initial treatment episode) functional outcome at discharge, utilizing a known, validated predictor (an ODI change score equal to or greater than 50% from inception to discharge; Flynn et al., 2002 and Childs et al., 2004) was unknown as prior to this investigation, no clinical data for this type of analysis was available. Therefore, a preliminary analysis was undertaken to explore the potential.

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Consequently, the ODI improvement score (0-100%) was transformed into a binary, categorical outcome (achieved or did not achieve  $\geq 50\%$  improvement). Out of the 59 patients who provided data at both inception and discharge, 50 (84.7%) achieved, at discharge, an overall outcome in ODI change score in excess of 50% improvement. Furthermore, Altman (1991; p284-285) advises that in cases where natural regression to the mean might be a covariant factor in the findings (eg. age and duration of symptoms prior to commencement of treatment), it is necessary to include these factors within the analysis, and therefore, the model included the main independent variable (SCR at inception) and two covariant factors; age and duration of symptoms.

The full model, containing all predictors, was statistically significant, Chi Squared (3, n=59) = 25.19,  $p < 0.0005$ , indicating that the model was able to distinguish between respondents who reported an improvement > 50% in ODI

function and those who did not achieve 50% improvement. The model as a whole explained between 34.7% (Cox & Snell R square) and 60.5% (Nagelkerke R squared) of the variance in ODI change scores and correctly classified 86.4% of cases. As shown in the table below, all three of the independent variables made a unique significant contribution to the model (SCR at inception, symptom duration and age). The strongest predictor of reporting an improvement in ODI score >50% was the max treatment SCR at inception, recording an odd ratio of 1.029 ( $p = 0.042$ ).

**Table :** Logistic regression predicting likelihood of achieving a 50% improvement in ODI score from inception to discharge

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
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