ELECTRICAL STIMULATION TO IMPROVE PROPRIOCEPTION IN THE NORMAL KNEE

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ABSTRACT

Amber Collins: Electrical Stimulation to Improve Proprioception in the Normal Knee
(Under the direction of Paul Weinhold)

Proprioception is the conscious and unconscious perception of joint position and movement in space. Deficits in knee proprioception are known to occur after specific knee injuries and may increase the risk of acute knee injury. These deficits have also been shown to have a role in the progression of knee osteoarthritis. Stochastic resonance electrical stimulation may be a novel way of improving knee proprioception by increasing the output of sensory systems. This study was designed to demonstrate whether any differences exist in proprioception in the normal knee when subject to the combination of subthreshold electrical stimulation and a neoprene knee sleeve. We found that joint position sense was best during the sleeve/stimulation condition in the partial weight bearing task and best during the sleeve/no stimulation condition in the nonweight bearing task. These results are promising for future applications of subthreshold electrical stimulation therapy in osteoarthritis patients.

To my husband and family whose love, endless encouragement, and support made this

possible.

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LIST OF ABBREVIATIONS AND SYMBOLS

CNS   Central Nervous System

-E/-S   No Electrical Stimulation and No Sleeve

+E/-S Electrical Stimulation and No Sleeve

-E/+S No Electrical Stimulation and Sleeve

+E/+S Electrical Stimulation and Sleeve

FWB   Full Weight Bearing

ICC   Intraclass Correlation Coefficient

IRB   Institutional Review Board

IPRC   Injury Prevention Research Center

JPS   Joint Position Sense

MCL   Motor Control Lab

NWB   Non Weight Bearing

mA   milliamp

µA   microAmp

PES   Pulsed Electrical Stimulation

PWB   Partial Weight Bearing

OA   Osteoarthritis

SNR   Signal-to-Noise Ratio

1. Introduction

1.1 Osteoarthritis

It is estimated that by the year 2030, 20 percent of Americans--about 70 million people--will have passed their 65th birthday, and will be at risk for osteoarthritis. Osteoarthritis (OA) is the most common joint disorder throughout the United States, with OA of the knee being especially common and debilitating. 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 joint stress. A study by Felson et al.[1] stated that men whose jobs required knee bending and at least medium physical demands had higher rates of knee OA (43.4%) versus those men whose jobs required neither (26.8%). Several studies have shown that OA 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[2-5]. A study by Sharma et al.[4] looked at proprioception in patients who were affected by OA in only one knee and compared it to the contralateral unaffected knee. They found proprioceptive deficits in the contralateral knee of equivalent magnitude to that of the affected limb, which suggests a role for impaired proprioception in the development of OA. Abnormal proprioception may result in impairment of neuromuscular responses which can expose joints to improper loading during the gait cycle. This improper loading may cause abnormal wear of the joint and may initiate or accelerate the disease process 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 cutaneous sensory receptors[6]. The concept of stochastic resonance has been applied clinically at the knee with success in improving balance control in older adults[7]. While this particular study did not directly measure knee proprioception, it did suggest the potential for electrical noise stimulation to improve knee joint proprioception, as previous studies have demonstrated a correlation between balance ability and knee joint proprioception in older adults[8].

In considering the use of noise stimulation for improving knee proprioception, a practical consideration is how the electrical stimulation will be applied. A simple means of applying the stimulation electrodes would undoubtedly be by incorporating them into a soft or hard knee brace. As studies have documented the ability of braces or sleeves to improve joint proprioception, an additional question this study attempted to answer was if electrical stimulation can improve proprioception beyond the tactile stimulation provided by a brace alone[9-12]. This research idea can be explored in different patient populations, one of which is previously described, OA patients. With success in improving the proprioception of OA patients, electrical stimulation could be used to slow the progression of the many other diseases and injuries affected by proprioceptive deficits or possibly prevent their onset in people susceptible to these diseases or prone to injury. Examples of this may include improving balance in stroke patients, reducing the occurrence of ulcers in diabetic patients by improving their loading patterns through enhanced proprioception, improving joint loading after total joint replacement by improving proprioception, and reducing joint degeneration

after intraarticular fracture by improving proprioception and facilitating more effective joint loading.

The elderly population could potentially benefit from this research idea as well. Balance, which is linked to proprioception, is altered in elderly people and this can lead to falls. Previous studies have looked at stimulation to improve balance in the elderly and diabetic patients but there has been no research which looks at the use of electrical stimulation to specifically improve proprioception in these populations[7, 13, 14].

1.2 Importance of Testing in Normals

Before looking for proprioceptive improvements with electrical stimulation in OA patients for which recruitment efforts would be more complex, we believed it would be most worthwhile to conduct initial work in normal uninjured subjects. This was done in order to evaluate the ability of electrical stimulation to improve proprioception as compared to other methods (knee brace or sleeve) that are known to improve proprioception in normals and in populations with proprioceptive deficits. Proprioception in nondiseased subjects is assumed normal, and therefore, any improvements seen in normal subjects who are not afflicted with proprioceptive deficits may be assumed to be more substantial in a patient population whose proprioception is abnormal such as OA patients. By successfully showing an improvement in proprioception in normal subjects, we believed this would better demonstrate the potential for utilizing this method in a number of clinical populations with proprioceptive deficits including the OA patient population that we wish to target next.

It is our hope that the success of this project will lead to the evaluation of the method of subthreshold electrical stimulation to improve proprioception in the clinical populations mentioned previously.

1.3 Specific Aims and Hypothesis

The objective of this project is to evaluate proprioception in the normal knee under various combinations of sleeve and electrical stimulation conditions.

AIM 1: To determine whether random subthreshold electrical stimulation applied at the normal knee will improve proprioception. Previous studies have examined the effects of stimulation in improving balance in the elderly and diabetic patients but have not yet looked at improving proprioception through subthreshold electrical stimulation.

Hypothesis 1: We hypothesize that proprioception will be more accurate during the sleeve/stimulation condition compared to the no sleeve/no stimulation control condition.

AIM 2: To determine whether the application of electrical stimulation improves proprioception beyond that seen by a neoprene knee sleeve alone.

Hypothesis 2: We hypothesize that proprioception will improve with the application of electrical stimulation and sleeve beyond the improvement seen with the sleeve alone.

AIM 3: To characterize how improvements in proprioception with the combinations of sleeve/no sleeve and stimulation/no stimulation conditions differ with a partial weight bearing and a nonweight bearing task.

Hypothesis 3.1: We hypothesize that proprioception will be more accurate during the sleeve/stimulation condition than the no sleeve/no stimulation control condition in the partial weight bearing task

Hypothesis 3.2: We also hypothesize that proprioception will be more accurate during the sleeve/no stimulation condition than the no sleeve/no stimulation control condition in the nonweight bearing task.

2. Background

2.1 The Cycle of Osteoarthritis

Osteoarthritis is the most common form of arthritis and it affects millions of people in the United States. Since the prevalence of this disease increases with age, it is becoming more and more important to find solutions as the baby boomer generation grows older. The exact mechanism by which age predisposes individuals to osteoarthritis is unclear. It is speculated that biochemical changes in aging cartilage make it more susceptible to damage and degradation[15]. The specific cause of Osteoarthritis (OA) is not known but it is thought to be caused by a combination of biomechanical and biochemical factors. The amount of research performed to determine the causes continues to grow. Currently, possible causes include genetics, dietary intake, low bone density, obesity, muscle weakness, and joint laxity among others. Additionally, some cases of OA have arisen from joint injury. All of these risk factors are especially important in weight bearing joints, particularly the knee. Of particular importance to the onset and progression of OA is the concept of proprioception, the process of presenting the central nervous system with data relating to joint position, force, and motion. These data are processed at conscious and unconscious levels in order to initiate motor responses. OA leads to altered proprioception, which may lead to abnormal joint wear, causing disease progression. In one study which examined whether proprioception is worse in the arthritic knee versus the contralateral unaffected knee, Sharma et al. discuss potential directions in the relationship between impaired proprioception and knee osteoarthritis[4]. One of the theories is that proprioceptive impairment present in a knee with

established OA may have contributed to and/or resulted from the disease itself. They

speculate that disruption of components located along the afferent pathways may lead to

repetitive, abnormal loading across the articular surface of the knee which would result in

OA. Alternatively, impairment of knee joint position sense might result from the

pathological changes that arise from OA such as the destruction or disturbance of capsule,

ligament, muscle, and tendon mechanoreceptor function. In summary, there are two main

pathways which are illustrated in figure 1: A. OA results from proprioceptive deficits or B.

Proprioceptive deficits result from the pathological factors of the disease. Pathological

factors are likely to exert their effects in knee OA progression by affecting the material

properties of the knee and thus changing the ability to bear load.

(Pathway A)

Poor spatial and temporal coordination of limb position and muscle activity ⟶ Increased load

Impaired knee proprioception

Knee OA

Loss or abnormal function of mechanoreceptors

Capsule, ligament, and muscle pathology

(Pathway B)
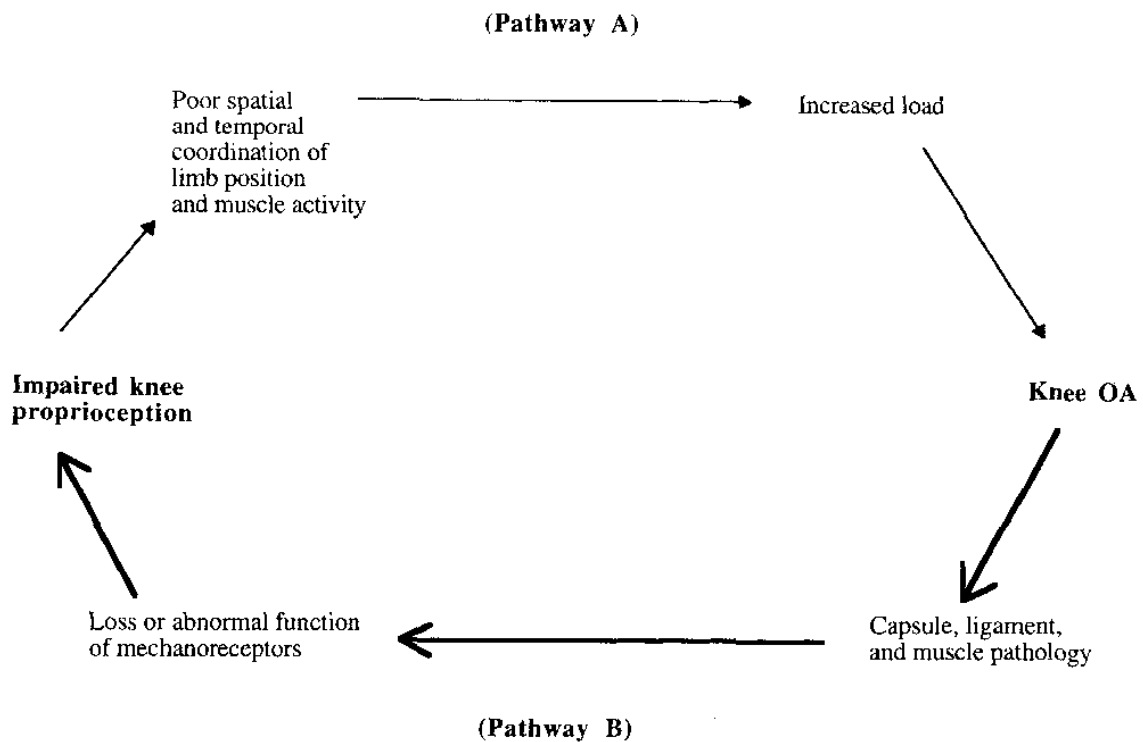
Figure 1. The osteoarthritis cycle theory [4]

Ultimately, OA diseases are manifested by morphologic, biochemical, molecular, and

biomechanical changes of both cells and matrix which lead to softening, fibrillation, and loss

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of articular cartilage. Although biomechanical factors are likely to contribute to the pathogenesis of knee OA, their exact mechanism of altering joint morphology is not known. Studies have shown a strong significant association between both the degree of foot rotation during gait and the line of progression and the magnitude of knee adduction moment [16, 17]. Further studies involving knee adduction moment are required to better understand the biomechanical pathogenesis of OA.

When clinically pronounced, OA is characterized by joint pain, tenderness, limitation of movement, crepitus, and variable degrees of inflammation. The thought that OA may result from proprioceptive deficits is a clinically relevant idea, because treatment of the proprioceptive impairment may result in a disease-modifying effect rather than simply treating the symptoms of the condition. Thus, the electrical stimulation method being investigated in this thesis for its ability to improve proprioception has the potential to be a disease-modifying treatment for OA. While this research does not focus on OA specifically, it does set out to determine if improvements in proprioception can be made at the normal knee with the stochastic resonance electrical stimulation technique.

2.2 Functional Anatomy of the Knee

Before beginning a discussion regarding proprioception of the knee and possible mechanisms of action of electrical stimulation, it is important to review the functional anatomy of the knee.
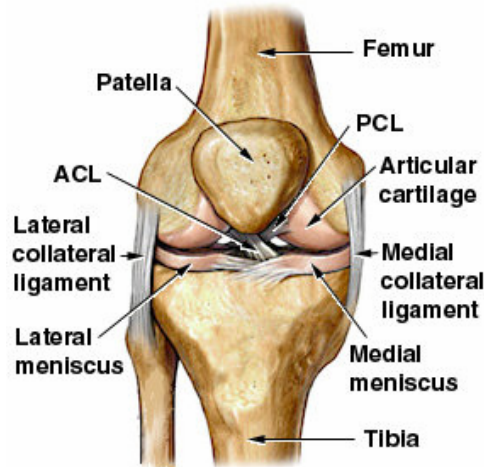
Figure 2. Anatomy of the knee (frontal view)[18]

The knee is made up of four joints: patellofemoral (where the femur connects with the knee cap), tibio fibular (where the tibia connects with the fibula), lateral tibio femoral, and medial tibio femoral. Bones of these joints are held in place primarily by passive restraints, or ligaments. The joints themselves are further supported by dynamic restraints, or muscles. Located between the femur and the tibia are the menisci (pads of cartilage) which serve to absorb shock transmitted from the bones upon impact. The knee moves primarily in extension and flexion with slight secondary movements of translation and rotation. Knee flexion and extension are achieved through contributions of several major muscle groups spanning the joint. The quadriceps muscle group on the anterior portion of the upper leg helps to straighten the knee from a bent position while the hamstring muscle group located at the posterior of the upper leg work to bend the knee from extension to flexion. Below the patella are two important muscles, the gastrocnemius and soleus which are responsible for foot extension during walking.

2.3 Proprioception and Sensory Processing

It is important to understand the basics of sensory information processing when dealing with the concept of proprioception. Limb position and movement are the products of multisite sensory input which is received and processed by the central nervous system (CNS). The CNS receives information from three main systems: somatosensory, vestibular, and the visual systems. This research is geared primarily towards somatosensation which is often referred to as proprioception. The somatosensory system's main function is to process information regarding touch, pressure, joint displacement, and movement. In addition to detecting postural sway, the somatosensory system has been suggested to trigger coordination of postural responses through neuromuscular pathways that are organized with mechanoreceptors of various types [19]. Feedback from the system is thought to allow adjustment of motor programs during tasks such as walking on irregular ground. Peripheral afferents such as those sensory receptors contained in muscle, skin or in the joints, visual receptors, and vestibular receptors provide the central nervous system with information regarding their environmental conditions.

2.3.1 Important Sensory Receptors

Knowledge of position, both static and dynamic, depends on knowing the degrees of angulation of all joints in all planes and their rates of change. Therefore, multiple types of receptors, including skin tactile receptors and deep tissue receptors, help to determine joint angulation and are used in combination to determine joint position sense [20]. While it has long been debated as to whether cutaneous, joint, or muscle receptors are most important to the maintenance of balance, contemporary belief is that all receptors contribute. Specifically, this paper will discuss receptors found both cutaneously and in the structures of the knee

joint which include: Pacinian corpuscles, Golgi joint receptors, Golgi tendon receptors, Ruffini endings, and muscle spindles.

Pacinian corpuscles detect pressure changes and they function to communicate information with the brain about limb movement. The pacinian corpuscles are fast adapting mechanoreceptors, which means they are very sensitive to small deformations caused by pressure and 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 they are fast adapting. 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.

However, unlike pacinian corpuscles, Ruffini endings are slow adapting which means they may detect changes in tissue stresses and strains as well as continue to signal for prolonged periods of time. In addition, Ruffini endings register both static and dynamic factors. Both Pacinian corpuscles and Ruffini endings are found cutaneously as well as in the ligaments, joint capsule and menisci.

Golgi receptors are found 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 slow adapting and 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 [20]. 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[6]. Additionally, the information that emerges from the muscle spindle is not perceived by the sensory cortex, thus showing its role in the subconscious regulation of motion.

Cutaneous (skin) afferents are also thought to contribute somewhat to joint proprioception, but joint and muscle afferents are thought to have a much greater affect on proprioception. One possible explanation for this is that the cutaneous afferents play more of a role during the NWB task than they do during the PWB task where functional proprioception is determined by joint and muscle afferents. This idea will be discussed in more detail in section 2.6 which discusses the role of the neoprene knee sleeve.

2.3.2 Vestibular and Vision

The vestibular and vision systems also play a role in maintaining the body's awareness of position and movement. The orientation of a person's eyes and head relative to their surroundings contribute to body awareness. One study tested the visual threshold for perception of sway during standing in humans and found that the eyes were the only contributing modality, demonstrating that visual input provides a sensitive means of perceiving sway [21]. The vestibular system supplies information to the CNS regarding

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gravitational, linear, and angular accelerations of the head relative to surrounding space [19].

Once received by the central nervous system, the information is processed and motor control

arises by way of spinal reflexes and information is transferred directly to specific muscle

groups which contract accordingly to generate body movement.   Visual input is not relevant

to this study as the use of a blindfold during all testing eliminates their contributions.   The

use of headphones works to eliminate any auditory cues which would allow the subject to

determine their relative position. Despite the use of headphones, there are other parts of the

vestibular system which could contribute to detection of position sense.

2.4 Techniques to Measure Proprioception

2.4.1 Measuring Proprioception

Proprioception is divided into two categories and is traditionally measured by analyzing

one of the two: the sense of static position (joint position sense) which is used in this study

and the sense of dynamic motion (kinesthesia). Kinesthesia is determined by looking at the

threshold to detection of passive motion, while joint position sense is measured by looking at

the reproduction of specific joint angles. Both are measured in terms of angles, with large

variations existing with each approach. Because of the amount of variation with each

technique, comparison between studies is difficult. Presently, there are a variety of different

ways to measure proprioception, but no consensus has been reached as to the best method. A

study by Beynnon et al. compared joint kinesthesia and joint position sense as methods to

measure knee proprioception[22].   Joint kinesthesia is typically measured by passive motion

of the knee by the investigator at a fixed rate. With this method, the subject's legs are

supported by an external device while they sit in a chair. Visual observation of the legs is

eliminated and the test leg is slowly flexed at a fixed rate. The measurement taken is the

magnitude of flexion (or extension) that the leg has moved when the subject detects motion

of that leg. Joint position sense, however, does not rely on detection of motion, but rather the

subject's ability to accurately reproduce predetermined joint angles. The joint position sense

technique most commonly used in the orthopaedic literature involves passively setting the

knee index angle with movement of the leg into extension from flexion followed by active

reproduction of the angle by the subject [22]. The difference in set index angle and

reproduced angle is measured. Differences in data analysis also exist and include the

measurement of real mean error or absolute mean error, where the absolute value of the real

error is taken.

2.4.2 Equipment Used to Measure Proprioception

Differences also exist in the equipment used to measure joint angles. Such equipment

includes flexometers, electromagnetic tracking systems, and electrogoniometers.

Flexometers such as the one seen in figure 3 utilize a gravity needle within the device to

determine degree of motion of major segments [23]. The instrument is fastened to the lateral

side of the upper leg (approximately 20 cm proximal to the knee joint) and the center of the

dial aligned with the tip of the greater trochanter of the femur. While the subject moves into

knee flexion, the movement of the gravity needle within the flexometer provides an estimate

about joint angulation.
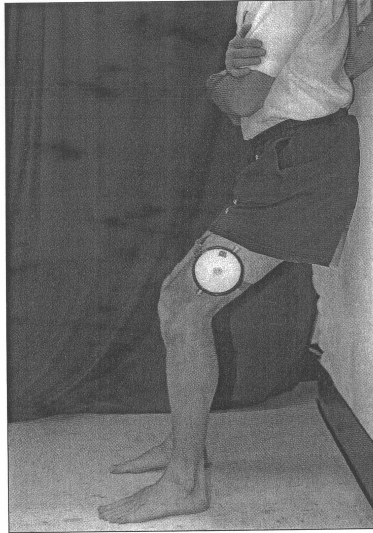
Figure 3. Knee Flexometer used in a partial weight bearing task

The electromagnetic tracking system is used to measure relative motion of limb segments in real time without requiring a line of sight.   While there may be benefits to using this system, its use was not feasible in this study as the metal of the PWB setup would interfere with the electromagnetic tracking system causing it to work improperly.

Electrogoniometers are designed in various forms. One form involves two adherent pieces, one that adheres to the femur and the other that adheres to the tibia along the limb line and are connected by a spring which contains a strain gauge (see figure 4).

Figure 4. One elecrogoniometer configuration which measures joint angle with the strain gauge located in the connecting spring

While this setup would prevent problems due to constant removal and placement of the electrogoniometer between sleeve conditions, it was not used in this study because of the

interference with the neoprene sleeve, as the sleeve would interfere with joint angle measurements by the spring if the sleeve were to be placed on top of the electrogoniometer. This study instead utilizes an electrogoniometer with a potentiometer center piece and two linkages that are placed along the femur and tibial lines. The apparatus lies on top of the neoprene sleeve once it is applied and is rigid enough that the sleeve does not affect its ability to accurately measure joint angles (see Figure 12).

2.4.3 Real and Absolute Error Measurements

Additionally, the method of data analysis can vary. Some studies compare real errors, while others compare absolute errors. While real error calculations consider both direction and magnitude, absolute errors consider only magnitude because the absolute value of the real error is taken, and the concept of overshooting or undershooting target angles is not relevant. The error term variations are what provide information about the precision of angle reproduction, and this precision can be described in terms of error standard deviations. Several approaches have been used to match the target angle: active matching with the same leg, active matching with the contralateral leg, representation of the perceived angle on a visual analogue model, active tracking with the contralateral limb, and passive matching with the same leg in which case the subject indicates when they have reached the index angle by depressing a switch or providing verbal cues[2, 3, 9-12, 24-27].

As a result of differences in experimental techniques and methods of data analysis, it is difficult to compare joint position sense across various studies. One study by Beynnon et al. tested several combinations of joint position sense techniques and analyzed both the real and absolute error measurements[22]. They found that while the use of real error scores may

provide precise and repeatable results, this analysis technique may fail to find differences that exist when the absolute error score is used instead.

2.5 Non-weight bearing vs. Weight-bearing

Another concern for investigators is whether their desired method of proprioception measurement should be performed under non weight-bearing or weight-bearing conditions. Researchers in recent years have begun to increasingly recommend weight bearing over nonweight bearing tasks during joint position sense testing[25]. The argument is that weight bearing tasks involve more cutaneous, muscular and articular mechanoreceptors than the alternative nonweight bearing tasks. Several studies have looked at the significance of weight bearing during static and dynamic joint position sense testing [24-26]. However, most studies will also evaluate the nonweight bearing task because some lower limb functions such as the swing phase of walking are nonweight bearing [24, 26]. One study by Stillman et al found position sense to be significantly more accurate in the weight bearing task than in the nonweight bearing [26]. This particular study found a significant difference in the accuracy of angular repositioning between weight bearing and nonweight bearing with less deviation from the predetermined angle during the weight bearing task. One possible explanation is that while bearing weight, muscular and articular proprioceptors within the joint itself provide feedback regarding position and motion unlike the nonweight bearing task, where cutaneous receptors play the major role with interjoint receptors having little to no affect on proprioception. Specifically, Golgi tendon organs are excited due to muscle activation and receptors in the articular cartilage and menisci are excited by joint compression.

Additionally, some studies prefer to test in a full weight bearing (FWB) position rather than in a PWB position because of the increased accuracy of joint position sense. A study by Bullock-Saxton set out to identify the influence of age on knee joint position sense accuracy and compare this accuracy during full and partial weight bearing conditions [25]. Subjects were divided into three age groups and it was determined that subjects in all three groups performed better in the full weight bearing (FWB) than in the partial weight bearing (PWB). While a FWB condition may have produced more accurate results than the partial weight bearing condition, we elected to utilize the PWB condition in our study because patient populations that may be tested in the future may experience less pain in the PWB condition.

2.6 Active vs. Passive Knee Positioning

Various approaches to the assessment of joint position sense have been used which include the degree of joint loading, how the subject indicates knowledge of the position, initial joint movement to the target angle, and lastly how the joint is repositioned (active or passive). Each of these approaches could influence the degree of sensory input provided when the subject is required to make a judgment about joint position sense. Many experiments involving joint position sense have used NWB conditions and reproduction of a passively attained index angle. Additionally, functional weight bearing tests in which active reproduction of an actively attained criterion angle have also been used to determine joint position sense. A study by Beynnon et al. tested seven different joint position sense techniques for knee flexion and extension in four different groups of subjects [22]. The seven different techniques were combinations of passive or active positioning into flexion or extension followed by analog representation, and active flexion or extension in either seated

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or standing subject position. The investigators found that the combination of passive positioning from flexion into extension followed by active extension while seated was the most accurate and repeatable.

It is thought that with active reproduction increased motor units are recruited causing increased activation of the muscle spindles, thereby possibly enhancing joint position acuity further. As a result, this study will utilize active reproduction of both an actively produced criterion angle (PWB) and a passively produced criterion angle (NWB).

2.7 Knee Sleeve

An additional component of this study is determining the effect of wearing a neoprene knee sleeve on proprioception, as numerous studies have shown proprioception improves through its use [9-12, 27, 28]. One study in particular demonstrated an improvement in joint position sense in the active, nonweight bearing task, but not in the active, weight bearing task when wearing a knee sleeve [10]. These results agreed with those from a previous study by Birmingham and may be related to an increase in muscle activity and joint compression resulting from increased signals of sensory receptors demonstrated during weight bearing activities [27]. It is likely that improved proprioception during weight bearing results more from deep tissue receptors as they contribute a greater percentage of overall proprioceptive input during weight bearing than NWB. Most of the current research focuses on the ability of knee braces to improve proprioception in the anterior cruciate deficient or impaired knee. Studies have suggested that the true benefits of knee functional braces are not through biomechanical reinforcement but rather through proprioceptive enhancement[11, 12, 27].

2.8 Stochastic Resonance

Stochastic resonance is an idea in which nonlinear system responses to weak input signals are optimized with the presence of a specific non-zero level of noise(mechanical or electrical). It is thought to work by altering the transmembrane potential of neurons, causing a depolarization of the cell. This depolarization lowers the threshold, making it more likely that an action potential will result. Somatosensation is responsible for providing feedback regarding position and movement and deficits in somatosensation can lead to postural instability. Recently, the idea of stochastic resonance has been tested as a means of enhancing somatosensory function. In a study by Cordo, muscle-spindle receptor sensitivity to weak movement signals was enhanced by the introduction of noise through the tendon of the parent muscle [6]. The idea of enhanced somatosensory function through the use of stochastic resonance has been tested in various subject populations including diabetics, stroke patients, the elderly, patients with Parkinson's disease, and patients with functional ankle instability[7, 13, 29, 30].

Priplata et al. found that postural sway was reduced with the application of mechanical noise in stroke, diabetic and elderly subjects (figure 5). They also reported that higher levels of baseline postural sway were correlated with greater improvements in balance control with the applied noise [13]. A study by Ross et al. concluded that stochastic resonance stimulation might be an alternative therapy for functionally instable ankles since this stimulation may improve dynamic stability quicker than coordination training alone [29]. Haas, on the other hand, found no significant improvements in leg proprioception with the application of random whole body vibration (average frequency 6 Hz +/- 1 Hz) [30].
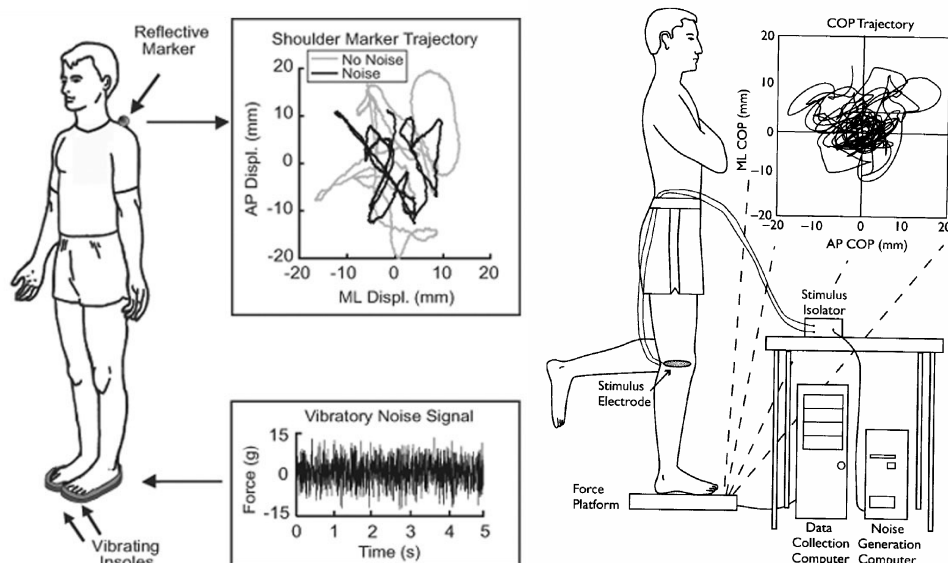
Figure 5. The reduction of postural sway with the application of a vibratory noise signal in a study by Priplata et al. investigating diabetic and elderly patients (left)[13]. Gravelle et al. investigated stochastic electrical stimulation applied at the knee (right)[7].

Additionally, Gravelle et al. investigated the effects of stochastic electrical stimulation signals specifically applied at the knee and found a reduction in center of pressure trajectory [7]. Specifically, the medial-lateral and anterior-posterior centers of pressure were reduced.

A reasonable question may be how stochastic resonance works to improve balance since balanced is linked with proprioception. The relationship of balance and proprioception is that balance involves both proprioception (afferent) and a motor output (efferent) component. Reduced sway is believed to be due to enhanced proprioception which could be due to stochastic resonance. Stochastic resonance is thought to cause small changes in receptor transmembrane potentials which depolarize the nerve cells, bringing them closer to threshold and making it more likely than an action potential will result. A study by Collins et al. found increased cutaneous detection of subthreshold indentation while subthreshold vibration was applied [31]. In this study, indentations were made to the tip of each subject's right middle digit and each subject was presented with subthreshold stimulus plus noise or no

stimulus plus noise. The subjects were instructed to indicate when they detected the stimulus. The investigators quantified the percentage of trials for which a subject correctly identified the presentation of stimulus or no stimulus and this was taken as *% correct*. The dashed line in Figure 6 indicates a significance level which shows that up to a certain input noise level, accuracy of detection is significant but then significance is lost if excessive noise is applied.
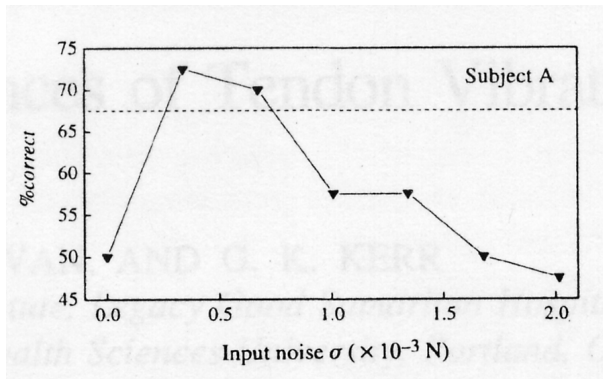
Figure 6. Increased cutaneous detection with the application of subthreshold noise. [31]

Another study by Cordo et al. supports this concept by showing increased relative muscle spindle output with the application of subthreshold tendon vibration [6].
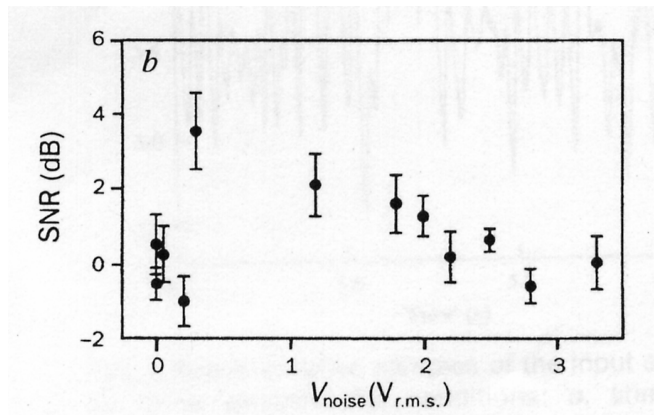
Figure 7. Increased relative muscle spindle output with the application of subthreshold tendon vibration. [6]

The investigators of this study recorded the firing activity of individual muscle-spindle afferents from both the wrist and hand extensor muscles from the radial nerve in healthy human subjects. Random noise was applied by a tendon stimulator to stretch the muscle. Noise intensity was varied between trials. The signal-to-noise ratio (SNR) was calculated and defined as the ratio of the strength (area) of the signal peak to the mean amplitude of the background noise at the specific input noise frequency. The output signal-to-noise assesses the coherence of the system response. Figure 7 indicates that as input noise intensity increased, the output SNR rapidly increased to a peak and then slowly decreased. Therefore, in the presence of a specific non-zero level of noise, the sensitivity of muscle spindle receptors to weak input signals is optimized.

Additionally, the exact placement of the electrodes which deliver the electrical stimulation is important. To date, no research has been done on the optimal placement of stimulus electrodes. However, acupuncture therapy as a treatment for symptomatic knee OA can be referenced for location of optimal treatment of pain. Three points around the knee joint were indicated as electroacupuncture points for indications of knee pain or motor impairment of the knee [32]. They are yanglinquan, yinlinquan, and dubi which are the inferior-lateral, inferior-medial, and superior-lateral areas of the knee joint, respectively. A fourth point, the superior-medial was added by the investigators to complete the paired orientation of the two electrode pairs.

2.8.1 Lasting Effects of Stochastic Resonance

While the immediate efficacy of stochastic resonance has been explored in multiple studies, there has not been an investigation into the potential long term effects of this therapy. By analyzing the results of specific subgroups of the subjects tested in this thesis study, we

hope to determine if there is any indication of sustained effects of the stimulation. Presumably, if there are lasting effects one would expect errors to decrease for the control condition when the control condition is later in the sequence of conditions presented to the subject.

2.8.2 Additional effects of Electrical Stimulation

In addition to improving proprioception, there may be other effects of this therapy. One study which used an electrically coupled knee brace looked at pulsed electrical stimulation (PES) to treat general knee OA [33]. Before beginning the 3 month study, the investigators looked at a 1 month randomized, double-blind, placebo-controlled trial which showed that a prototype device for delivering the PES to the knee improved symptomatic OA pain, physician global evaluation, and patient knee function assessment. Unfortunately, the precise method of action of PES in human knee OA has yet to be determined, but it is believed to be by way of influencing cartilage metabolism.

Electrical stimulation may also prove beneficial in other applications that suffer from abnormal proprioception besides OA. One study indicated Parkinson's patients suffered from proprioceptive deficits [30]. Additionally, patients who have had a total joint replacement as well as patients who have had intraarticular fracture may suffer from proprioceptive deficits if neurological pathways are affected. Also, one study demonstrated less accurate and less consistent knee joint position sense in people suffering from patellofemoral pain syndrome compared to control subjects [34]. There are many injured populations, including the ones previously mentioned, which could possibly benefit from electrical stimulation therapy.

2.9 Current Osteoarthritis Therapies

Currently, there are several options for treating osteoarthritis. Acetaminophen is the initial drug of choice for systemic treatment of symptomatic OA of the knee. Also, the use of topical analgesics is an option. Capsaicin cream or methylsalicylate are appropriate either together or as separate remedies. If pain does not subside with the above mentioned treatments, the use of nonsteroidal antiinflammatory drugs (NSAIDS) is an option. However, the use of NSAIDS can lead to gastric complications.

Other treatment options include physical therapy exercises and treatment programs, cortisone injections, and the most extreme option is total joint replacement [35, 36]. Additionally, acupuncture is a current symptomatic treatment for OA in Asian countries and increasingly in western countries [32]. Research into the mechanism of acupuncture pain relief has produced two widely accepted theories: 1. activation of the gate control system and 2. stimulation of the neurochemical release in the central nervous system. Acupuncture treatment has been shown to increase endorphin production which is why it is deemed an effective treatment for symptomatic OA.

While physical therapy programs have been shown to improve function and cortisone and acupuncture treat one of the disease symptoms by reducing pain, none of these options treat the disease itself. If abnormal loading of the knee joint is a key contributor to the progression of disease with OA, then improving proprioception through electrical stimulation may be an effective disease modifying therapy. If proprioception is improved, this may lead to more normal joint loading and less wear of the knee joint.

3. Research Design and Methods

3.1 Research Design Specific Aims and Hypothesis

The objective of this project is to evaluate proprioception in the normal knee under various combinations of sleeve and electrical stimulation conditions.

AIM 1: To determine whether random subthreshold electrical stimulation applied at the normal knee will improve proprioception. Previous studies have examined the effects of stimulation in improving balance in the elderly and diabetic patients but have not yet looked at improving proprioception through subthreshold electrical stimulation.

Hypothesis 1: We hypothesize that proprioception will be more accurate during the sleeve/stimulation condition compared to the no sleeve/no stimulation control condition.

AIM 2: To determine whether the application of electrical stimulation improves proprioception beyond that seen by a neoprene knee sleeve alone.

Hypothesis 2: We hypothesize that proprioception will improve with the application of electrical stimulation and sleeve beyond the improvement seen with the sleeve alone.

AIM 3: To characterize how improvements in proprioception with the combinations of sleeve/no sleeve and stimulation/no stimulation conditions differ with a partial weight bearing and a nonweight bearing task.

Hypothesis 3.1: We hypothesize that proprioception will be more accurate during the sleeve/stimulation condition than the no sleeve/no stimulation control condition in the partial weight bearing task.

Hypothesis 3.2: We also hypothesize that proprioception will be more accurate during the sleeve/no stimulation condition than the no sleeve/no stimulation control condition in the nonweight bearing task.

3.2 Institutional Review Board

This study was approved by The University of North Carolina at Chapel Hill's Institutional Review Board. An initial application for approval was submitted January 8, 2007 and was reviewed by the board February 5, 2007. After reviewing the application, the IRB stated there were a few minor contingencies to be addressed prior to full approval. These concerns were addressed, changes were made to the application and full approval was granted on February 26, 2007 with expiration set for February 26, 2008.

3.3. Subject Information

3.3.1. Recruitment

Subjects were recruited from the student body population at UNC Chapel Hill. Upon completion of a statistical power analysis, we determined that testing 24 subjects would be sufficient to yield an angle reproduction improvement of 30% with a standard deviation of the absolute error of angle reproduction of 50% of the mean. A power of 0.8 and significance level of 0.05 were used. Additionally, to allow for an unbiased investigation

with regard to gender, 12 males and 12 females were recruited for participation.   Before

beginning the study, four subjects were tested in order for the investigator to finalize the

equipment setup as well as steps for each task. The data acquired from these four "practice"

subjects was not used for any statistical calculations nor is it included in the results of this

study.

3.3.2. Exclusion Criteria

A mass email was sent out to the UNC Chapel Hill student body seeking participation of

subjects meeting the following criteria:

1. No history of functional instability of the knee joint
2. No current knee injuries or functional instability that limits knee function
3. Subjects were physically active (At least 1.5 hours/week of cardiovascular or resistance training).
4. Subjects were between the ages of 18-35 years old.
5. No signs or symptoms of knee injury (swelling, loss of function)
6. No known neurological conditions which may prevent the subject from sensing motion or feeling pain
7. No previous knee surgery
8. Subjects were required to not be pregnant
9. No history of cardiac arrhythmia
10. No history of gait or postural disorders, seizures, diabetes, fainting, peripheral neuropathy, stroke or motion sickness
11. Subjects were required to not have a cardiac pacemaker or drug delivery pump

Exclusion of subjects older than 35 years was necessary because of the amount of age-related

joint degeneration in a subject at this age. Even in a subject with no previous injuries, a

subject greater than 35 years of age may have a preexisting proprioceptive deficit without

their knowledge. This study focused on normal subjects with no proprioceptive deficits.

3.3.3. Study Questionnaire

Each subject was asked to complete a questionnaire prior to the start of the study (see

Appendix A) The questionnaire asked for age, gender, weight, height, dominant leg (R/L),

the amount of physical activity per week (in hours), as well as questions regarding the exclusion criteria previously mentioned. Collection of subject information such as age, weight, etc. allows the investigator to form further conclusions regarding proprioceptive acuity in relation to subject demographics. It also opens the door for future determinations about gender based differences in relation to similar studies.

3.4. Study Design

Subjects had their proprioception evaluated while performing both a partial weight bearing (PWB) and a nonweight bearing (NWB) task. A PWB task was used instead of a full weight bearing task, as during future studies with an OA population, the subjects may not tolerate full weight bearing because of knee pain. Testing was performed on the subject's dominant knee, where dominance was defined as the limb used to kick a soccer ball. During all tasks, the subject was either actively or passively moved to a target angle of 30 degrees for the "teaching" task. Upon reaching this position, the subject was asked to actively reproduce this angle. Similar studies have used target angles in the range of 20 to 40 degrees because this range simulates stance phase flexion during walking, and is reported to be strongly associated with proprioceptive feedback during normal walking [3]. To prevent any memorization effect of the target angle, a "dummy" 60 degree target angle was also incorporated into the PWB test sequences and a "dummy" 50 degree target angle was incorporated into the NWB test sequences using 3 different staging patterns yielding 24 testing sequences (see Table 2). Both proprioceptive tests were carried out under the following four conditions: no electrical stimulation/no sleeve, electrical stimulation/no sleeve, no electrical stimulation/sleeve, and electrical stimulation/sleeve. The sequence of the conditions was assigned to each subject

using a counterbalance design. Table 1 shows the 8 test sequences that were used for the

four conditions.

	A	B	C	D
1	+E/-S	-E/-S	-E/+S	+E/+S
2	-E/+S	+E/+S	-E/-S	+E/-S
3	-E/-S	+E/-S	+E/+S	-E/+S
4	+E/+S	-E/+S	+E/-S	-E/-S
5	+E/-S	-E/-S	+E/+S	-E/+S
6	+E/+S	-E/+S	-E/-S	+E/-S
7	-E/+S	+E/+S	+E/-S	-E/-S
8	-E/-S	+E/-S	-E/+S	+E/+S

Table 1. Listing of the 8 test sequences combining the 4 test conditions. A-D represent different stages of the test sequence. Note: +E=electrical stimulation, -E=no electrical stimulation, +S=sleeve on, -S=sleeve off

These sequences were designed to allow for the sleeve to remain on the subject once put in

place in order to minimize the times the sleeve was placed and removed. In addition, these

test sequences assured that each testing condition occurred with equal incidence at all stages

of the sequence (i.e. elimination of the potential for an order effect). Also, by

counterbalancing the sequences, any time or practice effects were minimized.

Sex	PWB/NWB	1st Task Sequence		A	B	C	D	E	F	2nd Task Sequence
M	PWB	1	1	+E/-S	60deg	-E/-S	60deg	-E/+S	+E/+S	23
M	PWB	2	2	-E/+S	60deg	+E/+S	60deg	-E/-S	+E/-S	21
M	PWB	3	3	-E/-S	60deg	+E/-S	60deg	+E/+S	-E/+S	22
M	PWB	4	4	+E/+S	60deg	-E/+S	60deg	+E/-S	-E/-S	24
M	PWB	5	5	+E/-S	60deg	-E/-S	+E/+S	60deg	-E/+S	19
M	PWB	6	6	+E/+S	60deg	-E/+S	-E/-S	60deg	+E/-S	20
M	NWB	7	7	-E/+S	50deg	+E/+S	+E/-S	50deg	-E/-S	17
M	NWB	8	8	-E/-S	50deg	+E/-S	-E/+S	50deg	+E/+S	18
M	NWB	9	1	+E/-S	-E/-S	50deg	-E/+S	50deg	+E/+S	14
M	NWB	10	2	-E/+S	+E/+S	50deg	-E/-S	50deg	+E/-S	13
M	NWB	11	3	-E/-S	+E/-S	50deg	+E/+S	50deg	-E/+S	16
M	NWB	12	4	+E/+S	-E/+S	50deg	+E/-S	50deg	-E/-S	15
F	PWB	13	1	+E/-S	60deg	-E/-S	-E/+S	60deg	+E/+S	10
F	PWB	14	2	-E/+S	60deg	+E/+S	-E/-S	60deg	+E/-S	9
F	PWB	15	3	-E/-S	60deg	+E/-S	+E/+S	60deg	-E/+S	12
F	PWB	16	4	+E/+S	60deg	-E/+S	+E/-S	60deg	-E/-S	11
F	PWB	17	5	+E/-S	60deg	-E/-S	60deg	+E/+S	-E/+S	7
F	PWB	18	6	+E/+S	60deg	-E/+S	60deg	-E/-S	+E/-S	8
F	NWB	19	7	-E/+S	50deg	+E/+S	50deg	+E/-S	-E/-S	5
F	NWB	20	8	-E/-S	50deg	+E/-S	50deg	-E/+S	+E/+S	6
F	NWB	21	5	+E/-S	-E/-S	50deg	+E/+S	50deg	-E/+S	2
F	NWB	22	6	+E/+S	-E/+S	50deg	-E/-S	50deg	+E/-S	3
F	NWB	23	7	-E/+S	+E/+S	50deg	+E/-S	50deg	-E/-S	1
F	NWB	24	8	-E/-S	+E/-S	50deg	-E/+S	50deg	+E/+S	4

Table 2. Listing of the 24 total test sequences that incorporate the dummy target angles for the PWB and NWB tasks. A-F represent different stages of the test sequence.

The dummy target angle stages used the electrical stimulation and sleeve condition of the previous stage of the test sequence. One sequence was assigned to each subject for his/her first task (PWB or NWB). The second task was then completed with the sequence number shown in Table 2 above. To illustrate this point, Male #1 performed the following test order for the first task sequence: +E/-S, 60deg., -E/-S, 60deg., -E/+S, +E/+S, and the following test order for the second task sequence: -E/+S, +E/+S, 50deg, +E/-S, 50deg, -E/-S. This 2nd task sequence was designed such that the first test condition was the exact opposite of the condition used in the first stage of the 1st task sequence. Half of the subjects (both male and female) performed the PWB task first, while the other half performed the NWB task first. Assigning test sequences 1-12 to the males and 13-24 to the females assured that within each

gender that each testing condition occurred with equal incidence in each of the stages of the testing sequence. Each subject performed 3 trials at each testing condition for each task, PWB or NWB for a total of 36 trials.

3.5. Study Procedure

Upon recruitment of each subject, the investigator determined whether the subject met the inclusion criteria. The subject then completed the study questionnaire and signed their informed consent (Appendix A, D). The subject then began the testing steps.

3.5.1. PWB steps

1. The PWB steps were demonstrated by the investigator while seated on the sliding platform and the subject was instructed on what will follow.
2. The subject was then seated on the sliding platform in a partial weight bearing position, the investigator found the lateral and medial knee joint space, 2cm above and below, and placed the electrodes. The electrodes were not removed between tasks.
3. The subject was positioned on the sliding platform and the foot of the dominant limb was placed on the heel wedge.
4. The neoprene knee sleeve was placed over the knee (if applicable for the first task condition).
6. Once the sleeve was in place and the subject was comfortable, the electrogoniometer was positioned (potentiometer was aligned with the lateral femoral condyle), and the straps were adjusted.
7. The investigator ensured all equipment was connected and reading correctly.
8. The subject was positioned with his/her limb that was not being tested tucked and resting on the metal extension to the platform.
9. The headphones and blindfold were then placed on the subject and the electronic switch was handed to them.
10. Practice runs were performed until the subject was comfortable with the procedure.
11. Once comfortable with the procedure, the subject was then actively moved into flexion until instructed to stop by the investigator.
12. The subject then depressed the electronic switch and maintained this position for 5 seconds.
13. After 5 seconds the subject returned to full extension.

14. White noise in the headphones was started after 5 seconds of the subject resting at full extension.
15. The investigator then tapped the subject on their nontest knee and this instructed the subject to reproduce the position.
16. Once the subject reached what they perceived to be the target angle, he/she depressed the switch and maintained the position for 5 seconds.
17. After 5 seconds, the subject then returned to full extension.
18. Steps 11 through 17 were repeated three times for each of the conditions.
19. If the PWB task was the last task, the investigator determined the threshold level of stimulus by increasing the stimulus level and having the subject tell the investigator at which point they felt the stimulus.

3.5.2. NWB steps

1. The investigator ensured the electrodes, electrogoniometer, and knee sleeve (if applicable) were in place.
2. The subject was positioned on the bench seated upright with his/her legs hanging over the edge of the bench and their knee popliteal space a few centimeters off the bench edge to eliminate tension cues.
3. The investigator ensured all electronic equipment was reading properly and that the angle of knee flexion at rest was within 70 to 80 degrees.
4. The subject was instructed on the steps that were to follow.
5. A practice trial was performed by passive movement of the subject's knee by the investigator into extension to a certain angle.
6. The subject was instructed to depress the time switch once the target angle was reached and the investigator said "OK".
7. Upon depression of the switch, the knee was held in place by the investigator for 5 seconds and was then brought back to the original, resting position.
8. After 5 seconds in the resting position, the investigator began the headphone noise and tapped the subject on their nontest knee to signal them to begin the reproduction part of the trial.
9. Once the subject was tapped, they actively moved to the flexion angle which they perceived to be the same as the target angle and depressed the electronic switch once they were in that position.
10. The subject maintained the position for 5 seconds and then returned to the relaxed position to end the practice trial.
11. The investigator ensured the subject understood the task, at which point testing began.
12. The process in steps 5-10 was repeated three times for each testing condition.

20. If the NWB task was the last task, the investigator determined the subject's threshold level of stimulus by increasing the stimulus level and having the subject tell the investigator at which point he/she detect the stimulus.

3.5.3. Stimulus Threshold to Detection

Upon completion of all study tasks, the stimulus threshold to detection was determined for each subject using a component of the Labview VI designed by Afferent, Inc. The purpose of determining the subject's threshold for stimulus detection was to ensure their detection level was higher than the 50 μA test level. Initially, the subject's threshold for detection was to be determined before the study began, but we felt this would provide the subject with false sensations of detecting the stimulus during the test. The stimulus was administered at 0.1milliAmps/Volt within the "Test Stimulus" program and each electrode pair, inferior and superior, was tested separately. Once the program was set to run, the investigator would enter an electrical stimulus amplitude which would provide a threshold value in microAmps. For example, a stimulus amplitude of 0.50 would correlate to a threshold value of 50 microAmps. The stimulus amplitude was continually ramped up by 0.10 until the subject could detect the stimulus or until the value reached 150 microAmps, whichever came first. All but 2 of the 26 subjects had detection levels higher than the test stimulus level. These 2 subjects were excluded from the study because they could detect the 50 μA test level.

3.6. Equipment

3.6.1. PWB setup

Both the PWB and NWB joint proprioceptive tests evaluated the subjects' joint position sense, and determined the subject's ability to actively reproduce a target knee flexion angle.

As previously mentioned, a PWB task was preferred over a FWB task because future studies may involve OA patients, and FWB tasks could be painful in this population. During the PWB task, each subject was positioned on a sliding, relatively frictionless platform that was reclined approximately 20 degrees relative to the horizontal. Similar to other studies, a supporting foam heel wedge was placed under the heel of the test limb, placing the heel in slight plantar flexion in order to decrease tension cues generated by the triceps surae during the knee flexion tests [3, 25]. The non-test limb was flexed at the hip and knee, allowing the foot to rest upon the sliding platform. As a result, the subject simulated single leg stance in a partial weight bearing condition (see figure 8).
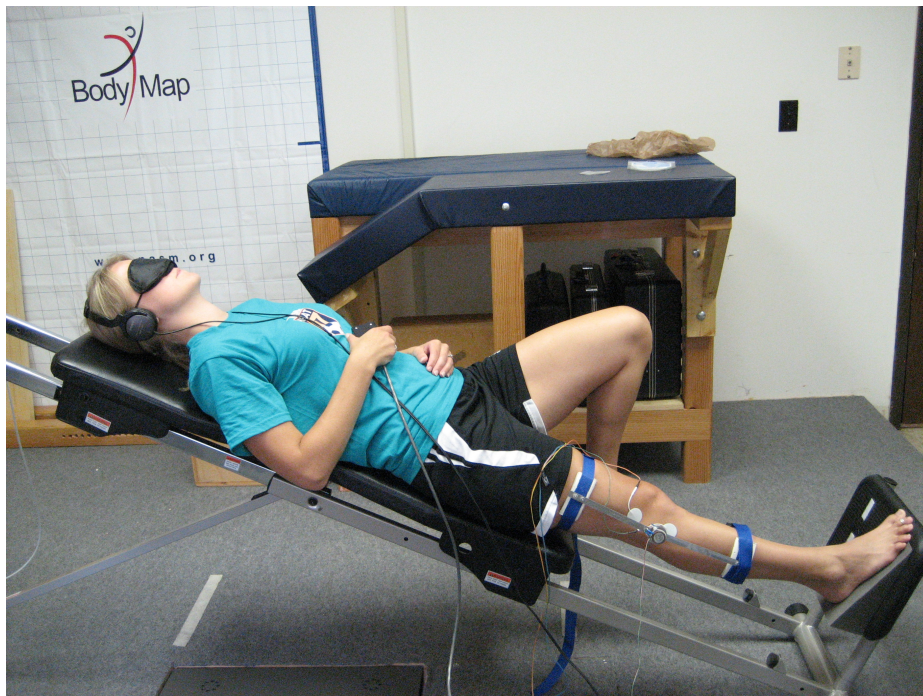
Figure 8. Partial weight bearing setup

During the knee flexion tests, the target angle of 30 degrees was chosen with a 60 degree "dummy" angle incorporated into the sequence. This target angle was chosen to simulate the positioning of the knee soon after foot contact during the early stance phase of gait. The

starting position was in full knee extension in single leg stance, and the subjects moved into flexion during each trial.

3.6.2. NWB setup

Unlike the PWB setup, during the NWB setup the subject was seated on an upright bench and the knee was tested moving from a starting position of approximately 70°- 80° flexion into extension (Figure 9). This test simulated the positioning of the knee during the swing phase of gait prior to foot contact on the ground. The target angle for this task was also chosen to be 30 degrees but a 50 degree "dummy" angle was incorporated into these sequences rather than the 60 degree angle previously mentioned for the PWB task. The 50 degree dummy angle was chosen because during the NWB task, the subjects' joint angle at rest was approximately between 70 and 80 degrees rather than 90 degrees.
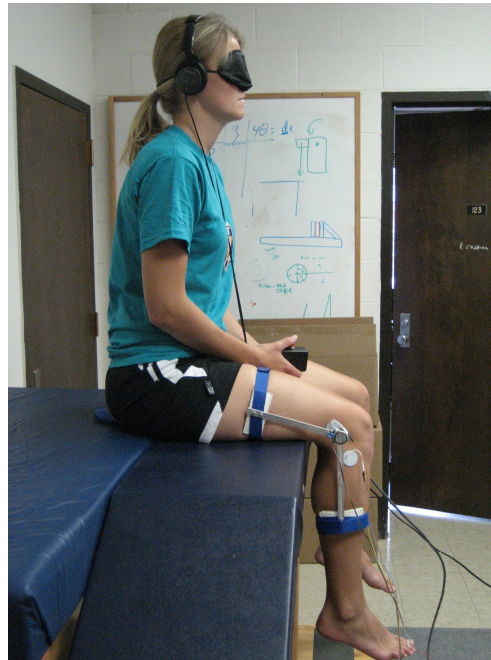
Figure 9. Nonweight bearing setup

In order to ensure the subject felt sufficient displacement of their limb from rest during the dummy sequences, the target dummy angle was chosen to be 50 degrees rather than 60 degrees.

3.6.3. Electrical Stimulation Setup

One of the aims of this study was to determine whether subthreshold electrical stimulation improves proprioception beyond that seen with a neoprene sleeve alone. All equipment utilized to deliver the subthreshold electrical stimulation was provided by Afferent Corporation. The system components included:

Laptop computer which runs a Labview program designed by Afferent personnel
National Instruments NI-6036E, Multifunction DAQ card
Two (2) AM2200 Analog Stimulus Isolators
Two (2) Battery Powered Error Isolation Boxes
Connector box (SCB-68) with 2 custom wired BNC outputs and 2 error inputs
Cables and connectors
Valutrode disposable Neurostimulation electrodes (4 per pack)
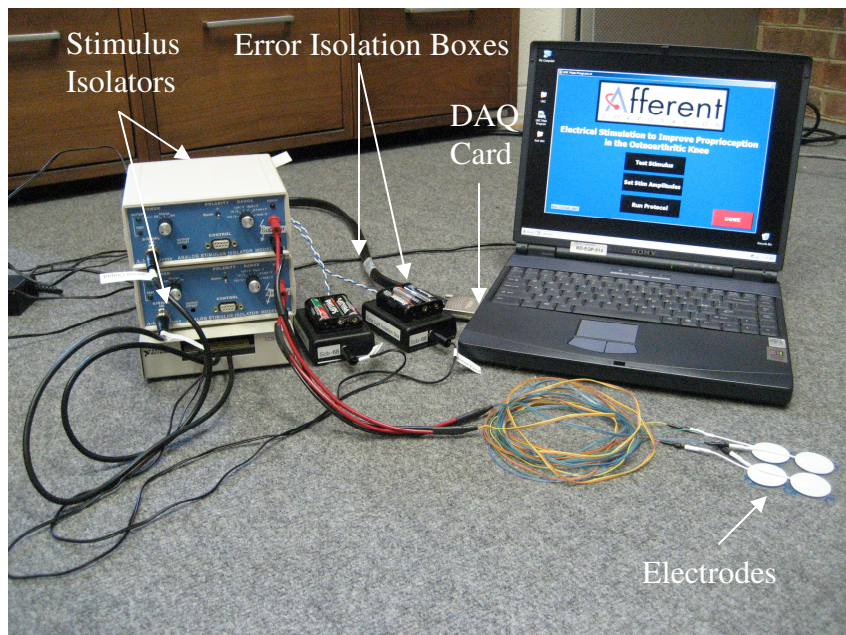
Figure 10. Electrical Stimulus equipment setup

Electrical stimulation was applied with an electrical stimulator device (Afferent Inc.) by way

of two pairs of self-adhesive surface electrodes placed alone or beneath the neoprene sleeve.

The two electrode pairs (an electrode pair consists of one stimulator and one ground) were

placed at four locations along the knee joint line: superior-lateral, superior-medial, inferior-

lateral, and inferior-medial (see Figure 11). Once the electrodes were placed they remained

in position throughout testing.
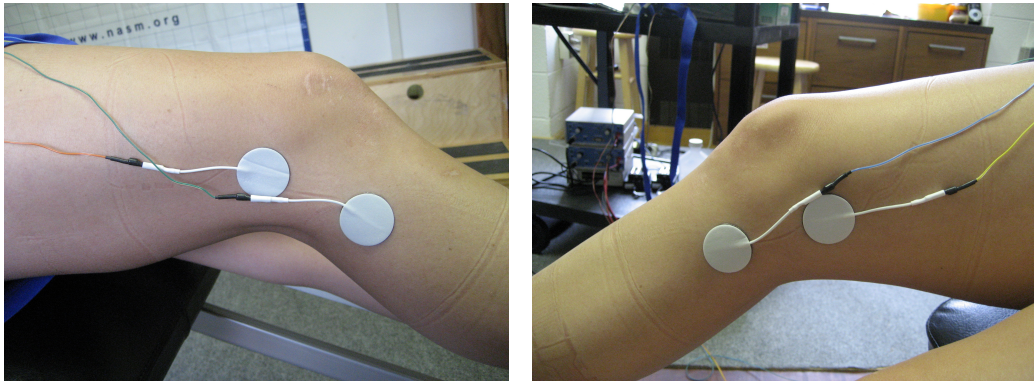
Figure 11. (Left) Lateral placement of the superior and inferior electrodes. (Right) Medial placement of the superior and inferior electrodes.
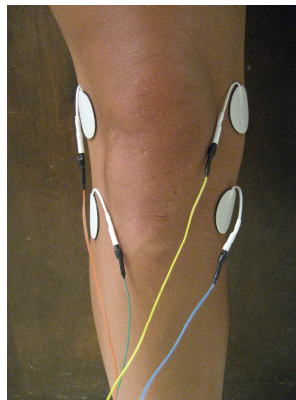
Figure 12. Frontal view of superior and inferior electrodes.

The electrodes were placed in such a way that the current was drawn laterally across the

knee. Each electrode is 1.5 cm in diameter and the superior and inferior electrodes were

placed approximately 2 cm above and below the joint line, respectively.

3.6.4. Electrogoniometer

Each subject's joint position sense was measured by their ability to actively reproduce a target knee flexion angle. Target angles were predetermined angles of knee flexion, and were measured using an electrogoniometer which gave an electronic readout of the knee angle with accuracy to less than 0.5°. The figure below illustrates the electrogoniometer and its proper placement about the knee joint (see Figure 12). The potentiometer, located at the point of knee flexion was placed above the lateral femoral condyle with both arms of the apparatus fixed along the femoral and tibial longitudinal axes.

Figure 13. Placement of the electrogoniometer about the knee joint in the NWB task.

Before use in this study, the potentiometer was calibrated in order to attain an accurate calibration constant which was entered into the Labview block diagram. In order to calibrate the electrogoniometer, the potentiometer was first detached from the metal arms and secured in a rotational stage with an accuracy of 0.1 degrees. Using a 5 volt power supply and setting the rotational stage to zero, the angle output (in volts) was read from the Elgon.v6 vi front

panel. This angle (in volts) was then entered in the program block diagram and once the new

value was entered, the program was started. The rotational stage angle ranged from 0 to 360

and the angle (in volts) displayed on the Labview front panel was recorded at every 5 or 10

degree turn on the rotational stage. Three trials were performed: Trial 1, 0° to 170°; Trial 2,

170° to 280°; Trial 3, 285° to 360° (see table 3). A line of best fit was determined for each set

of values for each trial and the three best fit line slopes were averaged to attain the new

calibration constant of 0.014433 volts/EU (engineering unit).

Trial 1		Trial 2		Trial 3	
Angle	Volts	Angle	Volts	Angle	Volts
0	1.62	170	4.07	285	0.54
10	1.76	175	4.15	290	0.61
20	1.91	180	4.22	295	0.68
30	2.05	185	4.29	300	0.76
35	2.12	190	4.36	305	0.83
40	2.2	195	4.43	310	0.9
45	2.27	200	4.51	315	0.97
50	2.34	205	4.58	320	1.05
55	2.41	210	4.65	325	1.12
70	2.63	215	4.72	330	1.19
80	2.77	220	4.79	335	1.26
90	2.92	225	4.87	340	1.33
100	3.06	230	4.94	345	1.41
105	3.13			350	1.48
110	3.21			355	1.55
115	3.28			360	1.62
120	3.35				
125	3.42				
140	3.64				
145	3.71				
150	3.79				
155	3.86				
160	3.93				
165	4				
170	4.07				
	0.014441		0.014418		0.014441
Calibration Constant (averaged across trials)		0.014433	(volts/degrees)		

Table 3. Potentiometer block calibration data for the three trials performed.

Once calibrated, the arms were then reattached to the potentiometer. The calibration constant was entered on the vi front panel along with the voltage value at 0° extension of the electrogoniometer arms.

3.6.5. Electronic Trigger

During both the PWB and the NWB testing sequences the subject was instructed to momentarily depress an electronic trigger when they arrived at the target angle and also when they felt they had reproduced that target angle. The electronic trigger used was a single pole double throw trigger designed to signal between 0V and 5V. When the trigger was depressed, the signal would rise from 0V to 5V, creating a positively sloped wave. The purpose of depressing the trigger once the desired angle was reached was to provide a time stamp on the front panel which showed the electrogoniometer angle waveform (see figure 14).
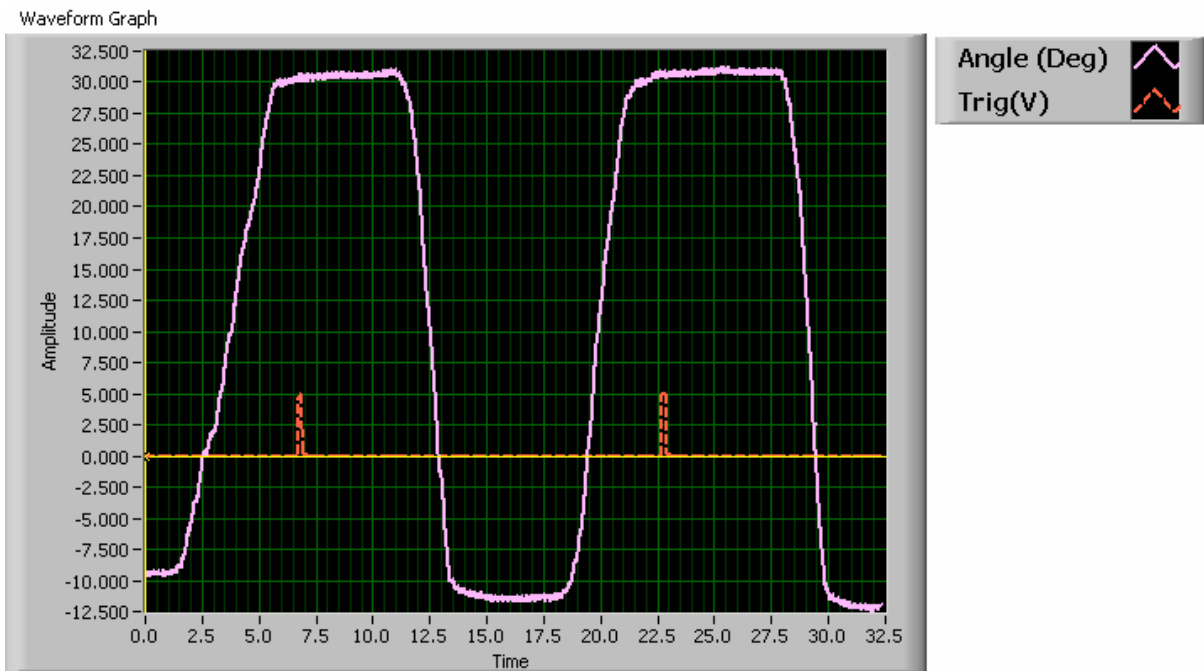
Figure 14. Labview front panel illustrating the electrogoniometer and trigger waveforms for a subject during the PWB task.

In figure 14, the red waveforms are the electronic trigger waveforms while the blue waveforms are the electrogoniometer waveforms. To relate trial steps to the figure above, this particular subject was told to depress the trigger once they had reached the target angle of 30 degrees at approximately 7 seconds. The subject then depressed the trigger at approximately 23 seconds to indicate they had reproduced the target angle.

3.6.6. Labview Software

For this project, Labview vi's were written both to collect the electrogoniometer and trigger data, and also to deliver the electrical stimulus. As explained in the previous section, a vi was written which captured the voltage output from the electrogoniometer (which corresponded to an exact angle measurement) and the electronic trigger. The program was designed to capture both an average reading and an instantaneous reading. Immediately after the trigger was depressed, the program would collect readings for 3 seconds and average them to determine a final average reading. The instantaneous reading, on the other hand, was taken immediately after the trigger was detected and no additional readings past that point were taken. The need for an instantaneous reading came about when it was noticed that some subjects were "drifting" at the target and reproduction angles, possibly due to fatigue. This can be seen in the figure below where the subject indicated they had reached the target angle of 30°, but within 5 seconds he/she had drifted to a new angle of approximately 34°.
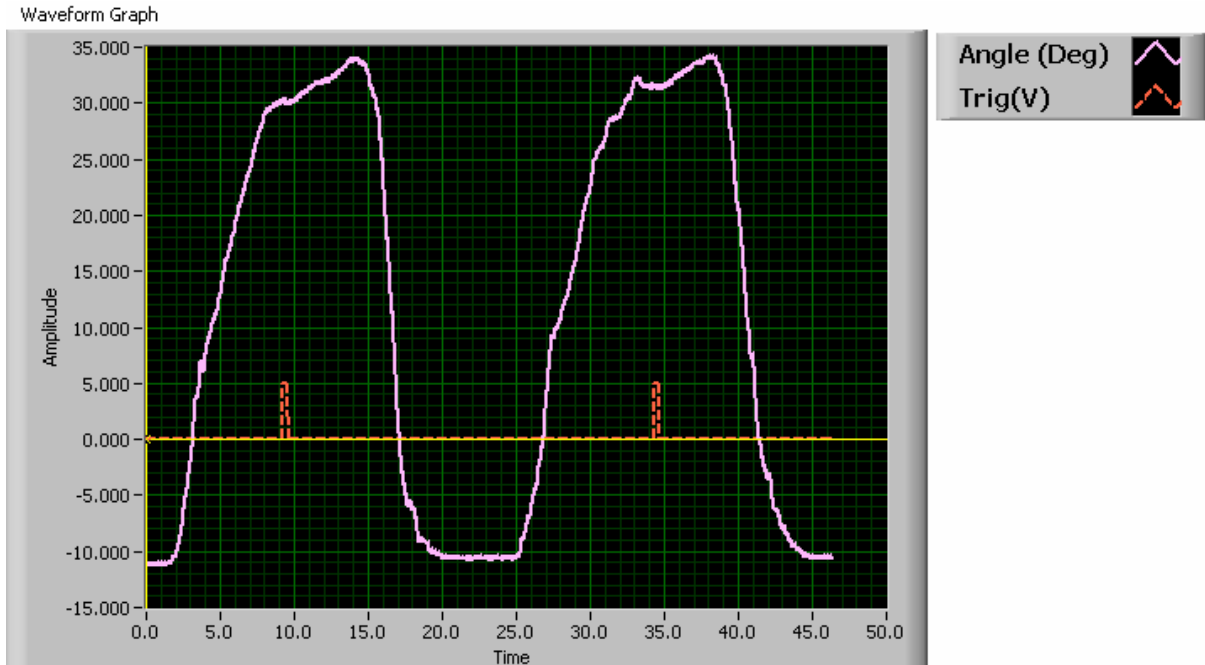
Figure 15. Labview front panel which illustrates "drifting" during a PWB task.

Most subjects who "drifted" only did so in the PWB task, presumably because it was more difficult to maintain the position while load bearing than while bearing no load.

3.6.7 Heel Wedge

In order to eliminate tension cues that may be provided by the triceps surae, a foam heel wedge was used (see figure 8). The wedge created slight plantar flexion which worked to reduce the influence of cues from the stretching of this muscle during the flexion tests. Several studies have also used heel wedges during the PWB task of their studies for the same reason [3, 25]. We elected to use a foam material for the heel wedge instead of something more rigid to provide additional comfort for the subject while he/she was simulating single-leg stance.

3.6.8 Blindfold/Headphones

An additional component of the study design is the exclusion of contributions made by the visual and auditory systems. This was done in order to isolate the somatosensory system as the main contributor to proprioception in this study. Several studies have either instructed the subject to close their eyes or placed a blindfold over the subject's eyes [3, 9-12, 24, 25, 37-40]. Following these studies, we elected to eliminate visual contribution by placing a blindfold over the subject's eyes during the entire test.

The vestibular system is also a factor in proprioceptive feedback in order to maintain proper balance. It supplies information that measures linear, gravitational, and angular accelerations of the head in relation to space, but does not provide information about orientation relative to external objects. Therefore, it plays only a minor role in the maintenance of balance when the visual and somatosensory systems are providing information. This may explain why so few studies incorporate white noise or the use of headphones to eliminate vestibular cues, mainly because headphones work to only eliminate auditory cues and do not deal with the other components of the vestibular system. Nonetheless, we felt it would be important to eliminate this contribution by playing white noise through a set of headphones worn by the subject during testing. The noise was only played during the reproduction portion of each trial in order for the subject to hear instructions from the investigator during the beginning parts of the study.

3.7 Statistics

Both a One-way and Two-way Analysis of Variance (ANOVA) repeated measure parametric and nonparametric (analysis based on ranks) tests were used to analyze the data. The Holm-Sidak test was used following One-way ANOVA for multiple comparisons. Both

One and Two-way ANOVA were performed using the absolute error means, real error means, and the standard deviation error means. The standard deviation errors were calculated by using the instantaneous target angle measurement as a reference point and subtracting the three second reproduced angle measurement. The two independent variables were sleeve status and stimulation status and the dependent variable was mean error score. The absolute mean error score was the absolute value of the difference between the target and reproduced knee joint angle averaged across three trials for each condition. Real mean error and standard deviation error scores were also measured.

The one-way ANOVA was conducted to determine differences in the measured variables with the testing condition for each task (PWB or NWB). The two-way statistical analysis specifically evaluated for a sleeve/stimulation interaction, a sleeve main effect, and a stimulation main effect. All significant effects were determined at a P value less than 0.05.

Additionally, a linear regression analysis was performed to compare both differences between the treatment error (with or without sleeve and/or with or without stimulation) and the control error (no stimulation/no sleeve) as well as to compare the difference between the control and treatment error with the control error.

4. Results

4.1. Subject Demographics

Twenty four uninjured, physically active males (n=12) and females (n=12) were tested for this study. Subjects were recruited from the UNC Chapel Hill student and faculty population. Subjects were 18-35 years old, had no history of knee surgery/injury/pain in their dominant knee, had no neurological conditions which could affect their balance or ability to detect motion, and were all physically active (at least 1.5 hours/week).   Subject demographic information is presented in the table below.   The BMI (Body Mass Index) was calculated using the subject's height in inches and their mass in pounds [41].

	Female (N=12)	Male (N=12)	Group (N=24)
Age (yr)	25.08 $\pm$ 3.99	24.58 $\pm$ 3.53	24.96 $\pm$ 3.72
Mass (kg)	61.42 $\pm$ 7.70	81.31 $\pm$ 13.00	68.91 $\pm$ 20.51
Height (in.)	64.75 $\pm$ 1.86	70.25 $\pm$ 1.60	67.65 $\pm$ 3.27
BMI	22.68 $\pm$ 2.43	25.52 $\pm$ 4.01	24.17 $\pm$ 3.61

Table 4. Mean ($\pm$SD) values for subject characteristics

4.2. Absolute Mean Error

Each subject performed knee joint position sense testing in both a NWB and a PWB task. There were 6 conditions within each task: NE/NS (control), NE/S, E/S, E/NS, and two dummy angles (50 and 60 degrees for NWB and PWB, respectively). The dummy angle conditions within both the PWB and NWB tasks were not considered in the data analysis as they were placed in the study to eliminate memorization effects only.

In each trial, the trigger was depressed by the subject to indicate target and reproduced joint angle position attainment. The absolute difference between the target and reproduced angle was taken for each of the three trials within each condition and averaged. Both an instantaneous and a 3 second average measurement were taken once the electronic trigger was depressed by the subject that indicated arrival at the target and reproduced angle. For this data analysis, only the instantaneous measurement was used in keeping with previous studies which have evaluated joint position sense. The instantaneous measurement means and statistics for each task within each of the four testing conditions are demonstrated below.

4.2.1. NWB Absolute Mean Error

During the NWB task, the subject's knee was passively flexed by the investigator to either 30 degrees or the 50 degree dummy angle. During the second part of each trial, the subject actively reproduced the position previously attained. The NWB absolute mean errors were averaged over the 24 subjects. The condition means and standard deviations are presented in Figure 16 and Table 5.
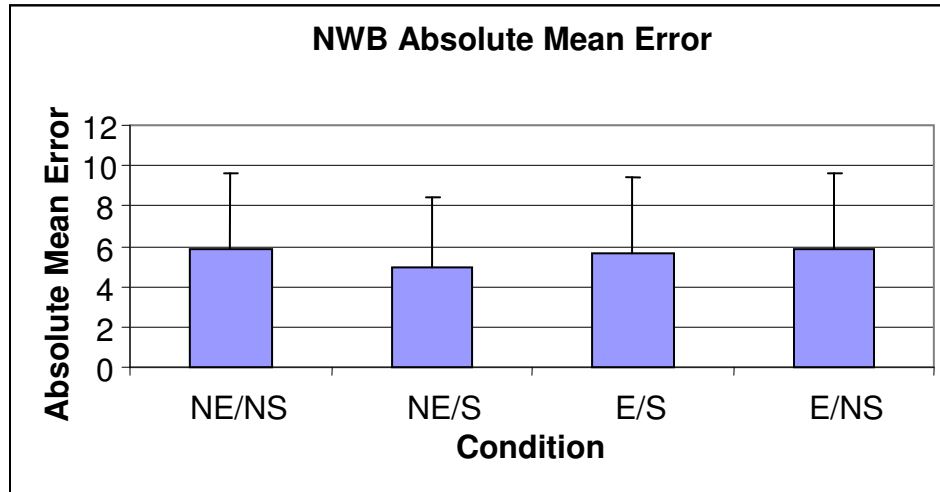
Figure 16. NWB Absolute Mean Errors (+/- SD) by Condition (NE=No Electrical Stimulation, E=Electrical Stimulation, NS=No Sleeve, S=Sleeve)

The main difference we saw during the nonweight bearing task was that errors were less in the NE/S group compared with the NE/NS control condition.

Condition	Mean Absolute Degrees of Error ($\pm$SD)
No Electrical Stimulation/No Sleeve	5.8571 ($\pm$3.7969)
No Electrical Stimulation/Sleeve	4.9584 ($\pm$3.5155)
Electrical Stimulation/Sleeve	5.6929 ($\pm$3.7318)
Electrical Stimulation/No Sleeve	5.8945 ($\pm$3.7392)

Table 5. NWB Absolute Mean Errors with Standard Deviation by condition

	One-way ANOVA		Two-way ANOVA		
Parametric	**One-way ANOVA**	p=0.207	**Two-way ANOVA**	Sleeve level	p=0.2116
				Stimulation level	p=0.2401
				Interaction	p=0.2338
Nonparametric (ranks)	**One-way ANOVA**	p=0.3691	**Two-way ANOVA**	Sleeve level	p=0.391
				Stimulation level	p=0.246
				Interaction	p=0.382

Table 6. NWB Absolute Mean Error Statistical p values (* indicates significance)

One-way parametric ANOVA showed no significant difference between the treatment groups. Since the data strayed from normality, a Friedman repeated measures analysis of variance on ranks was performed, but it did not show significance. Frequency distributions of all four conditions were performed to demonstrate conformance or nonconformance to normality (see Figures 17-20). Skewness and Kurtosis values are also listed with skewness values of $\pm$2 and kurtosis values of $\pm$7 being within an acceptable range.
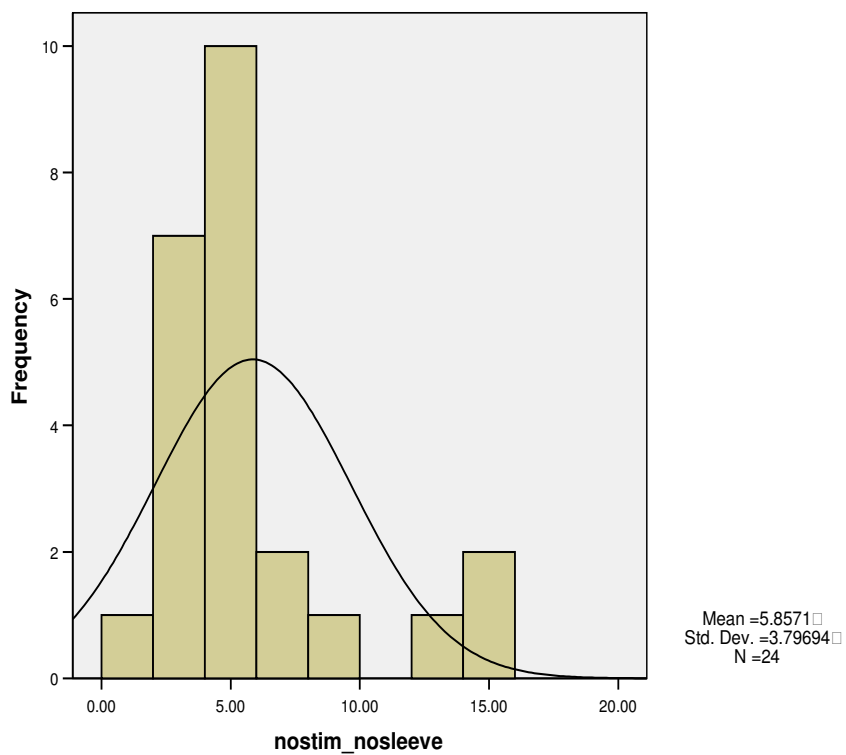
Figure 17. NWB NE/NS Condition Histogram. Skewness=1.78, Kurtosis=2.47
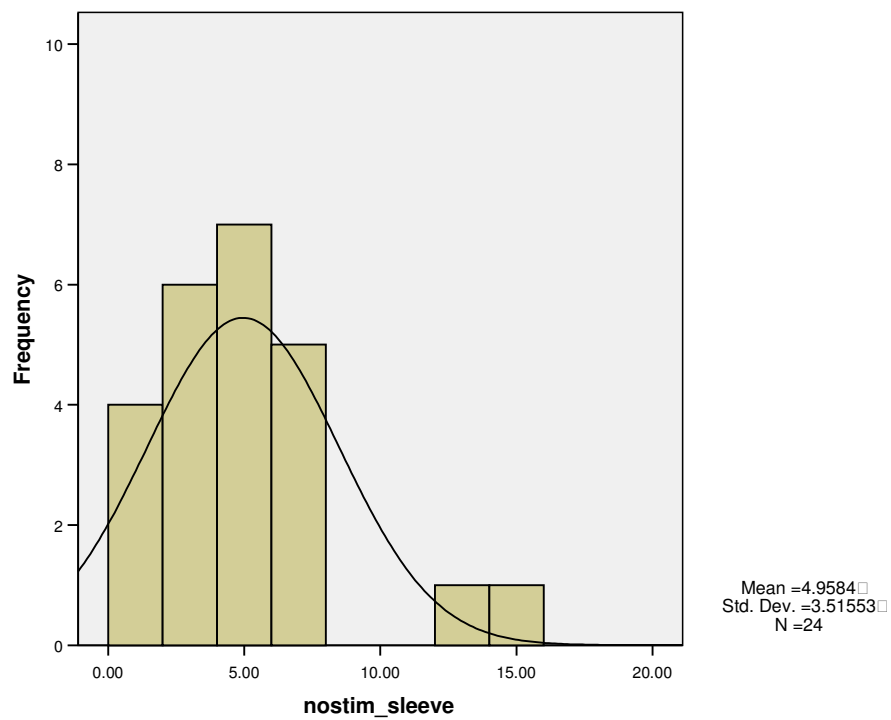
Figure 18. NWB NS/S Condition Histogram. Skewness=1.72, Kurtosis=3.87
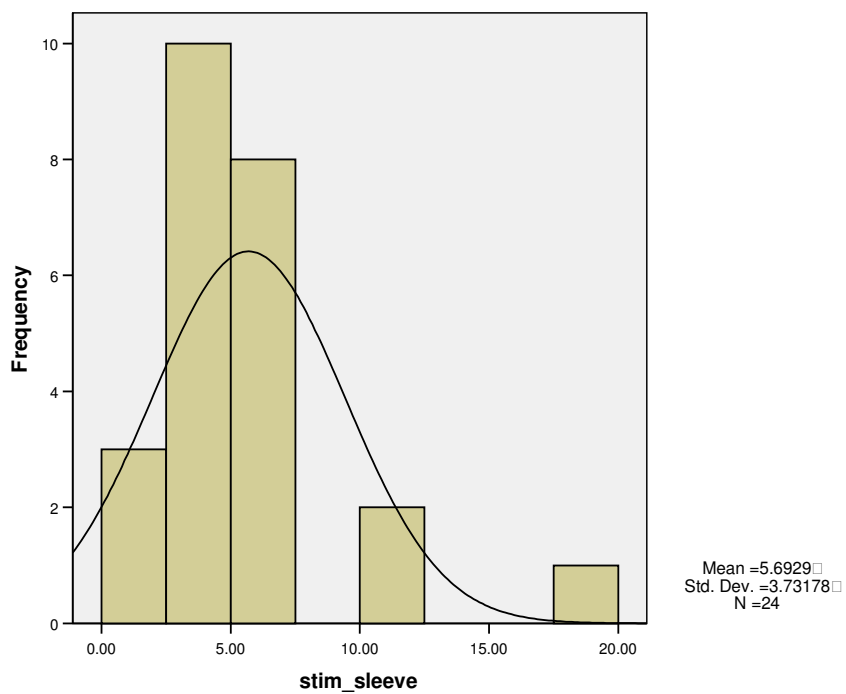
Figure 19. NWB E/S Condition Histogram. Skewness=2.52*, Kurtosis=8.27* (*indicates outside of acceptable range for normality)
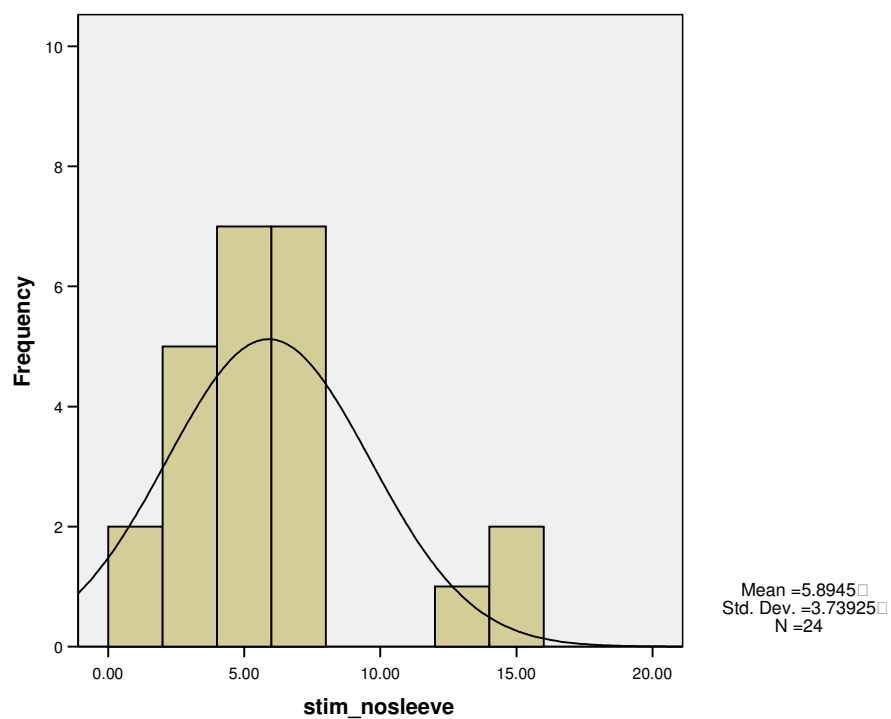
Figure 20. NWB E/NS Condition Histogram. Skewness=1.41, Kurtosis 1.83

Two-way parametric ANOVA was performed and no significance was detected between the different levels of stimulation, the different levels of sleeve, or between the interaction of the two. The average means for each of the three trials within each condition were transformed to ranks in the SigmaStat software and a two-way ANOVA was performed on ranks, but no significant differences were detected. When the data do not follow a normal distribution, using the ranks of observations rather than the observations themselves is an option. This allows for information about the relative size of responses to be maintained but it is not necessary to make assumptions about the sample distributions.

4.2.2. PWB Absolute Mean Error

Unlike the NWB task, the subject actively flexed his/her knee until told to stop by the investigator during the first part of the PWB task. The subject then actively reproduced the target angle. The absolute difference in the target and reproduced angle was taken as the measurement of interest.
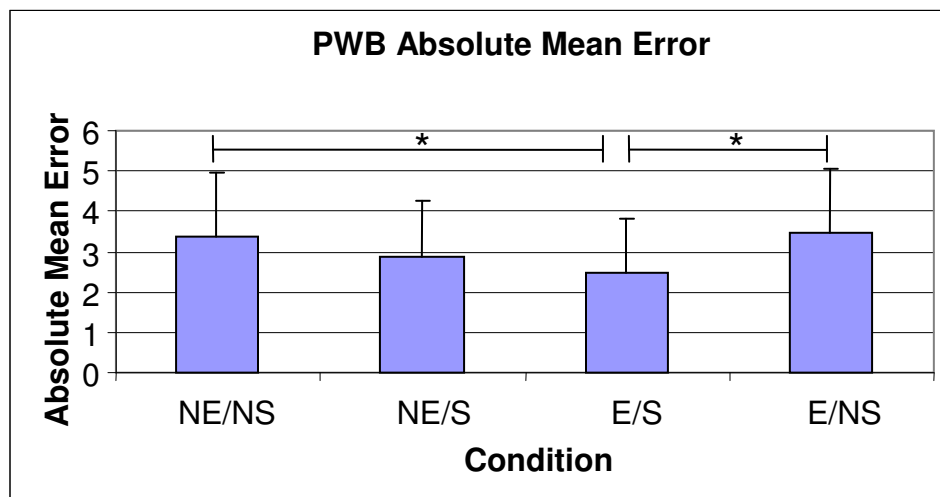
Figure 21. PWB Absolute Mean Error by condition (* indicates multiple comparison significant differences)

The main difference we saw with the PWB task was a significant decrease in the

Stimulation/Sleeve condition compared with the No Stimulation/No Sleeve control condition.

Table 7 shows the mean error for the E/S condition (2.48) is less than the control mean error

(3.35). Additionally, the absolute mean error significantly increased from the E/S condition

to the E/NS condition (3.48).

Condition	Mean Absolute Degrees of Error (+SD)
No Electrical Stimulation/No Sleeve	3.3472 (±1.6306)
No Electrical Stimulation/Sleeve	2.8698 (±1.4133)
Electrical Stimulation/Sleeve	2.4835 (±1.3173)
Electrical Stimulation/No Sleeve	3.4809 (±1.5842)

Table 7. PWB Absolute Mean Errors with Standard Deviation by condition

The difference between the control condition mean error and the stimulation/sleeve condition

mean error was 0.8637 degrees. Since there have been no previous studies that examine the

effects of stimulation and sleeve on reproduction of knee joint angle, there are no data for

comparison. However, this difference was the largest among the other two conditions when

compared with the control.

	One-way ANOVA		Two-way ANOVA		
Parametric	**One-way ANOVA**	p=0.0488*	**Two-way ANOVA**	Sleeve level	p=0.0177*
				Stimulation level	p=0.6655
				Interaction	p=0.3039
Nonparametric (ranks)	**One-way ANOVA**	p=0.145	**Two-way ANOVA**	Sleeve level	p=0.013*
				Stimulation level	p=0.672
				Interaction	p=0.247

Table 8. PWB Absolute Mean Error Statistical p values (* indicates significance)

Unlike the NWB task, the One-way parametric ANOVA showed a significant difference between the treatment groups during the PWB task. The Holm-Sidak method of pairwise multiple comparisons was used to find specific significant differences. A significance difference was detected between the E:NS vs. E:S groups and between the NE:NS vs. E:S groups.

Frequency distributions were also performed on the PWB data to determine conformance or nonconformance with normality. As is indicated by the figures below, skewness and kurtosis values were closer to zero than in the NWB task which indicates a better conformance to normality (see figure 22-25). However, a Friedman repeated measures analysis of variance on ranks was performed despite the better conformance to normality, but it did not show significance.

Mean =3.3472
Std. Dev. =1.63056
N =24
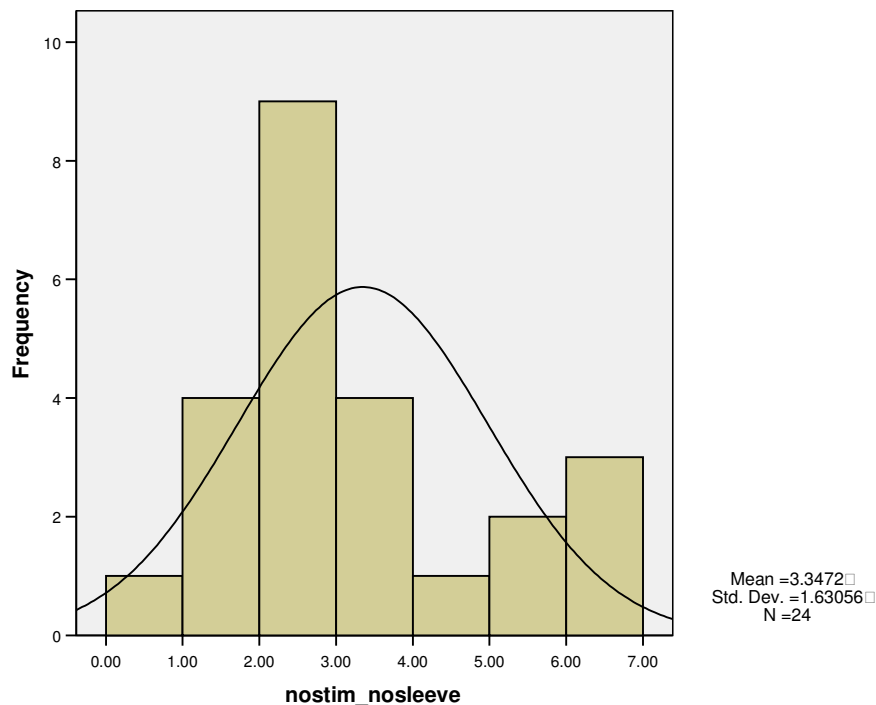
Figure 22. PWB NE/NS Condition Histogram. Skewness=0.75, Kurtosis=-.11
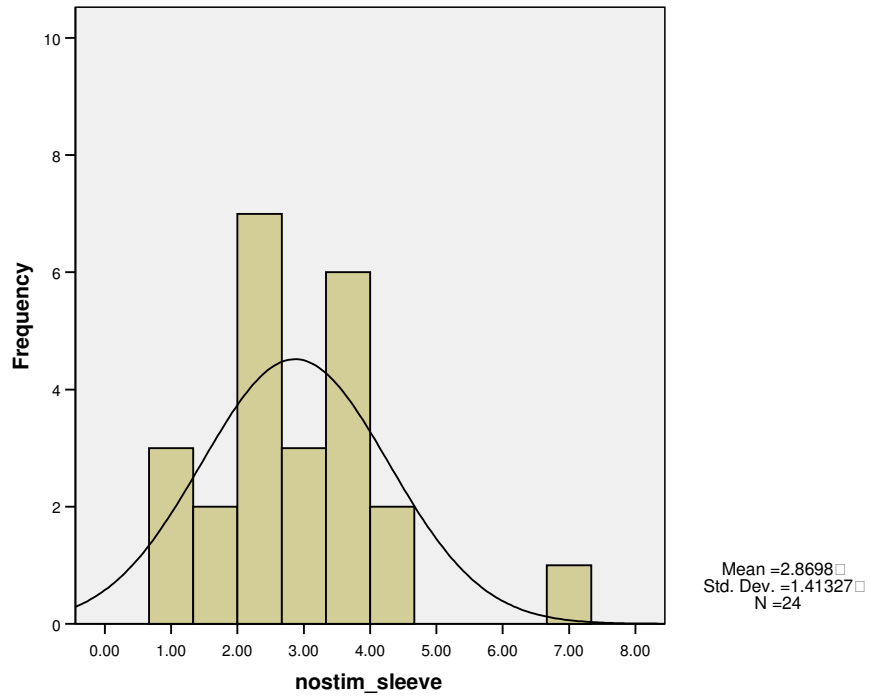
Figure 23. PWB NE/S Condition Histogram. Skewness=1.13, Kurtosis=2.98
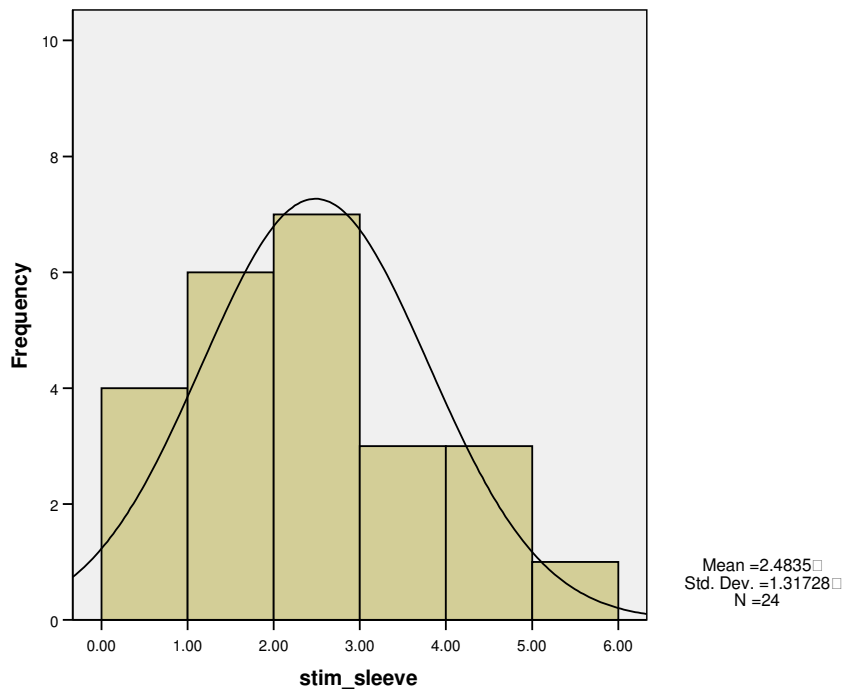
Figure 24. PWB E/S Condition Histogram. Skewness=0.68, Kurtosis=-0.23
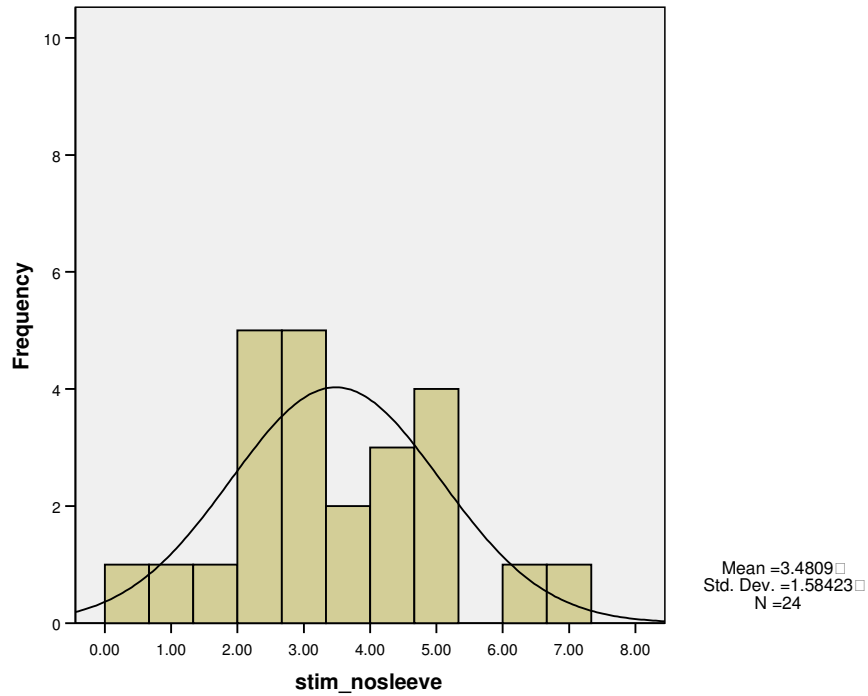
Figure 25. PWB E/NS Condition Histogram. Skewness=0.25, Kurtosis=0.29

Two-way parametric ANOVA was performed and a significant difference was detected between the different levels of sleeve, but not between the different levels of stimulation or between the interaction of the two. The average means for each condition were transformed to ranks in the SigmaStat software and a two-way ANOVA was performed on ranks. The nonparametric analysis found the same significances as the parametric analysis.

4.3. Real Mean Error

Similar to the Absolute Mean Error, the Real Mean Error was also recorded during each trial. However, the absolute value of each real mean error was not taken as it was for the absolute mean error. Real mean error was calculated by subtracting the target angle measurement from the reproduced angle measurement. This allows for analysis of

"undershooting" or "overshooting" target and reproduction angles. The figure below

illustrates the real mean errors and their standard deviations for the NWB task.

4.3.1. NWB Real Mean Error
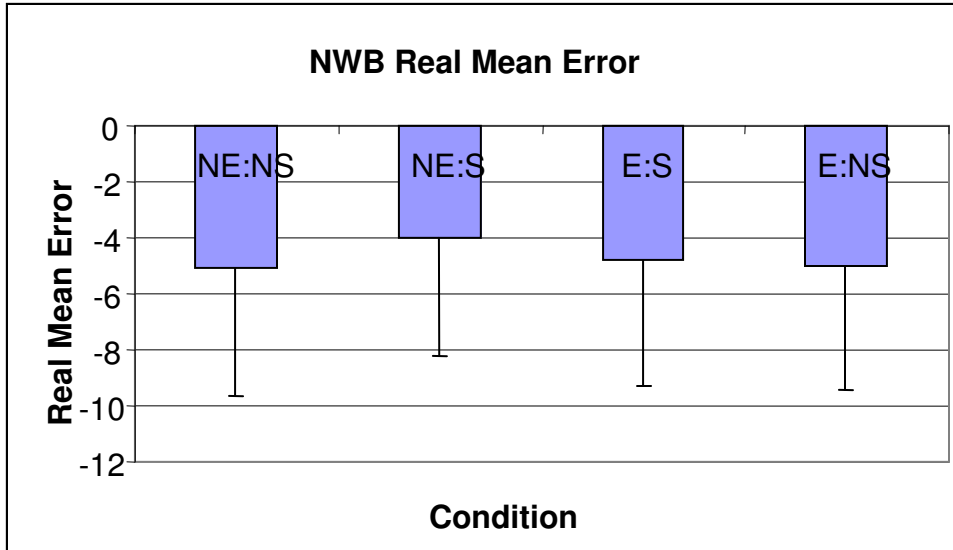
Figure 26. NWB Real Mean Error by condition

As it is seen in the figure above (Fig. 26), the NWB real mean errors were all negative. As

the knee was moving into full knee extension (electrogoniometer reading= 0°) during this

task, a negative difference between the reproduced angle and the target angle indicates

"overshooting". Overshooting implies that when asked to reproduce the target knee angle,

subjects would overestimate and attain an angle between 0° and 30°.

Condition	Mean Absolute Degrees of Error ($\pm$SD)
No Electrical Stimulation/No Sleeve	-5.076 ($\pm$4.552)
No Electrical Stimulation/Sleeve	-4.024 ($\pm$4.208)
Electrical Stimulation/Sleeve	-4.770 ($\pm$4.480)
Electrical Stimulation/No Sleeve	-5.031 ($\pm$4.389)

Table 9. NWB Real Mean Errors with Standard Deviation by condition

One-way parametric ANOVA showed no significant difference between the treatment groups. Even though the data followed a normal distribution, a Friedman repeated measures analysis of variance on ranks was performed, but it did not show significant differences either.

Parametric	One-way ANOVA	p=0.263	Two-way ANOVA	Sleeve level	p=0.192
				Stimulation level	p=0.372
				Interaction	p=0.294
Nonparametric	One-way ANOVA	p=0.5419	Two-way ANOVA	Sleeve level	p=0.299
				Stimulation level	p=0.4042
				Interaction	p=0.4006

Table 10. NWB Real Mean Error Statistical p values. (* indicates significance)

Two-way parametric ANOVA was performed and no significant differences were detected between the different levels of stimulation, the different levels of sleeve, or with the interaction of the two. One-way ANOVA found no significant differences between the measured variables with the testing condition. The average means for all trials within each condition were transformed to ranks in the SigmaStat software and a two-way ANOVA was performed on ranks due to failed normality in the two-way analysis. However, no significant differences were detected.

4.3.2. PWB Real Mean Error

Unlike the NWB real mean errors, the PWB real errors were positive which is shown in the figure below (Figure 27). As the knee was moving into greater knee flexion during this task, a positive difference between the reproduced angle and the target angle indicates that the subjects tended to "overshoot" the target angle.
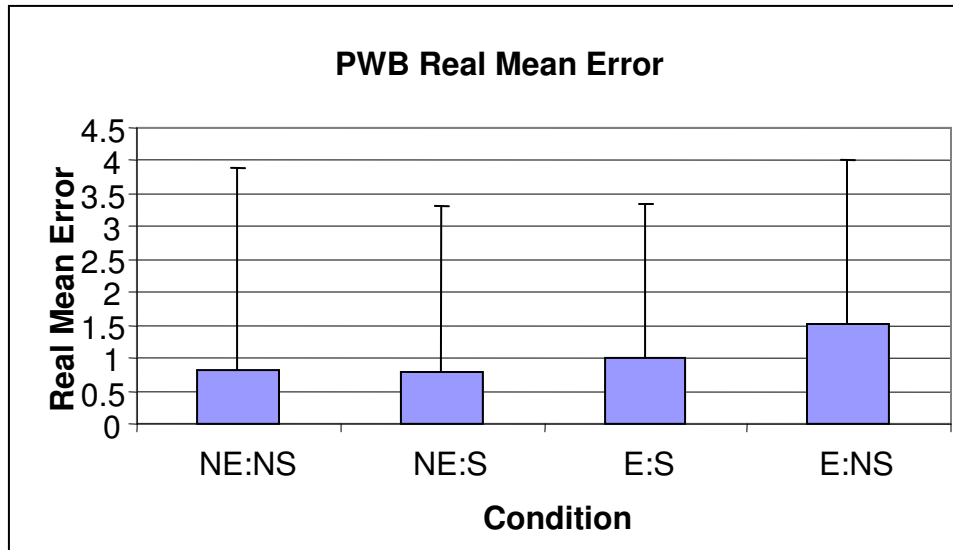
Figure 27. PWB Real Mean Errors with Standard Deviation

The condition means and standard deviations are given in the table below (Table 11).

Condition	Mean Absolute Degrees of Error (±SD)
No Electrical Stimulation/No Sleeve	0.809 (±3.075)
No Electrical Stimulation/Sleeve	0.779 (±2.526)
Electrical Stimulation/Sleeve	1.008 (±2.327)
Electrical Stimulation/No Sleeve	1.518 (±2.499)

Table 11. PWB Real Mean Errors with Standard Deviation by Condition

Parametric and nonparametric One and Two-Way ANOVA were performed to determine
whether significant differences exist between the different treatment groups.

	One-way ANOVA		Two-way ANOVA		
Parametric	**One-way ANOVA**	p=0.591	**Two-way ANOVA**	Sleeve level	p=0.517
				Stimulation level	p=0.255
				Interaction	p=0.610
Nonparametric (ranks)	**One-way ANOVA**	p=0.3476	**Two-way ANOVA**	Sleeve level	p=0.3847
				Stimulation level	p=0.2492
				Interaction	p=0.6803

Table 12. PWB Real Mean Error Statistical p values (*indicates significance)

One-way parametric ANOVA showed no significant difference between the treatment groups. Even though the data followed a normal distribution, a Friedman repeated measures analysis of variance on ranks was performed, but it did not show significant differences either. Two-way parametric ANOVA was performed and no significant differences were detected between the different levels of stimulation, the different levels of sleeve, or with the interaction of the two. Due to nonconformance to normality during the two-way analysis the average means of all trials within each condition were transformed to ranks and a two-way ANOVA was performed on ranks, but no significant differences were detected.

4.4. Standard Deviation Error

In addition to the absolute and real mean errors, a standard deviation error was recorded. The standard deviation error was calculated by using the instantaneous target angle measurement as a reference point and subtracting the three second reproduction angle measurement.

4.4.1. NWB Standard Deviation Error

The standard deviation of each measurement was taken and the difference between the target and reproduced standard deviation measurement was averaged across all 24 subjects. The standard deviation means and their standard deviations are shown in figure 28 and listed in table 13.
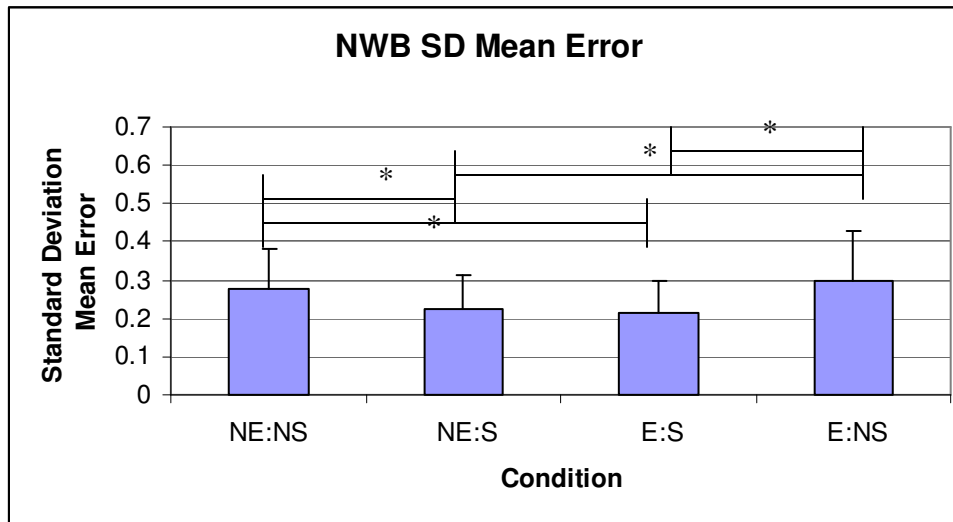
Figure 28. NWB Standard Deviation Mean Error by condition (* indicates significance between groups)

Condition	Mean Absolute Degrees of Error ($\pm$SD)
No Electrical Stimulation/No Sleeve	0.2754 ($\pm$0.105)
No Electrical Stimulation/Sleeve	0.2249 ($\pm$0.088)
Electrical Stimulation/Sleeve	0.2128 ($\pm$0.087)
Electrical Stimulation/No Sleeve	0.2963 ($\pm$0.133)

Table 13. NWB SD Mean Errors with Standard Deviations by condition

An interesting point to note is that the standard deviation mean error is lowest during the electrical stimulation/sleeve (E/S) condition rather than during the no electrical stimulation/sleeve condition (NE/S). This may demonstrate that the mean error varies less during the E/S condition while performing the NWB task. While both the E/S and NE/S

conditions produce the lowest standard deviation mean error, it is interesting to note that the

E/NS condition had little effect on the standard deviation mean error. In fact the error during

this condition was higher than the control condition.

Parametric	One-way ANOVA	p=0.002*	Two-way ANOVA	Sleeve level	p=0.007*
				Stimulation level	p=0.760
				Interaction	p=0.229
Nonparametric	One-way ANOVA	p=0.039*	Two-way ANOVA	Sleeve level	p=0.015*
				Stimulation level	p=1.00
				Interaction	p=0.434

Figure 29. NWB SD Mean Error Statistical p values (* indicates significance)

One-way ANOVA revealed significant differences between treatments. The Holm-Sidak

method of multiple comparisons showed that significant differences were detected

specifically between the E:NS and E:S, E:NS and NE:S, NE:NS and E:S, and NE:NS and

NE:S groups.

4.4.2. PWB Standard Deviation Error

Condition standard deviation means along with their respective standard deviations are

illustrated in Figure 30 and listed in Table 14.
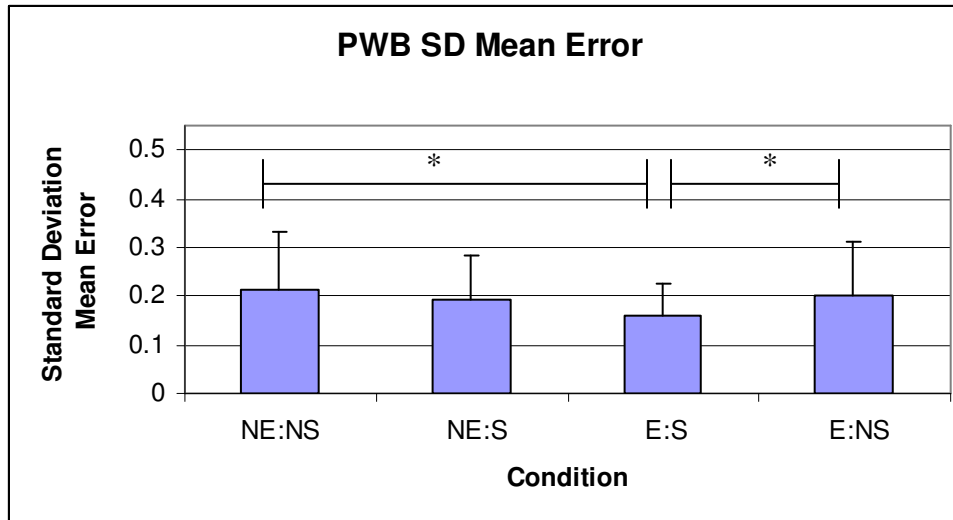
Figure 30. PWB SD Mean Error by condition (* indicates significance between groups)

Table 14 shows that standard deviation mean errors were lowest during the

stimulation/sleeve (E/S) condition and greatest during the control (NE/NS) condition. The

low standard deviation mean errors during the E/S condition demonstrate that overall, the

subject's ability to maintain the desired angle varied less compared with the control condition

(NE/NS). These data support the idea that the combination of stimulation and sleeve

provides for accurate joint position sense.

Condition	Mean Absolute Degrees of Error ($\pm$SD)
No Electrical Stimulation/No Sleeve	0.214 ($\pm$0.1195)
No Electrical Stimulation/Sleeve	0.192 ($\pm$0.091)
Electrical Stimulation/Sleeve	0.162 ($\pm$0.063)
Electrical Stimulation/No Sleeve	0.201 ($\pm$0.11)

Table 14. PWB SD Mean Error with Standard Deviation by condition

Statistical analysis showed that significant differences were present with the parametric

analysis but not with the nonparametric analysis. One-way parametric ANOVA showed

significant differences and the Two-way ANOVA also picked up significant differences but only with the level of sleeve present.

Parametric	**One-way ANOVA**	p=0.033*	**Two-way ANOVA**	Sleeve level	p=0.039*
				Stimulation level	p=0.093
				Interaction	p=0.490
Nonparametric	**One-way ANOVA**	p=0.384	**Two-way ANOVA**	Sleeve level	p=0.242
				Stimulation level	p=0.086
				Interaction	p=0.4601

Table 15. PWB SD Error Statistical p values (*indicates significance)

One-way ANOVA revealed significant differences between treatments. The Holm-Sidak method of multiple comparisons showed that significant differences were detected specifically between the E:NS vs. E:S and NE:NS vs. E:S groups.

4.5. Regression Analysis

Additionally, we investigated whether the control mean absolute error would affect the difference of mean errors between the control condition (NE:NS) and the three remaining test conditions (i.e. improvement in positioning).

4.5.1. NWB Absolute Mean Error Regression Analysis

Correlation coefficients (R) range from -1 to 1, with -1 demonstrating corresponding variables vary in opposite directions, a value of 1 shows the variables vary together with a strong relationship, and 0 demonstrates a completely independent relationship.

The NE/NS-NE/S condition had a low coefficient 0.309 (P=0.142). The NE/NS-E/S condition was correlated more highly with a coefficient of 0.540 that showed significance (P=0.006) which means that the difference between the control condition (NE/NS) mean error and the E/S condition mean error was most strongly related to the control condition mean error itself. The last condition (NE/NS-E/NS) had a correlation (0.145) closer to zero which implies a more independent relationship (P=0.499).

Linear Regression NE:NS vs. NE:NS-NE:S
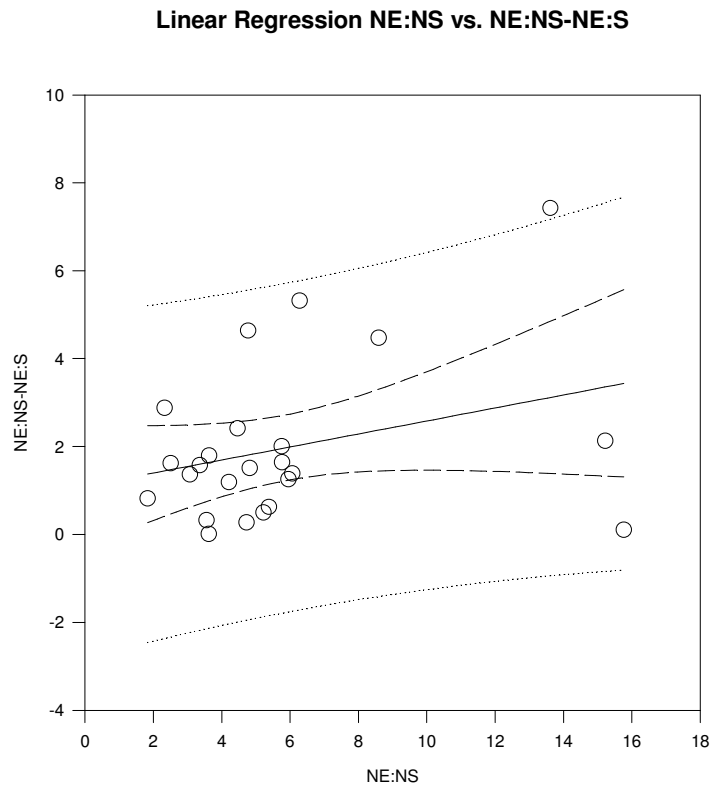
Figure 31. NWB Regression Analysis of NE:NS vs. NE:NS-NE:S (p=0.142, R=0.309)

Linear Regression NE:NS vs. NE:NS-E:S
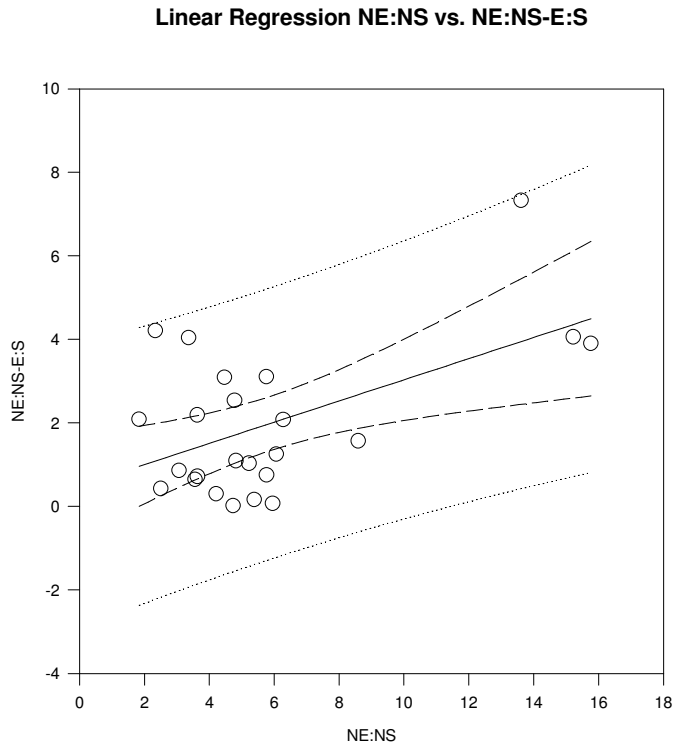
Figure 32. NWB Regression Analysis of NE:NS vs. NE:NS-E:S (p=0.006*, R=0.540)

Linear Regression NE:NS vs. NE:NS-E:NS
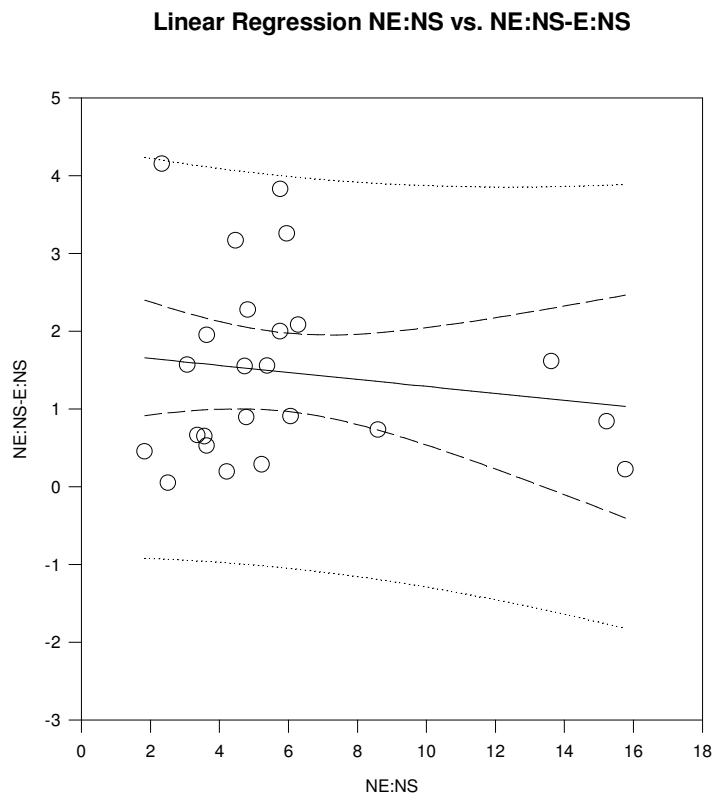
Figure 33. NWB Regression Analysis of NE:NS vs. NE:NS-E:NS (p=0.499, R=0.145)

4.5.2. PWB Absolute Mean Error Regression Analysis

A linear regression analysis was performed on the control condition and the difference between the control condition and the three remaining conditions specific to the PWB task. A significant relationship was detected between the control and the difference in control and NE/S condition (R=0.618, P=0.001) and between control and the difference in control and E/S condition (R=0.780, P<0.001). However, the correlation between the control and the difference in control and E/NS condition (R=0.151, P=0.480) was not significant.

PWB Linear Regression NE:NS vs. NE:NS-NE:S
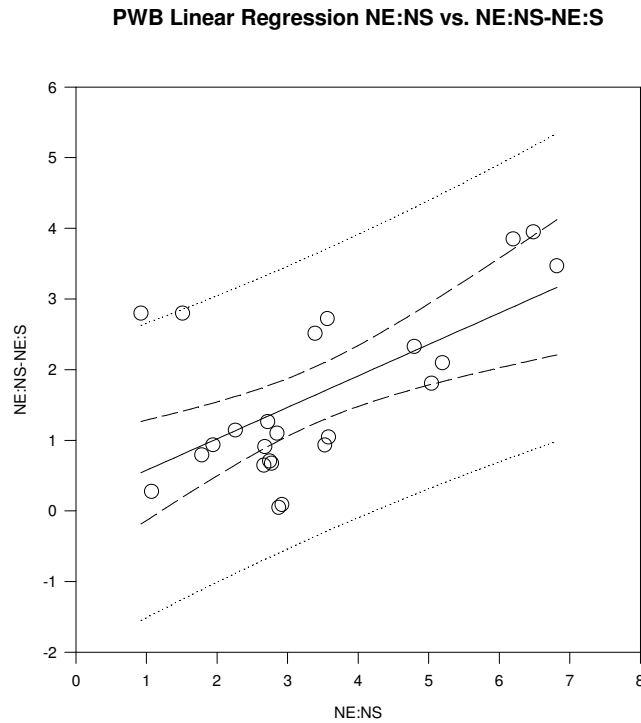
Figure 34. PWB Regression Analysis of NE:NS vs. NE:NS-NE:S (p=0.001*, R=0.618)

PWB Linear Regression NE:NS vs. NE:NS-E:S
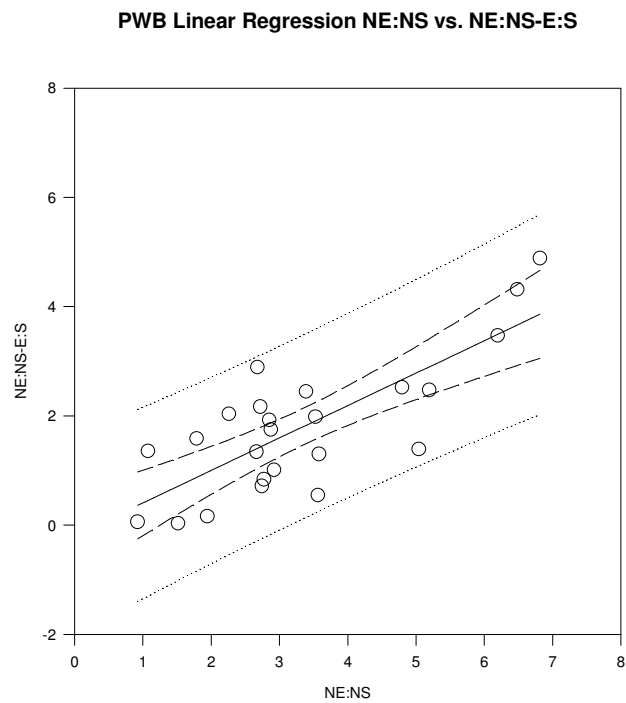
Figure 35. PWB Regression Analysis of NE:NS vs. NE:NS-E:S (p<0.001*, R=0.780)

PWB Linear Regression NE:NS vs. NE:NS-E:NS
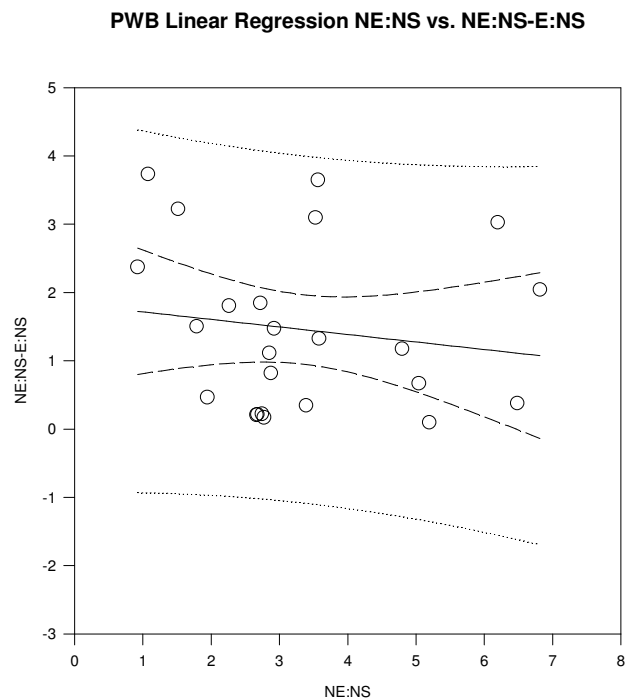
Figure 36. PWB Regression Analysis of NE:NS vs. NE:NS-E:NS (p=0.480, R=0.151)

4.6. Exclusion of 6 subjects

After examining the above correlations and observing the trend for greater improvement in absolute error with the E/NS and NE/S conditions when greater errors were initially present in the control condition, we were curious as to how the statistics might change for a sample of subjects with greater absolute error in the control condition. We simulated a sample of subjects with greater absolute error for the control condition by excluding subjects from our original set of subjects who had an absolute error less than 2 degrees for their control condition in the PWB task.

4.6.1. Exclusion of 6 subjects (PWB data)

Partial weight bearing data for the 18 remaining subjects is shown below (Figure 37, Table 16).
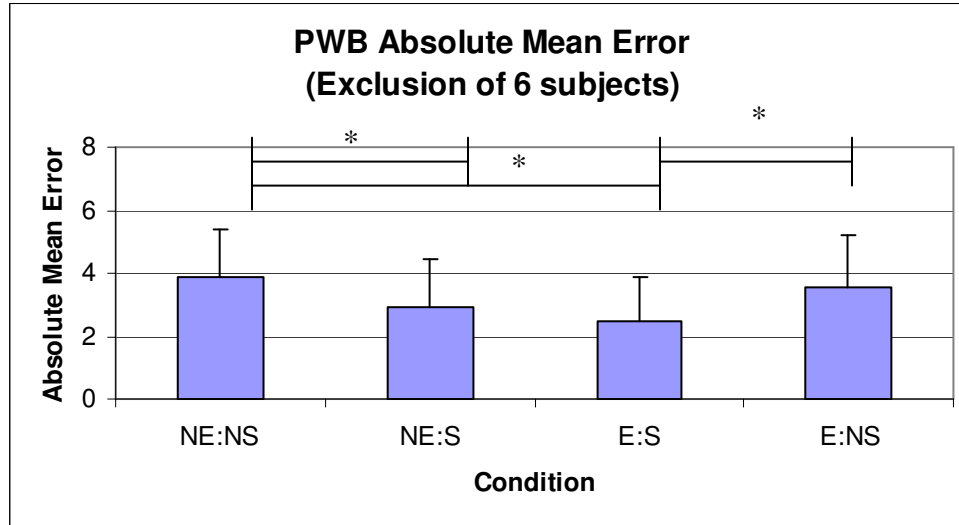
Figure 37. PWB Absolute Mean Error (Exclusion of 6 subjects, * indicates significance between groups)

It is important to note that during the PWB task errors in the E/S condition were less than the control condition.

Condition	Mean Absolute Degrees of Error ($\pm$SD)
No Electrical Stimulation/No Sleeve	3.901 ($\pm$1.468)
No Electrical Stimulation/Sleeve	2.943 ($\pm$1.479)
Electrical Stimulation/Sleeve	2.496 ($\pm$1.346)
Electrical Stimulation/No Sleeve	3.548 ($\pm$1.684)

Table 16. PWB Absolute Mean Error with Standard Deviation (Exclusion of 6 subjects)

The statistical analysis performed on the PWB task data revealed significant differences

between treatments, specifically with the level of sleeve condition.

	One-way ANOVA		Two-way ANOVA		
Parametric	**One-way ANOVA**	p=0.0122*	**Two-way ANOVA**	Sleeve level	p=0.011*
				Stimulation level	p=0.260
				Interaction	p=0.837
Nonparametric	**One-way ANOVA**	p=0.0137*	**Two-way ANOVA**	Sleeve level	p=0.005*
				Stimulation level	p=0.267
				Interaction	p=0.761

Table 17. PWB Absolute Mean Error Statistical p values (Exclusion of 6 subjects, * indicates significant differences)

4.7. Effects of Testing Conditions for Each Gender

A component of the study that was added was analysis of statistical differences in response

to the testing conditions for each gender. Twenty four subjects were tested and composed of

12 females and 12 males.

4.7.1. NWB Error Gender Based Differences

Comparison of male and female condition means with standard deviations during the

NWB task is shown below (Figure 38, Table 18).
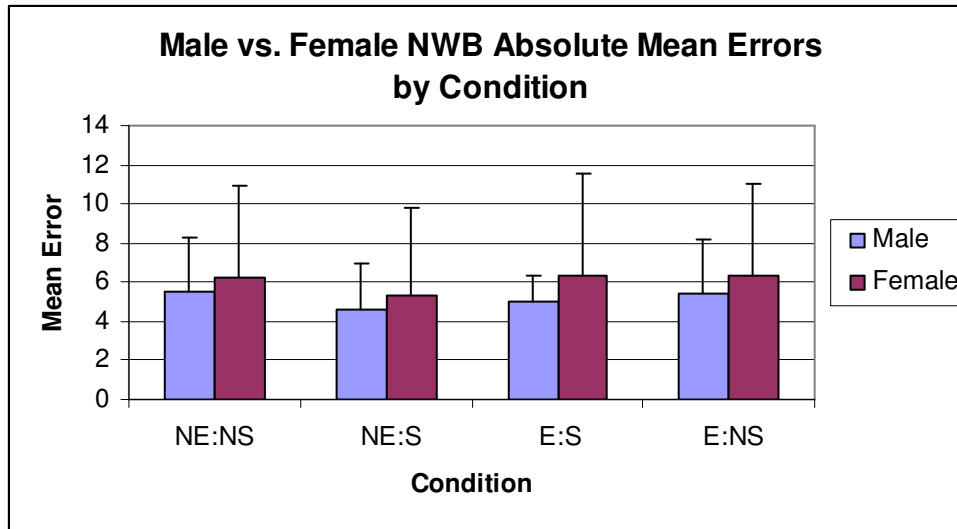
Figure 38. NWB Error Means (+/- SD) Gender Based Differences by condition

Condition	Mean Absolute Degrees of Error (+SD)	
	Male	Female
No Electrical Stimulation/No Sleeve	5.528 (+2.736)	6.186 (+4.735)
No Electrical Stimulation/Sleeve	4.590 (+2.317)	5.327 (+4.492)
Electrical Stimulation/Sleeve	5.015 (+1.331)	6.371 (+5.133)
Electrical Stimulation/No Sleeve	5.408 (+2.74)	6.381 (+4.608)

Table 18. NWB Gender Based Differences in Mean and Standard Deviation

As can be seen in the table above, mean errors and standard deviations were higher in

females for each condition.

Female	**Parametric**	**One-way ANOVA**	p=0.365	**Two-way ANOVA**	Sleeve level	p=0.420
					Stimulation level	p=0.177
					Interaction	p=0.398
	Nonparametric	**One-way ANOVA**	p=0.572	**Two-way ANOVA**	Sleeve level	p=0.526
					Stimulation level	p=0.180
					Interaction	p=0.471
Male	**Parametric**	**One-way ANOVA**	p=0.590	**Two-way ANOVA**	Sleeve level	p=0.364
					Stimulation level	p=0.758
					Interaction	p=0.420
	Nonparametric	**One-way ANOVA**	p=0.475	**Two-way ANOVA**	Sleeve level	p=0.837
					Stimulation level	p=0.823
					Interaction	p=0.824

Table 19. NWB Gender Based Difference Statistical p values (*indicates significance)

No significant differences were detected between treatments in male or female subgroups.

However, significant trends can be seen in Table 18 above with the difference between

NE/NS and NE/S conditions for both sexes being the highest of all conditions.

4.7.2. PWB Instantaneous Error Gender Based Differences

Male and female mean errors by condition during the PWB task are illustrated below

(Figure 39, Table 20).
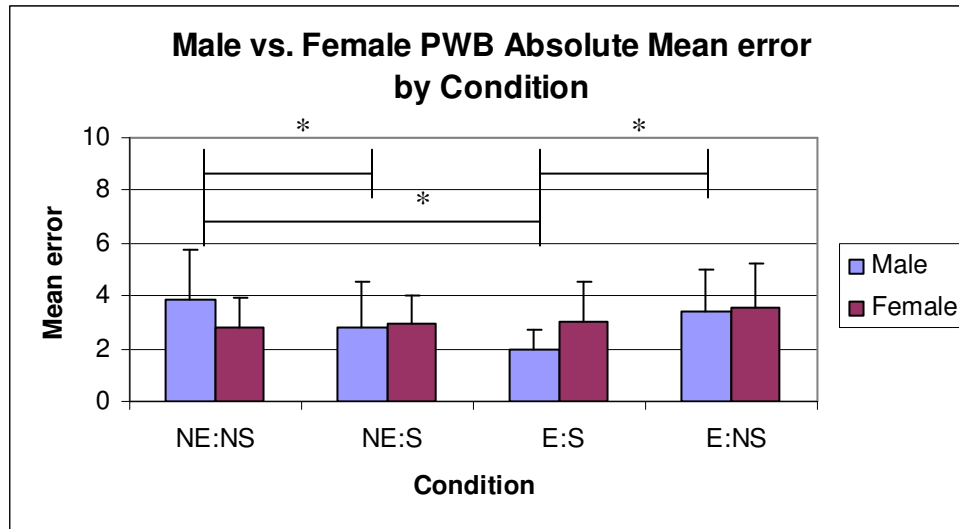
Figure 39. PWB Gender Based Differences

Condition	Mean Absolute Degrees of Error ($\pm$SD)	
	Male	Female
No Electrical Stimulation/No Sleeve	3.855 ($\pm$1.940)	2.840 ($\pm$1.111)
No Electrical Stimulation/Sleeve	2.809 ($\pm$1.730)	2.931 ($\pm$1.084)
Electrical Stimulation/Sleeve	1.943 ($\pm$0.797)	3.024 ($\pm$1.535)
Electrical Stimulation/No Sleeve	3.432 ($\pm$1.532)	3.530 ($\pm$1.702)

Table 20. PWB Gender Based Differences in Means and Standard Deviation

Unlike the NWB task, all female condition mean errors are not greater than the male condition mean errors in the PWB task. However, the female error standard deviations are less during the PWB task compared with the NWB task. These differences in standard deviation demonstrate that females vary greatly in their ability to accurately reproduce joint angles while in a nonweight bearing condition.

		One-way ANOVA		Two-way ANOVA			
Female	Parametric	One-way ANOVA	p=0.621	Two-way ANOVA	Sleeve level		p=0.584
					Stimulation level		p=0.424
					Interaction	p=0.406
	Nonparametric	One-way ANOVA	p=0.801	Two-way ANOVA	Sleeve level		p=0.738
					Stimulation level		p=0.432
					Interaction	p=0.486
Male	Parametric	One-way ANOVA	p=0.003*	Two-way ANOVA	Sleeve level		p=0.009*
					Stimulation level		p=0.039*
					Interaction	p=0.561
	Nonparametric	One-way ANOVA	p=0.0046*	Two-way ANOVA	Sleeve level		p=0.006*
					Stimulation level		p=0.074
					Interaction	p=0.416

Table 21. PWB Gender Based Difference Statistical p values (* indicates significance)

One and Two-way ANOVA revealed no significant differences for females when broken down by gender. However, it is important to note that there were several significant differences in the male group. Most importantly, the level of stimulation was significant during the parametric analysis. Both male and female subgroups passed normality during the One-way ANOVA but both groups failed normality during the Two-way ANOVA. The Holm-Sidak method of multiple comparisons revealed significant differences in the male subgroup between the NE:NS vs. E:NS, NE:NS vs. NE:S, and E:NS vs. E:S groups.

4.8. Electrical Stimulation Lasting Effects

To determine whether the application of electrical stimulation had any lasting effects on the errors of the control condition, we looked at the control condition error relative to its place in the task sequence. We felt that any lasting effects would be brought out by a decrease in the control condition error as it progressed further along within the task sequence. For example, the control condition error would be the greatest in task #1 where it was first within the sequence and the error would be the least in task #6 where the control condition is the last in the sequence. The following figure shows the control condition means within each task (#1-6).
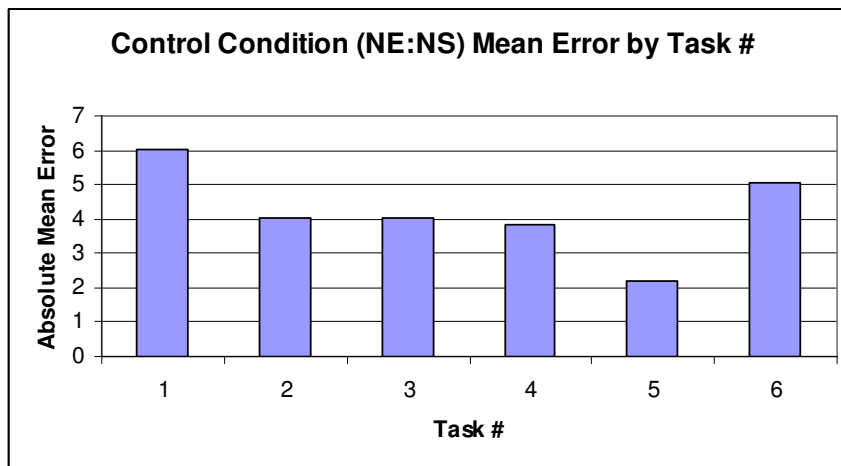
Figure 40. Control Condition (NE:NS) Absolute Mean Error by Task #

The figure above illustrates that while there could be a significant trend through the first five task sequences, the control condition error in task #6 is greater than the preceding errors. One-way ANOVA revealed no significant differences between task # and absolute mean error (P=0.357 nonparametric, P=0.324 parametric).

5. Discussion

Osteoarthritis is thought to be caused by and contribute to proprioceptive deficits. Analysis of joint position sense is a method of measuring proprioception and if a therapy has the ability to improve a person's joint position sense and thus their proprioception, that specific therapy may be a method of delaying osteoarthritis onset and progression. In looking at the concept of stochastic resonance as applied through electrical stimulation, it became apparent that in order for this therapy to be applied clinically, it must be applied through some type of garment or knee brace. Several studies have examined the efficacy of neoprene knee sleeve both on normal subjects and those suffering from ACL injury/reconstruction, and found that joint position sense is more accurate with a sleeve compared to a no sleeve condition [10, 12, 27, 42].

Our purpose was to determine whether subthreshold electrical stimulation applied at the knee would improve proprioception. We set out to determine whether the stimulation would improve proprioception beyond that seen with a sleeve alone and we hypothesized that the addition of stimulation to the sleeve condition would further improve proprioception. And lastly, we wanted to determine if the degree of improvement seen through the combinations of sleeve/no sleeve and stimulation/no stimulation conditions varies during the partial and non weight bearing tasks. We hypothesized that proprioception would be more accurate during the sleeve/stimulation condition than the no sleeve/no stimulation control condition specifically in the partial weight bearing task. We also hypothesized that proprioception

would be more accurate during the sleeve/no stimulation condition than the no sleeve/no stimulation control condition in the nonweight bearing task specifically in the nonweight bearing task.

5.1. Analysis of Results

5.1.1. Absolute Mean Error

During each trial an instantaneous measurement of the joint flexion angle was taken upon depression of an electronic trigger. All results presented in the preceding results section were instantaneous measurements in keeping with other studies that evaluated joint position sense.

Data analysis of the absolute mean errors from joint position sense testing did not reveal any treatment main effects in the NWB task. The main difference within this task that we anticipated to observe was that proprioception would be more accurate during the NE/S condition compared with the NE/NS control condition. While significant differences were not detected between the sleeve levels, stimulation levels, or the interaction of the two, a promising trend was shown as the mean error of the sleeve alone condition was the lowest of the four conditions. Several studies have documented the effects of a neoprene sleeve on joint position sense[10, 12, 27]. Birmingham et al. (1998) demonstrated a 1.2^{o} decrease in absolute mean error when a sleeve was added during a sitting open kinetic chain exercise[27]. Herrington et al. demonstrated a 0.6^{o} difference in mean absolute error between the no sleeve and sleeve conditions while seated in a NWB position[12]. Additionally, Birmingham et al. (2000) found that mean absolute error scores decreased by 0.8^{o} with the application of a neoprene sleeve[10]. Specific to this study, we saw a 0.91^{o} difference in mean absolute error when the sleeve was added compared with the control

condition (NE/NS). Despite being unable to detect a significant effect of the sleeve, positive trends were shown towards a sleeve effect in the NWB condition.

The chief effect we hoped to show during the PWB task was a decrease in absolute mean error with the stimulation and sleeve combined when compared with the no stimulation, no sleeve control condition. We felt that seeing a decrease in this condition was most important because in the future the electrical stimulation therapy would be incorporated into a knee brace to be used in a clinical setting. We hypothesized that joint position sense would be most accurate during the stimulation/sleeve condition as more mechanoreceptors would be stimulated in a load bearing task. We felt that the neoprene sleeve would increase the cutaneous receptor contribution to joint position sense. Since the idea of measuring joint position sense while applying electrical stimulation and wearing a knee sleeve is novel, there is no previous literature available for comparison. A significant difference was detected between treatment conditions in the PWB task when looking at the effect of the presence of the sleeve. This is further demonstrated by the means for the 4 conditions. The mean error score is lowest when both the stimulation and sleeve are present, but actually highest when no sleeve is present and the stimulation is acting alone, showing the importance of the presence of the sleeve. Additionally, all absolute mean error scores were less than those during the NWB task, which agrees with previous literature showing joint position sense to be more accurate during a load bearing condition[24, 26].

5.1.2. Regression Analysis

When comparing the control condition to the difference between the control condition and the three remaining conditions in the NWB task, only one correlation was significant, namely NE/NS vs. NE/NS-E/S. Specific to the PWB task, two significant relationships were found:

NE/NS vs. NE/NS-NE/S and NE/NS vs. NE/NS-E/S. By taking the difference between the control and the remaining conditions and then comparing that with the control itself, the level of improvement from the control condition was correlated with the control condition error.

Results from the regression analysis led us to wonder whether small mean errors in the control condition would mean treatments presented in the three remaining conditions would have no effect on absolute mean error because the error was already minimized. As a result, we excluded the six subjects whose control condition mean error was below 2° and looked at the condition means. While mean errors were slightly higher for all conditions in the NWB task relative to the entire subject data set, no additional significant differences between treatments was detected. Mean errors also increased in the PWB task compared to the mean errors of the entire subject pool but not to the extent as with the NWB task. A significant difference between treatment groups, specifically the effect of the sleeve was detected. Overall, by excluding 6 subjects no additional significance or reduction of mean errors was achieved.

5.1.3. Additional Results

Additionally, real mean error and standard deviation mean error were measured. Unlike the absolute mean error, the absolute value was not taken for the real mean error. An interesting point to note is the presence of target angle "overshooting" and "undershooting". During the PWB task, small positive real mean errors indicate that subjects tended to slightly "overshoot" the target angle when reproducing it. Subjects would also generally "overshoot" the target angle when in the NWB position. This may have been overcompensation as a result of reduced mechanoreceptor activity and feedback in a nonweight bearing task. As it

was described in the background section, cutaneous receptors alone instead of joint and tissue receptors are thought to play the dominant role in exercises that bear no load.

Standard deviation mean errors were measured as well to show the amount of variation present during the holding period for all of the conditions in both the NWB and PWB tasks. Results indicate that the electrical stimulation/sleeve condition had the least standard deviation for both tasks which could serve as further evidence for the benefits of this therapy. An additional point to make is that the control condition had the greatest deviation in the PWB task but it was the stimulation/no sleeve condition that showed the greatest deviation during the NWB task.

The subject data were also categorized according to gender in order to draw conclusions about any mean error differences in conditions specific to gender. When comparing males and females during the NWB task, no statistical distinctions could be made. There were no significant differences across gender for any condition which is in agreement with a previous study. However, this specific study by Hageman et al. tested for postural control not joint position sense[43]. They found no significant gender effects when testing for postural control in normal subjects.

One main observation also specific to gender worthy of mentioning in the present study is that females had greater absolute mean error scores than males during the NWB task. The standard deviation of the absolute mean error for the females was also considerably larger than the males'. On the other hand, males and females had generally the same absolute mean errors and standard deviations when looking at the PWB task. When comparing between conditions in the PWB task, a significant difference with the testing condition was detected in males for the presence of the sleeve and the presence of the stimulation, but no significant

differences were detected specific to females in either the PWB or the NWB task. When looking at gender based differences, the results of this study raise further questions about joint position sense in males compared to females. Possible explanations for these differences may include variation in body mass index or hormonal variation between gender.

5.2. Study Limitations

While we believe this study is important with valid results, it was not without limitations. One of which is that this study was performed on normal subjects whose proprioception is considered to be quite accurate. As a result, there is an inherent limitation on the amount of improvement that can be seen in the conditions. It is assumed that any improvements seen in normal subjects will be amplified in patients who have abnormal proprioception such as OA patients.

Lasting effects of the stimulation may have been a limitation as they could have affected results in subsequent conditions. An analysis was done to look at mean errors in the control condition relative to their location within the task sequence which showed no obvious lasting effects. However, there is a possibility that the stimulus may have some lasting effects that were not detected.

The fitting of the neoprene knee sleeve may have also been a limitation. The sleeve was fitted for each subject based on comfort and their positive response to the question "Does the brace feel secure but not excessively tight?". One study by Hassan et al. tested joint position sense in osteoarthritis subjects while the subjects wore one of two types of braces, one being looser than the other[44]. Although they found no significant differences between braces specific to proprioceptive acuity, they did find an improvement in acuity with the application of the looser bandage. They also found a significant reduction in pain while subjects wore

the looser bandage. Specific to our study, we felt the neoprene sleeve was fit securely enough to provide the necessary support required for this study, although the degree of support and cutaneous mechanoreceptor stimulation can vary and this variation should not be discounted.

Additionally, it may have been possible that subjects received cues from hip and ankle flexion despite the attempts to minimize ankle cues by the investigators in the form of a heel wedge. There was no way to eliminate hip flexion cues while performing the PWB task and this may have contributed to the subject's sensation of joint position. However, this effect would be constant across conditions.

The removal and placement of the electrogoniometer between sleeve conditions may have also been a limitation. During all trials in the PWB and NWB tasks the knee joint angle was measured by an electrogoniometer. A certain amount of inaccuracy among the knee angle measurement may have been present due to the removal and replacement of the electrogoniometer in order to take off or put on the knee sleeve. It was difficult to know whether the electrogoniometer was placed in the same exact position for each condition.

The use of a single target angle may have been a limitation. Also, the small sample size may have prevented detection of a significant sleeve effect in NWB and a greater improvement in stimulation/sleeve condition compared to the sleeve alone in the PWB task.

5.3. Clinical Relevance

We feel the findings of this study are clinically significant. One study by Kirkley et al. demonstrated that small improvements can be seen in patients with osteoarthritis while wearing a knee brace and that these improvements, specifically decreased pain and improvement in the disease-specific quality of life, can increase function[45]. Another study

by Hurley and Scott showed that exercise regimes can improve quadriceps strength[46]. These strength increases were associated with a reduction in disability and an increase in function. These studies show that small differences in functional measurements resulting from a treatment method are related to differences in clinical outcome measures. These differences in clinical outcome measures determine clinical significance.

Findings from other studies showing a decrease in joint position sense with the application of a neoprene sleeve while performing a NWB task were confirmed by the results of this study[11, 12, 27]. Additionally, significant differences in absolute mean error between treatments during the PWB task were seen. This provides promise to the idea of incorporating subthreshold electrical stimulation into a knee sleeve as a therapy for improving proprioception. Numerous studies have documented proprioceptive deficits in OA patients, and we feel this population may benefit from the stimulation therapy[2-4, 37, 47, 48]. Also, we feel any patient population whose proprioception is abnormal may benefit from this therapy. This may include patients suffering from intraarticular fracture, Parkinson's disease, diabetes, stroke, or those patients who have had a total joint replacement.

5.4. Future Research

The results of this study show promise towards an effective therapy for treating proprioceptive deficits. We feel more research is necessary to determine the effect of subthreshold electrical stimulation on joint position sense in OA patients. Future research with these patients would require slight modifications to the study protocol such as a fewer number of trials with each condition, reduced time to hold the knee in the target position, and a lower angle of platform inclination during the PWB task. The availability of OA patients at

UNC Hospital would allow for easier recruitment of a large number of subjects. By increasing the subject number from 24 which was used in this study, we may improve the ability to detect significant differences between conditions. Future studies would involve an investigation of biomechanical loading changes that result from improved proprioception. Additionally, future studies with OA patients will allow for additional conclusions to be drawn about the effectiveness of this therapy and its potential for clinical use in other populations who suffer from abnormal proprioception.

5.5. Conclusions

Certain conclusions can be drawn from the results presented in this study. We first hypothesized that proprioception would be more accurate during the stimulation/sleeve condition compared to the control condition. We found that proprioception is improved during the PWB task when the stimulation is combined with the neoprene knee sleeve compared with the control condition. However, this condition was not found to be significantly different from the control condition during the NWB task.

We also hypothesized that the application of electrical stimulation would improve proprioception beyond that seen through tactile stimulation of a neoprene knee sleeve alone. During the PWB task, the mean error was the lowest in the stimulation/sleeve condition. The no stimulation/sleeve condition mean error was slightly higher than the stimulation/sleeve condition. The stimulation/sleeve condition mean error was significantly lower than the control condition, thus providing support for our hypothesis that proprioception was more accurate during the stimulation/sleeve condition compared to the control condition. However, no such conclusions can be drawn in the NWB task. Data for the NWB task

indicate the sleeve alone has the greatest effect with the addition of stimulation having little to no additional effect.

Lastly, we set out to determine if the degree of improvement through the combination of the sleeve/no sleeve and stimulation/no stimulation conditions varies during the PWB and NWB tasks. We found that overall, the combination of stimulation/sleeve has the greatest effect in the PWB task and that joint position sense was most affected by the no stimulation/sleeve condition in the NWB task.

APPENDIX A: Subject Questionnaire

Date & Time:_____

Age:_____

Sex: M/F

Weight:_____ Height:_____

Which is your dominant Leg (R/L)?:_____

How many hours/week are you physically active?_____
        (cardiovascular or resistance training)

Do you have any signs or symptoms of knee injury (i.e. pain, swelling, loss of function)?
Yes   No

Have you previously had knee surgery?
Yes   No

Do you have any known neurological conditions which may prevent you from sensing motion or feeling pain?
Yes   No

Do you have knee instability (determined by a feeling of "giving way")?
Yes   No

Do you suffer from any vestibular or somatosensory deficits which would cause dizziness, vertigo or imbalance?
Yes   No

Do you have a history of gait or postural disorders, seizures, diabetes, fainting, peripheral neuropathy, stroke or motion sickness?
Yes   No

Do you have a cardiac pacemaker or drug delivery pump?
Yes   No

Do you have a history of cardiac arrhythmia?
Yes   No

Are you pregnant?
Yes   No

For investigator use only:
Subject ID:_____
1st Task Sequence # (1-24):_____
2nd Task Sequence # (1-24):_____

APPENDIX B: Subject recruitment announcement

Researchers in the Orthopaedics and Sports Medicine Research Laboratories are conducting a study at UNC-Chapel Hill to determine whether proprioception is improved with the application of low level (below threshold of detection) electrical stimulation on the normal knee. We are looking for healthy volunteers between the ages of 18-35 years to participate as subjects in a research study investigating proprioception in the normal knee.

To enroll in this study, you must not have a history of knee injury or any neurological conditions, and you must not have previously had knee surgery. You must not be pregnant and you must be physically active.

You will be asked to perform knee flexion and extension exercises while electrical stimulation is applied to your knee at levels below your threshold of detection of them. Participation in this study will last approximately 2 hours.

You will not be paid for your participation in this study.

If you are interested in participating in this study or would like more information, please call:
Amber Collins (919) 966-1212 or email amcollin@email.unc.edu

This study is approved by Biomedical IRB (# 07-0030).

APPENDIX C: IRB application

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

Title of Study: Electrical Stimulation to Improve Proprioception in the Knee
Date: 1-8-07

Name and degrees of Principal Investigator: Amber Collins, BS
Department: Orthopaedics, Biomedical Engineering   Mailing address/CB #: 134 Glaxo Biotechnology
Bldg. CB# 7546 101A Mason Farm Rd. Chapel Hill, NC 27599
UNC-CH PID: Pager:
Phone #: 919-966-1212   Fax #: 919-966-3349   Email Address: amcollin@email.unc.edu

For trainee-led projects: __ undergraduate _X_ graduate __ postdoc __ resident __ other
Name of faculty advisor: Paul Weinhold, Ph.D.
Department: Orthopaedics, Biomedical Engineering   Mailing address/CB #: 134 Glaxo Biotechnology 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

Name, phone number, email address of project manager or coordinator, if any:

List **all other project personnel** including co-investigators, and anyone else who has contact with subjects or identifiable data from subjects: Dr. Troy Blackburn, Amber Collins, Dr. Joanne Jordan, and Dr. Chris Olcott

Name of funding source or sponsor:
_X_ not funded __ Federal __ State __ industry __ foundation __ UNC-CH
__ other (specify):   **Sponsor or award number**:

Include following items with your submission, where applicable.
- Check the relevant items below and include one copy of all checked items 1-11 in the order listed.
- Also include two additional collated sets of copies (sorted in the order listed) for items 1-7.
- → **Applications may be returned if these instructions are not followed.**

Check	Item	Total No. of Copies
☐	1. This application. One copy must have original PI signatures.	3
☐	2. Consent and assent forms, fact or information sheets; include phone and verbal consent scripts.	3
☐	3. HIPAA authorization addendum to consent form.	3
☐	4. All recruitment materials including scripts, flyers and advertising, letters, emails.	3
☐	5. Questionnaires, focus group guides, scripts used to guide phone or in-person interviews, etc.	3
☐	6. Protocol, grant application or proposal supporting this submission; (e.g., extramural grant application to NIH or foundation, industry protocol, student proposal).	3
☐	7. Documentation of reviews from any other committees (e.g., GCRC, Oncology Protocol Review Committee, or local review committees in Academic Affairs).	3
☐	8. Addendum for Multi-Site Studies where UNC-CH is the Lead Coordinating Center.	1
☐	9. Data use agreements (may be required for use of existing data from third parties).	1
☐	10. Documentation of required training in human research ethics for all study personnel.	1
☐	11. Investigator Brochure if a drug study.	1

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

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?	__	_X_
A.2.2. Surveys, questionnaires, interviews, or focus groups with subjects?	_X_	__
A.2.3. Videotaping, audiotaping, filming of subjects (newly collected or existing)?	__	_X_

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)? *If yes*, give age range: to   years ....
	_X_
	__
	__
	__
	__
	__
	__
		__
		_X_
		_X_
		_X_
		_X_
		_X_
		_X_

A.2.5. a. Is this a multi-site study (sites outside UNC-CH engaged in the research)?
    b. Is UNC-CH the sponsor or lead coordinating center?
        If yes, include the ***Addendum for Multi-site Studies where UNC-CH is the Lead Coordinating Center***.
        If yes, will any of these sites be outside the United States?
            If yes, provide contact information for the foreign IRB.
	__
	__
	
	__
		_X_
		_X_
		
		__

A.2.6. Will there be a data and safety monitoring committee (DSMB or DSMC)?	__	_X_
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?	__ __	_X_ _X_

A.2.8. a. Investigational drugs? (provide **IND #**   )
    b. Approved drugs for "non-FDA-approved" conditions?
    All studies testing substances in humans must provide a letter of acknowledgement from the UNC Health Care Investigational Drug Service (IDS).
	__
	__
		_X_
		_X_

A.2.9. Placebo(s)?	__	_X_
A.2.10. Investigational devices, instruments, machines, software? (provide **IDE #**)	_X_	__
A.2.11. Fetal tissue?	__	_X_
A.2.12. Genetic studies on subjects' specimens?	__	_X_
A.2.13. Storage of subjects' specimens for future research? *If yes, see instructions for **Consent for Stored Samples**.*	__	_X_
A.2.14. Diagnostic or therapeutic ionizing radiation, or radioactive isotopes, which subjects would not receive otherwise? *If yes, approval by the **UNC-CH Radiation Safety** Committee is required.*	__	_X_
A.2.15. Recombinant DNA or gene transfer to human subjects? *If yes, approval by the **UNC-CH Institutional Biosafety** Committee is required.*	__	_X_
A.2.16. Does this study involve UNC-CH cancer patients? *If yes, submit this application directly to the **Oncology Protocol Review Committee**.*	__	_X_
A.2.17. Will subjects be studied in the General Clinical Research Center (GCRC)? *If yes, obtain the **GCRC Addendum** from the GCRC and submit complete application (IRB application and Addendum) to the GCRC.*	__	_X_

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.

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:		
(a) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with the sponsor of this study?	__ yes	_X_ no
(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?	__ yes	_X_ no
(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?	__ yes	_X_ no
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?	__ yes	_X_ no
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?	__ yes	_X_ no

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.

The purpose of this study is to evaluate knee proprioception with and without the application of electrical stimulation. A knee sleeve will also be introduced to determine its effect. Twenty-four healthy, physically active subjects will be tested. Participant exclusion is detailed in the Inclusion/Exclusion criteria section. Each subject will be tested in both a non-weight bearing (NWB) and a partial-weight bearing (PWB) setup. Within each setup the subject will be tested under four conditions: no electrical stimulation/no sleeve, electrical stimulation/no sleeve, no electrical stimulation/sleeve, and electrical stimulation/sleeve, 3 trials each. During each trial, the subject will be asked to actively reproduce a target angle of knee flexion. A second "dummy angle" will be introduced to decrease the risk of a memorization effect. The difference in target and reposition angles will be examined.

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 in normal adults and whether this improvement is superior to 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 twenty-four healthy subjects in the age range of 18-35 years. Attempts will be made to recruit twelve males and twelve females in order to achieve an adequate gender spread. We will also attempt to recruit subjects of various ethnic backgrounds. Subjects for this study will be volunteers who have no history of knee injury, no previous knee surgeries, and no neurological conditions. Additional exclusion criteria are detailed in the following section.

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. No history of functional instability of the knee joint
2. No current knee injuries or functional instability that limits knee function
3. Patients are physically active (perform cardiovascular or resistance training at least 1.5 hours/week)
4. Patients are between the ages of 18-35 years.

The exclusion criteria for study participants are as follows:
1. Any signs or symptoms of knee injury (swelling, pain, loss of function).
2. Self reported knee instability (determined as a feeling of "giving way").
3. Any known neurological conditions which may prevent the patients from sensing motion or feeling pain.
4. Subjects have previously had knee surgery.
5. Subjects are not physically active (less than 1.5 hours/week).
6. Subjects are not between the ages of 18-35 years. Exclusion of subjects after 35 years is necessary because the amount of joint wear in a patient with no previous injuries older than 35 is such that a preexisting proprioceptive deficit may exist without the subject's knowledge. This study aims to focus on normal subjects with no proprioceptive deficits.
7. Any known vestibular deficits or somatosensory deficits or any other balance disorder that may affect his/her performance.
8. Score less than or equal to 12 on the knee joint function assessment tool questionnaire.
9. History of gait, postural, neurological disorders, seizures, diabetes, fainting, peripheral neuropathy, stroke, and motion sickness.
10. Existing cardiac pacemakers or drug delivery pumps which may be interfered with by the electrical stimulators.
11. History of cardiac arrhythmia.
12. Participants should not be pregnant. Pregnant women have increased laxity in the joints which can cause proprioceptive deficits and this study aims to focus on normal subjects with no proprioceptive deficits.

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.

Twenty-four healthy, physically active subjects will be recruited for this study. Once this subject expresses an interest in participating in the study, they will be asked a series of questions.

The participants will also be asked whether they have any history of knee injury, whether they have any neurological conditions, balance conditions or vision deficits, whether they have previously had knee surgery, and whether they have any feelings of "giving way" in their knee. They will also be asked if they have a cardiac pacemaker, drug delivery pump, a history of cardiac arrhythmia, or

if they are pregnant. If the subject answers yes to any of the preceding question, they will be excluded from the study. Once a subject is determined eligible, they will be asked to fill out an informed consent form as well as a questionnaire before beginning the tests. The questionnaire will contain questions about the subject's age, weight, gender, and height.

Subjects will have their knee proprioception evaluated while performing both a partial-weight bearing (PWB) and a non-weight bearing (NWB) task. A PWB task will be used instead of a full weight bearing task as during potential future studies with an osteoarthritic population the subjects may not tolerate a full weight bearing task because of knee pain.   Tests will be performed on the subject's dominant knee where dominance will be defined as the limb that the subject would use to kick a soccer ball.   Both proprioceptive tests will be carried out under the following four conditions:
1. No electrical stimulation/no neoprene sleeve
2. Electrical stimulation/no neoprene sleeve
3. No electrical stimulation/neoprene sleeve
4. Electrical stimulation/neoprene sleeve.

The sequence of the conditions will be assigned to each subject using a counterbalance design. The table below (Table 1) illustrates the test sequences including the second "dummy angle" of 60° that will be used for each subject to decrease the risk of a memorization effect. The 60° angle task will use the conditions of the task before it. To illustrate this point, Male 1 task B which incorporates the 60° angle instead of the 30° angle will have the electrical stimulation/no sleeve condition.

Table 1

	1st Task							2nd Task
Sex	Sequence	A	B	C	D	E	F	Sequence
M	1	+E/-S	60deg	-E/-S	60deg	-E/+S	+E/+S	23
M	2	-E/+S	60deg	+E/+S	60deg	-E/-S	+E/-S	21
M	3	-E/-S	60deg	+E/-S	60deg	+E/+S	-E/+S	22
M	4	+E/+S	60deg	-E/+S	60deg	+E/-S	-E/-S	24
M	5	+E/-S	60deg	-E/-S	+E/+S	60deg	-E/+S	19
M	6	+E/+S	60deg	-E/+S	-E/-S	60deg	+E/-S	20
M	7	-E/+S	60deg	+E/+S	+E/-S	60deg	-E/-S	17
M	8	-E/-S	60deg	+E/-S	-E/+S	60deg	+E/+S	18
M	9	+E/-S	-E/-S	60deg	-E/+S	60deg	+E/+S	14
M	10	-E/+S	+E/+S	60deg	-E/-S	60deg	+E/-S	13
M	11	-E/-S	+E/-S	60deg	+E/+S	60deg	-E/+S	16
M	12	+E/+S	-E/+S	60deg	+E/-S	60deg	-E/-S	15
F	13	+E/-S	60deg	-E/-S	-E/+S	60deg	+E/+S	10
F	14	-E/+S	60deg	+E/+S	-E/-S	60deg	+E/-S	9
F	15	-E/-S	60deg	+E/-S	+E/+S	60deg	-E/+S	12
F	16	+E/+S	60deg	-E/+S	+E/-S	60deg	-E/-S	11
F	17	+E/-S	60deg	-E/-S	60deg	+E/+S	-E/+S	7
F	18	+E/+S	60deg	-E/+S	60deg	-E/-S	+E/-S	8
F	19	-E/+S	60deg	+E/+S	60deg	+E/-S	-E/-S	5
F	20	-E/-S	60deg	+E/-S	60deg	-E/+S	+E/+S	6
F	21	+E/-S	-E/-S	60deg	+E/+S	60deg	-E/+S	2
F	22	+E/+S	-E/+S	60deg	-E/-S	60deg	+E/-S	3
F	23	-E/+S	+E/+S	60deg	+E/-S	60deg	-E/-S	1
F	24	-E/-S	+E/-S	60deg	-E/+S	60deg	+E/+S	4

The second task sequence (PWB or NWB) will be the opposite conditions as in the first task for sequence A (NWB or PWB). Participants will be blind as to the task sequence to which they are assigned.   These sequences were designed to allow for the sleeve to remain on the subject once put in place in order to minimize the times the sleeve was placed and removed. In addition, these test sequences assure that each testing condition occurs with equal incidence at all stages of the sequence. Both the PWB and NWB joint proprioceptive tests will evaluate the subjects' joint position sense by determining the subject's ability to actively reproduce a target knee flexion angle.   Target angles will be defined as angles of knee flexion actively set by the subject and will be measured using an electrogoniometer which will give an electronic readout of the knee angle within an error of 0.5 degree.   Electrical stimulation will be applied by self-adhesive surface electrodes placed alone or beneath the neoprene sleeve. Each electrode is 1.5 inches in diameter and we anticipate using a current less than 5 mA. Although the current will be less than 5 mA, it will vary between subjects depending on the subject's level of detection. The two electrode pairs (an electrode pair consists of one stimulator and one ground) will be placed at four locations along the knee joint line in such as way that the current will be drawn laterally across the knee. The electrical stimuli will be applied in the form of a white noise signal low-pass filtered to 100Hz and applied to the electrode through a stimulus isolator. Initially each subject's threshold for detection of the electrical stimulus will be determined for each electrode location. During the

proprioceptive tests the amplitude of stimulation will be set to 50% of the threshold for detection. Electrodes will remain in place for all testing conditions. Electrodes will be reused between subjects but will be swabbed with alcohol between subjects.

Each subject will undergo 3 trials of proprioceptive testing for each testing condition during both the NWB and PWB tasks at a target of 30° of knee flexion as well as a dummy 60° angle. Subjects will be blindfolded and wear headphones playing white noise during all tests to eliminate visual and auditory cues. During the NWB task, the subject will be seated on an upright bench and their knee will be tested moving from a starting position of 90° flexion into extension. This test will simulate the positioning of the knee during the swing phase of gait prior to foot contact on the ground. For the PWB task the subject will lie flat on their back on a sliding reclined (20°) platform relative to the horizontal that is relatively frictionless. The starting position will be in full knee extension in single leg stance and the subjects will move into flexion. The subject's dominant leg will be tested. This test will simulate the positioning of the knee soon after foot contact during the early stance phase of gait. During the PWB task a wedge at the base of the subject's heel will be used to put the ankle in such a position as to eliminate passive tension ques from specific ankle muscle groups. For each task a trial will begin with the investigator telling each subject to flex their knee from the starting. The subject will hold the limb at the target position for 5 seconds and then return to the starting position. After returning to the starting position and holding for 5 seconds, the subject will then actively attempt to reposition the limb at the target angle. Once they reach what they perceive as the target angle they will depress an electronic switch which will provide a time stamp and they will hold their limb for 5 seconds. The reposition angle will be recorded and the absolute difference between the reposition and target angle will be computed as the absolute error for each trial and averaged across the three trials. The entire testing sequence will be repeated for each trial. Each subject will perform all 18 trials for each task (PWB and NWB).

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

After the subject expresses an interest in study participation and it is determined that they meet all the qualifications they will be contacted to schedule a testing session. 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 direct benefits for the healthy, normal patients involved in this study. However, scientific knowledge gained could allow us to consider an injured/diseased population which may benefit from the success of the study being described here. If results show a difference in normal patients, the hope is that a difference can be shown in patients with osteoarthritis. Osteoarthritic patients with a deficit in proprioception could see improvements in joint proprioception as a result of electrical stimulation. Abnormal wear of the knee may decrease, thereby possibly slowing the progression of the disease and reducing pain and discomfort.

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 risk of ligament strain, 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 during potential future studies with an osteoarthritic population since these subjects may not tolerate a full weight bearing task. During the non-weight bearing task, the patient will be in a seated position on an upright 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. Attempts to minimize risk will involve recruitment of healthy, physically active volunteers with no previous knee injuries.
Subject identification will remain confidential.

Each electrical stimulating device is built with a safety switch. A safety switch is in place so that the subject will not be injured from the very low electricity of the stimulating device. We will also use a level of electricity that is 50% of threshold detection as an additional safety precaution. If by chance there is an increase in the electrical output, the safety switch will detect the rise and the machine will cut off before the electricity is supplied to the subject.

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).

In deciding the appropriate number of test subjects required, a power analysis was completed. A power analysis for a paired t-test has indicated that for a standard deviation of the absolute error of angle reproduction of 50% of the mean and an expected improvement in angle reproduction of 30% with electrical stimulation, an N of 24 subjects would be required for a power of 0.8 and significance level of 0.05. 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 of 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 3 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   _**X**_ Yes   *If yes, check all that apply*:

a.   _**X**_Names

b.   __   Telephone numbers

c.   _**X**_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, characteristic or code, 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. **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).

Patient information will be attained upon completion of the study questionnaire. The subject's name will be linked to a numbered identifier through a spreadsheet which will be maintained by the study investigator in a locked cabinet located by a locked laboratory office. Access to the study information will only be given to members of the research team.

A.4.11. **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.

> _**X**_ No one
> __ Coordinating Center**:**
> __ Statisticians**:**
> __ Consultants**:**
> __ Other researchers**:**
> __ Registries**:**
> __ Sponsors:
> __ External labs for additional testing:
> __ Journals:
> __ Publicly available dataset:
> __ Other:

A.4.12. **Data security for storage and transmission**. Please check all that apply.

For electronic data:
> __ Secure network   _X_ Password access   __ Encryption
> __ Other (describe):
> _X_ Portable storage (e.g., laptop computer, flash drive)
> *Describe how data will be protected for any portable device:* A laptop will serve as the portable storage. Information contained in the laptop will be restricted by password.

For hardcopy data (including human biological specimens, CDs, tapes, etc.):
> __ Data de-identified by research team (stripped of the 18 identifiers listed in question 7 above)
> _X_ Locked suite or office
> _X_ Locked cabinet
> _X_ Data coded by research team with a master list secured and kept separately
> __ Other (describe):

A.4.13. **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**.

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. The investigators of this study will obtain informed consent from study subjects 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.

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 your IRB for further guidance.

Subjects for this study will be recruited from the University of North Carolina at Chapel Hill student and employee population. The principal investigator (Amber Collins) will recruit all subjects by sending an email to the Biomedical Engineering as well as the UNC Chapel Hill email listserve. The investigator will strive to recruit an equal number of male and female participants as well as minority subjects. The investigator will communicate with potential subjects privately and will not discuss details of the subject's involvement with anyone except the subject.

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.	Will the information collected be limited only to that necessary to contact the subjects to ask if they are interested in participating in the study?

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

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

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 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 email through a computer that is password protected. Testing materials will not be mailed and all communication prior to testing will be done over the phone or email.

B.6. **Inducements for participation.** Describe all inducements to participate, monetary or non-monetary. If monetary, specify the amount and schedule for payments and 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). Include food or refreshments that may be provided.

Subjects will not be compensated for their participation in this study.

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.

APPENDIX D: Subject Consent Form

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

IRB Study #_____
Consent Form Version Date: _____

Title of Study: Electrical Stimulation to Improve Proprioception in the Normal Knee

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. Troy Blackburn, Dr. Chris Olcott, and Dr. Joanne Jordan
Faculty Advisor: Dr. Paul Weinhold
Funding Source: Not Applicable
Study Contact telephone number: 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?
Osteoarthritis (OA) is the most common joint disorder throughout the United States, with OA of the knee being especially common and debilitating. 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 joint stress. We plan to test the hypothesis that electrical stimulation can enhance proprioception in normal knees first, and then progress to testing in patients with osteoarthritis. The purpose of this study is to evaluate knee proprioception in normal subjects with and without both the application of electrical stimulation and the use of a neoprene sleeve.
Abnormal proprioception may result in impairment of neuromuscular responses which can expose joints to improper loading during the gait cycle. This improper loading can cause abnormal wear of the joint and may initiate or accelerate the disease process 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 cutaneous sensory receptors. The concept of stochastic resonance has been applied clinically at the knee with success in improving balance control in older adults.
Electrical stimulation will be applied in below threshold detection levels. The electrical stimulators have safety switches which will serve to protect the subject from dangerous levels of stimulation.

The aims of the study are:
Aim 1: To determine whether proprioception is improved by wearing a neoprene sleeve alone.
Aim 2: To determine whether electrical stimulation can improve proprioception beyond the tactile stimulation provided by the neoprene sleeve alone.
Aim 3: To determine the degree of improvement through the combination of the sleeve/no sleeve and stimulation/no stimulation conditions during two tasks, partial weight-bearing and non weight-bearing.

Are there any reasons you should not be in this study?
You should not be in this study if:
13. You have any signs or symptoms of knee injury (swelling, pain, loss of function).
14. You have self reported knee instability (determined as a feeling of "giving way").
15. You have any known neurological conditions which may prevent you from sensing motion or feeling pain.

16. You have previously had knee surgery.
17. You are not physically active (less than 1.5 hours/week).
18. You are not between the ages of 18-35 years.
19. You have any known vestibular deficits or somatosensory deficits or any other balance disorder.
20. You have a history of gait, postural, neurological disorders, seizures, diabetes, fainting, peripheral neuropathy, stroke or motion sickness.
21. You have an existing cardiac pacemaker or drug delivery pump.
22. You have a history of cardiac arrhythmia.
23. You are pregnant.

How many people will take part in this study?
If you decide to be in this study, you will be one of approximately 24 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, whether you have previously had knee surgery, whether you are pregnant, whether you have any previous or current neurological conditions, whether you have a cardiac pacemaker or drug delivery pump, and whether you have any feelings of "giving way" in your knee. You will also be asked which knee is your dominant knee. Limb dominance will be defined as the limb you would use to kick a ball.

The test session will consist of two tasks, six conditions during each task. You will perform a total of 36 trials. The two tasks involved in this study are a non weight bearing task (NWB) and a partial weight bearing task (PWB).

Both proprioceptive tasks (NWB and PWB) will be carried out under the following four conditions: no electrical stimulation/no sleeve, electrical stimulation/no sleeve, no electrical stimulation/sleeve, and electrical stimulation/sleeve. The sequence of the conditions will be assigned to you using a counterbalance design. In addition, these test sequences assure that each testing condition occurs with equal incidence at all stages of the sequence.

During each trial, the investigator will set up the equipment according to which condition under the specific task you are to complete. You will be blindfolded and wear headphones playing white noise during all tests.

During the NWB task, you will be seated on an upright bench and your knee will be tested moving from a starting position of 90° flexion into extension.

For the PWB task you will lay flat on your back on a sliding reclined (20° relative to the horizontal) platform that is relatively frictionless. The starting position will be in full knee extension in single leg stance, and you will move into flexion. 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 passive tension ques from specific ankle muscle groups.

For each task, a trial will begin with your limb being moved (NWB=passively by the investigator, PWB=actively by the subject) from the starting position to the target position (either 30° or 60°). You will hold your limb at the target position for 5 seconds. After returning to the starting position and holding for 5 seconds, you will then actively attempt to reposition your limb at the target angle. When you feel that you have reproduced the target angle, you will depress an electronic switch to provide a time stamp and hold your limb position for 5 seconds.

What are the possible benefits from being in this study?
There is little chance you will benefit from being in this research study. The goal of this study is to gain knowledge that may help people in the future who suffer from knee injury/disease.

What are the possible risks or discomforts involved with being in this study?
As with any physical activity, there is a risk of spraining a ligament or straining a muscle 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.

Each electrical stimulating device is built with a safety switch. A safety switch is in place so that you are not injured from the very low electricity of the stimulating device. If by chance there is an increase in electrical output, the safety switch 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 unrecognized risks that might occur.

What if we learn about new findings or information during the study?
You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

How will your privacy be protected?

No subjects 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.

Your data will be coded with a number and stored in the computer. No one other than the study investigators, Paul Weinhold, Amber Collins, Troy Blackburn, Joanne Jordan, and Chris Olcott will have access to the computer or the number that identifies your data.

What will happen if you are injured by this research?
All research involves a 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 not receive anything for taking part in this study.

Will it cost you anything to be in this study?
It will not cost you anything to be involved 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.

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.

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Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. 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

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