Exploring the changes in pain, function and sympathetic activity when a thoracic spine manipulation is used as an adjunct to the treatment of Achilles tendinopathy

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Abstract

Achilles tendinopathy is a common musculoskeletal condition that contributes to pain and disability in both the active and sedentary populations. It’s pathogenesis is complex, and therefore it can be difficult to treat. For this reason, there are continuing investigations exploring new treatment options. Recently, there is increasing interest in the mechanisms through which spinal mobilisation techniques achieve hypoalgesia. Hypoalgesia is observed to occur together with excitation of the sympathetic nervous system. However, there is an absence of current data investigating the mechanisms through which manipulation, distinct from a mobilisation technique, might influence pain in the treatment of AT. There is also an absence of data regarding the longer-term effects of these techniques on pain and function. Recent studies identified changes in autonomic behaviour in Achilles tendons with tendinopathy: it is anticipated these changes might contribute to the mechanism of pain, and perhaps the pathogenesis of AT. Therefore, the effect of spinal manipulation on the autonomic nervous system may be highly important in the treatment of AT. With this in mind, an investigation into the effect of spinal manipulation on longer-term outcome measures of pain and function, together with an assessment of changes in autonomic function, is justified.

Aims:

1. Complete a systematic review on the studies that have investigated the effect of spinal mobilisation on the sympathetic nervous system.
2. Review the literature investigating the effect of spinal manipulation on the sympathetic nervous system.
3. Design a pilot study to assess for changes in pain and function between two groups of participants with Achilles tendinopathy.
4. Investigate changes in sympathetic activity following spinal manipulation.
5. Assess the effectiveness of the study protocols and procedures.

Methods:
The systematic review was completed according to PRISMA (www.prisma-statement.org) guidance.

For the pilot study, a total of 17 participants were randomised into either the manipulation group or the standard care group. Each group received a standardised eccentric exercise regime, and received two physiotherapy appointments per week, for four weeks, to monitor their exercise regime. In addition, the manipulation group received manipulation to the thoracic spine during each visit. After the initial four-week period participants were offered one follow-up appointment to monitor their exercise regime every two weeks until the end of the trial.

The Victorian Institute of Sports Assessment – Achilles questionnaire, and a pain score were used to assess for changes in pain and function at baseline; week four and week 12. Changes in heart rate and blood pressure were used to assess for changes in sympathetic nervous system activity following spinal manipulation or a rest intervention.

**Data Analysis:**

An analysis of covariance (ANOVA) assessed for changes within and between groups over the 12-week trial period.

**Results:**

Results of the systematic review established there was strong evidence for sympathetic excitation following spinal mobilisation.

Results of the pilot study demonstrated a significant difference in VISA-A scores within (p<0.01) and between groups (p<0.01), favouring the manipulation group. A significant difference in pain scores within (p<0.01) and between groups (p=0.03) was also demonstrated, favouring the manipulation group. There was no statistically significant change in blood pressure or heart rate within or between groups.
Conclusion:

This evidence suggests that a thoracic spine manipulation, as an adjunct to eccentric exercises, may be of benefit in the treatment of Achilles tendinopathy. The measures used here did not suggest an effect mediated by the ANS.
Acknowledgements

It’s hard to convey how truly grateful I am for the support I have received during this write-up.

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During this write up I sustained a severe concussion, during which time I could not continue with my research for a period of eight moths. I would like to express a very heartfelt and special thank you to Chris Higgs for his support and assistance in collecting the last of the outcome data. Thank you also to Karen Keith (Clinical co-ordinator), for making a treatment room and staff available for this trial. Thank you also to all other staff and administrators involved in this trial, including Dr. Ewan Kennedy, Kelly Anderson, Christina Hughson, Fay Devlin and Nicola Clarke, for their assistance.

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<th>Description</th>
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<tbody>
<tr>
<td>ACH</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>ANS</td>
<td>Autonomic nervous system</td>
</tr>
<tr>
<td>AT</td>
<td>Achilles tendinopathy</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CGRP</td>
<td>Calcitonin gene related peptide</td>
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<tr>
<td>ECM</td>
<td>Extra cellular matrix</td>
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<tr>
<td>ELPCT</td>
<td>Edge light pupil cycle time (reflex)</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>HVLAT</td>
<td>High velocity low amplitude thrust</td>
</tr>
<tr>
<td>IL-1;4;6;10</td>
<td>Interleukin-1;4;6;10</td>
</tr>
<tr>
<td>IPAG</td>
<td>Lateral column of periaqueductal gray area</td>
</tr>
<tr>
<td>MMP</td>
<td>Matrix metalloproteinase</td>
</tr>
<tr>
<td>MT</td>
<td>Manual therapy</td>
</tr>
<tr>
<td>nAChR</td>
<td>Nicotinic acetylcholine</td>
</tr>
<tr>
<td>NPRS</td>
<td>Numeric pain rating scale</td>
</tr>
<tr>
<td>NMDAR1</td>
<td>N-methyl-D-aspartate receptor type 1</td>
</tr>
<tr>
<td>NS</td>
<td>Nervous system</td>
</tr>
<tr>
<td>PEDro</td>
<td>Physiotherapy evidence database</td>
</tr>
<tr>
<td>PeNS</td>
<td>Peripheral nervous system</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
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<tr>
<td>PNS</td>
<td>Parasympathetic nervous system</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>SNS</td>
<td>Sympathetic nervous system</td>
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<tr>
<td>SoNS</td>
<td>Somatic nervous system</td>
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<tr>
<td>SP</td>
<td>Substance P</td>
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<tr>
<td>TNF-α</td>
<td>Tumour necrosis factor alpha</td>
</tr>
<tr>
<td>TNFR1 and 2</td>
<td>Tumour necrosis factor receptor 1 and 2</td>
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<tr>
<td>VISA-A</td>
<td>Victorian institute of sports assessment - Achilles</td>
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Publications

The systematic review, presented as Chapter 4 of this Masters thesis has been accepted for publication, pending very minor changes, by the journal Manual Therapy (Appendix A).
1 Introduction
Rehabilitation from Achilles tendinopathy (AT) is complex and can take months or longer to restore the tendon to a pain-free state (Alfredson & Öhberg, 2005; Meyer, Tumilty, & Baxter, 2009). A non-invasive treatment intervention that would facilitate a more rapid return to function and assist in the reduction of pain, would be highly desirable.

Anecdotally, spinal manipulation has yielded positive results when used in the treatment of AT. The autonomic nervous system (ANS), which is intricately linked with immune response, has been implicated in AT (Andersson, Danielson, Alfredson, & Forsgren, 2008; Danielson, Alfredson, & Forsgren, 2007). A theoretical basis for a positive response in AT recovery following manipulation of the spine might be the association between spinal manipulation and the modulation of ANS behaviour (refer to section 3.4.2).

The primary aim of this Masters thesis is to assess the effectiveness of the study protocol and procedures. The secondary aim to assess the potential added benefit (effectiveness) of spinal manipulation when applied in addition to a standard care intervention of an eccentric exercise regime, for the treatment of AT. This study will also assess for putative changes in sympathetic nervous system (SNS) outcome measures following manipulation, in an attempt to further explore the association between spinal manipulation and ANS behaviour. To the best of the author's knowledge, this will be the first longitudinal trial (12-weeks) that will investigate the effect of spinal manipulation on pain and functional outcome measures. It is also the only trial to investigate the effects of spinal manipulation as an adjunct to exercise treatment for AT. This is important as treatment techniques that might offer more rapid improvements in the recovery from AT are highly sought after.

Chapter 2 of this thesis explores the definition, pathogenesis, mechanism of pain and treatment interventions for AT. Recent histopathological findings indicate both inflammatory and degenerative changes in AT (Alfredson, Pietilä, Jonsson, & Lorentzon, 1998; Rees, Stride, & Scott, 2013; Schubert, Weidler, Lerch, Hofstädter, & Straub, 2005; van Sterkenburg & van Dijk, 2011). However, it is not completely understood if these changes are a result of, or a contributing factor towards the development of this condition. Similarly, the mechanisms of pain are not fully understood. There appears to be some evidence that the development of small blood vessels (neovascularisation) that grow into the tendon may contribute to the mechanisms of pain (Alfredson, Öhberg, & Forsgren, 2003; L Öhberg & Alfredson, 2002). In addition, biomechanical and autonomic changes (i.e. the development of sympathetic nerve fibres in the walls of the neovessels) associated with AT might also contribute to the
mechanism of pain (Andersson, Danielson, Alfredson, & Forsgren, 2007(a); Danielson et al., 2007; Lintz et al., 2011). These theories are discussed in Chapter 2, together with an overview of the various treatment approaches that are currently used. In particular, the effectiveness and mechanism of eccentric exercises, which are used as the standard care intervention in the current pilot study, are discussed.

The aim of Chapter 3 is to provide contextual background for this thesis. The term manipulation and mobilisation are defined for the purpose of this Masters thesis. An overview of the ANS is also provided, together with findings from studies that have investigated the effect of spinal manipulation on ANS activity.

Among manual therapists there are some technical terms that may infer different treatment techniques, thus creating confusion around the nomenclature used in manual therapy (MT). For example, the term manipulation might infer soft tissue massage, or it might infer a high velocity, low amplitude thrust (HVLAT) manipulation applied to a joint. An understanding of the subtle differences between spinal manipulation and mobilisation techniques are important to the context of this thesis. Spinal mobilisation techniques involve gentle, repeated, rocking movements applied to a spinal segment that does not extend the joint beyond its natural range (Maitland, Hengeveld, Banks, & English, 2005), while manipulation techniques passively extend the spinal joint beyond its natural physiological range (Bronfort, Haas, Evans, & Bouter, 2004). As previously mentioned, there is a lack of studies investigating the effect of manipulation on the ANS. However, the few studies that have investigated this topic are discussed in Chapter 3.

Although there is some variation between a mobilisation and manipulation technique, it is anticipated they might have a similar influence on the ANS. Therefore it is considered that studies investigating the effect of spinal mobilisation on the ANS are relevant studies to review as they might contribute towards contextual background and facilitate a better understanding of the potential for manipulation. The aim of Chapter 4, therefore, is to complete a systematic review on the effect of spinal mobilisation on SNS activity: a branch of the ANS. The clinical implications of these results are considered in detail and suggestions for future research are made.

Chapter 5 presents the pilot study that has been run as part of this Masters thesis. The aims of this pilot study have already been outlined in the abstract of this thesis. In summary, they are to assess the trial protocols and procedures; the effectiveness of spinal manipulation as an
adjunct to a standard care intervention in the treatment of AT, and also to assess for changes in SNS activity between participants that received either the spinal manipulation or the control intervention (rest). A theoretical framework of other potential pathways, through which manipulation might influence the mechanisms of pain in AT is presented in the final Chapter of this thesis: Chapter 6.
2 Tendinopathy
2.1 Overview of this chapter

The current Masters thesis investigates the effect of manipulation in addition to eccentric exercises for the treatment of AT. The aim of this chapter is to clarify the working definition of the term AT in the context of this thesis. The main theories that explain the pathogenesis and mechanism of pain in AT are considered important information as modulation of these variables might result in more effective treatment interventions. For example, SNS activity may be implicated in the mechanisms of pain in AT (section 2.4.3), therefore a treatment intervention that might influence this behaviour may be of therapeutic benefit. Finally, current treatment options are outlined. This section focuses on eccentric exercises, which form the standard care intervention in the current pilot study (Chapter 5).

2.2 Definition of the term tendinopathy

There is much debate over the terms tendinitis, tendinosis and tendinopathy. Previously these terms have been used interchangeably, but correct use of the terminology is highly important as the terms indicate a different pathogenesis, and therefore a different treatment approach.

The term tendinitis infers an inflammatory component, and for the vast majority of the 1990s and early 2000s this term was used to describe all pain arising from the tendon (Rees et al., 2013). Treatment was focused on methods to reduce inflammation such as the RICE protocol (rest, ice, elevation and compression); non-steroidal anti-inflammatory drugs (NSAIDS) and corticosteroids. Histological studies had already demonstrated the apparent absence of acute inflammatory cells (Puddu, Ippolito, & Postacchini, 1976), but it was not until the early 2000s that clinicians began to understand this new perspective on the pathological tendon. Focus then shifted to histological findings that identified collagen separation, specifically an increase in ground substance, an increase in tenocytes, degeneration of the extra cellular matrix (ECM) and the development of neovessels (i.e. neovascularisation) (Alfredson et al., 1998; Fredberg & Stengaard-Pedersen, 2008; Riley, 2004; van Sterkenburg & van Dijk, 2011), all indicative of tendon degeneration. Tendinosis, inferring degenerative changes, quickly became the prevailing diagnostic term for chronic (greater three months duration) tendon pain.

In the past decade degenerative theories (i.e. tendinosis) have dominated. More recently, the move away for a diagnosis of tendinosis, to one of tendinopathy, has proven to be more
reflective of the pathogenesis. Advances in technology have led to the identification of a number of inflammatory reactions in symptomatic tendons, (Gotoh, Hamada, Yamakawa, Inoue, & Fukuda, 1998; Schubert et al., 2005; Sullo, Maffulli, Capasso, & Testa, 2001; Zhang & Wang, 2010), verifying early assumptions of an inflammatory component. Therefore, the term tendinopathy, currently, denotes pathological tendons with both degenerative and inflammatory changes.

However, there remains some confusion over the diagnosis of tendinopathy in the clinical setting among manual therapists, where advanced histopathological studies are generally not carried out. A combination of tendon pain and impaired performance may constitute a diagnosis among some clinicians (Alfredson & Öhberg, 2005; Alfredson et al., 2003). Other clinical diagnoses require the presence of swelling together with the loss of function (K. M. Khan, Cook, Bonar, Harcourt, & Åstrom, 1999). In addition, there are a number of clinical tests (refer to Appendix B) known to improve the likelihood of accurately diagnosing AT in the clinical setting that may be used. Nonetheless, there is currently a general agreement that tendinopathy, and specifically AT, is a clinical, rather than laboratory, diagnosis (Gaida et al., 2012).

For the purpose of this thesis the term AT refers to chronic (greater than three months) mid-portion Achilles tendon pain and dysfunction, that exhibits histopathological evidence of degenerative and inflammatory changes. For the purpose of the feasibility trial that follows in Chapter 5, this condition is diagnosed clinically, without histopathological evidence (refer to Appendix B). The term tendinosis refers to tendons with evidence of degeneration, without features of pain or swelling. And finally the term tendinitis refers to tendons with evidence of inflammatory changes in the absence of degenerative changes. The focus of this thesis is solely on AT.

2.3 Achilles tendon structure

The Achilles tendon, which is formed from the soleus and gastrocnemius muscle, is the strongest tendon in the body (O'Brien, 1992). Distally, these muscles form an aponeurosis, from which the Achilles tendon arises. The point at which the soleus contributes fibres to the Achilles, the tendon fibres begin to rotate, forming a spiral. It is this point that some author’s postulate has the lowest vascular supply (Curwin & Stanish, 1984; Stanish, Curwin, &
Mandel, 2000). The spiral orientation of tendon fibres allow for elongation, elastic recoil and the release of energy (Jonsson, 2009). Between two and seven centimetres above the Achilles tendon insertion onto the calcaneus, the spiral becomes more apparent.

Medial to the Achilles tendon, the plantaris tendon is located; both the Achilles and plantaris tendons are enclosed by a loose paratendon. The loose paratendon is a membrane consisting of two layers: a deep layer and a superficial layer. The deep layer is surrounding, and in contact with, the epitenon and a superficial layer, the peritenon (Kvist, 1991).

The tendon organ itself is made up of fibres, fascicles and tertiary bundles, all held together in the loose paratendon sheath (Figure 2-1).
Collagen bundles, cells and ground substance make up the Achilles tendon. The collagen fibres, which are the basic unit of the tendon, generally lie in a parallel arrangement, although the fibres within them can be orientated in longitudinal, transverse and horizontal directions, which improves the tensile properties of tendon (Jonsson, 2009; Jozsa & Kannus, 1997). Apart from attaching muscle to bone, the main function of tendons is to store and release energy, and transfer the force produced by the muscle to produce movement (O'brien, 1992).

The paratendon provides a superficial blood supply to the Achilles tendon (Andersson et al., 2008; Danielson et al., 2007), and is poorly innervated by nerve fibres from the sural nerve (Jonsson, 2009); although recently general, sensory and ANS components have been identified in the tendon itself (Bjur, Alfredson, & Forsgren, 2005; Danielson, Andersson, Alfredson, & Forsgren, 2008).

2.4 Achilles tendinopathy

2.4.1 Overview

Although many different theories have been proposed (Åström & Rasing, 1995; Jonsson, 2009; Kvist, 1991), the pathogenesis of AT remains unclear. It is generally agreed that the causes are multifactorial, involving both intrinsic and extrinsic factors (Kannus et al., 2002; Paavola et al., 2002; Soma & Mandelbaum, 1994; Tumilty, 2010). For a detailed discussion on these influences, the reader is referred Carcia, Martin, Houch and Wukich (2010).

As discussed above (section 2.2) the past decade has seen AT described primarily in terms of degenerative changes. However, studies have identified numerous inflammatory reactions within the tendon proper and paratendon (Gotoh et al., 1998; Schubert et al., 2005; Sullo et al., 2001; Zhang & Wang, 2010). Clinicians and researchers have recently been encouraged to revisit the evidence for inflammation (Rees et al., 2013), as the most current findings indicate that inflammation is likely to be an on-going feature of AT. Although modern tools are advancing our understanding of the histopathological features in symptomatic AT, the exact
aetiology of this condition is yet to be clarified.

What follows is a summary of the findings that outline the degenerative and inflammatory changes in symptomatic AT. These changes are intricately linked. For example, an inflammatory response that leads to the expression of interleukins (described below), contributes to the degradation of the ECM. ECM provides the tendon with its structural support, a reduction in which may result in other degenerative changes. For this reason, it is difficult to describe features of inflammation and degeneration in isolation, as previous authors have generally done. The following section will outline inflammatory and degenerative findings together, as there is now evidence that these reactions and biochemical changes may be occurring concurrently in AT.

2.4.2 Healthy situation

Morphologically, healthy tendons consist of parallel bundles of collagen fibrils. Between the collagen bundles is ground substance, made up of fibroblasts and proteoglycans (van Sterkenburg & van Dijk, 2011), which influence the mechanical properties of the tendon by contributing to its viscoelasticity (O'brien, 1992). Proteoglycans, which consist of a protein core with attached glycosaminoglycans (GAGs) (Xu & Murrell, 2008), are important as they retain water for turgidity (Yanagishita, 1993). In addition to water retention, other important physiological functions of these proteins are ion transport, the diffusion of nutrients, resisting compressive forces, mediating cell matrix interactions and resistance of sequestration of enzymes and growth factors in the matrix (Hardingham & Fosang, 1992). Fibroblast type cells, which are elongated tenocytes, are the dominant cells in tendon tissue.

2.4.3 Pathological situation

Degenerative changes such as collagen separation and thinning; ECM degradation; decreased amounts of type I collagen (which gives tendons inherent strength) and increased amounts of type III collagen (a weaker type of collagen); and increased amounts of ground substance (Åström & Rausing, 1995; Jozsa & Kannus, 1997; Puddu et al., 1976; van Sterkenburg & van Dijk, 2011) have all been identified in symptomatic AT. In addition, an abundance of inflammatory reactions occurring in AT have also been identified (see below).
The presence of macrophages and T and B lymphocytes has been identified, indicating a strong inflammatory and immune response (Schubert et al, 2005). Interleukin expression stimulated by cytokines (e.g. IL-6), and macrophage-derived enzymes (e.g. cyclo-oxygenase) that contribute to the degradation of the ECM, have also been identified and confirm an inflammatory reaction in tendinopathy (Rees et al., 2013; Schubert et al., 2005; Sullo et al., 2001; Zhang & Wang, 2010). Increases in the amount and size of tenocytes, in response to cytokines and growth factors, are a frequently observed phenomenon. A recent study that explored the expression of tumour necrosis factor-alpha (TNF-$\alpha$) and its receptors tumour necrosis factor receptor one (TNFR1) and tumour necrosis factor receptor two (TNFR2), identified the very first evidence of a TNF-$\alpha$ system in the tenocytes of the Achilles tendon. Gaida (2012) identified more intense immunoreactions for TNFR1 in the tenocytes of pathological Achilles tendons (i.e. more widened and rounder in appearance), compared to the spindle, elongated shape of tenocytes in healthy tendons, indicating an up-regulated TNF-$\alpha$ system in pathological Achilles tendons.

Microdialysis has demonstrated high levels of glutamate in Achilles tendons (Alfredson & Öhberg, 2005; Alfredson et al., 2003). Moreover, the glutamate receptor N-methyl-D-aspartate receptor type one (NMDAR1) and its activated state phosphorylated NMDAR1 (phosphor-NMDAR1), which are known triggers for a number of chronic pain disorders, have recently been identified in tendinopathic tendons compared to healthy tendons (Schizas et al., 2012) (please refer to section 2.5.2 for a deeper discussion on these findings).

Altered concentrations of enzymes such as matrix metalloproteinase (MMPs) are well documented (Corps et al., 2006; Rees et al., 2013). These enzymes regulate the degradation and remodelling of the ECM, and are therefore important for the maintenance of the structural integrity of the tendon. In pathological conditions, it is understood that cytokines such as interleukin-1 (IL-1); interleukin-4 (IL-4); interleukin-6 (IL-6); interleukin-10 (IL-10); TNF $\alpha$; and growth factors stimulate the production of MMPs, further disrupting the balance between synthesis and degradation of ECM (Corps et al., 2006; Meller, Li, & Tseng, 2000; Tumilty, 2010).

Vascularity is increased. Neovascularisation is the formation of functional microvascular networks (neovessels) that have been found to be present in symptomatic AT, but not in pain free, healthy tendons (Alfredson & Öhberg, 2005). Sympathetic and sensory nerve fibres accompany the ingrowth of blood vessels into the Achilles tendon (Andersson et al., 2008).
Interestingly, in both patella and Achilles tendinopathy the perivascular innervation is primarily sympathetic in origin (Andersson et al., 2008; Danielson et al., 2007), suggesting a strong sympathetic influence in symptomatic AT. Animal studies have demonstrated that the sensory nerve ingrowth is a reaction to repetitive loading (Messner, Wei, Andersson, Gillquist, & Räsänen, 1999) and a response to injury (Ackermann, Ahmed, & Kreicbergs, 2002), in the Achilles tendons of rats.

Finally, the tenocytes in both healthy and pathological Achilles and patella tendons have shown evidence of a local, non-neuronal production of acetylcholine (ACh) and nicotinic and muscarinic ACh receptors (nAChR and mAChR respectively) i.e. a non-neuronal ACh system (Bjur, Danielson, Alfredson, & Forsgren, 2008; Danielson et al., 2007). This is similar to the behaviour of tenocytes in the synovium of patients with severe degenerative conditions such as rheumatoid arthritis and osteoarthritis (Forsgren, Grimsholm, Jönsson, Alfredson, & Danielson, 2009). It is of importance as ACh can modulate the activity of inflammatory cells. Locally produced ACh is likely to have proliferative, angiogenic, wound healing and immunomodulatory functions, and may result in significant anti-inflammatory effects (Forsgren et al., 2009; Wang, Iosifidis, & Fu, 2006).

In summary, there are a number of biochemical changes identified in symptomatic tendons, which interfere with the structural integrity and viscoelastic properties of the tendon. Many of these are discussed later in this chapter (please refer to section 2.4). Theories that attempt to explain how these changes have come about in AT (i.e. pathogenesis) are broadly grouped into two categories: the biomechanical hypothesis (Wang et al., 2006) and the biochemical hypothesis (Danielson et al., 2008). These are outlined below and the reader is referred to Wang, Iosifidis and Fu (2006) and Danielson (2009) for a deeper discussion on these theories.

2.4.4 The biomechanical hypothesis
This theory explains how chronic repetitive damage to tendons could accumulate over time, leading to tendinopathy. Progressive and gradual overload of the Achilles tendon results in matrix abnormalities (Danielson et al., 2008; Wang et al., 2006). These changes can have a detrimental effect on the viscoelastic properties (stress/strain, hysteresis) of the tendon. If the tendon cannot store and release energy efficiently, it’s ability to repair structural damage is
diminished (Jozsa & Kannus, 1997; Tumilty, 2010), demonstrating a chronic failure to heal following micro-traumas or overuse.

The difference between the energy stored and released (a function of the tendons viscoelastic property) is given off as heat (Riemersma & Schamhardt, 1985). An increase in load placed on the tendon, increases hysteresis and therefore the heat given off. This is important as temperatures above 42.5°C may cause cell death in vitro (Hall, 1994). Excessive heat has also been shown to increase the level of pro-inflammatory cytokines (Hosaka et al., 2006), thus exacerbating the problem.

As summarised by Tumilty (2010) the biomechanical hypothesis could be simply defined as failure of the tendon to cope with the loads placed upon it. Matrix abnormalities result in changes in the tendon’s viscoelastic properties; the results of which are excessive heat and potentially cell apoptosis.

2.4.5 The biochemical hypothesis

The production of local signalling substances such as substance P (SP), Ach, TNF and catecholamines, in response to tendon loading, are the basis of this hypothesis i.e. mechanotransduction (Andersson et al., 2008; Danielson, 2009; Tumilty, 2010).

TNF-α is an important cytokine in tendon tissue. For example, in torn supraspinatus tendons TNF-alpha messenger ribonucleic acid (mRNA) is increased 11 fold (Miller et al., 2005); cultured avian tendon cells exposed to a combination of TNF-alpha, an increased temperature and mechanical stress led to reduction of pro-collagen mRNA expression (Pan & Halper, 2003). Cultured human tenocytes treated with TNF-α demonstrated reduced type 1 collagen deposition and up-regulation in the expression of pro and immunoregulatory cytokines (John et al., 2010). TNF-α is involved in the regulation of mechanotransduction in human vascular smooth muscle cells, and is generally accepted as an important molecule in mechanotransduction. In a recent study Gaida (2012) postulated that the TNF-α system is involved in the mechanotransductive response to tendon loading by facilitating communication between tenocytes.

Other biochemical changes influence the interaction between glycoproteins, proteoglycans, and collagen, which determines the morphology and structure of the tendon (Tumilty, 2010).
It is believed that these substances not only affect pain, but also influence the vascularity and structure of tendon tissue. However, it is not known whether these changes are a causative factor, or a consequence of, tendinopathy. The reader is referred to section 2.5 for a deeper discussion on the effects these biochemical changes are having on the tendon.

2.4.6 Clinical presentation
The symptoms of mid-portion AT include painful swelling, generally between two and seven centimetres proximal to its insertion into the calcaneus, and stiffness, especially after a period of rest. The onset can be traumatic or atraumatic, and must be present for a period of three months or longer (Khan, Cook, Maffulli, & Kannus, 2000). The diagnosis of AT is complex as it can co-exist with paratendinopathy, and is based on a combination of history taking and clinical findings.

For the purpose of this current pilot study (Chapter 5), the clinical diagnosis of AT was based on a combination of history taking, combined with positive results in a combination of three tests: tenderness on palpation; a positive arc sign and a positive result in The Royal London Hospital test (Appendix B). When the three methods were combined, the overall sensitivity (i.e. the likelihood the tests will be positive if AT is present) was 0.586 with a confidence interval (CI) of 0.469–0.741. The overall specificity was 0.833 (CI, 0.758–0.889) (Maffulli, Wong, & Almekinders, 2003). These tests are described in Appendix B.

2.5 Aetiology of pain
2.5.1 Neovascularisation
The source of pain, although not clear, is speculated to be due, in part, to neovascularisation (Öhberg & Alfredson, 2004). A recent study has demonstrated that site of maximal pain, tenderness on palpation, maximal tendon thickness and neovascularisation are anatomically associated. In a study of 29 painful Achilles tendons, Divani et al (2010) identified a significant association between clinically determined pain and neovascularisation ($r = 0.85, p < 0.001$), patient reported pain ($r = 0.91; p < 0.001$), maximal tendon thickness ($r = 0.91; p < 0.001$) and maximal thickness and maximal neovascularisation ($r = 0.86; p < 0.001$).
Accompanying the ingrowth of blood vessels into the Achilles tendon are a substantial amount of sympathetic and sensory nerve fibres (Andersson et al., 2007(a), 2008; Danielson et al., 2008). In pathological situations, an interaction between the sympathetic nerves and the sensory afferents leading to the release of noradrenaline from the sympathetic terminals, is postulated to occur (Danielson et al., 2007). This affects the adrenergic receptors on the sensory nerves that are present, resulting in nociceptive signals. Therefore, it would appear that neovascularisation, in the presence of sympathetic nerve fibres, may play a significant role in the manifestation of pain in tendinopathy.

Eradication of the neovessels, and therefore the accompanying nerve fibres, through a variety of different interventions (discussed in section 2.6) is generally associated with positive outcomes (Alfredson & Öhberg, 2005; Cook, Malliaras, De Luca, Ptasznik, & Morris, 2005; Maquirriain, Ayerza, Costa-Paz, & Muscolo, 2002; Öhberg & Alfredson, 2004; Peers & Lysens, 2005; Steenstra & van Dijk, 2006; van Sterkenburg & van Dijk, 2011).

However, there is no established technique for quantitatively measuring neovascularisation in tendons, and there have been substantial discrepancies among reports on the occurrence of neovascularisation in symptomatic tendons. Some authors have demonstrated no association between neovascularisation and pain in symptomatic AT. For example, Zanetti (2003) identified that only 54% (n = 55) of symptomatic Achilles tendons exhibited neovascularisation on power doppler ultrasound. Khan (2003) demonstrated that only 63% (n = 55) of symptomatic Achilles tendons exhibited neovascularisation on ultrasound and MRI imaging, indicating that the source of pain must be emanating from a different structure. The reason for the discrepancy is not known, but it may be a combination of a number of factors. Most studies that have investigated the presence of neovascularisation as an outcome variable are heterogeneous in their methodology, using different outcome measures to assess pain and function, and investigating neovascularisation using different imaging tools. Furthermore, as previously mentioned, there is no established technique to assess neovascularisation. These factors are likely to confound results, thus making it difficult to establish the prevalence of neovascularisation in symptomatic AT. Information concerning neovascularisation is important when deciding on a treatment intervention, especially considering that many of the current treatment approaches are focused on influencing neovascular activity.
2.5.2 Biochemical changes

As mentioned previously (section 3.4.5), it is not known whether all the biochemical changes observed in tendinopathy are a causative factor, or a consequence of, tendinopathy, although it must be mentioned that some changes are a response to loading or underuse, which subsequently signal degeneration.

The number of nociceptive SP and calcitonin gene related peptide (CGRP, which can function as a vasodilator) positive nerve fibres are significantly increased in chronic tendinopathy (Forsgren et al., 2009; Öhberg, Lorentzon, & Alfredson, 2001; Schubert et al., 2005). In nociception, CGRP augments the effects of SP (Schubert et al., 2005), increasing the nociceptive signal. Due to the lack of blood vessels in the tendon proper, it is also postulated that neurogenic inflammation occurs in an effort to repair damaged tissue (van Sterkenburg & van Dijk, 2011). Interestingly, painful neurogenic inflammation is mediated through SP and CGRP, providing further evidence that these elevated neuropeptides may have a significant role to play in mechanism of pain. However, this alone does not explain the mechanism of pain as non-symptomatic tendons have demonstrated similar histopathological changes (Gaida et al., 2012; van Sterkenburg & van Dijk, 2011).

Elevated levels of glutamate (Alfredson, Ljung, Thorsen, & Lorentzon, 2000; Alfredson & Öhberg, 2005; Alfredson, Thorsen, & Lorentzon, 1999) and glutamate receptors (Schizas et al., 2012) have been observed in tendinopathic tissue. An early study demonstrated that a significant drop in mean pain scores following an exercise intervention for symptomatic AT was not associated with a change in levels of glutamate. Therefore, the authors concluded, glutamate must not play a role in pain generation in tendinopathy (Alfredson et al., 2003). However, the glutamate receptors NMDAR1 or, as its activated form is known, phosphor-NMDAR1, were not measured. The role of glutamate receptors in the pathogenesis of bone and joint disorders and the development and maintenance of chronic pain in conditions such as rheumatoid arthritis are well established (Hinoi & Yoneda, 2011). A recent study that analysed immunohistochemical differences between symptomatic patella tendons and healthy controls identified that glutamate receptors NMDAR1 and its activated form phosphor-NMDAR1, together with SP were present in both the symptomatic tendons and healthy controls. However, tendinopathic samples exhibited significantly increased levels of glutamate receptors NMDAR1, phosphor-NMDAR1 and SP compared to healthy controls (p=0.03; p=0.23 and p=0.04 respectively) (Schizas et al., 2012). Therefore, the authors
hypothesised that the pathogenesis of tendinopathy may be related to the up-regulation of SP co-existing with glutamate receptors NMDAR1 and phosphor-NMDAR1, similar to changes observed in rheumatoid and osteoarthritis. Furthermore, it has been speculated that as glutamate is itself a weak vasodilator, it may in some instances be involved in stimulating neovascularisation, thus contributing further to the experience of pain in tendinopathy (Alfredson & Öhberg, 2005).

Up-regulation of TNFR1 in the tenocytes of pathological Achilles tendons results increased signalling for inflammatory responses and cell apoptosis, which may contribute to the mechanisms of pain in AT (Gaida et al., 2012).

### 2.5.3 Extra-tendinous biomechanical factors

Interestingly, invaginated plantaris tendons on the medial aspect of the Achilles tendon have been demonstrated in a recent study (Alfredson, 2011(b); Spang et al., 2013). Histopathologically, the plantaris tendons demonstrated typical degenerative changes, and release of the tendon resulted in relief of Achilles tendon symptoms (Alfredson, 2011(b)), indicating that plantaris tendon may be a source of symptom in in individuals with medial AT pain. Further to this, it has also been demonstrated that the plantaris tendon is stiffer and stronger than the Achilles tendon (Lintz et al., 2011). As this tendon is located very close to the Achilles tendon, theoretically, it may compress it, tethering the AT and/or initiating an inflammatory response (Lintz et al., 2011; Spang et al., 2013). However, the plantaris tendons described were harvested from only six cadavers, and it was not reported if the cadavers used had a past history of AT, or whether or not they had previously been symptomatic. Authors concluded that results may implicate the plantaris tendon as a biomechanical factor that may contribute to symptoms of AT, but neither of these finding were evident in the Achilles tendons that were harvested together with the plantaris tendons in this study. More research in this area is need before further speculation can be made.

### 2.5.4 Summary

In summary, the aetiology of pain in AT is not understood. From the theories that have been presented it would appear that the aetiology is multifactorial and could potentially arise from changes in structures surrounding the Achilles tendon. It is not known whether the
biochemical changes described in the above section, and section 2.4.3 are a result of, or causative factors, contributing to AT. It would appear that the pathogenesis of AT and the mechanism of pain might be linked. It would also appear that the pathogenesis of pain might involve not only the presence of biochemical changes, but also the presence of sympathetic changes potentially in the form of the ingrowth sympathetic nerve fibres that have been identified in recent studies.

2.6 Treatment options

Although the pathogenesis and aetiology of AT are not completely clear, there is a general agreement that there is a failure of the healing/remodelling response in symptomatic tendons. A variety of different treatment options are available that attempt to restore this process and see it to conclusion. These include injection therapies, electrotherapy modalities and eccentric exercises. However, some of these approaches lack scientific evidence (Jonsson, Alfredson, Sunding, Fahlström, & Cook, 2008), and others have provided mixed results (Andres & Murrell, 2008; McLauchlan & Handoll, 2001; Tumilty, 2010). The current feasibility trial (Chapter 5) focuses on an eccentric exercise regime. Therefore, the following section will outline the main findings in the injection and electrotherapy approaches, while the eccentric exercise regime will be explained in more detail.

2.6.1 Injection therapies

Various injection therapies that include injecting corticosteroids, platelet rich plasma and sclerosant injections therapies, to name a few, have demonstrated mixed results. Cortisone injections have received the most attention in the literature. Over the past decade, the use of corticosteroid injections has become less popular (Rees et al., 2013). In elbow tendinopathies (i.e. lateral epicondylitis) and AT they have demonstrated effectiveness in reducing pain and swelling in the short term (Bisset, Paungmali, Vicenzino, & Beller, 2005; Capasso, Testa, Maffulli, & Bifulco, 1997; Fredberg & Ostgaard, 2009; Rees et al., 2013). Studies have shown that they provide short-term relief, but no long-term benefit (Gill, Gelbke, Mattson, Anderson, & Hurwitz, 2004; Jones et al., 2006; Kleinman & Gross, 1983). A Cochrane review on the efficacy of cortisone injection for rotator cuff disease has demonstrated short-
term benefits over placebo (Buchbinder et al., 2006). In instances of severe pain it would appear that cortisone injections might have an important role for short-term relief of pain.

Platelet rich plasma injections, although demonstrated to be effective in the reduction of pain in lateral epicondylia (Michna & Hartmann, 1989) have been found to be of no additional benefit in the treatment of AT (de Vos et al., 2010). Injection of sclerosants such as polidocanol outside the tendon, into the blood vessels, has demonstrated promising results (Alfredson & Öhberg, 2005; Lind, Öhberg, & Alfredson, 2006). Although sclerosant therapy has been criticised as it often requires multiple injection treatments with between six and eight weeks in-between each injection (Alfredson, 2011(a)).

**2.6.2 Electrotherapy modalities**

Electrotherapy modalities include extracorporeal shockwave therapy (ESWT), low level laser therapy (LLL) and ultrasound therapy (US). ESWT has been demonstrated mixed results. Costa et al (2005) did not identify any clinical improvement following ESWT treatment. Rompe, Furia and Maffulli (2008) demonstrated improvements in pain following ESWT, compared to a program of eccentric exercises, although in a subsequent study they concluded that a combination approach i.e. ESWT combined with an eccentric exercise program, provided the best results (Rompe, Furia and Maffulli 2009). More studies are necessary before a conclusion can be drawn on the efficacy of ESWT in the treatment of AT.

Results from six RCTs that have investigated the effect of LLLT on Achilles tendon healing, have demonstrated mixed results (Bjordal et al., 2008; Darre et al., 1994; Meier & Kerkour, 1988; Stergioulas, Stergioula, Aarskog, Lopes-Martins, & Bjordal, 2008; Tumilty et al., 2008; Tumilty et al., 2010). However, a recent systematic review with meta-analysis has demonstrated favourable outcomes when treatment parameters recommended by the World Association of Laser Therapy (WALT) are followed (Tumilty et al., 2008). Finally, there is no evidence for the use of US therapy in the treatment of Achilles tendon pain (Jonsson et al., 2008; Robertson & Baker, 2001).
2.6.3 Strength training

Loading of the Achilles tendon and muscles that contribute to its formation has a positive influence on collagen alignment (Kannus et al., 2002). In the treatment of AT, eccentric exercises appear to be of more benefit than concentric exercise (Jonsson, 2009; Mafi, Lorentzon, & Alfredson, 2001), and are frequently considered the gold standard intervention for this condition. This Masters thesis focuses on eccentric exercises; therefore the following section will focus on eccentric exercises.

Curwin and Standish were the first to prescribe a program of eccentric exercises for the treatment of tendinopathy (Curwin & Stanish, 1984). They recommended that patients progress to a moderate load, and gradually increase the speed with which the exercise was preformed (Curwin & Stanish, 1984). In the decade that followed, Alfredson et al (1998) built on their protocol, with a number of distinguishing features. In contrast with recommendations made by Curwin and Standish (1984), Alfredson et al (1998) recommended that patients with AT should focus on loading the tendon into pain, while standing on the affected leg, under a controlled speed. It was recommended this regime be carried out twice daily, seven days a week for a period of 12-weeks (Appendix C).

Systematic reviews have demonstrated that the heavy-load eccentric exercise regime is effective in reducing symptoms of AT and facilitating a return to physical activity (Kingma, de Knikker, Wittink, & Takken, 2007; Magnussen, Dunn, & Thomson, 2009) they are, nonetheless, generally very positive outcomes. Although later studies have not reported the very high success rates that were originally reported by Alfredson et al (1998). A number of studies have assessed the long-term (greater than three years) effects of the eccentric exercise regime, which also demonstrates promising results (de Jonge et al., 2010; Gärdin, Movin, Svensson, & Shalabi, 2010; Öhberg & Alfredson, 2004; Van der Plas et al., 2012). However, it must be noted that participants were generally free to receive other interventions during the long-term follow-up period (mean of five years). Therefore, it is not clear if the improvements are a direct result of the eccentric exercise regime, a result of another intervention (which is not documented sufficiently to form an opinion in the above studies) or a regression towards the mean during the follow-up period. Finally, debate remains over a clinically effective dose for these exercises. In a recent review Meyer et al (2009) found that due to insufficient reporting on compliance data it has not been possible to establish the optimum dose, frequency and duration to carry out the eccentric exercise regime. Nonetheless, the Alfredson
et al (1998) protocol for the heavy-load eccentric exercise regime (Appendix C) has been widely used with positive clinical results.

The scientific mechanism responsible for the reduction in pain and return to function following a protocol of eccentric exercises is not clear. Eradication of neovessels, improved collagen synthesis and reduced hysteresis are among the theories. Alfredson and Öhberg (2005) have postulated that the high dose of eccentric exercises, on a frequent basis may be sufficient to damage, injure or destroy the neovessels. Langberg (2001) demonstrated an increase in collagen synthesis correlated with a decrease in pain, following the eccentric exercise regime in injured tendons, potentially explaining their effect. Heavy load exercise has also been demonstrated increase the diameter and tensile strength of tendons, while decreasing collagen maturation (Kjaer, 2004; Langberg et al., 2001; Michna & Hartmann, 1989). However, the relationship between the magnitude of exercise and rate of collagen synthesis is not known. Kubo et al (2002) have demonstrated that stretching exercises performed in weight bearing reduces hysteresis and therefore the heating effect on the tendon, summarised by Tumilty (2010). This is of importance as temperatures above 42.5°C have been shown to cause apoptosis (Birch, Wilson, & Goodship, 1997), and lead to increased levels of inflammatory cytokines (Hosaka et al., 2006).

In conclusion, the mechanism behind the beneficial effects of eccentric exercises is not entirely clear. Most authors agree that eccentric exercises result in positive outcomes for the treatment on AT. However, there is debate and confusion over the optimum dose, frequency and duration of this regime (Meyer et al., 2009).

2.7 Summary

For the purpose of this thesis the term AT is defined as chronic (i.e. greater than three months) mid-portion Achilles tendon pain combined with diminished physical performance, and degenerative and inflammatory changes identified through histopathological, immunochemical or gene expression analyses. For the purpose of the feasibility trial that follows (Chapter 5), AT will be diagnosed clinically without the use of imaging to confirm the diagnosis.

There are a number of theories that attempt to explain the pathogenesis, and mechanism of pain, in AT. These factors appear to be interwoven. It is difficult to assess their individual
Contribution to the pathogenesis, and mechanism of pain, in AT, but it is postulated that a combination of these biochemical changes (in response to overuse or underuse) affects the structural integrity and vascularity of the tendon proper, perpetuating the condition. The variety of interventions available to treat this condition reflects the lack of understanding regarding its pathogenesis. Systematic reviews have confirmed that an eccentric exercise regime has a positive effect on pain and functional outcomes.
3 Manipulation and it’s influence on the autonomic nervous system
3.1 Overview of this Chapter

This chapter provides an overview of MT and the nervous system (NS). It provides a definition of terms that will be used throughout this thesis, and establishes the contextual background for the current pilot study. An explorative literature search on studies that have investigated the effect of spinal manipulation on the ANS is completed. This information is important as it highlights what is already known about the effect of spinal manipulation on ANS activity. Deficiencies in current research will be addressed in the pilot study that follows in Chapter 5.

3.2 Overview of manual therapy

3.2.1 Origins of manual therapy

It is clear from early reports that MT is an ancient, and well-established health care intervention. Traditionally, it has been used to exorcise spirits or demons, treat spinal deformities, and relieve pain, weakness and/or stiffness in the body. Soft tissue massage and manipulation of the peripheral and spinal joints are some of the oldest remedies known to man. During the time of Hippocrates (460 BC), spinal deformities were treated with MT techniques such as traction (Pettman, 2007). An Iranian physician, Abu’ Ali Ibn Sina (960-1037 AD), progressed many of the techniques used by Hippocrates by combining them with direct pressure on the spine (Pettman, 2007); these are perhaps the earliest documented form of spinal mobilisations as they are known today.

Today there are a wide variety of manual therapists adhering to different professional regulating bodies. In terms of clinical MT, the work of physiotherapists, osteopaths, and chiropractors frequently overlap. Clinicians within these fields utilise similar treatment techniques, although the language used to document them varies; the contrary is also true. This can be confusing when reading about MT, as different professionals frequently use the same technical terms, but infer a different MT technique: the commonly used term manipulation is sometimes used to describe very different techniques. It is therefore critical to clarify the definition of the terms spinal mobilisation and manipulation for the context of this thesis.
3.2.2 Definitions of manual therapy techniques

The term spinal mobilisation refers to passive, oscillatory movements applied to a spinal segment, which move it to the end of its available range (Maitland et al., 2005). The terms spinal mobilisation and mobilisation are used interchangeably throughout this thesis.

As previously shortened (Chapter 1), the term HVLAT manipulation refers to all forms of thrust manipulation performed on the spine that passively extend the joints beyond their natural range (Bronfort et al., 2004). For the purpose of this thesis the term manipulation or spinal manipulation infers a HVLAT manipulation applied to the spine.

As previously stated, a manipulation technique is considered to be technically similar to a mobilisation technique, and therefore it is considered they might have a similar effect on the ANS. It is acknowledge that in the clinical setting there might be a variety of opinions on the topic of whether or not a HVLAT technique is a progression of a mobilisation technique. However for the purpose of this thesis a HVLAT is considered a progression of a mobilisation technique (Bronfort et al, 2004)).

3.3 The nervous system

3.3.1 Overview of the nervous system

The NS is categorised into the central nervous system (CNS) and the peripheral nervous system (PeNS). Although anatomically separate, these two systems often function synergistically. They are made up of specialised cells called neurons, which vary in size and shape according to their function (Palastanga, Field, & Soames, 2006). Although neurons differ structurally according to their function, there are some basic, characteristic components that are common to all neurons of the NS (Figure 3-1).
3.3.2 Central nervous system

The CNS consists of the brain, the brain stem and the spinal cord, which are protected by the skull, the vertebral column, the meninges and the blood-brain barrier (Palastanga et al., 2006). These centres integrate and co-ordinate all of the information that they receive from elsewhere in the body.

3.3.3 Peripheral nervous system

The PeNS includes all parts of the NS that lie outside the CNS (i.e. cranial nerves, spinal nerves and their branches). It consists of nerve fibres that connect the CNS to limbs and organs by transmitting sensory and motor information about the target organ, to and from the
CNS (Michael-Titus, Revest, & Shortland). Unlike the CNS, the PeNS is not protected, and is therefore vulnerable to mechanical injury (Standring, 2008).

The PeNS has two major components: the ANS and the somatic nervous system (SoNS). Some textbooks also include the sensory systems. The SoNS is involved with voluntary control of skeletal movements, while the sensory nervous systems (e.g. visual and auditory) are concerned with the processing of sensory information (Standring, 2008). Further consideration of the somatic and sensory systems is beyond the scope of this thesis.

The ANS acts primarily as an involuntary control system and is located in the medulla oblongata of the brain stem. An understanding of the two primary sub-categories in the ANS: the SNS and the parasympathetic nervous system (PNS) is important background information for this thesis. Below is a schematic representation of the PeNS (Figure 3-2).

![Figure 3-2 A schematic representation of the PeNS](image)
3.3.3.1 Sympathetic nervous system

Within the SNS there are two types of neurons, pre- and post-ganglionic neurons that transmit information between the CNS and the body. The pre-ganglionic neurons arise from the thoracolumbar region, specifically between segments T1 and L2. Connections between these two neurons (ACh is the neurotransmitter), generally occur within the para-vertebral ganglia that are located in pairs on either side of the vertebrae (Michael-Titus et al.; Palastanga et al., 2006; Standring, 2008). These fibres form the sympathetic chain (figure 3-3), which runs from the base of the skull to the coccyx.

The location of the sympathetic chain is of significant importance as it has been proposed that different forms of MT directly stimulate the sympathetic chain ganglia, thereby modulating SNS activity (discussed in Chapter 4, section 4.2.4).

![Sympathetic chain ganglia](http://quizlet.com/10440688/print)

**Figure 3-3** Sympathetic chain ganglia

*Adapted from [http://quizlet.com/10440688/print](http://quizlet.com/10440688/print)*
3.3.3.2 Parasympathetic nervous system

Similar to the SNS, the PNS also contains pre-and post-ganglionic neurons. The pre-ganglionic neurons arise from the CNS with spinal nerves S2-4 (i.e. sacral nerve 2-4) and C3; 5; 7 and10; i.e. cranial nerves (Standring, 2008). The pre- and post-ganglionic neurons generally connect at a ganglion that is either very close to or embedded in their target organ. ACh, which is the major primary neurotransmitter for all autonomic ganglia, is released when these two neurons meet.

3.4 Effect of manipulation on the Autonomic Nervous System

3.4.1 Overview

There are two distinct literature searches included in this thesis: one on the effect of spinal mobilisation on the SNS, and one on the effect of spinal manipulation on the ANS (i.e. SNS and/or PNS changes). A systematic review on the former is presented in Chapter 4. A summary of the latter is presented below.

It should be emphasised that although there are a number of published studies that investigate the effect of manipulation on the ANS, there are very few studies that have defined manipulation as it is defined for the purpose of this Masters thesis. The studies included in the following review have defined manipulation as it has been defined for the purpose of this thesis (please refer to section 3.2.2 for definition).

3.4.2 Effect of manipulation on the Autonomic Nervous System

Data from studies that have investigated this topic have been summarised in Table 2-1 below. The following is not a systematic review, but a summary of findings from a literature search. The electronic databases Ovid Medline, Embase, AMED, PEDro and the Cochrane library were all searched from inception to May 2012. In addition, reference lists from appropriate papers were also searched. As emphasised below, methodological procedures in the following studies are heterogeneous, and in general, have been poorly described making it difficult to comment on (or critique) the procedures undertaken.

The majority of clinical trials (only one of which was a randomised controlled trial; RCT) that investigated the effect of manipulation on the ANS have demonstrated that manipulation
influences ANS activity (Gibbons, Gosling, & Holmes, 2000; Harris & Wagnon, 1987; Kappler & Kelso, 1984; Teodorczyk-Injeyan, Injeyan, & Ruegg, 2006; Welch & Boone, 2008). However, recent findings by Sillevis, Cleland, Hellman and Beekhuizen (2010) and Puhl and Injeyan (2012) challenge these results. Changes in physiological responses that are generally under the control of the ANS, have been demonstrated in four (Gibbons et al., 2000; Harris & Wagnon, 1987; Kappler & Kelso, 1984; Welch & Boone, 2008) of the six studies that have been identified, the remaining two studies (Puhl & Injeyan, 2012; Sillevis et al., 2010) demonstrated no change in ANS activity following manipulation. Although the majority of studies support a change in ANS activity, it is noted that the two studies that contradict these findings are high quality RCTs and therefore considered to be a higher level of evidence compared to the clinical trials that demonstrated changes in ANS activity following manipulation.

In total there were two studies that focused on changes in distal skin temperature (Harris & Wagnon, 1987; Kappler & Kelso, 1984), that demonstrated somewhat mixed results. Harris and Wagnon (1987) assessed 197 healthy participants for their study, and identified a significant difference in changes in skin temperature that was dependent on the area of the spine manipulated. Manipulation of the thoracic and upper lumbar region (specifically between T1-L2) resulted in a significant decrease in skin temperature (p<0.001), and conversely manipulation of the lower lumbar spine or cervical spine (specifically L4/5 and between C1-C7) resulted in a significant increase in skin temperature (p<0.001). The authors proposed that the anatomical proximity of the sympathetic nerve fibres accounted for the changes in SNS activity following manipulation of the thoracic spine; while the proximity of parasympathetic nerve fibres emanating from cervical and sacral segments accounted for changes consistent with PNS activity (Harris & Wagnon, 1987). This has been coined the theory of ‘regional bias’, i.e. the region of the spine manipulated modulates a specific ANS response. However, there has been little scientific research into this topic, and it is beyond the scope of this Masters thesis to investigate it further.

Kappler and Kelso (1984) demonstrated changes in skin temperature in six of the 15 symptomatic participants in their trial. Changes in skin temperature were consistent with an increase in PNS activity following manipulation of the thoracic spine (i.e. an increase in skin temperature). However, the authors did not report by how much the temperature increased, therefore it is not possible to deduce whether or not the changes were significant. Also, information on participants that did not experience changes in skin temperature was not
provided, and therefore it is difficult to postulate on the possible mechanisms responsible for these differences.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Participants</th>
<th>Intervention</th>
<th>Control/Comparator</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kappler and Kelso, 1984</td>
<td>15 symptomatic (male and female) participants</td>
<td>Manipulation applied to thoracic spine (between T2-T5, depending on hypomobile segment)</td>
<td>No</td>
<td>Skin temperature measured on dorsum of hand, upper back and entire spine</td>
<td>Segmental increase in skin temp for 6 participants (amount of change not reported)</td>
</tr>
<tr>
<td>Harris and Wagnon, 1984</td>
<td>196 non-symptomatic (male and female) participants</td>
<td>Manipulation applied to spine (therapists discretion i.e. cervical, thoracic or lumbar spine manipulated depending on clinical findings of biomechanical dysfunction)</td>
<td>Not clear</td>
<td>Skin temperature measured at finger tips</td>
<td>Manipulation applied between T1-L3, significant decrease skin temperature (p=0.001) (i.e. SNS excitation). Manipulation applied to C1-C7; L4/5 demonstrated significant increase in skin temperature (i.e. PNS excitation)</td>
</tr>
<tr>
<td>Gibbons, Gosling and Holmes, 2006</td>
<td>13 healthy (male) participants</td>
<td>Manipulation applied to cervical spine segments C1/2</td>
<td>No</td>
<td>Edge light pupil cycle time (ELPCT) reflex</td>
<td>Significant (p=0.002) difference in ELPCT reflex before and after manipulation</td>
</tr>
<tr>
<td>Teodorczyk-Injeyan, Injeyan and Ruegg, 2006</td>
<td>64 healthy (male and female) participants</td>
<td>Manipulation applied between T1-6 (therapist manipulated hypomobile segment)</td>
<td>Venepuncture procedure Sham manipulation procedure</td>
<td>Blood and serum levels of tumour necrosis factor-α (TNF-α), interleukin-1Beta (IL-1β) and substance P (SP)</td>
<td>Venepuncture and sham group demonstrated increase in TNF-alpha and IL-Beta following intervention. Manipulation group demonstrated a decrease in TNF-alpha and IL-1Beta following manipulation.</td>
</tr>
<tr>
<td>Welch and Boone, 2008</td>
<td>40 healthy (male and female) participants</td>
<td>Manipulation applied to the cervical and thoracic spine (therapist manipulated hypomobile segments on assessment)</td>
<td>No</td>
<td>Blood pressure and pulse rate Heart rate variability measured for 7 participants</td>
<td>Diastolic BP dropped significantly (p=0.38), and PR increased significantly (p=0.044) in participants receiving cervical manipulation. Non-significant decrease in PR following thoracic spine manipulation</td>
</tr>
<tr>
<td>Sillevis, Cleland, Hellman and Beekhuizen, 2010</td>
<td>100 symptomatic (male and female) participants</td>
<td>Manipulation applied to T3/4 segment only</td>
<td>Placebo group</td>
<td>Pupil diameter Visual analogue of pain (VAS) score</td>
<td>No changes in pupil diameter following manipulation No significant differences in VAS scores between groups</td>
</tr>
<tr>
<td>Puhl and Injeyan, 2012</td>
<td>38 healthy (male and female) participants</td>
<td>Manipulation applied between T1-6 (therapist manipulated hypomobile segment)</td>
<td>Sham manipulation procedure</td>
<td>Blood plasma concentrations of norepinephrine (NE) and epinephrine (E)</td>
<td>No measurable effect on plasma concentrations of E and NE</td>
</tr>
</tbody>
</table>

Table 3-1 Data extraction sheet
Methodologic procedures were not described in sufficient detail to enable judgment to be made on the internal or external validity (i.e. the reliability that the study answered what it intended to answer and also the extent to which the tests in each study measured what they intended to measure) of either of the above studies. Furthermore, neither study included a control or sham intervention group. In summary, the results of the above studies are heterogeneous, but overall they appear to suggest that manipulation results in changes in ANS activity.

Other studies have demonstrated significant changes in pulse rate (PR), blood pressure (BP) and the edge light pupil cycle time (ELPCT) reflex (p=0.044; p=0.380 and p=0.002 respectively), a reflex under the exclusive control of the ANS, following spinal manipulation (Gibbons et al., 2000; Welch & Boone, 2008).

Welch and Boone (2008) assessed 40 healthy volunteers and manipulated hypomobile segments in their cervical and thoracic spines. Changes in PR and BP immediately before and 15 minutes after spinal manipulation were recorded. The results demonstrated a significant decrease in diastolic BP following cervical spine manipulation together with a significant increase in PR, indicative of PNS activation. In contrast, a substantial decrease in PR following manipulation of the thoracic spine was also observed. This is indicative of SNS excitation, however, this change was not statistically significant. There was no comparator group in the above study, and the lack of methodological reporting has meant that it is not possible to identify how many spinal segments, and specifically which segments, were manipulated. Although this deficiency in reporting means that the trial is not reproducible, it nonetheless identified significant changes in ANS activity following manipulation of the cervical spine.

Gibbons, Gosling and Homes (2000) have demonstrated a significant change in the ELPCT (see above) reflex immediately following manipulation to the cervical spine (specifically C1/2). The reflex was found to be significantly (p=0.002) faster following manipulation of C1/2. ELPCT is one of the eyes light reflexes, which remains unaffected by visual acuity, refractive error, eye colour, pupil size or gender, and is under the direct control of sympathetic and parasympathetic branches of the ANS (Gibbons et al., 2000). These results demonstrate a distal physiological response to manipulation. Each of the above studies, although they have measured varying physiological responses of the ANS, support changes in ANS activity following spinal manipulation.
In contrast to the above findings, Sillevis, Cleland, Hellman and Beckhuizen (2010) and Puhl and Injeyan (2012) have demonstrated no change in ANS activity following manipulation of the spine. Sillevis et al (2010) measured changes in pupil diameter between 2 groups: a manipulation group (n=50), and a sham manipulation group (n=50), as an indicator of ANS activity (Sillevis et al., 2010). The pupil is innervated exclusively by the ANS. PNS activity facilitates constriction of the pupil and SNS activity facilitates dilation of the pupil. Thus, the balance between SNS and PNS activity determines the pupil’s diameter. It was assessed continuously for 60 seconds immediately before directly following the manipulation or sham manipulation intervention. Results demonstrated no significant changes in pupil diameter in the manipulation group.

Changes in blood plasma concentrations of norepinephrine (NE) and epinephrine (E) have also been used to assess for changes in SNS activity (Puhl & Injeyan, 2012). Circulating levels of NE and E are an accepted method of measuring the overall sympathetic and adrenal activity of the body (Grassi & Esler, 1999; Oeltmann, Carson, Shannon, Ketch, & Robertson, 2004). The results of this well executed study demonstrated no measurable change in blood plasma levels of NE and E after manipulation, within the manipulation group. These two latter studies (Puhl & Injeyan, 2012; Sillevis et al., 2010) contradict the findings of earlier research and highlight the need for more scientific research on this topic.

### 3.5 Summary

The effects of spinal manipulation on the ANS have not been fully elucidated. Studies have identified a variety of responses. Only two studies (Kappler & Kelso, 1984; Sillevis et al., 2010) have been carried out on the patient (i.e. symptomatic) population. One of these studies demonstrated a change in ANS activity (Kappler & Kelso, 1984), in contrast to the more recent study that demonstrated no change (Sillevis et al., 2010). Similarly, the majority of studies that have assessed for changes in ANS activity in the healthy (i.e. non-symptomatic) population have demonstrated a variety of ANS responses. These studies are heterogeneous in their methodology and some are inadequately reported, making it difficult to draw a definitive conclusion. In the past four years (i.e. between 2008 and 2012), there have been only two (published) studies that have been identified on this topic. Considering the recent findings of a change in SNS activity that may be associated with the mechanism of pain in AT, it is of interest to manual therapists to establish the effect that spinal manipulation might have on the ANS.
In conclusion, further clarification on this topic is necessary. From published studies it would appear that manipulation has a varied effect on both the patient and healthy population.

Chapter 4 offers a systematic review of the effect of spinal mobilisations on the SNS. These recent studies are of a high quality and it is anticipated the results of the systematic review might contribute towards a better understanding of the potential effects that manipulation might have on ANS activity.
4 Systematic Review
4.1 Overview of this chapter
As discussed in Chapter 3 (refer to section 3.4.2 and 3.4.3), studies investigating the effect of manipulation on the ANS use varying methodologies, and some lack sufficient detail to allow for a complete evaluation of the study procedure. Therefore it is difficult to compare and evaluate these studies. Given the above limitations of the above studies it was considered more appropriate to include them in a literature review, and focus the systematic review on higher quality, more clearly defined studies. The following section contains a systematic review of the effect of spinal mobilisation on the SNS. It is hoped that information gathered from these studies might better inform the manual therapist of the potential of a manipulation technique, as technically a manipulation is considered a progression of a mobilisation (refer to section 3.2.2). This chapter contains a systematic review of the effect of spinal mobilisations on SNS outcome measures. To better inform clinical decision making the literature is evaluated and the clinical implications of spinal mobilisation are highlighted in terms of its effect on the SNS.

4.2 A systematic review investigating the effects of spinal mobilisations on the Sympathetic Nervous System

4.2.1 Introduction
As discussed in chapter 3, the term spinal mobilisation and the term mobilisation alone describe passive, oscillatory movements applied to the spine (Maitland et al., 2005). The terms HVLAT manipulation, spinal manipulation or manipulation alone all infer the same technique on the spine that passively extend the joints beyond their natural range (Bronfort et al., 2004).

Gate-control mechanisms (Melzack & Wall, 1967) together with other biomechanical effects (Evans, 2002) formed early hypotheses on the mechanisms of pain relief and beneficial effect following MT intervention. However, recent studies have reported a multi-system neurophysiological response that involves excitation of the SNS (McGuiness, Vicenzino, & Wright, 1997; Sterling, Jull, & Wright, 2001; Wright, 1995). The activity of the SNS is of fundamental importance to all manual therapists since the experience of pain is closely linked to sympathetic activity (Petersen, Vicenzino, & Wright, 1993). Specifically, diminished pressure pain thresholds have been consistently demonstrated, in healthy and patient
populations, together with SNS excitation, following different forms of MT (Cleland, Durall, & Scott, 2002(a); Cleland & McRae, 2002(b); McGuiness et al., 1997; Sterling et al., 2001).

The aim of this systematic review is to evaluate RCTs that investigated the effects of spinal mobilisations on SNS outcome measures, in the healthy and patient populations. The second aim of this review is to establish the level of evidence (Heymans, Van Tulder, Esmail, Bombardier, & Koes, 2004) for a change, either excitatory or inhibitory, in SNS outcome measures. The level of evidence for specific outcome measures is important as it will guide not only clinical decision making, but will also highlight some of the outcome measures that could be used in future research investigating the SNS response to different forms of MT. The choice of outcome measures used in the pilot study (refer to Chapter 5) will be informed by the results of this review.

4.2.2 Methods

This systematic review has been completed in accordance with internationally recommended guidance: the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) (www.prisma-statement.org).

4.2.2.1 Literature search

The following electronic databases were searched for eligible trials (from database inception to May 2012): Ovid Medline, Embase, AMED, PEDro and the Cochrane library. Reference lists were also examined to identify any articles not captured in the electronic database search. Please see appendix D for an example of the search strategy used.

The search was restricted to RCTs conducted on humans and reported in English language. Only published material was included in the literature search.

4.2.2.2 Eligibility criteria

RCTs that investigated at least one sympathetic outcome measure during or immediately following spinal mobilisation were included. Spinal mobilisations were accepted in the form of passive accessory movements (Schmid, Brunner, Wright, & Bachmann, 2008). The control interventions considered acceptable were: no treatment, and/or placebo intervention. Both male and female volunteers between the ages of 18-65 years, in either a healthy or symptomatic population were considered eligible.
Investigations involving mobilisations with movement (MWMs), and HVLA thrust manipulations were excluded from this review to avoid grouping the effects of different MT techniques together.

4.2.2.3 Selection of studies
Potentially relevant articles were obtained in full text, and screened independently by two authors for inclusion and exclusion criteria.

4.2.2.4 Data extraction
Two authors independently extracted data from the studies, using a standardised form (Table 4-1). Inconsistencies were resolved by discussion between the two authors. Corresponding authors listed on the included articles were contacted for primary data to complete a meta-analysis, however the study data were not available and therefore it was not possible to carry out a meta-analysis.
4.2.2.5 RCT rating

The Cochrane Collaboration’s recommended tool for assessing risk of bias (RoB) was included in this review (Alderson, Green, & Higgins, 2004). The RoB assessment tool incorporates six primary sources for bias, and was used independently by two authors to classify the risk of bias in each study as a “high risk”, ‘low risk” or “unclear risk”. Differences in opinions were discussed and an agreement on judgments reached; it was not necessary to consult with the third author. Refer to Table 4-2 for an overview of these judgments.

PEDro, which is the Physiotherapy Evidence Database, contains randomised trials, systematic reviews and clinical practice guidelines in physiotherapy. The PEDro rating scale is an 11-point rating scale used to help individuals quickly assess the internal validity (criteria 2-9) and statistical interpretability of results from a trial (criteria 10-11). A score of 6 or above is considered a high-quality trial, while a score of below 6 is considered a low-quality trial (Grävare Silbernagel, Thomee, Thomee, & Karlsson, 2001; Martinez-Silvestrini et al., 2005; Roos, Engström, Lagerquist, & Söderberg, 2004). The maximum score achievable on the PEDro scale is 10/10; as the first criterion, which assesses the external validity of a trial, is not included in the final score (Appendix E). Each study was independently rated on this scale by two authors; disagreements were resolved by discussion and an agreement was reached for differing scores (Table 4-3).

Results of combined studies were also summarised using a best-evidence synthesis (Heymans et al., 2004). The level of evidence for specific SNS outcome measures was ranked according to the following criteria:

- “Strong” evidence: generally consistent findings in multiple high-quality RCTs.
- “Moderate” evidence: generally consistent findings in one high-quality RCT, plus one or more low-quality RCTs, or by generally consistent findings in multiple low-quality RCTs.
- “Limited” or “conflicting” evidence: only one RCT (either high or low quality) or inconsistent findings in multiple RCTs.
4.2.3 Results

4.2.3.1 Search strategy
The combined database search in MEDLINE, AMED and Embase yielded six RCTs eligible for inclusion in this review. Searches in PEDro and the Cochrane Controlled Trials register did not add any further articles. Searching the reference lists of key articles yielded a further two articles (McGuiness et al., 1997; Petersen et al., 1993) that were eligible for inclusion, and were not captured in the electronic search. Please refer to Figure 4-1 for a flow diagram of the study selection.

Figure 4-1 Study selection flow chart
4.2.3.2 Study characteristics

There were five studies that were crossover design, on a healthy population, that compared the intervention to both a placebo and a control condition. Two studies were conducted on a patient population (Sterling et al., 2001). Six of the eight studies included in this review applied spinal mobilisation to the cervical spine (Chiu & Wright, 1996; McGuiness et al., 1997; Petersen et al., 1993; Sterling et al., 2001; Vicenzino, Cartwright, Collins, & Wright, 1998(a), Vicenzino, Collins, Benson and Wright 1998(b)), one to the thoracic spine (Jowsey & Perry., 2010) and one applied the mobilisation to the lumbar spine (Perry and Green., 2008). All studies measured changes in sympathetic output during and/or immediately following each intervention using sympathetic outcome measures. Please review table 4-1 (data extraction sheet) for a summary of the study characteristics/

4.2.3.3 Synthesis of results

All studies ranked high on the PEDro rating scale, and are detailed in Table 4-2. Six of the eight studies reviewed did not provide adequate explanations of allocation concealment. Therefore, a judgment regarding the risk of bias that this procedure might have introduced could not be reached. Furthermore, the risk of attrition bias, and random sequence generation bias, could not be assessed from the information provided, in five and four of the studies respectively. Refer to Table 4-3 for a breakdown of the RoB judgements.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Participants</th>
<th>Intervention</th>
<th>Control/Comparator</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petersen et al (1993)</td>
<td>16 Healthy (male) subjects</td>
<td>GIII central PA C5 (oscillatory technique)</td>
<td>Placebo procedure</td>
<td>Skin conductance</td>
<td>SC: Significant increase in intervention procedure compared to placebo and control procedures. An increase in the order of 50-60% during intervention steadily decreasing to that of placebo after. Placebo consistently increased in the order of 30% during the intervention and 15-20% after. ST: Significant decrease in intervention procedure compared to control (change in the order of 1%), no significant difference between placebo and intervention procedure.</td>
</tr>
<tr>
<td>Chiu and Wright (1996)</td>
<td>16 Healthy (male) subjects</td>
<td>GIII central PA C5 @ 2Hz (oscillatory technique)</td>
<td>GIII central PA C5 @ 0.5Hz Placebo</td>
<td>Skin Conductance</td>
<td>SC: Significant increase in 2Hz group compared to control and 0.5Hz. 2Hz group increased in the order of 50-60%. ST: No significant difference in ST between 3 groups.</td>
</tr>
<tr>
<td>McGuinness et al (1997)</td>
<td>23 Healthy (male &amp; female) subjects</td>
<td>GIII central PA C5 (oscillatory technique)</td>
<td>Placebo procedure</td>
<td>Respiratory rate Blood pressure Heart rate</td>
<td>Significant increases in all outcomes in intervention group compared to control and placebo procedures. RR increased in the intervention group during treatment by 44%, Diastolic BP increased by 12.5% and systolic BP increased by 4.5%. HR increased in the order of 10.5%.</td>
</tr>
<tr>
<td>Vicenzino et al (1998a)</td>
<td>24 Healthy subjects</td>
<td>GIII left lateral glide C5 (oscillatory technique)</td>
<td>Placebo procedure</td>
<td>Respiratory rate Heart rate Blood pressure</td>
<td>Significant increase in all outcomes of the intervention procedure compared to control and placebo procedures. RR increased in the intervention group 36% compared to an increase of 13% and 14% in the placebo and control group respectively. HR increased in the intervention group 13% compared to 2% and 1% in the placebo and control group respectively. BP increased in the intervention group by 14% compared to 1% in the both the placebo and</td>
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<td>Subjects Details</td>
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<tr>
<td>Vicenzino et al (1998b)</td>
<td>24 subjects (male and female) with lateral epicondylia</td>
<td>GIII lateral glide (oscillatory technique)</td>
<td>Placebo procedure Control procedure Skin conductance Skin temperature Pressure pain &amp; thermal threshold Grip strength &amp; tension test 2b</td>
<td>Significant increase in all sympathetic measures in the treatment (P&lt;.03) intervention compared to placebo and control intervention. Significant increased in pressure pain threshold, grip strength test and upper limb tension test after the treatment intervention compared to placebo or control intervention. No significant change in thermal pain threshold between groups.</td>
<td></td>
</tr>
<tr>
<td>Sterling et al 2001</td>
<td>30 subjects (male &amp; female) – cervical pain &gt; 3months and dysfunction C5/6</td>
<td>GIII unilateral PA on symptomatic side (oscillatory technique)</td>
<td>Placebo procedure Control procedure Skin conductance Skin temperature Pressure pain &amp; Thermal threshold threshold EMG; VAS</td>
<td>SC: Significant increase in intervention procedure compared to placebo and control procedure. 16% change increase from baseline in the intervention group. ST: significant decrease in intervention procedure of -1.3 to -2.5%</td>
<td></td>
</tr>
<tr>
<td>Perry and Green (2008)</td>
<td>45 healthy (male) subjects</td>
<td>GIII unilateral (left) PA L4/5 @2Hz (oscillatory technique)</td>
<td>Placebo group Control group Skin conductance</td>
<td>SC: Significant side-specific increase on ipsilateral side in the intervention group, compared to placebo and control group. 13% increase from baseline during the intervention.</td>
<td></td>
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<tr>
<td>Jowsey and Perry (2010)</td>
<td>36 healthy (male &amp; female) subjects</td>
<td>GIII rotatory mobilisation T4 @ 0.5Hz (oscillatory technique)</td>
<td>Placebo group Skin conductance</td>
<td>SC: Significant side-specific increase in the intervention group compared to the placebo group. Increase in mean percentage change of 5.74% during the intervention compared to placebo and 16.84% post intervention compared to placebo.</td>
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Table 4-I Data extraction table
<table>
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<tr>
<th>References</th>
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Table 4-2 Pedro scores
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<th>Attrition bias</th>
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</tbody>
</table>

Table 4-3 Risk of bias assessment
Primary data was not available to complete a meta-analysis; one corresponding author replied to say the data was no longer available and the other corresponding author did not respond to the email. Overall, best-evidence synthesis indicated that there was strong evidence for statistically significant changes in skin conductance (SC), respiratory rate (RR), HR, and BP among the healthy population, following spinal mobilisation (Jowsey & Perry, 2010; McGuiness et al., 1997; Perry & Green, 2008; Petersen et al., 1993; Vicenzino et al., 1998). Limited evidence for significant changes in SC and skin temperature (ST) among the symptomatic population was established (Sterling et al., 2001). All changes were excitatory in nature; i.e. there was an increase in RR, HR, BP SC, and a decrease in ST following spinal mobilisation, compared to controls and placebo intervention, indicating sympathetic up-regulation in both the healthy and symptomatic population. This was the same whether the mobilisations were applied to the cervical, thoracic, or lumbar spine.

4.2.3.4 Additional information yielded from individual studies
Chiu and Wright (1996) compared the effects of different rates of mobilisation on sympathetic outflow rather than comparing mobilisation to placebo and control. These authors found that a higher rate of mobilisation (2Hz) led to significant increase in SC compared to a lower rate (0.5Hz), and to a control condition. No significant differences in skin temperature were identified between the two intervention groups and the control group.

Perry and Green (Perry & Green, 2008) found that a unilaterally applied posterior-anterior mobilisation at 2Hz to the left L4/5 zygapophyseal joint results in side-specific peripheral SNS changes (increase in SC) in the lower limbs compared to placebo and control.

4.2.4 Discussion
The primary aim of this review was to evaluate the literature pertaining to the effects of spinal mobilisations on SNS outcome measures, in both healthy and patient populations, irrespective of segmental level. The second aim was to establish the level of evidence for a change in sympathetic outcome measures.

Each of the high-quality RCTs included in this review established a statistically significant change, consistent with sympathetic excitation, in a variety of sympathetic outcome measures. These changes were observed following spinal mobilisations, and were compared to placebo and/or control interventions. Therefore, there is compelling evidence that spinal mobilisations result in an increase in sympathetic activity, irrespective of the segment mobilised. Findings
of a consistent trend towards sympathetic excitation, irrespective of the region of the spine that received the mobilisation are in contrast to the findings of Welch and Boone (2008) and Harris and Wagnon (1987), who demonstrated a regional bias (refer to Chapter 3, section 3.4.2). This may represent a different response of the SNS to spinal mobilisations compared to manipulations. However, overall there seems to be poor support from high-quality RCTs for the theory of a regional bias. This review revealed convincing evidence that the sympathetic response to spinal mobilisations is excitatory in nature, irrespective of the level of the spine mobilised.

4.2.4.1 Context of this research

Undoubtedly, the current findings are of significant interest to all manual therapists. To establish the clinical relevance of these findings, they will be examined in the context of pain modulating theories.

It is postulated that an area of the mid brain, the lateral column of the periaqueductal gray area (IPAG) mediates the response to mobilisation that includes SNS excitation and concurrent hypoalgesia (Evans, 2002; Sterling et al., 2001; Wright, 1995), through neural descending pathways. It is speculated that mobilisation of a spinal segment stimulates receptors present in joints, capsules, tendons and connective tissues, which are capable of directly or indirectly activating IPAG mechanisms (Schmid et al., 2008). Results from studies in this systematic review have consistently demonstrated increases in sympathetic activity, such as HR and SC. Sterling et al (2001) has also demonstrated concurrent hypoalgesia, consistent with IPAG-mediated effects (Kuraishi et al., 1991; Wright, 1995).

Another indicator of a multi-system response identified by studies in this review is peripheral vasoconstriction. This is demonstrated by a significant increase in BP (McGuiness et al., 1997; Vicenzino et al., 1998) together with a significant decrease in the ST of peripheral limbs (Chiu & Wright, 1996; Petersen et al., 1993; Sterling et al., 2001). Peripheral vascular control, which directly influences BP, is modulated by the IPAG (Carrive, 1991). Considering the above observations, it could be assumed that sympato-excitation is a centrally evoked response, likely to be modulated at least in part, through IPAG pathways.

It is hypothesised that direct stimulation of the sympathetic ganglia by mobilisation of the vertebrae, is a possible mechanism for the sympathetic response (Evans, 2002). The middle and inferior cervical ganglia, which are adjacent to C6 and C7 respectively, have postganglionic axons that project to the heart (Schmid et al., 2008). A number of authors in this review (Chiu & Wright, 1996; McGuiness et al., 1997; Petersen et al., 1993; Sterling et
al., 2001; Vicenzino et al., 1998) applied spinal mobilisations to the level of C5/6, potentially activating the adjacent ganglia, which may account for the increase in HR observed (Schmid et al., 2008). Many authors have cited the potential stimulation of sympathetic fibres through spinal mobilisations (Evans, 2002; Sterling et al., 2001), as a legitimate source of sympathetic excitation. After all, the sympathetic chain and accompanying ganglia, extend from the upper cervical vertebrae down to the coccyx (Palastanga et al., 2006). A mobilisation to a vertebral body in any region of the spine could stimulate local sympathetic fibres, side specific responses identified in two studies (Jowsey & Perry, 2010; Perry & Green, 2008) provides some support for this idea.

Finally, there is some speculation that joint oscillation may stimulate spinal reflex pathways (Dishman & Bulbulian, 2000; Jowsey & Perry, 2010). Interestingly, the application of an oscillatory technique is common to all studies in this review. In each study, the oscillatory technique resulted in statistically significant changes in sympathetic outcomes compared to a placebo and/or control. Further to this, recent research (Moulson & Watson, 2006; Moutzouri, Joanna, & Eudokia, 2012) that investigated the effects of a sustained glide applied to C5/6 and L4, respectively, demonstrated no significant change to SC between intervention and control conditions, during the treatment period. Thus supporting the theory that it is the oscillatory component of the technique that is central to generating the response observed (Jowsey & Perry, 2010).

4.2.4.2 Limitations of this review

One of the main limitations in scoring the studies for this review was the inflexibility of the PEDro rating criteria. All studies were systematically under-rated for criteria numbers six and nine of the PEDro rating scale. These criteria pertain to blinding of the therapist and either an intention to treat analysis or explicit confirmation that all participants received conditions as allocated. The design of these studies did not permit blinding of the therapists. The SNS responses are automatic in nature, and were electronically measured in each study. Whether or not blinding of the therapist or the assessor could affect the internal validity in this instance is debatable.

Spinal mobilisations were applied to the cervical spine in five of the seven studies included in this trial (Chiu & Wright, 1996; McGuiness et al., 1997; Petersen et al., 1993; Sterling et al., 2001; Vicenzino et al., 1998), therefore only two studies (Jowsey & Perry, 2010; Perry & Green, 2008) contributed to the finding about an overall excitatory response regardless of the level of the spine. Only one study (Sterling et al., 2001) investigated changes in sympathetic
outcome measures in a symptomatic population, diluting the level of evidence that could be established for this sub-group.

Another limitation of this review is that only English language studies were included. There is evidence that English language studies are more likely to be positive therefore potentially introducing a language bias (Egger et al., 1997). Also studies were restricted to those in published format. Publication bias may have been introduced. There is evidence to suggest that published studies are more likely to be positive (Easterbrook, Gopalan, Berlin, & Matthews, 1991).

4.2.4.3 Clinical implications and future research

Studies considered in this review have shown there could be potential to treat distal pain, more proximally. This is due to the connection between sympathetic excitation and pain modulation, as discussed in the literature (Petersen et al., 1993; Pickar, 2002; Sterling et al., 2001). In instances of acute injury, or in the presence of painful inflammation of the target area, it would be useful to treat centrally, away from the target area. According to the results of this review, it is likely that the response of the SNS would be the same (i.e. sympathetic excitation), regardless of the level of the spine that was mobilised.

To establish support for these claims, there is a need for future studies to investigate the effect of spinal mobilisation on non-segmental areas of pain. The current thesis is investigating the effectiveness of a thoracic spine manipulation, as an adjunct to treatment, on pain and functional outcome measures at a follow-up period of four and 12 weeks. Therefore, it will contribute towards an understanding of the non-segmental, longer-term effects of manipulation when used as an adjunct for the treatment of AT.

Previous high quality RCTs have focused on the response of the SNS among healthy volunteers. This review contained only one study (Sterling et al., 2001) that investigated responses among the patient population (i.e. symptomatic individuals). Future studies that established a consistent response among the patient population would directly influence the clinical applicability of this technique. This will be addressed in the current pilot study (Chapter 5), as only participants with AT will be enrolled on the trial. Studies included in the current systematic review focused primarily on the implications of increased SNS activity in terms of its endogenous analgesic effects, through LPAG-mediated pathways (Evans, 2002). Although this is of great importance, other effects of increased SNS activity that may have an impact on pain perception, such as vasoregulation, should also be investigated in future studies. As outlined in Chapter 2 of this thesis, the current literature proposes that
vasoregulation, or more specifically dysregulation, may contribute significantly to the pain experienced by AT sufferers.

### 4.2.5 Conclusion

All studies included in this review were deemed to be of a high quality, in accordance with the PEDro rating scale. Among the healthy population, strong evidence for sympathetic excitation following spinal mobilisation was established, irrespective of the segments mobilised. Only one study, which qualified for inclusion in this review, investigated changes in the patient population. There was strong evidence for changes in SC, HR, BP and RR, consistent with sympathetic excitation. There was limited evidence for changes in ST, consistent with sympathetic excitation. More studies investigating sympathetic activity following spinal mobilisations in the patient population are necessary. In the clinical context, this has important implications as sympathetic excitation occurs concurrently with hypoalgesia.

As mentioned earlier, it was hoped the above studies might contribute towards a better understanding of the effect that spinal manipulation might have on the ANS. To this end, they have contributed information through the different theories of IPAG and sympathetic ganglia stimulation (refer to section 4.2.4.1). These theories provide background information that assists in establishing an understanding of how manipulation might also influence the ANS.

The pilot study that follows (Chapter 5), is designed to assess the effect of manipulation on basic SNS outcome measures, consistent with outcome measures used the current systematic review, thus enabling comparison of result between studies. Outcome measures chosen for the current pilot study have been informed by the findings of the systematic review (section 4.2.3.3). To the best of the author’s knowledge, no previous research has looked at the longer-term implications on pain and functional outcome following manipulation in chronic pain conditions such as AT.

Therefore, the pilot study designed as part of this Masters thesis addresses a number of areas that are lacking in the currently available literature i.e. the following pilot study will be of a high level of evidence (i.e. an RCT), carried out on the patient population; it will use outcome measures consistent with those used in other studies this enabling a comparison of results; it will investigate longer term changes in pain and function when manipulation is used as an
adjunct to treatment and finally it is the first study to investigate the effect of a non-segmental manipulation (i.e. not related to the neurological level of the nerve root) in the recovery of AT.
5 Investigating the effect of spinal manipulation as an adjunct to treatment for Achilles tendinopathy; a pilot study
5.1 Introduction

The theories relating to pathogenesis and the mechanism of pain in AT were discussed in chapter 2. In summary, incomplete healing of the tendon as the basis for tendinopathy is a widely accepted theory. The resultant biochemical changes are implicated in the perpetuated degeneration and inflammation of the tendon, and are a possible mechanism of pain, although this relationship needs further clarification.

The mechanism of pain is an important consideration for manual therapists when deciding on how to treat AT. It is proposed that eccentric exercises reduce pain and improve functional outcome through the process of neovascularisation (Alfredson et al., 1998). An eccentric exercise protocol is the most commonly cited intervention currently used by manual therapists. However, it is not always successful and implementation of this regime is time consuming (i.e. 12 weeks). Recently, sympathetic changes (e.g. ingrowth of sympathetic nerve fibres in painful AT) have been implicated as a possible mechanism of pain in AT, although this is not completely understood.

Previous studies have demonstrated that specific MT techniques influence the activity of the SNS. Spinal mobilisation has received much attention and it has been demonstrated that mobilisations result in excitation of the SNS. However, the effect of spinal manipulation has received less attention. Spinal manipulation is considered by many to be a progression of a mobilisation technique, thus it might be of importance if SNS changes are implicated in AT. With this in mind the following pilot study has been designed to aid in the development of an adequately powered RCT to investigate the effects of spinal manipulation as an adjunct to treatment in AT. To the best of the author’s knowledge, this is the first study to investigate the effects of spinal manipulation as an adjunct for the treatment of AT. The current pilot study also assess for changes in SNS activity following manipulation. Therefore the aims of the current pilot study were:

(1) To assess for changes in pain and function between (and within) two groups of participants with AT: a manipulation group and a standard care group, over a period of 12-weeks.

(2) To assess for changes in BP and HR between (and within) two groups of participants with AT before and after the delivery of a manipulation or rest intervention.
To assess the effectiveness of the advertising and recruitment strategy by measuring the numbers of volunteers recruited over a specific period of time (six-weeks).

5.2 Methods

This section presents the methods used to investigate the null hypothesis.

Null hypothesis: There is no difference in improvements in AT between group A (the manipulation group) and group B (the standard care group).

Alternative hypothesis: Both groups will improve: group A will improve more than group B.

5.2.1 Study design

This was a 12-week parallel group RCT with repeated measures (feasibility) study. It was performed at the Otago School of Physiotherapy Clinics, Dunedin, New Zealand. The primary focus of this pilot study was on study design and the assessment of recruitment and treatment protocols. This study also measured changes in SNS outcome measures following spinal manipulation. Ethical approval was received from the Lower South Regional Ethics Committee of New Zealand (Appendix E).

5.2.2 Recruitment

Participants were recruited by placing an advertisement in the local newspaper on the 12th of July 2012. Sixty individuals responded to the advertisement and were assessed against the inclusion and exclusion criteria. Once consent was obtained, participants that met the inclusion criteria were enrolled on to the study (Appendix F). Instructions were given to restrict alcohol on the treatment days, to avoid exercising immediately prior to their appointment and to abstain from consuming caffeine for four hours before BP and HR measurements were taken, consistent with published protocol (Chiu & Wright, 1996; Moulson & Watson, 2006; Perry & Green, 2008; Petersen et al., 1993; Sterling et al., 2001; Vicenzino et al., 1998).

A total of 17 participants fulfilled the inclusion criteria and were subsequently randomised into either the manipulation group, or the standard care group (refer to 5.2.5 for randomisation technique).
5.2.3 Inclusion Criteria

Participants aged between 18 - 65 years old were eligible for inclusion. A diagnosis of AT was based upon accepted diagnostic criteria (Maffulli et al., 2003). Participants had to be available for two physiotherapy appointments per week, for the initial four weeks, and to remain compliant with the exercise protocol for a total of 12 consecutive weeks.

5.2.4 Exclusion criteria

Contraindications to a spinal manipulation such as: metastatic carcinoma; central nervous system disease e.g. transverse myelitis; myelopathy; pregnancy, manipulation is impractical at later stages and may result in a miscarriage; osteoporosis, as manipulation may cause a fracture; chronic back pain; neurological symptoms; bone disease; inflammatory arthropathies including ankylosing spondylosis and rheumatoid arthritis, as these diseases can affect spinal ligaments, which can subluxate following a manipulation. Other exclusion criteria included: congenital ankle or knee deformity; insertional tendinopathy, as they are known to be difficult to treat; bursitis (retrocalcaneal or Achilles); sudden unexplained weight loss; non-steroidal anti-inflammatory injection in the previous three months; adverse neural tension affecting the sciatic or sural nerves; positive straight leg raise causing pain to the Achilles region; inability to perform exercise for 15 minutes on a daily basis; failure to give consent to inform their GP of trial participation and finally, an inability to understand the study protocol and risks involved in participation.

5.2.5 Randomisation

A computer generated random numbers list was produced to ensure the treating physiotherapist remained blinded to group allocation until treatment commenced. Once invited to take part in the trial, participants selected a sealed opaque envelope, prepared by a blinded research assistant. Each envelope contained an individual study number and a group allocation letter. Participants were randomised into either the manipulation group (i.e. group A) or the standard care group (i.e. group B). Both groups received the heavy load eccentric exercise protocol (i.e. eccentric exercises are considered the standard care intervention for the treatment of AT) that lasted the duration of the trial (12-weeks).
5.2.6 Overview of the experimental procedure

During the initial four weeks of this trial, all participants attended the School of Physiotherapy (SOP) clinic for treatment appointments, twice per week. Immediately prior to the commencement of the initial treatment appointment, baseline measures of the primary outcome measures were recorded (refer to 5.2.8).

5.2.6.1 Flow of treatment appointments

Regardless of grouping, participants rested in a supine position for the initial five minutes of each appointment, and were discouraged from engaging in conversation during this time. BP and HR were electronically recorded together with the room temperature, by the treating physiotherapist. Following data collection participants from the manipulation group received a thoracic spine manipulation (refer to section 5.2.7 for manipulation procedure), while participants in the standard care group (group B) continued to rest for a further three minutes, i.e. three minutes was the time allotted to deliver the manipulation.

Following the manipulation or rest intervention, all participants continued to rest in a supine position for a further five minutes. The treating physiotherapist then recorded the second reading for BP, HR and room temperature.

Once these readings were taken, the eccentric exercise protocol was reviewed. Exercises were corrected and/or progressed as appropriate, according to the Alfredson et al protocol (Appendix C).

5.2.6.2 Manipulation procedure

Explanations of treatment reactions and possible adverse reactions were given as per standard operating procedures of the SOP clinic for the manipulation group. It was decided to perform the manipulation on the thoracic spine for a number of reasons. The authors were interested in non-segmental influences. Manipulation of the lumbar spine may have a segmental effect as the Achilles tendon is supplied by L5/S1. Manipulation of the cervical spine would involve more rigorous exclusion criteria, as there are significant risks associated with manipulating this area of the spine (Rivett, Thomas, & Bolton, 2005). Therefore, it was agreed to manipulate the thoracic spine.

The thoracic spine was assessed for hypomobility by performing posterior-anterior (PA) springing over spinous processes of the thoracic spine (Monaghan, 2001). The hypomobile
level was then manipulated. In the absence of hypomobility, it was agreed to manipulate the level at approximately T3/4.

To perform the manipulation, the participant was placed in a supine position, hands crossed in front of their chest, and gently rolled towards the therapist. The therapist placed their hand on the lower level of the hypomobile segment (or on T4) and clasped it between the middle finger and palmar aspect of the thumb. The therapist rolled the participant back onto the hand, and as the patient exhaled, the thrust was delivered. For each appointment, there was a successful cavitation on the first or second delivery of the thrust.

The lead researcher was responsible for treatment, monitoring of the eccentric exercise regime and recording the outcome measures for the manipulation group. A clinician at the SOP clinic, or a fourth year undergraduate physiotherapy student, was responsible for monitoring the eccentric exercise regime, and recording outcome measures for the standard care group.

5.2.7 Exercise protocol

All participants were instructed on how to perform the eccentric exercise on their affected side, according to the Alfredson et al protocol (1998). Exercises were completed in three sets of 15 repetitions, twice per day, seven days a week, for the duration of the trial (Appendix C).

According to the explanation of the Alfredson et al protocol (1998) the eccentric exercise is biased towards the gastrocnemius muscle with the affected knee straight, while the soleus muscle works harder with the affected knee bent. All exercises were performed on a step, and the load was gradually increased until the participant experienced discomfort. Once the participant could complete the recommended sets and repetitions comfortably, the load was again increased until they were exercising in discomfort, but not severe or disabling pain.

At the end of the four-week period participants were encouraged to continue with the eccentric exercises for a further eight weeks, in keeping with the original 12-week protocol (Alfredson et al., 1998). During this time, participants were offered a treatment appointment every two weeks if they wished to attend for continued monitoring of their exercise regime.
5.2.8 Outcome measures

The two primary outcome measures were the VISA-A questionnaire (Appendix G) and a pain scale; the NPRS (Appendix H). The secondary outcome measures, which were electronically recorded, were BP and HR. Primary outcome measures were recorded immediately prior to the commencement of the first treatment, at the end of week-four and finally at the end of week-12. Secondary outcome measures were recorded twice during every appointment, for the initial four weeks. What follows is a description of each of the outcome measures used.

The VISA-A questionnaire, which is a valid and reliable index for the measurement of AT severity, was developed by the Victorian Institute of Sport. It consists of eight questions that measure the domains of: (A) pain, (B) function in daily living and (C) sporting activity. The VISA-A questionnaire is frequently used in the published literature to measure functional outcome in AT, making it more accessible to compare results between studies (Robinson et al., 2001).

The NPRS for pain is used to help individuals evaluate their level of pain. The number “0” represents no pain and “10” represents the worst imaginable pain. The NPRS score is the average of three pains; the current, worst and best pain score in the preceding 24 hours.

BP and HR were measured using an electronic BP monitor (Omron T5 Model), placed over the brachial artery on the left hand of all participants. This device automatically determined the systolic and diastolic BP together with HR once the brachial cuff was inflated.

Although not an outcome measure, changes in room temperature were also recorded for inclusion in the statistical analysis, as temperature changes are known to affect sympathetic responses such as HR and BP.

5.2.9 Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS 20, SPSS Inc Chicago); alpha set to 0.05 (two-tailed). Normal descriptive statistics for the two groups, such as means and standard deviations, were calculated. Analysis was performed on raw scores on a modified intention to treat basis using repeated measures analysis of variance (ANOVA) for primary and secondary outcome measures, to assess for differences within and between groups over the 12-week trial period.
5.3 Results

The pilot study data was collected between 12\textsuperscript{th} July 2012 and the 30\textsuperscript{th} of October 2012. A total of 60 volunteers registered their interest; of these, 60 were screened, and 17 were recruited onto the trial, i.e. a recruitment rate of 28\%. This demonstrated the effectiveness of the advertising and recruitment strategy. One participant dropped out directly after randomisation, but before baseline measures were taken, citing change of mind as the reason for withdrawal. A second participant dropped out directly after baseline measures were taken, citing other time commitments as the reason for withdrawal; both participants belonged to the control group. In total, 15 participants completed the treatment and final assessment as described in the protocol according to group allocation. Refer to Figure 5-1 for the flow of study and also to Table 5-1 for demographic and baseline data.

![Figure 5-1 Study flow](image-url)
5.3.1.1 Repeated measures ANOVA for VISA-A

Repeated measures ANOVA on the VISA-A scores display a significant difference for ‘time’ within groups (F=15.22; df=2; p<0.01). The ‘time/group’ interaction is also significant (F=21.0; df=2; p<0.01) indicating the effect differs across time points and between groups. Observation of the means is important as it identifies if the trends are towards an improvement or a worsening of outcome measure.

Observation of the means is important as it identifies if the trends are towards an improvement or a worsening of outcome measure.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Manipulation group</th>
<th>Standard care group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47.1 ± 5.7</td>
<td>45 ± 9.0</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>8/2</td>
<td>1/4</td>
</tr>
<tr>
<td>VISA-A</td>
<td>55.1 ± 5.7</td>
<td>65.8 ± 8.1</td>
</tr>
<tr>
<td>Pain (NPRS)</td>
<td>3.0 ± 0.3</td>
<td>2.7 ± 0.5</td>
</tr>
<tr>
<td>BP (systolic)</td>
<td>126.7 ± 10.4</td>
<td>128.8 ± 17.7</td>
</tr>
<tr>
<td>BP (diastolic)</td>
<td>72.5 ± 6.5</td>
<td>71.2 ± 6</td>
</tr>
<tr>
<td>HR</td>
<td>62.8 ± 7.4</td>
<td>63.6 ± 13.6</td>
</tr>
</tbody>
</table>

Table 5-1 Demographic and baseline data

The mean VISA-A score for the manipulation group at baseline is lower (55.10), compared to the mean score at baseline for the standard care group (65.80), indicating the manipulation group had more severe AT symptoms at baseline. At week-four scores between groups are similar; 76.70 and 73.40 for the manipulation and standard care group respectively. At week-12, the mean is much higher for the manipulation group (82.00), compared to the standard care group (58.00), indicating a stronger improvement in the manipulation group. A lower
score (i.e. worsening of symptom) is identified between week-four and week-12 for participants in the standard care group (Table 5-2).

In summary, observation of the means (Figure 5-3) demonstrates improvements in both groups between baseline and week-four. There were continued improvements for the manipulation group between week-four and week-12. In contrast, a worsening of AT severity between week-four and week-12 was observed in the standard care group.

Figure 5-2 Profile of means for VISA-A scores
5.3.1.2 Repeated measures ANOVA for NPRS scores
Repeated measures ANOVA on the NPRS scores display a significant difference for ‘time’ within groups (F=8.79; df=2; p<0.01). The ‘time/group’ interaction is also significant (F=3.73; df=2 and p=0.03); indicating the effect differs across time points and between groups.

The mean for the manipulation group (0.93) is lower compared to the mean for the standard care group (2.66) at week-12, indicating a stronger hypoalgesia effect for the manipulation group at week-12 (Table 5-3). The means are similar at baseline (3.03 and 2.66) and week-four (1.13 and 1.46) for the manipulation and standard care group respectively. This is interesting as it indicates the most significant changes in NPRS scores between groups occurred between week-four and week-12, after the intervention phase had concluded and participants were expected to complete their exercise routine independently. Figure 5-4 displays the profile of the NPRS marginal means, between groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Time-point</th>
<th>Mean</th>
<th>Confidence Interval (Lower Bound)</th>
<th>Confidence interval (Upper Bound)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard Care</strong></td>
<td>Baseline</td>
<td>65.80</td>
<td>48.36</td>
<td>83.24</td>
</tr>
<tr>
<td></td>
<td>Week-4</td>
<td>73.40</td>
<td>61.33</td>
<td>85.47</td>
</tr>
<tr>
<td></td>
<td>Week-12</td>
<td>58.00</td>
<td>43.53</td>
<td>72.47</td>
</tr>
<tr>
<td><strong>Manipulation</strong></td>
<td>Baseline</td>
<td>55.10</td>
<td>42.77</td>
<td>67.43</td>
</tr>
<tr>
<td></td>
<td>Week-4</td>
<td>76.70</td>
<td>68.17</td>
<td>85.23</td>
</tr>
<tr>
<td></td>
<td>Week-12</td>
<td>82.00</td>
<td>71.77</td>
<td>92.23</td>
</tr>
</tbody>
</table>

Table 5-2 Descriptive means for VISA-A scores
Figure 5-3 Profile of means for NPRS scores

<table>
<thead>
<tr>
<th>Group</th>
<th>Time-point</th>
<th>Mean</th>
<th>Confidence Interval (Lower Bound)</th>
<th>Confidence interval (Upper Bound)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard Care</strong></td>
<td>Baseline</td>
<td>2.66</td>
<td>1.62</td>
<td>3.70</td>
</tr>
<tr>
<td></td>
<td>Week-4</td>
<td>1.46</td>
<td>0.77</td>
<td>2.15</td>
</tr>
<tr>
<td></td>
<td>Week-12</td>
<td>2.60</td>
<td>1.25</td>
<td>3.94</td>
</tr>
<tr>
<td><strong>Manipulation</strong></td>
<td>Baseline</td>
<td>3.03</td>
<td>2.30</td>
<td>3.77</td>
</tr>
<tr>
<td></td>
<td>Week-4</td>
<td>1.13</td>
<td>0.64</td>
<td>1.61</td>
</tr>
<tr>
<td></td>
<td>Week-12</td>
<td>0.93</td>
<td>-0.02</td>
<td>1.89</td>
</tr>
</tbody>
</table>

Table 5-3 Descriptive means for NPRS scores
5.3.1.3 Repeated measures ANOVA for changes in systolic blood pressure

Repeated measures ANOVA tests for statistically significant differences in BP before and after the manipulation and control (i.e. rest) intervention, over a period of four weeks. Scores for systolic changes are measured separately to diastolic changes.

Results indicate no statistically significant changes in systolic BP within or between groups (F=1.13; df = 1; p= 0.31 and F= 0.23; df = 1; p= 0.64 respectively), i.e. there is no significant change in systolic BP over time or between groups. Figure 5-5 displays the profile of the mean scores pre and post intervention (i.e. the intervention is manipulation for the manipulation group and rest for the standard care group).

![Systolic BP Graph](image)

Figure 5-4 Profile of means for Systolic BP
5.3.1.4 Repeated measures ANOVA for changes in diastolic blood pressure

Repeated measures ANOVA on the diastolic scores indicate no significant difference for ‘time’ within groups or ‘time/group’ interaction (F = 0.74; df = 1; p = 0.40; and F = 0.27; df = 1; p = 0.61 respectively), indicating no significant change over time and no significant change in diastolic BP between groups. Figure 5-6 displays the profile means for diastolic BP scores, between groups, before and after the intervention.

Figure 5-6 Profile of means for Diastolic BP

5.3.1.5 Repeated measures ANOVA for changes in HR

Repeated measures ANOVA on HR scores demonstrate no significant difference for ‘time’ within groups or ‘time/group’ interaction (F = 0.55; df = 1; p = 0.47 and F = 0.33; df = 1; p = 0.57 respectively), indicating no significant change over time or between groups (Figure 5-7).
5.3.1.6 Repeated measures ANOVA for changes in room temperature
Room temperature was stable throughout (Appendix I) therefore it is not possible or necessary to run the ANOVA for room temperature.

5.4 Discussion
The aims of this study were to:

1. Assess for changes in pain and function between (and within) two groups of participants with AT.
2. Investigate putative changes in SNS outcome measures (BP and HR) following spinal manipulation compared to a control intervention (rest).

3. To assess the effectiveness of the advertising and recruitment strategy by measuring the numbers of volunteers recruited over a specific period of time (six-weeks).

The following pages contain a discussion on the methodological procedures and aims of the current pilot study. Overall, the recruitment strategies and methodological procedures were found to be successful, however a number of methodological flaws were also identified. These flaws were due primarily to budget constraints and are discussed below.

### 5.4.1 Recruitment strategy

The recruitment strategy was successful in generating interest from 60 individuals with Achilles tendon pain. After initial screening, 17 volunteers met the inclusion and exclusion criteria, demonstrating a recruitment rate of 28%. A similar study, recruiting for AT (Tumilty et al., 2008), demonstrated a recruitment rate of 46%. The difference in success rates may be a reflection of the strict exclusion criteria for the current study. Volunteers with an on-going history of back pain (cervical, thoracic or lumbar) were excluded from this study.

As the recruitment strategy generated 60 willing volunteers, it is considered that this was a successful strategy for recruiting participants. Placing more than one advertisement in a local newspaper and extending the recruitment phase to longer than six weeks is likely to further improve the recruitment rate in future trials. The initial intention was to recruit 20 participants onto this trial, i.e. 10 per group, which might have been achieved if the recruitment phase was extended beyond six weeks.

### 5.4.2 Methodological procedures

The following paragraphs provide the rational for the methodological procedures that were followed.

As discussed in Chapter 2 (section 2.6.3), eccentric exercises are considered the gold standard treatment for AT. It was decided to use this intervention for the benefit of every volunteer in this study, regardless of group allocation. This ensures that none of the volunteers are denied treatment. A 12-week follow up period was chosen as it is expected that volunteers would
have returned to normal activities of daily living after 12-weeks of heavy load eccentric exercises (Alfredson et al., 1998).

The VISA-A questionnaire and NPRS scores were used as primary outcome measures as they have become accepted methods of measuring AT severity and pain intensity. The VISA-A questionnaire has been specifically designed for the measurement of AT severity, and according to published literature it is a valid and reliable tool (Robinson et al., 2001; Silbernagel, Thomeé, & Karlsson, 2005). Measuring the intensity of pain is complex, and trying to quantify the perception of pain may prove difficult for some individuals. Nonetheless, NPRS scores are reliable (ICC of 0.95) (McCarthy Jr et al., 2005), and produce data that can be statistically analysed. For these reasons, the VISA-A questionnaire and NPRS scores were chosen to measure the effect of treatments between groups.

A best-evidence synthesis (please refer to Chapter 4, section 4.2.2.3 and 4.2.3.3.) indicated that there was strong evidence for statistically significant changes in BP and HR, following excitation of the SNS. Measuring changes of other sympathetic responses such as SC or ST, involves the use of expensive equipment (e.g. the biopack system) that was not available for the purposes of this trial. For these reasons, it was decided to measure changes in BP and HR to assess for changes in sympathetic activity.

The strict inclusion and exclusion criteria were designed to maximize the likelihood of an accurate clinical diagnosis of AT, and recruiting these participants onto the trial. The comprehensive exclusion criteria were included to reduce the risk of recruiting participants with AT that had other health conditions or biomechanical dysfunctions that might not respond well (or in a predictable manner) to a thoracic spine manipulation.

5.4.3 Discussion of results

The results of the current pilot study demonstrated a significant difference between VISA-A and NPRS scores both between groups, and within groups over the 12-week trial period. An ANOVA measures change over time within and between groups i.e. change in VISA-A and NPRS scores between baseline and the end of week-12. The results from the ANOVA do not indicate between which time-points these changes were significant (i.e. if they were significant between baseline and week-four, or between week-four and week-12). For this reason, observation of the means was important (refer to section 5.3. for commentary and
Tables 5-2 and 5-3). In addition, observation of the means also demonstrated whether changes were indicative of an improvement or worsening of AT symptom.

Of note, the improvement in VISA-A scores in the manipulation group was almost three times greater compared to the amount of improvement in standard care group between baseline and week-four i.e. the standard care group improved by eight points, while in comparison the manipulation group improved by 21 points (Table 5-2). During this time both groups were completing the eccentric exercise protocol, but in addition the manipulation group received spinal manipulation twice a week. This might indicate that manipulation has contributed substantially to the change in scores. However, on closer examination of the published literature, Tumilty, McDonough, Hurley and Baxter (2012) demonstrated that after four-weeks of eccentric exercises, participants in both the control and the laser therapy group improved their VISA-A scores by at least 20 points, an overall improvement of 20% for each group. In another study Roos, Engström, Lagerquist and Söderberg (2004) demonstrated a 27% improvement in function and in pain scores following six-weeks of eccentric exercises. These figures are in line with improvements observed in the manipulation group of the current study, which demonstrated an improvement of 28% in VISA-A scores. During the same time, the standard care group demonstrated a mere 10% improvement in VISA-A scores: well below the anticipated outcome at that stage. An explanation for the substantially slow rate of improvement among the standard care participants between baseline and week four cannot be provided, however, a potential bias (the variability among therapists) that might have contributed to this unexpected finding is discussed in section 5.4.3.3.

Further to this, VISA-A and NPRS scores for participants in the standard care group diminished, indicating a worsening of symptom between week-four and week-12. During the same time, outcome measures for the manipulation group continued to improve (Tables 5-2 and 5-3). This finding is of significant concern and discussed in section 5.4.3.3. However, before potential explanations are offered, the minimal clinically important differences (MCID) and the effect size of these changes are considered.

5.4.3.1 Minimally important clinical difference
Calculation of the MCID is important as it represents clinically meaningful changes. This indicates the smallest difference that clinicians and patients would care about. There is little discussion in the literature regarding MCID scores for VISA-A and NPRS scores. Khan, Forster, Robinson, Cheong, Louis, Maclean and Taunton (2003) stated that 25-points is
clinically important. However, it is unclear how Khan et al (2003) arrived at this conclusion, as the paper they cite (Robinson et al., 2001) did not discuss MCID scores for the VISA-A questionnaire.

As summarised by Tumilty (Tumilty et al., 2010) it has been suggested that MCID has poor generalisability across groups and is best calculated from current clinical data. Therefore, in the current pilot study the MCID scores were calculated from the current data (e.g. 75% of the patient population scored a change of 20 points or more Hayley & Fragala-Pinkham, 2006). Using this approach with the pilot data, a MICD of 10 points for VISA-A and one point for NPRS was calculated for changes between baseline and week-four. Therefore changes in VISA-A scores greater than 10 points, and changes in NPRS scores greater than one point, are considered clinically meaningful between baseline and the end of week-four. A MCID of seven points for VISA-A and 0.67 points for NPRS was calculated for changes between week-four and week-12. Changes in VISA-A and NPRS scores that are clinically meaningful are highlighted in this section. This is followed by a discussion on the mechanisms that may have contributed to these changes.

The amount of change between different time-points, in VISA-A and NPRS scores are presented below (Tables 5-4 – 5-7). The series of small tables that follow highlight whether or not the changes were clinically significant. The symbol * denotes a negative change (i.e. a worsening of symptom)

| Manipulation group – VISA-A means |
|-----------------------------------|-----------------|----------------|
| Time-point                        | Change in score | Clinically important |
| Baseline – week 4                 | 21.6            | Yes             |
| Week 4 – week 12                  | 5.3             | No              |

Table 5-4 Manipulation group: changes in VISA-A scores
Improvements in VISA-A and NPRS scores (Tables 5-4 and 5-5), for the manipulation group are clinically meaningful between baseline and week-four. Although they continued to improve between week-four and week-12, improvements were not clinically meaningful during those time-points (i.e. they did not exceed MCID scores). Once the intervention ceased, the rate of improvement in the manipulation group slowed. It might therefore be argued that if the manipulation technique had contributed to the results, then it’s effect was relatively short term as the rate of improvement reduced once the intervention ceased (after week-four).
Clinically important improvements in NPRS scores, between baseline and week-four were identified in the standard care group (Table 5-6). Interestingly, improvements in VISA-A scores during the same time were not clinically important (Table 5-7). Interestingly, in contrast to scores observed in the manipulation group, VISA-A and NPRS scores exceeded the MCID value between week-four and week-12, indicating changes were clinically important. However, these changes were in a negative direction (Table 5-6 and 5-6), demonstrating a clinically important worsening of symptom. These findings are of concern and are not consistent with published reports that have demonstrated positive outcomes following an eccentric exercise regime. It is not known, but such scores might represent poor variability among participants between groups; even though participants were randomised to each group, the manipulation group consisted of twice as many participants as the standard care group. Participants in the standard care group might represent individuals that do not respond to eccentric exercise. Confounding factors are presented and discussed in section 5.4.3.3.

5.4.3.2 Effect size

Calculation of the effect size is important as it identifies the size of the difference between two groups. It is a measure of the size of the difference in VISA-A and NPRS scores between the manipulation and the standard care group. The effect size for VISA-A scores at week-four and week-12 were calculated to be 0.18 and 1.34 respectively, indicating a less than small effect size for VISA-A scores by the end of week-four, and a large effect size by the end of week-12 (Jack Cohen, 1988). The effect size for NPRS scores at the end of week-four and the end of week-12 were calculated to be 0.31 and 1.57 respectively, i.e. a small and large effect size respectively (please refer to Appendix J for effect size calculations). To detect a large effect between two groups at 80% power and a two tailed alpha of 0.05, a minimum of 26 participants per group (n=26) is required in each group (Jacob Cohen, 1992). Please refer to Appendix J for effect size and power calculation.

In light of the results of the current pilot study there are two important points to consider:

1. What are the mechanisms behind the worsening of symptom at the end of week-12 in the standard care group?

2. What are the mechanisms behind the continued improvements in the manipulation group?
5.4.3.3 Compliance

An obvious explanation for the disparity in results, once regular treatment and supervision ceased, is compliance with the exercise regime. Between week-four and week-12 all participants (regardless of grouping) were treated with the same eccentric exercise protocol (Appendix C), and therefore similar changes were expected between week-four and week-12 between groups.

However, participants in the manipulation and the standard care group received education and monitoring of the exercise regime from different clinicians, which may have influenced compliance (in terms of either exercise technique or exercise repetition). Participants in the manipulation group received education and monitoring from the lead researcher alone. Participants in the standard care group received education and monitoring by either a SOP clinician or a fourth year undergraduate physiotherapy student, depending on availability. It was not possible to arrange for a single, independent clinician to monitor the exercise regime for all participants, both the manipulation and the standard care group together, due to insufficient time and funding. Standardised information and exercise sheets describing the exercise protocol (Appendix C) were given to each participant regardless of grouping, and every care was taken to ensure clinicians gave uniform education and instruction on the exercise regime. Interestingly, even though every participant improved while under the direct supervision of a clinician or student during the initial four weeks, the standard care group improved at a rate well below the published norms, indicating there might have been a difference in compliance / technique between groups from baseline. Once discharged to self manage the manipulation group continued to improve. Without exception, every participant in the standard care group worsened, suggesting they might have followed the protocol incorrectly. Issues surrounding poor compliance or poor technique might result in systematically over-loading the Achilles tendon in an incorrect manner.

Mechanical loading of the Achilles tendon results in a biochemical response (mechanotransduction) that is necessary to maintain the viscoelastic properties and structural integrity of the tendon. Systematically over-loading the Achilles tendon in a non-uniform manner (i.e. poor technique) results in abnormal loading concentrations (Rees, Maffulli, & Cook, 2009), and therefore abnormal biochemical signalling responses.

It is proposed that these abnormal signalling responses might have included up-regulation of cytokines such as TNF-α by the tendon cells (Hosaka et al., 2006). Elevated levels of TNF-α are associated with mechanical deterioration of tendon tissue (Uchida et al., 2005), reduced type 1 collagen, cell apoptosis (Machner et al., 2003) and an up-regulated level of other
cytokines that are involved in inflammatory and nociceptive signalling (refer to Chapter 3). In summary, it is suggested that poor technique (or poor compliance) might have lead to an increase in non-uniform stress concentrations in the Achilles tendon and a subsequent flare-up in Achilles tendon symptoms, among participants that experienced a worsening of symptom.

It is not known for certain if poor technique, or poor compliance with the exercise protocol, might have contributed to the worsening of symptom. Participants were encouraged to attend clinic once every two weeks after the intervention ceased (i.e. between week-four and week-12) to receive supervision and continued guidance on the exercise regime. Continued, regular, follow-up appointments would have also resulted in early identification of a worsening in symptom. However, only two participants (both from the control group) attended for follow-up monitoring. Both of these participants attended during week six i.e. two-weeks after the intervention had ceased, and six-weeks before the trial finished. Upon review of the clinical notes that were documented during these follow-up appointments, it was observed that neither participant indicated any worsening of symptom at that time. In addition all participants were encouraged to contact either the clinical therapist; the lead researcher; the study supervisor or other members of the research team should they wish to discuss any elements of this participation that concerned them (please refer to Appendix C).

Considering the systematic worsening of symptom for every participant in the standard care group together with the initial slow rate of progress compared to improvements in published studies, it would appear that issues surrounding compliance (i.e. compliance with technique and/or exercise protocol) is the logical conclusion. In addition, it highlights a separate issue regarding supervision of exercise. The importance of close supervision, and thorough education of the exercise technique, throughout the entire eccentric exercise protocol (12 weeks in total), cannot be underestimated. The design of future trials should include more regular supervision of the exercise technique, for example, follow-up once a week for the 12-week rehabilitative period. In the current design participants were given the option to attend for supervision of exercise once every two weeks between week-four and week-12. The vast majority of participants declined this offer citing other time commitments. However, in retrospect, it is conceded this was of poor design. Future trials would improve the study design through closer monitoring of the exercise protocol. Bias could be further reduced through the use of a single (blinded) clinician available to supervise all participants taking part in the exercise regime, regardless of grouping.
The second important point to consider in light of the current results are the mechanisms behind the positive changes in outcome measures that were observed in the manipulation group.

5.4.3.4 Eccentric exercises
The positive results that were demonstrated for participants in the manipulation group are consistent with published findings (Alfredson et al., 1998; Jonsson et al., 2008; Öhberg & Alfredson, 2004; Tumilty, 2010; Tumilty et al., 2008). A discussion on the possible effects of eccentric exercises that might contribute to positive outcomes has been presented in Chapter 2 (section 2.5.4). In summary, the most commonly cited mechanism is the destruction of the neovessels and with them the sympathetic nerve ingrowth (Alfredson & Öhberg, 2005; Andersson et al., 2008; Danielson, 2009). In addition, loading tendons in a stretched position is known to reduce tendon hysteresis (refer to Chapter 3), and thus positively alter biochemical signalling of cytokines, contributing the structural integrity of the Achilles tendon.

Potential mechanisms through which manipulation might have contributed to the improvements in AT recovery observed in the manipulation group are explored in Chapter 6.

5.4.4 Limitations
There are a number of methodological flaws surrounding the current pilot study that should be addressed in future trials.

The responsibilities of the lead researcher were a substantial confounding factor. The lead researcher was responsible for screening all participants, assessing and recording primary outcome measures (VISA-A, NPRS), and treating all participants in the manipulation group. In addition the lead researcher assessed and recorded some of the final outcome measures for participants in the standard care group. Researcher bias, or participant desire to please the researcher might have influenced VISA-A and NPRS scores.

Undergraduate physiotherapy students and a clinician at the SOP clinic were responsible for monitoring and educating participants in the standard care group, introducing a further bias. Although students and the SOP clinician received thorough education on how to teach and monitor the eccentric exercise protocol, it would appear from the results at week-12 that participants in the standard care group might have managed their exercise regime different to participants in the manipulation group.
Confounding variables that might influence changes in sympathetic outcome measures include noise and humidity. In controlled laboratories these factors can be managed. In the current pilot study this was not possible, however, changes in room temperature were monitored throughout each appointment. The reading were stable suggesting temperature was not a confounding factor. Future studies that assess sympathetic output can eliminate the confounding variables mentioned above by carrying out the treatment appointments in a fully controlled laboratory setting.

As previously discussed, continued monitoring of the exercise regime is necessary to identify negative changes in AT symptom, and ensure continued participation on the trial is appropriate. Due to lack of clinician time and lack of funding to recruit other clinicians it was not feasible to continue monitoring each participant (both groups) three times a week for 12 weeks. Although it was not a requirement for inclusion, it was anticipated that participants would agree to attend once every two weeks once the intervention ceased. However, in light of the results, it is imperative that future trials continue to monitor participant progress on an on-going and regular basis throughout the entire duration of the trial.

Finally, sophisticated devices that assess for changes in a variety of physiological responses such as skin conduction and skin temperature exceeded the budget of this feasibility study. Forces exerted on participants to achieve a successful manipulation of the thoracic spine could potentially result in temporary changes in sympathetic responses such as BP and HR, although that was not the case in the current study. It is not known, but possibly the manipulation dose was insufficient to reach the threshold for an SNS effect. It is acknowledged that three (Harris and Wagnon, 1984; Gibbons et al, 2006; Welch and Boone 2008) of the six previous studies (Kappler and Kelso, 1984; Injeyan and Ruegy, 2006; Sillevis et al, 2010; Teodorczyk-Injeyan et al, 2006) investigating this topic have demonstrated significant changes in SNS activity following manipulation. Undoubtedly the design of the current study would be substantially improved through the use of more sophisticated equipment that would measure a broader variety of physiological sympathetic responses, such as the biopack system.

5.5 Summary

The methodology of this pilot study was successful in recruiting and retaining participants on this trial. The methodological procedures were rationalised through a combination of current evidence and available resources. Sympathetic response was measured by changes in BP and
HR. However, more advanced technologies that could assess for sympathetic changes such as distal skin temperature would be more suitable. The therapeutic effect of manipulation, over and above the effect of an eccentric exercise protocol, has been successfully measured using VISA-A and NPRS scores. Changes in VISA-A and NPRS scores both within and between groups, has been found to be significant. There was no statistically significant change in sympathetic responses (HR and BP) within or between groups immediately following the treatment intervention (i.e. rest or manipulation).

5.6 Conclusion

Results of this study reject the null hypothesis, which states that there is no difference in improvements in AT in the manipulation group (group A) compared to the standard care group (group B). This study has measured successfully what it intended to measure. Results suggest there may be benefit in the use of thoracic spine manipulation as an adjunct to treatment for AT. However definitive conclusions cannot be drawn due to the small number of participants that were assessed. Future trials that are sufficiently powered and address the methodological flaws of this study (refer 5.4.4) are urgently needed.
6 General Discussion
This thesis has investigated the effect of spinal manipulation over and above the effect of an eccentric exercise regime (Alfredson et al., 1998), for the treatment of Achilles tendinopathy (AT). In addition, it has attempted to measure changes in SNS activity both within groups, and between groups. The results demonstrated that there are statistically significant differences in VISA-A and NPRS scores between groups, and also within groups over the 12-week trial period. Changes in the sympathetic outcome measures (HR and BP) were not statistically significant. The findings of the current pilot study, together with the findings of the literature review (Chapter 3) and systematic review (Chapter 4), raise a number of issues that are of interest. These are considered in the following pages.

6.1 Overview of Achilles tendinopathy

The traditional clinical assessment has generally focused on identification of the patho-anatomical structure(s) responsible for the patient’s symptoms (Vicenzino, Hing, Rivett, & Hall, 2011). In the context of AT, identification of the patho-anatomical structure may not equate with a beneficial clinical outcome. AT is difficult to treat, as the pathogenesis and mechanism of pain are not completely understood. It can result from overuse and/or underuse of the Achilles tendon, and may or may not, involve an inciting injury. To complicate matters, Achilles tendons that demonstrate changes in biochemistry, vascularity and gene expression, may or may not be painful (Alfredson & Öhberg, 2005; Khan et al., 1999; Zanetti et al., 2003), although pain is more commonly observed than not. As the exact pathogenesis is not fully understood, recent intervention has focused on treating the mechanism of pain.

Analyses of histopathological reactions and gene expression have identified biochemical and gene related changes that are proposed to contribute to the mechanism of pain. Such studies have significantly improved our understanding of the complex interaction between biomechanical loading and biochemical stimulation. In the healthy tendon, these interactions result in the constant remodelling of the Achilles tendon. Numerous biological markers that are involved in the signalling of nociception and inflammation (e.g. TNF-α), which also influence the structural integrity of the Achilles tendon, have been identified (refer to Chapter 3). It is stressed that although this information has greatly advanced our knowledge of biochemical changes and how these changes might affect viscoelastic properties of the Achilles tendon, it has been difficult to postulate how the use of spinal manipulation might improve clinical and functional outcome in the treatment of AT.
There is increasing interest in the literature, in the possible involvement of the ANS in states of chronic (greater than three months) pain. Systemic and peripheral changes, under the control of the ANS, have been demonstrated in other chronic conditions such as low back pain and lateral epicondylia (Gockel, Lindholm, Niemisto, & Hurri, 2008; Smith, Christensen, Peck, & Ward, 1994). As summarised by Vicenzino, Hing, Rivette and Toby (2011), impaired sympathetic vasoconstriction in other pain conditions such as whiplash associated disorders are affiliated with poor functional outcomes (Sterling et al., 2001), which would suggest that SNS changes are implicated in the progression from the acute to chronic stages of pain. In regard to AT, there is some suggestion of autonomic involvement, although it’s significance has not been fully established. It has been demonstrated that sympathetic nerve fibres accompany the ingrowth of blood vessels into pathological Achilles tendons, and also the perivascular innervation is primarily sympathetic in origin, implicating SNS changes in AT. This is of particular interest to manual therapists as manipulation may alter ANS activity.

6.2 Effect of manual therapy on the Autonomic Nervous System

Studies have demonstrated a variety of ANS responses following manipulation (Gibbons et al., 2000; Harris & Wagnon, 1987; Kappler & Kelso, 1984; Sillevis et al., 2010; Teodorczyk-Injeyan et al., 2006; Welch & Boone, 2008). The majority of authors would agree that spinal manipulation significantly changes ANS activity (Gibbons et al., 2000; Harris & Wagnon, 1987; Kappler & Kelso, 1984; Teodorczyk-Injeyan et al., 2006; Welch & Boone, 2008). This has been measured by changes in autonomically controlled reflexes such as Edge light pupil cycle time (ELPCT) and physiological responses such as changes in skin temperature (Harris & Wagnon, 1987; Kappler & Kelso, 1984). However, it is conceded the quality if these studies are questionable; the reader is referred back to Chapter 3 (section 3.4.2) for a discussion on the quality of the above studies.

The results of the systematic review in Chapter 4 demonstrated that spinal mobilisations consistently resulted in SNS excitation regardless of the level of the spine that was mobilised. The initial intent of carrying out a systematic review (Chapter 4) on the effects of spinal mobilisations was to shed light on the potential effects of spinal manipulations as this was considered the most relevant source of high quality trials to review.

The current pilot study demonstrated that participants that received spinal manipulation responded better than participants that did not receive manipulation. Modulation of the behaviour of the ANS, through manipulation, might be of significant importance for the
Numerous authors have proposed a system of macrophage inhibition called the ‘cholinergic anti-inflammatory pathway’ (Borovikova et al., 2000; de Jonge & van der Zanden, 2005; Tracey, 2002). These studies imply that ACh, released in response to activation of certain nerve fibres (parasympathetic nerve fibres), has effects on local inflammation (Borovikova et al., 2000; Tracey, 2002; Watkins, Maier, & Goehler, 1995). ACh inhibits the synthesis of TNF-α and other cytokines that may be implicated in AT (Forsgren et al., 2009; Tracey, 2002). Drugs designed to up-regulate ACh are already successful in treating a number of chronic pain conditions (Forsgren et al., 2009).

The author of this current thesis proposes that it might be feasible to stimulate the cholinergic anti-inflammatory pathway through spinal manipulation. It is speculated that this could be achieved by altering the neuronal signaling in either the ANS (i.e. SNS and/or PNS activity) or the CNS, as ACh is the primary neurotransmitter for both systems. Refer to Figure 6-1 for a summary of these proposals.

The first proposal is based on the anatomical proximity of the paravertebral ganglia to the spinal column, which was discussed in Chapter 4. It was speculated that spinal mobilisations stimulate local paravertebral ganglia as they are situated very close to the spinal column. It is currently proposed that manipulation may have a similar effect on the paravertebral ganglia. Whether the manipulation technique stimulates sympathetic or parasympathetic nerve fibres, it is proposed that up-regulation or release of ACh is likely to occur, as ACh is the major neurotransmitter present in all autonomic ganglia (including the paravertebral ganglia).

The second proposal is based on the premise that spinal mobilisations stimulate local receptors that are present in joints, capsules, tendons and connective tissues, which are capable of directly or indirectly activating IPAG (refer Chapter 4, section 4.2.4.1). This area of the mid brain is implicated in co-ordinating a specific pain response that results in SNS excitation, facilitation of movement and immediate hypoalgesia (Boyling & Palastanga, 2004; Wright, 1995). The current pilot study did not utilise spinal mobilisations, however, it is proposed that spinal manipulation might have a similar influence onto the CNS. It is proposed that changes in central signalling (via stimulation of local receptors that are close to the spine) following a spinal manipulation are likely to involve up-regulation of ACh as ACh is the major neurotransmitter in both the ANS and CNS, potentially enabling the cholinergic anti-inflammatory pathway.

A recent study by Teodorczyk-Injeyan, Injeyan and Ruegg (2006) provides some support for the above theories. This study demonstrated that a single manipulation to the thoracic spine
(between T1-6) was sufficient to immediately down-regulate the body’s circulating levels of TNF-α and Interleukin-1 Beta (IL-1β) i.e. manipulation resulted in a measured anti-inflammatory response. The author postulated that down-regulation of the body’s inflammatory response occurred through an unknown pathway. The author of this current thesis proposes this result could be the first evidence that spinal manipulation stimulates the cholinergic anti-inflammatory pathway. However, little is known about this pathway. Although it is understood that parasympathetic nerve fibres release ACh when they connect at the ganglion (Standring, 2008), the mechanism through which sympathetic nerve fibres or the CNS might release ACh might be more complex. It is beyond the scope of this thesis to speculate further on these mechanisms. The above proposals are based on speculation and therefore caution is advised when interpreting these hypotheses.

Other central mechanisms that might also contribute to the positive responses to manipulation for the treatment of AT are summarised in the following paragraphs.

It is proposed that neuronal signalling from the ANS, in response to spinal manipulation, stimulates the hypothalamus. The hypothalamus links the nervous system to the endocrine and pituitary gland (Michael-Titus et al.; Standring, 2008) and is involved in a signalling system called the hypothalamic-pituitary-adrenal axis (HPA axis). One of the many functions of this axis is to help regulate the immune system. HPA signalling can have a direct effect on concentrations of the sympathetic neurotransmitters noradrenaline and adrenaline (Standring, 2008; Tracey, 2002). These neurotransmitters suppress inflammation by inhibiting the synthesis of TNF and other cytokines in local tissue, and stimulating the release of the potent anti-inflammatory cytokine Interleukin 10 (Tracey, 2002; Woiciechowsky et al., 1998). Through these mechanism, stimulation of the hypothalamus might be of therapeutic effect for the treatment of AT. Although, it must be conceded that a recent study (Puhl & Injeyan, 2012) found that manipulation of the thoracic spine resulted in no measurable change in plasma levels of norepinephrine and epinephrine. Therefore, more research is necessary on this topic to explore this theory further.

Finally, it is suggested that manipulation might contribute towards modulation of blood flow. Currently successful approaches in the treatment of AT are directed at controlling blood flow to the tendon. Peripheral vascular control is modulated, in part, by the IPAG (Carrive, 1991) and also by the activity of the SNS and PNS (see Chapter 2). It is proposed that manipulation might modulate blood flow through its combined effect on the ANS and the l(PAG).
However, it is cautioned that all of the above propositions are theoretical. It is not known if any of these theories might have a clinical effect. Signalling in the central and autonomic nervous system is complex, and far beyond the scope of this Masters thesis. Procedures such as Microdialysis in future studies would help establish the significance of any biochemical changes at the Achilles tendon immediately following spinal manipulation.
Figure 6-1 Proposed manipulation pathway

- Manipulation
  - Altered ANS activity
    - Up-regulation/release ACh
      - Cholinergic anti-inflammatory pathway
  - Altered CNS signalling
    - Stimulate hypothalamus
      - HPA axis
      - Stimulate (nor)adrenaline
        - Vasoregulation
    - Stimulate IPAG

- Decreased AT symptom
6.3 Conclusion

This is the first study to investigate the effect of spinal manipulation as an adjunct to treatment for AT. It is hoped the various limitations of the current pilot study (discussed in Chapter 5, section 5.4.4) might be addressed in future trials to better inform manual therapists on the efficacy of the use of spinal manipulation as an adjunction to eccentric exercises in the treatment of AT.

The pathway through which manipulation may have influenced the behaviour of this condition is unknown, but a number of propositions have been put forward.
7 References


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Appendix A: Letter of provisional acceptance from Manual Therapy

Manual Therapy
29/05/2013

To: kingston_laurn@hotmail.com

Ms. Ref. No.: YNATH-D-12-00184R2
Title: THE EFFECTS OF SPINAL MOBILIZATIONS ON THE SYMPATHETIC NERVOUS SYSTEM: A SYSTEMATIC REVIEW

Manual Therapy

Dear Ms. Laura Kingston,

Thank you very much for sending through the second revision of the above named manuscript to Manual Therapy Journal for reconsideration for publication. Your manuscript has now been re-reviewed and we feel your manuscript has much improved. However, Reviewer 2 still has some comments which need to be addressed which are enclosed for your information and use. Once these changes have been completed, then we can proceed to publication.

The consensus decision therefore is that the manuscript should be returned to you for very minor revisions and we would expect then to receive a revised manuscript from you within four weeks of this letter.

If you are submitting a revised manuscript, please also outline each change made (point by point) as raised in the reviewer comments and/or provide a suitable rebuttal to each reviewer comment not addressed. It is also mandatory to include a ‘clean’ copy of your revised manuscript, along with a copy that includes all amendments highlighted in red.

When revising your manuscript we would ask you to ensure that all referencing adheres to Manual Therapy Journal house style (see Guide for Authors). Therefore when citing multiple references within the text please list these in chronological order, earliest first, latest last.

To submit your revision, please do the following:

1. Go to:
2. Enter your login details
3. Click [Author Login]. This takes you to the Author Main Menu:
4. Click [Submissions Needing Revision]

Please note that this journal offers a new, free service called AudioSlides: brief, webcast-style presentations that are shown next to published articles on ScienceDirect (see also ). If your paper is accepted for publication, you will automatically receive an invitation to create an AudioSlides presentation.

I look forward to receiving your revised manuscript.

Please note that you have a maximum of 6 weeks to resubmit your revision, whereafter your paper will be withdrawn and must be submitted as a new manuscript online at
This will be handled as a new submission and sent to reviewers in the normal manner.

All good wishes,

Yours sincerely,

Ann Moore
Editor
Appendix B: Clinical tests to assess for Achilles tendinopathy (Maffulli et al., 2003)

I. Tenderness on palpation

With the patient in a prone position, the entire length of the Achilles tendon is palpated, gently squeezing the tendon between the thumb and index finger. Participants are asked to confirm whether or not there is tenderness on palpation. This test is considered if there is tenderness on palpation.

II. The painful Arc sign

The participant is asked to dorsi-flex and planter-flex the affected foot in a prone position. In tendinopathy, the area of swelling moves with ankle dorsi-flexion and plantar-flexion. In the absence of swelling the assessor performs the test on an area about 3 cm proximal to the Achilles insertion into the calcaneus.

III. The Royal London Hospital test

The participant is asked to actively dorsi-flex and plantar-flex the ankle once the maximal area of tenderness on palpation is identified. Once the ankle is maximally dorsi-flexed and plantar-flexed, the area of tenderness is again palpated. If the area of tenderness becomes less tender on palpation in maximal dorsi-flexion, the test is considered positive.

A combination of all three tests, together with a post-graduate level of clinical reasoning was used to clinically diagnose Achilles tendinopathy (AT).
Appendix C: Alfredson’s Heavy Load Eccentric Exercise Protocol (Alfredson et al 1998)

The assessor instructs participants on how to perform the eccentric exercises during the initial screening process. The technique is then monitored and modified by the treating physiotherapist or 4th year undergraduate student during the trial. Participants are instructed to perform the exercises two times daily, seven days a week for 12 weeks. During the 12-week training regimen, running is allowed only if it can be performed with mild discomfort and no pain.

The eccentric exercise regime incorporates two exercises; eccentric loading of the calf muscles with knee straight, and to maximize the activation of the deep calf muscle it is also performed with the knee bent. The daily regime is 15 repetitions done in 3 sets (3 X 15 twice per day with knee bent and knee straight). In the beginning the loading consists of the participants body weight, participants stand on their toes with all their body weight on the injured leg. The calf muscles are loaded by having the participant lower the heel beneath the forefoot. No following push up onto the toes is allowed; the non-injured leg is used to get back to the start position. Participants are told to expect some discomfort but to stop if the pain becomes disabling. Appendix H contains the pain scale (NPRS scale). For the purpose of this specific pilot study, it has been agreed with the Lower South Regional Ethics Committee that a score of 6 on the NPRS scale would represent the cut off point for severe pain elicited through exercise. Once the exercise regime can be completed without pain, participants must increase the loading by adding extra weight. This can be done by filling a backpack with successively more weight or by using a weight machine, provided at the School of Physiotherapy clinic.
Information sheet

Manipulative therapy and exercise therapy for the treatment of Achilles tendon pain

Information sheet for participants
You are invited to take part in a study to assess the effectiveness of spinal manipulation combined with specific tendon exercises (called eccentric exercises) to treat Achilles tendon pain. Spinal manipulation is a safe and effective form of manual therapy that helps improve the range of movement in the spine; it is commonly associated with an audible “popping” sound when it is delivered. Please read this information sheet carefully and take your time before deciding whether or not to take part in this study. If you decide to participate, we thank you. If you decide not to take part, there will be no disadvantage to you of any kind, you will still receive the usual treatment and we thank you for considering our request. Please be aware that you may decide at any time to withdraw from the project without any disadvantage to yourself of any kind.

I. If the physiotherapist feels it is not in your best interests, or should any harmful effects appear, your participation in the study will be terminated.

II. If you need an interpreter, one will be provided.

III. You may have a friend, family or whanau support to help you understand the risks/benefits of this study, and for any other explanation you may require.

IV. Your G.P. will be informed of your participation in this study.

V. At the end of the study on-going treatment will be provided under the normal ACC rules if required.
The aim of this project
The aim of this project is to investigate the effect of spinal manipulation in addition to specific tendon exercises (eccentric exercises), for the treatment of Achilles tendon pain.

Participants
If you are between the ages of 18-65 years old you may volunteer to take part. You must have pain in the region of your Achilles tendon, and must not have had surgery and not received any treatment or an injection into the tendon in the previous three months.
Study requirements
All participants in this study receive the standard treatment of exercise that has been shown to be effective as a stand-alone treatment.

Should you agree to participate in this study, you will be randomly allocated into one of two groups. Both groups will receive the standard form of care for this injury (eccentric exercises); one group will also receive in addition, spinal manipulation.

You will be assessed against outcome measures that assess your level of function and pain. During the trial, you will receive eight physiotherapy appointments during which time your exercises will be monitored, and a spinal manipulation given to the appropriate group. For the initial four weeks of this study, it is requested you attend physiotherapy twice weekly for treatment; during these appointments your blood pressure and respiratory rate will also be recorded. The trial runs for a total of 12 weeks, after the initial four weeks, you will be required to continue with your exercise routine at home, for a further eight weeks. During this eight-week period you are encouraged to attend clinic for continued monitoring of your exercise regime once every two weeks, at a time that is convenient for you. You will be free to contact the lead investigator or clinical physiotherapist at any time, and you are encouraged to contact either the lead investigator or clinical therapist should you become concerned for any reason, or in the unlikely event that you feel the exercise regime is contributing to your overall Achilles pain.

At the end of the trial, participants in the standard care group will be offered spinal manipulation, should they request it.

Exercise routine
You will be taught how to perform the exercise routine initially by the lead investigator (during your initial screening), and then by the clinician that will monitor your progress twice weekly for the initial four weeks. The exercises are to be performed twice daily, seven days a week, for 12 weeks. During this 12-week exercise regimen, running is allowed only if it can be performed with mild discomfort and no pain.

Follow up procedure and recording outcomes
At the end of week four and the end of week 12, you will be required to complete a questionnaire about your Achilles tendon pain and your level of function. A clinical therapist will be available to show you how to complete this questionnaire.
Benefits, Risks and Safety

I. Spinal manipulation is a safe and effective technique. It has been shown to reduce both acute and long standing tendon pain in other areas of the body.

II. The lead investigator will screen you to assess if it is safe and appropriate for you to participate in this study.

III. Although rare, spinal manipulation may cause a small amount of soreness along the spine. This soreness is temporary and should last no longer than several seconds to 24 hours.

IV. Muscle and tendon soreness during and after exercise may be experienced. Please be aware some soreness is to be expected and considered a good response when undertaking these exercises. If you are concerned, you are encouraged to discuss this with the clinical physiotherapist, or the lead researcher. Contact details are also provided at the end of this information sheet, should you wish to contact the study supervisor or other members of the research team.

V. Please be aware that every effort will be made to reduce the above risks. The physiotherapist providing the treatment will be an experienced practitioner, familiar with the procedure. S/he will follow strict guidelines to ensure your comfort and safety at all times.

VI. If you follow the exercise guidelines, it is expected that the severity of your Achilles tendon injury will be greatly reduced.

Data collection and use of information

The results of this project may be published but any data included will not be linked to any particular participant. At the end of the study, you are most welcome to request a copy of the results of this study. The data collected will be securely stored in such a way that only the principal investigator will have access to it. All personal information will be destroyed immediately after this study, except that, as required by the University’s research policy. The raw data, which supports the results of this study, will be retained in secure storage for 10 years, after which it will be destroyed.

If you have any Questions?
If you have any questions about our project or would like to report any concern regarding participation on this trial, either now or in the future, please feel free to contact either:

* Please note personal contact details were available to participants of the trial. For the purpose of printing this Masters thesis these personal details have been withdrawn.
Appendix D: Example of Search strategy
Database(s): Ovid MEDLINE(R) 1946 to Present with Daily Update

<table>
<thead>
<tr>
<th>Number</th>
<th>MeSH heading/key word</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>manipulation, spinal</td>
<td>996</td>
</tr>
<tr>
<td>2</td>
<td>Limit 1 to English language and humans</td>
<td>874</td>
</tr>
<tr>
<td>3</td>
<td>sympathetic nervous system/ or vasomotor system/</td>
<td>41,673</td>
</tr>
<tr>
<td>4</td>
<td>limit 3 to (english language and humans)</td>
<td>14,120</td>
</tr>
<tr>
<td>5</td>
<td>spinal mob*.mp.</td>
<td>399</td>
</tr>
<tr>
<td>6</td>
<td>limit 5 to (english language and humans)</td>
<td>352</td>
</tr>
<tr>
<td>7</td>
<td>2 and 4</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>limit 7 to randomized controlled trial</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>4 and 6</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>Limit 9 to randomized controlled trial</td>
<td>1</td>
</tr>
</tbody>
</table>
## Appendix E: PEDro scale

<table>
<thead>
<tr>
<th>PEDro scale</th>
<th>yes</th>
<th>no</th>
<th>where:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. eligibility criteria were specified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. allocation was concealed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. the groups were similar at baseline regarding the most important prognostic indicators</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. there was blinding of all subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. there was blinding of all therapists who administered the therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. there was blinding of all assessors who measured at least one key outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by “intention to treat”</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. the results of between-group statistical comparisons are reported for at least one key outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. the study provides both point measures and measures of variability for at least one key outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The PEDro scale is based on the Delphi list developed by Verhagen and colleagues at the Department of Epidemiology, University of Maastricht (Verhagen AP et al (1998). The Delphi list: a criteria list for quality assessment of randomised clinical trials for conducting systematic reviews developed by Delphi consensus. Journal of Clinical Epidemiology, 51(12):1235-41). The list is based on “expert consensus” not, for the most part, on empirical data. Two additional items not on the Delphi list (PEDro scale items 8 and 10) have been included in the PEDro scale. As more empirical data comes to hand it may become possible to “weight” scale items so that the PEDro score reflects the importance of individual scale items.

The purpose of the PEDro scale is to help the users of the PEDro database rapidly identify which of the known or suspected randomised clinical trials (ie RCTs or CCTs) archived on the PEDro database are likely to be internally valid (criteria 2-9), and could have sufficient statistical information to make their results interpretable (criteria 10-11). An additional criterion (criterion 1) that relates to the external validity (or “generalisability” or “applicability” of the trial) has been retained so that the Delphi list is complete, but this criterion will not be used to calculate the PEDro score reported on the PEDro web site.

The PEDro scale should not be used as a measure of the “validity” of a study’s conclusions. In particular, we caution users of the PEDro scale that studies which show significant treatment effects and which score highly on the PEDro scale do not necessarily provide evidence that the treatment is clinically useful. Additional considerations include whether the treatment effect was big enough to be clinically worthwhile, whether the positive effects of the treatment outweigh its negative effects, and the cost-effectiveness of the treatment. The scale should not be used to compare the “quality” of trials performed in different areas of therapy, primarily because it is not possible to satisfy all scale items in some areas of physiotherapy practice.

Last amended June 21st, 1999
Notes on administration of the PEDro scale:

**All criteria**

Points are only awarded when a criterion is clearly satisfied. If on a literal reading of the trial report it is possible that a criterion was not satisfied, a point should not be awarded for that criterion.

**Criterion 1**

This criterion is satisfied if the report describes the source of subjects and a list of criteria used to determine who was eligible to participate in the study.

**Criterion 2**

A study is considered to have used random allocation if the report states that allocation was random. The precise method of randomisation need not be specified. Procedures such as coin-tossing and dice-rolling should be considered random. Quasi-randomisation allocation procedures such as allocation by hospital record number or birth date, or alternation, do not satisfy this criterion.

**Criterion 3**

Concealed allocation means that the person who determined if a subject was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated to. A point is awarded for this criterion, even if it is not stated that allocation was concealed, when the report states that allocation was by sealed opaque envelopes or that allocation involved contacting the holder of the allocation schedule who was “off-site”.

**Criterion 4**

At a minimum, in studies of therapeutic interventions, the report must describe at least one measure of the severity of the condition being treated and at least one (different) key outcome measure at baseline. The rater must be satisfied that the groups’ outcomes would not be expected to differ, on the basis of baseline differences in prognostic variables alone, by a clinically significant amount. This criterion is satisfied even if only baseline data of study completers are presented.

**Criterion 4, 7-11**

Key outcomes are those outcomes which provide the primary measure of the effectiveness (or lack of effectiveness) of the therapy. In most studies, more than one variable is used as an outcome measure.

**Criterion 5-7**

Blinding means the person in question (subject, therapist or assessor) did not know which group the subject had been allocated to. In addition, subjects and therapists are only considered to be “blind” if it could be expected that they would have been unable to distinguish between the treatments applied to different groups. In trials in which key outcomes are self-reported (eg, visual analogue scale, pain diary), the assessor is considered to be blind if the subject was blind.

**Criterion 8**

This criterion is only satisfied if the report explicitly states both the number of subjects initially allocated to groups and the number of subjects from whom key outcome measures were obtained. In trials in which outcomes are measured at several points in time, a key outcome must have been measured in more than 85% of subjects at one of those points in time.

**Criterion 9**

An intention to treat analysis means that, where subjects did not receive treatment (or the control condition) as allocated, and where measures of outcomes were available, the analysis was performed as if subjects received the treatment (or control condition) they were allocated to. This criterion is satisfied, even if there is no mention of analysis by intention to treat, if the report explicitly states that all subjects received treatment or control conditions as allocated.

**Criterion 10**

A between-group statistical comparison involves statistical comparison of one group with another. Depending on the design of the study, this may involve comparison of two or more treatments, or comparison of treatment with a control condition. The analysis may be a simple comparison of outcomes measured after the treatment was administered, or a comparison of the change in one group with the change in another (when a factorial analysis of variance has been used to analyse the data, the latter is often reported as a group × time interaction). The comparison may be in the form of analysis by intention to treat, if the report explicitly states that all subjects received treatment or control conditions as allocated.

**Criterion 11**

A point measure is a measure of the size of the treatment effect. The treatment effect may be described as a difference in group outcomes, or as the outcome in (each of) all groups. Measures of variability include standard deviations, standard errors, confidence intervals, interquartile ranges (or other quantile ranges), and ranges. Point measures and/or measures of variability may be provided graphically (for example, by SDs may be given as error bars in a Figure) as long as it is clear what is being graphed (for example, as long as it is clear whether error bars represent SDs or SEs). Where outcomes are categorical, this criterion is considered to have been met if the number of subjects in each category is given for each group.
Appendix F: Ethical approval

21 June 2012

Mr Steve Tumilty
University of Otago - School of Physiotherapy
School of Physiotherapy
Otago University
Dunedin

Dear Mr Tumilty

Re: Ethics ref: LRS/12/05/011 (please quote in all correspondence)

Study title: To investigate the effects of spinal manipulation for Achilles tendinopathy; a pilot study

Investigators: Mr Steve Tumilty, Laura Kingston, Dr Leica Claydon, Professor David Baxter

Sites: University of Otago

This study was given ethical approval by the Lower South Regional Ethics Committee on 21 June 2012.

- Part 4 signed by Dr Steve Tumilty
- Form A
- Protocol
- Consent Form
- Interview Guidelines
- End of Treatment Phase Questionnaire
- Compliance Log
- Advertisement
- Locality Assessment for University of Otago
- Signed Form A
- Letter dated 17 April 2012 from Ngai Tahu Research Consultation Committee
- Letter dated 8 June 2012 to Ngai Tahu in response
- Page 13 Participant Information Sheet

This approval is valid until 28 February 2013, provided that Annual Progress Reports are submitted (see below).

Access to ACC

For the purposes of section 32 of the Accident Compensation Act 2001, the Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out. Participants injured as a result of treatment received in this trial will therefore be eligible to be considered for compensation in respect of those injuries under the ACC scheme.

Amendments and Protocol Deviations

All significant amendments to this proposal must receive prior approval from the Committee. Significant amendments include (but are not limited to) changes to:
Maori consultation

NGĀI TAHU RESEARCH CONSULTATION COMMITTEE
TE KOMITI RAKAHU KI KĀI TAHU

17/04/2012 - 12
Wednesday, 18 April 2012

Dr Tumilty
School of Physiotherapy
Dunedin

Tēnā koe Dr Tumilty

Title: To investigate the effects of an osteopathic manipulation in chronic Achilles tendinopathy; A Pilot Study.

The Ngāi Tahu Research Consultation Committee (The Committee) met on Tuesday, 17 April 2012 to discuss your research proposition.

By way of introduction, this response from the Committee is provided as part of the Memorandum of Understanding between Te Rūnanga o Ngāi Tahu and the University. In the statement of principles of the memorandum, it states "Ngāi Tahu acknowledges that the consultation process outlined in this policy provides no power of veto by Ngāi Tahu to research undertaken at the University of Otago". As such, this response is not "approval" or "mandate" for the research, rather it is a mandated response from a Ngāi Tahu appointed committee. This process is part of a number of requirements for researchers to undertake and does not cover other issues relating to ethics, including methodology; they are separate requirements with other committees, for example the Human Ethics Committee, etc.

Within the context of the Policy for Research Consultation with Māori, the Committee base consultation on that defined by Justice McGechan:

"Consultation does not mean negotiation or agreement. It means: setting out a proposal not fully decided upon; adequately informing a party about relevant information upon which the proposal is based; listening to what the others have to say with an open mind (in that there is room to be persuaded against the proposal); undertaking that task in a genuine and not cosmetic manner. Reaching a decision that may or may not alter the original proposal."

The Committee considers the research to be of importance to Māori health.

The Committee notes and commends that ethnicity data is to be collected as part of the research project and recommends the use of the questions on self-identified ethnicity and descent, these questions are contained in the 2006 census.

The Committee notes the researchers have identified that a, “…protocol that is culturally sensitive to Māori will be strictly adhered to…,” and asks what the researchers understand by a “culturally sensitive protocol”. The Committee is also interested to know who the translator is.

The Ngāi Tahu Research Consultation Committee has membership from:

Te Rūnanga o Ōtākou Incorporated
Kāti Huirapa Rūnaka ki Puketeraki
Te Rūnanga o Moeraki
8th June 2012

Dr. Mark Brunton
Office of Maori Development

Study Title: To investigate the effects of an Osteopathic manipulation in chronic Achilles tendinopathy: a pilot study.

Dear Dr. Brunton,

Thank you for your response and feedback regarding this research project. The researchers involved in this project have taken the time to read the Māori Health publications on the Ministry of Health website, and appreciate The Committees recommendation.

In response to The Committees enquiry into the researchers understanding of a culturally sensitive protocol, the researchers would like to take the opportunity to explain their understanding of cultural sensitivity, and how this is incorporated into the research protocol; i.e. a culturally sensitive protocol.

The researchers understanding of cultural sensitivity involves, first of all, the researchers understanding and appreciation of their own cultural biases. Once this has been recognized and accepted, they can then acknowledge and accept the legitimate differences between their own culture, and that of the Māori. The researchers recognize and accept that Māori are a diverse population, and may exhibit different cultural biases depending on influences such as age, gender, political orientation and religion etc.

The researchers have considered their own cultural perspective and how this may hinder effective delivery of their service to Māori participants. The researchers understanding of a culturally sensitive protocol is one that advocates that all individuals involved in this research (of any ethnicity) acknowledge and respect these potential differences. Each individual on the current research team will strictly adhere to this culturally sensitive approach.

As employees of the University of Otago the researchers and the therapist involved in this study must follow the University’s policy (Policy 2.3.3 in the Policies and Procedures Handbook in the School of Physiotherapy clinic) for incorporating this approach into their practice at all times. Each staff member involved in this study attends at least one in-service dedicated to this topic per year, in accordance with University policy (Policy 2.3.3).
If a translator or interpreter is required by any of the participants involved in this research, one will be provided. Once it is known which dialect requires translation and/or interpretation, Dr. Jim Williams, at Te Tumu, will arrange for one to be provided. It is not possible to provide you with a name for the translator and/or interpreter, until it is known which dialect requires translation. There will be no cost to the participant for this service.

Finally, the researchers would also like to take this opportunity to inform The Committee of a minor change in title for this research project. The new title is: "To investigate the effects of spinal manipulation for Achilles tendinopathy: a pilot study".

I hope our responses answer your questions adequately.

Yours Sincerely

Dr. Steve Tumility
Appendix G: Consent Form

Consent form for participants

Manipulative therapy and exercise therapy for the treatment of Achilles tendon pain

Request form for an interpreter

<table>
<thead>
<tr>
<th>Language</th>
<th>Request in Language</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>English</td>
<td>I wish to have an interpreter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero</td>
<td>Ae</td>
<td>Kao</td>
</tr>
<tr>
<td>Cook Island</td>
<td>Ka inangaro au I tetai tangata uri reo</td>
<td>Ae</td>
<td>Kare</td>
</tr>
<tr>
<td>Fijian</td>
<td>Au gadreva me dua e vakadewa vosa vei au</td>
<td>Io</td>
<td>Sega</td>
</tr>
<tr>
<td>Niuean</td>
<td>Fia manako au ke fakaaoaga e taha tagata fakahokohoko kupu</td>
<td>E</td>
<td>Nakai</td>
</tr>
<tr>
<td>Samoan</td>
<td>Ou te mana’o ia I ai se fa’amatala upu</td>
<td>Ioe</td>
<td>Leai</td>
</tr>
<tr>
<td>Tokelaun</td>
<td>Ko au e fofou ki he tino ke fakaliliu te gagana Peletania kin a gagana o na motu o te Pahafika</td>
<td>Ioe</td>
<td>Leai</td>
</tr>
<tr>
<td>Tongan</td>
<td>Oku ou fiemaú ha fakatonulea</td>
<td>Io</td>
<td>Ikai</td>
</tr>
</tbody>
</table>
I have read the information sheet dated July 2012 for volunteers taking part in the study designed to assess the effectiveness of exercise and spinal manipulation to treat Achilles tendon injury. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I have had the opportunity to use whanau support or a friend to help me ask questions and understand the study.

- I understand that taking part in the study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way effect my future health care/continuing health care.
- I understand that my participation in this study is confidential and that no material, which could identify me, will be used in any reports on this study.
- I understand that the treatment, or investigation, will be stopped if it should appear harmful to me.
- I understand the compensation provisions for this study.
- I have had time to consider whether to take part.
- I know whom to contact if I have any side effects to the study.

I wish to receive a copy of the results through the post. YES/NO

Participants should be advised that a significant delay may occur between data collection and publication of results.

Alternatively, I would like the researcher to discuss the outcomes of the study with me. YES/NO

I agree to my G.P. or other current provider being informed of my participation in this study/the results of my participation in this study. YES/NO

I ………………………………………………..(type name) hereby consent to take part in this study.

……………………………………..…………………………
(Signature of participant) (Date)

………………………………………
(Signature of researcher) (Date)
Appendix H: Achilles VISA-A Questionnaire

The VISA-A questionnaire: An index of the severity of Achilles tendinopathy

**IN THIS QUESTIONNAIRE, THE TERM PAIN REFERS SPECIFICALLY TO PAIN IN THE ACHILLES TENDON REGION**

1. For how many minutes do you have stiffness in the Achilles region on first getting up?

<table>
<thead>
<tr>
<th>0 mins</th>
<th>100 mins</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
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<tr>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

2. Once you are warmed up for the day, do you have pain when stretching the Achilles tendon fully over the edge of a step? (keeping knee straight)

<table>
<thead>
<tr>
<th>strong severe pain</th>
<th>no pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
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<tr>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

3. After walking on flat ground for 30 minutes, do you have pain within the next 2 hours? (If unable to walk on flat ground for 30 minutes because of pain, score 0 for this question).

<table>
<thead>
<tr>
<th>strong severe pain</th>
<th>no pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>
4. Do you have pain walking downstairs with a normal gait cycle?

<table>
<thead>
<tr>
<th>Strong</th>
<th>Severe</th>
<th>Pain</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>No pain</td>
<td></td>
</tr>
</tbody>
</table>

5. Do you have pain during or immediately after doing 10 (single leg) heel raises from a flat surface?

<table>
<thead>
<tr>
<th>Strong</th>
<th>Severe</th>
<th>Pain</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
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6. How many single leg hops can you do without pain?

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7. Are you currently undertaking sport or other physical activity?

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<td>Full training ± competition but not at same level as when symptoms began</td>
<td>Competing at the same or higher level as when symptoms began</td>
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8. Please complete EITHER A, B or C in this question.

- If you have **no pain** while undertaking **Achilles tendon loading sports** please complete Q8a only.
- If you have **pain** while undertaking **Achilles tendon loading sports** but it does **not stop you from completing the activity**, please complete Q8b only.
- If you have **pain which stops you** from completing **Achilles tendon loading sports**, please complete Q8c only.

**A.** If you have **no pain** while undertaking **Achilles tendon loading sports**, for how long can you train/practise?

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**OR**

**B.** If you have some pain while undertaking **Achilles tendon loading sport**, but it does **not stop you from completing your training/practice** for how long can you train/practise?

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**OR**

**C.** If you have **pain that stops you** from completing your training/practice in **Achilles tendon loading sport**, for how long can you train/practise?

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**TOTAL SCORE** ( /100)
Appendix I: NPRS scoring scheme

NPRS scoring scheme

(Point to one number):

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## Appendix J: Raw data for primary and secondary outcome measures

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Appendix K: Effect size and power calculation

First of all, the pooled SD at baseline is calculated. As there are uneven numbers of participants in each group, the following calculation is used.

\[ \frac{\text{SD} \times 10 \text{ (i.e. the number of participants in the manipulation group)) + SD} \times 5 \text{ (i.e. the number of participants in the standard care group))}}{15 \text{ (i.e. the total number or participants that completed the trial.)}} \]

**For VISA-A calculation:**

\[ (13.7 \times 10) + (25.1 \times 5) \div 15 = 17.5 \text{ pooled SD at baseline} \]

**For NPRS**

\[ (0.9 \times 10) + (1.4 \times 5) \div 15 = 1.06 \text{ pooled SD at baseline} \]

To work out the effect size the following calculation is used:

Manipulation mean at time-point minus control mean at time-point ÷ pool SD at baseline

**VISA-A effect size at week 4**

\[ 76.7 – 73.4 \div 17.5 = 0.18 \text{ less than small effect size} \]

**VISA-A effect size at week 12**

\[ 82-58.5 \div 17.5 = 1.34 \text{large effect size} \]