

An Investigation into the use of Stochastic Resonance Electrical Stimulation and Knee Sleeve to Improve Proprioception, Postural Control, and Gait Biomechanics in the Osteoarthritic Knee.

Amber Taylor Collins

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Biomedical Engineering.

Chapel Hill
2010

Approved By:

Paul S. Weinhold, PhD

J. Troy Blackburn, PhD

Bing Yu, PhD

Joanne Jordan, MD

Mark Tommerdahl, PhD

ABSTRACT

AMBER COLLINS: An Investigation into the use of Stochastic Resonance Electrical Stimulation and Knee Sleeve to Improve Proprioception, Postural Control, and Gait Biomechanics in the Osteoarthritic Knee.
(Under the direction of Paul S. Weinhold)

Knee osteoarthritis (OA) is a common joint disorder and a leading cause of disability in the US. Current treatment options focus on symptom modification rather than preventing or delaying OA progression. Abnormal proprioception has been demonstrated in this population and improvements in proprioception may lead to secondary improvements in postural control and in walking biomechanics. Stochastic resonance (SR), a novel phenomenon in which the introduction of subthreshold electrical or mechanical “noise” into a sensory system increases its sensitivity to weak stimuli, may be a disease-modifying treatment by way of enhancing proprioception. By incorporation of SR into a knee sleeve for clinical applicability, we aimed to determine whether proprioception, postural control and gait biomechanics would improve in those with osteoarthritis of the knee.

Proprioception was assessed via joint position sense (JPS) in those with minimal to moderate, medial knee OA under several conditions that combine SR and a neoprene knee sleeve in both a partial weight bearing (PWB) and a nonweight bearing (NWB) task. Gait kinetics and kinematics as well as postural control were also assessed under similar treatment conditions combining SR and a knee sleeve.

JPS was improved with the combination of SR and a knee sleeve as well as with the sleeve alone in a PWB task relative to the control condition, with no difference between the

treatment conditions and no improvements in the NWB task. Similarly, gait kinetics and kinematics, and postural control measures improved with the combination of SR and a knee sleeve as well as with the sleeve alone compared to the control condition; however no improvements were seen between the combination of SR and knee sleeve and the sleeve alone conditions.

The improvement of JPS during a PWB task with a neoprene knee sleeve is a novel finding and these improvements in JPS may be the cause of further improvements in walking biomechanics and postural control measures when wearing a sleeve. However, there seems to be no added benefit of SR; perhaps optimization of SR's parameters may lead to future improvements with this therapy in those with knee OA or other populations with neuromuscular deficits.

To my husband BJ, I couldn't have done this without you.

ACKNOWLEDGEMENTS

In acknowledgement of all the advice and guidance provided throughout my graduate experience, I would like to thank my research advisor and committee chair, Paul Weinhold, as well as Troy Blackburn. I would also like to thank the other members of my committee for their guidance and support.

A special thank you goes to Afferent Corporation, the UNC Chapel Hill Department of Orthopaedics, and the Arthritis Foundation for their financial support, without which this research could not have been completed.

I'd like to thank the Orthopaedic residents for their help with subject recruitment and radiograph assessments. Also, I'd like to give a special thank you to the undergraduate and graduate research assistants who helped me during the countless hours of subject testing.

Above all, I would like to thank my family and friends whose love and support have helped me endure the long road of attaining my doctoral degree.

TABLE OF CONTENTS

LIST OF TABLES	xi
LIST OF FIGURES	xii
LIST OF ABBREVIATIONS	xiv
CHAPTER 1. INTRODUCTION	1
CHAPTER 2. BACKGROUND	3
2.1. Osteoarthritis	3
2.2. Treatment options	4
2.3. Proprioception	7
2.4. Proprioception and Knee OA	9
2.5. Knee OA Biomechanics	10
2.6. Knee OA Postural Control	14
2.7. Knee Braces/Sleeves	15
2.8. Stochastic Resonance	18
2.9. References	23
CHAPTER 3. SPECIFIC AIMS & HYPOTHESES	31
3.1. Specific Aim 1	31
3.2. Specific Aim 2	31
3.3. Specific Aim 3	32
CHAPTER 4. STOCHASTIC RESONANCE ELECTRICAL STIMULATION TO IMPROVE PROPRIOCEPTION IN KNEE OSTEOARTHRITIS	34

4.1. Introduction.....	34
4.2. Methods.....	36
4.2.1. <i>Patients</i>	36
4.2.2. <i>Study Design</i>	38
4.2.3. <i>Equipment</i>	39
4.2.4. <i>Procedure</i>	40
4.2.5. <i>Statistical Analysis</i>	42
4.3. Results.....	43
4.3.1. <i>PWB</i>	44
4.3.2. <i>NWB</i>	44
4.3.3. <i>Correlations</i>	45
4.4. Discussion	47
4.5. References.....	52
CHAPTER 5. THE IMPACT OF STOCHASTIC RESONANCE ELECTRICAL STIMULATION AND KNEE SLEEVE ON IMPULSIVE LOADING AND MUSCLE CO-CONTRACTION DURING GAIT IN KNEE OSTEOARTHRITIS	56
5.1. Introduction.....	56
5.2. Materials & Methods	58
5.2.1. <i>Subjects</i>	58
5.2.2. <i>Study Design</i>	59
5.2.3. <i>Gait Analysis</i>	60
5.2.4. <i>EMG measurements</i>	60
5.2.5. <i>SR stimulation and sleeve</i>	61
5.2.6. <i>Data Collection</i>	61

5.2.7. <i>Data Reduction</i>	62
5.2.8. <i>Statistical Analysis</i>	64
5.3. Results.....	65
5.3.1. <i>Subject Demographics</i>	65
5.3.2. <i>Loading Rate parameters</i>	66
5.3.3. <i>Kinematic parameters</i>	66
5.3.4. <i>EMG parameters</i>	67
5.3.5. <i>VL/LH co-contraction</i>	69
5.3.6. <i>VL/MH co-contraction</i>	70
5.4. Discussion	71
5.5. References.....	75
CHAPTER 6. THE ASSESSMENT OF POSTURAL CONTROL WITH STOCHASTIC RESONANCE ELECTRICAL STIMULATION AND A NEOPRENE KNEE SLEEVE IN THE OSTEOARTHRITIC KNEE	79
6.1. Introduction.....	79
6.2. Methods.....	81
6.2.1. <i>Subjects</i>	81
6.2.2. <i>Study Design</i>	81
6.2.3. <i>Data Collection</i>	82
6.2.4. <i>Data Reduction</i>	84
6.2.5. <i>Statistical Analysis</i>	85
6.3. Results.....	85
6.3.1. <i>Subject Demographics</i>	85
6.3.2. <i>COP displacement range</i>	86

6.3.3. <i>SD COP displacement</i>	88
6.3.4. <i>COP velocity</i>	89
6.3.5. <i>COP path length</i>	91
6.3.6. <i>Control condition comparison</i>	91
6.3.7. <i>Regression analysis</i>	92
6.4. Discussion	92
6.5. References.....	96
CHAPTER 7. A KINETIC AND KINEMATIC ANALYSIS OF THE EFFECT OF STOCHASTIC RESONANCE AND KNEE SLEEVE DURING GAIT IN OSTEOARTHRITIS OF THE KNEE	99
7.1. Introduction.....	99
7.2. Materials & Methods	101
7.2.1. <i>Subjects</i>	101
7.2.2. <i>Study Design</i>	102
7.2.3. <i>Data Collection</i>	103
7.2.4. <i>Data Reduction</i>	104
7.2.5. <i>Statistical Analysis</i>	106
7.3. Results.....	106
7.3.1. <i>Subject Demographics</i>	106
7.3.2. <i>Kinematic parameters</i>	107
7.3.3. <i>Kinetic parameters</i>	111
7.3.4. <i>Methodological Issue</i>	112
7.4. Discussion	113
7.5. References.....	116

CHAPTER 8. DISCUSSION.....	120
8.1. Limitations to Methodological Approach.....	120
8.2. Future Directions	124
8.3. Conclusions.....	125
8.4. References.....	128
APPENDIX A. IRB APPLICATION – JPS STUDY.....	129
APPENDIX B. SUBJECT CONSENT FORM – JPS STUDY	140
APPENDIX C. HIPAA AUTHORIZATION FORM – JPS STUDY	145
APPENDIX D. SUBJECT QUESTIONNAIRE – DEMOGRAPHIC	147
APPENDIX E. SUBJECT QUESTIONNAIRE – SELF REPORTED MEASURE OF KNEE INSTABILITY	148
APPENDIX F. SUBJECT QUESTIONNAIRE – KOOS KNEE SURVEY.....	149
APPENDIX G. JPS NWB SETUP	153
APPENDIX H. ELECTRODE PLACEMENT ABOUT THE KNEE FOR STUDIES 1 & 2.....	154
APPENDIX I. IRB APPLICATION – GAIT/POSTURAL CONTROL STUDY	155
APPENDIX J. SUBJECT CONSENT FORM – GAIT/POSTURAL CONTROL STUDY	167
APPENDIX K. HIPAA AUTHORIZATION FORM – GAIT/POSTURAL CONTROL STUDY	171

LIST OF TABLES

Table 1. Mean (+/- sd) demographic information for all test subjects- JPS	37
Table 2. Mean (+/- sd) absolute errors (degrees) for all conditions in both the PWB and NWB tasks. Significant differences were found between the average of the two control conditions (NE/NS) and NE/S as well as E75/S conditions (* indicates significant difference).	45
Table 3. Spearman correlation analysis results detailing the relationship between the control average (NE/NS) condition and various subject measures. Bold indicates significant correlations exist between the two measures.	47
Table 4. Mean (sd) demographics as well as subject reported pain, stiffness, functionality, and instability measures for all test subjects – Loading rate	59
Table 5. Mean (sd) kinematic and kinetic measures during gait within the three testing conditions. † indicates significant difference compared to the average control (NE:NSave). ‡ indicates significant difference compared to the sleeve alone condition, p<0.05. MF=max knee flexion; IC=initial ground contact.....	67
Table 6. Mean (sd) SEMG muscle activity (VL, MH, LH) during each of the three phases of gait (Preparatory, weight acceptance, midstance). Values are normalized to the average peak activity in the control conditions for that specific muscle. † indicates significant differences relative to the control condition (NE:NSave) by RMANOVA. ‡ indicates significant differences relative to the sleeve alone condition (NE:S) by RMANOVA (p<0.05). ^{A,B} indicates significant difference relative to the control ^A or sleeve ^B alone condition by paired t-test comparison of the difference between conditions of the uncorrected data and the quiet trial difference (p<0.025).	68
Table 7. Mean (sd) demographics as well as subject reported pain, stiffness, functionality, and instability measures for all test subjects – Postural Control	86
Table 8. 1 st , 2 nd and 3 rd quartile values for center of pressure range (mm) and standard deviation (mm) in the anterior-posterior and medial-lateral directions during single leg stance for all test subjects.	89
Table 9. Mean (sd) demographics as well as subject reported pain, stiffness, functionality, and instability measures for all test subjects - Kinetics & Kinematics	107
Table 10. Mean (sd) maximum and minimum values of all data (non-normalized as a % of stance) during the weight acceptance and midstance phases of gait. † indicates the presence of a significant difference between the treatment conditions and the control condition (NE:NSave), p<0.05. There were no significant differences between the two treatment conditions (NE/S, E75/S).....	109

LIST OF FIGURES

Figure 1. The osteoarthritis/proprioception cycle theory.....	10
Figure 2. PWB setup simulating single leg stance. Also shown are the electrolytic tilt sensors on the thigh and shank. SR stimulation electrode placement is also depicted here with only the lateral electrodes visible.....	42
Figure 3. Average absolute error for the three conditions (NE/NS, E75/S, and NE/S) in both the NWB and PWB tasks. * indicates significant differences between conditions at the end of the horizontal bar ($p<0.05$).	45
Figure 4. The relationship between the absolute error (degrees) of the average control condition (NE/NS0 and the improvement in absolute error seen in the E75/S condition relative to the average control condition in the PWB task.	46
Figure 5. Vertical component of ground reaction force demonstrating loading rate outcome measures with respect to the generated data plot from a sample test subject	63
Figure 6. Loading rate outcome measures within each of the three testing conditions. * indicates significant differences between conditions at the end of the horizontal bars, $p<0.05$	66
Figure 7. Co-contraction indices of the VL/LH muscle groups. *indicates significant differences (RMANOVA) between the conditions at the end of the horizontal bars, $p<0.05$. ^A indicates significant difference between the conditions at the end of the horizontal bars, by paired t-test comparison of the difference between conditions of the uncorrected data and a quiet trial co-contraction indices ($p<0.025$).	69
Figure 8. Co-contraction indices of the VL/MH muscle groups. *indicates significant differences (RMANOVA) between the conditions at the end of the horizontal bars, $p<0.05$. ^A indicates significant difference between the conditions at the end of the horizontal bars, by paired t-test comparison of the difference between conditions of the uncorrected data and a quiet trial co-contraction indices ($p<0.025$).	70
Figure 9. Subject setup during the balance assessment demonstrating single-leg stance.....	84
Figure 10. Stabilograms demonstrating the displacement of center of pressure in the anterior-posterior (AP) and medial-lateral (ML) directions during a single trial for three of the testing conditions: NE:NSave, NE:S, E150:S.	88
Figure 11. Results from the Friedman Repeated Measures ANOVA on ranks include median COP velocity (mm/s) in the anterior-posterior (AP) direction during all five testing conditions. * indicates a significant difference between conditions at the end of the horizontal bars.	90

Figure 12. Results from the Friedman Repeated Measures ANOVA on ranks include median COP velocity (mm/s) in the medial-lateral (ML) direction during all five testing conditions. No differences with treatment conditions were found ($p>0.05$).....	90
Figure 13. Results from the Frieman Repeated Measures ANOVA on ranks include median COP normalized total path length (mm) during all five testing conditions. * indicates a significant difference between conditions at the end of the horizontal bars.....	91
Figure 14. Average curves for all test subjects as a % of stance. Stance phase is defined as the point from heel contact through toe-off. (Left) Knee flexion/extension, adduction/abduction, internal/external angles during gait. (Right) Internal knee moments in the sagittal, frontal, and transverse planes. Knee flexion, adduction, and internal rotation angles and moments are positive. Solid black-NE/NSave; solid grey-NE/S; dashed-E75/S.	108
Figure 15. Knee flexion angle 100 ms prior to and after ground contact. Dashed vertical lines indicate the amount of time(ms) taken to prepare for ground contact. Preparatory time was defined as the period from minimum knee flexion angle to ground contact.....	111

LIST OF ABBREVIATIONS

*must be in alphabetical order starting here

AP	Anterior/Posterior
COP	Center of pressure
CNS	Central nervous system
DMOADs	Disease modifying osteoarthritis drugs
EMG	Electromyography
IC	Initial contact
IRB	Institutional Review Board
KOOS	Knee Injury and Osteoarthritis Outcome Score
KL	Kellgren-Lawrence
HST	Heel strike transient
LH	Lateral hamstring
MH	Medial hamstring
ML	Medial/Lateral
NWB	Nonweight bearing
NSAIDS	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
JPS	Joint position sense
PWB	Partial weight bearing
PES	Pulsed electrical stimulation
QA	Quick adapting
RMS	Root mean square

SA	Slow adapting
SR	Stochastic resonance
TENS	Transcutaneous electrical nerve stimulation
VL	Vastus lateralis
WOMAC	Western Ontario McMaster Universities

CHAPTER 1. INTRODUCTION

Osteoarthritis (OA) is a common joint disorder characterized by pain, disability, and loss of function. It is the most common joint disorder in the United States and is associated with significant health and welfare costs. OA of the knee is especially common and debilitating, and is one of the five leading causes of disability among non-institutionalized elderly men and women. Currently, there are many noninvasive symptom-modifying treatment options for knee OA including: weight loss, NSAIDS (nonsteroidal anti-inflammatory drugs), physical therapy, TENS (transcutaneous electrical nerve stimulation), knee braces, foot orthotics, and steroid injections. These treatments mainly serve as symptom-modifiers, reducing pain and improving function, with no attempt at preventing the onset or progression of knee OA. However, there are a few “disease-modifying” drugs currently being explored, but none have been approved by the FDA. One option designed to target the mechanical factors of knee OA, thus qualifying it as a potential disease-modifier, is the medial unloader brace which is designed to promote optimal alignment of the knee. Many speculate that knee braces and sleeves may function mainly by providing the perception of increased stability via an improvement in proprioception, rather than biomechanical reinforcement.

Proprioception is defined as the conscious and unconscious perception of limb movement and position in space, and is measured either through joint position sense or joint motion sense (kinesthesia). Studies have shown proprioception to be diminished in subjects with knee OA and to be less accurate during nonweight bearing tasks compared to weight

bearing tasks. An improvement in proprioception may, in fact, positively change how the knee joint is loaded during dynamic activities such as walking and during static balance. The use of knee braces and sleeves has been shown to cause such improvements in proprioception. Further, proprioception may also be enhanced through a novel concept known as stochastic resonance electrical stimulation (SR) in which the detection and transmission of weak signals is enhanced through subsensory electrical or mechanical stimulation. By applying SR stimulation, studies have previously shown improvements in tactile sensation, the sensitivity of muscle spindles, as well as balance in the elderly, those with diabetic neuropathy, and stroke.

We wish to investigate the use of SR in combination with a neoprene knee sleeve as a possible way to improve proprioception (measured by joint position sense) in both a weight bearing and nonweight bearing task in individuals with knee OA. The use of a neoprene knee sleeve in our study stems from the clinical application of this potential therapy where the SR stimulation would be incorporated into a brace or sleeve worn by the patient. It is important to note the potential cascade effect of enhanced proprioception where an improvement in one's proprioception may result in more appropriate joint loading during weightbearing, dynamic activities such as walking, thus reducing or preventing abnormal wear within the joint itself. Additionally, SR has shown promise in enhancing balance control in the elderly and this improved balance control may be the result of enhanced sensory proprioceptive input. As such, we also wish to explore the effects of SR combined with a knee sleeve on balance and walking biomechanics in subjects with knee OA.

CHAPTER 2. BACKGROUND

2.1. Osteoarthritis

Osteoarthritis (OA) is the most common form of arthritis with symptomatic knee OA occurring in roughly 6% of U.S. adults 30 years and older [1]. Forecasts indicate that by the year 2030, nearly 67 million people (roughly 25% of the US population) will have physician-diagnosed arthritis [2]. Its economic costs are enormous with an estimated \$185.5 billion increase in aggregate annual medical care expenditures [3].

Osteoarthritis is most commonly defined as a disease that results from the combination of mechanical and biological events that destabilize the joint and its normal degradation and synthesis of the natural tissues which exist in and around the joint. OA occurs when the equilibrium between breakdown and repair of the joint tissues is disturbed and becomes unbalanced. The disease not only affects articular cartilage but it also involves other components of the joint including ligament, capsule, synovial membrane, subchondral bone, and menisci. Its symptoms include joint pain, stiffness, tenderness, swelling, crepitus, and inflammation. Diagnosis of knee OA is primarily based on radiological evidence as some people are asymptomatic with knee OA graded radiographically based on the Kellgren-Lawrence grading system as follows: 0=normal, 1=possible osteophytic lipping, 2=definite osteophytes and possible joint space narrowing, 3=multiple, moderate osteophytes and definite joint space narrowing and some sclerosis and possible bone contour deformity, 4=large osteophytes, marked joint space narrowing, severe sclerosis, and definite bone contour deformity [4]. OA is specifically classified by the American College of

Rheumatology as either primary or secondary based on whether the cause of the disease is unknown (idiopathic, primary) or whether it results from a known medical condition or event (secondary) [5]. Primary OA risk factors include: advanced age, obesity, gender (with females at an increased risk), higher bone mineral density, and genetic predisposition. Age is the strongest determinant of OA and even though the mechanism by which age predisposes to osteoarthritis is unclear, it is known that aging cartilage is susceptible to injury and degradation [6]. Additionally, women are at greater risk of developing OA, most likely due to the changes in sex hormones after menopause and the effects these change have on the joint tissues [7]. Another important primary risk factor, and one that is preventable, is obesity. Obesity has been strongly linked to the development of OA, specifically knee OA, and results in high mechanical stress on the load bearing joint [8]. The secondary risk factors for OA include: trauma, acute joint injury, knee instability, proprioceptive deficits, muscle weakness, metabolic disorders, nutritional factors, and coronal malalignment. OA is a very common disease, especially in the older population with knee OA being especially common and debilitating, thus highlighting the importance for novel treatment options.

2.2. Treatment options

Currently, there are a multitude of treatment options for knee OA. However, most treatments focus solely on the improvement of pain and functionality with little attempt at disease-modification through the improvement of joint structure. One negative aspect of treatments focused on symptom modification is the risk of further disease progression through joint injury when the protective pain mechanism is not present. Some of the current symptom modifying, nonsurgical treatment options for knee OA include: NSAIDs (non-steroidal anti-inflammatory drugs), steroid injections, TENS (transcutaneous electrical nerve

stimulation), knee braces, foot orthotics, physical therapy, and weight loss. Many studies have reported relationships between obesity and knee osteoarthritis, thus demonstrating the importance of weight loss as a treatment for knee OA [1, 9, 10]. Felson et al. found that a weight loss of approximately 11 pounds or more over the course of 10 years decreased the odds for developing OA by more than 50% [11]. Physical therapy is another noninvasive option when treating the symptoms of knee OA. In a study by Deyle et al. 83 patients with knee osteoarthritis were randomly assigned to receive physical therapy which consisted of manual therapy and an exercise program performed at home, or a placebo group [12]. The investigators found improvements in the 6-minute walk distance as well as the pain, function and stiffness subscores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). NSAIDs are also a common treatment option with general use in OA as both an analgesic and an anti-inflammatory, thus functioning to reduce inflammation and joint pain. However, the use of NSAIDs has become more controversial in recent years because of its main side effect, gastrointestinal toxicity, which can lead to gastritis and ulceration. TENS therapy has also been investigated as a treatment option for knee OA, but is primarily indicated for the mediation of pain. One study by Taylor et al. determined that TENS therapy is effective in reducing pain specifically located at the knee compared to an inactive control device in a population with knee OA [13]. In another study, Lewis et al. found a significant reduction in pain when patients with knee OA self administered TENS three times daily for 30 to 60 minutes over the course of a three week period [14]. TENS therapy is a non-pharmacologic therapy which electrically stimulates the nerves surrounding the area of interest. It may function similar to the “Gate Control Theory” of pain perception in which pain nerve impulses are transmitted via small delta fibers while TENS stimulates

the larger beta fibers to transmit a faster impulse via the C-fibers, thus inhibiting pain signals from the smaller delta fibers. Intra-articular steroids have also been used to manage arthritic conditions with the goal of this treatment being improved functionality through pain reduction and a reduction in inflammation. Unfortunately, no long-term benefits have been found with intra-articular steroids and there is no evidence of the treatment producing a disease-modifying effect [15].

Over the past 2 decades, attempts have been made to slow or halt the progression of articular cartilage destruction, or “chondroprotection”, through the use of disease-modifying osteoarthritis drugs (DMOADs). However, currently there are no Food and Drug Administration (FDA) approved disease-modifying drugs available. In order to produce a disease-modifying effect a treatment must not only improve functionality, but must also improve the biological structure of the joint and its tissues as seen through radiographs or other imaging techniques. Other potential disease-modifying therapies include intra-articular viscosupplementation with hyaluronate-derived products. One such product, hyaluronic acid, is thought to improve elasticity and viscosity of the synovial fluid, both normally impaired in individuals with OA. Additionally, glucosamine and chondroitin are thought to aid in cartilage repair and/or slowing the destruction of cartilage, but currently it is unclear as to whether or not they actually work to improve symptoms and structure. One study found the glucosamine hydrochloride preparation was no more effective than placebo but the methodology of this study was later questioned [16] and until appropriately performed studies come to light, the efficacy of this potential treatment will not be known for sure.

2.3. Proprioception

The mechanical environment of the knee joint is also an important factor to consider when looking for potential disease-modifying treatments of OA. Alterations of the knee joint's mechanical environment can lead to adverse affects on load distribution. Knee laxity (frontal plane or varus-valgus laxity), which increases with age and is greater in women [17], and knee alignment (increased knee adduction during the stance phase of gait) [18] are important mechanical factors in knee OA. Lastly, proprioception is another important mechanical factor in this population and is defined as the conscious and unconscious perception of limb movement and position in space. Proprioception is an important component of the somatosensory system, providing for the stability of joints during both dynamic and static tasks. More specifically, the somatosensory system utilizes auditory, visual, and proprioceptive input to detect sensory stimuli such as pain, pressure and movement. Proprioception is measured two ways, either through joint position sense, or joint movement sense (kinesthesia). Joint motion sense and joint position sense are both achieved through the stimulation of specific peripheral mechanoreceptors within the knee joint, muscle and skin such as: pacinian corpuscles, golgi joint receptors, golgi tendon receptors, ruffini endings, and muscle spindles. Pacinian corpuscles mainly function to detect pressure changes and communicate with the central nervous system (CNS) concerning limb movement. They are quick adapting (QA) mechanoreceptors which means they are very sensitive to small deformations caused by pressure and they initiate discharge of electrical potentials only during the application or removal of a stimulus, or during acceleration or deceleration of a moving joint. With regard to vibration, pacinian corpuscles can detect signal vibrations from 30 to 800 cycles per second because of their quick adapting nature. At

joint angulation extremes, stretching of the ligaments and deep tissues around the joints is important for determining position. Pacinian corpuscles, as well as ruffini endings, detect these types of changes. Since pacinian corpuscles are responsive to very small mechanical deformations, it is possible their signal will be affected (enhanced) when the high frequency nature of SR is applied. Unlike pacinian corpuscles, ruffini endings are slow adapting (SA), which means they may detect changes in tissue stresses and strains over time as well as continue to signal for prolonged periods making them more ideal for detecting changes in static joint position. Both pacinian corpuscles and ruffini endings are found cutaneously as well as in the ligaments, joint capsule and menisci. Because these afferent receptors are located cutaneously as well as deep within the tissue, it is possible they are receptive to both the electrical stimulation and sleeve conditions presented in this research. Golgi receptors are another type of mechanoreceptor and they are present in the muscle tendons, menisci, and collateral and cruciate ligaments. There are two main types: golgi tendon receptors and golgi joint receptors which indicate their location by their name. Both golgi receptors are SA, have a high threshold for detection of mechanical deformation, and may continue to signal about the new tissue state for prolonged periods of time. They are responsible for sending information to the motor control systems in the CNS concerning muscle tension or changes in tension. For determining joint angulation in mid ranges of motion, muscle spindles are among the most important. Like the pacinian corpuscles, muscle spindles are adapted for detecting rapid rates of change. Muscle spindles contain both afferent and efferent innervation and they consist of short muscle fibers attached in series with a normal muscle fiber. Of particular importance to this research is the fact that muscle spindles are sensitive to weak movement signals, but this sensitivity can be enhanced by the introduction of noise

through the tendon of the parent muscle through a concept known as stochastic resonance (SR), which will be discussed later [19].

2.4. Proprioception and Knee OA

Proprioception is of particular importance to the onset and progression of knee OA. Proprioceptive deficits are prominent in many injured and diseased populations including patellofemoral pain syndrome [20], anterior cruciate ligament (ACL) injury or deficiency [21, 22], meniscal injury [23], Parkinson's disease [24], the elderly [25], and especially knee OA [25-30]. Specifically, anterior cruciate ligament and meniscal injury are two injuries shown to predispose one to develop knee OA [31]. Proprioceptive acuity may be related to the characteristics of gait, specifically those associated with improper loading of the joint. Radin et al. suggested the proprioceptive deficits present in prearthritic subjects may be the cause of a higher angular shank velocity, lower maximum knee flexion and ineffective quadriceps activation during gait [32]. One theory suggests that proprioceptive deficits may have contributed to and/or resulted from knee OA [29, 30]. This theory, initially mentioned in a study by Barrett et al. exploring the effects of an elastic bandage on knee position sense in normal and osteoarthritis knees [29], was later confirmed by Sharma et al [30]. Sharma et al. present the idea that the afferent components of the neuromuscular reflex pathway are disrupted, which results in harmful loading of the joint, and thus knee OA. Alternatively, knee proprioception impairments may result from mechanoreceptor destruction caused by the disease. In their study, Sharma et al. test the hypothesis that impaired proprioception is solely the result of knee OA by testing joint kinesthesia in both the affected and unaffected knee of unilateral OA patients. They concluded that there was no difference in proprioception between the affected and unaffected knee. These findings led the authors to

suggest that the relationship between knee OA and impaired knee proprioception is a cyclic one, rather than a direct cause and effect relationship (Figure 1).

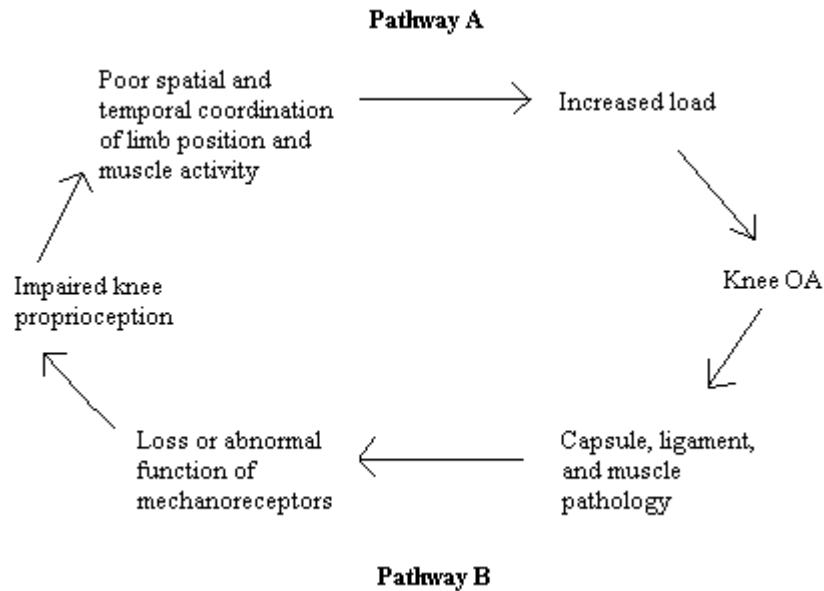


Figure 1. The osteoarthritis/proprioception cycle theory [30]

Additionally, studies have shown that decreasing sensory input in ACL transection animal models of OA result in more rapid progression of disease [33, 34]. Improving on proprioceptive impairments may lead to better spatial and temporal coordination of limb position, resulting in more normal load distribution within the joint and delayed progression or onset of knee OA.

2.5. Knee OA Biomechanics

In addition to proprioception, other mechanical factors have been shown to influence the progression of knee OA including malalignment and joint laxity. In the normal knee, it is estimated that approximately 60% to 80% of the body's weight passes through the medial compartment of the knee during the stance phase of gait. Increased knee adduction moments and increased compressive loads in the medial aspect of the knee joint are hallmarks of those

with medial knee OA [35]. Those with medial knee OA tend to have a greater varus alignment and combined with an increased knee adduction moment narrowing in the medial aspect of the tibiofemoral joint occurs [36]. As a result, the knee adduction moment has become a reliable measure of the load seen in the medial compartment of the tibio-femoral joint. Knee adduction moments are generated by the combination of the ground reaction force at heel strike (transmitted from the heel to the knee joint) and the perpendicular distance of this force from the center of the knee joint (moment arm). Additionally, studies that have compared walking mechanics in patients with knee OA to those of age-matched controls found that subjects with knee OA walked slower, had greater stance phase durations and shorter stride lengths as well as decreased knee range of motion [37-41]. Walking slower is a mechanism employed to reduce pain by decreasing knee joint moments and loads since higher walking speeds correlate with higher ground reaction forces. Landry et al. showed that higher peak knee adduction moments were present during a faster walking speed condition in subjects with moderate knee OA [42]. To further support this idea, Hunt et al. demonstrated increased peak knee adduction moments and moment arms in knees with OA compared to unaffected knees [43].

Increased impulsive loads have been suggested to be an initiator of OA through damage to cartilage [44] or by subchondral changes to bone that result in cartilage overload [45]. Further demonstrating that subchondral changes occur with higher loading rates Ewers et al. found higher surface fissuring at 12 months post impact of the cartilage when a high rate of loading was used compared to a lower loading rate [44]. In a healthy individual, the quadriceps acts to slow limb descent during gait, which results in decreased ground reaction forces and loading rates. However, those with knee OA demonstrate greater impulsive loads

possibly due to ineffective quadriceps activation prior to heel contact resulting in less dampening of the ground reaction force. Confirming this, Radin et al. demonstrated that patients who experience knee pain and who are presumed to be preosteoarthritic have a higher loading rate during heel strike compared to a control non-pain group [32]. Mundermann et al. compared patients with medial compartment knee OA with age-matched control subjects and showed that those with knee OA had a 50% higher loading rate than the control subjects just after heel strike [35]. Given the important role that proprioception plays in refining motor activity, it is likely that proprioceptive deficits would correlate with functional disability, specifically ineffective muscle activation of the quadriceps. Therefore, abnormal proprioception may be the cause of this ineffective quadriceps activation leading to higher impulsive loading rates and ground reaction forces demonstrated in the studies previously mentioned [32, 35].

In addition, there are other important biomechanic abnormalities such as knee joint angles and range of motion (ROM) that should be investigated in patients with knee OA. When measured in total knee extension and flexion, knee ROM has been shown to be significantly different in those with knee OA compared to a control group, presumably resulting from stiffness or swelling within the joint [37]. One study that looked at the secondary changes of gait in patients with knee OA found these patients made initial ground contact with the knee in 5.3° more extension than controls [35]. Referred to as the “stiffened knee response” the increased knee extension at ground contact is presumably a pain avoidance mechanism as well as a reaction to joint instability [37]. However, this response is detrimental because it results in decreased shock absorption and more of the ground contact force seen at heel strike being transmitted to the tibio-femoral joint. It is possible that those

who suffer from this “stiffened knee response” experience decreased proprioceptive input to the joints and surrounding muscles, which results in a feeling of instability. As a result of this instability, co-contraction of the hamstrings and quadriceps muscle groups occurs, which leads to a stiffened knee incapable of properly distributing forces seen during dynamic activities. Specifically, this co-contraction is detrimental because it allows for higher compressive forces to be seen by the joint, thus exacerbating tissue damage in the knee. Schmitt and Rudolph found higher co-contraction during weight acceptance and single-limb support while walking in knee OA subjects and they speculate this was because of the subject’s sense of knee instability [46] which was assessed from the Activities of Daily Living Scale of the Knee Outcome Survey. Hortobagyi et al. also looked at hamstring-quadriceps activation during walking, stair ascent and descent [47] in subjects with knee OA and age-matched control subjects. The authors found heightened co-activation of the two muscle groups during all three tasks and interpreted this much like other studies as a natural compensatory mechanism to a few of the abnormalities seen in subjects with knee OA, specifically in this case quadriceps weakness and pain.

In addition to increased co-contraction of the quadriceps and hamstrings patients with knee OA have demonstrated abnormal muscle activation of the individual quadriceps muscles. Quadriceps weakness has been shown in those with knee OA compared to control subjects [26]. More specifically, ineffective quadriceps activation has been suggested as the primary cause of the increased impulsive loading at heel strike due to the muscle’s inability to appropriately control limb descent just prior to heel contact [32]. Another study looking at this effect demonstrated delayed onset of the vastus medialis (VM) prior to heel strike when walking in an asymptomatic population with mild knee OA and found they all had more

pronounced heel-strike transients [48]. This notion may indicate that inappropriate activation of the VM is responsible for heightened heel strike transients and thus, greater impulsive loads. To further support this theory, Jefferson et al. studied the effects of quadriceps paralysis on impulsive loading and found that when the quadriceps were paralyzed, greater impulsive loads were seen at heel strike [49]. Yet another study was able to show delayed onset of the VM in subjects with knee OA, but this study looked at the effects during stair descent rather than walking [50]. The delayed VM activation prior to heel strike is another detrimental factor in this population serving to further degenerate the joint by allowing abnormally large compressive forces in the tibio-femoral joint during walking. In addition to the delayed onset of the VM, the activation period of the vastus lateralis is prolonged (approximately 1.5 times longer) in subjects with knee OA compared to a control group as Childs et al. were able to demonstrate during a stair descent task [37]. This study also demonstrated reduced knee flexion in the knee OA subjects, which in combination with the increased muscle activation period during the loading response phase of gait may be the result of joint stiffening as another way to minimize joint instability when descending stairs. Al-Zahrani et al. was able to isolate the rectus femoris (RF) muscle of the quadriceps muscle group in subjects with knee OA and found prolonged activation throughout the stance phase which corresponded with sustained knee joint moments, presumably to stabilize the joint during the weight transfer phase of gait [41].

2.6. Knee OA Postural Control

Taking afferent input from vestibular, visual, and proprioceptive pathways abnormal postural control has also been demonstrated in those with knee OA [27]. Postural control can be assessed statically where the ability to maintain upright position is assessed, or

dynamically where balance is assessed during execution of a movement. Postural control is generally assessed by displacement of the body's center of pressure where large excursions of the center of pressure are indicative of poor balance. The authors of the previously mentioned study suggested that observed increases in postural sway may have been due to impairments in quadriceps strength and proprioception which they also observed [27]. Hurley et al. also investigated balance in those with knee OA and its relationship to muscle sensorimotor function [26] and found diminished quadriceps activity, impaired proprioception, and decreased postural stability but no relationship was found between quadriceps weakness, impaired knee JPS, and decreased postural stability.

2.7. Knee Braces/sleeves

It is possible that the previously mentioned symptoms of knee OA (pain, decreased function, increased knee adduction moment, increased medial joint loads, increased impulsive loading and muscle co-contraction, and decreased knee flexion at contact) may be ameliorated through an improvement in proprioception. Several studies have demonstrated that proprioception can be enhanced from the use of knee sleeves, braces, and bandages in both normal subjects and those with knee OA [29, 51-53]. But these improvements are seen in non weightbearing (NWB) situations [51, 52] rather than during closed kinetic chain exercises, which may be because there is more proprioceptive input available in a weightbearing situation, thus minimizing any improvement by a knee sleeve. There are several types of knee braces and sleeves that have been investigated as a means of alleviating pain and improving function in knee OA [53-56]. They include elastic bandages, neoprene sleeves, hinged knee braces, and medial unloader braces. These knee braces and sleeves have also been investigated as a means of improving balance, proprioception, medial joint

loading, and mechanical stability in normal subjects [51, 57, 58] and in those with knee OA [52, 53, 55, 59, 60]. Hassan et al. found that pain, proprioceptive acuity, and static postural sway were all improved while wearing an elastic bandage in subjects with knee OA [53]. They speculated the main reason for these improvements was due to stimulation of cutaneous mechanoreceptors since it is currently thought that knee braces and sleeves effectively provide an added sensation of stability, rather than any biomechanical reinforcement itself. This enhanced sensation of stability may be related to the improvement in proprioceptive acuity seen by Herrington et al. [58]. They tested the effect of a neoprene knee sleeve on proprioceptive acuity of normal subjects and found a 28% improvement in the accuracy of an active tracking task, which is another way to measure proprioception.

Medial unloader braces have been looked at as a method for improving the symptoms of knee OA, such as heightened medial compressive forces in the medial aspect of the knee [61], pain [56], and functionality [62]. The main mechanism by which the medial unloader brace works is by placing the knee in a more valgus position and as the subject bends his/her knee the medial compartment of the knee is slightly unloaded, resulting in pain reduction and improved function. One study specifically measured the separation of the femoral condyle from the tibial plateau just after heel strike while wearing an unloader knee brace in patients with medial knee OA [54]. Using video fluoroscopy under weight-bearing conditions, the authors found medial condylar separation with corresponding pain relief in 78% of patients they tested. Specific to symptomatic improvement in knee OA, Matsuno et al. looked at the Generation II medial unloader knee brace and found that it improved pain during walking and stair ascent and descent, the femorotibial angle decreased, and quadriceps strength increased in 19 of the 20 patients tested [56]. Brouwer et al. also looked at the unloader

brace and found that subjects exhibited overall longer walking distances while wearing a brace compared to the control group [62]. However, Ramsey et al. demonstrated that neutral aligning braces performed as well as or better than the valgus aligning brace in reducing pain, disability, muscle co-contraction, and knee adduction excursions [55]. It is possible that the decreased muscle co-contraction seen in this study may have been caused by enhanced proprioception from simply wearing the knee brace. Additionally, several studies have demonstrated the long-term effectiveness of knee braces and sleeves. Birmingham et al. found that a neoprene knee sleeve was comparable to a functional knee brace after ACL reconstruction with respect to disease specific quality of life when examined over the course of several years [63]. Kirkley et al. found similar results in the disease specific quality of life between a medial unloader brace and a neoprene knee sleeve after six months [60]. In summary, research about the effects of braces for knee OA shows that wearing a knee brace compared to not wearing a brace may increase walking distance, reduce pain, and improve function and quality of life.

Another symptom of knee OA is increased external adduction moment, which causes higher loads to be placed in the medial compartment of the tibio-femoral joint of the knee. Foot orthotics such as lateral wedged insoles have been tested as a means of improving knee mechanics, specifically reducing the increased knee adduction moments, in those with medial compartment knee OA. Similar to knee braces and sleeves, the effectiveness of foot orthotics, specifically lateral wedged insoles remains inconclusive. Crenshaw et al. found no significant differences in hip, knee, or ankle joint angles or temporal or spatial parameters when testing the effects of a lateral wedged insole in healthy subjects [64]. However, the external varus moment and medial compartment loads were significantly reduced. The

authors suggested that pain relief and improved function seen in patients with knee OA while using lateral wedge insoles are likely the result of the reduced moment and compressive loads. Shimada et al. also looked at the effects of lateral wedged insoles and found a reduction in the peak external adduction moment of the knee in individuals with OA when a insole was applied compared to a control group [65]. One important thing to note about this study was that peak adduction moments were significantly improved in individuals with Kellgren and Lawrence grades I and II OA, but not in those with grades III and IV. The authors speculated this was because those with grades III and IV had severe varus deformities as well as changes in center of pressure and moment arms, thus the insole would not be sufficient to produce a measurable effect. A Cochrane review summarized the results of three insole studies and concluded that when wearing a lateral wedge compared to a neutral wedge, those with knee OA may not experience any difference in pain or knee function [66]. This further demonstrates the inconclusive findings of studies investigating the effect of lateral wedge insoles on the symptoms of knee OA.

2.8. Stochastic Resonance

In addition to the use of knee sleeves or braces, proprioception may also be enhanced through a phenomenon known as stochastic resonance (SR). SR has been shown to enhance muscle spindle output [67] and tactile sensation [68] in sensory systems through the introduction of mechanical noise. SR is a phenomenon in which the presence of a non-zero level of subsensory electrical or mechanical (vibratory) noise optimizes the system's response to a weak input signal in nonlinear systems. Cordo recorded the firing activity of individual muscle-spindle afferents of the wrist and hand extensor muscles and found that with a random noise input, the output signal-to-noise ratio increased, exhibiting clear

stochastic resonance behavior [67]. In another study, the ability of an individual to correctly identify indentations on his/her finger was improved when a non-zero level of noise was introduced to the system [68]. SR stimulation is different than other forms of electrical stimulation such as TENS and capacitively coupled, subsensory pulsed electrical stimulation (PES). PES has been demonstrated as an effective treatment modality for improving patient's pain, morning stiffness, and function during a 4 week randomized placebo-controlled trial [69]. In another study, Fary et al. demonstrated an improvement in pain, patient global assessment, and function in two of the three knee osteoarthritis patients they tested with long term use of PES (16 weeks) [70]. The exact method of action of PES is only speculative, but it is thought to work through pain mediation when the surrounding nociceptors and other pain-mediating receptors are stimulated. Seegers et al. demonstrated the capacity of PES to alter ATP (adenosine triphosphate) levels which they postulated would affect pain sensation through specific P2-purinergic receptors [71]. PES has also been speculated as a possible disease-modifying treatment since the use of PES in combination with electromagnetic fields has been shown to augment bone healing [72]. The main contrast between PES and SR stimulation is in their stimulation specifications. Typically, PES is pulsed, monophasic with a frequency of 100Hz, has a pulse width of 2ms and an adjustable intensity which is typically just below threshold. SR stimulation, on the other hand, is a random, biphasic, white noise signal with a 0-1000Hz bandwidth and zero mean. The two methods also differ in their theoretical method of activation. PES is proposed to activate nociceptors and other pain mediating receptors while SR stimulation seeks to modify those receptors responsible for detection of weak signals, possibly golgi organs, ruffini endings and other joint mechanoreceptors. Similar to PES, TENS therapy is an established

clinical tool for the management of pain and despite being used for decades, there is still a great deal of debate about its efficacy. However, contrary to PES and SR stimulation, TENS therapy works by administering much higher levels of stimulation at a higher fixed frequency. Typically, TENS is delivered at an amplitude of which the patient is tolerant, but unlike SR stimulation, TENS is biphasic and symmetrical with a pulse width of 200 μ s and a frequency of 100Hz. Several studies have shown improvements in balance control via postural sway when TENS is applied to the lower limb [73, 74]. Dickstein et al. showed that the mean sway velocity and the absolute values of the minimum and maximum medio-lateral and anterior-posterior velocity decreased when TENS was applied to the posterior aspect of the leg [74]. The authors then showed, in a separate study, that the mean sway velocity and medio-lateral COP dispersion decreased when TENS was applied to the lateral aspect of the knees [73].

Contrary to what most think concerning system “noise”, it can enhance the detection of subthreshold tactile stimuli. This concept of SR stimulation has been carried over into patient populations such as those suffering from stroke and diabetic neuropathy as well as the elderly population. In a study by Liu et al. the detection threshold of a vibratory stimulus at the fingertip was decreased when mechanical noise (random vibration with low intensity) was applied to the site of the test stimuli [75]. Dhruv et al. also investigated the effects of electrical noise stimulation on tactile sensation in the elderly and found a statistically significant increase in the number of tactile detections in 5 of the 9 subjects when electrical noise was applied [76]. SR has also been investigated as a means of improving balance in these populations [77-79]. Gravelle et al. tested the effects of low-level electrical noise applied at the knee on balance control in a healthy, elderly population and found significant

differences in the amount of anterior-posterior and medio-lateral center of pressure (COP) excursion compared to a young, healthy population [78]. More recently, Priplata et al. investigated the effects of subsensory mechanical noise applied on the soles of the foot on quiet-standing balance control in patients with diabetic neuropathy and stroke [77]. They found an overall reduction in all the measured sway parameters with the addition of mechanical noise and greater improvements in balance in those suffering from poorer balance control at baseline. Postural stability has also been improved through the application of electrical stimulation in those suffering from functional ankle instability (FAI) [80]. Ross looked at the single-leg balance performance of 12 subjects with FAI and found that with the application of electrical stimulation at specific muscle groups in the lower limb and ankle, the anterior-posterior and medial-lateral center of pressure velocities were significantly improved. SR might be applied in a population suffering from poor proprioception since one of the major components of a person's balance control is their proprioceptive ability.

Proprioception has been investigated in various populations. Specifically, joint position sense has been shown to be diminished in the elderly [29, 81] and in people with knee OA [25, 29]. Joint motion sense has been evaluated in both the affected and unaffected limb in patients who suffer from unilateral OA and no differences were found between limbs [28], which suggests that abnormal proprioception is not solely responsible for the onset of OA, but rather they have a cause and effect relationship [30]. The impaired proprioception in those with knee OA may explain the biomechanical changes this population displays during dynamic tasks. These biomechanical changes may include greater impulsive loading caused by poor temporal/spatial coordination of the limb, increased loading rates, increased axial loads, increased muscle co-contraction between the hamstrings and quadriceps muscle

groups and increased medial compartment loads. Since impaired proprioception may have a role in the progression of knee OA, improving proprioception may in fact prevent disease progression.

2.9. References

1. Felson, D.T. and Y. Zhang, *An update on the epidemiology of knee and hip osteoarthritis with a view to prevention*. Arthritis & Rheumatism, 1998. **42**: p. 1343-1355.
2. Hootman, J. and C. Helmick, *Projections of US prevalence of arthritis and associated activity limitations*. Arthritis & Rheumatism, 2006. **54**(1): p. 226-229.
3. Kotlarz, H., et al., *Insurer and Out-of-Pocket Costs of Osteoarthritis in the US*. Arthritis & Rheumatism, 2009. **60**(12): p. 3546-3553.
4. Kellgren, J.H. and J.S. Lawrence, *Radiological assessment of osteo-arthritis*. Annals of Rheumatic Diseases, 1957. **16**(4): p. 494-502.
5. Altman, R., et al., *Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association*. Arthritis & Rheumatism, 1986. **29**(8): p. 1039-1049.
6. Creamer, P. and M. Hochberg, *Osteoarthritis*. The Lancet, 1997. **350**(August 16): p. 503-508.
7. Hanna, F., et al., *Women have increased rates of cartilage loss and progression of cartilage defects at the knee than men: a gender study of adults without clinical knee osteoarthritis*. . Menopause, 2009. **16**(4): p. 666-670.
8. Hochberg, M. and M. Lethbridge-Cejku, *Epidemiologic considerations in the primary prevention of osteoarthritis*. , in *Osteoarthritis: public health implications for an aging population*., D. Hamerman, Editor. 1997, Johns Hopkins University Press: Baltimore. p. 169-186.
9. Felson, D.T., et al., *The prevalence of knee osteoarthritis in the elderly; The Framingham Osteoarthritis Study*. Arthritis & Rheumatism, 1987. **30**: p. 914-918.
10. van Saase, J.L., et al., *Osteoarthritis and obesity in the general population, A relationship calling for an explanation*. . Journal of Rheumatology, 1988. **15**: p. 1152-1158.

11. Felson, D., et al., *Weight loss reduces the risk for symptomatic knee osteoarthritis in women*. . Annals of Internal Medicine, 1992. **116**: p. 535-539.
12. Deyle, G., et al., *Effectiveness of manual physical therapy and exercise in osteoarthritis of the knee*. Annals of Internal Medicine, 2000. **132**(3): p. 173-181.
13. Taylor, P., M. Hallett, and L. Flaherty, *Treatment of osteoarthritis of the knee with transcutaneous electrical nerve stimulation*. Pain, 1981. **11**: p. 233-240.
14. Lewis, D., B. Lewis, and R. Sturrock, *Transcutaneous electrical nerve stimulation in osteoarthrosis: a therapeutic alternative?* Annals of Rheumatic Disease, 1984. **43**: p. 47-49.
15. Raynauld, J., C. Buckland-Wright, and R. Ward, *Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial*. Arthritis & Rheumatism, 2003. **48**(2): p. 370-377.
16. Clegg, D., D. Reda, and C. Harris, *Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis*. New England Journal of Medicine, 2006. **354**(8): p. 795-808.
17. Sharma, L., et al., *Laxity in healthy and osteoarthritis knees*. Arthritis & Rheumatism, 1999. **42**(861-870).
18. Sharma, L., et al., *Knee adduction moment, serum hyaluronan level, and disease severity in medial tibiofemoral osteoarthritis*. Arthritis & Rheumatism, 1998. **41**: p. 1233-1240.
19. Cordo, P., et al., *Noise in human muscle spindles*. Nature, 1996. **383**(October 31): p. 769-770.
20. Baker, V., et al., *Abnormal knee joint position sense in individuals with patellofemoral pain syndrome*. Journal of Orthopaedic Research, 2002. **20**: p. 208-214.
21. Beynnon, B., et al., *The effect of anterior cruciate ligament trauma and bracing on knee proprioception*. American Journal of Sports Medicine, 1999. **27**: p. 150-155.

22. Corrigan, J., W. Cashman, and M. Brady, *Proprioception in the Cruciate Deficient Knee*. The Journal of Bone and Joint Surgery, 1992. **74-B(2)**: p. 247-250.
23. Jerosch, J., M. Prymka, and W. Castro, *Proprioception of knee joints with a lesion of the medial meniscus*. Acta Orthopaedica Belgica, 1996. **62(1)**: p. 41-45.
24. Haas, C., et al., *Proprioceptive and sensorimotor performance in parkinson's disease*. Research in Sports Medicine, 2006. **14**: p. 273-287.
25. Pai, Y., et al., *Effect of age and osteoarthritis on knee proprioception*. Arthritis & Rheumatism, 1997. **40(12)**: p. 2260-2265.
26. Hurley, M., et al., *Sensorimotor changes and functional performance in patients with knee osteoarthritis*. Annals of the Rheumatic Diseases, 1997. **56**: p. 641-648.
27. Hassan, B., S. Mockett, and M. Doherty, *Static Postural Sway, Proprioception, and Maximal Voluntary Quadriceps Contraction in Patients with Knee Osteoarthritis and Normal Control Subjects*. Annals of Rheumatic Diseases, 2001. **60**: p. 612-618.
28. Garsden, L., Bullock-Saxton, JE., *Joint Reposition Sense in Subjects with Unilateral Osteoarthritis of the Knee*. Clinical Rehabilitation, 1999. **13**: p. 148-155.
29. Barrett, D.S., et al., *Joint Proprioception in Normal Osteoarthritic and Replaced Knees*. The Journal of Bone and Joint Surgery, 1991. **73(B)**: p. 53-56.
30. Sharma, L., et al., *Is Knee Joint Proprioception Worse in the Arthritic Knee Versus the Unaffected Knee in Unilateral Knee Osteoarthritis?* Arthritis & Rheumatism, 1997. **40(8)**: p. 1518-1525.
31. Lohmander, L., et al., *The long-term consequence of anterior cruciate ligament and meniscus injuries*. American Journal of Sports Medicine, 2007. **35(10)**: p. 1756-1769.
32. Radin, E.L., et al., *Relationship between lower limb dynamics and knee joint pain*. J Orthop Res, 1991. **9(3)**: p. 398-405.
33. Slowman-Kovacs, S.D., E.M. Braunstein, and K.D. Brandt, *Rapidly progressive Charcot arthropathy following minor joint trauma in patients with diabetic neuropathy*. Arthritis & Rheumatism, 1990. **33(3)**: p. 412-417.

34. O'Connor, B., et al., *Neurogenic Acceleration of Osteoarthritis*. The Journal of Bone and Joint Surgery, 1992. **74-A**(3): p. 367-376.
35. Mundermann, A., C.O. Dyrby, and T.P. Andriacchi, *Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking*. Arthritis Rheum, 2005. **52**(9): p. 2835-44.
36. Sharma, L., et al., *The role of knee alignment in disease progression and functional decline in knee osteoarthritis*. Journal of the American Medical Association, 2001. **286**(2): p. 188-195.
37. Childs, J., et al., *Alterations in lower extremity movement and muscle activation patterns in individuals with knee osteoarthritis*. Clinical Biomechanics, 2004. **19**(1): p. 44-49.
38. Kaufman, K.R., et al., *Gait characteristics of patients with knee osteoarthritis*. J Biomech, 2001. **34**(7): p. 907-15.
39. Baliunas, A., et al., *Increased knee joint loads during walking are present in subjects with knee osteoarthritis*. Osteoarthritis Cartilage, 2002. **10**(7): p. 573-579.
40. Messier, S., et al., *Osteoarthritis of the knee: Effects on gait, strength, and flexibility*. Archives of Physical and Medical Rehabilitation, 1992. **73**: p. 29-36.
41. Al-Zahrani, K.S. and A.M. Bakheit, *A study of the gait characteristics of patients with chronic osteoarthritis of the knee*. Disabil Rehabil, 2002. **24**(5): p. 275-80.
42. Landry, S.C., et al., *Knee biomechanics of moderate OA patients measured during gait at a self-selected and fast walking speed*. J Biomech, 2007. **40**(8): p. 1754-61.
43. Hunt, M., et al., *Associations among knee adduction moment, frontal plane ground reaction force, and lever arm during walking in patients with knee osteoarthritis*. Journal of Biomechanics, 2006. **39**: p. 2213-2220s.
44. Ewers, B.J., et al., *Rate of blunt impact loading affects changes in retropatellar cartilage and underlying bone in the rabbit patella*. Journal of Biomechanics, 2002. **35**(6): p. 747-755.

45. Radin, E.L., et al., *Response of joints to impact loading-III. Relationship between trabecular microfractures and cartilage degeneration*. Journal of Biomechanics, 1973. **6**(1): p. 51-54.
46. Schmitt, L.C. and K.S. Rudolph, *Influences on knee movement strategies during walking in persons with medial knee osteoarthritis*. Arthritis Rheum, 2007. **57**(6): p. 1018-26.
47. Hortobagyi, T., et al., *Altered hamstring-quadriceps muscle balance in patients with knee osteoarthritis*. Clinical Biomechanics, 2005. **20**(1): p. 97-104.
48. Liikavainio, T., et al., *Loading and gait symmetry during level and stair walking in asymptomatic subjects with knee osteoarthritis: importance of quadriceps femoris in reducing impact force during heel strike?* Knee, 2007. **14**(3): p. 231-8.
49. Jefferson, R.J., et al., *The role of the quadriceps in controlling impulsive forces around heel strike*. Proc Inst Mech Eng [H], 1990. **204**(1): p. 21-8.
50. Hinman, R.S., et al., *Delayed onset of quadriceps activity and altered knee joint kinematics during stair stepping in individuals with knee osteoarthritis*. Arch Phys Med Rehabil, 2002. **83**(8): p. 1080-6.
51. Birmingham, T.B., et al., *Effect of a Neoprene Sleeve on Knee Joint Position Sense During Sitting Open Kinetic Chain and Supine Closed Kinetic Chain Tests*. American Journal of Sports Medicine, 1998. **26**(4): p. 562-566.
52. Birmingham, T.B., et al., *Knee bracing for medial compartment osteoarthritis: effects on proprioception and postural control*. Journal of Rheumatology, 2001. **40**(3): p. 285-289.
53. Hassan, B.S., S. Mockett, and M. Doherty, *Influence of elastic bandage on knee pain, proprioception, and postural sway in subjects with knee osteoarthritis*. Annals of Rheumatic Diseases, 2002. **61**: p. 24-28.
54. Dennis, D.A., et al., *Evaluation of off-loading braces for treatment of unicompartmental knee arthrosis*. J Arthroplasty, 2006. **21**(4 Suppl 1): p. 2-8.

55. Ramsey, D., et al., *A mechanical theory for the effectiveness of bracing for medial compartment osteoarthritis of the knee*. The Journal of Bone and Joint Surgery, 2007. **89**(2398-2407).
56. Matsuno, H., K.M. Kadowaki, and H. Tsuji, *Generation II knee bracing for severe medial compartment osteoarthritis of the knee*. Archives of Physical Medicine and Rehabilitation, 1997. **78**(7): p. 745-749.
57. McNair, P., S. Stanley, and G. Strauss, *Knee bracing: Effects on proprioception*. Archives of Physical and Medical Rehabilitation, 1996. **77**: p. 287-289.
58. Herrington, L., *The effect of a neoprene sleeve on knee joint position sense*. Research in Sports Medicine, 2005. **13**: p. 37-46.
59. Chuang, S., et al., *Effect of knee sleeve on static and dynamic balance in patients with knee osteoarthritis*. Kaohsiung Journal of Medical Sciences, 2007. **23**(8): p. 405-410.
60. Kirkley, A., et al., *The effect of bracing on varus gonarthrosis*. The Journal of Bone and Joint Surgery, 1999. **81**: p. 539-548.
61. Lindenfeld, T.N., T.E. Hewett, and T.P. Andriacchi, *Joint loading with valgus bracing in patients with varus gonarthrosis*. Clinical Orthopaedics and Related Research, 1997(344).
62. Brouwer, R.W., et al., *Brace treatment for osteoarthritis of the knee: a prospective randomized multi-centre trial*. Osteoarthritis Cartilage, 2006. **14**(8): p. 777-83.
63. Birmingham, T., et al., *A randomized controlled trial comparing the effectiveness of functional knee brace and neoprene sleeve use after anterior cruciate ligament reconstruction*. American Journal of Sports Medicine, 2008. **36**(4): p. 648-655.
64. Crenshaw, S.J., F.E. Pollo, and E.F. Calton, *Effects of lateral-wedged insoles on kinetics at the knee*. Clin Orthop Relat Res, 2000(375): p. 185-92.
65. Shimada, S., et al., *Effects of disease severity on response to lateral wedged shoe insole for medial compartment knee osteoarthritis*. Arch Phys Med Rehabil, 2006. **87**(11): p. 1436-41.

66. Brouwer, R., et al., *Braces and orthoses for treating osteoarthritis of the knee (Review)*. The Cochrane Library, 2009(4).
67. Cordo, P., et al. , *Noise in human muscle spindles*. Nature, 1996. **383**(October 31): p. 769-770.
68. Collins, J.J., T.T. Imhoff, and P. Grigg, *Noise-enhanced tactile sensation*. Nature, 1996. **383**(6603).
69. Zizic, T., et al., *The treatment of osteoarthritis of the knee with pulsed electrical stimulation*. Journal of Rheumatology, 1995. **22**: p. 1757-1761.
70. Fary, R., N. Briffa, and T. Briff, *Effectiveness of pulsed electrical stimulation in the management of osteoarthritis of the knee: Three case reports*. . Physiotherapy Theory and Practice, 2009. **25**(1): p. 21-29.
71. Seegers, J., et al., *A pulsed DC electric field affects P2-purinergic receptor functions by altering the ATP levels in in-vitro and in vivo systems*. Medical Hypotheses, 2002. **58**: p. 171-176.
72. Aaron, R., D. Ciombor, and B. Simon, *Treatment of nonunions with electric and electromagnetic fields*. Clinical Orthopaedics, 2004. **419**: p. 21-29.
73. Laufer, Y. and R. Dickstein, *TENS to the lateral aspect of the knees during stance attenuates postural sway in young adults*. Scientific World Journal, 2007. **7**: p. 1904-1911.
74. Dickstein, R., Y. Laufer, and M. Katz, *TENS to the posterior aspect of the legs decreases postural sway during stance*. Neuroscience Letters, 2006. **393**: p. 51-55.
75. Liu, W., et al., *Noise-enhanced vibrotactile sensitivity in older adults, patients with stroke, and patients with diabetic neuropathy*. Archives of Physical Medicine and Rehabilitation, 2002. **83**: p. 171-176.
76. Dhruv, N.T., et al., *Enhancing tactile sensation in older adults with electrical noise stimulation*. NeuroReport, 2002. **13**(5): p. 597-600.

77. Priplata, A.A., et al., *Noise-Enhanced Balance Control in Patients with Diabetes and Patients with Stroke*. Annals of Neurology, 2005. **59**: p. 4-12.
78. Gravelle, D.C., et al., *Noise-Enhanced Balance Control in Older Adults*. NeuroReport, 2002. **13**(15): p. 1-4.
79. Hijmans, J., et al., *Effects of vibrating insoles on standing balance in diabetic neuropathy*. Journal of Rehabilitation Research & Development, 2008. **45**(9): p. 1441-1450.
80. Ross, S., *Noise-enhanced postural stability in subjects with functional ankle instability*. British Journal of Sports Medicine, 2007. **41**: p. 656-659.
81. Petrella, R., P. Lattanzio, and M. Nelson, *Effect of age and activity on knee joint proprioception*. American Journal of Physical Medicine & Rehabilitation, 1997. **76**(3): p. 235-241.

CHAPTER 3. SPECIFIC AIMS & HYPOTHESES

3.1. Specific Aim 1: To measure joint position sense (JPS) in subjects with knee osteoarthritis (OA) during both a partial weight bearing (PWB) and a nonweight bearing (NWB) task for the following conditions: no electrical stimulation/no sleeve (NE/NS), no electrical stimulation/sleeve (NE/S), 50 μ A electrical stimulation/sleeve (E50/S), 75 μ A electrical stimulation/sleeve (E75/S).

3.1.1. Hypothesis 1.1: Electrical stimulation will significantly improve JPS when combined with a knee sleeve (E50/S and E75/S) compared to the control (NE/NS) conditions during both the PWB and NWB tasks.

3.1.2. Hypothesis 1.2: Electrical stimulation will significantly improve JPS when combined with a knee sleeve (E50/S and E75/S) compared to a sleeve alone (NE/S) condition during both the PWB and NWB tasks.

3.1.3. Hypothesis 1.3: JPS will improve with the sleeve alone condition (NE/S) compared to the control (NE/NS) condition in the NWB task only.

3.1.4. Hypothesis 1.4: JPS will be superior when the 75 μ A level of stimulation is applied compared to the 50 μ A level in both the PWB and NWB tasks.

3.2. Specific Aim 2: To evaluate differences in ground reaction force (GRF) loading rates, knee kinetics, knee kinematics, and muscle activation patterns during gait in subjects with knee OA during the following conditions: no electrical stimulation/no sleeve (NE/NS), no electrical stimulation/sleeve (NE/S), electrical stimulation/sleeve (E75/S). Electrical stimulation will be at an amplitude of 75% of threshold level.

3.2.1. *Hypothesis 2.1:* Impulsive loading rates will decrease while vastus lateralis (VL) activation prior to heel strike and knee flexion angle at heel strike will increase with the application of stimulation and sleeve (E75/S) compared to the control condition (NE/NS).

3.2.2. *Hypothesis 2.2:* Maximum knee flexion angles will increase and maximum knee adduction angles will decrease during weight acceptance with the application of stimulation and a sleeve (E75/S) compared to the control condition (NE/NS). Internal knee extension moment will increase and internal knee abduction moment will decrease during weight acceptance with the application of stimulation and a sleeve (E75/S) compared to the control condition (NE/NS).

3.2.3. *Hypothesis 2.3:* The sleeve alone (NE/S) will not result in decreased loading rates or changes in knee angles compared to the control condition (NE/NS).

3.2.4. *Hypothesis 2.4:* The application of stimulation and a sleeve (E75/S) will decrease co-contraction of the quadriceps/hamstring muscle groups during weight acceptance and midstance compared to the control condition (NE/NS).

3.2.5. *Hypothesis 2.5:* The sleeve alone (NE/S) will not decrease muscle co-contraction during weight acceptance and midstance compared to the control condition (NE/NS).

3.3. Specific Aim 3: To evaluate postural control in subjects with knee OA during a single-leg balance task. Postural control will be evaluated during the following conditions: no electrical stimulation/no sleeve (NE/NS), no electrical stimulation/sleeve (NE/S), and stimulation/sleeve (E/S). Stimulation will be applied at 3 percentages of threshold: 75%, 100%, and 150%.

3.3.1. *Hypothesis 3.1:* The application of stimulation and sleeve (E75/S, E100/S, E150/S) will result in improvements in postural control measures (range, standard deviation, total path length, and mean velocity) compared to a control condition.

3.3.2. *Hypothesis 3.2:* Postural control measures (range, standard deviation, total path length, and mean velocity) will be further improved with the application of SR and sleeve compared to the sleeve alone condition.

3.3.3. *Hypothesis 3.3:* Postural control measures (range, standard deviation, total path length, and mean velocity) will differ when the SR amplitude is varied as a percentage of threshold.

CHAPTER 4. STOCHASTIC RESONANCE ELECTRICAL STIMULATION TO IMPROVE PROPRIOCEPTION IN KNEE OSTEOARTHRITIS

4.1. Introduction

Osteoarthritis (OA) is a common joint disorder characterized by pain, instability, and loss of function. It is the most common joint disorder in the United States and is associated with significant health and welfare costs [1]. Osteoarthritis of the knee is especially common and debilitating, and is one of the five leading causes of disability among non-institutionalized elderly men and women [1].

Mechanical factors such as obesity, trauma, high impact sports and repetitive stress activities are known risk factors in the development of OA of the knee [2, 3]. These factors lead to improper loading of the joint which can initiate the cascade of events resulting in OA. Likewise, abnormal position sense or proprioception results in improper loading of the joint. Proprioception is the conscious and unconscious awareness of body limb position and movement in space. Proprioceptive deficits are shown to be greater in an elderly population with knee OA compared to age-matched controls who themselves exhibit proprioceptive deficits compared to a younger population [4]. Poor load distribution across articular surfaces, uncoordinated muscular co-contraction, joint instability, and increased impact loading of the joint occur with knee OA [5-10], and it has been suggested that proprioceptive deficits may have a role in each of these effects [11, 12]. In addition, ACL and meniscal injuries increase a subject's risk of developing osteoarthritis of the knee [13] and are known

to cause proprioceptive deficits [14, 15]. Furthermore, in the canine ACL deficient model of knee OA, a dorsal root ganglionectomy to decrease proprioceptive sensory input in conjunction with an ACL transaction, results in a more rapid and severe development of OA [16]. Finally, studies of subjects with unilateral knee OA have shown an equivalent proprioceptive deficit in the contralateral knee, suggesting that the impaired proprioception in the affected knee is not simply a result of the disease process, but that it may be involved in the development and progression of knee OA [17]. This has led to the suggestion that treatment of the proprioception impairment may have a disease-modifying effect [17].

Many of the current treatments for knee OA focus on symptom modification and there is a great clinical need for a disease-modifying treatment in order to reduce healthcare costs and improve the quality of life for those suffering from this condition. Two common means by which proprioceptive acuity has been improved in knee OA subjects are muscle training exercises [18] and the wearing of knee braces or sleeves [19-21]. The improvements in proprioception acuity with a knee brace and sleeve have only been observed in the non weight-bearing knee, making the clinical relevance of this improvement uncertain.

One potential means of further enhancing the improvement in proprioception with a sleeve is by incorporating subsensory stochastic resonance (SR) electrical stimulation into the sleeve. SR stimulation is a type of electrical or mechanical stimulation that, at a subsensory level, has been shown to enhance the detection and transmission of weak sensory signals [22, 23]. SR is thought to work by altering the transmembrane potential of neurons, causing the resting membrane potential to approach threshold making it more likely that an action potential will result. SR has shown promise in improving balance in various populations including the elderly [24, 25], those with diabetic neuropathy [26], and those

recovering from stroke [27, 28]. As somatosensory feedback is an important component to the balance control system, it has been theorized that the improved balance observed with SR stimulation is a result of enhanced proprioceptive input [24]. In support of this suggestion and pertinent to the use of SR stimulation in knee OA, it has recently been demonstrated that applying SR electrical stimulation in concert with a sleeve at the knee in young healthy individuals can improve proprioception as measured by joint position sense testing during a partial weight-bearing task [29]. In contrast, the investigators demonstrated that the sleeve alone was unable to significantly improve joint position sense during the partial weight-bearing task.

The objective of this study was to determine the effect of a combination of SR electrical stimulation and a neoprene knee sleeve on joint position sense (JPS) in subjects with knee OA during both a non weight-bearing (NWB) and a partial weight-bearing (PWB) task. Our hypothesis was that joint position sense would be significantly improved with the application of stimulation and sleeve as compared with the application of a sleeve alone or no stimulation and no sleeve (control) during both the PWB and NWB tasks.

4.2. Methods

4.2.1. Patients

After receiving Institutional Review Board approval, 38 subjects (26 females, 12 males) with minimal to moderate (Grade 1 to 3) medial compartment knee OA were recruited for participation in the study (Table 1).

	<u>Male</u> <u>(n=12)</u>	<u>Female</u> <u>(n=26)</u>	<u>Total</u> <u>(n=38)</u>
Age	55.4 (11.0)	61.9 (10.0)	59.9 (10.6)
Weight (kg.)	94.7 (15.4)	71.7 (13.2)	79.0 (17.5)
Height (cm.)	181.9 (6.4)	165.5 (6.6)	171.5 (10.3)
BMI	28.6 (4.3)	26.2 (4.5)	27.0 (4.5)
KL grade (1 to 3)	2.5 (0.9)	2.4 (0.8)	2.4 (0.8)

Table 1. Mean (+/-sd) demographic information for all test subjects-JPS

Subjects' knee OA grade was assessed using the modified Kellgren/Lawrence grading system [30]. Subjects were included in the study if they had a diagnosis of medial compartment knee OA confirmed by a physician and if they demonstrated radiographic evidence of knee OA. Subjects were excluded from participation in the study if they were younger than 40 years of age, had any neurologic condition that would prevent them from sensing pain, were pregnant, used a pacemaker or any other implantable electronic device, had musculoskeletal disease or joint replacement within the tested lower extremity, a history of cardiac arrhythmia, gout, rheumatoid or other systemic inflammatory arthritis, or if they were morbidly obese (BMI >35). A decision was made to exclude those subjects with BMI greater than 35 in an attempt to eliminate as many extraneous variables as possible so the effect of SR stimulation on knee proprioception could be directly evaluated. Additionally, subjects who were unable to walk without an assistive device, had a steroid injection less than 3 months prior to participation, had a knee flexion contracture greater than 5 degrees and further flexion of less than 120 degrees, had an inability to perform the study tasks due to a medical condition, or were unable to understand the directions of the study were excluded from participation.

An orthopaedist assessed standing anterior-posterior radiographs with the knee in full extension to evaluate the severity of knee OA in the tibiofemoral joint using the modified Kellgren/Lawrence grading system [30, 31]. Felson et al. suggested knees should be

characterized as having radiographic OA if there is either an osteophyte of grade 2 or higher severity (on a 0-3 scale) present or with the presence of moderate to severe joint space narrowing (≥ 2 , on a 0-3 scale). Each knee was evaluated for the presence of osteophytes, joint space narrowing, sclerosis, and subchondral cysts, and was graded for overall evidence of OA as follows: 0=none; 1=questionable osteophyte(s) and or questionable joint space narrowing; 2=definite osteophyte(s) (at least small) with possible narrowing of the joint space or definite mild joint space narrowing with or without osteophytes; 3=definite moderate joint space narrowing (at least 50%), cysts or sclerosis may be present, and osteophytes are usually present; 4=severe joint space narrowing, at least some small definite osteophytes, possible sclerosis, and definite deformity of bone contour [30]. In this study, joint space narrowing was measured by the interbone distance on both the medial and lateral sides to ensure narrowing was greater on the medial side for this test population. Each subject's more severely affected knee was tested and in the case where both knees were equally affected, the subject's dominant limb was tested.

4.2.2. Study Design

Subjects performed JPS testing during PWB and NWB tasks. The order of these assessments was counterbalanced across subjects and stratified across sex such that half of the females and males performed the NWB task first and the other half performed the PWB task first. For each task, subjects were presented with conditions in the following sequence: no stimulation/no sleeve (control1 NE/NS), counterbalanced design of 3 conditions: no stimulation/sleeve, 50 μ A-RMS stimulation/sleeve, 75 μ A-RMS stimulation/sleeve (NE/S, E50/S, E75/S respectively), followed by a no stimulation/no sleeve condition (control2 NE/NS). This sequence was designed to present the treatment conditions in a

counterbalanced order and to assess any “lasting effects” of the electrical stimulation or the effects of fatigue by placing control conditions before and after all treatment conditions.

4.2.3. Equipment

Subjects were blinded as to whether or not the electrical stimulation was being applied due to its subsensory amplitude, and electrodes were adhered to the subject during all test conditions. Subsensory electrical stimulation was applied via an electrical stimulator device (Afferent Corporation, Providence, RI) through pairs of electrodes placed two centimeters above and below the medial and lateral joint line of the knee, respectively to create an alternating flow of current in the medial-lateral direction. An attempt was made to place the electrodes so as to increase the output of joint mechanoreceptors since it is clear that altered output of these receptors may contribute to proprioceptive deficits in knee OA and improving their sensitivity may help correct these deficits. Placing the electrodes further from the joint would lead to a higher involvement of the muscle receptors and it is less clear to what extent altered muscle receptor activity contributes to proprioceptive deficits in knee OA. Stimulation consisted of either a 50 μ A-RMS or 75 μ A-RMS Gaussian white noise signal (zero mean, s.d. = 0.05mA or 0.075mA, 0-1000Hz bandwidth) that was passed through a signal isolator for subject safety. Following completion of JPS testing, the stimulus level was incrementally increased to determine each subject’s threshold for detection separately in each pair of electrodes.

Before beginning JPS testing two electrolytic tilt sensors (Spectrotilt Model # 1188, Spectron Systems Technology, Hauppauge, NY) were strapped to the lateral side of both the shin and the thigh of the subject’s test limb to measure the knee flexion angle. Both sensor positions were defined along the long axis of each segment relative to the normal gravity

direction (in degrees). Upon movement, these positions (in degrees) were subtracted from one another to achieve an angle of knee flexion. The tilt sensors were calibrated before testing, and their measurement error was verified as less than 0.5° . Sensor data were captured at a frequency of 100Hz using LabVIEW software. Subjects also wore a neoprene knee sleeve during certain conditions in both the PWB and NWB task (Safe-T-Sport Model # 37-350, FLA Orthopaedics Inc., Miramar, FL). The sleeve was fit based on thigh girth measured approximately 4 inches above the center of the patella per the manufacturer's recommendations. During all testing subjects wore a blindfold in order to eliminate visual cues. Additionally, during the "reproduction" portion of each trial white noise was played in a set of headphones worn by the subject in order to eliminate auditory cues.

4.2.4. Procedure

Prior to participation, subjects read and signed an informed consent document. Subjects completed several questionnaires before testing began, the first of which was a measure of their self-reported knee instability adapted from the Knee Outcome Survey-Activities of Daily Living Scale [5, 32]. Subjects also completed the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index questionnaire which is used to assess functionality of their osteoarthritic knee as well as the degree of pain and stiffness which they encounter [33]. Lastly, subjects were asked to complete a short demographic questionnaire asking for their height, weight, sex, and knee affected with OA.

Each subject's knee range of motion was then evaluated using a handheld goniometer. Maximum knee extension was determined with each subject lying supine while a foam wedge positioned under the heel of the test limb placed the knee in maximum extension. The maximum knee flexion angle was determined with the subject lying prone

and the investigator passively flexing the knee to the point at which no additional flexion could occur without subject discomfort.

JPS was then tested during PWB and NWB tasks. During the NWB task, subjects were seated upright on a bench beginning in a position of 90° knee flexion moving into extension. Each trial began with the subject's limb passively moved to one of three target positions (30°, 40°, 20°) by the investigator and held there for approximately 5 seconds after which the limb was returned to the starting position. Following a 5 second rest period the subject was prompted (via a fingertap on the nontest limb) to actively reposition the test limb to the target position [34]. The subject indicated he/she had accurately repositioned the test limb by depressing an electronic switch that provided a time stamp on the kinematic data.

During the PWB task, subjects were positioned lying supine on a sliding reclined platform reclined 15° relative to the horizontal. A similar protocol was used by Bullock-Saxton et al. to assess knee joint position sense in a PWB setup [35]. Each trial began with the test limb fully extended and the nontest limb positioned on the platform, simulating single leg stance (Figure 2).

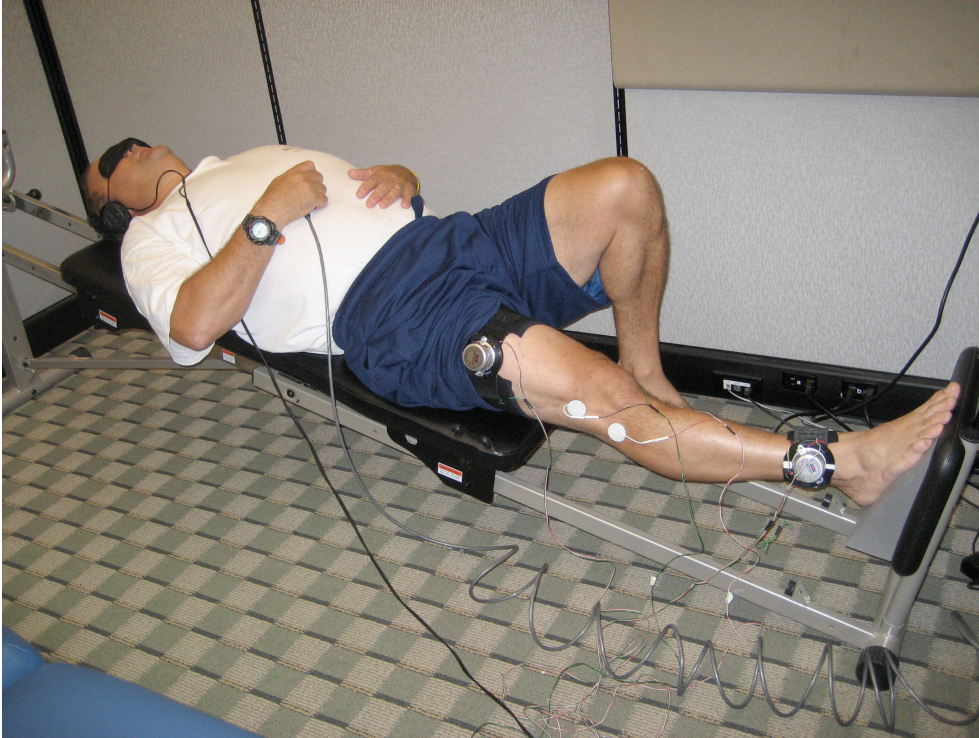


Figure 2. PWB setup simulating single leg stance. Also shown are the electrolytic tilt sensors on the thigh and shank. SR stimulation electrode placement is also depicted here with only the lateral electrodes visible.

A rigid foam wedge was placed under the heel of the test limb, producing slight plantar flexion and limiting passive tension cues from the ankle plantarflexors. Subjects actively flexed the test limb until instructed to stop at one of three predetermined target knee joint angles (20° , 25° , 30°). This position was maintained for 5 seconds and then the subject returned to the starting position. Following a 5 second rest, the subject was prompted (via a fingertap) to actively flex the knee in an effort to reproduce the target angle. During both the PWB and NWB tasks, the absolute difference between the target angle and the reproduced angle was calculated and averaged across the 5 trials within each condition.

4.2.5. Statistical Analysis

All statistical analyses were performed using SigmaPlot (Systat Software Inc., San Jose, CA). The number of subjects desired for testing was selected based on a pre-power

analysis that indicated an N of 52 subjects could detect a 20% difference between testing conditions for a power of 0.8, alpha of 0.05, and standard deviation of 50% of the control mean. Initially, a paired t-test was performed to compare JPS between the two control conditions. We found that the errors in the two control conditions differed in the NWB task. However, there were no differences between the two control conditions in the PWB task so the two control conditions were then averaged and used in subsequent analyses. If, on the other hand, both conditions were different in both tasks the first control condition errors would be used alone. Only the electrical stimulation level displaying the greatest average improvement relative to the control condition was used in statistical analyses in order to maintain statistical power. A one-way repeated measures analysis of variance (testing condition) was performed to determine if significant differences were present among the 3 resulting conditions (NE/NS, NE/S, E75/S) in both the PWB and NWB tasks. Further statistical differences between conditions were determined using Tukey's posthoc method of multiple comparisons ($p < 0.05$).

Regression analyses were performed to determine if improvements in JPS error resulting from the E75/S treatment condition were dependent on the magnitude of proprioceptive deficit during the control condition (NE/NS). Spearman correlations were also calculated to evaluate the correlation between the absolute error in the control (NE/NS), E75/S, and NE/S conditions and all WOMAC indices, the Self Reported Instability measures, BMI, Age, and KL grade.

4.3. Results

Thirty-eight patients (26 female, 12 male) with minimal to moderate, medial knee OA were tested. The mean age, BMI, and KL grade of these participants was 59.9 (± 10.6) years,

27.0 (± 4.5), and 2.4 (± 0.8), respectively (Table 1). While our pre-power analysis indicated an N of 52, a post power analysis following the testing of 38 subjects determined an N of 1164 (PWB) and 6910 (NWB) would allow for differences between the NE/S and E75/S conditions to be significant. Because of the enormous subject size required to detect differences at a 0.80 power level, a decision was made to discontinue testing at 38 subjects.

4.3.1. PWB

No significant difference was found between the two control conditions ($p=0.982$). The two stimulation/sleeve conditions (E50/S, E75/S) did not differ significantly from each other ($p=0.272$), though improvement via the E75/S condition was greater in magnitude. A significant effect of the testing condition was found in the PWB task. Specifically, the mean absolute error of the sleeve alone (NE/S, $2.9^\circ \pm 2.6^\circ$, $p=0.001$) and 75 μ A-RMS stimulation/sleeve (E75/S, $3.0^\circ \pm 2.3^\circ$, $p=0.006$) conditions were significantly decreased compared to the control condition (NE/NS, $3.7^\circ \pm 2.5^\circ$). Finally, the sleeve alone condition was not significantly different from either of the stimulation/sleeve conditions.

4.3.2. NWB

A trend for a difference ($p=0.054$) between the two control conditions was found. No significant differences between the treatment conditions were found (Figure 3, Table 2).

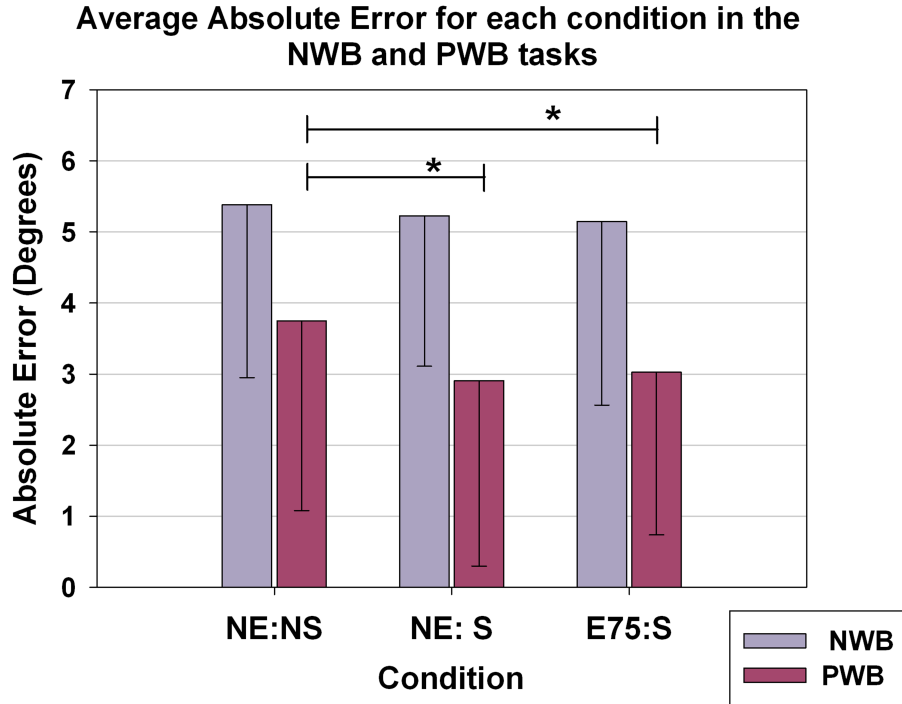


Figure 3. Average absolute error for the three conditions (NE/NS, E75/S and NE/S) in both the NWB and PWB tasks. * indicates significant differences between conditions at the end of the horizontal bar ($p < 0.05$).

	<u>PWB</u> <u>Mean (sd)</u> <u>95% CI</u>	<u>NWB</u> <u>Mean (sd)</u> <u>95% CI</u>
No Electrical Stimulation/No sleeve average (NE/NS)	*3.74 (2.50) 2.95 to 4.54	5.38 (2.43) 4.61 to 6.15
75uA Stimulation/Sleeve (E75/S)	*3.03 (2.29) 2.30 to 3.75	5.14 (2.58) 4.32 to 5.97
No Electrical Stimulation/sleeve (NE/S)	*2.91 (2.61) 2.08 to 3.74	5.23 (2.12) 4.55 to 5.90

Table 2. Mean (sd) absolute errors (degrees) for all conditions in both the PWB and NWB tasks. Significant differences were found between the average of the two control conditions (NE/NS) and NE/S as well as E75/S conditions (*indicates significant difference).

4.3.3. Correlations

Correlation analysis demonstrated a moderate correlation between the absolute error of the average control condition (NE/NS) and the improvement seen in the absolute error

with the E75/S treatment condition relative to the control condition ($R=0.556$, $p<0.005$, Figure 4) during the PWB task.

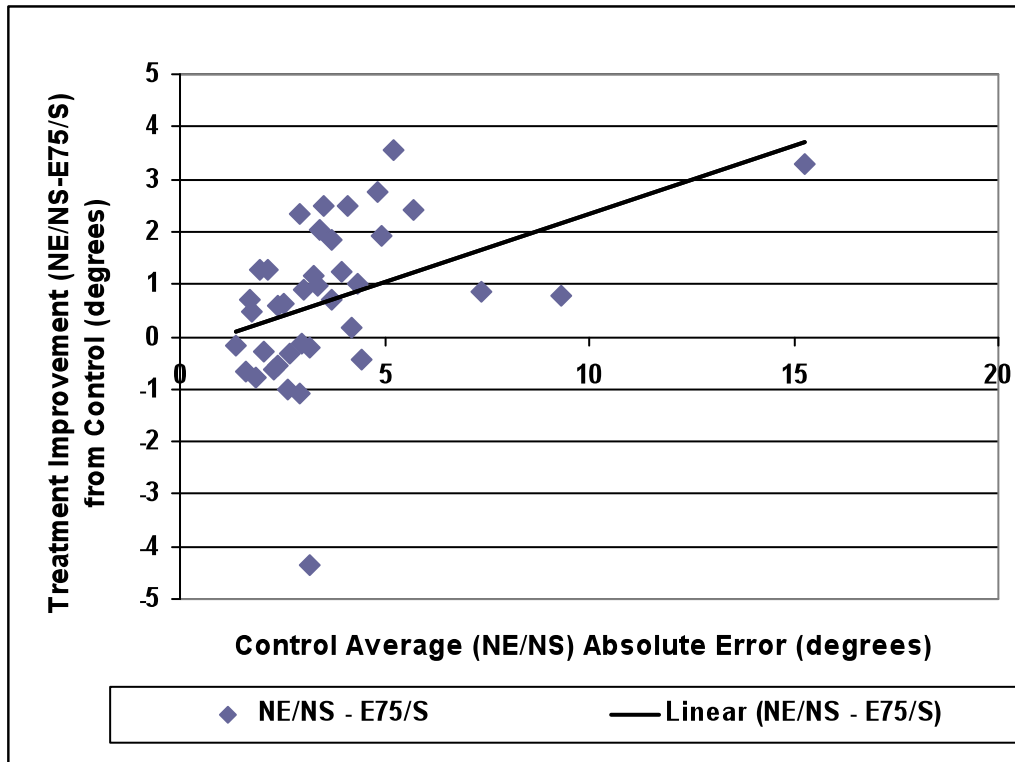


Figure 4. The relationship between the absolute error (degrees) of the average control condition (NE/NS) and the improvement in absolute error seen in the E75/S condition relative to the average control condition in the PWB task.

Similarly, a modest correlation was found between the absolute error of the average control condition (NE/NS) and the improvement seen in the absolute error with the sleeve alone (NE/S) condition relative to the control condition ($R=0.391$, $p<0.05$) during the PWB task. Significant correlations were also found between the control average absolute error seen in both the NWB and PWB tasks and the patient reported measures of functionality and instability (Table 3).

<u>Correlation Coefficient p-value</u>	<u>Age</u>	<u>BMI</u>	<u>KL grade</u>	<u>WOMAC</u>				<u>Self Reported Instability</u>
				<u>pain</u>	<u>stiffness</u>	<u>function</u>	<u>aggregate</u>	
PWB	0.140 0.399	-.0482 0.772	0.224 0.175	0.450 <0.05	0.462 <0.05	0.437 <0.05	0.473 <0.05	-.484 <0.05
NWB	0.0513 0.758	0.174 0.293	0.0884 0.596	0.435 <0.05	0.420 <0.05	0.521 <0.05	0.496 <0.05	-.340 <0.05

Table 3. Spearman correlation analysis results detailing the relationship between the control average (NE/NS) condition and various subject measures. Bold indicates significant correlations exist between the two measures.

The mean threshold for detection of electrical stimulation was determined for both the superior ($110.97\mu\text{A-RMS} \pm 44.50\mu\text{A-RMS}$) and inferior ($123.80\mu\text{A-RMS} \pm 40.15\mu\text{A-RMS}$) pairs of electrodes for the subjects.

4.4. Discussion

Our findings partially support our hypothesis, as an improvement in proprioception was found in the E75/S and NE/S conditions relative to the control condition during the PWB task. However, these conditions did not differ from each other. The improvement in knee proprioception during a physiologically relevant PWB task with application of a neoprene sleeve in subjects with knee OA is a novel finding. Previous studies have demonstrated improvements in knee JPS in knee OA subjects [20] and normal subjects [19, 21] during a NWB task with a neoprene sleeve, but this modality has been reported as ineffective during an axially-loaded closed kinetic chain task simulating WB [36, 37]. Evaluations of postural sway during single or dual leg stance have been used to assess joint proprioception indirectly, however, studies using this approach have been inconsistent in documenting an improvement in balance in knee OA subjects wearing a knee sleeve [20, 38]. Part of the motivation of the

current study was derived from previous balance studies demonstrating that SR electrical stimulation applied about the knee reduced postural sway in elderly subjects [24]. These findings and other SR somatosensory stimulation effects reported in the literature [22, 23, 25] led these investigators to theorize that enhanced knee proprioception was the mechanism by which improved postural control was achieved [24]. The lack of improvement in JPS during the E75/S condition relative to the NE/S condition in the current study does not appear to support the hypothesis that SR stimulation enhances proprioception as assessed via static JPS. However, it may be that the beneficial effects of SR stimulation on balance act by means other than enhancing the sensitivity of proprioceptors. Reeves et al. recently demonstrated in chronic low back pain subjects that SR stimulation had no effect on spine proprioception but did improve postural control and suggested that SR stimulation may shorten reflex delays allowing for more effective postural control during dynamic tasks [39]. If SR stimulation enhances balance via improvement of reflex characteristics, it would seem plausible that these changes may still improve knee joint loading during dynamic tasks such as walking. If future studies are able to demonstrate that SR stimulation applied in knee OA subjects can improve dynamic loading of the knee during walking, it would be helpful to identify the subpopulation of OA subjects that may most benefit from such a therapy. The moderate correlation observed between the improvement in JPS with the E75/S-RMS condition and JPS of the control condition is suggestive that individuals with poor proprioceptive acuity may benefit most from this therapy.

An additional question is whether the observed improvement in proprioception for the E75/S and NE/S conditions during the PWB task represents a clinically significant effect. Using a similar PWB methodology it has been demonstrated that the JPS error is 1.7° greater

in knee OA subjects compared to age matched controls and that the JPS error is 1.6° greater in elderly subjects (60-75 years) compared to young subjects (20-35 years) [40]. These findings suggest that a difference in JPS error of $1-2^{\circ}$ may be a clinically significant effect. Further support that the improvement in JPS observed in the sleeve conditions may be clinically significant comes from a prospective, randomized clinical trial of patients with varus gonarthrosis which found that wearing a knee sleeve for 6 months significantly improved the WOMAC stiffness score and the six minute walking distance relative to controls [41]. The significant correlations found between the subjects' JPS error in the control condition and the WOMAC scores or self-reported instability scores in our study suggest that the improvements in JPS error with the treatment condition may produce significant changes in disease severity and function. These correlations coincide with earlier reports that have found modest correlations between joint displacement detection thresholds and WOMAC scores in subjects with knee OA [4]. Finally, a recent longitudinal study demonstrated that JPS error had modest effects on the increase in pain and physical function limitations in knee OA [42].

While this study is novel and resulted in significant findings, it has several limitations. The fact that an improvement in JPS was not seen during both of the stimulation conditions (E50/S and E75/S) compared to the sleeve alone condition may be a result of an inadequate stimulation amplitude. Past SR stimulation studies have clearly demonstrated that an optimal stimulation level exists for increasing the sensitivity of somatosensory receptors to mechanical stimuli, and that stimulation outside of this optimal range may have little effect [22, 23]. The $50\mu\text{A}$ -RMS amplitude used in this study coincides with a level previously applied at the knee in elderly subjects that produced a significant improvement in postural

sway [24]. However, because the subjects in our study may have had more degeneration, it is unclear whether the two levels of stimulation applied were able to adequately penetrate each subject's tissue around the knee and sufficiently activate the muscle spindles and mechanoreceptors necessary for improvements in JPS. Past SR studies in the lumbar spine have demonstrated that stimulation levels at 50% of the subject's threshold for detection of the SR stimulus produced the greatest improvement in postural sway [39]. The 75 μ A-RMS stimulation level of our study was approximately 67.5% and 60.5% of each subject's detection threshold for the superior and inferior electrode pairs, respectively. However, it is unclear how the detection threshold coincides with the threshold of the mechanoreceptors which contribute to knee proprioception. Additionally, electrode placement may be another limitation. An effort was made to simulate the methods used in our previous work, in which an improvement was seen in the PWB task [8]. Although an attempt was made to surround the joint with SR stimulation, it is less clear what specific mechanoreceptors would be best to target in trying to correct the proprioceptive deficits in knee OA, which provides the opportunity for future study. Another limitation of this study is that testing sessions were somewhat lengthy and on several occasions subjects stated they lost focus, resulting in trial repeats. It is possible the loss of focus compounded with subject fatigue may have affected subject's ability to concentrate on the knee target angle, resulting in poor joint position sense error. This was particularly true during the NWB task, and may have contributed to the lack of differences among the conditions for this task. Lastly, there was a wide range of functionality and pain level from subject to subject and the subject's response to the treatment conditions may have been affected by their disease symptoms (functionality and pain).

While application of a neoprene sleeve was sufficient to enhance knee proprioception during the more functional PWB task in knee OA subjects, no further improvement in proprioception acuity was found with the addition of SR stimulation. Future work is necessary to determine if applying SR electrical stimulation at higher amplitudes tailored to each subject's threshold of detection will help demonstrate the benefits of SR to knee proprioception or if the benefits of SR stimulation to knee function may be more evident during dynamic tasks such as walking and single leg balance. Our findings also confirm that proprioception acuity is correlated with knee pain and function and suggest that the SR stimulation and sleeve therapy may be most beneficial to apply in patients with larger proprioceptive deficits.

4.5. References

1. *Osteoarthritis of the Knee: State of the Condition*. 2004, American Academy of Orthopaedic Surgeons.
2. Creamer, P. and M. Hochberg, *Osteoarthritis*. The Lancet, 1997. **350**(August 16): p. 503-508.
3. Felson, D.T. and Y. Zhang, *An update on the epidemiology of knee and hip osteoarthritis with a view to prevention*. Arthritis & Rheumatism, 1998. **42**: p. 1343-1355.
4. Pai, Y., et al., *Effect of age and osteoarthritis on knee proprioception*. Arthritis & Rheumatism, 1997. **40**(12): p. 2260-2265.
5. Fitzgerald, G., S. Piva, and J. Irrgang, *Reports of joint instability in knee osteoarthritis: Its prevalence and relationship to physical function*. Arthritis & Rheumatism, 2004. **51**(6): p. 941-946.
6. Hortobagyi, T., et al., *Altered hamstring-quadiceps muscle balance in patients with knee osteoarthritis*. Clinical Biomechanics, 2005. **20**(1): p. 97-104.
7. Mundermann, A., C.O. Dyrby, and T.P. Andriacchi, *Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking*. Arthritis Rheum, 2005. **52**(9): p. 2835-44.
8. Radin, E.L., et al., *Relationship between lower limb dynamics and knee joint pain*. J Orthop Res, 1991. **9**(3): p. 398-405.
9. Schmitt, L.C. and K.S. Rudolph, *Influences on knee movement strategies during walking in persons with medial knee osteoarthritis*. Arthritis Rheum, 2007. **57**(6): p. 1018-26.
10. Sharma, L., et al., *Knee adduction moment, serum hyaluronan level, and disease severity in medial tibiofemoral osteoarthritis*. Arthritis & Rheumatism, 1998. **41**: p. 1233-1240.
11. Sharma, L., *Proprioceptive Impairment in Knee Osteoarthritis*. Rheumatic Disease Clinics of North America, 1999. **25**(2): p. 299-314.

12. Swanik, C.B., et al., *The role of proprioception in patients with DJD and following total knee arthroplasty*, in *Proprioception and Neuromuscular Control in Joint Stability*, S.M.a.F. Lephart, Freddie H., Editor. 2000, Human Kinetics, Inc.
13. Lohmander, L., et al., *The long-term consequence of anterior cruciate ligament and meniscus injuries*. American Journal of Sports Medicine, 2007. **35**(10): p. 1756-1769.
14. Jerosch, J., M. Prymka, and W. Castro, *Proprioception of knee joints with a lesion of the medial meniscus*. Acta Orthopaedica Belgica, 1996. **62**(1): p. 41-45.
15. Corrigan, J., W. Cashman, and M. Brady, *Proprioception in the Cruciate Deficient Knee*. The Journal of Bone and Joint Surgery, 1992. **74-B**(2): p. 247-250.
16. O'Connor, B., et al., *Neurogenic Acceleration of Osteoarthritis*. The Journal of Bone and Joint Surgery, 1992. **74-A**(3): p. 367-376.
17. Sharma, L., et al., *Is Knee Joint Proprioception Worse in the Arthritic Knee Versus the Unaffected Knee in Unilateral Knee Osteoarthritis?* Arthritis & Rheumatism, 1997. **40**(8): p. 1518-1525.
18. Lin, D.H., et al., *Efficacy of 2 non-weight-bearing interventions, proprioception training versus strength training, for patients with knee osteoarthritis: a randomized clinical trial*. Journal of Orthopaedic & Sports Physical Therapy, 2009. **39**(6): p. 450-457.
19. McNair, P., S. Stanley, and G. Strauss, *Knee bracing: Effects on proprioception*. Archives of Physical and Medical Rehabilitation, 1996. **77**: p. 287-289.
20. Birmingham, T.B., et al., *Knee bracing for medial compartment osteoarthritis: effects on proprioception and postural control*. Journal of Rheumatology, 2001. **40**(3): p. 285-289.
21. Herrington, L., *The effect of a neoprene sleeve on knee joint position sense*. Research in Sports Medicine, 2005. **13**: p. 37-46.
22. Cordo, P., et al., *Noise in human muscle spindles*. Nature, 1996. **383**(October 31): p. 769-770.

23. Collins, J.J., T.T. Imhoff, and P. Grigg, *Noise-enhanced tactile sensation*. Nature, 1996. **383**(6603).
24. Gravelle, D.C., et al., *Noise-Enhanced Balance Control in Older Adults*. NeuroReport, 2002. **13**(15): p. 1-4.
25. Dhruv, N.T., et al., *Enhancing tactile sensation in older adults with electrical noise stimulation*. NeuroReport, 2002. **13**(5): p. 597-600.
26. Hijmans, J., et al., *Effects of vibrating insoles on standing balance in diabetic neuropathy*. Journal of Rehabilitation Research & Development, 2008. **45**(9): p. 1441-1450.
27. Liu, W., et al., *Noise-enhanced vibrotactile sensitivity in older adults, patients with stroke, and patients with diabetic neuropathy*. Archives of Physical Medicine and Rehabilitation, 2002. **83**: p. 171-176.
28. Priplata, A.A., et al., *Noise-Enhanced Balance Control in Patients with Diabetes and Patients with Stroke*. Annals of Neurology, 2005. **59**: p. 4-12.
29. Collins, A., et al., *The effects of stochastic resonance electrical stimulation and neoprene sleeve on knee proprioception*. Journal of Orthopaedic Surgery and Research, 2009. **4**(3).
30. Felson, D.T., et al., *The incidence and natural history of knee osteoarthritis in the elderly*. Arthritis & Rheumatism, 1995. **38**(10): p. 1500-1505.
31. Felson, D.T., et al., *Defining radiographic osteoarthritis for the whole knee*. Osteoarthritis and Cartilage, 1997. **5**: p. 241-250.
32. Irrgang, J., et al., *Development of a patient-reported measure of function of the knee*. The Journal of Bone and Joint Surgery, 1998. **80-A**(8): p. 1132-1145.
33. Bellamy, N., et al., *Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee*. J Rheumatology, 1988. **15**(2): p. 1833-1840.

34. Higgins, M. and D. Perrin, *Comparison of weight-bearing and non-weight bearing conditions on knee joint position sense*. Journal of Sports Rehabilitation, 1997. **6**: p. 327-334.
35. Bullock-Saxton, J., W. Wong, and N. Hogan, *The influence of age on weight-bearing joint reposition sense of the knee*. Experimental Brain Research, 2001. **136**: p. 400-406.
36. Birmingham, T.B., et al., *Effect of a Neoprene Sleeve on Knee Joint Position Sense During Sitting Open Kinetic Chain and Supine Closed Kinetic Chain Tests*. American Journal of Sports Medicine, 1998. **26**(4): p. 562-566.
37. Birmingham, T., et al., *Effect of a neoprene sleeve on knee joint kinesthesia: Influence of different testing procedures*. Medicine & Science in Sports & Exercise, 1999. **32**(2): p. 304-308.
38. Chuang, S., et al., *Effect of knee sleeve on static and dynamic balance in patients with knee osteoarthritis*. Kaohsiung Journal of Medical Sciences, 2007. **23**(8): p. 405-410.
39. Reeves, P., et al., *The effects of stochastic resonance stimulation on spine proprioception and postural control in chronic low back pain patients*. . Spine, 2009. **34**(316-321).
40. Garsden, L., Bullock-Saxton, J.E., *Joint Reposition Sense in Subjects with Unilateral Osteoarthritis of the Knee*. Clinical Rehabilitation, 1999. **13**: p. 148-155.
41. Kirkley, A., et al., *The effect of bracing on varus gonarthrosis*. The Journal of Bone and Joint Surgery, 1999. **81**: p. 539-548.
42. Felson, D.T., et al., *The effects of impaired joint position sense on the development and progression of pain and structural damage in knee osteoarthritis*. . Arthritis & Rheumatism, 2009. **61**(8): p. 1070-1076.

CHAPTER 5. THE IMPACT OF STOCHASTIC RESONANCE ELECTRICAL STIMULATION AND KNEE SLEEVE ON IMPULSIVE LOADING AND MUSCLE CO-CONTRACTION DURING GAIT IN KNEE OSTEOARTHRITIS

5.1. Introduction

Osteoarthritis (OA) is a common joint disorder affecting roughly 27 million people in the US [1] and contributes to significant health care costs [2]. The disorder involves chronic breakdown of cartilage within a joint and its associated risk factors for development include joint injury, obesity, and repetitive joint stress, among others. More specifically, alterations in the mechanical environment of the knee joint can lead to adverse effects on load distribution, resulting in abnormal wear within the joint. Reduced knee flexion excursion as well as heightened muscular co-contraction during the loading phase of gait are mechanical hallmarks of those with knee OA and together they represent what is known as the “stiffened knee response” [3, 4].

Repetitive impulsive loading, a reflection of both the force at ground contact otherwise known as the heel strike transient (HST) and the time to reach peak force, is another mechanical factor that may play a role in the progression of knee OA [5]. Animal studies investigating the effects of repetitive loading have demonstrated that microfractures are present in the trabecular bone of rabbits when subject to repetitive loading [6] and that greater cartilage fissuring results from the same magnitude impact loads applied at higher

loading rates [7]. Subsequently, bone remodeling produces stiffening of the subchondral bone, thus minimizing its ability to absorb impact forces resulting in joint degeneration.

Deficits in proprioception, which is defined as the perception of limb position and movement within space, could be the cause of ineffective muscle activation resulting in elevated impulsive loading. Also, these deficits may cause a pseudo instability resulting in increased muscular co-contraction as a way to restabilize the joint, but at the expense of increasing compressive stresses across the joint. Correcting these proprioceptive deficits through a phenomenon known as stochastic resonance (SR) may help slow disease progression by decreasing impulsive loading and improper muscle activation. SR is a concept in which low-level noise improves a given system's sensitivity to weak stimuli. Somatosensory application of subsensory SR stimulation has demonstrated improvements in tactile sensation [8], muscle spindle output [9], balance control [10, 11], and joint position sense [12]. Previous work has shown that a knee sleeve/brace can improve proprioception [13-15]. Thus, by combining SR stimulation with a sleeve, greater improvements in proprioception may result. By enhancing the sensitivity of one's sensory system, proprioceptive improvements may positively alter gait, resulting in more appropriate joint loading, thus possibly delaying onset and/or slowing progression of OA. As there is no previous research investigating the effects of a sleeve combined with SR electrical stimulation applied at the knee on gait or muscle activity, this study contributes novel information to the existing field of knowledge.

The purpose of this study was to determine whether the application of SR electrical stimulation combined with a knee sleeve could decrease the HST and ground reaction force (GRF) loading rate as well as decrease the muscle co-contraction activity occurring during

gait in subjects with OA of the knee. We hypothesized that the HST and GRF loading rates would be reduced at ground contact and muscular co-contraction between the hamstrings and quadriceps groups would decrease during the weight acceptance phase of gait with the application of a knee sleeve and further decrease with SR application.

5.2. Materials & Methods

5.2.1. Subjects

Following approval by the Institutional Review Board, 52 (30 females, 22 males) patients 40 years or older with minimal to moderate (Kellgren-Lawrence KL grade 1-3) medial knee OA and a physician's diagnosis of knee OA were recruited from the physician's practice within the Department of Orthopaedics. Prior to recruitment, subjects with a BMI of 35 or more, those who had a previously diagnosed neurological condition, used a pacemaker or other implanted electronic device, had a diagnosis of musculoskeletal disease other than their knee OA, or had a lower extremity joint replacement were excluded. Those subjects using an assistive device to walk, and those who had a previous injection of corticosteroid within 3 months prior to screening were also excluded. Subject demographics as well as self reported pain, stiffness, functionality, and instability measures are reported in Table 4.

	Male (n=22)	Female (n=30)	Total (n=52)
Age	58.6 (10.9)	63.0 (8.3)	61.2 (9.6)
Weight (kg.)	91.9 (12.4)	72.9 (12.7)	80.9 (15.7)
Height (cm.)	178.2 (8.1)	164.7 (6.4)	170.4 (9.8)
BMI	29.0 (4.1)	26.8 (4.2)	27.8 (4.3)
Kellgren-Lawrence grade (1 to 3)	2.3 (0.8)	2.1 (0.8)	2.2 (0.8)
WOMAC Index (pain)	4.0 (4.1)	4.2 (3.0)	4.1 (3.4)
(stiffness)	3.0 (2.1)	2.6 (1.6)	2.7 (1.8)
(function)	12.7 (12.7)	12.2 (9.3)	12.4(10.8)
WOMAC Aggregate	19.6 (18.1)	19.0 (13.2)	19.2 (15.3)
Self Reported Instability (part A)	3.5 (1.3)	4.0 (1.3)	3.8 (1.3)
Self Reported Instability (part B)	6.2 (14.0)	10.6 (23.8)	8.7 (20.2)

Table 4. Mean (sd) demographics as well as subject reported pain, stiffness, functionality, and instability measures for all test subjects.-Loading Rate.

Standing anterior-posterior radiographs taken with the knee in full extension were assessed by an orthopaedist to determine knee OA severity based on a modified Kellgren-Lawrence (KL) grading system [16, 17]. Joint space narrowing was ensured to be greater on the medial side by visual inspection of standing radiographs. Each subject's more severely affected knee, excluding knees with grade 4 OA, was chosen for testing and in instances where both knees were equally affected the subject's dominant knee was tested.

5.2.2. Study Design

Kinetic, kinematic, and electromyography (EMG) measures were recorded while subjects performed a 10-meter walk down a level platform. Each subject's threshold for detecting the SR stimulation was determined prior to gait analysis and a level of 75% of their threshold for detection was used for subsequent testing. During gait analysis, subjects were presented with four conditions in the following sequence: no electrical stimulation/no sleeve (control1 NE:NS1); counterbalance design of 2 treatment conditions: no stimulation/sleeve (NE:S), and 75% of threshold stimulation/sleeve (E75:S); followed by a no stimulation/no sleeve condition (control2 NE:NS2). Treatment conditions were presented in a

counterbalanced sequence design in order to control for any lasting effects of the electrical stimulation. Additionally, fatigue effects were assessed by comparing measures in the two control conditions placed before and after the treatment conditions.

5.2.3. Gait Analysis

Subjects were instructed to walk at a self-selected “fast” pace with the foot of their test limb landing on a nonconductive force plate (model 4060nc, Bertec Corp., Columbus, OH). Three electromagnetic position sensors (Flock of Birds, Ascension Technology Corp., Burlington, VT) were placed on the sacrum, thigh and shank of the test limb taking care to place them in areas of minimal subcutaneous tissue in order to minimize motion artifacts. The knee and ankle joint centers were defined as the midpoint between the digitized medial and lateral femoral condyles and medial and lateral malleoli, respectively. The hip joint center was determined using Leardini’s method [18]. Knee joint angles were determined as the motion of the tibial reference frame relative to the femoral reference frame where flexion-extension was about the y-axis, valgus-varus was about the x-axis, and internal-external rotation about the z-axis. Walking speed was measured using an infrared timing system (Sparq XLR8 Digital Timing System, Nike) to ensure walking speed did not vary by more than 10% between trials. In addition, mean forward velocity was calculated from the displacement of the sacral position sensor.

5.2.4. EMG measurements

Preamplified, surface electromyography (SEMG) electrodes (Delsys Inc., Boston, MA) were placed on the vastus lateralis (VL), medial hamstrings (MH), and lateral hamstrings (LH) to determine electrical activity of each muscle. Electrodes were placed

parallel to the muscle fibers over the longitudinal midline midbelly. A common reference electrode was placed over the posterior aspect of the ipsilateral wrist.

5.2.5. SR stimulation and sleeve

Two pairs of surface SR electrodes designed to deliver the electrical stimulation via an electrical stimulator device (Afferent Corporation, Providence, RI) were placed on the inferior and superior aspects of the knee joint line. Electrodes were placed approximately 2cm above and below the joint line as measured from the joint line to electrode pad circumference. Each pair consisted of one electrode placed medial to the joint centroid and one lateral in order to create an alternating flow of current in the medial-lateral direction. Stimulation consisted of a Gaussian white noise signal (zero mean, 0-1000Hz bandwidth) that was 75% of the subject's threshold level for detection determined prior to testing. SR threshold level for detection was determined by asking subjects to indicate at which amplitude they detected the presence of the electrical stimulation. SR electrodes remained in place during all testing conditions and subjects were blinded as to when the stimulation was applied.

Subjects also wore a neoprene knee sleeve during the no electrical stimulation/sleeve (NE:S) and stimulation/sleeve (E75:S) treatment conditions. The sleeve was fit based on the girth of the test limb's thigh measured approximately 4 inches above the patella center per manufacturer's recommendations (Safe-T-Sport Model# 37-350, FLA Orthopaedics Inc., Miramar, FL).

5.2.6. Data Collection

After explanation of the study procedures and the associated risks, informed consent was obtained from each subject. Subjects then completed a self-reported measure of knee

instability questionnaire adapted from the Knee Outcome Survey “Activities of Daily Living Scale” [19-21]. The questionnaire asked each subject to rate his/her instability (0 to 5 scale) by answering the question, “To what degree does giving way, buckling, or shifting of the knee affect your level of daily activity?” and indicating how many times he/she had experienced instability within 3 months prior to testing. Each subject then completed the Knee and Osteoarthritis Outcome Score (KOOS) survey, indicating within the week prior to testing how he/she felt about his/her knee symptoms, stiffness, pain, physical function, and overall quality of life [22]. Five valid gait trials within each of the four testing conditions were collected with a valid trial defined as one in which the subject correctly landed on the force plate with no variation in stride length. Data collection commenced 3s prior to ground contact and continued 2s after contact.

5.2.7. Data Reduction

Kinematic, kinetic and EMG data acquisition were synchronized using the Motion Monitor motion capture system (Innovative Sports Training, Chicago, IL). All kinetic and SEMG data were collected at 1440Hz while kinematic data were sampled at 144Hz and filtered at 6Hz using a 4th order, zero lag Butterworth filter. Data were reported during the three phases of gait: preparatory phase (100ms prior to initial ground contact through initial ground contact), weight acceptance phase (period from initial contact to peak knee flexion), and midstance (period from peak knee flexion to toe-off). Kinematic outcome measures include knee flexion angle at ground contact and forward velocity. Kinetic outcome measures include ground reaction forces in the anterior-posterior (x), medial-lateral (y), and superior-inferior (z) directions, which were acquired unfiltered and normalized to subject’s body weight (N). Loading rate measures were calculated from the vertical ground reaction

force (Fz) over increasing time domains in the following manner: 1.) Fz LR max (BW/s): the maximum slope from the 1st derivative of a 4th order polynomial fit between the point of initial ground contact and the peak heel strike transient (HST) 2.) Fz LR to HST (BW/s): the linear slope between the point of initial ground contact and the peak HST (Fz HST) and 3.) Fz LR to Peak (BW/s): the linear slope between the point of initial ground contact and the overall peak of the vertical ground reaction force (Fz Peak) (Figure 5).

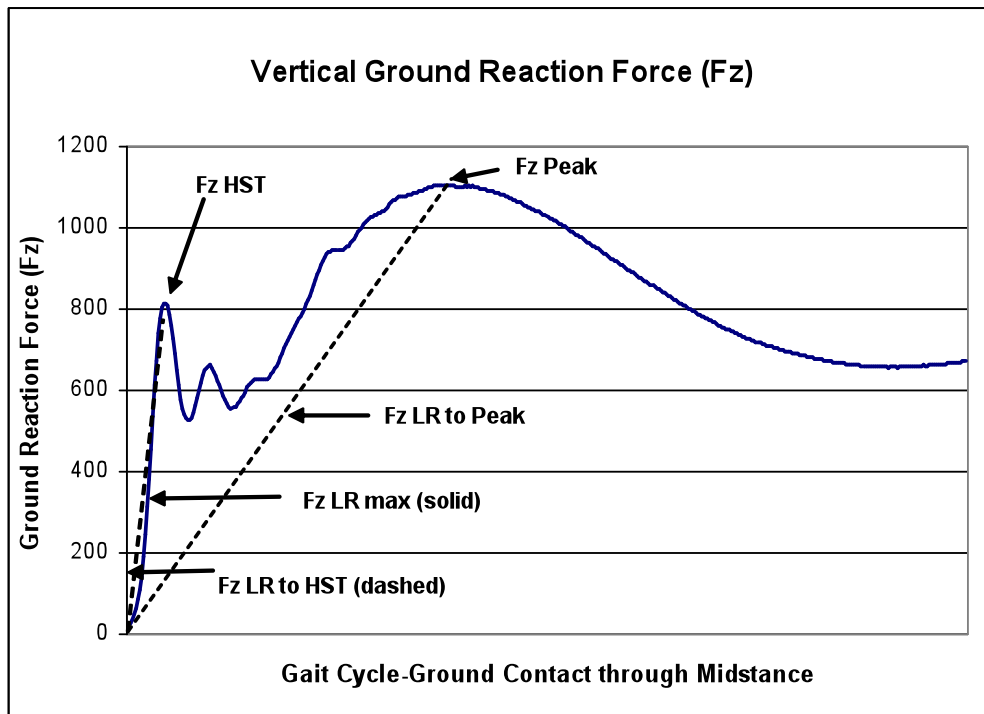


Figure 5. Vertical component of ground reaction force demonstrating loading rate outcome measures with respect to the generated data plot from a sample test subject.

The mean EMG amplitudes of all three muscles (VL, MH, LH) in each of the three phases of gait were calculated. These values were time normalized to 100 points as well as normalized to the average maximum activity of the specific muscle demonstrated during the control trials (NE:NS1 and NE:NS2) after signal processing. EMG data were bandpass filtered from 20 to 450Hz, using a 4th order Butterworth filter, notch filtered at 60Hz, full

wave rectified, and filtered at 20Hz using a zero lag 8th order Butterworth low pass filter to create a linear envelope. Additionally, EMG co-contraction values (VL/MH and VL/LH) were calculated according to a previously described method [4] as shown in the equation below:

Co-contraction index =

$$[\sum_{i=1}^{100} \{(\text{lower EMGi}/\text{higher EMGi}) * (\text{lowerEMGi} + \text{higher EMGi})\}]/100$$

In order to account for any leakage of the SR stimulation to the EMG signals, quiet trials of EMG were taken with the subject in a seated position with and without the stimulation applied. The difference in these mean EMG levels for the quiet trials was subtracted from the dynamic EMG levels on a point by point basis to compute a “corrected” set of EMG values in addition to an uncorrected data set. If this subtraction produced a EMG level less than the quiet trial non-stimulation condition, the quiet trial non-stimulated level was then substituted.

5.2.8. Statistical Analysis

All statistical analyses were performed using SigmaPlot (Systat Software Inc., San Jose, CA). Paired t-tests were performed to compare control condition values (NE:NS1, NE:NS2) for each measure ($p < 0.05$). The control values were then averaged and used in subsequent analyses to create three overall testing conditions (NE:NSave, NE:S, and E75:S). A one-way repeated measures analysis of variance (ANOVA) was performed to determine whether overall significant differences exist between conditions for each measure with further statistical differences between conditions assessed by the Student-Newman-Keuls posthoc method of multiple comparisons ($p < 0.05$). Both parametric and nonparametric analyses were performed in instances where the data did not adhere to normality.

Nonparametric analyses included the Friedman Repeated Measures ANOVA on ranks as

well as the Wilcoxon Signed Rank paired t-test. Statistical significance in the following results is reported from the appropriate test, either parametric or non-parametric.

As a sensitivity analysis, an alternative statistical approach was also used to assess differences in the EMG measures between the treatment conditions. In this approach, the differences between the quiet non-stimulated and stimulated EMG values were normalized by the mean peak EMG during the control trials. This quiet trial difference was then compared to the following differences in the uncorrected mean EMG data between the treatment conditions (E75:S-NE:S; E75:S-NE:NS) using a paired t-test and Bonferroni correction of the significance level. If the quiet trial difference and treatment condition differences were not found to differ the treatment condition difference was considered to be solely a result of leakage of the SR stimulation to the EMG signal. Using a similar approach, a quiet trial difference in the co-contraction indices was also computed and compared to treatment condition differences (E75:S-NE:S; E75:S-NE:NS) in the co-contraction indices for the uncorrected EMG data.

5.3. Results

5.3.1. Subject Demographics

Fifty-two patients (30 females, 22 males) with minimal to moderate, medial knee OA were tested with some patients displaying bilateral OA. Of the 52 subjects, 28 had grade 3 OA, 11 had grade 2, and 13 had grade 1 OA. The average WOMAC indices for pain, stiffness, and function as well as the aggregate (sum of all answers within the three indices) and self-reported instability measures are detailed in Table 4. Twenty-four subjects indicated they experienced no episodes of instability while only three subjects indicated they were severely affected with daily episodes of instability.

5.3.2. Loading Rate parameters

Loading rate parameters are presented in Figure 6 and Table 5. The heel strike transient peak (Fz HST), and loading rates calculated from ground contact to peak HST (Fz LR to HST) and the maximum loading rate to peak HST (Fz LR max) were significantly less for the NE:S and E75:S conditions than the control condition ($p<0.05$). Loading measures that did not differ include the overall ground reaction force peak (Fz peak) and the loading rate calculated from ground contact to the overall ground reaction force peak (Fz LR to peak). Loading measures were also assessed using the horizontal component of the ground reaction force (Fx), however these parameters did not differ between conditions.

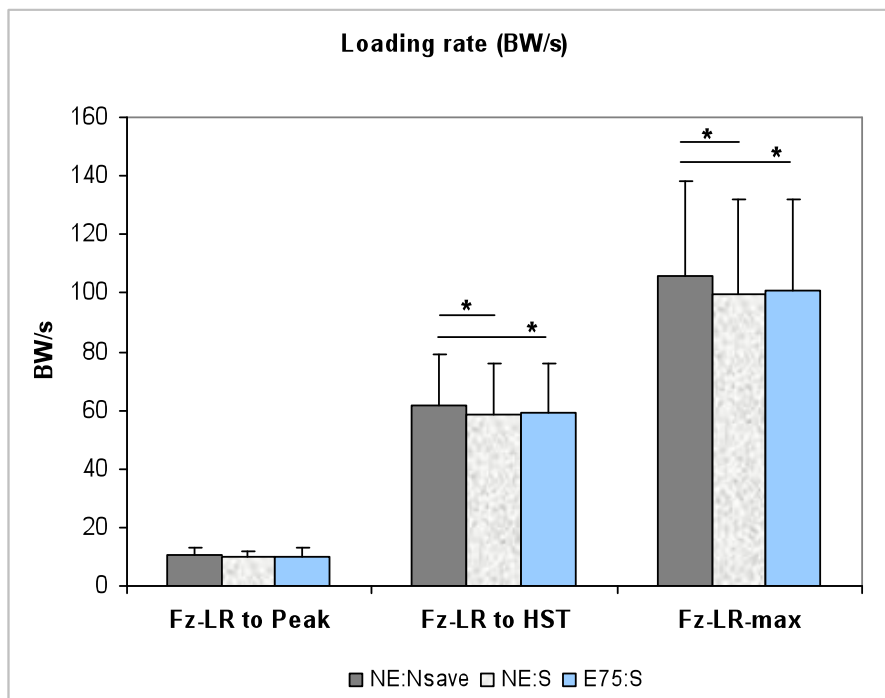


Figure 6. Loading rate outcome measures within each of the three testing conditions. *indicates significant differences between conditions at the end of the horizontal bars, $p<0.05$.

5.3.3. Kinematic parameters

Kinematic parameters are detailed Table 5. With the addition of a sleeve alone the knee flexion angle at initial ground contact significantly increased compared to the control

condition ($p<0.05$). Combining the sleeve with SR stimulation had the same affect compared to the control condition ($p<0.05$); however, the stimulation/sleeve (E75:S) and the sleeve alone (NE:S) conditions were not significantly different from each other. The mean forward velocity was not significantly different between conditions.

Kinematic measures	NE:NSave	NE:S	E75:S
Mean Forward Velocity (m/s)	1.47 (0.20)	1.47 (0.22)	1.47 (0.20)
Knee Flexion at contact (deg.)	12.56 (8.12)	14.44 (7.97) [†]	14.67 (8.03) [†]
Kinetic measures			
Fz-Peak (BW)	1.17 (0.13)	1.17 (0.14)	1.18 (0.13)
Fz-HST (BW)	0.73 (0.15)	0.70 (0.16) [†]	0.71 (0.15) [†]

Table 5. Mean (sd) kinematic and kinetic measures during gait within the three testing conditions. [†] indicates significant difference compared to the average control (NE:NSave). ^{*} indicates significant difference compared to the sleeve alone condition, $p<0.05$. MF=max knee flexion; IC=initial ground contact.

5.3.4. EMG parameters

Normalization parameters include the average \pm sd peak muscle activity (VL, MH, LH) over the 10 control trials, which were used for normalizing mean and peak muscle activity in each of the three gait phases (VL, 0.049 ± 0.0292 ; MH, 0.0472 ± 0.0259 ; LH, 0.0479 ± 0.0307). The non-normalized quiet trial values for each muscle during stimulation (VL, 0.0199 ± 0.0157 ; MH, 0.0054 ± 0.0031 ; LH, 0.0047 ± 0.0029) and no stimulation (VL, 0.0038 ± 0.0015 ; MH, 0.0031 ± 0.0013 ; LH, 0.0032 ± 0.0014) were used during the alternate statistical analysis. Quiet trial data indicated that some leakage of the SR stimulation to the EMG signal occurred. This in general resulted in the normalized EMG of the E75:S condition being significantly increased relative to the other conditions. As a result, our results will focus on statistical differences of the E75:S EMG data corrected for this leakage effect by using the quiet trial difference data. In all cases except where indicated, the secondary statistical analysis approach of comparing the quiet trial difference to the

differences between conditions (uncorrected data), produced similar statistical differences to that of the RMANOVA performed on the corrected E75:S EMG data. All normalized uncorrected and corrected EMG means for each phase are presented in Table 6.

Average corrected VL muscle activity during the preparatory phase of gait decreased with the sleeve alone ($p<0.05$) and further with the combination of sleeve and SR ($p<0.05$) compared to the control condition, with the two conditions (NE:S and E75:S) being significantly different from each other ($p<0.05$) (Table 6). During the weight acceptance phase of gait the addition of SR (E75:S) produced a significant decrease in corrected VL activity compared to the sleeve alone and control ($p<0.05$) which continued through the midstance phase ($p<0.05$).

EMG Measure	Phase	Normalized quietnstim-quietstim	NE:NSave	NE:S	E75:S	
					corrected	uncorrected
VL Mean	Prep	0.463 (0.553)	0.439 (0.110)	0.389 (0.110)†	0.320 (0.134)†‡	0.753 ^{A,B} (0.521)†‡
	Weight Acceptance		0.599 (0.059)	0.582 (0.085)	0.413 (0.148)†‡	0.839 ^{A,B} (0.404)†‡
	Midstance		0.231 (0.094)	0.215 (0.096)	0.186 (0.120)†‡	0.581 ^{A,B} (0.518)†‡
LH Mean	Prep	0.0695 (0.119)	0.549 (0.097)	0.566 (0.130)	0.541 (0.139)	0.592 (0.177)
	Weight Acceptance		0.342 (0.146)	0.347 (0.169)	0.335 (0.159)	0.379 (0.216)
	Midstance		0.219 (0.112)	0.209 (0.112)	0.222 (0.130)	0.267 (0.207)†‡
MH Mean	Prep	0.0529 (0.134)	0.543 (0.108)	0.570 (0.161)	0.527 (0.163)‡	0.595 ^B (0.197)†
	Weight Acceptance		0.331 (0.142)	0.338 (0.153)	0.320 (0.148)	0.384 (0.194)†‡
	Midstance		0.194 (0.098)	0.191 (0.100)	0.196 (0.122)	0.260 (0.189)†‡

Table 6. Mean (sd) SEMG muscle activity (VL, MH, LH) during each of the three phases of gait (Preparatory, weight acceptance, midstance). Values are normalized to the average peak activity in the control conditions for that specific muscle. † indicates significant differences relative to the control condition (NE:NSave) by RMANOVA. ‡ indicates significant differences relative to the sleeve alone condition (NE:S) by RMANOVA ($p<0.05$). ^{A,B} indicates significant difference relative to the control^A or

sleeve^B alone condition by paired t-test comparison of the difference between conditions of the uncorrected data and the quiet trial difference ($p<0.025$).

No significant differences were detected in the corrected LH activity between conditions within any of the phases of gait. Similarly, corrected MH activity was not different between conditions in the phases, except in the preparatory phase where a significant decrease was observed in the E75:S ($p<0.05$) condition compared to the NE: S and NE:Nsave conditions.

5.3.5. VL/LH co-contraction

Co-contraction of the VL/LH muscles significantly decreased in the preparatory phase with the addition of a sleeve alone ($p<0.05$) and decreased further with the addition of SR stimulation ($p<0.05$). These significant differences were carried over into the weight acceptance and midstance phases of gait (Figure 7).

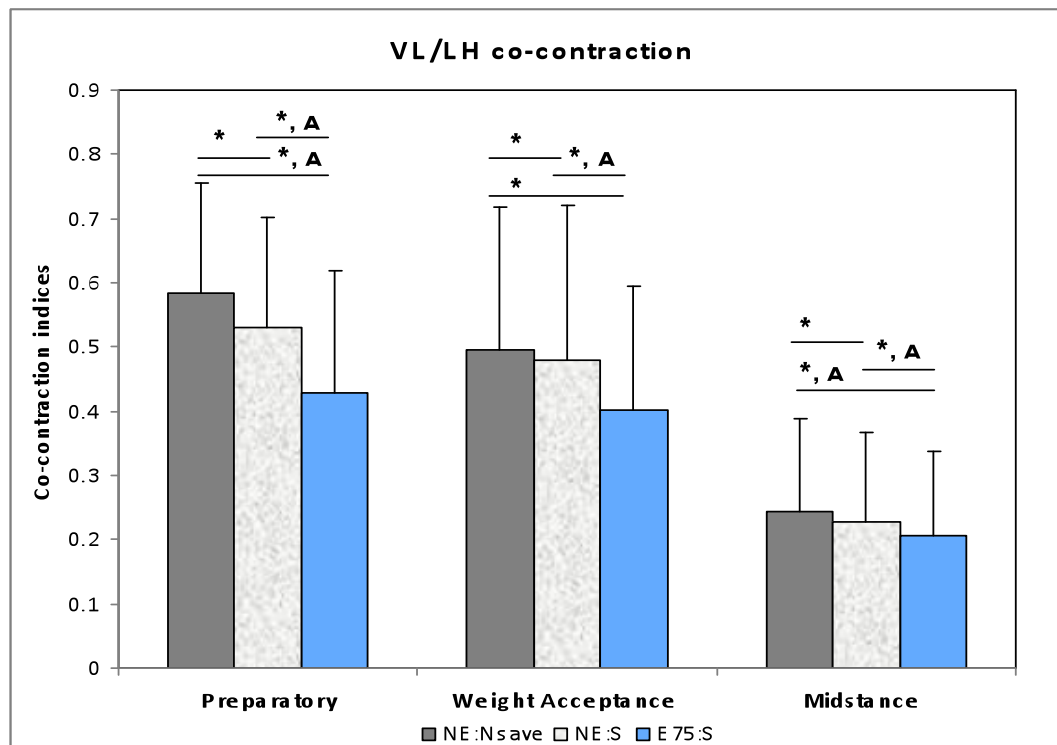


Figure 7. Co-contraction indices of the VL/LH muscle groups. *indicates significant differences (RMANOVA) between the conditions at the end of the horizontal bars, $p<0.05$. ^A indicates significant difference between the conditions at the end of the horizontal bars, by paired t-test comparison of the difference between conditions of the uncorrected data and a quiet trial co-contraction indices ($p<0.025$).

5.3.6. VL/MH co-contraction

Co-contraction of the VL/MH muscles significantly decreased in the preparatory phase for the sleeve alone ($p < 0.05$) and decreased further with the addition of SR stimulation ($p < 0.05$). When progressing to the weight acceptance phase of gait, significant decreases in the amount of co-contraction were found with the E75:S condition compared to NE:NSave and the NE:S ($p < 0.05$) conditions with there being no difference between the sleeve alone and the control condition. During the midstance phase of gait, the co-contraction indices in the E75:S and NE:S conditions were both significantly decreased compared to NE:NSave ($p < 0.05$).

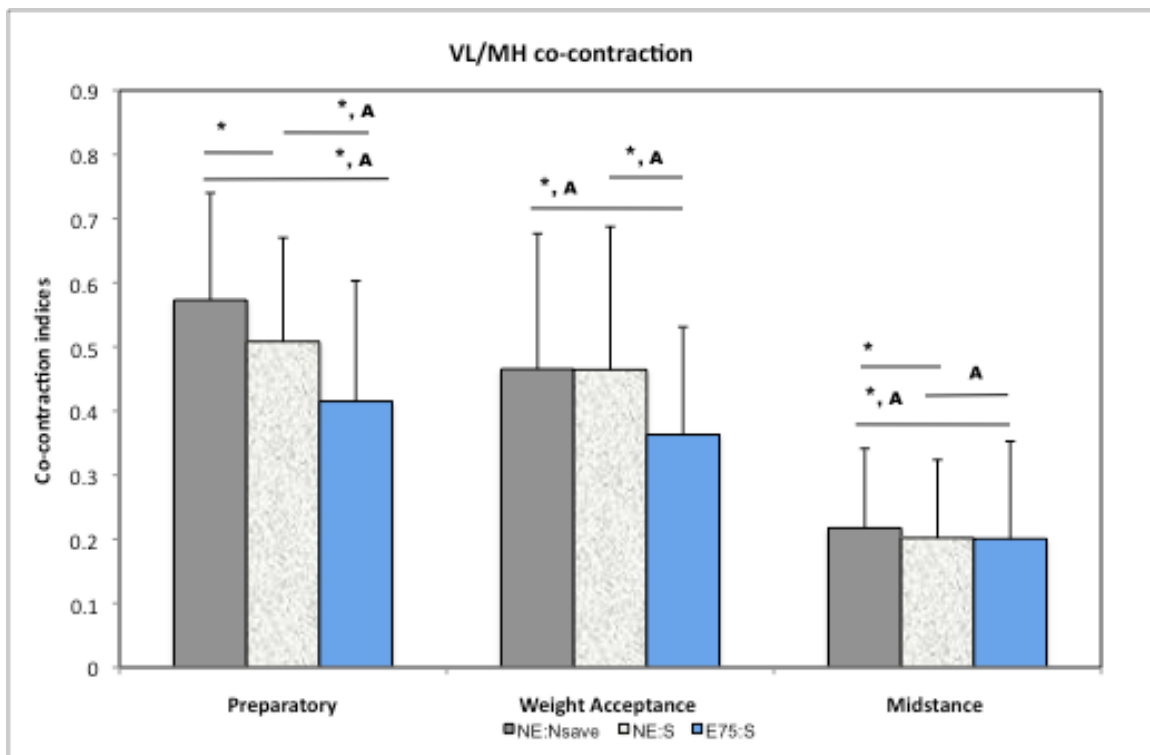


Figure 8. Co-contraction indices of the VL/MH muscle groups. *indicates significant differences (RMANOVA) between the conditions at the end of the horizontal bars, $p < 0.05$. ^A indicates significant difference between the conditions at the end of the horizontal bars, by paired t-test comparison of the difference between conditions of the uncorrected data and a quiet trial co-contraction indices ($p < 0.025$).

5.4. Discussion

Several biomechanical and muscular activation abnormalities are present in those with knee OA and include increased loading rates and reduced knee flexion at contact [23] as well as increased co-contraction of the quadriceps-hamstring muscle groups [24]. SR stimulation combined with a neoprene knee sleeve has proven to be effective in improving proprioception via joint position sense relative to a no sleeve, control condition in those with knee OA [25]. Previous studies investigating the effects of SR stimulation have found improvements in postural sway [10, 11, 26], tactile sensation [8], proprioception [27]. However, the present study is the first to investigate the effects of SR electrical stimulation combined with a neoprene knee sleeve on impulsive loading and muscle co-contractions in those with knee OA.

The significance of loading rate to the overall development and progression of knee OA has previously been demonstrated in animal studies [6, 7] with higher loading rates generating more surface fissuring of cartilage than lower loading rates [7]. Our results showed significant decreases in loading rates calculated over a shorter time domain with the application of a sleeve alone and in combination with SR whereas the loading rate calculated using the overall peak ground reaction force (Fz-LR to peak) did not. This is most likely the result of the significant decreases observed with the peak heel strike transient (Fz HST) between the sleeve alone and control condition as well as the stimulation/sleeve and control condition. The HST is a direct measure of the amount of load experienced during the impact at ground contact and decreases in this measure can translate into overall reductions in harmful load experienced at the knee. Our observed improvements in loading rate are likely a direct result of the increased knee flexion at ground contact as previous studies have found

an attenuation of shock loading with greater knee flexion [28]. In addition, Mundermann et al. demonstrated that subjects with knee OA landed in a more extended knee position with a greater loading rate than age matched control subjects [23], which may suggest that the observed increase in knee flexion at contact with the sleeve condition is a result of proprioceptive improvements, returning the gait pattern of OA subjects to a more normal pattern. The use of knee braces and sleeves to improve loading rate is limited to only one study in which the authors were able to reduce the loading rate at initial ground contact through the use of a knee brace designed to provide feedback to the user [29]. However, the use of a knee sleeve or simple, non-automated knee brace to reduce impact loading in knee OA has not been investigated. In the present study, our findings demonstrated significant increases in knee flexion at contact with the sleeve alone and in combination with SR stimulation though no differences were seen between the two treatment conditions, suggesting knee flexion increases at initial ground contact are due to the effect of a sleeve alone.

The increased knee flexion observed at ground contact may also be the result of the decreased co-contractions of both the VL/MH and VL/LH muscle groups seen during the preparatory and weight acceptance phases of gait, opposite to what is referred to as the “stiffened knee response” [30]. Decreases in muscle co-contraction with the application of SR or sleeve alone are likely the result of enhanced joint position sense (JPS), which may lead to a greater sense of increased stability of the joint. Previous studies have observed an improvement in JPS with a sleeve alone and a stimulation/sleeve condition compared to a control condition [25]. Those with knee OA likely demonstrate increased co-contraction of the hamstrings and quadriceps muscle groups as a way to improve the stability of the knee.

However, this strategy increases joint contact pressures, which exacerbates pain and degradation of the joint, thus highlighting the importance for treatment modalities targeting decreased muscle co-contraction.

The use of rigid braces has been investigated as a way to correct the muscular, biomechanical, and symptomatic differences present in knee OA [31-35]. Ramsey et al. found that the use of a rigid, neutrally aligning brace over a 2 week period reduced muscle co-contraction, pain, and knee adduction excursion angle [32] and suggested that the pain relief demonstrated in their study may be from decreased muscular co-contractions. Additionally, long term wear of neoprene sleeves has produced improvements in the disease-specific quality of life in knee OA as measured by the WOMAC index [36].

While this study presents novel information to the existing field of knowledge, it is not without limitations. Increased knee flexion observed in our study could be due to passive restraint effects of the sleeve. However, this is unlikely due to the fact that the sleeve was fit with the knee in full extension. Our results showed that the increase in mean uncorrected EMG activity was most likely due to a “leakage” effect of the SR stimulation and this should be considered when interpreting the resulting differences between conditions in the mean muscle amplitudes. Our effort to subtract out the SR stimulation signal was also a novel approach and may not have completely corrected the mean EMG data. However, our alternative statistical approach, which did not rely upon this correction procedure, found nearly equivalent statistical differences to the primary statistical approach, providing greater confidence that co-contraction levels are decreased in the SR stimulation group.

Additionally, it is possible the SR stimulation delivered was not at an optimal level. Some

subjects became confused and were not sure if they were detecting the stimulation during the threshold for detection procedure, so it is possible their detection amplitudes were incorrect.

We postulate that over time, decreases in loading rates experienced during gait may translate into improvements in functionality, and reductions in pain and stiffness. While the differences in loading rate seen in this study are small, and it is unknown what differences are considered clinically significant, these differences may grow with a more challenging task such as stair descent, with fatigue, or with prolonged use of a brace. Many studies have utilized a longer time domain when calculating loading rate, which diminishes the effect of initial impact [23, 37]. By considering the time at peak HST as the final time point for loading rate calculation, a more precise assessment can be made as to the loading rate experienced at contact.

Our hypothesis that SR stimulation combined with a neoprene knee sleeve would improve loading rate parameters was partially supported in that the HST peak and the shorter time scale loading rate measures were significantly reduced in the sleeve alone and the combination of sleeve and SR condition relative to the control. Despite these significant differences, there were no significant differences in the loading rate measures or HST peak between the two treatment conditions themselves. From this, we can conclude that our reductions in loading rate were likely the result of increased knee flexion at contact and decreased muscular co-contraction, possibly due to a greater sense of stability provided by the proprioceptive enhancing effects of the sleeve.

5.5. References

1. Helmick, C., et al., *Estimates of the prevalence of arthritis and other rheumatic conditions in the United States*. Arthritis & Rheumatism, 2008. **58**(1): p. 15-25.
2. Kotlarz, H., et al., *Insurer and out-of-pocket costs of osteoarthritis in the US*. Arthritis & Rheumatism, 2009. **60**(12): p. 3546-3553.
3. Childs, J., et al., *Alterations in lower extremity movement and muscle activation patterns in individuals with knee osteoarthritis*. Clinical Biomechanics, 2004. **19**(1): p. 44-49.
4. Schmitt, L.C. and K.S. Rudolph, *Influences on knee movement strategies during walking in persons with medial knee osteoarthritis*. Arthritis Rheum, 2007. **57**(6): p. 1018-26.
5. Collins, J.J. and M.W. Whittle, *Impulsive forces during walking and their clinical implications*. Clinical Biomechanics, 1989. **4**: p. 179-187.
6. Radin, E.L., et al., *Response of joints to impact loading-III. Relationship between trabecular microfractures and cartilage degeneration*. Journal of Biomechanics, 1973. **6**(1): p. 51-54.
7. Ewers, B.J., et al., *Rate of blunt impact loading affects changes in retropatellar cartilage and underlying bone in the rabbit patella*. Journal of Biomechanics, 2002. **35**(6): p. 747-755.
8. Collins, J.J., T.T. Imhoff, and P. Grigg, *Noise-enhanced tactile sensation*. Nature, 1996. **383**(6603).
9. Cordo, P., Et Al. , *Noise in human muscle spindles*. Nature, 1996. **383**(October 31): p. 769-770.
10. Gravelle, D.C., Et Al., *Noise-Enhanced Balance Control in Older Adults*. NeuroReport, 2002. **13**(15): p. 1-4.
11. Priplata, A.A., Et Al., *Noise-Enhanced Balance Control in Patients with Diabetes and Patients with Stroke*. Annals of Neurology, 2005. **59**: p. 4-12.

12. Collins, A., et al., *The effects of stochastic resonance electrical stimulation and neoprene sleeve on knee proprioception*. Journal of Orthopaedic Surgery and Research, 2009. **4**(3).
13. Birmingham, T.B., Et Al., *Effect of a Neoprene Sleeve on Knee Joint Position Sense During Sitting Open Kinetic Chain and Supine Closed Kinetic Chain Tests*. American Journal of Sports Medicine, 1998. **26**(4): p. 562-566.
14. Birmingham, T.B., et al., *Knee bracing for medial compartment osteoarthritis: effects on proprioception and postural control*. Journal of Rheumatology, 2001. **40**(3): p. 285-289.
15. Herrington, L., *The effect of a neoprene sleeve on knee joint position sense*. Research in Sports Medicine, 2005. **13**: p. 37-46.
16. Felson, D.T., et al., *Defining radiographic osteoarthritis for the whole knee*. Osteoarthritis and Cartilage, 1997. **5**: p. 241-250.
17. Felson, D.T., et al., *The incidence and natural history of knee osteoarthritis in the elderly*. Arthritis & Rheumatism, 1995. **38**(10): p. 1500-1505.
18. Leardini, A., et al., *Validation of a functional method for the estimation of hip joint centre location*. Journal of Biomechanics, 1999. **32**(1): p. 99-103.
19. Fitzgerald, G., S. Piva, and J. Irrgang, *Reports of joint instability in knee osteoarthritis: Its prevalence and relationship to physical function*. Arthritis & Rheumatism, 2004. **51**(6): p. 941-946.
20. Irrgang, J., et al., *Development of a patient-reported measure of function of the knee*. The Journal of Bone and Joint Surgery, 1998. **80-A**(8): p. 1132-1145.
21. Felson, D.T., et al., *Knee Buckling: Prevalence, Risk Factors, and Associated Limitations in Function*. Annals of Internal Medicine, 2007. **147**: p. 534-540.
22. Bellamy, N., et al., *Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee*. J Rheumatology, 1988. **15**(2): p. 1833-1840.

23. Mundermann, A., C.O. Dyrby, and T.P. Andriacchi, *Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking*. Arthritis Rheum, 2005. **52**(9): p. 2835-44.
24. Hortobagyi, T., et al., *Altered hamstring-quadriceps muscle balance in patients with knee osteoarthritis*. Clinical Biomechanics, 2005. **20**(1): p. 97-104.
25. Collins, A., et al., *Stochastic resonance electrical stimulation to improve proprioception in knee osteoarthritis*. The Knee, 2010. **Jul 22 [Epub ahead of print]**.
26. Ross, S., *Noise-enhanced postural stability in subjects with functional ankle instability*. British Journal of Sports Medicine, 2007. **41**: p. 656-659.
27. Reeves, P., et al., *The effects of stochastic resonance stimulation on spine proprioception and postural control in chronic low back pain patients*. . Spine, 2009. **34**(316-321).
28. Lafortune, M.A., E.M. Hennig, and M.J. Lake, *Dominant role of interface over knee angle for cushioning impact loading and regulating initial leg stiffness*. Journal of Biomechanics, 1996. **29**(12): p. 1523-1529.
29. Riskowski, J., et al., *Design and validation of a knee brace with feedback to reduce the rate of loading*. Journal of Biomechanical Engineering, 2009. **131**(8).
30. Lewek, M.D., K.S. Rudolph, and L. Snyder-Mackler, *Control of frontal plane knee laxity during gait in patients with medial compartment knee osteoarthritis*. Osteoarthritis Cartilage, 2004. **12**(9): p. 745-51.
31. Richards, J.D., et al., *A comparison of knee braces during walking for the treatment of osteoarthritis of the medial compartment of the knee*. Journal of Bone and Joint Surgery, 2005. **87-B**(7): p. 937-939.
32. Ramsey, D., et al., *A mechanical theory for the effectiveness of bracing for medial compartment osteoarthritis of the knee*. The Journal of Bone and Joint Surgery, 2007. **89**(2398-2407).
33. Brouwer, R.W., et al., *Brace treatment for osteoarthritis of the knee: a prospective randomized multi-centre trial*. Osteoarthritis Cartilage, 2006. **14**(8): p. 777-83.

34. Lindenfeld, T.N., T.E. Hewett, and T.P. Andriacchi, *Joint loading with valgus bracing in patients with varus gonarthrosis*. Clinical Orthopaedics and Related Research, 11/1997(344).
35. Lindenfeld, T.N., T.E. Hewett, and T.P. Andriacchi, *Joint loading with valgus bracing in patients with varus gonarthrosis*. Clinical Orthopaedics and Related Research, 1997(344).
36. Kirkley, A., et al., *The effect of bracing on varus gonarthrosis*. The Journal of Bone and Joint Surgery, 1999. **81**: p. 539-548.
37. Liikavainio, T., et al., *Loading and gait symmetry during level and stair walking in asymptomatic subjects with knee osteoarthritis: importance of quadriceps femoris in reducing impact force during heel strike?* Knee, 2007. **14**(3): p. 231-8.

CHAPTER 6. THE ASSESSMENT OF POSTURAL CONTROL WITH STOCHASTIC RESONANCE ELECTRICAL STIMULATION AND A NEOPRENE KNEE SLEEVE IN THE OSTEOARTHRITIC KNEE

6.1. Introduction

Osteoarthritis (OA) is a debilitating disease and is especially common in the elderly, affecting roughly 10% of those over the age of 65 [1]. Abnormal postural control [2] beyond that attributable to aging effects, as well as knee instability [3] have been demonstrated in those with knee OA and may put this population at greater risk of falling. Postural control is a reflection of sensory input (including proprioception), central processing, neuromuscular responses, and lower limb muscle strength. The abnormal postural control of knee OA may be a direct result of proprioceptive deficits, which are also known to exist in this population and exceed those of general aging effects [4-7]. Age has been demonstrated to have a detrimental effect on balance [8, 9], but this may be compounded in knee OA by the further impairment in one of the main components of balance, proprioception.

By improving proprioception, it is possible that balance itself may be improved. Birmingham et al. demonstrated improvements in proprioception with the use of a valgus producing brace in those with knee OA during a non-weightbearing joint position sense task [10]. A more recent study demonstrated that a neoprene knee sleeve produced a significant improvement in joint position sense in those with knee OA during a partial weightbearing task [11]. Improvements in sensory input (specifically proprioception) may translate into

improvements in balance, which may result in a reduction in the risk of falls in those with knee OA who are elderly in general and are more susceptible to falling.

The use of a knee sleeve/brace to improve balance in knee OA is limited to a few studies [10, 12, 13] with conflicting results. Chuang et al. demonstrated improvements in both static and dynamic balance with the use of a neoprene knee sleeve [12] and Hassan et al. showed significant reductions in postural sway with a loose elastic bandage [13].

Conversely, Birmingham et al. did not see a significant effect on balance with the use of a valgus producing brace [10]. Based on the conflicting results in the current literature, it is unclear whether postural control can be affected with the use of a knee sleeve.

A novel option for enhancing the ability of a sleeve to improve postural control may be by incorporating stochastic resonance (SR) electrical stimulation into the sleeve. SR stimulation has been investigated as a tool for improving postural control in a variety of diseased and injured populations [14-18]. SR is a phenomenon in which the sensitivity to weak stimuli is enhanced in sensory systems through the introduction of subsensory electrical or mechanical “noise”. It was first introduced as a way of improving tactile sensitivity [19] and muscle spindle output [20], but has since been investigated as a way of enhancing postural control in those with functional ankle instability [16], diabetic neuropathy [18], low back pain [17], older adults [14], and those who have suffered a stroke [15].

To date no studies exist examining the effects of SR electrical stimulation on balance in those with knee OA. By combining SR electrical stimulation and a neoprene knee sleeve, a novel clinical application arises in which balance may be improved in those with knee OA. The purpose of this study was to determine whether SR electrical stimulation combined with a neoprene knee sleeve would improve postural control outcome measures in those with knee

OA. Additionally, we investigated whether three different SR amplitudes, set as a percentage of the subject's threshold for detection, would have differential effects on balance.

6.2. Methods

6.2.1. Subjects

Fifty-two subjects (30 females, 22 males) with minimal to moderate (Kellgren-Lawrence KL grade 1 to 3), medial knee OA were recruited for participation in the study following Institutional Review Board approval. Subjects over the age of 40 years with a physician's diagnosis of knee OA were recruited from the physician's practice within the Department of Orthopaedics at the University of North Carolina at Chapel Hill. Those with a BMI of 35 or more, prior neurological impairments, a diagnosed musculoskeletal disease other than knee OA, use of a pacemaker or other implanted electronic device, use of a walking assistive device, or lower limb joint replacement were excluded. Additionally, those subjects who had received steroid injections within 3 months prior to screening were also excluded from participation. Each subject's standing anterior-posterior radiographs taken with the knee in full extension were assessed by a single orthopaedist in order to determine the severity of knee OA and grades were assigned based on a modified KL grading system [21, 22]. Each subject's more severely affected knee (excluding grade 4) was tested, and in instances where both knees were equally affected the subject's dominant limb was tested.

6.2.2. Study Design

Center of pressure (COP) displacements in the medial-lateral (ML) and anterior-posterior (AP) directions were assessed during single limb stance. Prior to testing, each subject's threshold for SR electrical stimulation detection was determined for both inferior and superior electrode pairs and three percentages of the subject's threshold for stimulation

detection were used for subsequent testing: 75%, 100%, 150%. Subject's threshold for stimulation detection was determined as the amplitude at which point he/she indicated the presence of electrical stimulation. During the balance assessment, six testing conditions were presented to each subject in the following sequence with subjects performing 3 trials in each condition: no electrical stimulation/no sleeve (control1 NE:NS); counterbalance of 4 treatment conditions: no stimulation/sleeve (NE:S), 75% electrical stimulation/sleeve (E75:S), 100% electrical stimulation/sleeve (E100:S), 150% electrical stimulation/sleeve (E150:S); followed by a second control condition (control2 NE:NS). In order to minimize fatigue/learning effects or any lasting effects of the electrical stimulation, treatments were presented in a counterbalanced manner with a control condition placed before and after the treatment conditions.

6.2.3. Data Collection

Informed consent was obtained from each subject after explanation of the study procedures and associated risks. Each subject then completed several questionnaires, the first of which was a self-reported measure of the amount of instability they had experienced that was adapted from the Knee Outcome Survey Activities of Daily Living Scale [23]. Within this questionnaire, subjects were asked to rate how episodes of giving way, buckling, or shifting of the knee affected their daily activities (0 to 5 scale) with 0 indicating the symptom prevents them from all activity and 5 indicating they do not experience the symptom. The second part of this questionnaire was derived from an article in which knee buckling was assessed in knee OA [24] and asked subjects how many times they had experienced the symptom within the previous 3 months. Subjects then completed the Knee and Osteoarthritis

Outcome Score (KOOS) survey, which asked subjects to rate how they felt about their knee pain, function, stiffness, and overall quality of life within the week prior to testing [25].

Two pairs of SR electrodes were placed on the medial and lateral aspects of the knee approximately 2 cm above and below the tibio-femoral joint line. The SR electrode placement pairs were designed to create an alternating flow of current in the medial-lateral direction. The delivered stimulation consisted of a Gaussian white noise signal (zero mean, 0-1000Hz bandwidth). The electrodes remained in place during the entire testing session and subjects were blinded as to whether or not the SR electrical stimulation was being delivered. Subjects were also fit for a neoprene knee sleeve per the manufacturer's recommendations (Safe-T-Sport Model #37-350, FLA Orthopaedics Inc., Miramar, FL).

Subjects performed the balance task barefoot and were asked to stand on their single test limb on a force plate (model 4060nc, Bertec Corp., Columbus, OH) while maintaining a forward focus with their hands on their hips for 20 seconds (Figure 9). A valid trial was determined to be one in which the subject would not grab onto the supporting safety frame or shift the location of their foot on the force plate. Subjects performed three practice trials prior to the start of data collection in order to become familiar with the task. Three valid trials were collected during each of the six testing conditions and subjects were given seated rest breaks of 30 seconds minimum in between trials and one minute between conditions.



Figure 9. Subject setup during the balance assessment demonstrating single-leg stance.

6.2.4. Data Reduction

Anterior-posterior (AP) medial-lateral (ML) locations of COP were collected at 1440Hz and filtered using a zero lag low-pass Butterworth filter with a cutoff frequency of 20 Hz. The resulting data from each trial were then analyzed to attain outcome measures including COP mean velocity in the AP and ML directions (COP-vel-AP, ML), the COP displacement range in both AP and ML directions (COP disp-AP, ML), the standard deviation of the COP displacement in both directions (SD COP disp-AP, ML), and the total path length of the COP was normalized to the duration of single leg stance excluding time of

touchdowns (Normalized COP Total Path Length). More specifically, total path length of the COP was only calculated during periods in which the subject was in single leg stance.

6.2.5. Statistical Analysis

All statistical analyses were performed using SigmaPlot (Systat Software Inc., San Jose, CA). The two control conditions (NE:NS1 and NE:NS2) were compared using a paired t-test to assess whether outcome measures were significantly different between the two conditions ($p < 0.05$). The control values were then averaged and used in subsequent analyses to create five overall conditions (NE:NSave, NE:NS, E75:S, E100:S, E150:S). A repeated measures analysis of variance (ANOVA) was used to assess differences between the five remaining conditions with posthoc testing performed using the Student-Newman-Keuls method of multiple comparisons ($p < 0.05$). As an exploratory analysis, the three stimulation/sleeve conditions (E75:S, E100:S, E150:S) were also compared using a repeated measures ANOVA to assess whether the stimulation level had an effect on the outcome measures ($p < 0.05$). Both parametric and nonparametric analyses were performed to account for non-normality of the data. Nonparametric analyses included Friedman Repeated Measures ANOVA on ranks and the Wilcoxon Signed Rank test. Lastly, a correlation analysis was performed between the COP outcome measures in both control conditions (NE:NS1 and NE:NS2) and the WOMAC indices (pain, stiffness, function, aggregate) and Self-Reported Instability measures ($p < 0.05$).

6.3. Results

6.3.1. Subject Demographics

Fifty-two patients with minimal to moderate, medial knee OA participated in this study (30 females, 22 males). Based on standing radiographs, all knees were verified to have

at least grade 1 OA with more severe joint space narrowing in the medial compartment.

Table 7 illustrates the subject demographics as well as WOMAC and Self-Reported

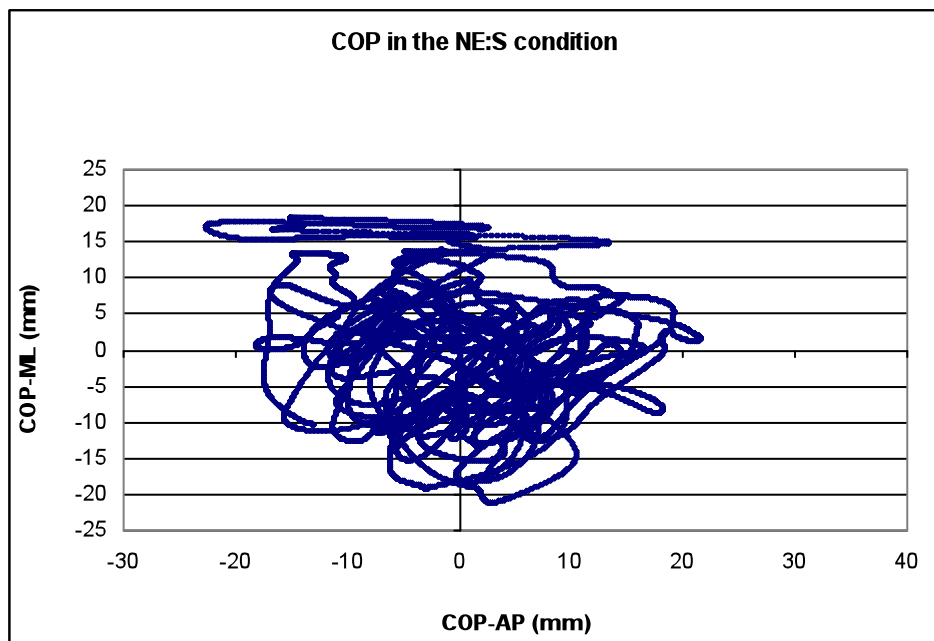
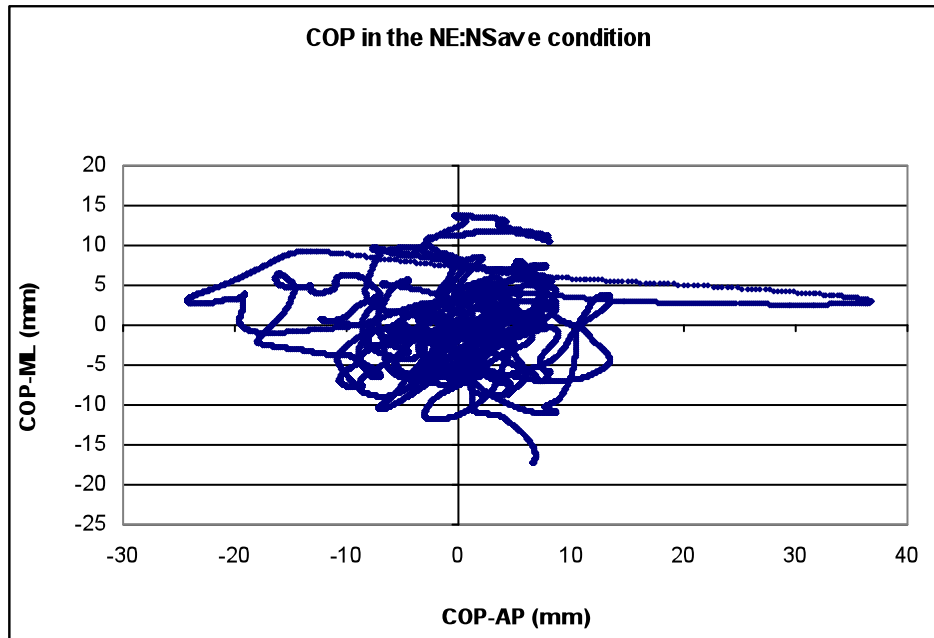
Instability outcome measures for all subjects.

	Male (n=22)	Female (n=30)	Total (n=52)
Age	58.6 (10.9)	63.0 (8.3)	61.2 (9.6)
Weight (kg.)	91.9 (12.4)	72.9 (12.7)	80.9 (15.7)
Height (cm.)	178.2 (8.1)	164.7 (6.4)	170.4 (9.8)
BMI	29.0 (4.1)	26.8 (4.2)	27.8 (4.3)
Kellgren-Lawrence grade (1 to 3)	2.3 (0.8)	2.1 (0.8)	2.2 (0.8)
WOMAC Index (pain)	4.0 (4.1)	4.2 (3.0)	4.1 (3.4)
(stiffness)	3.0 (2.1)	2.6 (1.6)	2.7 (1.8)
(function)	12.7 (12.7)	12.2 (9.3)	12.4(10.8)
WOMAC Aggregate	19.6 (18.1)	19.0 (13.2)	19.2 (15.3)
Self Reported Instability (part A)	3.5 (1.3)	4.0 (1.3)	3.8 (1.3)
Self Reported Instability (part B)	6.2 (14.0)	10.6 (23.8)	8.7 (20.2)

Table 7. Mean (sd) demographics as well as subject reported pain, stiffness, functionality, and instability measures for all test subjects-Postural Control.

6.3.2. COP displacement range

No significant difference between the five conditions was found for either the AP or ML directional COP displacement (Table 8). Additionally, no significant differences were seen between the three stimulation conditions. Figure 10 illustrates the center of pressure displacement for three of the testing conditions (NE:NSave, NE:S, E150:S) over a single trial for a single subject.



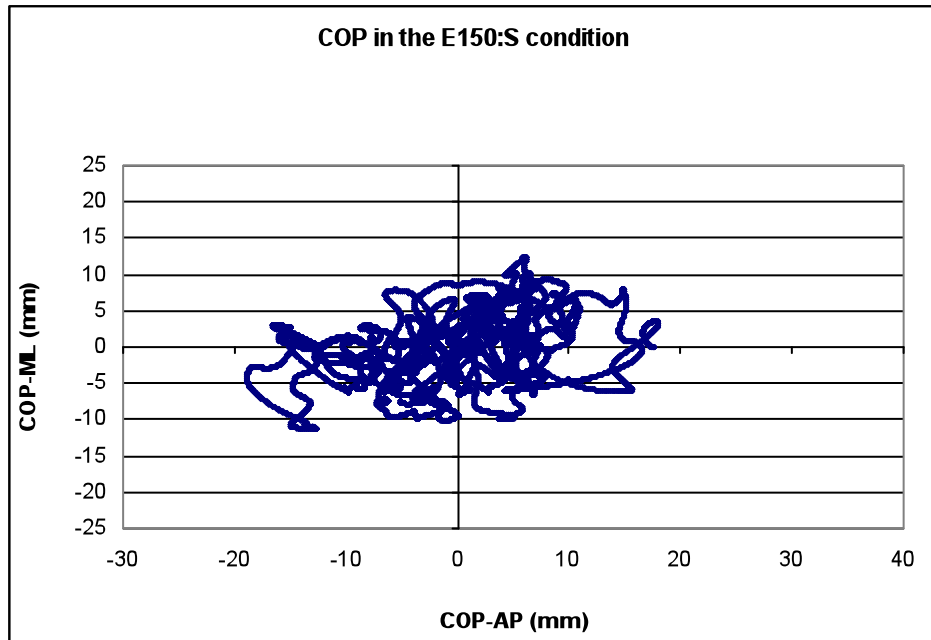


Figure 10. Stabilograms demonstrating the displacement of center of pressure in the anterior-posterior (AP) and medial-lateral (ML) directions during a single trial for three of the testing conditions: NE:NSave, NE:S, E150:S.

6.3.3. *SD COP displacement*

No significant difference was found between the five conditions for either the AP or ML directional COP displacement (Table 8). No significant differences were detected between the three stimulation conditions as well.

	1st quartile (25%)	2nd quartile (median)	3rd quartile (75%)
COP Range-AP (mm)			
NE:NSave	28.89	33.80	40.97
NE:S	28.58	33.32	40.88
E75:S	27.48	32.44	42.40
E100:S	27.47	33.02	38.64
E150:S	27.11	32.70	40.40
COP Range-ML (mm)			
NE:NSave	25.57	27.7	30.73
NE:S	24.02	27.56	32.11
E75:S	24.63	27.48	29.71
E100:S	25	27.49	31.18
E150:S	24.44	26.57	30.2
COP SD-AP (mm)			
NE:NSave	5.49	6.46	7.95
NE:S	5.29	6.68	7.81
E75:S	5.44	6.2	8.03
E100:S	5.12	6.29	7.9
E150:S	5.38	6.68	7.62
COP SD-ML (mm)			
NE:NSave	5.09	5.63	6.6
NE:S	5.19	5.81	6.9
E75:S	4.8	5.79	6.48
E100:S	5.02	5.81	6.61
E150:S	4.83	5.75	6.43

Table 8. 1st, 2nd and 3rd quartile values for center of pressure range (mm) and standard deviation (mm) in the anterior-posterior and medial-lateral directions during single leg stance for all test subjects.

6.3.4. COP velocity

A significant difference between the five conditions was observed in AP COP velocity ($p < 0.05$) with posthoc testing showing significant reductions in postural sway of the following conditions: NE:S, E75:S, E100:S, E150:S relative to the control, NE:NSave ($p < 0.05$) (Figure 11). However, no significant difference was observed between the five conditions for the ML direction (Figure 12) or between the three stimulation conditions for either AP or ML directions.

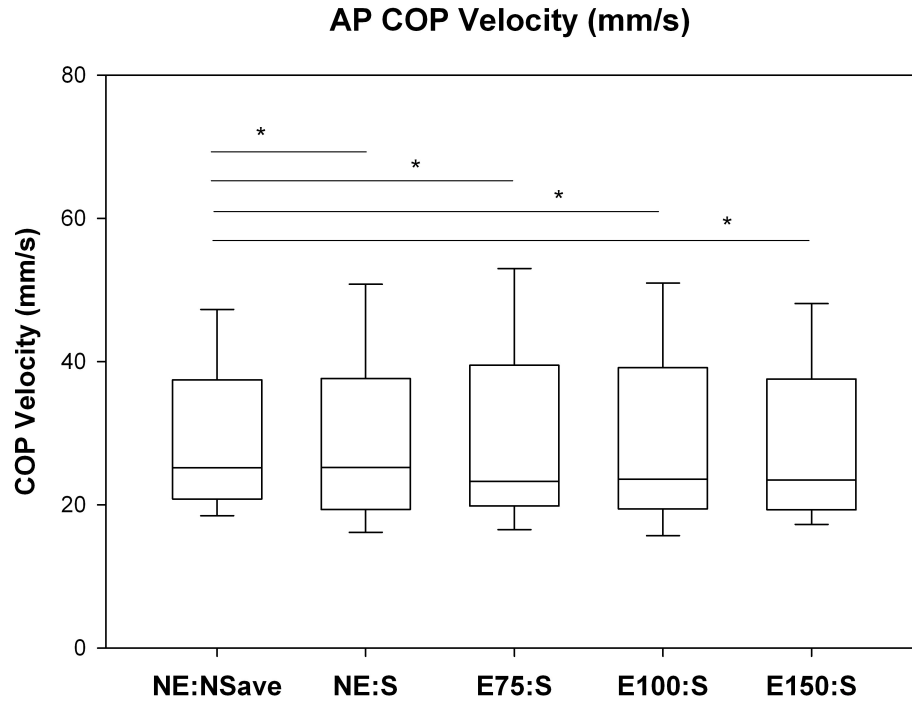


Figure 11. Results from the Friedman Repeated Measures ANOVA on ranks include median COP velocity (mm/s) in the anterior-posterior (AP) direction during all five testing conditions. * indicates a significant difference between conditions at the end of the horizontal bars.

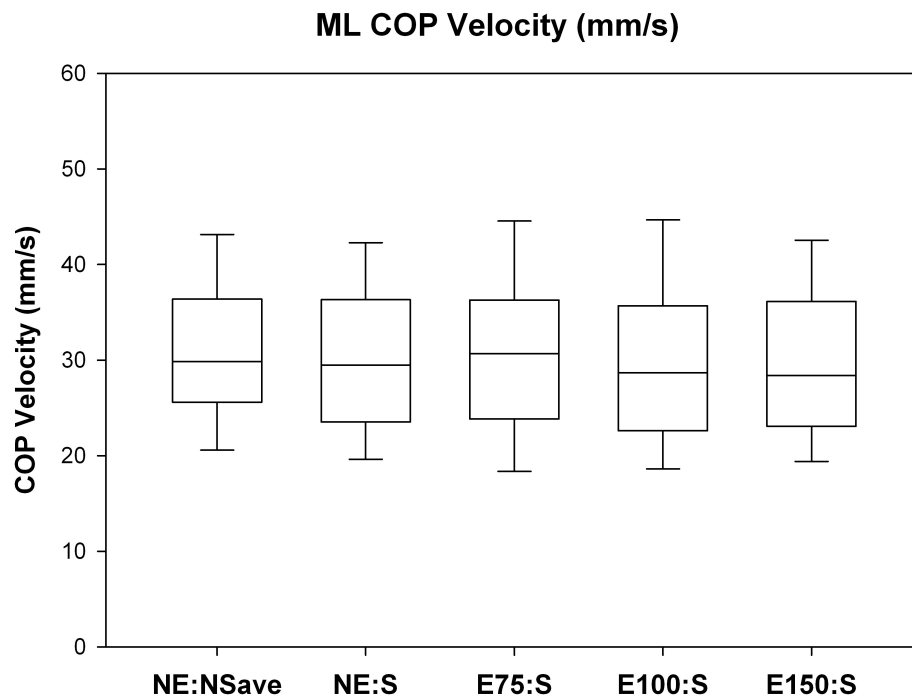


Figure 12. Results from the Friedman Repeated Measures ANOVA on ranks include median COP velocity (mm/s) in the medial-lateral (ML) direction during all five testing conditions. No differences with treatment conditions were found ($p > 0.05$).

6.3.5. COP Path Length

Box plots of the length of the path of the center of pressure during each of the five treatment conditions are illustrated in Figure 13. A significant effect of the treatment conditions was observed ($p < 0.05$) with significant reductions in postural sway for the following conditions: NE:S, E75:S, E100:S, E150:S relative to the control, NE:NSave ($p < 0.05$). No statistical differences were seen between the three stimulation conditions or between the stimulation and sleeve conditions.

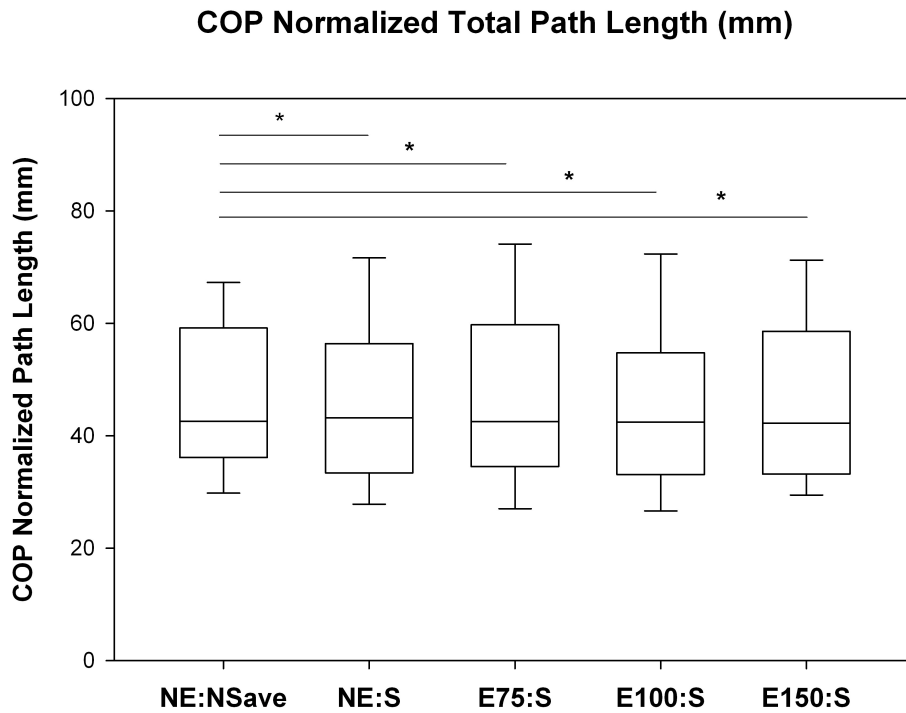


Figure 13. Results from the Friedman Repeated Measures ANOVA on ranks include median COP normalized total path length (mm) during all five testing conditions. * indicates a significant difference between conditions at the end of the horizontal bars.

6.3.6. Control Condition Comparison

The velocity of COP in both the AP and ML directions as well as the COP normalized path length were significantly reduced for the final control condition relative to

the initial control condition ($p < 0.001$ for all comparisons). The COP range in the AP and ML directions as well as the COP SD in AP and ML directions revealed significant reductions in most measures ($p < 0.05$ for all comparisons) relative to the initial control condition.

6.3.7. Regression Analysis

Results from the correlation analysis revealed no significant correlations between the COP and self-reported measures except between the Self Reported Instability part B measure and the COP velocity in the AP direction ($p = 0.00380$, $R = 0.282$) as well as the COP path length ($p = 0.0197$, $R = 0.229$); however the correlation coefficients did not indicate strong relationships between the measures.

6.4. Discussion

Wearing a knee brace/sleeve has been investigated as a possible way to improve balance, but with conflicting results [10, 12, 13, 26, 27]. Specifically looking at knee OA, Chuang et al. saw a significant 28% reduction in balance scores when wearing an elastic knee sleeve [12] while Hassan et al. found a smaller (3%) reduction in postural sway when wearing a loose elastic bandage [13]. Similarly, we found reductions in COP-Vel-AP (mm/s) and total path length (mm) when wearing a neoprene knee sleeve (1.64%, 1.99% respectively). The question of whether or not the differences observed in the present study are clinically significant should be addressed. In a study investigating postural control with the use of a custom fit brace following ACL reconstruction, Birmingham et al. questioned the clinical significance of the small improvements that were observed in an eyes open, stable surface single leg stance task [27]. These improvements did not carry over into more strenuous balance tasks, thus the authors questioned the clinical benefit of the subtle

neuromuscular adaptations resulting from the use of a brace. In a separate study, authors also questioned the clinical significance of a 3.68% reduction in COP path length when wearing a brace [10]. Such small differences in center of pressure path length, while statistically significant, may not be clinically significant as these improvements may not translate into a more strenuous, functionally relevant task. Lyytinen et al. assessed postural control in men with knee OA during a single-leg, eyes open task and found a non significant, 8.5% difference in the mean sway velocity between those with knee OA and age, sex-matched controls [28].

The SR electrical stimulation did not produce significant improvements in balance relative to the sleeve alone condition contrary to previous studies showing improvements in balance with SR stimulation without the presence of a sleeve [14-18]. However, these studies were investigating balance control in populations suffering from diseases and injuries other than knee OA. It is possible the present study was not able to detect differences solely because of the nature of knee OA. SR electrical stimulation aims to improve mechanoreceptor sensitivity, but in a population where those specific mechanoreceptors are degraded as a result of the disease it is possible no improvements can be attained. Additionally, the sleeve may have already been providing a SR effect through surface friction noise resulting in no added benefit from the SR stimulation.

Correlational analysis revealed weak to moderate relationships between the Self-Reported Instability measure and the COP velocity in the AP direction and total path length, indicating the results of the Self-Reported Instability questionnaire may serve as clinical predictors of poor postural control in knee OA subjects. This is especially important given postural sway has been shown to relate to some measures of the Falls Efficacy Scale [29].

Our study is limited by the fact that a learning effect was present. COP measures decreased from the first control condition (NE:NS1) to the second control condition (NE:NS2). This could be a result of subjects infrequently performing a single leg stance task on a daily basis such that a high learning curve was present in our study. It is possible that abnormal postural control in this population is not solely a result of mechanoreceptor insensitivity, but may be a more central processing issue where localized SR would be ineffective. In a study by Shakoor et al. vibratory perception threshold (VPT) was assessed in those with hip OA and age-matched controls along five lower and one upper extremity (radial head) site [30]. VPT was significantly greater at all sites in those with hip OA compared to controls, which the authors suggest is a result of generalized sensory deficits involving both the upper and lower extremity. Perhaps the sensory mechanisms necessary to maintain center of pressure are more generally diminished in this population due to central processing deficits, rather than localized to the lower extremity. Lastly, the SR amplitude may not have been at an optimal level and the procedure used to determine threshold values may need to be refined. SR is most effective at a certain amplitude, past which point no improvements in sensitivity are present [20]. Our previous work investigating JPS in knee OA delivered an SR amplitude approximately 50% of the subject's detection threshold with no observed effect of the SR beyond the sleeve [11]. However, Priplata et al. demonstrated that an SR mechanical stimulation amplitude of 75% of threshold produced the largest reductions in postural sway parameters [31]. Overall mean threshold values for the superior and inferior electrode pairs of all subjects was determined to be 141.5 μ A and 145.8 μ A, respectively, with delivered SR at 75%, 100%, and 150% of threshold. Our threshold test determined when a specific group of mechanoreceptors felt the stimulus, but these may not

be the best-suited receptors to sensitize as a way to affect balance. Additionally, some subjects were not sure if they were sensing the stimulation, which may have lead to an incorrect threshold value determination, and thus, the delivered stimulation may not have been at an optimal level.

The results of our study demonstrate the ability of a neoprene knee sleeve to reduce postural sway specific to the AP direction during a single-leg stance task in those with knee OA. However, the addition of SR electrical stimulation appeared to have no significant added benefit. The significant correlation between one Self-Reported Instability measure and the COP velocity and total path length may allow for better identification of those patients with greater balance deficits and greater risk of falling in knee OA subjects.

6.5. References

1. Felson, D.T., et al., *The prevalence of knee osteoarthritis in the elderly; The Framingham Osteoarthritis Study*. Arthritis & Rheumatism, 1987. **30**: p. 914-918.
2. Wegener, L., C. Kisner, and D. Nichols, *Static and dynamic balance responses in persons with bilateral knee osteoarthritis*. Journal of Orthopaedic & Sports Physical Therapy, 1997. **25**(1): p. 13-18.
3. Fitzgerald, G., S. Piva, and J. Irrgang, *Reports of joint instability in knee osteoarthritis: Its prevalence and relationship to physical function*. Arthritis & Rheumatism, 2004. **51**(6): p. 941-946.
4. Barrett, D.S., et al., *Joint Proprioception in Normal Osteoarthritic and Replaced Knees*. The Journal of Bone and Joint Surgery, 1991. **73**(B): p. 53-56.
5. Garsden, L., Bullock-Saxton, J.E., *Joint Reposition Sense in Subjects with Unilateral Osteoarthritis of the Knee*. Clinical Rehabilitation, 1999. **13**: p. 148-155.
6. Hassan, B., S. Mockett, and M. Doherty, *Static Postural Sway, Proprioception, and Maximal Voluntary Quadriceps Contraction in Patients with Knee Osteoarthritis and Normal Control Subjects*. Annals of Rheumatic Diseases, 2001. **60**: p. 612-618.
7. Sharma, L., et al., *Laxity in healthy and osteoarthritis knees*. Arthritis & Rheumatism, 1999. **42**(861-870).
8. Balow, R., et al., *Comparison of static and dynamic posturography in young and older normal people*. Journal of the American Geriatrics Society, 1994. **42**: p. 405-412.
9. Gu, M., et al., *Postural control in young and elderly adults when stance is perturbed: dynamics*. Journal of Biomechanics, 1996. **29**(3): p. 319-329.
10. Birmingham, T.B., et al., *Knee bracing for medial compartment osteoarthritis: effects on proprioception and postural control*. Journal of Rheumatology, 2001. **40**(3): p. 285-289.

11. Collins, A., et al., *Stochastic resonance electrical stimulation to improve proprioception in knee osteoarthritis*. The Knee, 2010. **Jul 22 [Epub ahead of print]**.
12. Chuang, S., et al., *Effect of knee sleeve on static and dynamic balance in patients with knee osteoarthritis*. Kaohsiung Journal of Medical Sciences, 2007. **23**(8): p. 405-410.
13. Hassan, B.S., S. Mockett, and M. Doherty, *Influence of elastic bandage on knee pain, proprioception, and postural sway in subjects with knee osteoarthritis*. Annals of Rheumatic Diseases, 2002. **61**: p. 24-28.
14. Gravelle, D.C., et al., *Noise-Enhanced Balance Control in Older Adults*. NeuroReport, 2002. **13**(15): p. 1-4.
15. Priplata, A.A., et al., *Noise-Enhanced Balance Control in Patients with Diabetes and Patients with Stroke*. Annals of Neurology, 2005. **59**: p. 4-12.
16. Ross, S., *Noise-enhanced postural stability in subjects with functional ankle instability*. British Journal of Sports Medicine, 2007. **41**: p. 656-659.
17. Reeves, P., et al., *The effects of stochastic resonance stimulation on spine proprioception and postural control in chronic low back pain patients*. . Spine, 2009. **34**(316-321).
18. Hijmans, J., et al., *Effects of vibrating insoles on standing balance in diabetic neuropathy*. Journal of Rehabilitation Research & Development, 2008. **45**(9): p. 1441-1450.
19. Collins, J.J., T.T. Imhoff, and P. Grigg, *Noise-enhanced tactile sensation*. Nature, 1996. **383**(6603).
20. Cordo, P., et al. , *Noise in human muscle spindles*. Nature, 1996. **383**(October 31): p. 769-770.
21. Felson, D.T., et al., *Defining radiographic osteoarthritis for the whole knee*. Osteoarthritis and Cartilage, 1997. **5**: p. 241-250.

22. Felson, D.T., et al., *The incidence and natural history of knee osteoarthritis in the elderly*. Arthritis & Rheumatism, 1995. **38**(10): p. 1500-1505.
23. Irrgang, J., et al., *Development of a patient-reported measure of function of the knee*. The Journal of Bone and Joint Surgery, 1998. **80-A**(8): p. 1132-1145.
24. Felson, D.T., et al., *Knee Buckling: Prevalence, Risk Factors, and Associated Limitations in Function*. Annals of Internal Medicine, 2007. **147**: p. 534-540.
25. Bellamy, N., et al., *Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee*. J Rheumatology, 1988. **15**(2): p. 1833-1840.
26. Kaminski, T. and D. Perrin, *Effect of prophylactic knee bracing on balance and joint position sense*. Journal of Athletic Training, 1996. **31**(2): p. 131-136.
27. Birmingham, T., et al., *Knee bracing after ACL reconstruction: effects on postural control and proprioception*. Medicine & Science in Sports & Exercise, 2000. **32**(2): p. 304-308.
28. Lyytinen, T., et al., *Postural control and thigh muscle activity in men with knee osteoarthritis*. Journal of Electromyography and Kinesiology, 2010. **20**(6): p. 1066-1074.
29. Hughes, M., et al., *The relationship of postural sway to sensorimotor function, functional performance, and disability in the elderly*. Archives of Physical and Medical Rehabilitation, 1996. **77**: p. 567-572.
30. Shakoor, N., et al., *Generalized vibratory deficits in osteoarthritis of the hip*. Arthritis & Rheumatism, 2008. **59**(9): p. 1237-1240.
31. Priplata, A., et al., *Enhancing human balance control by applying random vibrations to the ankle tendons*. 2006, The American College of Sports Medicine.

CHAPTER 7. A KINETIC AND KINEMATIC ANALYSIS OF THE EFFECT OF STOCHASTIC RESONANCE AND KNEE SLEEVE DURING GAIT IN OSTEOARHTRITIS OF THE KNEE

7.1. Introduction

Osteoarthritis (OA) is the most prevalent form of arthritis in the United States with knee OA being one of the five leading causes of physical disability in the elderly [1]. The mechanics of walking in those with knee OA have been thoroughly characterized in previous studies demonstrating that these patients walk slower [2] with reduced knee flexion [2, 3] and have higher external knee adduction moments during stance [4] compared to control subjects. Hurwitz et al. found that radiographic measures of medial knee OA severity were predictive of peak knee adduction moments [5]. In fact, those with a varus alignment at the knee joint are at a fourfold increased risk of disease progression [6, 7]. More specifically, higher external knee adduction moments are seen during the stance phase of gait solely due to the increased moment arm present in those with varus alignment [8]. Increased adduction moment places higher compressive loads on the medial compartment of the knee and the knee adduction moment is commonly used as a way to characterize this medial load [3, 9]. Increased dynamic loads experienced on the medial side of the knee may contribute to development or progression of knee OA. Many studies have focused on reduction of medial knee loads as a way to ameliorate pain and improve functionality. Medial unloading braces have been investigated as a way to reduce medial load by producing a counter valgus-producing, or external abduction moment via a three point bending system [10-13].

Interestingly, medial unloader braces that have been applied in a neutral alignment configuration have also shown an ability to reduce knee adduction excursion during walking, suggesting that aspects other than the valgus moment of the brace may be contributing to reductions in knee adduction [10].

While many studies have focused on the mechanical aspects of abnormal joint loading, less have addressed the neuromuscular components that may play a part [14]. It is widely known that proprioceptive deficits are present in those with knee OA [15-18] and these deficits can lead to mechanical abnormalities during dynamic activities such as gait. It is possible that inefficient mechanoreceptor activation may contribute to malalignment of the joint during dynamic activities. One such malalignment, varus alignment (knee adduction), has been shown to affect the mechanics of gait and this may lead to inappropriate joint loading and thus, disease progression. More importantly, correcting the proprioceptive deficits may allow for more appropriate mechanics during dynamic tasks. Knee sleeves have been shown to enhance proprioception and extended use of sleeves in populations at risk of OA progression have resulted in functional and quality of life benefits [13, 19]. However, comprehensive kinematic and kinetic analyses to determine the possible mechanism of the benefits of a sleeve are limited. A possible means of enhancing the proprioceptive benefits of a sleeve may be by stochastic resonance (SR), a phenomenon in which the sensitivity of a given system to weak stimuli is improved through the introduction of low-level noise. Subsensory SR stimulation has been demonstrated to improve mechanoreceptor sensitivity, specifically through improved tactile sensation [20], muscle spindle output [21], postural control [22, 23], and joint position sense [23]. SR stimulation has also recently been demonstrated to improve joint position sense when combined with a neoprene knee sleeve in

those with knee OA [24]. By enhancing mechanoreceptor sensitivity through SR stimulation, it may be possible to improve the mechanics of gait and thus delay onset and/or progression of OA.

The goal of this study was to determine whether SR electrical stimulation combined with a neoprene knee sleeve would affect knee kinematics and kinetics in the sagittal, frontal, and transverse planes. We hypothesized the adduction angle and resulting internal knee abduction moment would be reduced with the application of SR stimulation and sleeve. Also, we hypothesized that the knee flexion angle and resulting internal knee extension moment would increase in the stimulation/sleeve condition compared to the control condition. To our knowledge, no previous studies have investigated the use of SR stimulation combined with a neoprene knee sleeve to improve gait mechanics in those with knee OA.

7.2. Materials and Methods

7.2.1. Subjects

After approval by the Institutional Review Board, 35 subjects (19 females, 16 males) with mild to moderate (Kellgren-Lawrence KL grade 1 to 3) medial knee OA were recruited from the Orthopaedic Clinic for testing. All subjects gave their informed consent prior to testing. Only those patients 40 years or older with a BMI of 35 or less, no history of neurological or musculoskeletal disorders other than their knee OA, no implanted electronic devices, no lower limb joint replacement, and no previous steroid injections within 3 months prior to screening were included for participation. Patients with a prior knee OA diagnosis were prescreened using standing radiographs of the knee in full extension by an orthopaedic resident. Radiographs were assessed using a modified Kellgren and Lawrence grading scale

[25, 26] with 7 of the subjects having a grade of 1, indicating possible presence of osteophyte(s) and questionable joint space narrowing; 10 had a grade of 2, indicating definite osteophyte(s) with possible joint space narrowing; and the remaining 18 patients had a grade of 3, indicating moderate joint space narrowing combined with the presence of cysts or sclerosis and osteophytes. The medial and lateral compartments of the joint were both assessed to ensure narrowing in the medial side was greater. During testing, the subject's more severely affected knee was chosen for testing, but in instances where both knees were equally affected the subject's dominant knee was tested.

Prior to testing, subjects completed a self-reported measure of knee instability questionnaire which was adapted from the Knee Outcome Survey Activities of Daily Living Scale [27]. They were asked about the degree of "giving way, buckling, or shifting of the knee" in two parts: Part A asked for a rating on a scale of 0 to 5 where 5 indicates they do not experience episodes of buckling, giving way, or shifting of the knee and 0 indicates their activities are severely affected by this instability. Part B asked for the number of times the subject experienced episodes of giving way, buckling, or shifting of the knee within the previous three months. Additionally, subjects completed the Knee and Osteoarthritis Outcome Score (KOOS) survey, which asked for information concerning their pain, stiffness, physical function, and overall quality of life within the week prior to testing [28].

Subject demographics including age, weight, height, as well as measures of knee instability, pain, functionality, and stiffness are included in Table 9.

7.2.2. Study Design

Three-dimensional gait analysis was performed on all subjects' lower extremities during a 10-meter walk test. Subjects were instructed to walk at their own self-selected,

“fast” speed down a level walkway, ensuring the foot of their test limb landed appropriately on the force platform (model 4060nc, Bertec Corp., Columbus, OH). To ensure less than a 10% change in walking speed between trials, an infrared timing system was used (Sparq XLR8 Digital Timing System, Nike). Prior to testing, each subject’s threshold for detection of the SR stimulation was determined and a percentage (75%) of that level was used in subsequent testing. Subject’s threshold for detection was determined as the amplitude at which subjects indicated they felt the presence of the electrical stimulation. Subjects were presented with four testing conditions which occurred in the following sequence: control 1 (NE/NS1); counterbalance of two treatment conditions: no stimulation/no sleeve (NE/S) and stimulation/sleeve (E75/S); control 2 (NE/NS2). The two treatment conditions were presented in a counterbalanced fashion in order to control for any fatigue effects as well as any lasting effects of the stimulation.

7.2.3. Data Collection

Equipment used for analysis of gait included an electromagnetic tracking system (Flock of Birds, Ascension Technology Corp., Burlington, VT) with sensors placed on the sacrum, thigh, and shank. More specifically, the thigh sensor was placed on the lateral aspect of the thigh midway between the hip and knee joints, and the shank sensor was placed on the anterior-medial portion of the tibia taking care to place both sensors outside of the range of the knee sleeve. All kinematic data were sampled at 144Hz. A multicomponent force plate (Bertec, Columbus, OH) was also used for the analysis of gait kinetics. Data were collected from the data acquisition board which sampled data from the force plate at 1440Hz. Additionally, two pairs of SR surface electrodes were placed over the inferior and superior aspects of the knee joint line, approximately 2 cm above and below. Each pair of electrodes

delivered an alternating flow of current in the medial-lateral direction via an electrical stimulator device (Afferent Corporation, Providence, RI). Stimulation consisted of a Gaussian white noise signal (zero mean, 0-1000Hz bandwidth) at an amplitude of 75% of the subject's detection threshold. Subjects were blinded as to when the SR stimulation was applied and also wore a neoprene knee sleeve during the NE/S and E75/S treatment conditions. The sleeve was fit based on the subject's thigh circumference at a point approximately 4 inches above the center of the patella per the manufacturer's recommendations (Safe-T-Sport Model# 37-350, FLA Orthopaedics Inc., Miramar, FL). Data were collected 3 seconds prior to ground contact and continued 2 seconds after toe off. Five valid trials were recorded within each of the four testing conditions; a valid trial was defined as one in which the subject did not vary his/her stride length and landed appropriately on the force plate with the foot of the test limb. All data were collected and time synchronized using the Motion Monitor motion capture system (Innovative Sports Training, Chicago, IL). The standard range transmitter was used with 4 sensors, one of which was moveable and attached to a stylus for digitization of joints prior to data collection.

7.2.4. Data Reduction

Prior to data collection, a global axis system was established in which +x was in the direction the subject walked forward, +y to the forward facing subject's left, +z in the upward vertical direction. Joint angles were determined using the Euler angular convention with a y(medial-lateral), x(anterior-posterior), z(superior-inferior) order of rotation. For those subjects whose right limb was tested, flexion, adduction, and internal rotation (ER) were positive about the y, x, and z axes, respectively. Knee joint moments, angles and ground reaction forces (GRF) were output from Motion Monitor and further data processing

was performed using data processing software (Labview 7.1, National Instruments Inc., Austin, TX). The knee and ankle joint centers were defined as the midpoint between the medial and lateral femoral condyles and the midpoint between the medial and lateral malleoli, respectively. The hip joint center was defined using the Leardini method [29]. Kinematic data was filtered with a lowpass Butterworth filter at a cutoff frequency of 6Hz while kinetic data was filtered with a cutoff frequency of 40Hz. Kinetic variables of interest include flexion/extension, adduction/abduction, internal/external rotation moments, and ground reaction forces in the y, x, and z directions, respectively. All moments output through Motion Monitor were internal moments. Moments were normalized to the product of body weight (N) and height (m) while ground reaction forces were normalized to body weight (N) alone. Kinematic outcome measures included knee flexion/extension, adduction/abduction, and internal/external rotation angles, as well as the angular velocity 20ms prior to ground contact. Angles of knee motion were calculated with the distal segment motion relative to the more proximal motion (ie. shank relative to thigh). All variables except the angular velocity were identified during the stance phase of gait with weight acceptance defined as the period from initial contact to peak knee flexion, and midstance defined as the period from peak knee flexion to toe-off. The gait cycle was then normalized to attain a 100 point time scale across the stance phase for each measure. Each point was then averaged over all subjects to attain average curves for each measure as a percentage of stance (Figure 14). Figure 14 presents measures during the stance phase beginning at ground contact through weight acceptance, which occurs at approximately 20 to 40% of stance, and continuing through midstance, which ends at toe-off.

Additionally, the preparatory time taken before ground contact was calculated and defined as the time from minimum knee flexion angle to ground contact. The knee angular velocity was then calculated from the slope of the knee flexion angle at 20ms prior to ground contact.

7.2.5. Statistical Analysis

All statistical analyses were performed in SigmaPlot (Systat Software Inc., San Jose, CA). The two control conditions (NE/NS1 and NE/NS2) were compared via paired t-test ($p < 0.05$) to determine whether a fatigue/learning effect or lasting effect of the SR stimulation was present. The values for the two control conditions were then averaged, resulting in three final testing conditions (NE/NSave, NE/S, E75/S). All outcome measures were assessed using a repeated measures one-way analysis of variance (ANOVA) statistical test to determine if differences were present between the three testing conditions ($p < 0.05$). If an overall difference was detected, further statistical significance between conditions was assessed using the Student-Newman-Keuls posthoc method of multiple comparisons ($p < 0.05$). To account for non-adherence to normality, both parametric and nonparametric analyses were performed. Nonparametric analyses included the Friedman repeated measures ANOVA on ranks and the Wilcoxon signed rank test.

7.3. Results

7.3.1. Subject Demographics

Data were successfully collected from thirty-five patients (19 females, 16 males) with minimal to moderate, medial knee OA. Subject's weight (kg), height (cm), BMI, and WOMAC indices and Self-Reported Instability measures are detailed below (Table 9).

	Male (n=16)	Female (n=19)	Total (n=35)
Age	60.1 (10.1)	63.2 (8.6)	61.7 (9.3)
Weight (kg.)	92.2 (12.0)	73.0 (12.8)	81.8 (15.6)
Height (cm.)	178.6 (8.7)	164.5 (5.1)	170.9 (9.9)
BMI	29.0 (4.0)	26.9 (4.1)	27.9 (4.1)
Kellgren-Lawrence grade (1 to 3)	2.3 (0.8)	2.1 (0.8)	2.2 (0.8)
WOMAC Index (pain)	4.9 (4.3)	3.3 (2.7)	4.0 (3.6)
(stiffness)	3.6 (2.0)	2.3 (1.6)	2.9 (1.9)
(function)	15.4 (13.7)	9.7 (8.5)	12.3 (11.4)
WOMAC Aggregate	23.9 (19.3)	15.3 (11.9)	19.2 (16.1)
Self Reported Instability (part A)	3.3 (1.4)	4.2 (1.3)	3.7 (1.4)
Self Reported Instability (part B)	8.2 (16.1)	12.7 (29.0)	10.6 (23.7)

Table 9. Mean (sd) demographics as well as subject reported pain, stiffness, functionality, and instability measures for all test subjects-Kinetics & Kinematics.

7.3.2. Kinematic parameters

Knee flexion/extension, abduction/adduction, and internal/external rotation maximum and minimum angles in each phase are detailed in Table 10 and illustrated in Figure 14. The maximum and minimum knee flexion angles increased during the weight acceptance and midstance phases of gait in the NE/S and E75/S conditions relative to the NE/NSave condition ($p < 0.05$). However, there were no differences between the NE/S and E75/S conditions themselves.

Figure 14 demonstrates outcome measures normalized to a 100-point time scale with each time point averaged over the 35 subjects tested and beginning at initial ground contact and ending at toe-off. However, the values in Table 10 are maximum and minimum values during the weight acceptance and midstance phases as defined in section 7.2.4 in the absence of normalization as a percentage of stance.

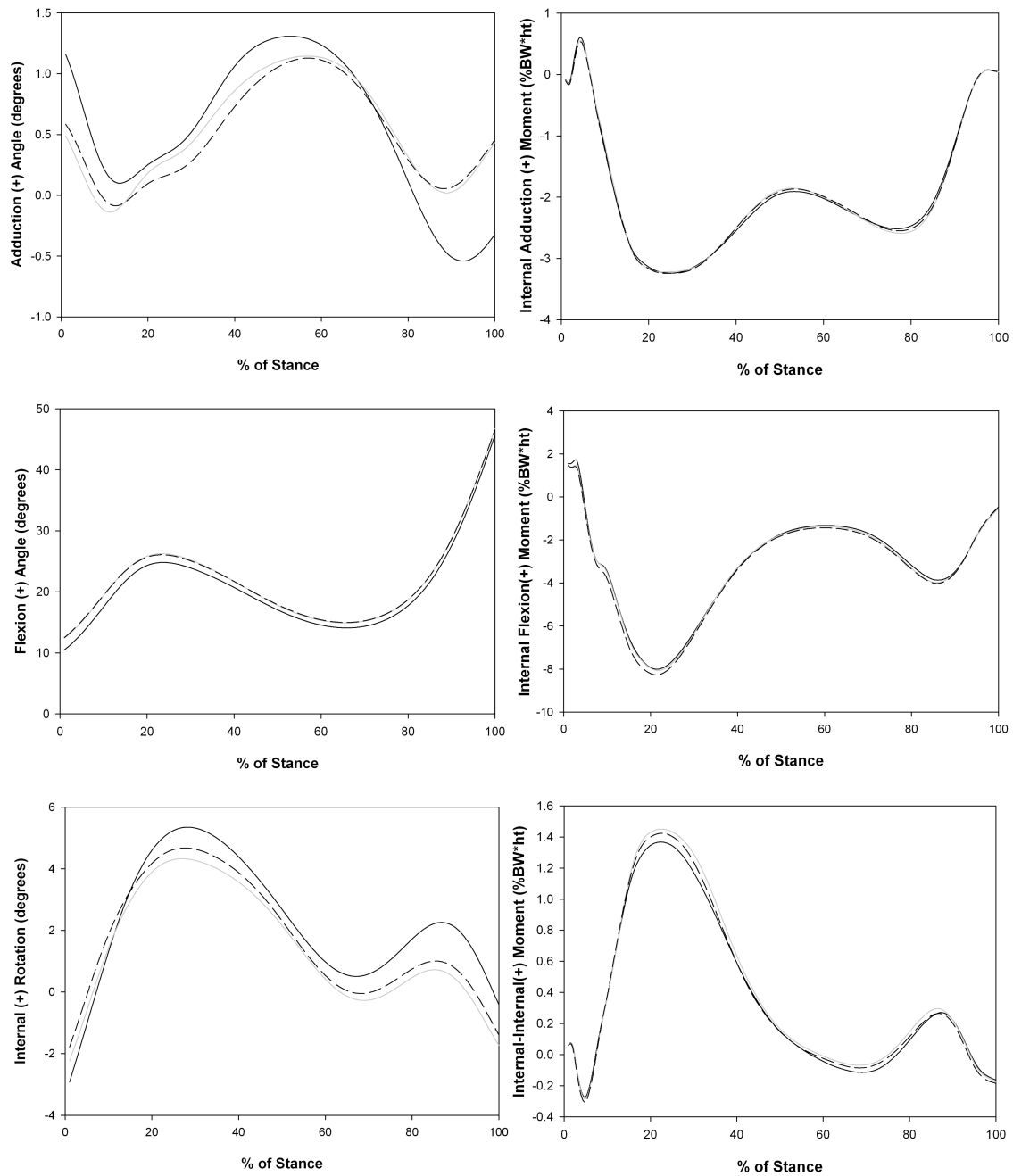


Figure 14. Average curves for all test subjects as a % of stance. Stance phase is defined as the point from heel contact through toe-off. (Left) Knee flexion/extension, adduction/abduction, internal/external angles during gait. (Right) Internal knee moments in the sagittal, frontal, and transverse planes. Knee flexion, adduction, and internal rotation angles and moments are positive. Solid black-NE/NSave; solid grey-NE/S; dashed-E75/S.

		Wt. Acceptance			Midstance		
Angle (degrees)		NE/NSave	NE/S	E75/S	NE/NSave	NE/S	E75/S
Adduction	max.	2.6 (5.1)	2.2 (6.2)	2.3 (6.0)	5.2 (5.7)	5.2 (6.7)	5.2 (6.4)
	min.	-1.2 (5.6)	-1.5 (6.2)	-1.6 (6.0)	-4.6 (6.3)	-3.9 (6.7)†	-3.9 (6.7)†
Flexion	max.	25.6 (9.8)	26.8 (9.2)†	26.8 (9.1)†	47.5 (11.0)	48.5 (10.7)†	48.5 (10.8)†
	min.	10.8 (8.1)	12.6 (7.9)†	12.8 (8.0)†	13.6 (9.0)	14.2 (8.6)†	14.1 (8.7)†
Internal rotation	max.	5.6 (6.2)	4.9 (6.0)†	5.2 (6.0)†	7.5 (5.6)	5.8 (5.5)†	6.1 (5.5)†
	min.	-3.0 (6.5)	-2.5 (7.0)	-2.1 (6.8)	-3.7 (7.5)	-4.3 (7.0)	-3.9 (6.8)
Internal Moment (%BW*ht)							
Adduction	max.	0.85 (0.68)	0.81 (0.66)	0.80 (0.67)	0.33 (0.52)	0.32 (0.43)	0.32 (0.45)
	min.	-3.5 (2.4)	-3.5 (2.5)	-3.5 (2.4)	-3.8 (2.0)	-3.9 (2.1)	-3.8 (2.1)
Flexion	max.	2.3 (0.9)	2.1 (0.9)†	2.0 (0.9)†	0.15 (0.9)	0.14 (0.9)	0.16 (0.9)
	min.	-8.2 (3.6)	-8.3 (3.5)	-8.5 (3.5)	-7.8 (3.2)	-8.0 (3.3)	-8.1 (3.2)†
Internal rotation	max.	1.5 (0.9)	1.6 (0.9)	1.6 (1.0)	1.4 (0.9)	1.5 (0.9)†	1.5 (0.9)†
	min.	-0.43 (0.3)	-0.43 (0.3)	-0.43 (0.3)	-0.53 (0.6)	-0.52 (0.5)	-0.51 (0.5)

Table 10. Mean (sd) maximum and minimum values of all data (non-normalized as a % of stance) during the weight acceptance and midstance phases of gait. † indicates the presence of a significant difference between the treatment conditions and the control condition (NE/NSave), $p < 0.05$. There were no significant differences between the two treatment conditions (NE/S, E75/S).

The minimum knee adduction angle was greater during midstance in the NE/S and E75/S conditions relative to the NE/NSave condition ($p < 0.05$), but was not different during weight acceptance. Additionally, there were no differences in the maximum knee adduction angles in midstance or weight acceptance. Maximum internal rotation angles were less during weight acceptance and midstance in the NE/S and E75/S conditions relative to the NE/NSave condition ($p < 0.05$). However, there were no differences in the minimum internal

rotation angles between NE/S and E75/S compared to NE/NSave. There were no differences in the above measures between the two treatment conditions (E75/S and NE/S).

The knee flexion angular velocity calculated 20ms prior to ground contact was significantly greater during the NE/S ($29.1\text{mm/s} \pm 39.5\text{mm/s}$) and E75/S ($25.8\text{mm/s} \pm 41.9\text{mm/s}$) conditions relative to the NE/NSave ($15.2\text{mm/s} \pm 45.4\text{mm/s}$) condition ($p < 0.005$) (Figure 15). Knee preparatory time also increased in the NE/S ($30.7\text{ms} \pm 15.3\text{ms}$) and E75/S ($30.0\text{ms} \pm 15.4\text{ms}$) conditions relative to the NE/NSave ($24.4\text{ms} \pm 14.1\text{ms}$) condition. The two treatment conditions (NE/S and E75/S) did not differ in angular velocity or knee preparatory time.

Additionally, differences between the two control conditions (NE/NS1 and NE/NS2) were observed. Specifically, the minimum knee flexion during midstance increased from the first to second control condition ($p < 0.05$) while the maximum knee flexion angle during weight acceptance decreased ($p < 0.05$). The minimum knee adduction angle during midstance and weight acceptance decreased, but the maximum angle during weight acceptance increased from the first to second control condition ($p < 0.05$). The minimum internal rotation angle during midstance was different between control conditions, decreasing from the first to second control conditions ($p < 0.05$). Angular velocity 20ms prior to ground contact as well as knee prep time decreased from the first to the second control condition ($p < 0.05$).

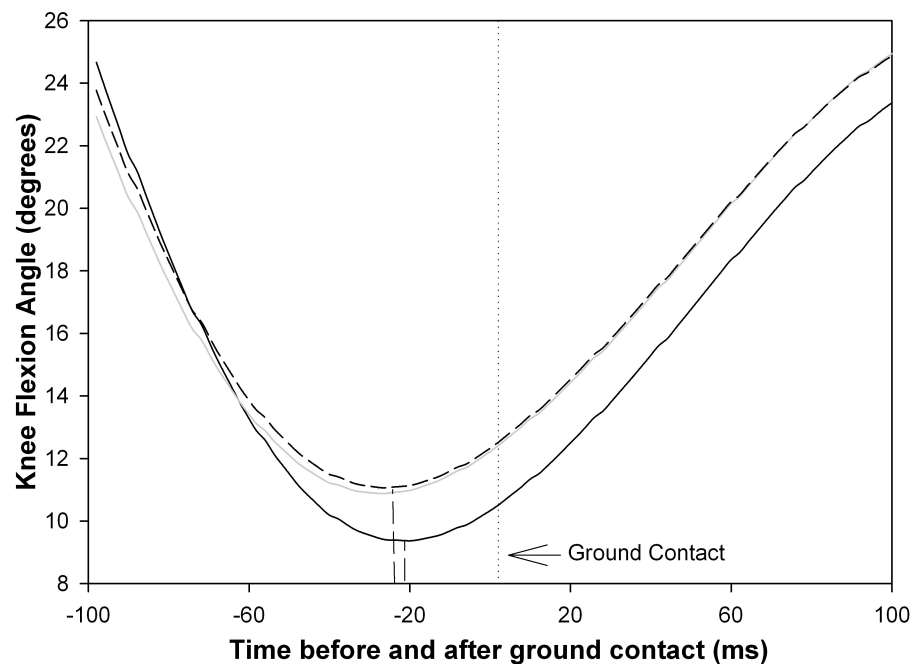


Figure 15. Knee flexion angle 100 ms prior to and after ground contact. Dashed vertical lines indicate the amount of time(ms) taken to prepare for ground contact. Preparatory time was defined as the period from minimum knee flexion angle to ground contact. Solid black-NE/NSave; solid grey-NE/S; dashed-E75/S

7.3.3. Kinetic parameters

The maximum internal extensor moment decreased in the NE/S and E75/S conditions relative to the control condition during the weight acceptance phase only ($p < 0.05$, Table 10). The minimum internal extensor moments were not different during the weight acceptance phase, but increased in only the E75/S condition relative to the control condition during midstance ($p < 0.05$). Maximum and minimum internal abduction moments were not different between conditions during either weight acceptance or midstance. The maximum internal rotation moment was greater during midstance in the NE/S and E75/S conditions relative to the control condition ($p < 0.05$). However, these differences were not present with the minimum internal rotation moments or during the weight acceptance phase of gait.

Sagittal, frontal, and transverse plane moments were not different between the two treatment conditions (NE/S and E75/S).

A paired t-test revealed significant differences between the two control conditions (NE/NS1 and NE/NS2), specifically the minimum sagittal plane moment during weight acceptance and midstance ($p < 0.05$) decreased from the first control to the second control condition. No differences were seen in frontal plane moments. However, nonparametric comparisons showed the maximum transverse moments decreased from the first to the second control condition in midstance and increased in weight acceptance from the first to the second control condition ($p < 0.05$).

7.3.4. Methodological Issue

Fifty-two subjects were originally recruited and tested in this study. Prior to the commencement of data analysis it was noticed in graphical animations of the data that the vertical ground reaction force was located in a more lateral position than the common position directly under the foot bearing weight in 17 of the 52 subjects. We suspected this was due to malalignment of the coordinate system of the forceplates and electromagnetic tracking sensors during setup. It is possible that some of these subjects' data were accurate, but the presence of high internal adduction moments in these 17 subjects was cause for exclusion. In order to help determine whether an error in alignment of the forceplates with the sensors was present, we compared the difference between the center of pressure (COP) and the ankle joint center (in both x and y directions) in subjects with highly positive internal adduction moments to those differences in subjects who did not have highly positive internal adduction moments. High internal adduction moments are not expected in a population with medial knee OA since studies have shown these subjects demonstrate high external adduction

moments [5, 8]. For those with highly positive internal adduction moments, the COP_y - $Ankle_y$ was significantly different between those with highly positive adduction moments and those who did not have highly positive adduction moments ($-0.0596m \pm 0.0406m$, $0.0207m \pm 0.0314m$, respectively, $p < 0.001$) where a negative sense indicated the COP was located 5.96cm lateral to the ankle joint center. However, no differences were seen in the x direction. These results suggested an error in forceplate alignment, resulting in the exclusion of those 17 subjects from further kinetic and kinematic data analyses.

7.4. Discussion

Previous studies have assessed the effects of medial unloader braces on external knee adduction moments [30], pain, functionality, and stability in knee OA [10, 11]. Medial unloading braces are specifically designed to unload the medial compartment of the knee by producing a knee abduction moment counter to the adduction moment experienced by those with medial knee OA. However, since knee sleeves are not rigid in nature and not designed to produce a counter abduction moment about the knee joint, it may be assumed that improvements seen in knee joint mechanics are through the perception of knee stability via improvements in proprioception. The increases in knee flexion angle as well as reductions in internal rotation angles seen in our study may be the result of these proprioceptive improvements. Many studies have demonstrated improvements in proprioception in those with knee OA while wearing a neoprene knee sleeve [24, 31, 32]. Perhaps the neoprene knee sleeve enhances cutaneous afferent sensitivity, which improves the subject's perception of knee position and motion coordination. These improvements may then result in a return to more normal joint angles and moments during gait.

The angular velocity of knee flexion calculated 20ms prior to ground contact showed significant increases with the sleeve alone and SR/sleeve conditions, indicating subjects demonstrated faster knee flexion in these conditions when preparing for impact. Additionally, with the application of the sleeve alone and SR/sleeve, subjects prepared longer in advance for ground contact. Previous studies have shown that subjects with knee OA land in greater knee extension with higher loading rates [8], which translates to a greater amount of load over a shorter time period being transferred to the knee joint. Landing in a less abrupt manner with the knee in greater flexion allows for better absorption of the loads experienced at ground contact and less load transfer to the knee joint, thus increases in knee flexion angular velocity and knee preparatory time are important for the improvement of joint loading. We also saw decreases in the internal knee angle of rotation with the application of a neoprene knee sleeve. These decreases are a new finding and demonstrate the ability of a neoprene knee sleeve to reduce internal knee rotation during stance.

We did not see further improvements in our measures with the application of SR electrical stimulation. It is possible the design of our study was a limiting factor and a greater effect may have been seen if the SR had been applied over a longer time period. Changes in joint kinetics and kinematics would possibly be more pronounced in a longitudinal study design where subjects receive the SR over a longer time course rather than a single testing session. SR electrical stimulation has not previously been applied in a patient population with joint degeneration and it may be that mechanoreceptor sensitivity within the joint cannot be enhanced because of that degeneration. Additionally, the procedure for determining each subject's SR stimulation detection threshold should be further refined as

studies have shown SR produces enhancements in sensitivity up to certain amplitudes; past that optimal amplitude SR may be ineffective [20].

The benefits of this study lie in the potential of a neoprene knee sleeve to positively affect knee joint angles and moments in those with knee OA during gait. Knee sleeves represent a cost-effective intervention and the efficacy of braces in maintaining high levels of activity in those with knee OA has been demonstrated [33]. Compliance with long-term use is promising as knee sleeves represent a non-surgical option that is less cumbersome than medial unloading braces for those with OA who desire to maintain an active lifestyle. In conclusion, our hypothesis that SR stimulation and sleeve would decrease both knee adduction angle and increase knee flexion angle was partially proven correct in that knee flexion angle decreased in the NE/S and E75/S conditions compared to the control, but no differences were seen in the adduction angle. Also, there were no differences in the internal knee abduction moments. However, internal knee flexion moments were reduced in the treatment conditions relative to the control but only within the weight acceptance phase and internal rotation moments were increased during midstance with the treatment conditions. Overall, there were no differences in the above measures between the treatment conditions themselves. From this, we may conclude that our increases in knee flexion angle and reductions in knee extension moments may be the result of proprioceptive enhancements provided by the sleeve alone, leading to a greater sense of stability and a return to a more appropriate loading pattern.

7.5. References

1. *Osteoarthritis of the Knee: State of the Condition*. 2004, American Academy of Orthopaedic Surgeons.
2. Kaufman, K.R., et al., *Gait characteristics of patients with knee osteoarthritis*. J Biomech, 2001. **34**(7): p. 907-15.
3. Baliunas, A., et al., *Increased knee joint loads during walking are present in subjects with knee osteoarthritis*. Osteoarthritis Cartilage, 2002. **10**(7): p. 573-579.
4. Landry, S.C., et al., *Knee biomechanics of moderate OA patients measured during gait at a self-selected and fast walking speed*. J Biomech, 2007. **40**(8): p. 1754-61.
5. Hurwitz, D., et al., *The knee adduction moment during gait in subjects with knee osteoarthritis is more closely correlated with static alignment than radiographic disease severity, toe out angle and pain*. Journal of Orthopaedic Research, 2002. **20**(1): p. 101-107.
6. Cerejo, R., et al., *The influence of alignment on risk of knee osteoarthritis progression according to baseline stage of disease*. Arthritis & Rheumatism, 2002. **46**(10): p. 2632-6.
7. Sharma, L., et al., *The role of knee alignment in disease progression and functional decline in knee osteoarthritis*. Journal of the American Medical Association, 2001. **286**(2): p. 188-195.
8. Mundermann, A., C.O. Dyrby, and T.P. Andriacchi, *Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking*. Arthritis Rheum, 2005. **52**(9): p. 2835-44.
9. Sharma, L., et al., *Knee adduction moment, serum hyaluronan level, and disease severity in medial tibiofemoral osteoarthritis*. Arthritis & Rheumatism, 1998. **41**: p. 1233-1240.
10. Ramsey, D., et al., *A mechanical theory for the effectiveness of bracing for medial compartment osteoarthritis of the knee*. The Journal of Bone and Joint Surgery, 2007. **89**(2398-2407).

11. Brouwer, R.W., et al., *Brace treatment for osteoarthritis of the knee: a prospective randomized multi-centre trial*. Osteoarthritis Cartilage, 2006. **14**(8): p. 777-83.
12. Lindenfeld, T.N., T.E. Hewett, and T.P. Andriacchi, *Joint loading with valgus bracing in patients with varus gonarthrosis*. Clinical Orthopaedics and Related Research, 11/1997(344).
13. Kirkley, A., et al., *The effect of bracing on varus gonarthrosis*. The Journal of Bone and Joint Surgery, 1999. **81**: p. 539-548.
14. Birmingham, T., et al., *Association among neuromuscular and anatomic measures for patients with knee osteoarthritis*. Archives of Physical and Medical Rehabilitation, 2001. **82**: p. 1115-1118.
15. Barrett, D.S., Et Al., *Joint Proprioception in Normal Osteoarthritic and Replaced Knees*. The Journal of Bone and Joint Surgery, 1991. **73**(B): p. 53-56.
16. Felson, D.T., et al., *The effects of impaired joint position sense on the development and progression of pain and structural damage in knee osteoarthritis*. . Arthritis & Rheumatism, 2009. **61**(8): p. 1070-1076.
17. Garsden, L., Bullock-Saxton, Je., *Joint Reposition Sense in Subjects with Unilateral Osteoarthritis of the Knee*. Clinical Rehabilitation, 1999. **13**: p. 148-155.
18. Sharma, L., *Proprioceptive Impairment in Knee Osteoarthritis*. Rheumatic Disease Clinics of North America, 1999. **25**(2): p. 299-314.
19. Birmingham, T., et al., *A randomized controlled trial comparing the effectiveness of functional knee brace and neoprene sleeve use after anterior cruciate ligament reconstruction*. American Journal of Sports Medicine, 2008. **36**(4): p. 648-655.
20. Collins, J.J., T.T. Imhoff, and P. Grigg, *Noise-enhanced tactile sensation*. Nature, 1996. **383**(6603).
21. Cordo, P., Et Al. , *Noise in human muscle spindles*. Nature, 1996. **383**(October 31): p. 769-770.

22. Priplata, A.A., Et Al., *Noise-Enhanced Balance Control in Patients with Diabetes and Patients with Stroke*. Annals of Neurology, 2005. **59**: p. 4-12.
23. Collins, A., et al., *The effects of stochastic resonance electrical stimulation and neoprene sleeve on knee proprioception*. Journal of Orthopaedic Surgery and Research, 2009. **4**(3).
24. Collins, A., et al., *Stochastic resonance electrical stimulation to improve proprioception in knee osteoarthritis*. The Knee, 2010. **Jul 22 [Epub ahead of print]**.
25. Felson, D.T., et al., *Defining radiographic osteoarthritis for the whole knee*. Osteoarthritis and Cartilage, 1997. **5**: p. 241-250.
26. Felson, D.T., et al., *The incidence and natural history of knee osteoarthritis in the elderly*. Arthritis & Rheumatism, 1995. **38**(10): p. 1500-1505.
27. Irrgang, J., et al., *Development of a patient-reported measure of function of the knee*. The Journal of Bone and Joint Surgery, 1998. **80-A**(8): p. 1132-1145.
28. Bellamy, N., et al., *Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee*. J Rheumatology, 1988. **15**(2): p. 1833-1840.
29. Leardini, A., et al., *Validation of a functional method for the estimation of hip joint centre location*. Journal of Biomechanics, 1999. **32**(1): p. 99-103.
30. Lindenfeld, T.N., T.E. Hewett, and T.P. Andriacchi, *Joint loading with valgus bracing in patients with varus gonarthrosis*. Clinical Orthopaedics and Related Research, 1997(344).
31. Birmingham, T., et al., *Effect of a neoprene sleeve on knee joint kinesthesia: Influence of different testing procedures*. Medicine & Science in Sports & Exercise, 1999. **32**(2): p. 304-308.
32. Herrington, L., *The effect of a neoprene sleeve on knee joint position sense*. Research in Sports Medicine, 2005. **13**: p. 37-46.

33. Pollo, F. and R. Jackson, *Knee Bracing for Unicompartmental Osteoarthritis*. Journal of the American Academy of Orthopaedic Surgeons, 2006. **14**(1): p. 5-11.

CHAPTER 8. DISCUSSION

Knee OA is an increasingly common and debilitating disease, thus the development of novel, disease modifying, treatment options is paramount. Knee sleeves and braces are commonly used as a means of improving the symptoms of disease but other avenues to delay or prevent disease progression should be explored. Stochastic resonance (SR) stimulation has been shown to enhance the sensitivity of sensory systems to weak stimuli and may improve proprioceptive deficits, a common occurrence in knee OA. Specifically, we set out to determine whether a clinically applicable therapy, SR combined with a neoprene knee sleeve, could improve proprioceptive deficits. We also explored whether these improvements in proprioception would translate into biomechanical improvements in functional tasks such as single-leg stance and walking.

8.1. Limitations to Methodological Approach

Proprioception was assessed via JPS during conditions combining SR and a neoprene knee sleeve. In this initial study, SR was delivered at two absolute amplitudes, 50 μA and 75 μA with subject's threshold for SR detection determined post testing. JPS was improved with the sleeve alone condition and the combination of the sleeve and 75 μA stimulation condition. The 75 μA amplitude/sleeve condition produced improvements in JPS and was approximately 64.5% and 60.5% of subjects' detection threshold for the superior and inferior electrode pairs, respectively. However, JPS was not significantly different between the 50 μA stimulation/sleeve condition and either the 75 μA stimulation/sleeve or the no

stimulation/no sleeve conditions. These absolute amplitudes were in line with those previously used during balance assessments [1, 2]. The results of this initial study led us to conclude that SR should be delivered at a higher amplitude and that delivering it as a percentage of subject's threshold of detection determined prior to testing during subsequent studies may be more effective.

Postural control and gait were later assessed in this population with both assessments performed during the same testing session. During pilot testing of gait analysis, it was observed that the SR signal was interfering with the EMG recordings of muscle activity. We experimented with the location of the superior SR electrode pair as well as the ground electrode in order to avoid SR's interference with the EMG recordings. We found the optimal placement of SR electrodes and the ground electrode was with SR electrodes placed 2cm above and below the knee joint line and the ground electrode placed on the posterior aspect of the ipsilateral wrist. A decision was also made to have subjects perform two "normalizing" quiet trials while in a seated position, assuming minimal muscle activation would be occurring while seated. During the first quiet trial, subject's muscle activity was recorded while no SR was applied. SR was then applied and muscle activity was recorded during the second quiet trial. The resulting EMG activity was then used to normalize EMG activity recorded during regular testing at times when SR was applied. It was also noticed during pilot testing that the interference of the SR signal on the EMG signal seemed to be concentrated at a frequency of 60Hz and a decision was made to account for this during data analysis with a 60Hz notch filter.

During the analysis of EMG data, several steps were taken to account for the interference of SR during the stimulation/sleeve condition. EMG amplitude for all three

muscles (VL, MH, LH) was collected during the two quiet trials and subtracted to attain a normalizing value for each muscle. This normalizing value (ex. VL quiet_stimulation – VL quiet_nostimulation) was then subtracted from the mean muscle activity (ex. VL) during the stimulation/sleeve condition in order to give a corrected data set. Upon initial inspection of the resulting data, the “corrected” values were negative in some instances, indicating the data were overcorrected at these points. As a result, the quiet_nostimulation value for each specific muscle was substituted in instances where the corrected value (ex. VL activity – (VLquiet_stimulation-VLquiet_nostimulation)) was less than the quiet_nostimulation value. To determine whether the SR had a physiologic effect on EMG activity or if differences were solely due to “leakage”, a secondary statistical analysis was performed on the uncorrected data looking at the difference between the muscle activity during the quiet_stimulation trial and quiet_nostimulation trial (ex. Quiet_stimulation – quiet_nostimulation) compared to the difference between muscle activity during the E75/S and NE/S conditions (ex. E75/S – NE/S) (See section 5.2.8). Our rationale was that differences between the two groups would indicate that a physiologic effect is present whereas no differences would indicate only the presence of a leakage effect of the SR. If the quiet trial difference was significantly greater than the E75/S-NE/S difference, we believed a physiologic effect of the SR to decrease muscle activity is present. If, however, the quiet difference was significantly less than the E75/S-NE/S difference, we believed a physiologic effect to increase muscle activity is present. The primary statistical analysis showed that the increases in uncorrected mean VL muscle activity were most likely due to a leakage effect of the SR stimulation. Once the VL data were “corrected”, muscle activity decreased which indicated the presence of a physiologic effect of the SR to decrease muscle activity. The same approach was taken when

determining differences between co-contraction levels. Correspondingly, the alternative statistical approach demonstrated similar statistical results for uncorrected co-contraction levels as the primary approach. Our primary statistical analysis demonstrated decreases in co-contraction levels and these may be a direct result of decreases in corrected mean VL activity, and may therefore be viewed with greater confidence as being different between conditions due to a physiologic effect.

Lastly, the angular convention used during gait analysis was that following the right hand rule such that adduction and internal rotation angles and moments for right limbed subjects were positive while abduction and external rotation angles and moments were positive for left limbed subjects. When analyzing this data, a decision was made to “correct” data of subjects whose left knee was tested by multiplying the angles and moments in the frontal and transverse planes by negative one. This was done in order to place all data in the same sense so that maximum and minimum measures could be correctly determined. Upon further inspection of the data, it appeared that in 17 subjects the vertical ground reaction force, which is normally located directly under the foot that is bearing weight, was located in a more lateral position possibly due to the malalignment of the forceplate and electromagnetic sensors during. Data from these 17 subjects demonstrated highly positive internal adduction moments, which is the opposite of what is expected in this population. We looked at the difference between the x coordinate of the ankle joint center and center of pressure (COP) in the anterior-posterior(x) direction as well as in the medial-lateral(y) direction for subjects who had high internal adduction moments and compared those values with those who did not have high internal adduction moments. The presence of a statistical difference in COP distance from ankle joint center between subjects with high internal

adduction moments and subjects who did not have a high internal adduction moment suggested an error in forceplate alignment, which resulted in the exclusion of those 17 subjects from further kinetic and kinematic data analyses (See section 7.3.4.).

8.2. Future Directions

This research investigating potential disease-modifying therapies in knee OA contributes novel information and future studies should build on the present findings. First, an alternative method for determining subject's threshold for SR electrical stimulation detection should be investigated. Throughout testing, it became apparent that the determination of subject's SR detection threshold is subjective in nature. Often, subjects became confused as to whether they were sensing the stimulation. It is possible subject's became accustomed to the SR and their sensation diminished through the threshold detection protocol. Future studies should impose a stepwise method of SR detection threshold in which SR is applied at a specific amplitude then turned off, at which point the subject is asked whether they detected the stimulation. This method may minimize confusion for the subject and allow for a more discrete detection of threshold amplitude. Additionally, the location of SR application should be explored. Specifically, the mechanoreceptors and muscle spindles that are activated during the delivery of SR electrical stimulation should be identified. It is possible muscle spindles are the best targets for SR therapy as previous studies have demonstrated enhancement of muscle-spindle receptors when SR was applied through the tendon of the parent muscle [3]. Future studies should explore whether moving the superior pair of SR electrodes more superiorly over the quadriceps and hamstrings muscle groups in order to target the muscle-spindle receptors would render SR more effective.

It would also be interesting to determine whether those with greater walking mechanic abnormalities, such as increased loading rates and heel strike transients (HST), would better benefit from the combination of SR and a knee sleeve. Greater abnormalities may translate into greater improvements and future studies should investigate this reasoning while incorporating the alternative SR detection threshold determination protocol mentioned previously. Perhaps postural control should also be reassessed in future studies using the alternative SR detection threshold protocol in addition to alternative placement of the SR electrodes as previously mentioned.

Future studies should also investigate the long-term effects of SR and sleeve therapy. Despite the fact that JPS did not improve from the first control condition to the second indicating no prolonged effect of the SR with respect to JPS, it may be possible that JPS would improve over a longer period with daily use of a brace that incorporates SR. Changes in gait biomechanics may also become more pronounced with daily use of an SR brace and measures such as impulsive loading, knee adduction moments, and knee flexion at heelstrike should be assessed at varying time points during a longitudinal study.

8.3. Conclusions

Our first aim was to determine whether proprioception via joint position sense (JPS) could be improved when a neoprene knee sleeve was applied and further improved with the addition of both a 50 μ A and 75 μ A level of SR stimulation during both a NWB and a PWB task. We also aimed to determine whether JPS would improve with a sleeve alone during the NWB task. JPS was significantly improved in the PWB task alone with the use of a knee sleeve and when the knee sleeve was combined with a 75 μ A level of SR stimulation.

However, no improvements were seen in the NWB task and no improvements were seen between the treatment conditions (E50/S and E75/S).

Secondly, we aimed to determine whether loading rates and the heel strike transient (HST) would decrease during gait while knee flexion angle at heel strike and vastus lateralis (VL) activation would increase with the application of SR combined with a sleeve and when the sleeve was applied alone. Our results showed loading rates and HST decreased while knee flexion angle increased in both treatment conditions (NE/S and E75/S). Mean VL corrected muscle activity decreased in both the E75/S and NE/S conditions compared to the control which is the opposite of what we expected. This decreased mean VL activity during in the E75/S condition may have been a result of improper correction of the data as our correction procedure was a novel approach (Chapter 5). The above measures were not different between the NE/S and E75/S conditions. However, co-contraction levels were reduced with the application of a neoprene knee sleeve and were further reduced with the application of SR. Furthermore, knee flexion angles increased during weight acceptance and midstance with a sleeve alone and with the combination of stimulation/sleeve. There were no differences in knee adduction angles; however, internal rotation angles were reduced during both weight acceptance and midstance with the combination of stimulation and sleeve and the sleeve alone. The internal knee flexion moment decreased and internal rotation moments increased with the use of a knee sleeve and SR and a neoprene knee sleeve, but no differences were seen between the treatment conditions and no differences were seen in the knee adduction moment between any of the conditions.

Lastly, we aimed to determine whether postural control could be improved with the combination of SR and a knee sleeve and with the knee sleeve alone. Our results

demonstrated differences in two of the postural control measures; specifically the COP mean velocity in the anterior-posterior directions and the COP total path length decreased with use of a knee sleeve and in combination with SR stimulation. However, no differences were seen between the treatment conditions.

Our overall hypothesis of this research is that correction of proprioceptive deficits may influence postural control and walking biomechanics in subjects with knee OA. Correction of proprioception was attempted through the use of SR electrical stimulation combined with a neoprene knee sleeve. While our results seem to indicate there is no added benefit of the SR to JPS, postural control, and most of the biomechanical measures during gait, the clinical benefit of a knee sleeve should not be discounted. The sleeve itself demonstrated improvements in proprioception, postural control, and gait biomechanics. Neoprene knee sleeves are a non-invasive, less cumbersome option and with the improvements in gait biomechanics and postural control demonstrated in this study, neoprene knee sleeves may be a disease-modifying option. Future studies should focus on the determination of optimal SR parameters and whether it is a viable treatment option in those with knee OA under these parameters. Determination of the optimal parameters of SR in a knee OA population may translate into clinical improvements with its use, making it a viable treatment option.

8.4. References

1. Gravelle, D.C., et al., *Noise-Enhanced Balance Control in Older Adults*. NeuroReport, 2002. **13**(15): p. 1-4.
2. Ross, S., et al., *Enhanced balance associated with coordination training with stochastic resonance stimulation in subjects with functional ankle instability: an experimental trial*. . Journal of Neuroengineering and Rehabilitation, 2007. **4**(47).
3. Cordo, P., et al. , *Noise in human muscle spindles*. Nature, 1996. **383**(October 31): p. 769-770.

APPENDIX A: IRB Application – JPS study

Part A.1. Contact Information, Agreements, and Signatures

Date: 7-24-08

Title of Study: Electrical Stimulation to Improve Proprioception in Knee Osteoarthritis

Name and degrees of Principal Investigator: Paul Weinhold, Ph.D.

Department: Orthopaedics, Biomedical Engineering Mailing address/CB #: 134 Glaxo Bldg., CB# 7546, 101A Mason Farm Rd., Chapel Hill, NC 27599

UNC-CH PID: 701583613

Pager:

Phone #: 919-966-1212

Fax #: 919-966-3349

Email Address: weinhold@med.unc.edu

For trainee-led projects: ☐ undergraduate ☐ graduate ☐ postdoc ☐ resident ☐ other

Name of faculty advisor: Paul Weinhold, Ph.D.

Department: Orthopaedics, Biomedical Engineering

Mailing address/CB #: 134B Glaxo Bldg., CB# 7546, 101A Mason Farm Rd., Chapel Hill, NC 27599

Farm Rd., Chapel Hill, NC 27599

Phone #: 919-966-9077

Fax #: 919-966-3349

Email Address: weinhold@med.unc.edu

Center, institute, or department in which research is based if other than department(s) listed above: Department of Exercise and Sports Science

Name of Project Manager or Study Coordinator (if any):

Department:

Mailing address/CB #:

Phone #:

Fax #:

Email Address:

List **all other project personnel** including co-investigators, and anyone else who has contact with subjects or identifiable data from subjects. **Include email address for each person who should receive electronic copies of IRB correspondence to PI:** Amber Collins (amcollin@email.unc.edu), Dr. Paul Weinhold (weinhold@med.unc.edu), Dr. Chris Olcott (colcott@med.unc.edu), Dr. James Meeker, Dr. J. Troy Blackburn, Dr. Doug Dirschl, Dr. Bing Yu, Dr. Joanne Jordan, Dr. Jodie Miles.

Name of funding source or sponsor (please do not abbreviate): UNC University Research Council Award & Arthritis Foundation.

☐ not funded ☐ Federal ☐ State ☐ industry ☒ foundation ☒ UNC-CH

☐ other (specify):

For industry sponsored research (if applicable):

Sponsor's master protocol version #:

Version date:

Investigator Brochure version #:

Version date:

Any other details you need documented on IRB approval:

RAMSeS proposal number (from Office of Sponsored Research): 08-2450

Principal Investigator: I will personally conduct or supervise this research study. I will ensure that this study is performed in compliance with all applicable laws, regulations and University policies regarding human subjects research. I will obtain IRB approval before making any changes or additions to the project. I will notify the IRB of any other changes in the information provided in this application. I will provide progress reports to the IRB at least annually, or as requested. I will report promptly to the IRB all unanticipated problems or serious adverse events involving risk to human subjects. I will follow the IRB approved consent process for all subjects. I will ensure that all collaborators, students and employees assisting in this research study are informed about these obligations. All information given in this form is accurate and complete.

Signature of Principal Investigator

Date

Faculty Advisor if PI is a Student or Trainee Investigator: I accept ultimate responsibility for ensuring that this study complies with all the obligations listed above for the PI.

Signature of Faculty Advisor

Date

Note: The following signature is not required for applications with a student PI.

Department or Division Chair, Center Director (or counterpart) of PI: (or Vice-Chair or Chair's designee if Chair is investigator or otherwise unable to review): I certify that this research is appropriate for this Principal Investigator, that the investigators are qualified to conduct the research, and that there are adequate resources (including financial, support and facilities) available. If my unit has a local review committee for pre-IRB review, this requirement has been satisfied. I support this application, and hereby submit it for further review.

Signature of Department Chair or designee

Date

Print Name of Department Chair or designee

Department

Part A.2. Summary Checklist *Are the following involved?*

	Yes	No
A.2.1. Existing data, research records, patient records, and/or human biological specimens?	<u> X </u>	<u> </u>
A.2.2. Surveys, questionnaires, interviews, or focus groups with subjects?	<u> X </u>	<u> </u>
A.2.3. Videotaping, audiotaping, filming of subjects, or analysis of existing tapes?	<u> </u>	<u> X </u>
A.2.4. Do you plan to enroll subjects from these vulnerable or select populations: a. UNC-CH students or UNC-CH employees? b. Non-English-speaking? c. Decisionally impaired? d. Patients? e. Prisoners, others involuntarily detained or incarcerated, or parolees? f. Pregnant women? g. Minors (less than 18 years)? <i>If yes</i> , give age range: to years	<u> </u> <u> </u> <u> </u> <u> X </u> <u> </u> <u> </u> <u> </u>	<u> X </u> <u> X </u> <u> X </u> <u> </u> <u> X </u> <u> X </u> <u> X </u>
A.2.5. a. Are sites outside UNC-CH engaged in the research? b. Is UNC-CH the sponsor or lead coordinating center for a multi-site study? <i>If yes</i> , include the Addendum for Multi-site Studies . <i>If yes</i> , will any of these sites be outside the United States ? <i>If yes</i> , is there a local ethics review committee agency with jurisdiction? (provide contact information)	<u> </u> <u> </u> <u> </u> <u> </u>	<u> X </u> <u> X </u> <u> </u> <u> </u>
A.2.6. Will this study use a data and safety monitoring board or committee? <i>If yes:</i> UNC-CH School of Medicine DSMB? (must apply separately) Lineberger Cancer Center DSMC? Other? Specify:	<u> </u> <u> </u> <u> </u> <u> </u>	<u> X </u> <u> </u> <u> </u> <u> </u>
A.2.7. a. Are you collecting sensitive information such as sexual behavior, HIV status, recreational drug use, illegal behaviors, child/physical abuse, immigration status, etc? b. Do you plan to obtain a federal Certificate of Confidentiality for this study?	<u> </u> <u> </u>	<u> X </u> <u> X </u>
A.2.8. a. Investigational drugs? (provide IND #) b. Approved drugs for “non-FDA-approved” conditions? <i>All studies testing substances in humans must provide a letter of acknowledgement from the UNC Health Care Investigational Drug Service (IDS).</i>	<u> </u> <u> </u>	<u> X </u> <u> X </u>
A.2.9. Placebo(s)?	<u> </u>	<u> X </u>
A.2.10. Investigational devices, instruments, machines, software? (provide IDE #)	<u> X </u>	<u> </u>
A.2.11. Fetal tissue?	<u> </u>	<u> X </u>
A.2.12. Genetic studies on subjects’ specimens?	<u> </u>	<u> X </u>
A.2.13. Storage of subjects’ specimens for future research? <i>If yes, see instructions for Consent for Stored Samples.</i>	<u> </u>	<u> X </u>
A.2.14. Diagnostic or therapeutic ionizing radiation, or radioactive isotopes, which subjects would not receive otherwise? <i>If yes, approval by the UNC-CH Radiation Safety Committee is required.</i>	<u> </u>	<u> X </u>
A.2.15. Recombinant DNA or gene transfer to human subjects? <i>If yes, approval by the UNC-CH Institutional Biosafety Committee is required.</i>	<u> </u>	<u> X </u>
A.2.16. Does this study involve UNC-CH cancer patients? <i>If yes, submit this application directly to the Oncology Protocol Review Committee.</i>	<u> </u>	<u> X </u>
A.2.17. Will subjects be studied in the General Clinical Research Center (GCRC)? <i>If yes, obtain the GCRC Addendum from the GCRC and submit complete application (IRB application and Addendum) to the GCRC.</i>	<u> </u>	<u> X </u>
A.2.18. Will gadolinium be administered as a contrast agent?	<u> .. </u>	<u> .. X </u>

The following questions apply to **all investigators and study staff** engaged in the design, conduct, or reporting results of this project **and/or their immediate family members**. For these purposes, "family" includes the individual's spouse and dependent children. "Spouse" includes a person with whom one lives together in the same residence and with whom one shares responsibility for each other's welfare and shares financial obligations.

<p>A.3.1. Currently or during the term of this research study, does any member of the research team or his/her family member have or expect to have:</p> <p>(a) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with the sponsor of this study?</p> <p>(b) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with an entity that owns or has the right to commercialize a product, process or technology studied in this project?</p> <p>(c) A board membership of any kind or an executive position (paid or unpaid) with the sponsor of this study or with an entity that owns or has the right to commercialize a product, process or technology studied in this project?</p>	<p>___ yes</p> <p>___ yes</p> <p>___ yes</p>	<p>_x_ no</p> <p>_x_ no</p> <p>_x_ no</p>
<p>A.3.2. Has the University or has a University-related foundation received a cash or in-kind gift from the sponsor of this study for the use or benefit of any member of the research team?</p>	<p>___ yes</p>	<p>_x_ no</p>
<p>A.3.3. Has the University or has a University-related foundation received a cash or in-kind gift for the use or benefit of any member of the research team from an entity that owns or has the right to commercialize a product, process or technology studied in this project?</p>	<p>___ yes</p>	<p>_x_ no</p>

If the answer to ANY of the questions above is yes, the affected research team member(s) must complete and submit to the Office of the University Counsel the form accessible at <http://coi.unc.edu>. List name(s) of all research team members for whom any answer to the questions above is yes:

Signature of Principal Investigator

Date

Signature of Faculty Advisor

Date

For all questions, if the study involves only secondary data analysis, focus on your proposed design, methods and procedures, and not those of the original study that produced the data you plan to use.

A.4.1. Brief Summary. Provide a *brief* non-technical description of the study, which will be used in IRB documentation as a description of the study. Typical summaries are 50-100 words. *Please reply to each item below, retaining the subheading labels already in place, so that reviewers can readily identify the content.*

Purpose: The purpose of this study is to evaluate knee proprioception with and without the application of electrical stimulation and a neoprene knee sleeve in subjects with knee osteoarthritis.

Participants: Fifty-two (26 males, 26 females) with radiological evidence of medial compartment knee osteoarthritis will be tested. Participant exclusion is detailed in the Inclusion/Exclusion criteria section.

Procedures (methods): Each subject will be tested during both a non-weight bearing (NWB) and a partial-weight bearing (PWB) task. With each task the subject will be tested under four conditions: no electrical stimulation/no sleeve (NE/NS), no electrical

stimulation/sleeve (NE/S), 50 μ A electrical stimulation/sleeve (E50/S), and 75 μ A electrical stimulation (E75/S), 5 trials each. During each trial, the subject will be asked to actively reproduce a target angle of knee flexion. The average difference in target and reproduction angles (i.e. joint position sense error) will be the primary evaluation measure. In addition, the subjects will complete a functional activity questionnaire and a self-reported rating of knee instability questionnaire. The scores of the questionnaires will be correlated with the joint position sense error.

A.4.2. Purpose and Rationale. Provide a summary of the background information, state the research question(s), and tell why the study is needed. If a complete rationale and literature review are in an accompanying grant application or other type of proposal, only provide a brief summary here. If there is no proposal, provide a more extensive rationale and literature review, including references.

Osteoarthritis is the most common joint disorder in the United States with osteoarthritis of the knee being the most debilitating. The exact cause of the disorder is unknown, but it is thought to result from a combination of several factors such as age, excessive weight, joint injury, and joint stress. Several studies have shown that osteoarthritic patients in comparison to age-matched controls have a deficit in proprioception, which is the conscious and unconscious awareness of body limb position and movement in space. A person with abnormal proprioception may have an impairment of neuromuscular responses which can expose the knee joint to improper loading during the gait cycle. This improper loading can cause abnormal wear of the joint and may initiate or accelerate the progression of osteoarthritis. If impaired proprioception contributes to osteoarthritis, then a possible means to slow the progression of the disease may be through a principle known as stochastic resonance. Stochastic resonance is a phenomenon in which low levels of random noise stimulation (electrical/mechanical) have been shown to enhance the detection and transmission of weak signals in sensory systems such as muscle spindles or skin sensory receptors.

The research question we wish to answer is whether the application of low-level electrical stimulation at the knee can improve joint proprioception significantly in patients with medial compartment knee osteoarthritis and whether this improvement is superior to the control condition (NE/NS) and any improvement seen by solely wearing a neoprene sleeve over the knee. This study is needed in order to determine whether the application of electrical stimulation could serve as a therapeutic tool for patients with osteoarthritis of the knee.

A.4.3. Subjects. *You should describe the subject population even if your study does not involve direct interaction (e.g., existing records).* Specify number, gender, ethnicity, race, and age. Specify whether subjects are healthy volunteers or patients. If patients, specify any relevant disease or condition and indicate how potential subjects will be identified.

This study will be composed of fifty-two patients with medial compartment knee osteoarthritis (OA). Attempts will be made to recruit twenty-six males and twenty-six females in order to achieve an adequate gender spread. We will also attempt to recruit subjects of various ethnic backgrounds. Subjects will be included if they are greater than 40 years of age. A diagnosis of moderate medial compartment knee OA will be made by a UNC orthopaedist upon grading standing radiographs in the anterior-posterior view with the knee in extension.

A.4.4. Inclusion/exclusion criteria. List required characteristics of potential subjects, and those that preclude enrollment or involvement of subjects or their data. Justify exclusion of any group, especially by criteria based on gender, ethnicity, race, or age. If pregnant women are excluded, or if women who become pregnant are withdrawn, specific justification must be provided.

The inclusion criteria for study participants are as follows:

1. Have a physician diagnosis of knee OA
2. Show radiologic evidence of moderate knee OA in the medial compartment. (Kellgren/Lawrence [K/L] grade of 1, 2, or 3; Kellgren & Lawrence 1957)
3. Subjects will also be required to have a smaller interbone distance at the narrowest point of the medial compartment compared with the lateral compartment.
4. Patients are older than 40 years.

The exclusion criteria for study participants are as follows:

1. Any neurologic condition.
2. Pregnancy. Pregnant women have increased laxity in the joints which can cause proprioceptive deficits and this study aims to focus on proprioceptive deficits specific to the OA condition alone.
3. Use of a pacemaker, other implantable electronic device, or external catheter.
4. Musculoskeletal disease or joint replacement in the lower extremities other than knee OA
5. Diagnosis of gout, rheumatoid or other system inflammatory arthritis, obesity (BMI>35)
6. Unable to walk without an assistive device
7. Steroid injection in the knee in the last 3 months
8. Knee flexion range of motion less than 5-120 degrees
9. History of cardiac arrhythmia. .
10. Inability to perform requested tasks because of their medical condition

A.4.5. Full description of the study design, methods and procedures. Describe the research study. Discuss the study design; study procedures; sequential description of what subjects will be asked to do; assignment of subjects to various arms of the study if applicable; doses; frequency and route of administration of medication and other medical treatment if applicable; how data are to be collected (questionnaire, interview, focus group or specific procedure such as physical examination, venipuncture, etc.). Include information on who will collect data, who will conduct procedures or measurements. Indicate the number and duration of contacts with each subject; outcome measurements; and follow-up procedures. If the study involves medical treatment, distinguish standard care procedures from those that are research. If the study is a clinical trial involving patients as subjects and use of placebo control is involved, provide justification for the use of placebo controls.

Fifty-two patients with moderate, medial compartment knee OA will be recruited for this study from the patients of Dr. Chris Olcott of the Orthopaedic Clinic at UNC. Dr. Olcott will put in a request to UNC Physicians and Associates to generate a list of his patients with a billing code of knee OA. In this listing he will request that they also include the medical record number of the patient. Using the medical record number of the listing, Dr. Olcott or the orthopaedic resident, Dr. James Meeker or Dr. Jodie Miles, will use the PACS system to review digital standing AP radiographs, which were taken as part of the patient's standard care, of the patients affected knee to determine if they have the proper disease severity in the medial compartment (Kellgren/Lawrence [K/L] grade of 1, 2, or 3; Kellgren & Lawrence 1957). Dr. Olcott or the resident will then use this shortened list of patients that meet the disease severity criteria to review the patient's medical information in WEBCIS to identify those patients that also meet the rest of the exclusion/inclusion criteria. Once these potential subjects have been identified from this review, this patient list (name and phone number) will be distributed to Amber Collins so that she can contact these patients by phone to determine their interest in participating in the study.

If the subject is interested in participating in the study, the subject will be asked a series of questions to again determine if they qualify to enroll in the study based on the inclusion/exclusion criteria. If the patient is not interested in participating in the study, their contact information will be destroyed by shredding hardcopy documents and deleting contact information from spreadsheet digital files listing potential subjects. For the subjects interested in participating in the study, a meeting will be scheduled with Amber Collins to enroll the subject, conduct the joint position sense tests, and complete the questionnaires.

At the enrollment meeting, Amber Collins will provide a brief overview of the procedures involved with the testing and will then ask the subject to fill out the informed consent form. After completing the consent form, subjects will complete a questionnaire which contains questions about the subject's age, weight, gender, height, and knee range of motion.

Note: Procedures similar to what is described below for this study were approved by the IRB for use in normal subjects under Study #: 07-0030.

Subjects will have their knee proprioception evaluated while performing both a partial-weight bearing (PWB) and a non-weight bearing (NWB) task. Tests will be performed on the patient's osteoarthritic knee. Both proprioceptive tasks will be carried out under the following four conditions:

1. No electrical stimulation/No sleeve (NE/NS)
2. No electrical stimulation/Sleeve (NE/S)
3. 50 μ A electrical stimulation/Sleeve (E50/S)
4. 75 μ A electrical stimulation/Sleeve (E75/S).

The sequence of the conditions will be assigned to each subject using a counterbalanced design. A repeated-measures design will be used to compare the four conditions within subjects. Each subject will perform joint position sense testing for both a PWB and NWB task with half of the females and males performing the NWB task first and the other half the PWB task first. For each task the conditions will be presented in the following sequence: control1 (NE/NS), counterbalance design of the 3 conditions (NE/S, E50/S, E75/S), control2 (NE/NS). While our past studies have not indicated any "lasting effect" of the electrical stimulation after it is stopped, this sequencing will be used to help control for this and allow us to examine for such an effect. Subjects will be blinded to if electrical stimulation is being given during testing. The number of subjects was selected based on a pre-power analysis which indicated that an N of 52 subjects could detect a 20% difference between groups for a power of 0.8, alpha of 0.05, and standard deviation of 50% of the control mean.

Electrical stimulation will be applied with an electrical stimulator device (Afferent Corporation, Providence, RI) by a pair of self-adhesive surface electrodes (Model Platinum 03-053T, Scrip) placed 2cm above the joint line and another pair placed 2cm below the joint line on the medial and lateral aspects of the knee. These electrodes will remain in place during all testing conditions. Stimulation will consist of a 50 μ A or 75 μ A Gaussian white noise signal (zero mean, s.d. = 0.05mA, 0-1000 Hz bandwidth). To isolate the electrical current, the signals will be passed through a current-controlled stimulus isolator with a 1 mA/V conversion (Model 2200, A-M Systems). At the end of the joint position sense testing the current stimulus will be progressively increased to determine the subject's threshold of detection and the current level will be recorded. Electrodes will not be reused between subjects.

Prior to beginning the joint position sense testing an electrogoniometer will be secured by straps to the limb. The electrogoniometer will be calibrated before and at the end of the study and has demonstrated a nominal error of less than 0.2 degrees. The electrogoniometer will be interfaced with a PC data acquisition board to acquire the knee flexion angle in real-time (100Hz) along with an electronic trigger signal indicating when the subject has reached the target angle of joint position testing. The neoprene sleeve will be a self-adjustable velcro type in order to eliminate the need for removal of the electrogoniometer to remove a nonadjustable sleeve. The subjects will be asked to find a comfortable tension for the sleeve for extended use and we will mark the position of overlap of the velcro elements so that equivalent tension can be used with each testing condition.

For the NWB task the subject will be reclined back 20° from the vertical to prevent excessive tension in the hamstrings as they extend their knee. Their knee will be tested from a starting position of 90° flexion moving into extension. Subjects will be blindfolded and wear headphones playing white noise during all tests to eliminate visual and auditory cues. A trial will begin with the subject's limb being moved slowly (NWB=passively by the investigator, PWB=actively by the subject) from the starting position to the target position. The subject will hold the limb at the target position for 3 seconds. After returning to the starting position and holding for 3 seconds, the subject will then actively attempt to reposition the limb at the target angle. When the subject feels they have reproduced the target angle, he/she will depress an electronic switch to provide a time stamp and hold for 3 seconds. The reposition angle will be recorded and the absolute and real difference between the reposition and target angle will be computed. The real and absolute error for each trial will then be averaged across 5 trials. The entire testing sequence will be repeated for each trial. In order to prevent memorization of the target angle, the angle will be randomly varied to be 20 (twice), 30 (once) or 40 (twice) degrees for the 5 trials of the NWB task.

For the PWB task the subject will lie flat on his/her back on a sliding reclined (15° relative to the horizontal) platform that is relatively frictionless. The starting position will be in full knee extension in single leg stance, and the subjects will move into flexion. During

the PWB task a wedge at the base of heel will be used to put the ankle in plantar flexion to limit passive tension cues from ankle muscle groups. The remaining aspects of the PWB testing will be similar to the NWB tests with the exception that target angles will be randomly varied to be 20(twice), 25(once), and 30 degrees (twice). The PWB nature of the task is viewed as a more desirable task for knee OA subjects as a full weight-bearing task may cause pain in some subjects. As the PWB is more demanding, the subjects will be given an opportunity to rest between trials.

A graduate student (Amber Collins) will perform all subject recruitment, testing, data collection, and data analysis as a part of the student's doctoral dissertation.

The test session will last approximately 2 hours. Follow up visits are not required.

A.4.6. Benefits to subjects and/or society. Describe any potential for direct benefit to individual subjects, as well as the benefit to society based on scientific knowledge to be gained; these should be clearly distinguished. Consider the nature, magnitude, and likelihood of any direct benefit to subjects. If there is no direct benefit to the individual subject, say so here and in the consent form (if there is a consent form). Do not list monetary payment or other compensation as a benefit.

There are no immediate direct benefits for the knee OA patients involved in this study. However, scientific knowledge gained from the study may allow for the development of a brace or sleeve that incorporates electrical stimulation to be used as a therapy in OA patients to improve their knee proprioception. Improvement of proprioception in knee OA patients may decrease abnormal loading and wear of the knee and thereby possibly slow the progression of the disease, reduce pain and improve function.

A.4.7. Full description of risks and measures to minimize risks. Include risk of psychosocial harm (e.g., emotional distress, embarrassment, breach of confidentiality), economic harm (e.g., loss of employment or insurability, loss of professional standing or reputation, loss of standing within the community) and legal jeopardy (e.g., disclosure of illegal activity or negligence), as well as known side effects of study medication, if applicable, and risk of pain and physical injury. Describe what will be done to minimize these risks. Describe procedures for follow-up, when necessary, such as when subjects are found to be in need of medical or psychological referral. If there is no direct interaction with subjects, and risk is limited to breach of confidentiality (e.g., for existing data), state this.

As with any activity, there is a minor risk of muscle strain or joint pain while performing the partial weight bearing task. The partial weight bearing task will be used instead of a full weight bearing task to minimize the risk of knee pain experienced by the subjects. During the non-weight bearing task, the subject will be in a seated position on a slightly reclined bench with their back supported in order to minimize the risk of any back pain and to increase the subject's stability while seated on the bench. Subject identification will remain confidential.

A minimal risk of electrical shock is present in working with any electrical equipment. The electrical stimulation system will be supplying currents below the subject's threshold of detection and are at a harmless level. The stimulus-isolator of the electrical stimulation system has optically isolated outputs and the maximum current the output can deliver is $\pm 5\text{mA}$ when set at its highest range. This current level is still at an intensity that is accepted to be harmless. The system is designed with a safety measure such that if the stimulus-isolator malfunctions and the output stimulus increases greater than the desired input stimulus, then the stimulus is automatically turned off. Additionally, the entire system administering the stimulation will be freestanding, battery powered and will not be connected to an outlet in order to ensure the stimulation delivered is not higher than desired.

In the case of an unanticipated or adverse event either Dr. Chris Olcott (Tuesday and Thursdays; Pager #: 216-2048) or Dr. Douglas Dirschl (Monday, Wednesday, and Friday; Pager #: 216-1902) who are both orthopaedic physicians will be able to be contacted for medical advice. In addition, a third year orthopaedic resident who is conducting a year of research, Dr. James Meeker (Pager #: 216-5883) or Dr. Jodie Miles (Pager#: 216-0365) will also be available to be contacted for medical advice at all times.

A.4.8. Data analysis. Tell how the qualitative and/or quantitative data will be analyzed. Explain how the sample size is sufficient to achieve the study aims. This might include a formal power calculation or explanation of why a small sample is sufficient (e.g., qualitative research, pilot studies).

The number of subjects was selected based on a pre-power analysis and indicated that an N of 52 subjects could detect a 20% difference between groups for a power of 0.8, alpha of 0.05, and standard deviation of 50% of the control mean. A two-way repeated measures analysis of variance will be performed for both the partial and non-weight bearing tasks to determine if electrical stimulation or the presence of the knee sleeve influenced the angle reproduction absolute error. The Holm-Sidak mean comparison test will be used to determine statistical differences ($p < 0.05$) in the mean reproduction angle between the four testing conditions for each task. Additionally, the intraclass correlation coefficient will be calculated for each of the trials under all of the testing conditions to assess the reliability of the data.

A.4.9. Will you collect or receive any of the following identifiers? Does not apply to consent forms.

☐ No ☒ Yes *If yes, check all that apply:*

- a. ☒ Names
- b. ☒ Telephone numbers
- c. ☐ Any elements of dates (other than year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death. For ages over 89: all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 and older
- d. ☐ Any geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code
- e. ☐ Fax numbers
- f. ☐ Electronic mail addresses
- g. ☐ Social security numbers
- h. ☒ Medical record numbers
- i. ☐ Health plan beneficiary numbers
- j. ☐ Account numbers
- k. ☐ Certificate/license numbers
- l. ☐ Vehicle identifiers and serial numbers (VIN), including license plate numbers
- m. ☐ Device identifiers and serial numbers (e.g., implanted medical device)
- n. ☐ Web universal resource locators (URLs)
- o. ☐ Internet protocol (IP) address numbers
- p. ☐ Biometric identifiers, including finger and voice prints
- q. ☐ Full face photographic images and any comparable images
- r. ☐ Any other unique identifying number, code, or characteristic, other than dummy identifiers that are not derived from actual identifiers and for which the re-identification key is maintained by the health care provider and not disclosed to the researcher

A.4.10. Identifiers in research data. Are the identifiers in A.4.9 above linked or maintained with the research data?

☐ yes ☒ no

A.4.11. Confidentiality of the data. Describe procedures for maintaining confidentiality of the data you will collect or will receive. Describe how you will protect the data from access by those not authorized. How will data be transmitted among research personnel? Where relevant, discuss the potential for deductive disclosure (i.e., directly identifying subjects from a combination of indirect IDs).

The listing of knee OA subjects with their medical record number will be recorded in a spreadsheet in Dr. Olcott's locked office. Dr. Olcott will only share this information with the residents assisting with the project, Dr. Meeker and Dr. Miles. Dr. Olcott will only provide the name, phone number, radiographic grade, and interbone distance measurements of potential subjects to Amber Collins who will then be contacting these individuals to determine their willingness to participate in the study. This information will be shared with Amber Collins by means of a digital spreadsheet file that is password protected. Potential subjects unwilling to participate in the study will be deleted from this file. The enrolled subject's name will be linked to a numbered identifier through a password protected spreadsheet which will be maintained by Amber Collins in a locked cabinet located in a locked laboratory office. Access to the enrolled subject's study information will only be given to members of the research team thru a password protected spreadsheet which include the subjects numbered identifier, but not their name.

A.4.12. Data sharing. With whom will *identifiable* (contains any of the 18 identifiers listed in question A.4.9 above) data be shared outside the immediate research team? For each, explain confidentiality measures. Include data use agreements, if any.

- ☒ No one
- ☐ Coordinating Center:
- ☐ Statisticians:
- ☐ Consultants:
- ☐ Other researchers:
- ☐ Registries:
- ☐ Sponsors:
- ☐ External labs for additional testing:
- ☐ Journals:
- ☐ Publicly available dataset:
- ☐ Other:

A.4.13. Data security for storage and transmission. Please check all that apply.

For electronic data:

- ☐ Secure network ☐ Password access ☐ Encryption
- ☐ Other (describe):
- ☒ Portable storage (e.g., laptop computer, flash drive)
- Describe how data will be protected for any portable device:*

For hardcopy data (including human biological specimens, CDs, tapes, etc.):

- ☐ Data de-identified by research team (stripped of the 18 identifiers listed in question A.4.9 above)
- ☒ Locked suite or office
- ☒ Locked cabinet
- ☒ Data coded by research team with a master list secured and kept separately
- ☐ Other (describe):

A.4.14. Post-study disposition of identifiable data or human biological materials. Describe your plans for disposition of data or human biological specimens that are identifiable in any way (directly or via indirect codes) once the study has ended. Describe your plan to destroy identifiers, if you will do so.

After completion of the study, hardcopy data will be stored for a period of 5 years. It will then be shredded after this period.

Part A.5. The Consent Process and Consent Documentation (including Waivers)

The standard consent process is for all subjects to sign a document containing all the elements of informed consent, as specified in the federal regulations. Some or all of the elements of consent, including signatures, may be altered or waived under certain circumstances.

- If you will obtain consent in any manner, complete **section A.5.1**.
- If you are obtaining consent, but requesting a waiver of the requirement for a signed consent document, complete **section A.5.2**.
- If you are requesting a waiver of any or all of the elements of consent, complete **section A.5.3**.
- If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a *limited waiver of HIPAA authorization*. This is addressed in section B.2.

You may need to complete more than one section. For example, if you are conducting a phone survey with verbal consent, complete sections A.5.1, A.5.2, and possibly A.5.3.

A.5.1. Describe the process of obtaining informed consent from subjects. If children will be enrolled as subjects, describe the provisions for obtaining parental permission and assent of the child. If decisionally impaired adults are to be enrolled, describe the provision for obtaining surrogate consent from a legally authorized representative (LAR). If non-English speaking people will be enrolled, explain how consent in the native language will be obtained. Address both written translation of the consent and the availability of oral interpretation. *After you have completed this part A.5.1, if you are not requesting a waiver of any type, you are done with Part A.5.; proceed to Part B.*

Children, decisionally impaired adults, and non-English speaking people will not be enrolled in this study. After potential subjects have been identified and contacted by phone, the investigators of the study will obtain informed consent from study subjects during the enrollment visit by providing a consent document detailing the study and all risks involved. Subjects will be asked to sign the consent document as evidence of their understanding of the study.

A.5.2. Justification for a waiver of written (i.e., signed) consent. *The default is for subjects to sign a written document that contains all the elements of informed consent.* Under limited circumstances, the requirement for a signed consent form may be waived by the IRB if either of the following is true.
Chose only one:

- a. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., study topic is sensitive so that public knowledge of participation could be damaging). ___ yes ___ no

Explain.

- b. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (e.g., phone survey).

Explain.

___ yes ___ no

If you checked "yes" to either (and you are not requesting a waiver in section A.5.3) consent must be obtained orally, by delivering a fact sheet, through an online consent form, or be incorporated into the survey itself. Include a copy of the consent script, fact sheet, online consent form, or incorporated document.

→ If you have justified a waiver of written (signed) consent (A.5.2), you should complete A.5.3 *only* if your consent process will not include all the other [elements of consent](#).

A.5.3. Justification for a full or partial waiver of consent. *The default is for subjects to give informed consent.* A waiver might be requested for research involving only existing data or human biological specimens (see also Part C). More rarely, it might be requested when the research design requires withholding some study details at the outset (e.g., behavioral research involving deception). In limited circumstances, parental permission may be waived. This section should also be completed for a waiver of HIPAA authorization if research involves Protected Health Information (PHI) subject to HIPAA regulation, such as patient records.

☒ Requesting **waiver of some elements** (specify; see SOP 28 on the IRB web site): 28.1.5 (Waiver of HIPAA authorization in order to review patient medical records initially to identify potential subjects and then contact them to recruit as subjects)

☐ Requesting **waiver of consent entirely**

If you check either of the boxes above, answer items a-f.. To justify a full waiver of the requirement for informed consent, you must be able to answer "yes" (or "not applicable" for question c) to items a-f. **Insert brief explanations that support your answers.**

a. Will the research involve no greater than minimal risk to subjects or to their privacy? ☒_X_ yes ☐ no

The subjects will be performing tasks that they routinely perform during daily living activities. The electrical stimulation is at a subthreshold level and is harmless.

b. Is it true that the waiver will *not* adversely affect the rights and welfare of subjects? *(Consider the right of privacy and possible risk of breach of confidentiality in light of the information you wish to gather.)* ☒_X_ yes ☐ no

The subject's medical records will only be reviewed by their orthopaedic physician (Chris Olcott) or the resident assisting with the project. Only the subject's phone number, name, and knee OA disease severity grade will be given to the research team member (Amber Collins) that will be contacting the subject to recruit them for the study.

c. When applicable to your study, do you have plans to provide subjects with pertinent information after their participation is over? *(e.g., Will you provide details withheld during consent, or tell subjects if you found information with direct clinical relevance? This may be an uncommon scenario.)* ☐ yes ☒_X_ not applicable

All other components of written consent will be acquired after the subject is recruited.

d. Would the research be impracticable without the waiver? *(If you checked "yes," explain how the requirement to obtain consent would make the research impracticable, e.g., are most of the subjects lost to follow-up or deceased?). Without the waiver the research would be impractical as our recruiting process would be terribly inefficient in that we would have to contact many more people who do not meet the basic inclusion/exclusion criteria prior to finding potential subjects that do meet the criteria. In addition, we would need for the potential subjects to have an AP radiograph of their knee taken or for their current physician to allow us access this information and the subject may still not qualify for enrollment in the study if they do not meet the radiographic knee OA disease criteria.* ☒_X_ yes ☐ no

e. Is the risk to privacy reasonable in relation to benefits to be gained or the importance of the knowledge to be gained? ☒_X_ yes ☐ no

The risk of privacy is minimal as only the patient's orthopaedic physician and the assisting resident will be reviewing the medical information. The knowledge gained from this study has the potential to be developed into a new therapy for slowing the progression of knee OA that could help millions of patients.

If you are accessing patient records for this research, you must also be able to answer "yes" to item f to justify a waiver of HIPAA authorization from the subjects.

f. Would the research be impracticable if you could not record (or use) Protected Health Information (PHI)? *(If you checked "yes," explain how not recording or using PHI would make the research impracticable.)* ☒_X_ yes ☐ no

Without the waiver the research would be impractical as our recruiting process would be terribly inefficient in that we would have to contact many more people who do not meet the basic inclusion/exclusion criteria prior to finding potential subjects that due meet the criteria. In addition, we would need for the potential subjects to have an AP radiograph of their knee taken or for their current physician to allow us access to this information and the subject may still not qualify for enrollment in the study if they do not meet the radiographic knee OA disease criteria.

Part B. Questions for Studies that Involve Direct Interaction with Human Subjects
→ *If this does not apply to your study, do not submit this section.*

B.1. Methods of recruiting. Describe how and where subjects will be identified and recruited. Indicate who will do the recruiting, and tell how subjects will be contacted. Describe efforts to ensure equal access to participation among women and minorities. Describe how you will protect the privacy of potential subjects during recruitment. *For prospective subjects whose status (e.g., as patient or client), condition, or contact information is not publicly available (e.g., from a phone book or public web site), the initial contact should be made with legitimate knowledge of the subjects' circumstances. Ideally, the individual with such knowledge should seek prospective subjects' permission to release names to the PI for recruitment. Alternatively, the knowledgeable individual could provide information about the study, including contact information for the investigator, so that interested prospective subjects can contact the investigator. Provide the IRB with a copy of any document or script that will be used to obtain the patients' permission for release of names or to introduce the study. Check with the IRB for further guidance.*

Fifty-two patients with moderate, medial compartment knee OA will be recruited for this study from the patients of Dr. Chris Olcott of the Orthopaedic Clinic at UNC. Dr. Olcott will put in a request to UNC Physicians and Associates to generate a list of his patients with a billing code of knee OA. In this listing he will request that they also include the medical record number of the patient. Using the medical record number of the listing, Dr. Olcott or the orthopaedic residents, Dr. James Meeker or Dr. Jodie Miles, will use the PACS

system to review digital standing AP radiographs, which were taken as part of the patient's standard care, of the patients affected knee to determine if they have the proper disease severity in the medial compartment (Kellgren/Lawrence [K/L] grade of 1, 2, or 3; Kellgren & Lawrence 1957). Dr. Olcott or the resident will then use this shortened list of patients that meet the disease severity criteria to review the patient's medical information in WEBCIS to identify those patients that also meet the rest of the exclusion/inclusion criteria (See section 4.4). Once these potential subjects have been identified from this review, this patient list (name and phone number) will be distributed to Amber Collins so that she can contact these patients by phone to determine their interest in participating in the study. This list will be distributed to Amber Collins by means of a password protected spreadsheet file.

If during the initial telephone call to contact the potential subject it is determined the person is interested in participating in the study and qualifies for enrollment, the subject will be scheduled for a enrollment/testing meeting where their written consent will be acquired. If the patient is not interested in participating in the study, their contact information will be destroyed by shredding hardcopy documents and deleting contact information from spreadsheet digital files listing potential subjects.

We are planning that half of the enrolled subjects will be women in order to have equal representation of this gender. We will attempt to enroll subjects from all minorities.

B.2. Protected Health Information (PHI). If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a *limited waiver of HIPAA authorization*. If this applies to your study, please provide the following information.

- a. Under this limited waiver, you are allowed to access and use only the minimum amount of PHI necessary to review eligibility criteria and contact potential subjects. What information are you planning to collect for this purpose?

The patients' medical record will be reviewed to confirm that they meet the following inclusion and exclusion criteria.

The inclusion criteria for study participants are as follows:

1. Have a physician diagnosis of knee OA
2. Show radiologic evidence of moderate knee OA in the medial tibial-femoral compartment based on a standing Anterior-Posterior radiograph. (Kellgren/Lawrence [K/L] grade of 1, 2, or 3; Kellgren & Lawrence 1957)
3. Subjects will also be required to have a smaller interbone distance at the narrowest point of the medial compartment compared with the lateral compartment.
4. Patients are older than 40 years.

The exclusion criteria for study participants are as follows:

1. Have any neurologic condition.
2. Pregnancy. Pregnant women have increased laxity in the joints which can cause proprioceptive deficits and this study aims to focus on proprioceptive deficits specific to the OA condition alone.
3. Use of a pacemaker, other implantable electronic device, or external catheter
4. Musculoskeletal disease or joint replacement in the lower extremities other than knee OA
5. Diagnosis of gout, rheumatoid or other system inflammatory arthritis, obesity (BMI>35)
6. Unable to walk without an assistive device
7. Steroid injection in the knee in the last 3 months
8. Knee flexion range of motion less than 5-120 degrees
9. History of cardiac arrhythmia.
10. Inability to perform requested tasks because of their medical condition

- b. How will confidentiality/privacy be protected prior to ascertaining desire to participate?

A listing of potential subjects for the study that are patients of Dr. Olcott will be generated where the listing will include the subjects' medical record #. This listing will be kept in a password-protected spreadsheet file in Dr. Olcott's locked office. Dr. Olcott and the resident assisting with the project will review the subject's medical information to determine if they fulfill the inclusion/exclusion criteria. A new listing will be generated of the patients that fulfill the criteria and this listing (name and phone #) will be distributed to Amber Collins who will then contact the patients to determine their willingness to participate in the study. This new listing will be kept in a password-protected spreadsheet file in Amber Collins' office in a locked-laboratory.

- c. When and how will you destroy the contact information if an individual declines participation?

Patients who decline to participate in the study will be deleted from the spreadsheet file listing of potential subjects and any hardcopies of their contact information will be shredded.

B.3. Duration of entire study and duration of an individual subject's participation, including follow-up evaluation if applicable. Include the number of required contacts and approximate duration of each contact.

The duration of each individual subject's participation is approximately 2 hours. Follow up evaluations are not required, but we may wish to enroll the subjects in a subsequent study filed under a different IRB application.

B.4. Where will the subjects be studied? Describe locations where subjects will be studied, both on and off the UNC-CH campus.

The subjects will be studied on the UNC-CH campus in the Motor Control Lab which is located in Fetzer Gym, room 126, CB# 8700

B.5. Privacy. Describe procedures that will ensure privacy of the subjects in this study. Examples include the setting for interviews, phone conversations, or physical examinations; communication methods or mailed materials (e.g., mailings should not indicate disease status or focus of study on the envelope).

Privacy of the subjects in this study will be ensured by procedures such as private communication via the phone. Testing materials will not be mailed and all communication prior to testing will be done over the phone. Joint position sense testing of the subjects will be carried out with no other individuals other than the research team in the laboratory.

B.6. Inducements for participation. Describe all inducements to participate, monetary or non-monetary. If monetary, specify the amount and schedule for payments and if/how this will be prorated if the subject withdraws (or is withdrawn) from the study prior to completing it. For compensation in foreign currency, provide a US\$ equivalent. Provide evidence that the amount is not coercive (e.g., describe purchasing power for foreign countries). Be aware that payment over a certain amount may require the collection of the subjects' Social Security Numbers. If a subject is paid more than \$40.00 at one time or cumulatively more than \$200.00 per year, collection of subjects' Social Security Number is required (University policy) using the Social Security Number collection consent addendum found under [forms on the IRB website](#) (look for Study Subject Reimbursement Form).

Subjects will be compensated for their participation in this study at a rate of \$100 for the entire testing session. If the subject fails to complete the testing session, they will be compensated in proportion to the percentage of the testing session that was completed.

B.7. Costs to be borne by subjects. Include child care, travel, parking, clinic fees, diagnostic and laboratory studies, drugs, devices, all professional fees, etc. If there are no costs to subjects other than their time to participate, indicate this.

There are no costs to the subject other than their time to participate.

Part C. Questions for Studies using Data, Records or Human Biological Specimens without Direct Contact with Subjects
→ *If this does not apply to your study, do not submit this section.*

C.1. What records, data or human biological specimens will you be using? (check all that apply):

- ☐ Data already collected for another research study
- ☐ Data already collected for administrative purposes (e.g., Medicare data, hospital discharge data)
- ☒ Medical records (custodian may also require form, e.g., HD-974 if UNC-Health Care System)
- ☐ Electronic information from clinical database (custodian may also require form)
- ☐ Patient specimens (tissues, blood, serum, surgical discards, etc.)
- ☐ Other (specify):

C.2. For each of the boxes checked in 1, how were the original data, records, or human biological specimens collected? Describe the process of data collection including consent, if applicable.

The medical records of the patients of Dr. Olcott were collected as part of their care in the UNC-Health Care System. Dr. Olcott will be reviewing these records to find subjects that meet the study inclusion and exclusion criteria.

C.3. For each of the boxes checked in 1, where do these data, records or human biological specimens currently reside?

The medical records that we wish to review reside in the PACS and WEBCIS systems for the Department of Orthopaedics of the UNC Health Care System.

C.4. For each of the boxes checked in 1, from whom do you have permission to use the data, records or human biological specimens? Include data use agreements, if required by the custodian of data that are not publicly available.

Dr. Olcott is the patient's physician and he or the assisting resident will be reviewing the medical records information. We will complete whatever custodian forms the UNC Health Care System requires of to perform this review.

C.5. If the research involves human biological specimens, has the purpose for which they were collected been met before removal of any excess? For example, has the pathologist in charge or the clinical laboratory director certified that the original clinical purpose has been satisfied? Explain if necessary.

☐ yes ☐ no ☐ not applicable (explain)

C.6. Do all of these data records or specimens exist at the time of this application? If not, explain how prospective data collection will occur.

☒ yes ☐ no If no, explain

APPENDIX B: Subject consent form – JPS study

University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Adult Subjects
Biomedical Form

IRB Study # 08-0664

Consent Form Version Date: 9-5-08

Title of Study: Electrical Stimulation to Improve Proprioception in Knee Osteoarthritis

Principal Investigator: Dr. Paul Weinhold

UNC-Chapel Hill Department: Orthopaedics

UNC-Chapel Hill Phone number: 919-966-9077

Email Address: weinhold@med.unc.edu

Co-Investigators: Amber Collins, Dr. Chris Olcott, Dr. J. Troy Blackburn, Dr. Doug Dirschl, Dr. Bing Yu, Dr. Joanne Jordan, Dr. Jodie Miles

Faculty Advisor: Dr. Paul Weinhold

Funding Source: Arthritis Foundation

Study Contact telephone number: 919-966-1212

Study Contact email: amcollin@email.unc.edu

What are some general things you should know about research studies?

You are being asked to take part in a research study. To join the study is voluntary.

You may refuse to join, or you may withdraw your consent to be in the study, for any reason.

Research studies are designed to obtain new knowledge that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher, your health care provider, or the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

The purpose of this research study is to learn about the ability of a low level electrical stimulation to improve a person's position sense (proprioception) of their knee joint in subjects with knee osteoarthritis (OA). The low level electrical stimulation is harmless and will be applied at levels below your ability to sense them. Osteoarthritis (OA) is the most common joint disorder throughout the United States, with OA of the knee being especially common and painful. The exact cause of osteoarthritis is not known, but it is thought that it may result from a combination of several factors such as age, excessive weight, joint injury, and improper loading of the joint. If a person is unable to position their knee properly (poor proprioception) during walking and other activities, this may expose the knee joint to higher levels of loading. This improper loading may cause abnormal wear of the joint and may accelerate the disease process of osteoarthritis. If poor positioning of the knee during daily activities contributes to osteoarthritis, then a possible means to slow the disease may be through a new type of low level electrical stimulation.. This new type of low level electrical stimulation is believed to help a person in sensing the position of their knee during activities. This type of electrical stimulation has been applied at the knee in older adults to improve balance. The low level electrical stimulation is harmless and will be applied at levels below your ability to sense them. If you should sense the stimulation, it will merely feel like a slight itching sensation.. In addition, safety precautions have been built into the stimulation system to prevent exposure to any harmful levels of stimulation if there should be any malfunction of the equipment.

We plan to test if low level electrical stimulation can improve a person's ability to sense their position of their knee in patients with medial compartment knee osteoarthritis. The purpose of this study is to evaluate knee joint position sense in knee osteoarthritis subjects with and without both the application of electrical stimulation and the use of a neoprene knee sleeve.

The aims of the study are:

Aim 1: To determine whether proprioception can be improved with electrical stimulation and wearing a neoprene sleeve.

Aim 2: To determine whether proprioception can be improved by wearing a neoprene knee sleeve alone.

Aim 3: To determine whether electrical stimulation can improve proprioception beyond that provided by the neoprene knee sleeve alone.

You are being asked to be in the study because you are 40 years or older and have mild or moderate knee OA in the medial compartment of your knee as evaluated by your physician and indicated by the x-ray films of your knee.

Are there any reasons you should not be in this study?

You should not be in this study if:

1. You have any condition that affects your nerve tissues.
2. You are pregnant.
3. You have a pacemaker, other implantable electronic device, or tube implanted into your vein or body cavity.
4. You have a musculoskeletal disease or joint replacement in your legs other than knee OA.
5. You have a diagnosis of gout, rheumatoid or other systemic inflammatory arthritis, or a BMI>35.
6. You are unable to walk without an assistive device.
7. You have had a steroid injection in your knee in the last 3 months.
8. Your knee flexion range of motion is less than 5-120 degrees. (We will assist you in evaluating this).
9. You have a history of cardiac arrhythmia.
10. You are unable to perform the requested tasks because of your medical condition.

How many people will take part in this study?

If you decide to be in this study, you will be one of approximately 52 people in this research study.

How long will your part in this study last?

Your participation in this study will last approximately 2 hours. Only one test session is necessary, follow-up visits are not required.

What will happen if you take part in the study?

During your testing session, the following will occur:

First, the investigator will collect information about your height, weight and age in the form of a written questionnaire. Next, you will complete a questionnaire about your functional activity and knee pain. Finally, you will answer a question about any knee instability you experience during daily activities. For the questionnaires, you may choose not to answer a question for any reason; however we may not be able to include you in the study if you do not answer all the questions.

During the testing session you will be required to perform two different tasks multiple times (a total of 50 trials). You will be required to complete the two different activities under several testing conditions. These testing conditions will be with or without wearing a neoprene knee sleeve and with or without receiving the low level electrical stimulation. During the activities you will be required to move your knee to different positions and then try to reproduce these positions. In one activity you will be seated (non-weight bearing task; NWB), while in the other activity you will be reclined on a sliding inclined platform while supporting yourself on one leg (partial weight bearing task; PWB).

Similar to flipping a coin the sequence of the test conditions used will be assigned to you randomly. In addition, you will not be told (Blinded) when you are receiving the electrical stimulation and the stimulation is below the level that most people can feel so you will be unaware of it. During each trial, the investigator will set up the equipment according to which condition you are to complete. You will be blindfolded and will wear headphones playing white noise during all tests.

Each task will be shown to you by the investigator. You will be given a chance to practice the task before the testing begins. During the NWB task (see Figure 1.), you will be seated on a bench and your knee will be moved from a bent knee position towards a straight leg position and returned.

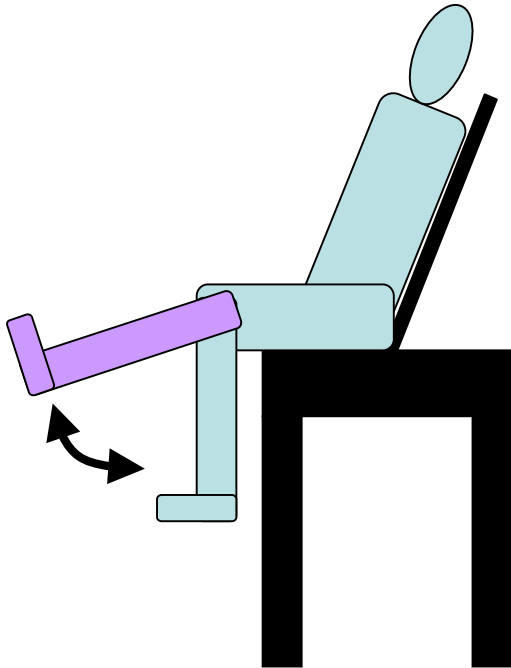


Figure 1. Diagram of the NWB task.

For the PWB task you will lay flat on your back on a sliding reclined platform (15° relative to the horizontal) while bearing weight on one leg (Figure 2). The starting position will be in straight leg position, and you will move into a bent knee position and then return.. During this task a wedge at the base of your heel will be used to put the ankle in such a position as to limit sensory information from your ankle. You will be given a chance to rest as needed during these tasks.

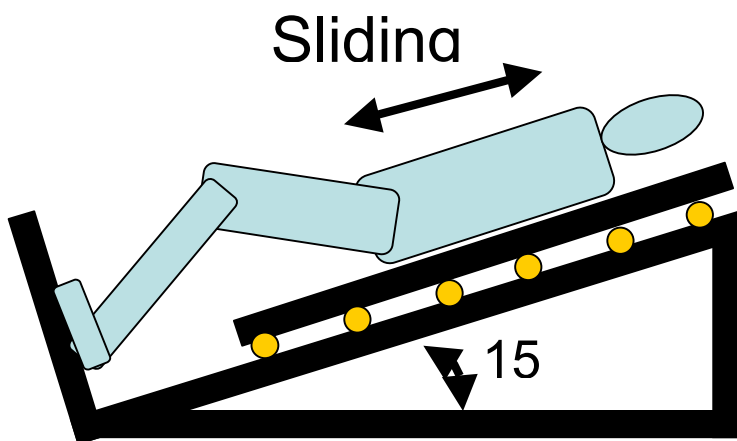


Figure 2. Diagram of PWB task.

At the end of testing session, we will gradually increase the amplitude of the electrical stimulus to determine at what level you sense the stimulus. The stimulus will feel like a slight itching sensation, and will remain harmless to you.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. You will not benefit personally from being in this research study. The

results of this study could lead to the development of a new brace that could provide such electrical stimulation so that it might be used to slow the disease progression of knee OA and improve function.

What are the possible risks or discomforts involved with being in this study?

As with any physical activity, there is a minor risk of muscle strain or joint pain in your knee while performing the tasks in this study. We are asking you to perform tasks that you may have never performed. Although they are not difficult, there is always a risk of injury. We cannot guarantee that you will not incur an injury from your participation in this study. Each task will be demonstrated for you so that you may see the level of difficulty.

A minimal risk of electrical shock is present in working with any electrical equipment. The electrical stimulation system supplies electrical currents that are below your ability to detect them and are at a harmless level. Each electrical stimulating device is built with safety measures and is battery-powered so that it is only able to provide electrical currents at harmless levels. The safety measures are in place to prevent you from being stimulated at higher electricity levels than intended. If by chance there is an increase in electrical output, the safety measures will detect the rise and the machine will cut off before the electricity is passed onto you.

In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to the researchers.

What if we learn about new findings or information during the study?

If any subjects prior to your testing session experience an unanticipated event during their testing session we will provide you with this new information prior to you participating in the study.

How will your privacy and confidentiality be protected?

Neither your name, social security number or other personal information will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

In order to assure the confidentiality of your personal medical information only your physician (Dr. Chris Olcott) and the orthopaedic resident assisting him will be allowed to review your personal medical information and this will only be done to assess if you qualify to participate in the study. Only your name, phone number, information about the X-rays films of your osteoarthritic knee, and your qualification status for the study will be provided by the physician and resident to the other investigators. Initially, your name will be coded with a number and this information will be stored in a separate password-protected file and computer in a locked office. In order to assure the confidentiality of your data, additional data collected during the study will only be saved with your numeric code and your name will not appear. The additional data collected during the study will be saved with your numeric code on a separate password-protected spreadsheet file on a computer in a locked office. No one other than the study investigators Chris Olcott, Paul Weinhold, Amber Collins, Troy Blackburn, Joanne Jordan, Doug Dirschl, Jodie Miles and Bing Yu will have access to the computer, the password, the files or the numeric code that identifies your data.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. However, by signing this form, you do not give up any of your legal rights.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Will you receive anything for being in this study?

You will be receiving \$100 in the form of a check for taking part in this study. You will receive this at the end of the testing session. If you do not complete the entire testing sequence (50 trials) your payment will be in proportion to the number of trials of the testing sequence that you complete.

Will it cost you anything to be in this study?

It will not cost you anything to participate in this study.

What if you are a UNC student?

You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

What if you are a UNC employee?

Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

Who is sponsoring this study?

This research is partially funded by the UNC University Research Council. This means that the research team is being funded by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

What if you have questions about your rights as a research subject?

All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Title of Study: Electrical Stimulation to Improve Proprioception in Knee Osteoarthritis

Principal Investigator: Paul Weinhold

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time and have had them satisfactorily answered. I voluntarily agree to participate in this research study.

Signature of Research Subject

Date

Printed Name of Research Subject

Signature of Person Obtaining Consent

Date

Printed Name of Person Obtaining Consent

APPENDIX C: HIPAA Authorization form – JPS study

University of North Carolina-Chapel Hill

HIPAA Authorization for Use and Disclosure of Health Information for Research Purposes

IRB Study #08-0664

Title of Study: Electrical Stimulation to Improve Proprioception in Knee Osteoarthritis

Principal Investigator: Paul Weinhold

Mailing Address for UNC-Chapel Hill Department: UNC Orthopaedic Research Labs, 134B Glaxo Bldg., CB# 7546, 101A Mason Farm Rd., Chapel Hill, NC 27599

This is a permission called a "HIPAA authorization." It is required by the "Health Insurance Portability and Accountability Act of 1996" (known as "HIPAA") in order for us to get information from your medical records or health insurance records to use in this research study.

1. If you sign this HIPAA authorization form, you are giving your permission for the following people or groups to give the researchers certain information (described in #2 below) about you:

Any health care providers or health care professionals or health plans that have provided health services, treatment, or payment for you such as physicians, clinics, hospitals, home health agencies, diagnostics centers, laboratories, treatment or surgical centers, including but not limited to the UNC Health Care System.

2. If you sign this HIPAA authorization form, this is the health information about you that the people or groups listed in #1 may give to the researchers to use in this research study:

11. Musculoskeletal: Medical records will be reviewed for evidence of musculoskeletal disease or joint replacement in the lower extremities other than knee OA. Records will be reviewed for any diagnosis of gout, rheumatoid or other system inflammatory arthritis. Radiographs of the knees will be examined to grade the severity of knee osteoarthritis.

Subject's Initials: _____

12. Neurologic: Medical records will be reviewed for any diagnosis or evidence of a neurologic condition that may influence their sensory perception.

Subject's Initials: _____

3. The HIPAA protections that apply to your medical records will not apply to your information when it is in the research study records. Your information in the research study records may also be shared with, used by or seen by the sponsor of the research study, the sponsor's representatives, officials of the IRB, and certain employees of the university or government agencies if needed to oversee the research study. HIPAA rules do not usually apply to those persons. The informed consent document describes the procedures in this research study that will be used to protect your personal information. You can also ask the researchers any questions about what they will do with your personal information and how they will protect your personal information in this research study.

4. If this research study creates medical information about you that will go into your medical record, you may not be able to see the research study information in your medical record until the entire research study is over.

5. If you want to participate in this research study, you must sign this HIPAA authorization form to allow the people or groups listed in #1 on this form to give access to the information about you that is listed in #2 on this form. If you do not want to sign this HIPAA authorization form, you cannot participate in this research study. However, not signing the authorization form will not change your right to treatment, payment, enrollment or eligibility for medical services outside of this research study.

6. This HIPAA authorization will stop when the results of this study are submitted for publication.

7. You have the right to stop this HIPAA authorization at any time. HIPAA rules are that if you want to stop this HIPAA authorization, you must do that in writing. You may give your written stop of this HIPAA authorization directly to Principal Investigator or researcher or you may mail it to the department mailing address listed at the top of this form, or you may give it to one of the researchers in this study and tell the researcher to send it to any person or group the researcher has given a copy of this HIPAA authorization. Stopping this HIPAA authorization will not stop information sharing that has already happened.

8. You will be given a copy of this signed HIPAA authorization.

Signature of Research Subject

Date

Print Name of Research Subject

For Personal Representative of the Research Participant (if applicable)

Print Name of Personal Representative: _____

Please explain your authority to act on behalf of this Research Subject:

I am giving this permission by signing this HIPAA Authorization on behalf of the Research Participant.

Signature of Personal Representative

Date

APPENDIX D: Subject questionnaire-Demographic

Date & Time: _____

Age: _____

Sex (M/F): _____

Weight: _____ Height: _____

Knee affected with osteoarthritis? (Right or Left) _____

For investigator use only:

Knee Flexion Range of Motion 5-125° at least (Y/N): _____

Calculated BMI (<35): _____

Subject ID: _____

1st Task Sequence # : _____

2nd Task Sequence #: _____

Level of current at detection: _____

APPENDIX E: Subject questionnaire-Self Reported Measure of Knee Instability

Instructions: The following questionnaire is designed to determine the symptoms and limitations that you experience because of your knee while you perform your usual daily activities. Please answer the question by circling the number of the statement that best describes your condition.

A. “To what degree does giving away, buckling, or shifting of the knee affect your level of daily activity?” (circle the number of the statement that best describes your condition.)

0 = The symptom prevents me from all activity.

1 = The symptom affects my activity severely.

2 = The symptom affects my activity moderately.

3 = The symptom affects my activity slightly.

4 = I have the symptom but it does not affect my activity.

5 = I do not have giving away, buckling, or shifting of the knee.

B. “How many times in the past 3 months have you experienced an episode of giving away, buckling, or shifting of the knee?”

_____ (Indicate number of times)

For investigator use only:

Date: _____

Subject ID: _____

APPENDIX F: Subject questionnaire- KOOS Knee Survey

Knee and Osteoarthritis Outcome Score (KOOS), English version LK1.0

APPROVED - 199, UNC-CH

SEP 16 2009¹

KOOS KNEE SURVEY

Today's date: ____/____/____

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to do your usual activities.

Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms

These questions should be answered thinking of your knee symptoms during the **last week**.

S1. Do you have swelling in your knee?

Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐

S3. Does your knee catch or hang up when moving?

Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐

S4. Can you straighten your knee fully?

Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never ☐

S5. Can you bend your knee fully?

Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never ☐

Stiffness

The following questions concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

Pain

P1. How often do you experience knee pain?

Never	Monthly	Weekly	Daily	Always
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

What amount of knee pain have you experienced the **last week** during the following activities?

P2. Twisting/pivoting on your knee

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

P3. Straightening knee fully

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

P4. Bending knee fully

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

P5. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

P6. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

P7. At night while in bed

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

P8. Sitting or lying

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

P9. Standing upright

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A1. Descending stairs

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

A2. Ascending stairs

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A3. Rising from sitting

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

A4. Standing

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

A5. Bending to floor/pick up an object

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

A6. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

A7. Getting in/out of car

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

A8. Going shopping

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

A9. Putting on socks/stockings

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

A10. Rising from bed

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

A11. Taking off socks/stockings

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

A12. Lying in bed (turning over, maintaining knee position)

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

A13. Getting in/out of bath

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

A14. Sitting

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

A15. Getting on/off toilet

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

SP2. Running

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

SP3. Jumping

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

SP4. Twisting/pivoting on your injured knee

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

SP5. Kneeling

None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Quality of Life

Q1. How often are you aware of your knee problem?

Never	Monthly	Weekly	Daily	Constantly
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

Not at all	Mildly	Moderately	Severely	Totally
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Q3. How much are you troubled with lack of confidence in your knee?

Not at all	Mildly	Moderately	Severely	Extremely
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Q4. In general, how much difficulty do you have with your knee?

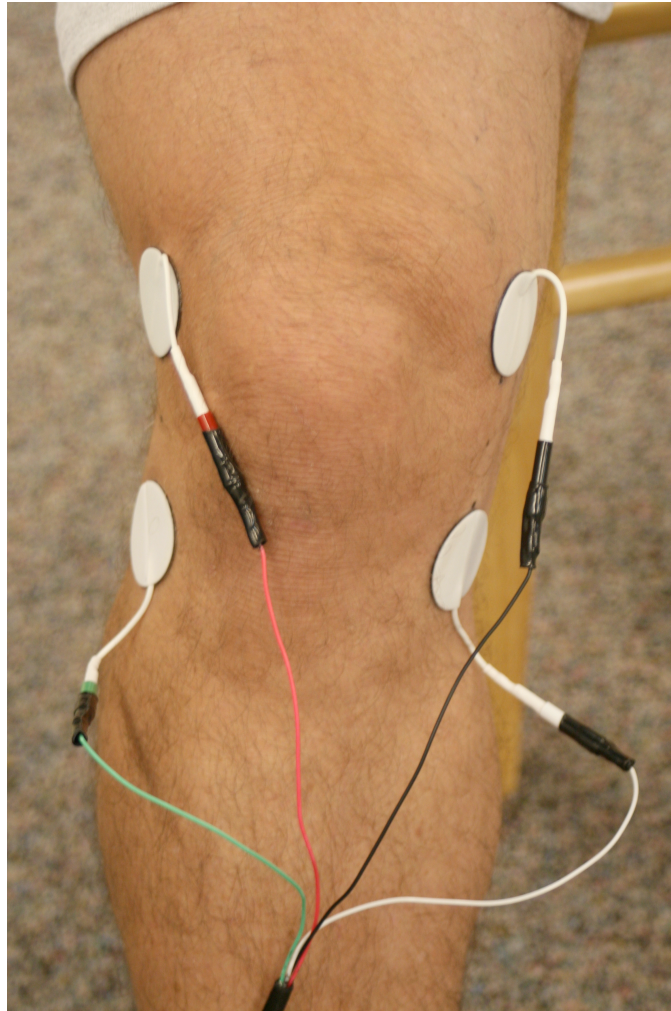
None	Mild	Moderate	Severe	Extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Thank you very much for completing all the questions in this questionnaire.

APPENDIX G: JPS NWB setup



APPENDIX H: Electrode placement about the knee for Study 1 and 2



APPENDIX I: IRB application – Gait/Postural Control study

Part A.1. Contact Information, Agreements, and Signatures

Date: 10/13/09

Title of Study: Electrical Stimulation to Improve Walking Biomechanics in Knee Osteoarthritis, IRB Study # 09-1516

Name and degrees of Principal Investigator: Amber Collins, MS

Department: Orthopaedics, Biomedical Engineering Mailing address/CB #: 134 Glaxo Bldg., CB# 7546, 101A Mason Farm Rd., Chapel Hill, NC 27599

UNC-CH PID: 701583613

Pager:

Phone #: 919-966-1212

Fax #: 919-966-3349

Email Address: amcollin@email.unc.edu

For trainee-led projects: ☐ undergraduate ☒ graduate ☐ postdoc ☐ resident ☐ other

Name of faculty advisor: Paul Weinhold, Ph.D.

Department: Orthopaedics, Biomedical Engineering

Mailing address/CB #: 134B Glaxo Bldg., CB# 7546, 101A Mason Farm Rd., Chapel Hill, NC 27599

Phone #: 919-966-9077

Fax #: 919-966-3349

Email Address: weinhold@med.unc.edu

Center, institute, or department in which research is based if other than department(s) listed above: Department of Exercise and Sports Science

Name of Project Manager or Study Coordinator (if any):

Department:

Mailing address/CB #:

Phone #:

Fax #:

Email Address:

List **all other project personnel** including co-investigators, and anyone else who has contact with subjects or identifiable data from subjects. **Include email address for each person who should receive electronic copies of IRB correspondence to PI:** Amber Collins (amcollin@email.unc.edu), Dr. Paul Weinhold (weinhold@med.unc.edu), Dr. Chris Olcott (colcott@med.unc.edu), Dr. J. Troy Blackburn, Dr. Doug Dirschl, Dr. Bing Yu, Dr. Joanne Jordan, Dr. Bikramjit Singh.

Name of funding source or sponsor (please do not abbreviate): UNC University Research Council Award & Arthritis Foundation.

☐ not funded ☐ Federal ☐ State ☐ industry ☒ foundation ☒ UNC-CH

☐ other (specify):

For industry sponsored research (if applicable):

Sponsor's master protocol version #:

Version date:

Investigator Brochure version #:

Version date:

Any other details you need documented on IRB approval:

RAMSeS proposal number (from Office of Sponsored Research): 08-2450

Principal Investigator: I will personally conduct or supervise this research study. I will ensure that this study is performed in compliance with all applicable laws, regulations and University policies regarding human subjects research. I will obtain IRB approval before making any changes or additions to the project. I will notify the IRB of any other changes in the information provided in this application. I will provide progress reports to the IRB at least annually, or as requested. I will report promptly to the IRB all unanticipated problems or serious adverse events involving risk to human subjects. I will follow the IRB approved consent process for all subjects. I will ensure that all collaborators, students and employees assisting in this research study are informed about these obligations. All information given in this form is accurate and complete.

Signature of Principal Investigator

Date

Faculty Advisor if PI is a Student or Trainee Investigator: I accept ultimate responsibility for ensuring that this study complies with all the obligations listed above for the PI.

Signature of Faculty Advisor

Date

Note: The following signature is not required for applications with a student PI.

Department or Division Chair, Center Director (or counterpart) of PI: (or Vice-Chair or Chair's designee if Chair is investigator or otherwise unable to review): I certify that this research is appropriate for this Principal Investigator, that the investigators are qualified to conduct the research, and that there are adequate resources (including financial, support and facilities) available. If my unit has a local review committee for pre-IRB review, this requirement has been satisfied. I support this application, and hereby submit it for further review.

Signature of Department Chair or designee

Date

Print Name of Department Chair or designee

Department

Part A.2. Summary Checklist *Are the following involved?*

	Yes	No
A.2.1. Existing data, research records, patient records, and/or human biological specimens?	<u>_X_</u>	<u>__</u>
A.2.2. Surveys, questionnaires, interviews, or focus groups with subjects?	<u>_X_</u>	<u>__</u>
A.2.3. Videotaping, audiotaping, filming of subjects, or analysis of existing tapes?	<u>__</u>	<u>_X_</u>
A.2.4. Do you plan to enroll subjects from these vulnerable or select populations: a. UNC-CH students or UNC-CH employees? b. Non-English-speaking? c. Decisionally impaired? d. Patients? e. Prisoners, others involuntarily detained or incarcerated, or parolees? f. Pregnant women? g. Minors (less than 18 years)? <i>If yes</i> , give age range: to years	<u>__</u> <u>__</u> <u>__</u> <u>_X_</u> <u>__</u> <u>__</u> <u>__</u>	<u>_X_</u> <u>_X_</u> <u>_X_</u> <u>__</u> <u>_X_</u> <u>_X_</u> <u>_X_</u>
A.2.5. a. Are sites outside UNC-CH engaged in the research? b. Is UNC-CH the sponsor or lead coordinating center for a multi-site study? <i>If yes</i> , include the Addendum for Multi-site Studies . <i>If yes</i> , will any of these sites be outside the United States ? <i>If yes</i> , is there a local ethics review committee agency with jurisdiction? (provide contact information)	<u>__</u> <u>__</u> <u>__</u> <u>__</u>	<u>_X_</u> <u>_X_</u> <u>__</u> <u>__</u>
A.2.6. Will this study use a data and safety monitoring board or committee? <i>If yes:</i> UNC-CH School of Medicine DSMB? (must apply separately) Lineberger Cancer Center DSMC? Other? Specify:	<u>__</u> <u>__</u> <u>__</u> <u>__</u>	<u>_X_</u> <u>__</u> <u>__</u> <u>__</u>
A.2.7. a. Are you collecting sensitive information such as sexual behavior, HIV status, recreational drug use, illegal behaviors, child/physical abuse, immigration status, etc? b. Do you plan to obtain a federal Certificate of Confidentiality for this study?	<u>__</u> <u>__</u>	<u>_X_</u> <u>_X_</u>
A.2.8. a. Investigational drugs? (provide IND #) b. Approved drugs for “non-FDA-approved” conditions? <i>All studies testing substances in humans must provide a letter of acknowledgement from the UNC Health Care Investigational Drug Service (IDS).</i>	<u>__</u> <u>__</u>	<u>_X_</u> <u>_X_</u>
A.2.9. Placebo(s)?	<u>__</u>	<u>_X_</u>
A.2.10. Investigational devices, instruments, machines, software? (provide IDE #)	<u>_X_</u>	<u>__</u>
A.2.11. Fetal tissue?	<u>__</u>	<u>_X_</u>
A.2.12. Genetic studies on subjects’ specimens?	<u>__</u>	<u>_X_</u>
A.2.13. Storage of subjects’ specimens for future research? <i>If yes, see instructions for Consent for Stored Samples.</i>	<u>__</u>	<u>_X_</u>
A.2.14. Diagnostic or therapeutic ionizing radiation, or radioactive isotopes, which subjects would not receive otherwise? <i>If yes, approval by the UNC-CH Radiation Safety Committee is required.</i>	<u>__</u>	<u>_X_</u>
A.2.15. Recombinant DNA or gene transfer to human subjects? <i>If yes, approval by the UNC-CH Institutional Biosafety Committee is required.</i>	<u>__</u>	<u>_X_</u>
A.2.16. Does this study involve UNC-CH cancer patients? <i>If yes, submit this application directly to the Oncology Protocol Review Committee.</i>	<u>__</u>	<u>_X_</u>
A.2.17. Will subjects be studied in the General Clinical Research Center (GCRC)? <i>If yes, obtain the GCRC Addendum from the GCRC and submit complete application (IRB application and Addendum) to the GCRC.</i>	<u>__</u>	<u>_X_</u>
A.2.18. Will gadolinium be administered as a contrast agent?	<u>..__</u>	<u>.._X_</u>

Part A.3. Conflict of Interest Questions and Certification

The following questions apply to **all investigators and study staff** engaged in the design, conduct, or reporting results of this project **and/or their immediate family members**. For these purposes, "family" includes the individual's spouse and dependent children. "Spouse" includes a person with whom one lives together in the same residence and with whom one shares responsibility for each other's welfare and shares financial obligations.

<p>A.3.1. Currently or during the term of this research study, does any member of the research team or his/her family member have or expect to have:</p> <p>(a) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with the sponsor of this study?</p> <p>(b) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with an entity that owns or has the right to commercialize a product, process or technology studied in this project?</p> <p>(c) A board membership of any kind or an executive position (paid or unpaid) with the sponsor of this study or with an entity that owns or has the right to commercialize a product, process or technology studied in this project?</p>	<p>___ yes</p> <p>___ yes</p> <p>___ yes</p>	<p><u>_x_</u> no</p> <p><u>_x_</u> no</p> <p><u>_x_</u> no</p>
<p>A.3.2. Has the University or has a University-related foundation received a cash or in-kind gift from the sponsor of this study for the use or benefit of any member of the research team?</p>	<p>___ yes</p>	<p><u>_x_</u> no</p>
<p>A.3.3. Has the University or has a University-related foundation received a cash or in-kind gift for the use or benefit of any member of the research team from an entity that owns or has the right to commercialize a product, process or technology studied in this project?</p>	<p>___ yes</p>	<p><u>_x_</u> no</p>

If the answer to ANY of the questions above is yes, the affected research team member(s) must complete and submit to the Office of the University Counsel the form accessible at <http://coi.unc.edu>. List name(s) of all research team members for whom any answer to the questions above is yes:

Certification by Principal Investigator: By submitting this IRB application, I (the PI) certify that the information provided above is true and accurate regarding my own circumstances, that I have inquired of every UNC-Chapel Hill employee or trainee who will be engaged in the design, conduct or reporting of results of this project as to the questions set out above, and that I have instructed any such person who has answered "yes" to any of these questions to complete and submit for approval a Conflict of Interest Evaluation Form. I understand that as Principal Investigator I am obligated to ensure that any potential conflicts of interest that exist in relation to my study are reported as required by University policy.

Signature of Principal Investigator

Date

Faculty Advisor if PI is a Student or Trainee Investigator: I accept ultimate responsibility for ensuring that the PI complies with the University's conflict of interest policies and procedures.

Signature of Faculty Advisor

Date

Part A.4. Questions Common to All Studies

For all questions, if the study involves only secondary data analysis, focus on your proposed design, methods and procedures, and not those of the original study that produced the data you plan to use.

A.4.1. Brief Summary. Provide a *brief* non-technical description of the study, which will be used in IRB documentation as a description of the study. Typical summaries are 50-100 words. *Please reply to each item below, retaining the subheading labels already in place, so that reviewers can readily identify the content.*

Purpose: The purpose of this study is to evaluate balance during a single-leg stance balance assessment and to evaluate ground reaction forces, knee biomechanics, and muscle activation patterns during walking in subjects with mild to moderate medial knee osteoarthritis (OA) with and without the application of electrical stimulation and a neoprene knee sleeve.

Participants: Fifty-two with radiological evidence of medial compartment knee osteoarthritis will be tested. Attempts will be made to recruit an even number of males and females for participation. Participant exclusion is detailed in the Inclusion/Exclusion criteria section below.

Procedures (methods): After the completion of the WOMAC and Self-Reported Measure of Instability questionnaires, subjects will have then threshold to detection of electrical stimulation determined. Subjects will then conduct a balance performance assessment in a single-leg stance during the following three conditions NE/NS (no electrical stimulation/no sleeve), NE/S (no electrical stimulation/sleeve), and E/S (electrical stimulation/sleeve). Three different electrical stimulation levels will be tested. These three levels will be percentages (75%, 100%, and 150%) of the subject's threshold of detection and will be determined prior to the balance assessment. This will be followed by a gait analysis while subjects walk at a predetermined speed during the same three conditions. Only one stimulation level will be used during gait analysis and will be determined as the level at which the subject's balance performance is best. Knee biomechanics, muscle activation patterns and ground reaction forces will be recorded during walking with both the balance performance test and gait analysis repeated multiple times for each testing condition.

A.4.2. Purpose and Rationale. Provide a summary of the background information, state the research question(s), and tell why the study is needed. If a complete rationale and literature review are in an accompanying grant application or other type of proposal, only provide a brief summary here. If there is no proposal, provide a more extensive rationale and literature review, including references.

Osteoarthritis is the most common joint disorder in the United States with osteoarthritis of the knee being the most debilitating. The exact cause of the disorder is unknown, but it is thought to result from a combination of several factors such as age, excessive weight, joint injury, and joint stress. Several studies have shown that osteoarthritic patients in comparison to age-matched controls have abnormal balance as well as abnormal biomechanics and muscle co-activation of the quadriceps and hamstrings muscles during walking. The abnormal biomechanics and heightened muscle co-activation result in improper loading of the joint which can cause abnormal wear and may initiate or accelerate the progression of osteoarthritis. If abnormal biomechanics and muscle co-activation contribute to osteoarthritis, then a possible means to slow the progression of the disease may be through a principle known as stochastic resonance. Stochastic resonance is a phenomenon in which low levels of random noise stimulation (electrical/mechanical) have been shown to enhance the detection and transmission of weak signals in sensory systems such as muscle spindles or skin sensory receptors.

The research question we wish to answer is whether the application of low-level electrical stimulation applied at the knee in combination with a neoprene knee sleeve can improve balance, knee biomechanics and muscle co-activation of the quadriceps and hamstrings significantly in patients with mild to moderate medial compartment knee osteoarthritis. We want to determine whether these improvements are superior to a control condition (NE/NS) and any improvement seen by solely wearing a neoprene sleeve (NE/S) over the knee. This study is needed in order to determine whether the application of electrical stimulation could serve as a therapeutic tool for patients with osteoarthritis of the knee.

A.4.3. Subjects. *You should describe the subject population even if your study does not involve direct interaction (e.g., existing records).* Specify number, gender, ethnicity, race, and age. Specify whether subjects are healthy volunteers or patients. If patients, specify any relevant disease or condition and indicate how potential subjects will be identified.

This study will be composed of fifty-two patients with mild to moderate medial compartment knee osteoarthritis (OA). Attempts will be made to recruit twenty-six males and twenty-six females in order to achieve an adequate gender spread. We will also attempt to recruit subjects of various ethnic backgrounds. Subjects will be included if they are greater than 40 years of age. A diagnosis of mild to moderate medial compartment knee OA will be made by a UNC orthopaedist upon grading standing radiographs in the anterior-posterior view with the knee in full extension. We will also attempt to recruit the same subjects who participated in our previous study, "Electrical Stimulation to Improve Proprioception in Knee Osteoarthritis" (Study # 08-0664).

A.4.4. Inclusion/exclusion criteria. List required characteristics of potential subjects, and those that preclude enrollment or involvement of subjects or their data. Justify exclusion of any group, especially by criteria based on gender, ethnicity, race, or age. If pregnant women are excluded, or if women who become pregnant are withdrawn, specific justification must be provided.

The inclusion criteria for study participants are as follows:

5. Have a physician diagnosis of knee OA
6. Show radiologic evidence of moderate knee OA in the medial compartment. (Kellgren/Lawrence [K/L] grade of 1, 2, or 3; Kellgren & Lawrence 1957)
7. Subjects will also be required to have a smaller interbone distance at the narrowest point of the medial compartment compared with the lateral compartment.
8. Patients are older than 40 years.

The exclusion criteria for study participants are as follows:

13. Any neurologic condition.
14. Pregnancy. Pregnant women have increased laxity in the joints which can cause proprioceptive deficits and this study aims to focus on proprioceptive deficits specific to the OA condition alone.
15. Use of a pacemaker, other implantable electronic device, or external catheter.
16. Musculoskeletal disease or joint replacement in the lower extremities other than knee OA
17. Diagnosis of gout, rheumatoid or other system inflammatory arthritis, obesity (BMI>35)
18. Unable to walk without an assistive device
19. Steroid injection in the knee in the last 3 months
20. Knee flexion range of motion less than 5-120 degrees
21. History of cardiac arrhythmia. .
22. Inability to perform requested tasks because of their medical condition

A.4.5. Full description of the study design, methods and procedures. Describe the research study. Discuss the study design; study procedures; sequential description of what subjects will be asked to do; assignment of subjects to various arms of the study if applicable; doses; frequency and route of administration of medication and other medical treatment if applicable; how data are to be collected (questionnaire, interview, focus group or specific procedure such as physical examination, venipuncture, etc.). Include information on who will collect data, who will conduct procedures or measurements. Indicate the number and duration of contacts with each subject; outcome measurements; and follow-up procedures. If the study involves medical treatment, distinguish standard care procedures from those that are research. If the study is a clinical trial involving patients as subjects and use of placebo control is involved, provide justification for the use of placebo controls.

Fifty-two patients with mild to moderate, medial compartment knee OA will be recruited for this study from the patients of the Department of Orthopaedics at UNC. Dr. Olcott will put in a request to UNC Physicians and Associates to generate a list of patients with a billing code of knee OA. In this listing he will request that they also include the medical record number of the patient. Using the medical record number of the listing, Dr. Olcott or the orthopaedic resident, Dr. Bikramjit Singh, will use the PACS system to review digital standing AP radiographs, which were taken as part of the patient's standard care, of the patients affected knee to determine if they have the proper disease severity in the medial compartment (Kellgren/Lawrence [K/L] grade of 1, 2, or 3; Kellgren & Lawrence 1957). Dr. Olcott, the resident or Amber Collins will then use this shortened list of patients that meet the disease severity criteria to review the patient's medical information in WEBCIS to identify those patients that also meet the rest of the exclusion/inclusion criteria. Once these potential subjects have been identified from this review, this patient list (name and phone number) will be distributed to Amber Collins so that she can contact these patients by phone to determine their interest in participating in the study. We will also attempt to recruit subjects that have participated in our previous study, "Electrical Stimulation to Improve Proprioception in Knee Osteoarthritis" (study # 08-0664).

If the patient is interested in participating in the study, they will be asked a series of questions to again determine if they qualify to enroll in the study based on the inclusion/exclusion criteria. If the patient is not interested in participating in the study, their contact information will be destroyed by shredding hardcopy documents and deleting contact information from spreadsheet digital files listing potential subjects. For the subjects interested in participating in the study, a meeting will be scheduled with Amber Collins to enroll the subject, conduct the balance performance tests and gait analysis, and complete the questionnaires.

Subjects will also be recruited through a flyer which is posted in the Orthopaedic clinic. This flyer has been approved for use in study #08-0664. When patients respond to the flyer, they will be asked a series of questions by Amber Collins in order to determine whether they qualify. If they qualify, their name and age will then be forwarded to the orthopaedic resident and Dr. Olcott who will examine the patient's standing radiographs. If the patient meets all of the exclusion criteria, they will be scheduled for testing. If, on the other hand, they must be excluded, their information will be shredded.

After the patient has been recruited and scheduled, they will be tested. When the subject arrives Amber Collins will provide a brief overview of the procedures involved with the testing and will then ask the subject to fill out the informed consent form. After completing the consent form, subjects will complete a questionnaire which contains questions about the subject's age, weight, gender, height, and knee range of motion. Subjects will also complete the WOMAC (Western Ontario and McMaster Universities) Osteoarthritis Index questionnaire and a Self-Reported Measure of Instability which asks questions regarding their current level of pain, stiffness, and functionality of the osteoarthritic knee. Subjects will then have their body fat percentage measured using a bioelectric impedance analyzer. Electrodes will be placed on the subject's right wrist and right ankle and a nondetectable, low amplitude current will be sent through the body. This procedure has been utilized numerous times in various studies and has been shown to be a safe and noninvasive method for determining body composition. The piece of equipment that will be used is the Valhalla Scientific Medical Body Composition Analyzer, model 1990B, and is currently on the market for use with this application.

At the beginning of the testing session the electrical stimulus level will be progressively increased to determine the subject's threshold of detection and this current level will be recorded. Electrical stimulation will be applied with an electrical stimulator device (Afferent Corporation, Providence, RI) by a pair of self-adhesive surface electrodes (Model Platinum 03-053T, Scrip) placed 2cm above the joint line and another pair placed 2cm below the joint line on the medial and lateral aspects of the knee. These electrodes will remain in place during all testing conditions. Stimulation will consist of a Gaussian white noise signal (zero mean, s.d. = 0.05mA, 0-1000 Hz bandwidth). During the balance assessment, the exact amplitude will be percentages of the subject's threshold to detection. To isolate the electrical current, the signals will be passed through a current-controlled stimulus isolator with a 1 mA/V conversion (Model 2200, A-M Systems). Electrodes will not be reused between subjects.

Preamplified surface electromyography (EMG) electrodes will be placed over the vastus lateralis (VL), vastus medialis (VM), lateral hamstrings (LH), and medial hamstrings (MH) muscles to assess muscle activity. The EMG signals obtained during subsequent gait analysis will be normalized to the mean peak EMG signal in the control condition.

Subjects will have their balance, muscle activity, and gait analyzed under the following three conditions:

5. No electrical stimulation/No sleeve (NE/NS)
6. No electrical stimulation/Sleeve (NE/S)
7. Electrical stimulation/Sleeve (E/S)*

*3 different stimulation levels will be used during the balance assessment and will be determined as percentages (75%, 100%, and 150%) of the subject's threshold to detection of electrical stimulation. During gait analysis only one of the three stimulation levels will be used (75%).

The sequence of the conditions will be assigned in the following manner: control1 (NE/NS), counterbalance design of the 2 conditions (NE/S, E/S), control2 (NE/NS). A repeated-measures design will be used to compare the conditions within subjects. Based on subject's average threshold of detection (125 μ A) from our previous study (IRB# 08-0664) and the fact that the highest level we will apply will be 150% of subject's threshold, we anticipate the highest current we will use in this study to be approximately 188 μ A.

Immediately prior to the evaluation of gait parameters during a walking test, subject's balance will be assessed. Subjects will maintain their balance on a single leg (affected knee) while standing barefoot on a force plate up to 15 seconds with eyes open with a steady forward focus. A U-shaped wooden frame that is waist high will be positioned to surround each subject during the balance assessment in order to provide support in case the subject becomes unbalanced. Unless necessary, the subject will be instructed not to touch the frame, but instead place their hands on their hips while performing the single-leg stance.

Following the balance assessment, subject's gait will be analyzed while walking along a 10-meter walkway at a predetermined speed making sure to land with their test limb on a non-conductive force plate. Five valid trials will be collected per each of the testing conditions. The ground reaction forces and moments will be sampled via a non-conductive force plate (model 4060nc, Bertec Corp., Columbus, OH). The subject's kinematic data will be collected by two electromagnetic tracking sensors secured on the anteromedial shank and lateral thigh. Kinematic variables to be evaluated will include the peak knee flexion angle, peak extension angle, flexion/extension excursion, peak abduction angle, peak adduction angle, and abduction/adduction excursion.

A graduate student (Amber Collins) will perform all subject recruitment, testing, data collection, and data analysis as a part of the student's doctoral dissertation.

The test session will last approximately 2 hours. Follow up visits are not required.

A.4.6. Benefits to subjects and/or society. Describe any potential for direct benefit to individual subjects, as well as the benefit to society based on scientific knowledge to be gained; these should be clearly distinguished. Consider the nature, magnitude, and likelihood of any direct benefit to subjects. If there is no direct benefit to the individual subject, say so here and in the consent form (if there is a consent form). Do not list monetary payment or other compensation as a benefit.

There are no immediate direct benefits for knee OA patients involved in this study. However, scientific knowledge gained from the study may allow for the development of a brace or sleeve that incorporates electrical stimulation to be used as a therapy in OA patients to improve their knee biomechanics and muscle activation patterns. An improvement of knee biomechanics and muscle co-activation of the hamstrings and quadriceps in knee OA patients may decrease abnormal loading and wear of the knee. This, in turn could possibly slow the progression of the disease resulting in a reduction in pain while improving function.

A.4.7. Full description of risks and measures to minimize risks. Include risk of psychosocial harm (e.g., emotional distress, embarrassment, breach of confidentiality), economic harm (e.g., loss of employment or insurability, loss of professional standing or reputation, loss of standing within the community) and legal jeopardy (e.g., disclosure of illegal activity or negligence), as well as known side effects of study medication, if applicable, and risk of pain and physical injury. Describe what will be done to minimize these risks. Describe procedures for follow-up, when necessary, such as when subjects are found to be in need of medical or psychological referral. If there is no direct interaction with subjects, and risk is limited to breach of confidentiality (e.g., for existing data), state this.

As with any activity, there is a minor risk of muscle strain or joint pain while performing the balance assessment or gait analysis. Subjects will be asked to walk at a predetermined speed, but care will be taken to ensure the subject is comfortable with and able to walk at this speed safely. Subjects will also be allowed to rest and take breaks between trials. Subject identification will remain confidential.

A minimal risk of electrical shock is present in working with any electrical equipment. The body composition analyzer is designed to deliver safe and noninvasive current to the subject. The level of current will be nondetectable. The electrical stimulation system will be supplying currents at the level of the subject's threshold of detection and are at a harmless level. The stimulus-isolator of the electrical stimulation system has optically isolated outputs and the maximum current the output can deliver is \pm 5mA when set at its highest range. This current level is still at an intensity that is accepted to be harmless. The system is designed with a safety measure such that if the stimulus-isolator malfunctions and the output stimulus increases greater than the desired input stimulus, then the stimulus is automatically turned off. Additionally, the entire system administering the stimulation will be freestanding, battery powered and will not be connected to an outlet in order to ensure the stimulation delivered is not higher than desired.

It is possible that subjects may have an itchy feeling or tingling sensation at the electrodes during testing. If this occurs, the feeling will be temporary and will subside once the electrical current is no longer being administered. Subjects will experience no long-term discomfort as a result of the stimulation. It is also possible that subjects will experience the usual knee discomfort associated with their knee osteoarthritis during testing.

In the case of an unanticipated or adverse event either Dr. Chris Olcott (Tuesday and Thursdays; Pager #:216-2048) or Dr. Douglas Dirschl (Monday, Wednesday, and Friday; Pager #: 216-1902) who are both orthopaedic physicians will be able to be contacted for medical advice. In addition, a third year orthopaedic resident who is conducting a year of research, Dr. Bikramjit Singh (Pager#: 216-5854) will also be available to be contacted for medical advice at all times.

A.4.8. Data analysis. Tell how the qualitative and/or quantitative data will be analyzed. Explain how the sample size is sufficient to achieve the study aims. This might include a formal power calculation or explanation of why a small sample is sufficient (e.g., qualitative research, pilot studies).

The number of subjects was selected based on a pre-power analysis and indicated that an N of 52 subjects could detect a 20% difference between groups for a power of 0.8, alpha of 0.05, and standard deviation of 50% of the control mean. A two-way repeated measures analysis of variance will be conducted on all outcome measures.

A.4.9. Will you collect or receive any of the following identifiers? Does not apply to consent forms.

☐ No ☒ Yes *If yes, check all that apply:*

- s. ☒ Names
- t. ☒ Telephone numbers
- u. ☐ Any elements of dates (other than year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death. For ages over 89: all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 and older
- v. ☒ Any geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code
- w. ☐ Fax numbers
- x. ☐ Electronic mail addresses
- y. ☐ Social security numbers
- z. ☒ Medical record numbers
- aa. ☐ Health plan beneficiary numbers
- bb. ☐ Account numbers
- cc. ☐ Certificate/license numbers
- dd. ☐ Vehicle identifiers and serial numbers (VIN), including license plate numbers
- ee. ☐ Device identifiers and serial numbers (e.g., implanted medical device)
- ff. ☐ Web universal resource locators (URLs)
- gg. ☐ Internet protocol (IP) address numbers
- hh. ☐ Biometric identifiers, including finger and voice prints
- ii. ☐ Full face photographic images and any comparable images
- jj. ☐ Any other unique identifying number, code, or characteristic, other than dummy identifiers that are not derived from actual identifiers and for which the re-identification key is maintained by the health care provider and not disclosed to the researcher

A.4.10. Identifiers in research data. Are the identifiers in A.4.9 above linked or maintained with the research data?

☐ yes ☒ no

A.4.11. Confidentiality of the data. Describe procedures for maintaining confidentiality of the data you will collect or will receive. Describe how you will protect the data from access by those not authorized. How will data be transmitted among research personnel? Where relevant, discuss the potential for deductive disclosure (i.e., directly identifying subjects from a combination of indirect IDs).

The listing of knee OA subjects with their medical record number will be recorded in a spreadsheet in Dr. Olcott's locked office. Dr. Olcott will only share this information with the resident assisting with the project, Dr. Singh, as well as Paul Weinhold and Amber Collins. Dr. Olcott will provide the name, phone number, radiographic grade, and interbone distance measurements of potential subjects to Amber Collins who will then be contacting these individuals to determine their willingness to participate in the study. This information will be shared with Amber Collins by means of a digital spreadsheet file that is password protected. Potential subjects unwilling to participate in the study will be deleted from this file. The enrolled subject's name will be linked to a numbered identifier through a password protected spreadsheet which will be maintained by Amber Collins in a locked cabinet located in a locked laboratory office. Access to the enrolled subject's study information will only be given to members of the research team thru a password protected spreadsheet which include the subjects numbered identifier, but not their name.

A.4.12. Data sharing. With whom will *identifiable* (contains any of the 18 identifiers listed in question A.4.9 above) data be shared outside the immediate research team? For each, explain confidentiality measures. Include data use agreements, if any.

- ☒ No one
- ☐ Coordinating Center:
- ☐ Statisticians:

- ☐ Consultants:
- ☐ Other researchers:
- ☐ Registries:
- ☐ Sponsors:
- ☐ External labs for additional testing:
- ☐ Journals:
- ☐ Publicly available dataset:
- ☐ Other:

A.4.13. Data security for storage and transmission. Please check all that apply.

For electronic data:

- ☐ Secure network ☐ Password access ☐ Encryption
- ☐ Other (describe):
- ☒ Portable storage (e.g., laptop computer, flash drive)

Describe how data will be protected for any portable device:

Data contained on the portable device will be protected through the use of a password on each of the data containing files. The password will be required to access these files and only the study investigators will have access to this password. The portable storage device will remain in the possession of study investigators at all times.

For hardcopy data (including human biological specimens, CDs, tapes, etc.):

- ☐ Data de-identified by research team (stripped of the 18 identifiers listed in question A.4.9 above)
- ☒ Locked suite or office
- ☒ Locked cabinet
- ☒ Data coded by research team with a master list secured and kept separately
- ☐ Other (describe):

A.4.14. Post-study disposition of identifiable data or human biological materials. Describe your plans for disposition of data or human biological specimens that are identifiable in any way (directly or via indirect codes) once the study has ended. Describe your plan to destroy identifiers, if you will do so.

After completion of the study, hardcopy data will be stored for a period of 5 years. It will then be shredded after this period.

Part A.5. The Consent Process and Consent Documentation (including Waivers)

The standard consent process is for all subjects to sign a document containing all the elements of informed consent, as specified in the federal regulations. Some or all of the elements of consent, including signatures, may be altered or waived under certain circumstances.

- If you will obtain consent in any manner, complete **section A.5.1**.
- If you are obtaining consent, but requesting a waiver of the requirement for a signed consent document, complete **section A.5.2**.
- If you are requesting a waiver of any or all of the elements of consent, complete **section A.5.3**.
- If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a *limited waiver of HIPAA authorization*. This is addressed in section B.2.

You may need to complete more than one section. For example, if you are conducting a phone survey with verbal consent, complete sections A.5.1, A.5.2, and possibly A.5.3.

A.5.1. Describe the process of obtaining informed consent from subjects. If children will be enrolled as subjects, describe the provisions for obtaining parental permission and assent of the child. If decisionally impaired adults are to be enrolled, describe the provision for obtaining surrogate consent from a legally authorized representative (LAR). If non-English speaking people will be enrolled, explain how consent in the native language will be obtained. Address both written translation of the consent and the availability of oral interpretation. *After you have completed this part A.5.1, if you are not requesting a waiver of any type, you are done with Part A.5.; proceed to Part B.*

Children, decisionally impaired adults, and non-English speaking people will not be enrolled in this study. After potential subjects have been identified and contacted by phone, the investigators of the study will obtain informed consent from study subjects during the enrollment visit by providing a consent document detailing the study and all risks involved. Subjects will be asked to sign the consent document as evidence of their understanding of the study.

A.5.2. Justification for a waiver of written (i.e., signed) consent. *The default is for subjects to sign a written document that contains all the elements of informed consent.* Under limited circumstances, the requirement for a signed consent form may be waived by the IRB if either of the following is true.

Chose only one:

a. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., study topic is sensitive so that public knowledge of participation could be damaging). ☐ yes ☐ no

Explain.

b. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (e.g., phone survey). ☐ yes ☐ no

Explain.

If you checked "yes" to either (and you are not requesting a waiver in section A.5.3) consent must be obtained orally, by delivering a fact sheet, through an online consent form, or be incorporated into the survey itself. Include a copy of the consent script, fact sheet, online consent form, or incorporated document.

→ If you have justified a waiver of written (signed) consent (A.5.2), you should complete A.5.3 *only* if your consent process will not include all the other [elements of consent](#).

A.5.3. Justification for a full or partial waiver of consent. *The default is for subjects to give informed consent.* A waiver might be requested for research involving only existing data or human biological specimens (see also Part C). More rarely, it might be requested when the research design requires withholding some study details at the outset (e.g., behavioral research involving deception). In limited circumstances, parental permission may be waived. This section should also be completed for a waiver of HIPAA authorization if research involves Protected Health Information (PHI) subject to HIPAA regulation, such as patient records.

☒ Requesting **waiver of some elements** (specify; see SOP 28 on the IRB web site): 28.1.5 (Waiver of HIPAA authorization in order to review patient medical records initially to identify potential subjects and then contact them to recruit as subjects)

☐ Requesting **waiver of consent entirely**

If you check either of the boxes above, answer items a-f.. To justify a full waiver of the requirement for informed consent, you must be able to answer "yes" (or "not applicable" for question c) to items a-f. **Insert brief explanations that support your answers.**

a. Will the research involve no greater than minimal risk to subjects or to their privacy? ☒ yes ☐ no
The subjects will be performing tasks that they routinely perform during daily living activities. The electrical stimulation is at a subthreshold level and is harmless.

b. Is it true that the waiver will *not* adversely affect the rights and welfare of subjects? (*Consider the right of privacy and possible risk of breach of confidentiality in light of the information you wish to gather.*) ☒ yes ☐ no
The subject's medical records will only be reviewed by an orthopaedic physician (Dr. Chris Olcott), the resident assisting with the project, or Amber Collins. Only the subject's phone number, name, and knee OA disease severity grade will be given to the research team member (Amber Collins) that will be contacting the subject to recruit them for the study.

c. When applicable to your study, do you have plans to provide subjects with pertinent information after their participation is over? (e.g., *Will you provide details withheld during consent, or tell subjects if you found information with direct clinical relevance? This may be an uncommon scenario.*) ☐ yes ☒ not applicable
All other components of written consent will be acquired after the subject is recruited.

d. Would the research be impracticable without the waiver? (*If you checked "yes," explain how the requirement to obtain consent would make the research impracticable, e.g., are most of the subjects lost to follow-up or deceased?*). ☒ yes ☐ no
Without the waiver the research would be impractical as our recruiting process would be terribly inefficient in that we would have to contact many more people who do not meet the basic inclusion/exclusion criteria prior to finding potential subjects that do meet the criteria. In addition, we would need for the potential subjects to have an AP radiograph of their knee taken or for their current physician to allow us to access this information and the subject may still not qualify for enrollment in the study if they do not meet the radiographic knee OA disease criteria.

e. Is the risk to privacy reasonable in relation to benefits to be gained or the importance of the knowledge to be gained? ☒ yes ☐ no
The risk of privacy is minimal as only the patient's orthopaedic physician, the assisting resident, and Amber Collins will be reviewing the medical information. The knowledge gained from this study has the potential to be developed into a new therapy for slowing the progression of knee OA that could help millions of patients.

If you are accessing patient records for this research, you must also be able to answer "yes" to item f to justify a waiver of HIPAA authorization from the subjects.

f. Would the research be impracticable if you could not record (or use) Protected Health Information (PHI)? ☒ yes ☐ no
(*If you checked "yes," explain how not recording or using PHI would make the research impracticable.*)
Without the waiver the research would be impractical as our recruiting process would be terribly inefficient in that we would have to contact many more people who do not meet the basic inclusion/exclusion criteria prior to finding potential subjects that due meet the criteria. In addition, we

would need for the potential subjects to have an AP radiograph of their knee taken or for their current physician to allow us access to this information and the subject may still not qualify for enrollment in the study if they do not meet the radiographic knee OA disease criteria.

Part B. Questions for Studies that Involve Direct Interaction with Human Subjects
→ *If this does not apply to your study, do not submit this section.*

B.1. Methods of recruiting. Describe how and where subjects will be identified and recruited. Indicate who will do the recruiting, and tell how subjects will be contacted. Describe efforts to ensure equal access to participation among women and minorities. Describe how you will protect the privacy of potential subjects during recruitment. *For prospective subjects whose status (e.g., as patient or client), condition, or contact information is not publicly available (e.g., from a phone book or public web site), the initial contact should be made with legitimate knowledge of the subjects' circumstances. Ideally, the individual with such knowledge should seek prospective subjects' permission to release names to the PI for recruitment. Alternatively, the knowledgeable individual could provide information about the study, including contact information for the investigator, so that interested prospective subjects can contact the investigator.* Provide the IRB with a copy of any document or script that will be used to obtain the patients' permission for release of names or to introduce the study. Check with the IRB for further guidance.

Fifty-two patients with mild to moderate, medial compartment knee OA will be recruited for this study from the patients of the Department of Orthopaedics at UNC Chapel Hill. Dr. Olcott will put in a request to UNC Physicians and Associates to generate a list of his patients with a billing code of knee OA. In this listing he will request that they also include the medical record number of the patient. Using the medical record number of the listing, Dr. Olcott or the orthopaedic resident, Dr. Bikramjit Singh will use the PACS system to review digital standing AP radiographs, which were taken as part of the patient's standard care, of the patients affected knee to determine if they have the proper disease severity in the medial compartment (Kellgren/Lawrence [K/L] grade of 1, 2, or 3; Kellgren & Lawrence 1957). Dr. Olcott, the resident, or Amber Collins will then use this shortened list of patients that meet the disease severity criteria to review the patient's medical information in WEBCIS to identify those patients that also meet the rest of the exclusion/inclusion criteria (See section 4.4). Once these potential subjects have been identified from this review, this patient list (name and phone number) will be distributed to Amber Collins so that she can contact these patients by phone to determine their interest in participating in the study. This list will be distributed to Amber Collins by means of a password protected spreadsheet file.

If during the initial telephone call to contact the potential subject it is determined the person is interested in participating in the study and qualifies for enrollment, the subject will be scheduled for an enrollment/testing meeting where their written consent will be acquired. If the patient is not interested in participating in the study, their contact information will be destroyed by shredding hardcopy documents and deleting contact information from spreadsheet digital files listing potential subjects.

We are also planning to recruit subjects by posting a flyer in the Orthopaedic Clinic (refer to study # 08-0664) which has already been approved for use. Patients will call the number listed on the flyer (Amber Collins) and they will be asked a series of basic questions to ensure they meet the exclusion criteria. If they meet all the criteria, their name and age will be provided to the resident assisting with the project in order to look up the patient in the patient data base. Once the patient is found in the database, their standing radiographs will be analyzed by the resident and Dr. Olcott to further determine if the patients qualify for the study.

We are planning that half of the enrolled subjects will be women in order to have equal representation of this gender. We will attempt to enroll subjects from all minorities.

B.2. Protected Health Information (PHI). If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a *limited waiver of HIPAA authorization*. If this applies to your study, please provide the following information.

- a. Under this limited waiver, you are allowed to access and use only the minimum amount of PHI necessary to review eligibility criteria and contact potential subjects. What information are you planning to collect for this purpose?

The patients' medical record will be reviewed to confirm that they meet the following inclusion and exclusion criteria.

The inclusion criteria for study participants are as follows:

1. Have a physician diagnosis of knee OA
2. Show radiologic evidence of moderate knee OA in the medial tibial-femoral compartment based on a standing Anterior-Posterior radiograph. (Kellgren/Lawrence [K/L] grade of 1, 2, or 3; Kellgren & Lawrence 1957)
3. Subjects will also be required to have a smaller interbone distance at the narrowest point of the medial compartment compared with the lateral compartment.
4. Patients are older than 40 years.

The exclusion criteria for study participants are as follows:

11. Have any neurologic condition.
12. Pregnancy. Pregnant women have increased laxity in the joints which can cause proprioceptive deficits and this study aims to focus on proprioceptive deficits specific to the OA condition alone.
13. Use of a pacemaker, other implantable electronic device, or external catheter

14. Musculoskeletal disease or joint replacement in the lower extremities other than knee OA
15. Diagnosis of gout, rheumatoid or other system inflammatory arthritis, obesity (BMI>35)
16. Unable to walk without an assistive device
17. Steroid injection in the knee in the last 3 months
18. Knee flexion range of motion less than 5-120 degrees
19. History of cardiac arrhythmia.
20. Inability to perform requested tasks because of their medical condition

b. How will confidentiality/privacy be protected prior to ascertaining desire to participate?

A listing of potential subjects for the study that are patients of Dr. Olcott will be generated where the listing will include the subjects' medical record #. This listing will be kept in a password-protected spreadsheet file in Dr. Olcott's locked office. Dr. Olcott, the resident assisting with the project and Amber Collins will review the subject's medical information to determine if they fulfill the inclusion/exclusion criteria. A new listing will be generated of the patients that fulfill the criteria and this listing (name and phone #) will be distributed to Amber Collins who will then contact the patients to determine their willingness to participate in the study. This new listing will be kept in a password-protected spreadsheet file in Amber Collins' office in a locked-laboratory.

Additionally, patients who respond to the posted flyer will be screened for participation in the study. If they qualify, their information will be kept in a password-protected spreadsheet file in Amber Collins' office in a locked laboratory. If the patient does not qualify for participation, their information will be shredded.

c. When and how will you destroy the contact information if an individual declines participation?

Patients who decline to participate in the study will be deleted from the spreadsheet file listing of potential subjects and any hardcopies of their contact information will be shredded.

B.3. Duration of entire study and duration of an individual subject's participation, including follow-up evaluation if applicable. Include the number of required contacts and approximate duration of each contact.

The duration of each individual subject's participation is approximately 2 hours. Follow up evaluations are not required.

B.4. Where will the subjects be studied? Describe locations where subjects will be studied, both on and off the UNC-CH campus.

The subjects will be studied on the UNC-CH campus in the Sports Medicine Research Laboratory in Fetzer Gym, Room 06F

B.5. Privacy. Describe procedures that will ensure privacy of the subjects in this study. Examples include the setting for interviews, phone conversations, or physical examinations; communication methods or mailed materials (e.g., mailings should not indicate disease status or focus of study on the envelope).

Privacy of the subjects in this study will be ensured by procedures such as private communication via the phone. Testing materials will not be mailed and all communication prior to testing will be done over the phone. The balance assessment and gait analysis of the subjects will be carried out with no other individuals other than the research team in the laboratory.

B.6. Inducements for participation. Describe all inducements to participate, monetary or non-monetary. If monetary, specify the amount and schedule for payments and if/how this will be prorated if the subject withdraws (or is withdrawn) from the study prior to completing it. For compensation in foreign currency, provide a US\$ equivalent. Provide evidence that the amount is not coercive (e.g., describe purchasing power for foreign countries). Be aware that payment over a certain amount may require the collection of the subjects' Social Security Numbers. If a subject is paid more than \$40.00 at one time or cumulatively more than \$200.00 per year, collection of subjects' Social Security Number is required (University policy) using the Social Security Number collection consent addendum found under [forms on the IRB website](#) (look for Study Subject Reimbursement Form).

Subjects will be compensated for their participation in this study at a rate of \$100 for the entire testing session. If the subject fails to complete the testing session, they will be compensated in proportion to the percentage of the testing session that was completed.

B.7. Costs to be borne by subjects. Include child care, travel, parking, clinic fees, diagnostic and laboratory studies, drugs, devices, all professional fees, etc. If there are no costs to subjects other than their time to participate, indicate this.

There are no costs to the subject other than their time to participate.

Part C. Questions for Studies using Data, Records or Human Biological Specimens without Direct Contact with Subjects

→ ***If this does not apply to your study, do not submit this section.***

C.1. What records, data or human biological specimens will you be using? (check all that apply):

- ☒ Data already collected for another research study
- ☐ Data already collected for administrative purposes (e.g., Medicare data, hospital discharge data)
- ☒ Medical records (custodian may also require form, e.g., HD-974 if UNC-Health Care System)

- ☐ Electronic information from clinical database (custodian may also require form)
- ☐ Patient specimens (tissues, blood, serum, surgical discards, etc.)
- ☐ Other (specify):

C.2. For each of the boxes checked in 1, how were the original data, records, or human biological specimens collected? Describe the process of data collection including consent, if applicable.

Data collected from a previous research study (IRB # 08-0664) will be referred to for statistical analysis purposes only. Data collection from this study can be viewed within the IRB application. Subjects gave their informed consent prior to completion of the study. The medical records of the patients of UNC Department of Orthopaedics were collected as part of their care in the UNC-Health Care System. Dr. Olcott will be reviewing these records to find subjects that meet the study inclusion and exclusion criteria.

C.3. For each of the boxes checked in 1, where do these data, records or human biological specimens currently reside?

The medical records that we wish to review reside in the PACS and WEBCIS systems for the Department of Orthopaedics of the UNC Health Care System.

C.4. For each of the boxes checked in 1, from whom do you have permission to use the data, records or human biological specimens? Include data use agreements, if required by the custodian of data that are not publicly available.

Dr. Olcott is a physician in the UNC Orthopaedic Clinic where the subjects are receiving care and he, the assisting resident, and Amber Collins will be reviewing the medical records information. We will complete whatever custodian forms the UNC Health Care System requires to perform this review.

C.5. If the research involves human biological specimens, has the purpose for which they were collected been met before removal of any excess? For example, has the pathologist in charge or the clinical laboratory director certified that the original clinical purpose has been satisfied? Explain if necessary.

☐ yes ☐ no ☐ not applicable (explain)

C.6. Do all of these data records or specimens exist at the time of this application? If not, explain how prospective data collection will occur.

☒ yes ☐ no If no, explain

APPENDIX J: Subject consent form – Gait/Postural Control study

University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Adult Subjects
Biomedical Form

IRB Study # 09-1516

Consent Form Version Date: _____

Title of Study: Electrical Stimulation to Improve Walking Biomechanics in Knee Osteoarthritis

Principal Investigator: Amber Collins

UNC-Chapel Hill Department: Orthopaedics

UNC-Chapel Hill Phone number: 919-966-1212

Email Address: amcollin@email.unc.edu

Co-Investigators: Dr. Paul Weinhold, Dr. Chris Olcott, Dr. J. Troy Blackburn, Dr. Doug Dirschl, Dr. Bing Yu, Dr. Joanne Jordan, Dr. Bikramjit Singh

Faculty Advisor: Dr. Paul Weinhold

Funding Source: Arthritis Foundation, UNC University Research Council Award

Study Contact telephone number: 919-966-1212

Study Contact email: amcollin@email.unc.edu

What are some general things you should know about research studies?

You are being asked to take part in a research study. To join the study is voluntary.

You may refuse to join, or you may withdraw your consent to be in the study, for any reason.

Research studies are designed to obtain new knowledge that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher, your health care provider, or the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

The purpose of this study is to evaluate balance during a single-leg stance balance assessment and to evaluate ground reaction forces, knee biomechanics, and muscle activation patterns during walking in subjects with mild to moderate medial knee osteoarthritis (OA). Osteoarthritis (OA) is the most common joint disorder throughout the United States, with OA of the knee being especially common and painful. The exact cause of osteoarthritis is not known, but it is thought that it may result from a combination of several factors such as age, excessive weight, joint injury, and improper loading of the joint. If a person is unable to position their knee properly (poor proprioception) during walking and other activities, this may expose the knee joint to higher levels of loading. This improper loading may cause abnormal wear of the joint and may accelerate the disease process of osteoarthritis. If poor positioning of the knee during daily activities contributes to osteoarthritis, then a possible means to slow the disease may be through a new type of low level electrical stimulation. This new type of low level electrical stimulation is believed to help a person in sensing the position of their knee during activities. This type of electrical stimulation has been applied at the knee in older adults to improve balance. The low level electrical stimulation is harmless and will be applied at three different levels. These three levels will be percentages (75%, 100% and 150%) of the level at which you can feel the stimulation. If you should sense the stimulation, it will merely feel like a slight itching or tingling sensation. In addition, safety precautions have been built into the stimulation system to prevent exposure to any harmful levels of stimulation if there should be any malfunction of the equipment.

The aims of the study are:

Aim 1: To determine whether knee kinetics, kinematics, and muscle activation patterns can be improved with electrical stimulation and wearing a neoprene sleeve.

Aim 2: To determine whether knee kinetics, kinematics, and muscle activation patterns can be improved by wearing a neoprene knee sleeve alone.

Aim 3: To determine whether electrical stimulation can improve kinetics, kinematics, and muscle activation patterns beyond that provided by the neoprene knee sleeve alone.

Aim 4: To determine whether the application of electrical stimulation in combination with a knee sleeve can improve balance.

You are being asked to be in the study because you are 40 years or older and have mild to moderate knee Osteoarthritis (OA) in the medial compartment of your knee as evaluated by your physician and indicated by the x-ray films of your knee.

Are there any reasons you should not be in this study?

You should not be in this study if:

23. You have any condition that affects your nerve tissues.
24. You are pregnant.
25. You have a pacemaker, other implantable electronic device, or tube implanted into your vein or body cavity.
26. You have a musculoskeletal disease or joint replacement in your legs other than knee OA.
27. You have a diagnosis of gout, rheumatoid or other systemic inflammatory arthritis, or a BMI>35.
28. You are unable to walk without an assistive device.
29. You have had a steroid injection in your osteoarthritic knee in the last 3 months.
30. Your knee flexion range of motion is less than 5-120 degrees. (We will evaluate this during your testing session).
31. You have a history of cardiac arrhythmia.
32. You are unable to perform the requested tasks because of your medical condition.

How many people will take part in this study?

If you decide to be in this study, you will be one of approximately 52 people in this research study.

How long will your part in this study last?

Your participation in this study will last approximately 2 hours. Only one test session is necessary, follow-up visits are not required.

What will happen if you take part in the study?

During your testing session, the following will occur:

First, the investigator will collect information about your height, weight and age in the form of a written questionnaire. Next, you will complete a questionnaire about your functional activity and knee pain. Finally, you will answer a questionnaire about any knee instability you experience during daily activities. For the questionnaires, you may choose not to answer a question for any reason; however we may not be able to include you in the study if you do not answer all the questions. Before testing begins, your body fat percentage will be measured by having several electrodes placed on your right hand and right foot while a low amplitude, nondetectable current is delivered to your body. This method has been proven to be safe and will not harm you.

During the testing session you will be required to perform several different tasks multiple times. First, your threshold of detection of the electrical stimulation will be evaluated. We will use this value to determine the percentage levels that will be used during testing. Following this, surface electrodes will be placed over specific muscles of your leg to assess your muscle activity during testing.

Your balance will then be assessed during a single-leg stance in the following three conditions:

1. No electrical stimulation/No sleeve (NE/NS)
2. No electrical stimulation/Sleeve (NE/S)
3. Electrical stimulation/Sleeve (E/S)

These conditions will be presented to you in random order during the study. You will be asked to maintain your balance on a single leg (leg with affected knee) while standing barefoot on a force plate for up to 15 seconds with your eyes open and a steady forward focus. You will be positioned on the force plate with a wooden U-shaped frame surrounding you in order to prevent falling. Your balance performance will be assessed multiple times with and without electrical stimulation and a neoprene knee sleeve. Three levels of stimulation will be used during the balance assessment and will be determined as percentages of your threshold of detection (75%, 100% and 150%).

Following the balance performance assessment, you will be asked to perform a series of 5 walking trials during each of the same three conditions (NE/NS no stimulation/no sleeve, NE/S no stimulation/sleeve, E/S stimulation/sleeve). Only one of the three stimulation levels will be used during the walking trials. We will place two sensors on your lower limb: one will be placed on your shin and the other will be placed on your thigh. You will be asked to walk at a predetermined speed down a 10 meter walkway during each trial. Each trial will be performed five times for each of the three conditions.

Similar to flipping a coin the sequence of the test conditions used will be assigned to you randomly. In addition, you will not be told (Blinded) when you are receiving the electrical stimulation. During each trial, the investigator will set up the equipment according to which condition you are to complete.

Each task will be shown to you by the investigator. You will be given a chance to practice the task before the testing begins and you will be given a chance to rest as needed during these tasks.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. You will not benefit personally from being in this research study. The results of this study could lead to the development of a new brace that could provide electrical stimulation so that it might be used to slow the disease progression of knee OA and improve function.

What are the possible risks or discomforts involved with being in this study?

As with any physical activity, there is a minor risk of muscle strain or joint pain in your knee while performing the tasks in this study. We are asking you to perform tasks that you may have never performed. Although they are not difficult, there is always a risk of injury. We cannot guarantee that you will not incur an injury from your participation in this study. Each task will be demonstrated for you so that you may see the level of difficulty. It is also possible that you may experience your usual amount of discomfort associated with your knee osteoarthritis during the study.

A minimal risk of electrical shock is present in working with any electrical equipment. The body composition analyzer is designed to deliver safe and noninvasive levels of current. These levels are nondetectable and will not harm you. The electrical stimulation system supplies electrical currents that are at a harmless level. Each electrical stimulating device is built with safety measures and is battery-powered so that it is only able to provide electrical currents at harmless levels. Safety measures are in place to prevent you from being stimulated at higher electricity levels than intended. If by chance there is an increase in electrical output, the safety measures will detect the rise and the machine will cut off before the electricity is passed onto you.

It is possible that you may have an itchy feeling or tingling sensation at the electrodes during testing. If this occurs, the feeling will be temporary and will subside once the electrical current is no longer being administered. You will not experience any long-term discomfort as a result of the stimulation.

In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to the researchers.

What if we learn about new findings or information during the study?

If any subjects prior to your testing session experience an unanticipated event during their testing session we will provide you with this new information prior to you participating in the study.

How will your privacy and confidentiality be protected?

Neither your name nor other personal information will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

In order to assure the confidentiality of your personal medical information only your physician, the orthopaedic resident assisting him, Paul Weinhold, and Amber Collins will be allowed to review your personal medical information and this will only be done to assess if you qualify to participate in the study. Only your name, phone number, information about the X-rays films of your osteoarthritic knee, and your qualification status for the study will be provided by the physician and resident to the other investigators. Initially, your name will be coded with a number and this information will be stored in a separate password-protected file and computer in a locked office. In order to assure the confidentiality of your data, additional data collected during the study will only be saved with your numeric code and your name will not appear. The additional data collected during the study will be saved with your numeric code on a separate password-protected spreadsheet file on a computer in a locked office. No one other than the study investigators Chris Olcott, Paul Weinhold, Amber Collins, Troy Blackburn, Joanne Jordan, Doug Dirschl, Bikramjit Singh and Bing Yu will have access to the computer, the password, the files or the numeric code that identifies your data.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. However, by signing this form, you do not give up any of your legal rights.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Will you receive anything for being in this study?

You will be receiving \$100 in the form of a check for taking part in this study. You will receive this at the end of the testing session. If you do not complete the entire testing sequence your payment will be in proportion to the amount of the study you complete.

Will it cost you anything to be in this study?

It will not cost you anything to participate in this study.

What if you are a UNC student?

You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

What if you are a UNC employee?

Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

Who is sponsoring this study?

This study is funded by the Arthritis Foundation and is partially funded by the UNC University Research Council. This means that the research team is being funded by the sponsors for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

What if you have questions about your rights as a research subject?

All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Title of Study: Electrical Stimulation to Improve Walking Biomechanics in Knee Osteoarthritis

Principal Investigator: Amber Collins

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time and have had them satisfactorily answered. I voluntarily agree to participate in this research study.

Signature of Research Subject

Date

Printed Name of Research Subject

Signature of Person Obtaining Consent

Date

Printed Name of Person Obtaining Consent

APPENDIX K: HIPAA Authorization form-Gait/Postural Control study

University of North Carolina-Chapel Hill

HIPAA Authorization for Use and Disclosure of Health Information for Research Purposes

IRB Study # 09-1516

Title of Study: Electrical Stimulation to Improve Walking Biomechanics in Knee Osteoarthritis

Principal Investigator: Amber Collins

Mailing Address for UNC-Chapel Hill Department: UNC Orthopaedic Research Labs, 134 Glaxo Bldg., CB# 7546, 101A Mason Farm Rd., Chapel Hill, NC 27599

This is a permission called a "HIPAA authorization." It is required by the "Health Insurance Portability and Accountability Act of 1996" (known as "HIPAA") in order for us to get information from your medical records or health insurance records to use in this research study.

1. If you sign this HIPAA authorization form, you are giving your permission for the following people or groups to give the researchers certain information (described in #2 below) about you:

Any health care providers or health care professionals or health plans that have provided health services, treatment, or payment for you such as physicians, clinics, hospitals, home health agencies, diagnostics centers, laboratories, treatment or surgical centers, including but not limited to the UNC Health Care System.

2. If you sign this HIPAA authorization form, this is the health information about you that the people or groups listed in #1 may give to the researchers to use in this research study:

33. Musculoskeletal: Medical records will be reviewed for evidence of musculoskeletal disease or joint replacement in the lower extremities other than knee OA. Records will be reviewed for any diagnosis of gout, rheumatoid or other system inflammatory arthritis. Radiographs of the knees will be examined to grade the severity of knee osteoarthritis.

Subject's Initials: _____

34. Neurologic: Medical records will be reviewed for any diagnosis or evidence of a neurologic condition that may influence their sensory perception.

Subject's Initials: _____

3. The HIPAA protections that apply to your medical records will not apply to your information when it is in the research study records. Your information in the research study records may also be shared with, used by or seen by the sponsor of the research study, the sponsor's representatives, officials of the IRB, and certain employees of the university or government agencies if needed to oversee the research study. HIPAA rules do not usually apply to those persons. The informed consent document describes the procedures in this research study that will be used to protect your personal information. You can also ask the researchers any questions about what they will do with your personal information and how they will protect your personal information in this research study.

4. If this research study creates medical information about you that will go into your medical record, you may not be able to see the research study information in your medical record until the entire research study is over.

5. If you want to participate in this research study, you must sign this HIPAA authorization form to allow the people or groups listed in #1 on this form to give access to the information about you that is listed in #2 on this form. If you do not want to sign this HIPAA authorization form, you cannot participate in this research study. However, not signing the authorization form will not change your right to treatment, payment, enrollment or eligibility for medical services outside of this research study.

6. This HIPAA authorization will stop when the results of this study are submitted for publication.

7. You have the right to stop this HIPAA authorization at any time. HIPAA rules are that if you want to stop this HIPAA authorization, you must do that in writing. You may give your written stop of this HIPAA authorization directly to Principal Investigator or researcher or you may mail it to the department mailing address listed at the top of this form, or you may give it to one of the researchers in this study and tell the researcher to send it to any person or group the researcher has given a copy of this HIPAA authorization. Stopping this HIPAA authorization will not stop information sharing that has already happened.

8. You will be given a copy of this signed HIPAA authorization.

Signature of Research Subject

Date

Print Name of Research Subject

For Personal Representative of the Research Participant (if applicable)

Print Name of Personal Representative: _____
Please explain your authority to act on behalf of this Research Subject:

I am giving this permission by signing this HIPAA Authorization on behalf of the Research Participant.

Signature of Personal Representative

Date