Promoting Neurological Recovery by Maximising Sensory-Motor Activation during Stepping and Walking: Development and Assessment of Robotics-Assisted Delivery Platforms

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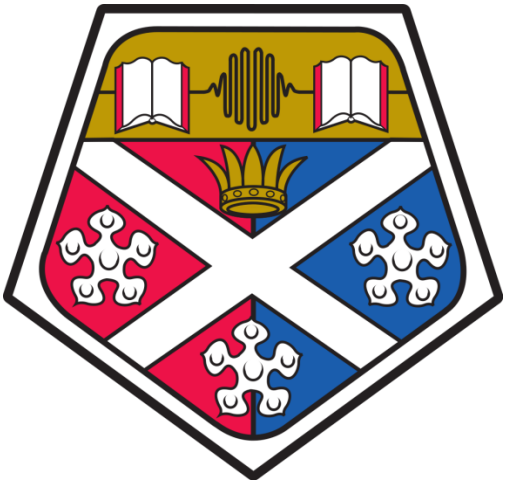
A thesis presented in fulfilment of the requirements for the degree of Doctor of Philosophy



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Copyright Statement

Signed:

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Dedicated

to my inspiring parents and sisters,

without them none of my succeeds would be possible

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Abstract

Spinal cord injury results in severe physical disability and a wide range of progressive medical complications. The main challenge for clinicians and neuroscientists is to develop methods for enhancing recovery after spinal cord injury. New researches have demonstrated that robotic or manual assisted treadmill training can have long lasting positive effects on the recovery of locomotion in incomplete SCI human patients. By moving limbs and progressively modifying body weight support, the patterned sensory information arising from the robotic or manual guidance of movement is considered to increase the potential for the gait recovery.

Commonly, deficits in walking in incomplete spinal cord injured patients are often revealed as deficits in ankle control. Accordingly, it is believed that successful recovery of stepping requires a degree of sparing in sensory and motor pathways that subserve ankle control. We therefore have begun experiments that examine ways to facilitate activation in pathways that influence the ankle joint control and that can be used within the context of body weight support rehabilitation programs.

The work focused on developing a system for vibratory stimulation of the foot sole that can act as a surrogate stimulus for ground contact and also we studied the physiological effects of vibration in spinal and supraspinal levels.

Findings in this thesis demonstrated that short periods of foot vibrotactile stimulation can produce measureable effect at cortical and spinal level in normal subjects. The findings suggest that activation of foot mechanoreceptors using localized vibrotactile stimulation interact with spinal inhibitory control mechanism contributing to the control of locomotion in human. This type of stimulation will most likely can have practical benefits for normalising gait and restoring reflex modulation during gait training. Finding in this study showed that an insole device can make this happen and can be used in gait training of SCI subjects.

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List of Abbreviations

ADLs Assess Activity of Daily Living

ANOVA Analysis of Variance

ASIA American Spinal Injury Association

BWS Body Weight Support

BWSTT Body Weight Support Treadmill Training

CC Cingulate Cortex

CPG Central Pattern Generator

CST Corticospinal Tracks

C-T Conditioning Test Intervals

DSEP Dermatomal Somatosensory Evoked Potential

DTI Diffusion Tensor Imaging

ECD Equivalent Current Dipole

EEG Electroencephalography

EP Evoked Potential

EPSP Excitatory Postsynaptic Potential

FIM Functional Independent Measure

H-reflex Hoffman Reflex

JSP Joint Position Sense

MBI Modified Barthel index

MN Motor Neuron

MTP Metatarsus Heads

QIF Quadriplegia Index of Function

S1 Contralateral Primary Somatosensory Cortex

S2 Bilateral Secondary Somatosensory Cortex

SCI Spinal Cord Injury

SCIM Spinal Cord Independence Measurement

SEP Somatosensory Evoked Potential

SNR Signal to Noise Ratio

SOL Soleus

SR Stochastic Resonance

SSEP Somatosensory Evoked Potentials

TA Tibialis Anterior

Td Conditioning Time Delay Intervals

TMS Transcranial Magnetic Stimulation

WBV Whole Body Vibration

Contents

CHAPTER 1
Introduction

Any damage to the spinal cord is termed as spinal cord injury (SCI) and results in life long and currently irreversible changes to the person's motor, sensory and autonomic functions. The influence of spinal cord injury on person's life depends on the severity and location of the injury and on their access to acute and chronic medical care and well managed rehabilitation post-injury. It impacts on independence and the ability of patients to lead normal daily lives without care and support. Accordingly, as a lifelong condition it carries an economic burden for the sufferer and for the health/benefit system supporting the patient. In UK there are over 1000 new cases of spinal cord injury every year and it is assumed that around 40,000 people are suffering from spinal injury in the country. The main causes of SCI in UK are falls, road accidents and sport injuries (Apparelyzed, 2014).

The spinal cord is not just a cable of nerves that connects areas of the brain to rest of the body but it is responsible for directing the functional motor, sensory and autonomic tasks that operate largely independently of the higher brain. These tasks range from basic reflexes to the complicated polysynaptic and multisegmental reflexes that help regulate functions as diverse as postural control and the emptying of the bowel or bladder. The most obvious outcome of spinal cord is loss of mobility or sensation below the injury site. The extent of the loss of these functions is based on the severity of injury and the level of the spinal cord damage. The higher the level of injury from sacral to cervical the more disabling the condition will be. In a similar way, the more extensive the severity of the damage at a particular level the greater the loss of function. SCI patients face many problems linked to the degree of anatomical damage and the consequential impairment of physiological control over bladder, bowel, cardiovascular, respiratory and sexual functions. Secondary complications associated with pressure sores, spasticity, autonomic dysreflexia and chronic neuropathic pain all further impact on the SCI patients' life.

SCI patients are categorised on the basis of the segmental level of the injury (e.g. C3, T12, L1 etc.) and whether the level of injury is complete or incomplete. Complete spinal cord injury is refer to any injury to the spinal cord that cause complete loss of function and sensory perception below the point of injury. Incomplete injury, is referred to a spinal cord injury in which some feeling or movement is still preserved below the point of injury (Apparelyzed 2014). In recent years American Spinal Injury Association (ASIA) scoring system has become a common clinical tool to capture this information and the related motor and sensory impairments association with the injury (Apparelyzed, 2014). The ASIA scoring system is globally recognised and used in spinal injury clinics not only to assess patients on admission but to chart any progress they may make over time. Patients with incomplete lesions are classified as ASIA B, C or D and have some preserved feelings or movements below the point of injury. The ASIA A patients on the other hand have no preserved voluntary or sensory perception below the level of injury (Apparelyzed, 2014).

Regaining or restoring the lost functions that the spinal cord is responsible for is extremely important for the patient. Statistics report that around 35% of the SCI patients state that the inability to walk creates daily problems for them and the loss of the ability to walk is considered as one of the most devastating disability impacts for SCI patients (Branco et al., 2007). The inability in walking varies from complete paralysis (wheelchair bound) to functional walkers who are able to demonstrate some level of walking usually with the aid of assistive technology aids such as frames or crutches. However, for patients with high levels of SCI injury conventional walking aids limit the independent use of hand and arm function during standing and walking.

During the last decades one of the main challenges for clinicians and neuroscientists was to develop methods for enhancing recovery after spinal cord injury. Much of this effort has been directed to regenerative medicine where the primary objective is to repair the damaged spinal cord. However, even today only limited success in animal models has been achieved and no effective regenerative treatment is likely to reach the clinic in the short term. Nevertheless, the work in this area has promoted renewed interest in neurorehabilitation and plasticity as promoter

of functional recovery post injury, particularly in incomplete SCI where some degree of recovery can be expected over time.

For many years the prevailing assumption was that the nervous system is hard-wired and is not capable of repairing itself and recovery cannot happen after injury. Accordingly, rehabilitation focused on training people to work on improving the capabilities to adapt to motor and sensory loss and to use assistive technologies such as wheelchairs for mobility. These rehabilitation strategies enable patients to compensate and modify what they do in order to perform tasks needed to achieve their goals in activities of daily living. However these approaches do not use the natural capacity of the nervous system and the spinal cord to adapt thorough neuroplasticity in relation to the demands placed on it through conditioning and repetition (Behrman et al., 2014). Evidence from basic science shows that after injury, the nervous system still can learn and adapt and change the strength of connections. The recognition that plasticity can be influenced within a rehabilitation context has opened the way to develop new intensive rehabilitation techniques that aim to drive this inherent capacity of the nervous system to support functional recovery (Behrman et al., 2014). These findings are particularly compelling in the recovery of locomotion after SCI. New researches have demonstrated that treadmill training can have long lasting positive effects on the recovery of locomotion in SCI human patients and animals. In spinal animals, locomotor activity can be restored by appropriate locomotor training with body weight support (Lavrov et al., 2010) (Hodgson et al., 1994). Based on the positive results found in animals studies, body weight support treadmill training is seen as a useful method for recovery of walking in acute incomplete spinal injured human patients (Hornby et al., 2005) (Thomas & Gorassini, 2005) (Knikou, 2010b). A recent study also shows that the treatment of patients suffering from complete spinal cord injury might be possible by transplanting cells from the nasal cavity into the spinal cord following by intensive body weight support treadmill training (Tabakow et al., 2014).

Body weight support treadmill training involves assisted stepping over a motorized treadmill with some percentage of the patient's body weight being supported by an overhead harness system. The current clinical treatment protocols involve manual assisted therapies or robotic actuators that act on the limbs. The

manual protocol is labour-intensive and physically demanding on the therapy team. Usually up to 3 physiotherapists/trainers are required for manual treadmill training therapy in which the trunk and limb movements to stimulate walking are produced by manual manipulation of the patient. The manually assisted therapy is tiring for the therapy team as each session should be more than 30mins of walking and this should be repeated daily over the course of 6-8 week. The therapists also have to work against the resistance of spasticity and unwanted reflexes.

The alternative approach that has been introduced to limit the burden on the rehab team is the use of robotic rehabilitation devices. These devices aim to reduce the dependency on therapist time and intervention and also provide a more consistent rehabilitation regime. One commercial system is the Hokoma Lokomat® which can provide automatic assistance in step production during body weight assisted treadmill training. It is suggested that these robotic assistant devices can enhance the motor recovery in SCI patients by providing highly repeated and task specific practices of stepping over treadmill in SCI patients (Hornby et al., 2005).

The success of body weight support treadmill protocol in human and animal studies is attributed to plasticity in the spinal cord caused by the repetitive movements inducing movement related proprioceptive feedback to the CNS. Providing patterned sensory information driven by treadmill training can activate and regulate the spinal circuits responsible for locomotion in human patients and spinal animals. By moving limbs and trunk on the treadmill, the patterned sensory information arising from the movement will increase the potential for the recovery of walking after neurologic injuries (Harkema, 2001). Spinal networks in animals and human can be shown to be responsive to this form of sensory training which in turn promotes the functional efferent signals necessary for basic stepping of occur. For patients with incomplete spinal cord injury treadmill training has been demonstrated to have positive effects on unassisted over ground walking (Knikou 2010b).

Physiological studies on human and animal locomotion show that there are neural networks (referred to as “Central Pattern Generators” (CPGs)) responsible to produce rhythmic movements like walking and running. These locomotor circuits are activated by functional training which provide appropriate afferent feedback (Hubli & Dietz, 2013). Afferent feedbacks from joints, muscle, and tendons influence the

step cycle timing by blocking or inducing switching between of the stance and swing phase of the step cycle (Sayenkoet al., 2009) (Dietz et al., 2002). Among these sensory feedbacks, the plantar cutaneous afferents are considered as an important source of information on foot placement, pressure, step progress, and body stability. Any reduction in the tactile sensation at the sole can be hypothesised to impact on gait and balancing stability as observed in patients suffering from diabetic neuropathy (Priplata et al., 2006). The role of plantar cutaneous stimulation in modulating the excitability of muscles controlling the ankle movement and human balance control in respect to the location of stimulation has been also been studied in healthy human subjects (Sayenkoet al., 2009). It has been shown that different areas of the foot sole contribute differently to human balance control and reflex excitability of the muscles surrounding the ankle joint.

In the current body weight training protocols, the level of body weight support given to patients in combination with guided limb movements begins at 80-100% of body weight. This is then reduced as training progresses over period of weeks. A consequence of the high levels of body weight support needed for training to progress is that the sensory feedback from the foot sole is diminished during stance. The foot pressure plays an important role in modulating the reflex patterns during walking and there is a potential option to artificially compensate for the reduced feedback through the use of cutaneous stimulation during appropriate phases of the gait cycle.

Maintained feedbacks of sensory signals arising from the foot are considered important for the recovery of walking in SCI patients and spinal animals (Duysensa et al., 1998) (Conway & Knikou, 2008) (Côté & Gossard, 2004). The plantar cutaneous feedback is believed to influence extensor and flexor reflex patterns in a phase dependent manner during locomotion and therefore support the appropriate activation of muscles during stepping. In this thesis an underlying hypothesis is that by combining cutaneous feedback with body weight support locomotor training (or any other training method); the enhanced sensory feedback provided will interact with locomotion generating mechanisms to assist in generating a more effective recovery of walking.

Researches on animals have revealed that the spinal cord plays the main role in generating locomotor patterns and that higher brain centres are mainly involved in initiating locomotion, stepping over obstacles, and adaptation to environmental, motivational conditions including visual adjustments of gait patterns (MacKay-Lyons & Marilyn, 2002). Non-invasive studies in human subjects suggested that there is dependency between the locomotor circuits at the spinal level and higher brain networks. In support of this, the excitability of the corticospinal pathway has been shown to be modulated during locomotion cycles and it directly contributes to the activation of lower limb muscles during walking. The influence is being most clear in the ankle muscles active during the swing phase of walking (Barthélemy et al., 2010). This correlates with the well-known drop foot syndrome seen in stroke patients and for incomplete SCI patients the walking deficits often reveal as deficits in ankle control Based on this observation it would seem appropriate to believe that the recovery of stepping in incomplete SCI patients through the use of body weight support therapies requires a degree of sparing in corticospinal pathways that contribute to ankle joint control. Due to the inter dependency between sensory motor processing in the brain and spinal cord this research also consider that the successful recovery of walking requires sensory and motor pathways associated with ankle function to be operational and that targeting therapy to promote plasticity in these pathways will lead to improved stepping in patients.

This project will investigate sensory stimulation methods that will target those pathways that support corticospinal control of the ankle and also can modulate pattern generation in a phase dependent manner. Such sensory stimulation could then be incorporated into gait training paradigms such as Hocoma-Lokomat® in order to improve the rehabilitation outcome. By replicating the pattern of plantar skin stimulation an augmented phase dependent sensory feedback that is analogous to weight bearing stimulation of skin afferents can be generated despite higher levels of body weight support. To achieve this, localized vibration stimulation of the different foot sole zones synchronized with gait kinematics was planned. This type of stimulation is pain free, easy to control and can stimulate receptors likely to also be recruited during walking. A vibratory shoe was designed which can be integrated to devices like Lokomat® or can operate independently based on the foot ground

contact reaction force. The designed vibratory shoe can stimulate different regions of the foot sole synchronized with the gait phases during treadmill training. We also demonstrated the physiological effects of localized vibrotactile stimulation on both spinal and cortical neural circuits using commonly available electrophysiological methods meaning that in clinical studies the effects of the stimulations can be readily monitored.

CHAPTER 2
Literature Review

2.1 Spinal Cord Injury

Any injury to the spinal cord, caused by a trauma, is called Spinal Cord Injury (SCI). It is life altering, difficult to treat and leads to lifelong health care costs. Over 12000 new cases of SCI are reported every year in USA (Branco et al., 2007). The average age of the new SCI patient (28.7 years) is lower than many the other conditions affecting a person's functional capability (e.g. stroke, movement disorders, etc.). Statistics show that the majority of SCI patients are not employed and most are not able to return to their jobs after injury. SCI has a tremendous effect on the patients, their quality of life and that of their families. Economically, the main costs include initial high hospitalization care costs, prolonged rehabilitation costs and the provision of specialist assistive technologies, drugs and home modifications (Branco et al., 2007).

SCI is the second most significant cause of paralysis in USA after stroke and most of the SCI patients consider one of their most devastating disabilities as their inability to walk and perform voluntary movements. Poor mobility contributes to higher health care costs and the lower rate of employment. A main topic of this thesis is the drive to develop ways to assist in the rehabilitation of walking in patients with SCI.

2.2 Locomotion

Understanding everyday tasks like walking and running have been the focus of study for many neuroscientists, biomechanists and clinicians. There have been many studies on the individual components of the process but we still don't have a full understanding of the neural mechanisms and the control of human locomotion (Duysensa et al., 1998).

The spinal cord is involved into many complex voluntary and involuntary motor tasks including the control of walking and works with higher centres to coordinates the timing and the pattern of movements for each joint during walking. The entire system of neural networks is also able to respond and adapt motor output to external challenges such as obstacle avoidance or changes in surface properties to ensure stability and the smooth progression of the movement. This shows that the nervous systems integrates information from a large flow of sensory input and use this information to perform movement that are task and goal dependent (McCrea, 2001).

In animals and human walking is controlled by organization of neural networks specialized in repeating a particular motor movement. In locomotion the term Central Pattern Generator (CPG) is often used to represent these specialized neuronal networks (Grillner & Wallen, 1985).

2.3 Central Pattern Generator

There are specialized neural networks that are able to generate appropriate muscle patterns that produce rhythmic actions like: walking, breathing, mastication or other rhythmical activities. These self-sustaining patterns are capable of being generated without continuous higher centre drive. In vertebrates research it has demonstrated that for locomotion the networks of the spinal cord are critical to pattern generation and that these networks have properties that contribute to many adaptive mechanisms that characterise walking behaviour. (Grillner & Wallen, 1985). Nevertheless, supraspinal signals are critical in controlling the initiation, termination, inhibition and modification of CPG in many species. During walking, spinal and supraspinal circuits use movement related sensory feedback to modify the step. Importantly, elements of these feedbacks may act directly on CPG mechanism to provide appropriate signals to respond to the environmental demands. The functional output of CPG is very responsive to the environmental needs. It receives specific sensory information and changes the motor output proper to the environmental need without any supraspinal interference.

The general model for locomotion is based on data obtained from animal's studies. It has been found that there are some similarities in neural control of locomotion between human and animals (Nielsen & Jens, 2003) (McCrea, 2001). The basic patterns of locomotion in human and vertebrates may be similar but amplitudes and functions of bursts of activity may differ. For example the paraspinal muscles in humans are used in balance control but not in cats. Another example could be hip extensors which are used for balance control in human but in cats are used as propulsion muscles. Comparing the human and the vertebrate's model of locomotion shows that not only there is not such a fundamental difference between the neural networks of human and other vertebras but also indeed striking similarities exists (Duysensa et al., 1998).

2.3.1 CPG in Animals and Human

Experiments in human volunteers and patient groups with SCI and stroke suggest that there is little fundamental difference between locomotion generation in humans and other animals in relation to the likelihood of a CPG system controlling walking in humans. These similarities therefore also open the debate on how knowledge of locomotor restoration in experimental animals can be translated to the rehabilitation of spinal cord injured (SCI) patients.

In 19th century, Flourens observed locomotor patterns in spinal injured animals (Morton & Bastian, 2004) but viewed the spinal cord as a conductor rather than a generator of activity. Others over the years also reported similar observations in adult animals with Graham Brown early in the 20th century concluding that the spinal cord controls gait using central and reflex mechanisms (Guertin, 2012) (Guertin, 2009). The stereotypic phase-dependent gait patterns in adult animals depend on activation and proper coordination of a large group of muscles. These patterns are formed in early life and appear hard to change once developed (Forssberg et al., 1983) (Gordon et al., 1986).

The most convincing evidence which proves the existence of CPG in animals was the demonstration of fictive locomotion. Fictive locomotion is observation of locomotor like discharges in the motor nerves of animals paralysed by

neuromuscular blocking agents. The locomotor patterns occur in the absence of actual movement and without movement related sensory feedback thereby providing strong evidence for a central rhythm generation of the basic step cycle. Although in animals there is a wealth of data that proves the existence of CPG, there is a little knowledge in humans about the neural networks that act like a CPG. In the context of humans the key question is whether there is a CPG and where is it located.

The idea that there is a basic similarity in spinal locomotor circuitry in animals and human is supported by experiments performed on patients suffering from complete spinal cord injury. If a spinal injured human patients receives the same sensory inputs (as they used to receive during gait before injury), similar locomotion patterns will be observed which are related to the provided sensory information (Wernig & Müller, 1992) (Harkema et al., 1997). Based on these finding it is suggest that the neurons inside the human spinal cord are able to receive the sensory information, process them and generate proper output to coordinate movements between limbs (Forssberg, 1985) (Harkema, et al., 1997) (Visintin & Barbeau, 1989) (Dietz et al., 1995) (Dietz et al., 1998).

In cats it has been shown that neural networks that are responsible to generate gait patterns are located along the spinal cord and the brain stem (Dietz et al., 1999). In humans Dietz (Dietz et al., 1999) noted that SCI patients with the higher levels of injury produce more normal gait patterns. This suggests that CPG neurons are not restricted to any specific level of the spinal cord but may be distributed throughout the spinal cord from thoracolumbar to cervical levels (Dietz et al., 1999).

From clinical view, it is not very helpful to find convincing evidence of where these neurons are placed exactly. The key thing is that whether the spinal circuits after the lesion can handle the remaining input to facilitate the generation of locomotor patterns (Harkema, 2001).

2.3.2 Supraspinal Activation of CPG

It has been found that locomotion in human and animals depends on three major factors: supraspinal structures, spinal networks, and afferent pathways (Duysensa et

al., 1998). When a spinal injury occurs, the residual supraspinal and afferent signals becomes extremely important within a rehabilitation context (Edgerton & Reggie, 2008). In animals the neural networks in higher centres are considered important for gait initiation and the spinally located CPG will retain the capacity to generate locomotion patterns even in the absence of supraspinal signals if proper sensory information is provided (Nielsen & Jens, 2003) (Drew et al., 1996). These studies show that cats with complete lesion of the motor cortex are still capable of over ground walking when placed on treadmill. This type of locomotion is due to the activation of CPG and reflex modulation of output pathways by repetitive sensory feedbacks arising from the limbs, foot, tendons and joints. In cats, some of the corrective reflexes are integrated at spinal level while in the human they are more dependent on supraspinal levels and on cortical signals (Nielsen & Jens, 2003).

Our knowledge about the suprasegmental control of human locomotion and the role of the motor cortex is limited and depends on the information coming from experiments on animals (Capaday et al., 1999). The activity of spinal locomotion networks in human is more dependent on supraspinal signals than the other animals. In human subjects a significant amount of activity in sensorimotor cortex has been observed during real and imaginary walking. Corticospinal tract is also highly excited during walking. By removing the corticospinal contribution using a week Transcranial Magnetic Stimulation (TMS) the EMG activity of the active muscles during uncomplicated treadmill walking is depressed (Thomas & Gorassini, 2005) (Petersen et al., 2012). This shows the important role of motor cortex and the corticospinal tract in human locomotion. Some experiments suggest that motor cortex may not be part of the central neural system involved in timing the motor neurons activity during the step cycle but it is more closely linked to segmental motor circuits controlling ankle muscles during human walking (Capaday et al., 1999). However the role of motor cortex and the corticospinal tracts in still not fully understood yet.

2.3.3 Influence of Sensory Afferents on CPG

Sensory feedback is an essential component in motor control and is critical in modifying the output of CPG in order to facilitate the adaption to environmental

needs. Afferent feedbacks are important in stabilizing the motor control systems and, modulation of reflex pathways to ensure motor output is appropriate for the ongoing task and posture. It has been shown that all types of sensory information can affect and modulate motor output. In locomotion sensory feedback regulates the step cycle by controlling the duration and adjusting the muscle activates during the different gait phases (Fouad & Pearson, 2004).

The phasic sensory information coming from the lower limb afferents are therefore important elements in the rehabilitation and recovery of locomotion after SCI (Fouad & Pearson, 2004). Spinal networks in animals and human will adapt in response to intensive interactive training (Harkema, 2001). It has been shown that, in cats with spinal cord lesion, locomotion can be restored by appropriate programmes of daily treadmill training. Providing movement related proprioceptive sensory information through treadmill training can active and regulate spinal circuits responsible for locomotion in human and animals (Barbeau et al., 1987). By moving limbs and trunk on treadmill, sensory feedback will assist recovery by conditioning appropriate pathways and promoting plasticity after neurologic injury (Harkema, 2001).

In general the most studied sensory feedback sources that can access and influence CPGs fall in to three main categories. Two of them are related to load, and one is related to hip position (Pearson & Keir, 1993). Proprioceptive afferents in extensor muscles and exteroceptive afferents from mechanoreceptors in the foot sole provide the load receptor input and the muscles around the hip contribute to the joint position input (Pearson & Keir, 1993).

Pang and Yang (Pang & Yang, 2002) studied the role of load and stretch receptors in initiation of the swing phase and control of balance in the stance phase in health human subjects. They used infants for their study because the effect of changes in hip position is not easy to study in adult humans (In infants stepping is mainly controlled by circuitry in the spinal cord and brainstem). They placed a piece of cardboard under the infants' foot and they realised that by pulling the cardboard in different directions the subject leg is also displaced in a particular direction and simultaneously unloaded. The swing phase was immediately started. Based on these findings they suggested that hip extension and load reduction are two major factors

that control the transient from stand to swing phase in either forward or even backward walking. They also realised that load feedback is always necessary to initiate the swing phase (Pang & Yang, 2002).

2.4 The Role of Cutaneous Feedback in the Control of Locomotion

The role of hindpaw cutaneous feedback has been studied extensively in intact and spinal cats. It was suggested by Sherrington (Sherrington, 1910) based on observations following nerve section that in healthy cats, cutaneous afferents are not an essential element in controlling locomotion. This view is backed by more recent work by Bouyer and Rossignol (Bouyer & Rossignol, 2003). They cut the cutaneous nerves at ankle level in healthy cats at both sides and observed that the denervation caused well-identified but minor changes in the locomotor pattern which were gradually compensated. Based on these findings it can be concluded that the generation of the locomotor patterns does not depend on the cutaneous afferents in healthy animals (Bouyer & Rossignol, 2003) (Bolton & Misiaszek, 2009). Importantly, researchers suggest that cutaneous afferents may play a regularity roll in modify the step cycle (McCrea, 2001). This can make an appropriate response to modify the muscle response to avid obstacles (Bouyer & Rossignol, 2003). Cutaneous afferents therefore seem to be involved in supporting the necessary motor compensations that follow perturbed stepping. The effects of cutaneous afferent activity are highlighted when the animal tries to walk on slopes or challenging surfaces. It has been shown that foot placement errors occur if cutaneous afferents are blocked (Bouyer & Rossignol, 2003). This supports the view that cutaneous information is important for correct kinematic expression and adaptation to the environmental demands (Bouyer & Rossignol, 2003) (Gossard et al., 1990).

Locomotion in spinal cats also becomes more dependent on the cutaneous sensory information than in the intact animal. After spinalization, the cutaneous sensory inputs become very important for functional expression of locomotion (Bouyer & Rossignol, 2003). In a study by Bouyer and Rossignol (Bouyer & Rossignol, 2003) they realised that complete cutaneous denervation at the ankle level in cats before and after spinalization will cause permanent locomotor deficit in spinal

animals but not in healthy ones. The observed defect was more prominent in inability to lift the foot during the swing phase (Bouyer & Rossignol, 2003). Based on their findings it was suggested that cutaneous afferent feedback contributes toward providing the sensory cues indicative of load bearing and help adapting walking speed to the treadmill velocity. The lack of cutaneous feedback also reduces the muscle EMG patterns. It has been shown that by preserving a minimal cutaneous feedback, the animal is still able to place the foot correctly and support its weight (Bouyer& Rossignol, 2003).

In human the relationship between motor control and the sensory feedback are in two forms. The sensory information mediates error signals due to an external perturbation or they contribute directly to the motoneuronal drivers (Nielsen & Sinkjaer, 2002). In humans the integration of the sensory afferents and the motor command happens at all levels of the CPG (Nielsen & Sinkjaer, 2002) and any loss in cutaneous sensory information will lead to unstable locomotion. Even a small cutaneous sensation can be functionally critical (Gravano et al., 2011) (Van Wezel et al., 2000). The skin of the foot is innervated by the sural, posterior tibial, and superficial peroneal nerves. Only the sural nerve is a purely cutaneous nerve and accordingly much of the research using electrical stimulation of cutaneous afferent has used the sural nerve. However, anatomically the sural nerve only innervates a small area of lateral dorsal and plantar foot skin (see Figure **2-1**).

The low-threshold cutaneous receptors in the sole of the foot inhibit the initiation of the swing phase; promote stance phase and helps for correct foot placement in locomotion (Knikou, 2007). Mechanoreceptors from the human foot sole can influence spinal pathways and having been shown to participate in reflex regulation and sensory gaiting during stepping (Knikou & Conway, 2007).

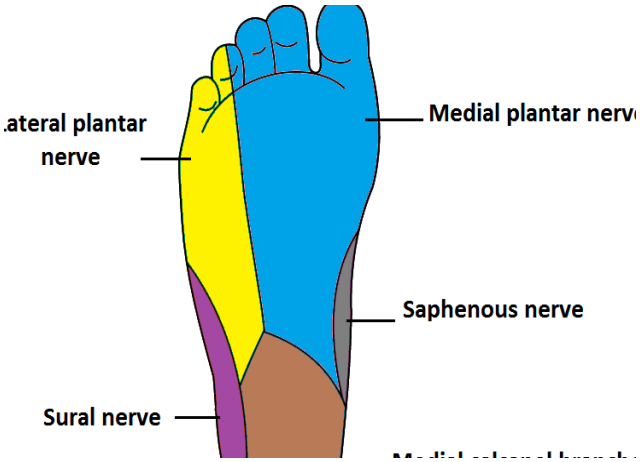


Figure 2-1. Segmental distribution of the cutaneous nerves of the sole of the foot.

2.5 Role of Motor Cortex and Corticospinal Tract in Locomotion

A common observation in patients recovered from stroke or incomplete SCI is the presence of drop foot during the swing phase of walking. Foot-drop is characterized by the inability of the patient to actively dorsiflex the ankle (Knutsson & Richards, 1979). The deficit is the result of a combination of increased activity in ankle extensors coupled with a decrease in producing ankle flexor moments. Clinical observations backed by lesion experiments in animals strongly implicate damage to the corticospinal tract or the loss of transmission via this pathway as the main cause of the drop foot syndrome (Thomas & Gorassini, 2005). The implication is that for the control of ankle function during locomotion in humans an intact functioning of corticospinal tract is essential and therefore interaction between cortical and spinal processes is an integral aspect of gait control in humans (McKay et al., 2005).

Studies using fMRI and Transcranial Magnetic Stimulation (TMS) in healthy subjects and stroke patients show the abnormalities in the level of motor performance of the ankle extensor and flexor muscles are directly related to the disruption in the sensory motor cortex region (Capaday et al., 1999) (Dobkin et al., 2004). In spinal injured patients, the drop foot is also one of the frequent permanent functional deficits and as mentioned above is associated with damage to regions of the cord where the corticospinal tracks (CST) are located. Recent human studies verify this

and thereby directly demonstrate that activity transmitted via the CST significantly contributes to the pattern of muscle activity during swing and that drop foot deficits correlate with the extend of corticospinal tract injury (Thomas & Gorassini, 2005) (Barthélemy et al., 2010). In this regard it is also believed from experiments using TMS and EMG coherence analysis that the cortical drive to lower limb muscle is preferentially directed to muscle groups that display activity deficit in drop foot cases. For example, it has been shown that Tibialis Anterior (TA) muscle receives more monosynaptic corticospinal drive than soleus (SOL) and that coherence measures related to motor unit coupling of cortical origin are more preserved in pre-tibial muscles than other lower limb muscle groups (Petersen et al., 2003) (Barthélemy et al., 2010). Accordingly, clinical observation and physiological experimentation is coming to the view that during human locomotion (in both stance and swing phase) the corticospinal pathway is more linked to the regulation of ankle flexor activity than it is linked to the ankle extensor (soleus) muscles. It has been suggested that non-cortical pathways may provide the primary drive to muscles activity during the stance phase of walking (Capaday et al., 1999).

2.6 Spinal Reflexes and Locomotion

A reflex is generally defined as an involuntary response to a sensory stimulus and according to Clarac (Clarac, 2012) Jean Astruc (1684-1766) was the first to use the term “reflex” to describe the initiation of a motor response using the metaphor of light reflecting from a mirror. However, the important role of reflexes and sensory information in regulating movements was not known until the seminal works of the late nineteen and early twentieth century physiologists including Sir Charles Sherrington.

Often considered as part of a hierarchical system reflexes are viewed as the lowest level of organisation generating behaviour in motor control systems. This makes them interesting to study from a number of standpoints relating to how they contribute to coordinated motor behaviour but also how the simplest reflex pathways can be used as tools to explore more complex function and pathways within the CNS.

The functional role of reflex pathways in locomotion has always been an interest to researchers and the modulations of reflexes during walking have been extensively studied in many animal species and man (Zehr & Stein, 1999). These studies show that reflex modulation is behaviourally relevant to the task and have phase dependency, meaning that they contribute positively to the body ability to adapt the step cycle to changes in terrain and environment. Reflexes have functional roles during human locomotion but the actual role of reflexes in human locomotion is still unclear. Some reflexes are strongly controlled by the central pattern generator during locomotion so it is important to understand the modulation of reflexes during different gait phases. This is also known as the phase-dependent reflex modulation during locomotion (Zehr & Stein, 1999).

In human subjects stretch applied to muscle evokes a number of reflex components of varying latencies. For example, stretch of ankle dorsiflexors generate components labelled M1 (short latency ~44ms), M2 (~69ms) and M3 (~95ms) (Petersen et al., 1998). The earliest of the reflex peaks (M1) is mainly mediated by the monosynaptic Ia pathway to the spinal motoneurons. The later components (specifically M3) are likely to include transcortical pathways (Petersen et al., 1998) (Corden et al., 2000). There has been much debate on the M2 pathway but this component of the stretch reflex is considered to be too short to be a transcortical pathway reflex and persist in the lower limbs of patients with injury to supraspinal pathways and therefore is most likely to be generated by spinal pathways (Petersen et al., 1998).

What is certain is that the monosynaptic reflexes responses (M1) are purely spinal and can be evoked using low threshold electrical stimulation of muscle nerves. In these cases the reflex response is often referred to as a Hoffman reflex or H-reflex (Hoffmann, 1910). The study of this reflex has become a useful tool to explore changes in excitability in neuronal pathways during behaviour and it has been extensively used to explore central nervous system activity during gait (Knikou, 2008). For example, many studies have reported on H-reflex modulation during gait and for H-reflexes recorded in ankle extensor muscles the common view is that during the swing phase there is a decrease in the amplitude of the reflex that is not simply the consequence of a change in background muscle activity. The consensus

view being that in lower limb muscles, the neural circuits that generate locomotion patterns also modulate the excitability of H-reflex transmission. This is also true for the short latency stretch reflex (M1) (Baken et al., 2005). In the section that follows, work using the H-reflex as a probe of neuronal pathways and excitability changes will be reviewed.

2.7 Hoffman Reflex

There are four common methods to study the reflex functions in humans (Zehr & Stein, 1999):

- Hoffman reflex (H-reflex) (Hoffmann, 1910) (Misiaszek, 2003).
- Stretch reflex (Miles et al., 2004).
- Modulation curves of the rectified and averaged EMG signals (Reaz et al., 2006).
- Post stimulation time histogram of motor unit firing rates (Norton et al., 2008).

From these methods the most accessible and experimentally convenient way to study presynaptic modulation of the reflex pathways and improve our knowledge about the short latency stretch reflex (M1) modulation in humans is to study the H-reflex (Andersen & Sinkjaer, 1999).

H-reflex or Hoffmann reflex was first described by the German physician, Paul Hoffman in 1910 (Hoffmann, 1910). It was widely used in late twentieth century as a neurophysiology tool to measure the effects of Ia afferent monosynaptic projections to α-motoneurons. It was also used to investigate the inhibitory or excitatory effects of specific pathways on α-motoneurons activation (Chen & Zhou, 2011a).

Using the H-reflex it became feasible to compare the muscle activity in a subject using amplitude and the latency from the EMG signal (Staceyet al., 2010). Through conditioning the H-reflex it is possible to look at converging inputs, the timing relations between different pathways and whether they have excitatory or inhibitory components all through non-invasive testing in conscious humans. Accordingly, the H-reflex is a useful electrophysiological tool and can be also be of

value clinically, for example, it has been used in the diagnosis of radiculopathy at the lumbosacral spinal level (Alrowayeh & Sabbahi, 2011a). It can also provide insight in the adaptive plasticity arising in spinal reflex pathways after rehabilitation training in patients (Sayenko et al., 2010). H-reflex in motor control research is a probe for adaptations in the function of spinal structures with training, following injury or disease, or with therapeutic interventions (Knikou, 2008).

2.7.1 Evoking the H-reflex

H-reflex is an electrical equivalent of monosynaptic stretch reflex. It is generated by trans-cutaneous electrical stimulation of a muscle nerve. At the lowest thresholds of electrical stimulation the H-reflex is seen on its own due to the recruitment of the largest group of Ia afferents in the stimulated muscle nerve. With increases in the strength of electrical stimulation additional smaller afferent fibres are recruited and alpha motor axons within the nerve also begin to be excited. This gives rise to an antidromic and orthodromic activation of the stimulated motor fibres with the orthodromic stimulation resulting in a direct EMG response in the muscle which is often referred to as M-wave. The direct EMG response that makes up the M-wave occurs at a shorter latency than the H-reflex mediated by the monosynaptic activation of motoneurons by the stimulated Ia afferents (Chen & Zhou, 2011a).

M-wave is of value as a measure of stimulus strength and consistency. It also allows normalisation across subjects as it gives an indication of the percentage of α-motoneurons within a pool being activated. Magnitude of M-wave depends on the muscle fibre length, placement of the recording and stimulation electrodes and the strength of stimulus (Chen & Zhou, 2011b).

H-wave is with the result of excitatory postsynaptic potential (EPSP) in motoneurons. The amplitude of H-reflex depends on the number of motor units recruited to the reflex and changes in this in response to conditioning can indicate excitatory or inhibitory actions affecting the motoneuronal pool (Chen & Zhou, 2011a).

Ia afferent fibres have larger diameter than motor fibres so they have smaller excitation threshold. If the electrical stimulation intensity is low, the recorded signal will be H-reflex and M-wave will disappear. At very high intensity, the evoked potential will propagate in both directions on α-motoneuron axon. The ascending action potential will collide with the descending one from the spinal cord so H-reflex will become very small or disappear. By increasing the stimulation the M-wave will become larger and H-wave will become smaller. The M-wave will increase until it gets to its maximum amplitude (M_{max}). Changes in the amplitude of H-wave under different conditions can be explained by at least three possibilities: (1) alteration in the excitability of the motoneurons; (2) variation in the amount of neurotransmitter released by the afferent terminals; or (3) variation in the intrinsic properties of the motoneurons. H-reflex has been tested under different experimental conditions and the studies show that it is a reliable tool in repeated tests (Chen & Zhou, 2011a).

2.8 Reflex Modulation of Soleus Muscle

The triceps surae is a muscle group located at the back portion of the lower leg (calf). These muscles (lateral and medial gastrocnemius and soleus) act on the foot through the Achilles tendon. These muscles are innervated by tibial nerve and their function is to induce plantar flexion and stabilization of the ankle during walking. Soleus is a single-joint plantar flexor whereas gastrocnemius is a two joint muscle crossing both the ankle and knee joints. Soleus is considered to have its main role in low level force contributions to postural control where the gastrocnemius is more active in phasic activities such as walking, running and jumping. Forward propulsion of the body during locomotion is given by the soleus where gastrocnemius is responsible for vertical body support (McGowan et al., 2008) (Makihara & Yukiko, 2011). Soleus is mostly innervated by S1 nerve root where gastrocnemius is more innervated by L5 (Alrowayeh et al., 2011b). H-reflex recording from gastrocnemius allows a reliable examination of the L5 nerve root where H-reflex recordings from SOL provide S1 diagnosis in patients (Edamura et al., 1991) (Alrowayeh & Sabbahi, 2009). SOL muscle was selected as a good candidate (among triceps surae group muscles) to study the relative role of the central versus peripheral mechanism in

human gait (Morin & Pierrot, 1977). SOL is active in most of the stand phase during human locomotion (Yang et al., 1991) and there is evidence that reflex responses of ankle extensors and flexor muscles play an important role in contributing to the activity in the early stance phase of human locomotion and help to secure foot placement around heel strike (Nakazawa et al., 2004a).

Any change in the amplitude of SOL H-reflex under a give condition reflects the change in the excitability of the corresponding reflex pathway. To study excitatory or inhibitory effects of a specific sensory stimulation (cutaneous stimulation, heat, attention, change in the joint angle and etc.) on the excitability of the segmental reflex pathways, usually the conditioned response of SOL H-reflex is studied (Manella, 2011).

2.8.1 Effect of Loading on Sol H-reflex

Natural walking patterns induce cyclical periods of alternating limb loading as walking propels the person forward. Limb loading can active many sensory receptors including: Golgi tendons organs, muscle spindles and mechanosensitive cutaneous receptors located in the foot. The exact functional role of each type of receptors is not well understood because they cannot be easily studied separately. These receptors interact with each other and with CPG to generate locomotion patterns (Gravano et al., 2011). The soleus H-wave modulation is the result of interactions between sensory afferents, spinal and supraspinal networks (Conway & Knikou, 2008).

Among all sensory feedbacks contributing to motor control during walking, the plantar cutaneous afferents in the foot sole are considered to provide important information on foot placement, pressure, step progression, and postural body stability during walking. Accordingly, it is expected that sensory information coming from the foot sole has an important role in sensory regulation of walking. The primary role of plantar cutaneous feedback is in stabilizing the foot during the stand phase of walking (Conway & Knikou, 2008) (Knikou, 2010b). Cutaneous afferents of the foot sole adjust the excitability of the spinal pathways that innervate the muscle acting on ankle joint (Sayenkoet al., 2009). The influence of load receptors on the modulation of the cutaneous reflexes in human healthy and spinal injured subjects has been

previously studied and it is shown that loading modulates the H-reflex excitability in healthy and spinal cord injured subjects (Conway & Knikou, 2008) (Bastiaanse et al., 2000). The common finding is that mechanical plantar loading generates significant inhibition in the SOL H-reflex pathway. This modulatory effect can therefore be used as a way to support phase dependent excitability changes in spinal cord injured subjects where the normal pattern of gait induced reflex excitability changes is lost (Conway & Knikou, 2008) (Dietz et al., 2009).

Excitation of the foot sole cutaneous afferents using electrical stimulation of the nerves generates a cutaneous reflexes during locomotion which is considered to play an important role in balance control while walking (Nakazawa et al., 2004b) (Sayenkoet al., 2009). Studies using electrical stimulation of cutaneomuscular afferents from plantar nerves has demonstrate a complex synaptic actions on active ankle muscles (Knikou & Conway, 2007). It has been shown that electrical stimulation of the cutaneous afferents generates a complex excitatory and inhibitory effect in a wide range of lower limb muscles which also depends on the phase of the walking (Sayenko et al., 2007) (Bastiaanse et al., 2000) (Delwaide, 1981b). The generated reflexes are task-dependent and posture-dependent demonstrating the highly adaptive nature of spinal circuits and factors that contribute to transmission of pathways across and between spinal segments. (Nakajima et al., 2009).

Stimulating different regions of the foot has demonstrated different effects on the SOL H-reflex excitability. In sitting and standing non-noxious electrical stimulation at 2 times the perceptual threshold of the heel region in healthy human subject has an excitatory effect on SOL H-reflex but stimulation the fore-medial and fore-lateral has inhibitory effects (Nakajima et al., 2006). This suggests that effects of cutaneous afferent into the motoneurons in the lower limb muscle are highly organized in a topographic manner (Sayenko et al., 2007) (Sayenkoet al., 2009) (Nakajima et al., 2009). It should be noted that there is a contradiction in literature about the effect of electrical cutaneous nerve stimulation and the amplitude modulation of SOL H-reflex. Some groups have report the inhibitory effect of plantar cutaneous afferents and some have reported the opposite. For example Goulart (Goulart et al., 2000) measured the excitability of SOL H-reflex after electrical stimulation of the mixed posterior tibial nerve and reported a strong inhibition of

SOL H-reflex. Knikou (Knikou, 2007) also reported the inhibition of SOL H-reflex after stimulation the medial plantar nerve in healthy subjects and facilitation in spinal injured patients. On the other hand, Sayenko revealed that cutaneous stimulation of the foot around the heel facilitates the SOL H-reflex in healthy subjects. This contradiction could be explained by the fact that tibial nerve stimulation might produce a mixed reflex effect (tibial nerve arises from different branches) (Sayenkoet al., 2009) (Sayenko et al., 2007).

2.8.2 Effect of Skin Brushing on Sol H-reflex

The main difference between stimulating the skin receptors by cutaneous tactile stimulation and electrical stimulation of the sensory nerve is that the cutaneous tactile stimulation generates a spatial pattern of afferent discharge than the more synchronized volley which would be produced by electrical stimulation. Natural stimulation has been used for a long time to alter muscle tone in those groups of muscles whose normal functionality has been affected due to neurological problems. These methods include brushing of the skin, icing and scratching of the skin (Doeringer et al., 2010) (Rood, 1954). These methods are less often used in clinical application and they are mainly described in paper and textbooks. It has been shown that cutaneous stimulation strongly modulates the excitability of many reflex pathways. Based on these finding it is suggested that cutaneous stimulation will have potential benefits for patients with neuromuscular disorders. The effect of skin brushing has been investigated previously (Matyas & Spicer, 1980) (Garland & Hayes, 1987) (Davey et al., 1991). It has been reported that brushing of the skin facilitates the voluntary muscle contraction in TA muscle in patients suffering from foot drop (Garland & Hayes, 1987).

Modulation (inhibition) in H-reflex excitability of triceps surae muscles has also been reported in healthy subjects when the skin overlying the muscle was stimulated by brushing or scratching. Stimulation of the cutaneous receptors of the skin overlying the triceps surae by brushing significantly inhibits the SOL H-reflex amplitude in healthy subjects. The inhibition demonstrates no long-lasting effect. It has been reported that duration of brushing does not affect the magnitude of inhibition but there seems to be a relationship between frequency of brushing and

inhibition in SOL H-reflex. Increasing the frequency of brushing slightly increased the degree of inhibition. This could be due to intense stimulation of the receptors which will lead to less recovery or adaptation time (Edin et al., 1995). Brushing bigger or smaller regions of the skin also produces more or less inhibition in the SOL H-reflex which is due to stimulating more or less number of receptors overlying under the skin (Edin et al., 1995) (Wood et al., 1998). By removing the tactile stimulation the H-reflex is recovered to its nominal value (Wood et al., 1998). Inhibitory effects of tactile cutaneous stimulation could useful in clinical applications for reducing spasticity. Possible mechanism for modulation of the H-reflex after cutaneous tactile stimulation includes:

- Presynaptic inhibition of the Ia afferent terminals
- inhibition of Alpha-motoneurones mediated by cutaneous input to Ib inhibitory interneurons
- Cutaneous inhibition of gamma-motoneurons

In summary, it has been shown that different skin areas of the foot provide specific tactile information about events that are encountered during locomotion. Cutaneous afferents information from different zones of the feet provides postural and body loading information to the CNS and can induce adapted regulative postural responses (Kavounoudias et al., 1998). In cats it has been shown that tapping different regions of the foot elicits different reflex responses in leg muscles. In human studies it has been also been shown that non-nociceptive stimulation of the sural, posterior tibial, and superficial peroneal nerves elicits different reflex responses (Van Wezel et al., 1997). This variation in response is believed to reflect the different anatomical skin areas each nerve innervates and the location specific nature of sensory feedback. This location-specific information is incorporated in a functional way in reflexes during locomotion (Van Wezel et al., 1997).

2.8.3 Effect of Muscle and Tendon Vibration on SOL H-reflex

Recent methods introduced to enhance neuromuscular performance in athletic training and in rehabilitation of patients include Whole Body Vibration (WBV) and

direct muscle and tendon vibration. WBV generates repetitive mechanical stimulation that acts on the subjects' body while standing on a vibratory platform. The effects of WBV are poorly understood and its effectiveness as an intervention is not proved (Sayenko et al., 2010). For example Lau (Lau et al., 2012) reported that WBV exercise protocol is not effective in improving neuromotor function in chronic stroke patients.

The tonic vibration reflex is a well described reflex increase in motor output associated with muscle receptor activation during low amplitude vibration and there is a long history of experimental studies investigating the neurophysiological effects of applying vibration to muscles or tendons (Arcangel et al., 1971) (Burke et al., 1976). The tonic vibration reflex is related to the stretch reflex and relies on the high sensitivity of the primary and secondary afferent terminals of the muscle spindle to small amplitude vibration. Nevertheless, it is also known that Ia afferent transmission to networks within the spinal cord is also reduced by transcutaneous muscle or tendon vibration, an action mediated through an increase in presynaptic inhibition (Ritzmann et al., 2011). This opens up the possibility of using vibration as a means of influencing spinal reflex excitability and transmission and may be the basis for reports for the therapeutic benefits of whole body vibration in neurological patients (Sayenko et al., 2010).

Spinal injured people often complain about involuntary reflex evoked muscle activities. This type of muscle activity also impacts on spasticity and clonus. Muscle vibration can only act by producing central actions mediated via the sensory systems it activates and subsequent modulation of the spinal and transcortical reflex activity. With reports of WBV producing sustained increases in balance control for up to 6 weeks in patients with chronic stroke there appears to be opportunities to use this form of intervention as an aid to rehabilitation (Van Nes et al., 2004) and clearly more work in this area is needed to verify its effectiveness and mechanisms of action.

Controlled and targeted muscle vibration has suppressive effect on spinal reflexes. The mechanisms for this depressive action are summarised by Ritzmann and Sayenko (Ritzmann et al., 2011) (Sayenko et al., 2010):

- Vibration induces repetitive reflex activation of the muscle. The reduction in the amplitude of H-reflex could be explained by post-activation (homosynaptic) depression. Due to repetitive afferent activation, there will be a reduction in transmitter release over time. This will reduce the H-reflex during and shortly after applying vibration
- Reduction in the H-reflex amplitude after tendon vibration is assumed to be due to increase in Ia afferent presynaptic inhibition

2.8.4 Effect of Body Posture on SOL H-reflex

In humans SOL H-reflex modulation is also linked to posture and orientation of the body with respect to gravity. In standing, the depression of the SOL H-reflex is greater compared to sitting and it should be noted that this difference could be attributed to the effects of loading in the limbs and afferent feedback from the foot during standing (Van Wezel et al., 1997). During walking SOL H-reflex is also greatest during the stance phase when the subject requires the most muscle effort to support the trunk and propel the body forward. Conversely, the SOL H-reflex is smallest during the swing phase when extensor muscle loading is at its lowest and the foot is not in contact with the ground (Van Wezel et al., 1997). Knikou (Knikou & Rymer ,2002) also studied the effects of changes in hip joint angle on SOL H-reflex in healthy subjects. She realised that in supine position, flexion of the hip significantly depressed SOL H-reflex excitability up to 50% and significant facilitation of the H-reflex (up to 200%) happens when the hip joint is extended. Her finding proofs that spinal mechanisms are mediated with hip joint angle.

2.9 Activity-Based Recovery Therapy

Activity-based restorative therapy has been introduced over the last 15 years and is defined as: “an intervention that tries to restore neurologically lost functions” (Sadowsky & McDonald, 2009). Activity-based therapy tries to activate the nervous system below the level of lesion (Dromerick et al., 2006). To achieve this, a specific

task has to be repeated and practiced with the goal to induce activity driven plasticity that can aid in re-establishing lost function (Behrman et al., 2007).

The general and prevailing view of the central nervous system as a hard wired system has been changed through improved understanding of concepts such as neuroplasticity as a basis for successful rehabilitation. Conventional rehabilitation planning which has traditionally been based on using the compensatory and adaptation changes in performance are now changing to capitalise on the potential for neuroplastic changes to have positive impact on performance. Using these concepts some new rehabilitation methods are being introduced (Behrman et al., 2007). These techniques use the new fundamental methods to overcome shortcomings raised by paralysis. The new approaches, try to active the neurological circuits below and above the level of injury by stimulating the nervous system (Behrman et al., 2007).

From animals studies it was discovered that CNS is able to reorganize at multiple levels. So it is possible to have a significant recovery after injury so long as there are key neuroanatomical and physiological substrates to work with in relation to sensory/proprioceptive input paths and motor output channels. The CNS reorganization has been reported at different levels like: cortical, subcortical, spinal cord and peripheral nervous system. This reorganization can have different origins like: synaptic plasticity, sprouting, creation of new connections and re-myelination (Wang et al., 2011) (Goldshmit et al., 2008).

Locomotor training using body weight support over a moving treadmill is known as one of the most accepted activity based therapy methods. The improved ambulatory ability has been achieved using treadmill training in SCI patients. A key aspect of this training method is the high number of steps that can be practised and the recreation of kinematics that are analogous to that achieved during normal gait. In 1970s, treadmill training technique was tested on animals as part of experimental studies and was successfully translated to human subjects in 1987 (Lovely et al., 1986b) (Grillner & Rossignol, 1978) (Barbeau et al., 1987). It has been now accepted that Body Weight Support Treadmill Training (BWSTT) provides a suitable

place valuable method for SCI patients to repeat the sensorimotor experience of walking.

2.9.1 Body Weight Support Treadmill Training

It has been shown that cat's lumbar spinal cord generates rhythmic locomotor pattern when appropriate repetitive sensory information is exposed to it (Brown, 1911) (Grillner, 1973) (Lovely et al., 1986a). In spinal transected animals research studies have shown that the spinal cord is able to produce rhythmic alternating movements of the hindlimbs when the animal is placed over a moving treadmill. These animals, with training, are able to make some limited stepping but they are not able to support themselves. By fixing their chest and both forelimbs on a small carriage, they will be able do some movements similar to the normal gait. At the onset of training, the animal's weight was partially supported over the treadmill. The weight support was gradually reduced over time as walking ability of the animal was improved due to the training. After several months of training, the animal regained locomotor ability remarkably similar to the healthy cats and the EMG activity patterns were also similar to the healthy cats (Lovely et al., 1986a). Successful recovery of the locomotion ability in spinal cats has to be due to the training induced reactivation or reorganisation of spinal locomotor circuits. There has been some evidence on the change in the properties of the CPG after training (Pearson & Rossignol, 1991). It was found out that the trained cats also had significant improvement in locomotion speed, increase in step quality and step length and improvement in weight bearing and walking stability at higher speeds. These factors are also related to the training intensity (De Leon et al., 1998).

One of the important factors in the post injury recovery after treadmill training is the initiation of training after spinal injury is implemented. Studies show that better results can be achieved by earlier training post injury. Other parameters like treadmill speed and limb loading are also important. This information can be useful when applying and developing treadmill training protocols for human subjects.

The work in cats has also been repeated in other species most notably the rat with a similar result (Wenger et al., 2014). This highlight a general principle that in adult mammalian, nervous system is able to adapt and learn to produce locomotion

patterns when the appropriate sensory information is provided at the right time and with an adequate dose and intensity. Depending on the motor task, different pathway will adapt in response to motor training. The afferent signalling during motor task is considered by spinal cord as individual pattern of sensory input for a given phase of a specific motor task. The task specific afferent inputs can be effectively interpreted by the spinal cord over time when the task it is practised or repeated. The spinal cord in spinalized mammals therefore appears to be able to process sensory patterns and relearn to produce motor output that relate to the practiced task even in the absence of supraspinal signals. In humans evidence that the human spinal cord has a similar ability to learn when proper sensory information related to a specific motor task is provided. A typical example for this type of training is locomotor training (Harkema, 2001). Most of the studies in human locomotor training use similar parameters as were used in training cats which is referred as "rules of spinal locomotion" (Wernig et al., 1995). The rule says that the appropriate sensory input (treadmill speed, joint movements and etc.) related to successful execution of the task should be provided during the training process.

The first body weight supporting treadmill system for human studies was designed and trialled in Montreal by Barbeau in 1987 (Barbeau et al., 1987). This system was designed based on the experiences gained through animal studies. In the Montreal system patients could be given varying levels of body weight support while suspended over a moving treadmill. As the treadmill belt moved a team of therapist would manually move the patient's limbs in a way to simulate the kinematics and foot contact of walking. The system allowed the main three necessary components of locomotion to be catered for posture, balance and coordination of stepping (Barbeau et al., 1987). The training system was made of a treadmill, mounting frame, and body weight support apparatus.

The main objective of this type of training is to promote coordinated and purposeful movement of the limbs and trunk via the provision of sensory information to spinal cord. Some of the key rules in locomotor training are (Harkema, 2001):

- Generating stepping velocity similar to the normal walking
- Providing normal load patterns on the stand limb
- Keeping the subject's trunk and head upright and extended

- Approximating the kinematic of the hip, knee and ankle similar to the normal walking
- Synchronizing the extension of the hip in stance phase and loading of one limb with simultaneous unloading of the contralateral limb (Harkema, 2001)
- The arms should be able to swing easily by minimizing the weight bearing on them

The above rules increase the sensory stimulation to the spinal cord and CPG. Most of these rules are currently used in clinics that use therapists to manually interact to control the patients stepping, but the development and optimisation of this form of locomotor training is still evolving and also carries a significant resource commitment.

The experiments on human incomplete SCI subjects show that BWSTT can effectively improve their over ground locomotion after several weeks of training. The patients are trained typically for an hour and are conducted daily or semi-daily for approximately 6-8 weeks. After completing the training sections most of the patients are also able to do some of their daily duties. Two main positive outcome of the body weight support treadmill training are better modulation patterns of EMG activity and better body weight support but there has been reported other positive effects which can be summarized as:

- An increase in the walking speed and the covered distance (Wernig & Müller, 1992)
- The need for the assistant was gradually declined. (Dobkin et al., 1995)
- Some of the incomplete spinal injured patients could found their locomotion ability without assistant (Wernig & Müller, 1992)
- In incomplete spinal injured patient, the initial amount of body weight support was about 80-100%, but it was decreased after weeks of training in many patients. In some cases, the body weight support was also decreased to 0% (Wernig & Müller, 1992) (Wernig et al., 1995)

- The EMG of muscles of the lower extremities in both complete and incomplete spinal injured patients shows better modulation patterns after training

It is also notable that the decrease in the Body Weight Support (BWS) is not because of the increase in the muscle strength (Edgerton et al., 2004). It has been shown that behavioural recovery after SPI is due to the spinal re-circuitry (Galen et al., 2014). The lower EMG amplitude in SCI patients compared to healthy subjects could be due to the reduction or loss of input from supraspinal pathways to the locomotor centres in spinal cord. Clinically spinal injured patients that are trained on the treadmill show improvement in their locomotion on the treadmill but they are not able to walk over ground. This shows that although providing proper sensory information to the spinal cord can generate locomotion signals but its sustainability highly dependent on the supraspinal signals (Harkema, 2007). Currently popular weight training methods are two types: Manual ones that utilizes some skilled physiotherapist and robotic ones that uses robotic technology.

In treadmill training, various tasks should be performed synchronously and sequentially. There has been a growing interest in using robotic devices to assist locomotor training. The robotic assistance is an external skeleton with motors that can provide proper force on hip and knees (Sai et al., 2009). Robotic devices provide weight support and move the patient's hindlimbs in preprogramed step trajectories. The robot's assistance is proportional to the patient's ability in walking. As they learn to walk the machine provides less support. Although there are many advantages in using robotic devises but manual assistances provides better adjustment of the patient's individual stimulation need (Fouad & Pearson, 2004). The main advantage of manual training is that it can be adjusted on the specific needs of the subject. The trainers can adopt and change the training to maximize the sensory cue (Meyer-Heim et al., 2007). In the manual method, usually four skilled trained physiotherapists are required. The risk of injury is high while training and the training cost is quite high. The training sections are short because training sections are very exhaustive for therapist (Wirz et al., 2011).

Robotic method needs less human interface and the risk of injury is lower than the manual method. There is also no assistant fatigue and therefore it has the capability to prolong time for locomotor training compared to manually one (Wirz et al., 2011). This method cannot adapt quickly to the patient's needs and therefore is not as effective as the manual one. The robotic systems are suitable in applications that proper controlled over physical motion and force are required (Sai et al., 2009). Some studies tried to compare the robotic method with the manual training but they couldn't prove that the robotic one is better that the manual one.

2.10 Measurements of Recovery in SCI Patients

The terms recovery and measurement are linked in spinal cord injury outcomes and many methods of measuring motor behaviour are in use but the majority are based on observation, subjective evaluation and interpretation (Geisler et al., 2001). The common outcome measures include the following (Carmen & Edelle, 2003) (Catz et al., 2007):

- Functional Independent Measure (FIM)
- Spinal cord independence measurement (SCIM)
- Modified Barthel index (MBI)
- Quadriplegia Index of Function (QIF)
- Assess activity of daily living (ADLs)

All these tools are based on measuring ability of the patients to perform a functional task and therefore may not be very suitable for measuring subtle recovery in motor or sensory systems after training. Recently, many researchers have looked to identify those factors and markers that can predict the likelihood of recovery in SCI patients. The so far identified factors are (Winchester et al., 2009):

- Severity of injury
- Time of injury
- Level of lesion
- Walking speed before starting the training
- Preservation of pin prick sensation

- Motor score
- Spasticity
- Voluntary voiding the bowels and bladder.

It is still not clear that which of these factors can best be considered as prognostic measures for SCI recovery. There are also 3 main methods which are used in evaluating changes after SCI: anatomical and functional MRI, transcranial magnetic stimulation (TMS) and somatosensory evoked potentials (SSEP) (Fehlings et al., 1989).

Using MRI and diffusion tensor imaging (DTI) it will be possible to provide high-resolution structural images of the lesion and measuring the white matter integrity. Researchers have tried to correlate structural and functional brain and spinal cord changes with functional recovery (like open-field locomotion, grid walking and etc.) data to find a relationship between the MRI data from the spinal cord and brain as markers in SCI rehabilitation (Sundberg et al., 2010) (Deo et al., 2006) (Lammertse et al., 2007).

Transcranial magnetic stimulation (TMS) is a painless and non-invasive tool for electrical stimulation of cerebral cortex and spinal roots and evaluating the motor pathways in CNS. TMS allows monitoring the changes in motor function and evaluating the effects of the different rehabilitation approaches after injury. It provides reliable information about the conduction properties of the corticospinal tracts and motor control after SCI. Unfortunately, the results of TMS studies are often divergent, and should be replicated in a larger sample of subjects (Nardone et al., 2014) (Ellaway et al., 2007).

2.10.1 SSEP as a Tool to Measure the Recovery in SCI

The measurable electrical fields resulting from the response of a neurone or combination of neurones to an imposed stimulus is often referred to as an Evoked Potential (EP). Analysis of the evoked potentials can provide valuable information on CNS pathways and neuronal processing. During the past century, evoked potentials have evolved from a scientific tool to a standard clinical tool routinely

used in the diagnosis of neurological cases (Nuwer, 1998). SSEP are non-invasive, easy to perform and can be measured with relatively low cost equipment. Applications cover the sensory modalities of vision, hearing, and somatic sensation. Current methods can measure the primary sensory pathways and higher order cognitive function. The application of EPs can be summarized as (Nuwer, 1998):

- It can be used to quantify patient symptoms and aid diagnosis of lesions when signs or symptoms are unclear
- It can be used to find silent lesions
- To assign an anatomical degree of impairment along a pathway
- To get information about the general category of the pathology
- To track the changes in the patient's status over time

EPs are used to measure the functionality of known pathways or processing capabilities in the nervous system. They are sensitive to find abnormalities even when there is not any functional deficit evident in the patient (silent Lesions). Most EPs have fixed shape, delay and amplitude and are repeatable when tested on year to year basis. They also can be studied without the need for the explicit cooperation of the patient (unconscious or otherwise incapacitated). The most commonly employed sensory EP studies are tests of the visual, auditory and somatosensory systems. In the case of the somatosensory system the test is often referred to as a somatosensory evoked potential (SSEP).

The most common way to generate SEPs is to use electrical stimulation. Generally a square wave of 100-500μs is delivered using a constant voltage or constant current stimulator. The short electric shock will, if above threshold for afferents in the peripheral nerve, generate a synchronous afferent volley of action potentials that will lead to activation of pathways within the CNS which is turn will result in the activation of appropriate sensorimotor areas of the brain that can be measured using EEG electrodes placed on the scalp. There are many factors that affect the normal SSEP some of the main ones are: age, body height and gender, skin and core temperature, attention and drugs (Mauguiere et al., 1999).

SSEPs can also be created by adequate stimulation of sensory systems, for example flashes of light generate visual EPs and different types of mechanical stimuli of the skin can physiologically activate specific cutaneous mechanoreceptors (Hämäläinen et al., 1990). Some studies show that mechanical stimulation (using vibratory pulses) of the skin elicits qualitatively different responses in the EEG in comparison to electrical stimulation and this difference is believed to reflex the activation of different pathways in each case (Cheyne et al., 2000).

There have been many studies to determine the relationship between SSEP and prediction of recovery in SCI patients (Tzvetanov et al., 2003) (Tzvetanov & Rousseff, 2005) (Li et al., 1990). Somatosensory evoked potential mainly inform on the integrity of dorsal column ascending pathways in SCI patients and can assist in assessing the sensory completeness of lesions by SSEPs in response to stimuli delivered below the level of a lesion. In the complete spinal injured patient no SSEP from below the lesion should be identifiable. Observation of SSEPs or how they may change post injury (both latency and the amplitude) in cases of SCI may be used to chart the improvement of sensory function in patients. But on the other hand others have suggested that SSPE do not give additional prognostic information to the clinical examination (Fehlings et al., 1989). SSEP are most useful in those patients that ASIA impairments scale or clinical examinations are limited due to the patient being unresponsive or otherwise uncooperative with the tester.

2.10.2 Vibrotactile SEPs

The ability of living organs to react and adapt to externally applied forces is an essential aspect of motor control. Cutaneous mechanoreceptors transfer tactile information crucial in discriminating vibration, pressure, edge and texture and ultimately in the multimodal sensory perception of touch. Within non-hairy or glaborous skin there are four main types of low threshold mechanoreceptors: Pacinian corpuscles, Meissner's corpuscles, Merkel's discs, and Ruffini endings. Properties of these receptors have been widely studied and are recently reviewed by Zimmerman (Zimmerman et al., 2014). Afferent fibres from cutaneous mechanoreceptors transmit tactile information to CNS. These mechanoreceptors are

activated in response to the mechanical forces like vibration and pressure and are located distal end of the sensory neurons. The sensory information gathered by these receptors is transmitted to the CNS using Aβ afferents (Chung et al., 2013). Meissner corpuscles detect low frequency activations (5-50Hz) and pacinian corpuscles detect vibration stimuli in the range of 50-400HZ (Chung et al., 2013). Merkel's discs are located in the epidermis and provide information regarding to light pressure and texture and are most sensitive to low frequencies up to 15Hz. The spindle-shaped Ruffini corpuscles exist only in the glabrous dermis and subcutaneous tissue of humans as well as in ligaments and tendons. They are sensitive to skin stretch and sustained pressure. These receptors do not elicit any particular tactile sensation when stimulated electrically (Zimmerman et al., 2014).

The human mechanosensation system plays an important role in many applications and helps in tactile object recognition, grip control and locomotion. Somatosensory information about the foot contact along with other postural control mechanism is part of the sensory triggers that contribute to patterns of neuromuscular synergies and therefore the process of walking (Kremneva et al., 2012). Understanding how human mechanosensation systems respond and process external mechanical forces is important in designing gait rehabilitation machines. Somatosensory evoked potentials in response to natural skin stimulation provide an accessible way to study the pathways used for processing tactile stimulations and can therefore be applied within the context of SCI to determine what pathways and modalities are necessary in gait rehabilitation.

SEPs generated by electrical nerve stimulation have been widely studied but there has not been much study using mechanical stimulation. The advantage of using electrical stimuli is that it directly stimulates axons so the generated EPs are synchronised to a clear afferent volley, are large and distinguishable with high signal to noise ratio (SNR) (Spackman et al., 2006). The electrical stimulation is also easy to use in clinical applications. However, the major weakness of electrical SEPs is the lack of specificity regarding to the fibre type being activated. Tactile stimuli provide a more natural recruitment of afferents than electrical stimuli but they have not been widely studied in part due to the need for more complex equipment, difficulty in

synchronisation of afferent populations and the effects of electromagnetic noise from mechanical actuators (Jousmäki & Hari, 1999).

SEPs from mechanical stimulation resulting from vibration and tapping have been studied for the human hand and the corresponding early/mid-latency SEP components identified (Hari, 1980). The recorded EPs were in many respects similar to the EPs elicited by auditory, visual stimuli and painful stimulations. Depending on the frequency, vibration pulse width and the location of stimulation different component latencies have been reported by authors. In general a typical waveform of the mechanical stimulation is an M-shaped pattern followed by large negative-positive-negative waves (see Figure **2-2**) (Hari, 1980) (Yamauchi et al., 1981). A large negative slow wave component at 150ms and a large sustained negative peak at 400-700ms post vibration onset have been reported by many authors (Yamauchi et al., 1981) (Hari, 1980).

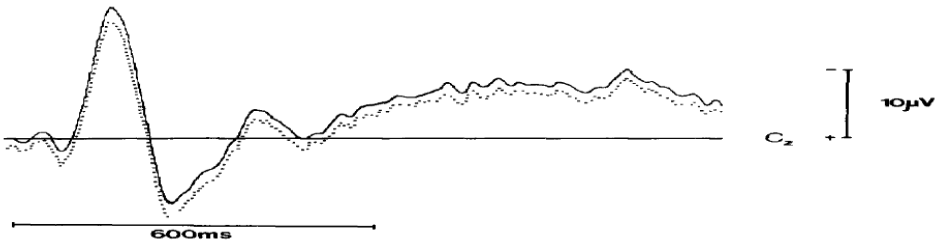


Figure 2-2. Evoked potentials recorded from Cz elicited by vibratory bursts (60 Hz, 600 ms) delivered to the back of the hand. Image taken from (Hari, 1980).

The time course of the vibrotactile SEPs are very similar to that of some other slow waves that are related to the orienting sensation (Hari, 1980) and it has been suggested that any stimuli which can elicit a large negative sustained slow deflecting component in the EEG signal may active neural circuits associated with the orienting reflex (Naatanen & Michie, 1979) (Hari, 1980) (Woodman & Geoffrey, 2010) suggesting a generalised response to proprioceptive related afferents. It is well established that peak components of 120ms or more are related to the perception of stimulation (Johnson et al., 1975).

Somatosensory EPs are mainly generated in contralateral primary somatosensory (S1), bilateral secondary somatosensory cortex (S2) and cingulate cortex (CC) in human (Hu et al., 2012). S1 receives information from the opposite side of the body and S2 receives information bilaterally. Mechanical sensory information is transmitted to cortex in a segregated way so different tactile mechanical stimuli cause diverse somatosensory cortical responses. Electroencephalography in human following different mechanical stimulation of the skin reveals that there is a difference in somatosensory cortical activity recorded from scalp after vibration and fluttering. The sensation of flutter is produced when mechanical vibrations are in the range of 5–50 Hz (Hämäläinen et al., 1990) (Han et al., 2013). Further, fMRI studies also show that S1 is more active when fluttering and S2 shows a dominant activity after vibration (Harrington et al., 2001). A bilateral response in the S2 following vibrotactile stimulation of the hand and foot sole has been reported by some authors (Golaszewski et al., 2005) (Hämäläinen et al., 1990) (Kany & Treede, 1997). The effects of changing the frequency and vibration pulse width have been studied before for hand and finger regions but not in low limb which is in our interest in this research (Kekoni et al., 1997) (Baba et al., 2001) (Harrington et al., 2001) (Chung et al., 2013). The surface compliance at the foot sole is much smaller than palm of the hand so in order to activate the sensory cortex and elicit a measurable response much stronger vibration stimulation is usually needed (Golaszewski et al., 2005). This might cause electromagnetic noise interference with recording devices which will be discussed in detail in next chapter.

2.11 Stochastic Resonance Theory

Stochastic resonance (SR) is a nonlinear phenomenon where adding a proper amount of noise to the signal source can improve the detection of a weak stimuli. It mainly occurs in a threshold measurement system (electronic device; a natural cell, organ or organism). SR happens when the signal-to-noise ratio of the system increases for moderate values of noise intensity. It often occurs in bistable systems or in systems with a sensory threshold and when the input signal to the system is "sub-threshold". For lower noise intensities, the signal does not cause the device to cross the

threshold, so little signal is passed through it. For large noise intensities, the output is dominated by the noise, also leading to a low signal-to-noise ratio. For moderate intensities, the noise allows the signal to reach threshold, but the noise intensity is not so large to swamp it.

For stochastic resonance to happen three criteria should met: there must be a nonlinear input output relationship (an example is the nervous system), the input or the source signal must be below the threshold (like foot pressure when high percentage of body weight support is used during treadmill walking) and a random noise at proper amplitude (like vibration) must be added to the source signal. If these conditions meet the output will yield a better measurement of the signal compared to the system without noise.

Physiological experiments on human shows that adding noise to the sensory stimulation will increase the human perception. The stochastic resonance effect has been studied in visual, auditory and tactile sensory stimulations (McDonnell et al., 2009).

2.11.1 Improvement of Plantar tactile Sensitivity Using Vibration

Human balance control highly depends on feedback from plantar skin receptors (Priplata et al., 2006). Subsiding of the sensory input from foot sole will increase postural instability during standing or walking and is mainly observed in patients suffering from diabetes or Parkinson (Priplata et al., 2006). The generated stochastic resonance effect using vibration has been considered to compensate the decrease of plantar tactile sensation and improve the stability of gait in patients suffering from reduced sensation on the plantar feet (Satoshi et al., 2011). Vibration is non-invasive and accessible as a stimulation technique through small, low cost, mass produced electrical mechanical devices. Vibration provides a simple way to locally activate low threshold cutaneous mechanoreceptors and generate a synchronised form of sensory feedback that can influence the activity of neural circuits in CNS. Usually vibrating insoles are placed inside the patient's shoes to increase the plantar tactile sensitivity by applying vibrating noise to the sole of foot. Proprioceptive feedback can be perturbed by stimulating foot mechanoreceptors using vibration to enhance gait stability. Somatosensory stimulation using vibration has been proved to be an

effective method to improve balance control in these patients (Priplata et al., 2006). Psychophysical experiments in humans show that adding a certain amount of noise (vibration) to the mechanical stimulations may significantly enhance the ability of the subject to detect the tactile stimuli (Collins et al., 1996) (Martínez et al., 2007). Adding a certain amount of noise (vibration) to the mechanical tactile stimuli will also increase the amplitude of the EEG responses evoked in the somatosensory cortical regions (Manjarrez et al., 2002).

2.12 Mechanical Stimulation of the Foot as an Augmented Sensory Input

Sensory information from the muscles, tendons, joint receptors and foot cutaneous receptors reflect information about loading (Gravano et al., 2011). As foot contact pressure is an important sensory input during gait and any loss or decrease in cutaneous sensory information may contribute to unstable locomotion, even a small cutaneous sensation can be functionally critical. There has been number of ways proposed for enhancing the cutaneous load related output from the foot during walking or treadmill training in patients and can be summarized as:

- Non-nociceptive electrical nerve stimulation (Knikou, 2007)
- Ankle foot loading Device (Gordon et al., 2009)
- Pneumatic insole method (Gravano et al., 2011)
- Step synchronized insoles vibration method (Novak & Novak, 2006)

The non-nociceptive electrical nerve stimulation is mainly used to study and test the cutaneous reflexes rather than imitate or to restore the sensory feedback from the foot sole during walking.

The ankle loading and compression of the foot are associated with improvement in ankle joint position sense (JSP). These devices are specifically used to unilaterally load the ankle and foot during robotically assisted airstepping (Gordon et al., 2009). These devices apply dorsiflexor torque about the ankle joint during the stance phase. Studies show that both SCI and healthy subjects showed a significant

increase in hip extension torque during the stance phase of the walking when using the ankle-foot load device. Figure **2-3** shows the device designed by Gorden (Gordon et al., 2009).

The Pneumatic insole method is a non-invasive technique for augmenting the sensory input from the foot sole in stance phase of locomotion. Using this method it will be possible to restore contact forces and provide a temporal sequence of forefoot and heel stimulation under body weight support conditions. This device is made of pneumatic insoles for each leg to mechanically stimulate the foot soles to raises the pressure inside the shoes during treadmill walking (see Figure **2-4**). Experiments show that foot compression using Pneumatic insole does not, changes in the motor patterns in healthy participants during step-synchronized foot pressure application (this device has not been tested on patients suffering from loss in cutaneous sensory information yet). Pneumatic insoles cannot provide reliable sensory cues about the position of the contact surface. it is suggested that using light touch to stimulate the foot receptors might provide better results as light touch contact may provide better position feedback and enhance the control of walking than compression (Gravano et al., 2011) (Jeka et al., 1997).

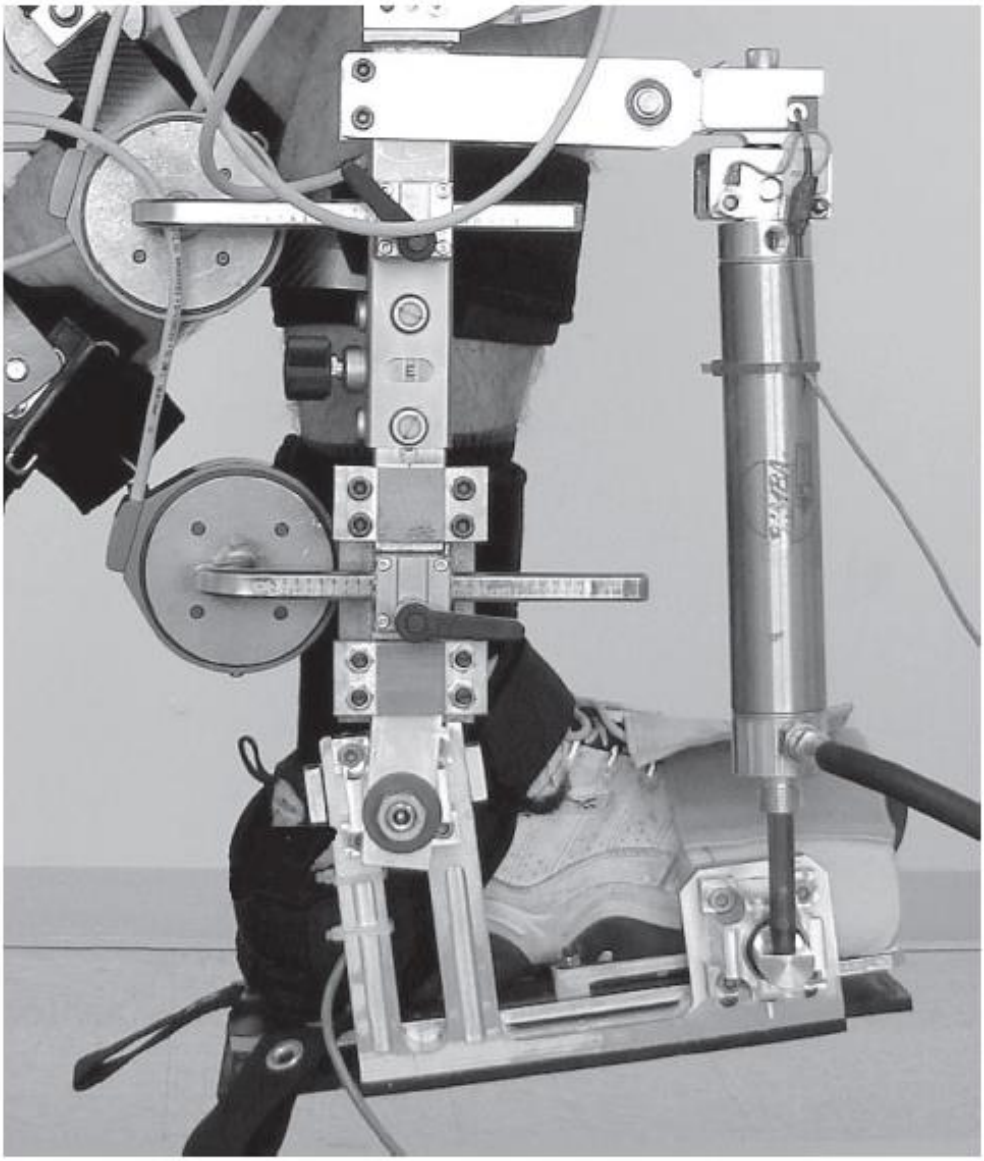


Figure 2-3. Ankle orthosis which was used to mechanically stimulate the load receptors of the ankle and foot during stepping movements. The pneumatic cylinder creates a dorsiflexion torque when pressurized. Image taken from (Gordon et al., 2009).

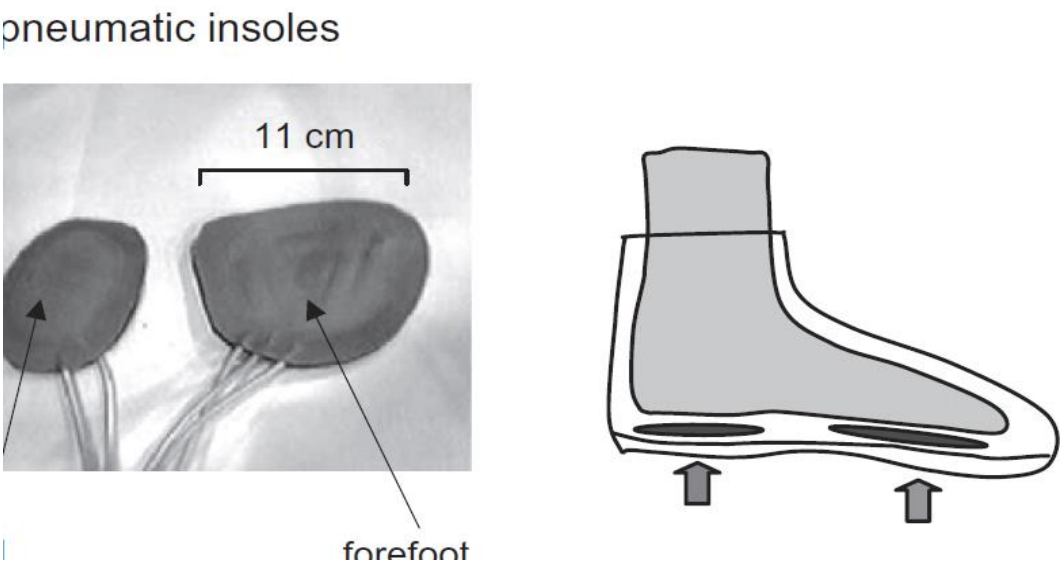


Figure 2-4. Pneumatic insoles used to mechanically stimulate the foot soles. Image taken from (Gravano et al., 2011).

In contrast to mechanical compression of the foot, suprathreshold vibration of the foot sole in healthy subjects enhances the proprioceptive feedback and improves quite standing due to the stochastic resonance theory (Novak & Novak, 2006). During static standing, the vibratory stimulation of the different regions of the foot has been reported to have different effects on postural control (see Figure 2-5). Vibratory stimulation of the forefoot zones in healthy subjects moves the centre of pressure slightly forward. Stimulation of the rear foot zones has the same effect but with an opposite direction of the body tilt (Novak & Novak, 2006).

Positive effect of foot vibration has also been demonstrated in patients suffering from Parkinson (Novak & Novak, 2006). Additional mechanical noise (vibration) applied to the foot sole will improved quiet-standing balance in patients suffering from reduced sensation of the plantar feet (Priplata et al., 2003) (Priplata et al., 2006). It has been shown that vibration stimulation of foot mechanoreceptors synchronized with gait phase (during the stand phase) will improve stepping in patients suffering from Parkinson's disease (Novak & Novak, 2006). Improvements in patients walking are assumed to be due to the increased awareness of foot placement caused by stochastic resonance generated by vibration stimulation (Novak & Novak, 2006).

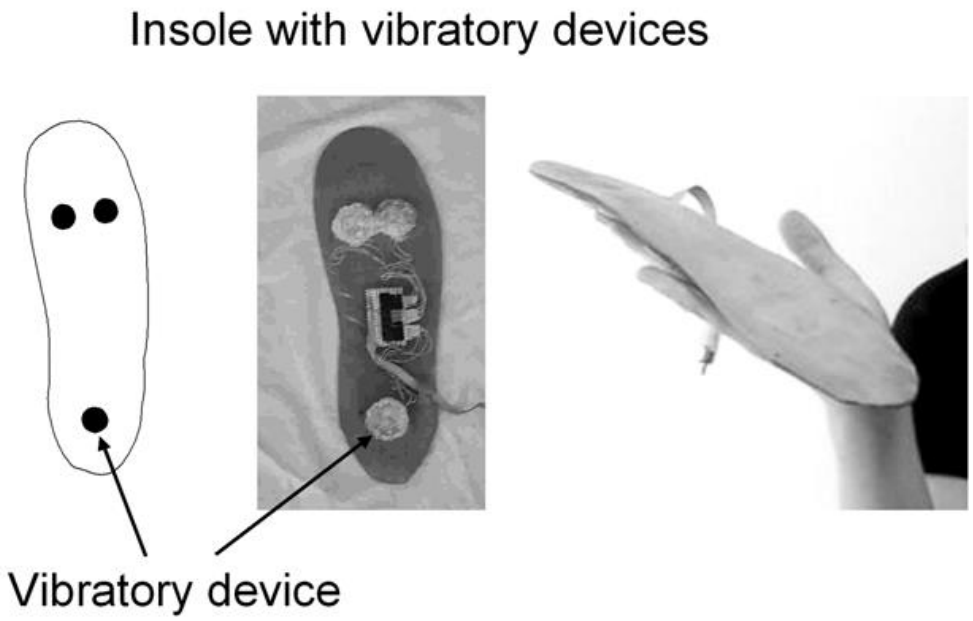


Figure 2-5. Schematic diagram that shows the insole with the vibratory device. The Vibratory device consists of a vibration disk motor (diameter 18 mm). Image taken from (Novak & Novak, 2006).

In this research we hypothesized that localised vibrotactile stimulation of foot mechanoreceptors synchronized with the gait kinematic might also have beneficial effects for SCI patients when being trained using bodyweight support treadmill devices. Unlike the ankle foot loading device, vibration stimulation is easy to implement and control and also provides more reliable sensory cues about the position of the contact surface which is missing in pneumatic insoles. Before applying this method to patients some physiological experiments need to be conducted to proof the effectiveness of this method in healthy subjects. The major question we are trying to answer in the rest of the thesis is that if it is possible demonstrate measurable effects in both spinal and cortical levels after localised vibrotactile simulation of different foot zones? Can these effects facilitate activation in pathways that influence the ankle joint control? And can this type of stimulation be used within the context of body weight support rehabilitation programs for gait?

CHAPTER 3
Cortical Somatosensory Evoked Potentials Elicited by Vibrotactile Sole Stimulation

3.1 Abstract

Mechanical stimuli stimulate a distinct group of skin mechanoreceptors which contribute differently to tactile and vibrotactile sensations (Hämäläinen et al., 1990). The main method of investigating the effective transmission of vibrotactile sensory activation through the pathways of the central nervous system to the cortical level is to look at the vibration induced somatosensory evoked potential (SEP). This chapter will investigate the cortical evoked potentials that result when stimulating the foot sole using mild cutaneous localized vibratory stimulation. Vibratory of the foot sole was chosen over electrical stimulation in these experiments because it is pain free and provides a natural way to activate skin mechanoreceptors that are sensitive to touch, pressure and vibration (Hämäläinen et al., 1990). These are receptor subtypes that are likely to be activated during stance phase of walking. By analysing the characteristic features of these evoked signals, it will be possible in later studies to incorporate the monitoring of this type of signal in patients undergoing gait retraining to determine if transcortical activation plays a role in successful rehabilitation. At the present time the main objectives of this work are:

- Attempt to determine the SEP feature components
- Measuring the effects of changing the vibration pulse width and skin area on the SEP waveform
- Characterise the time and frequency domain features of vibrotactile SEPs evoked from the lower limb

3.2 Vibrotactile Stimulation Apparatus

Stimulating skin surface via mechanical transducers has been used to study the flutter and vibration effects in both psychophysical and neurophysiological studies (Tannan et al., 2005). Usually mechanical transducers which can deliver sinusoidal stimuli at frequency range (1-250Hz with amplitudes size of 0-1000μm) are used to activate wide range mechanoreceptors in the skin. We investigated several different types of mechanical transducers to find a stimulator with the capability to assess the vibrotactile SEPs under a range of stimulation conditions. Three different types of the mechanical transducers have been evaluated and a foot-rest platform was built that allows the vibration transducer to be placed beneath the foot sole at key anatomical locations. The selected transducer was then used to stimulate three different sites (first and fifth metatarsal heads and heel) at different vibration durations (50ms, 75ms and 110ms) at 100Hz.

3.2.1 Micro Vibrators

The first group of vibrators that were tested are micro vibrators (Pager Motors) by Precision Microdrives (Precision Microdrives). These vibrators are mainly used by mobile/cell phone manufacturers. They operate within the range of 1.5-3V and work based on a brushed coreless cylinder design. Their weight varies from 25- 200g.

These vibrators were first used to generate vibration stimuli. After doing some initial recordings it was found out that these transducers induce large and significant levels of electromagnetic noise when used in combination with electrophysiological recording systems. Figure **3-1** shows the average SEP dominated by the interference generated by the device. A single trial record is shown in Figure **3-2**. Given the need to be able to monitor early components of the SEP, this type of device was not investigated further.

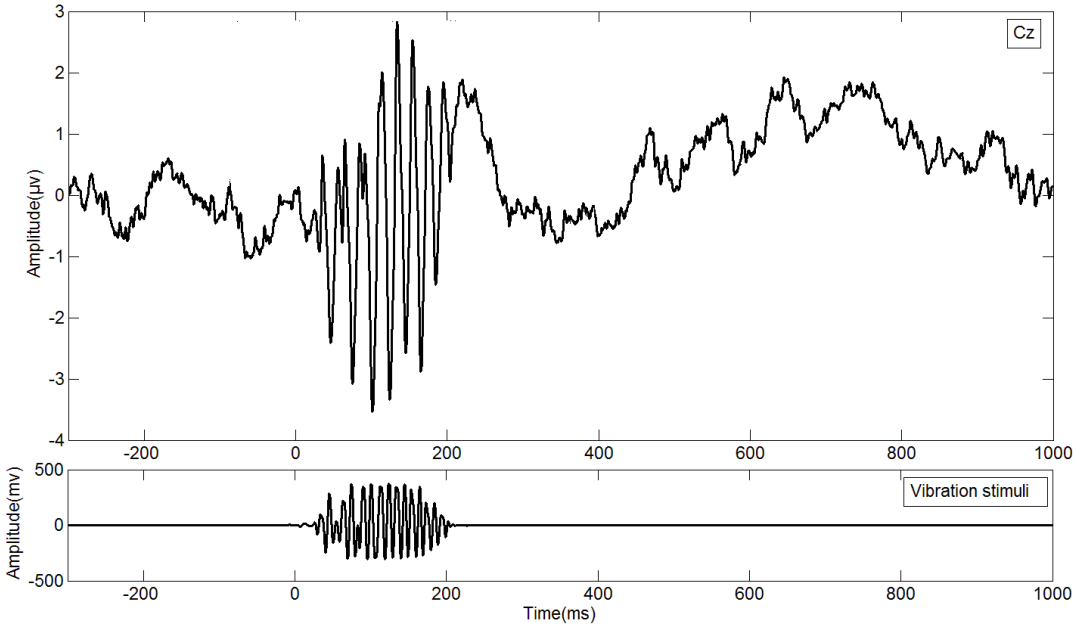


Figure 3-1. The mechanical transducer (Pico Vibe 9mm vibration motor 307-100) generates a huge amount of electromagnetic noise which masks the SEP components after averaging. The foot sole of one of the subjects was stimulated using vibrotactile stimuli generated using a micro vibrator. In total 600 stimuli were applied to the subject's foot and averaged. The plot shows the averaged SEP recorded from Cz. The vibration stimuli were applied at 100HZ with the pulse width of ~200ms.

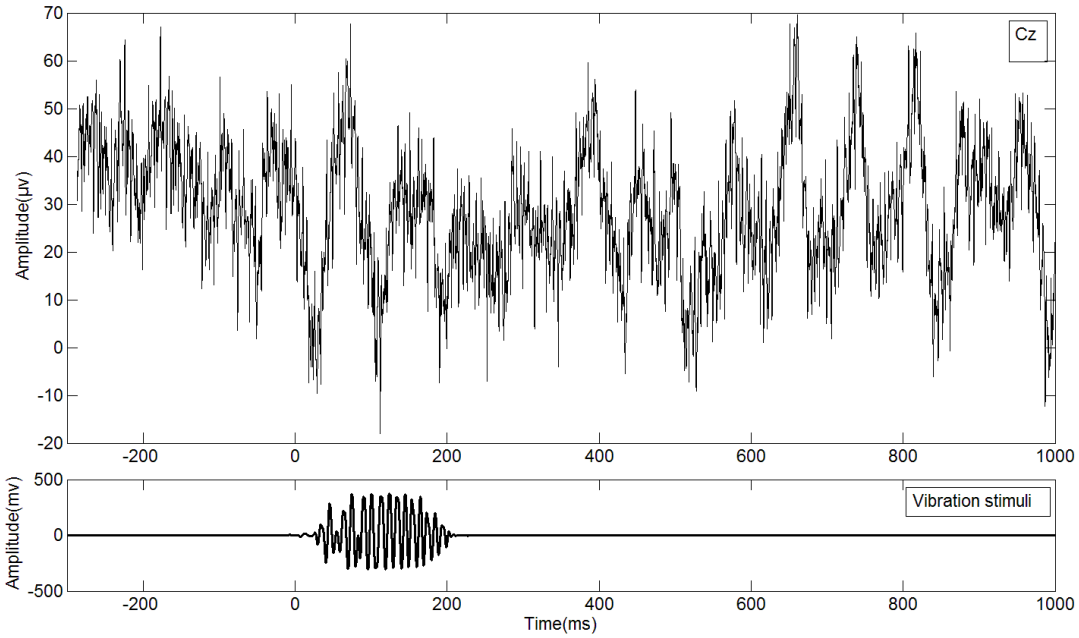


Figure 3-2. The plot shows a single trial record SEP recorded from Cz. The vibration stimuli were applied at 100HZ with the pulse width of ~200ms. The electromagnetic noise is not recognizable on the raw EEG data.

3.2.2 Neurothesiometer

This is a commercial device which is used in quantitative sensory testing. In practice it is used to report on the perceptual vibratory threshold of patients with peripheral neuropathy. The device can produce vibration stimulation at a single frequency of 100Hz and has variable but uncalibrated amplitude adjustment. However, like the micro vibrators the major problem with this vibrator is that it produces a large level of electromagnetic noise which makes it difficult to use it in electrophysiological monitor tests. Its design also makes it impractical to use the device in walking rehabilitation as it is a hand held instrument (Diaped, 2015).

3.2.3 LDSV101 Permanent Magnet Shaker

LDSV101 produced by Ling Dynamic Systems Ltd (Brüel & Kjær) is designed to be used in laboratory conditions. This vibrator has a lightweight moving armature and has been designed allowing a wide frequency range response. Our initial tests showed that electromagnetic field generated by this device is weak, and the noise has minimal effect on electrophysiological monitoring (EEG).

This vibrator is a suitable stimulator in neurophysiologic studies and for examining the sensory pathways activated by controlled vibratory stimuli. This vibrator was therefore adopted for subsequent experiments on normal subjects. To monitor the vibrator output during the experiments, an analog accelerometer was also attached to the vibrator.

3.2.4 The Vibrator Driver

LDSV101 is a linear motor and is driven with DC pulses. The frequency of the vibrator can be controlled by changing the frequency of the input pulses. To generate stimuli that can be used in measuring vibrotactile SEPs, short repeatable vibration pulses are required.

Two function generators EM135L were used to drive the vibrator. The signal generators have two isolated output. One output was used as a trigger and the other

output was used to drive the vibrator (see Figure **3-3**). Two signal generators share the same common reference and the body of the vibrator is also connected to the reference port. Using this setup it is possible to control the vibration frequency and pulse width. All devices are powered through an isolated medical power supply. The smallest vibration pulse width that can be generated by this setup is ~50ms.

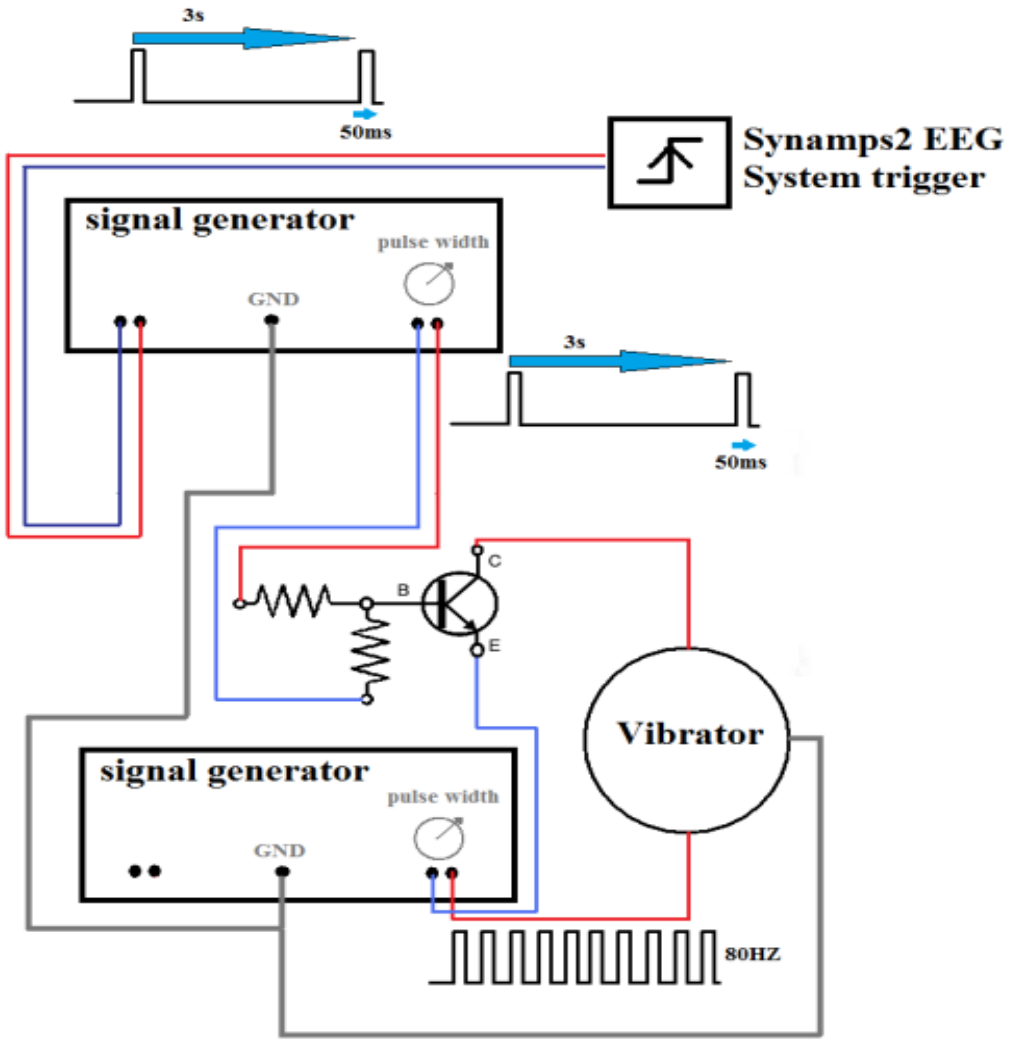


Figure 3-3. The schematic of the vibrator driver. Two function generators EM 135L were used to drive the vibrator. One of the function generator controls the pulse width and the other one control the pulse duration.

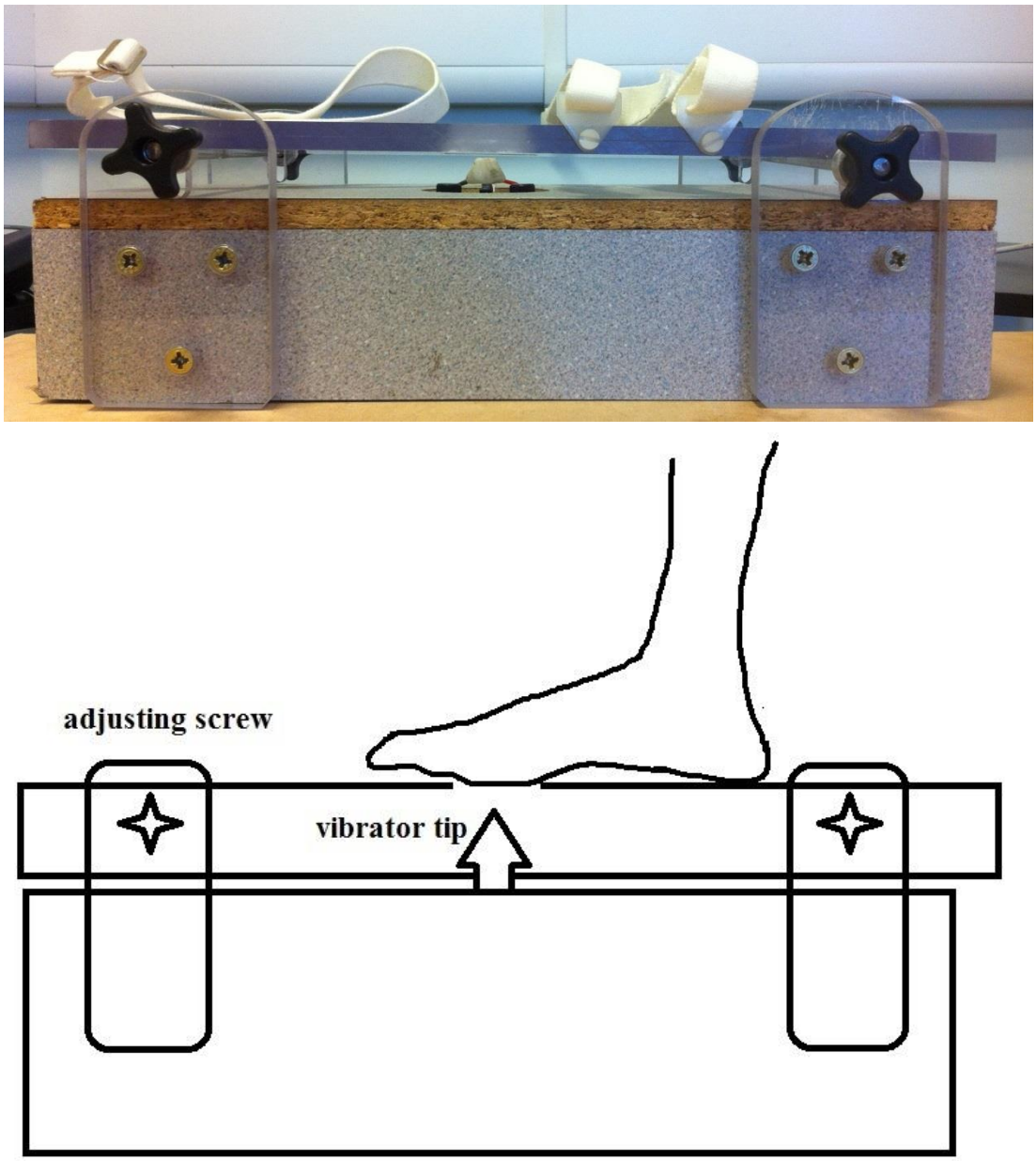


Figure 3-4. A custom-built mechanical stimulus generator system is used for proper positioning of the subject's plantar surface. There are two screws in the top and the bottom of the platform. By turning the screws, it is possible to adjust the top platform height up to 3cm.

The vibrator was mounted into a wooden apparatus that allowed the foot of the participant to be secured and permitted the sinusoidal vibrotactile inputs to be directed to the foot sole regions of interest. A rigid plastic pyramid shell with contact surface of ~0.3cm^2 served as the vibrator head actuator. The body of the platform is made of MDF, and the other parts are made of acrylic. The platform dimension is 38×15×8cm^3. There are two adjustment screws in the top and the bottom of the

platform. By turning the adjusters, it is possible to adjust the top platform height by 3cm. This allows the vibrator to be positioned in an optimal way for each subject (see Figure **3-4**). It should be mentioned that the vibrator generates a constant displacement (~0.5cm) of the shaft. To adjust the vibration amplitude the end of the shaft displacement has to be adjusted relative to the skin surface.

3.3 Subject Recruitment

All the subjects that participated in this study were recruited on voluntary basis. The "Health status assessment prior to the test" form was used to consider the health situation of subjects. The main inclusion criteria were:

- Healthy subjects with no previous history of neurological problems
- 18-65 years of age
- No structure surgically implanted cardiovascular, orthopaedic or neurological device

Those people who matched the criteria signed the consent form. The aim and the details of the experiments were explained verbally. All the experiments were carried out in the biomechanics lab in the University of Strathclyde. All the subjects undertook a familiarization session before doing the experiment. During the sessions subjects were introduced to the experiment procedure. Subjects were asked to avoid having tea or coffee within 2 hours prior to the experiment. This study was covered under a general ethics policy for the neurophysiology group approved by the department of Bioengineering at the University of Strathclyde.

3.4 SEP Recording

Subjects were asked to sit on a chair in a comfortable position and put their right foot on the top platform. The foot was held using two straps to prevent movements on the platform (see Figure **3-4**). The height of the platform was then adjusted to a position where the subject reported feeling the tip of the vibrator actuator (vibration sensation threshold) while the vibrator was constantly vibrating. The experiments were

conducted in a quiet room and subjects were asked to keep their eyes open and remain stable. Subjects were asked to use earplugs so there was no auditory sensation of the vibration stimuli and no SEP without skin contact.

SEPs were recorded using 17[1] Ag/AgCl sintered electrodes placed on the scalp using a commercial electrode cap (EasyCAp). Electrodes formed a 17 electrode montage around Cz in accordance with the 10-20 system (see Figure **3-5**). This montage ensures a good coverage of the foot region in the brain. The EEG recording was monopolar and was referenced to a non-cephalic reference point using the linked ear electrodes2. After positioning the cap the scalp skin was cleaned using an abrasive solution applied to the tip of a cotton bud and electrode gel introduced into the cup of each electrode. Manipulating a cotton bud inserted through the electrodes and performing gentle abrasion was done until the contact impedance fell below 5Ω. All channels were sampled at 10KHz using the Synamps2 amplifier. The amplifier gain was set to 1000 and the data were filtered by a band-pass filter at 0.5-500Hz. EEG data were analysed offline using SCAN software.

3.5 Experiment 1: Modulation of the SEP Wave By Increasing in the Stimuli Duration

3.5.1 Method

The aim of current study was to evaluate the effect of increasing the vibration pulse width on cortical SEPs. 9 right handed healthy volunteers (21-36 years old) were recruited for this experiment and all signed the written contest form. The cortical evoked potentials were obtained by applying vibration stimulation to the plantar surface of the right foot using the wooden platform described previously. The platform height was adjusted to a level where subjects could just feel the vibration (sensation threshold). If vibration was perceived in the tested area, this was indicated by the subject by a verbal response.

[1]SPEs were recorded from: FP2, AFz, Fz, FCz , Cz, CPz, Pz, C3, C4, CP3, CP4, P3, P4
[2] Non-cephalic electrodes are used to remove far fields noises which affects all the electrodes on the scalp

Vibration stimuli (~100Hz) at the sensation threshold were delivered to the first metatarsal head of the right foot in all the subjects. Experiment consisted of 3 different pulse train duration scenarios all tested in a single test session. Testing each scenario took approximately 30 minutes to complete and during the test subjects received vibration stimuli with fixed vibration duration. After finishing the test, subject had a break and the test was repeated using different pulse duration. In total three different vibration stimuli were applied at ~100HZ at sensation level with the stimulus durations of 50ms, 75ms and 110ms repeated every 3s (see Figure **3-6** and Figure **3-7**). In total 1800 stimuli were recorded from each subject. The large number of collected data samples was performed to allow acceptable and reliable averaging to be performed. The stimuli were averaged and the cortical components determined.

3.5.2 Data Analysis

The recorded data was checked visually and epoch containing artefacts were rejected. The raw data were epoch using routines provide by SCAN software. The epoch length was set to [-300ms 800ms] relative to time of stimuli onset. The epoch data were averaged and baseline corrected. All the SEPs measurements were based on peak to peak values. The SPSS program was used for statistical analysis.

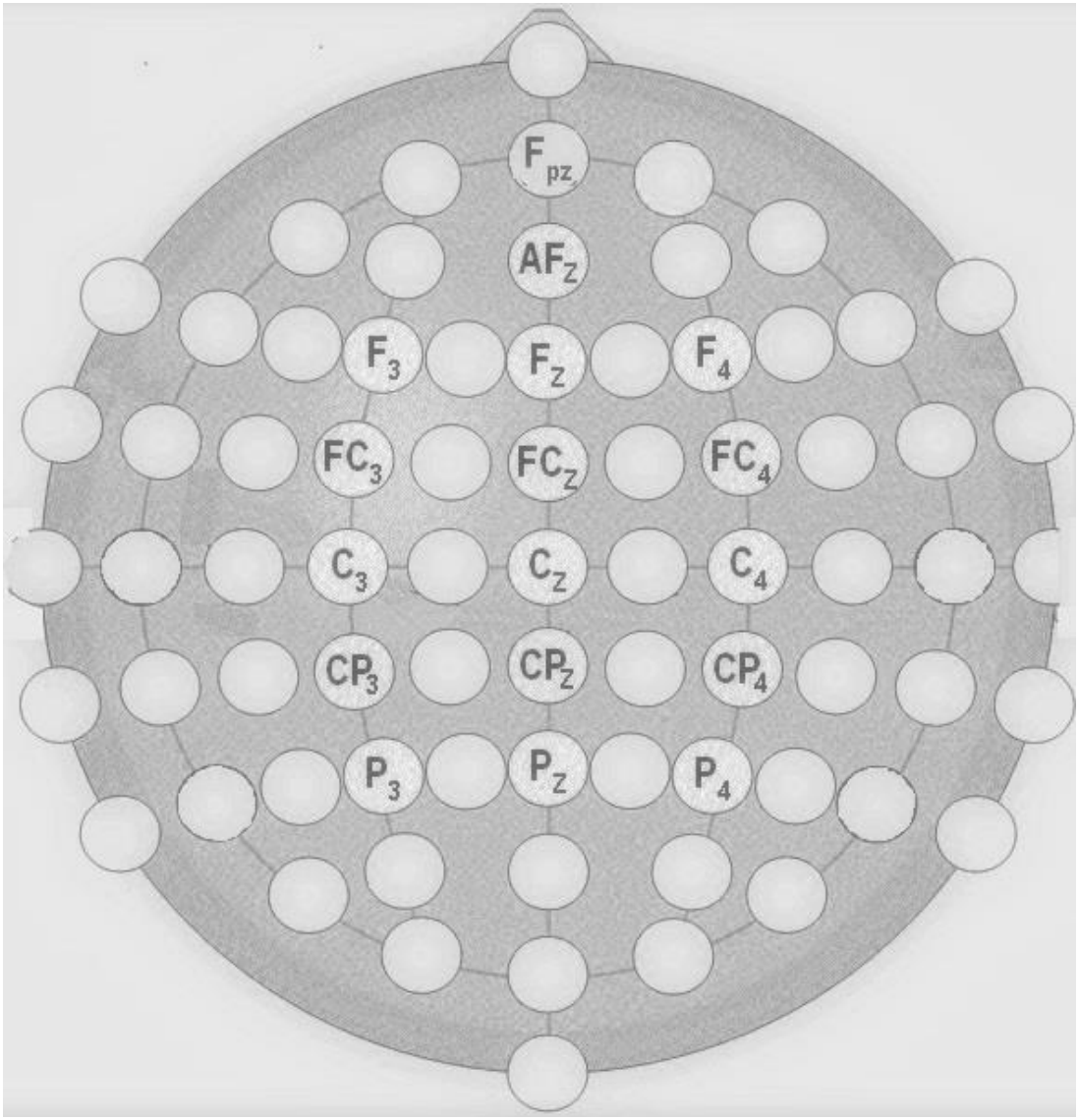


Figure 3-5. 17 electrodes around Cz according to 10-20 system were used for recording vibrotactile SEPs.

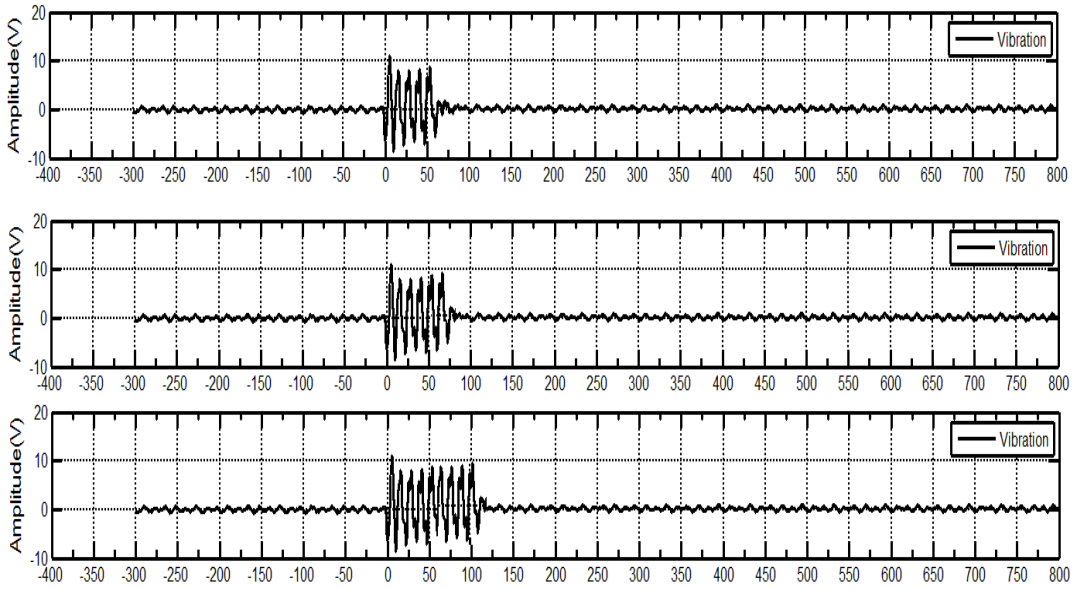


Figure 3-6. From top to bottom, three vibration stimuli at different pulse widths (50ms, 75ms and 110ms) were applied to the plantar surface of the foot to evoke vibrotactile SEPs. The vibration frequency was also fixed at ~100HZ. The time axis is in millisecond.

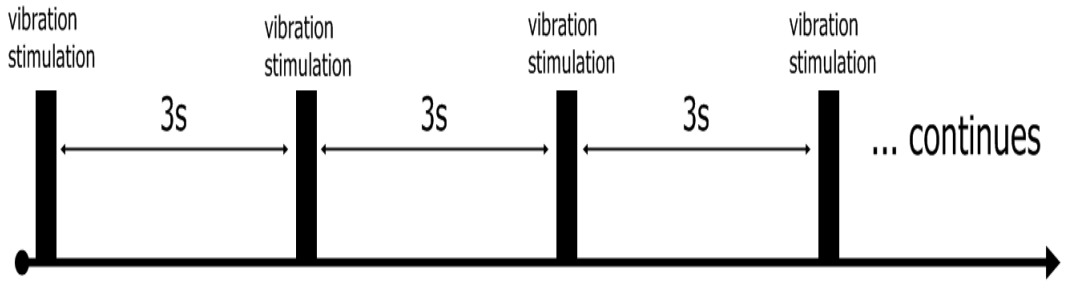


Figure 3-7. Vibration stimuli was repeated every 3s to evoke SEP. In total around 1800 stimuli were applied to the each subject.

3.5.3 Results

The averaged measurements obtained from the 9 subjects are shown in Figure **3-8**, Figure **3-9** and Figure **3-10** for different stimulus duration. The monopolar SEP only contains far field components so further derivation of the monopolar recording is needed to remove the far field waveforms and reveal the early components. This can be achieved by linear derivation of monopolar data. Using this technique it will be possible to identity near-field generator signals. Data recorded from Cz, FCz and linear derivation of monopolar data acquired between FCz and Cz are shown coloured to identify individuals in these graphs.

Grand averages across all subjects grouped based on the stimuli pulse widths are shown in Figure **3-11**, Figure **3-12** and Figure **3-13**. Comparing evoked potentials recorded from different subjects under identical experiments conditions reveals some inter subject variability in the early components (<100ms). By studying the grand averages across all subjects and the average data obtained from each individual subjects it could be seen that the first consistently recognizable early response is a positive peak appearing at ~80-100ms relative to the stimuli onset. In FCz-Cz derivation following linear derivation of monopolar data most of subjects showed a SEP component during 80-100ms relative to the stimulation onset (this suggests that this component is a near field component). The early response is followed by large negative and positive peak at 150ms and 220-250ms respectively. 10 subjects displayed these SEP components after vibrotactile stimulation. A late negative deflection is also observed at 350-400ms (N400) in 11 subjects. Using convention these waveforms can be named as: P100, N150, P250 and N400.

For better comparison the grand averaged data across all subjects (Figure **3-11**, Figure **3-12** and Figure **3-13**) are plotted in one graph which is shown in Figure **3-14**. Identified components (P100, N15, P220 and N400) are also indicated in Figure **3-14**. The results indicate that increasing the vibration pulse width slightly enhances the SEP waveform. The averaged data across all subjects recorded from 12 different scalp land marks are plotted Figure **3-15**. That early components show a lateral localisation in the foot area but the large comments are bilaterally distributed over the whole scalp. Figure **3-16** and Figure **3-17** show the peak to peak amplitude of the averaged SEPs at 13 different anatomical landmarks. Paired sample T-test shows that longer vibration pulse width elicited an increase in peak to peak amplitude of the recorded SEPs but this increase not significant.

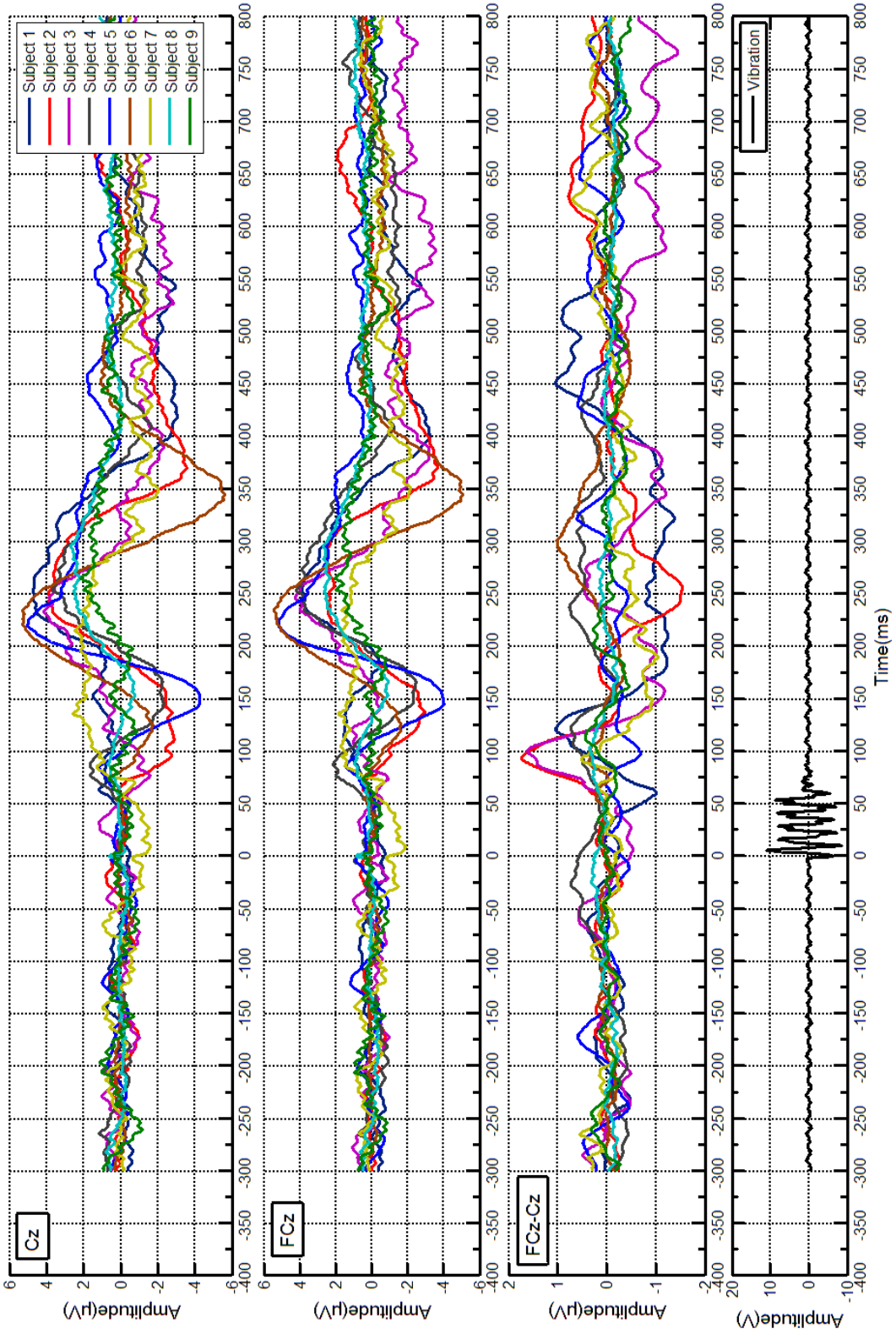


Figure 3-8. Time domain waveforms recorded after vibrotactile stimulation of the first metatarsus head in 9 subjects. The vibration pulse width was set to 50ms at 100Hz. The graphs shows SEPs recorded from Cz, FCz, FCz-Cz (linear derivation of monopolar data) and the vibration waveform from top to bottom respectively.

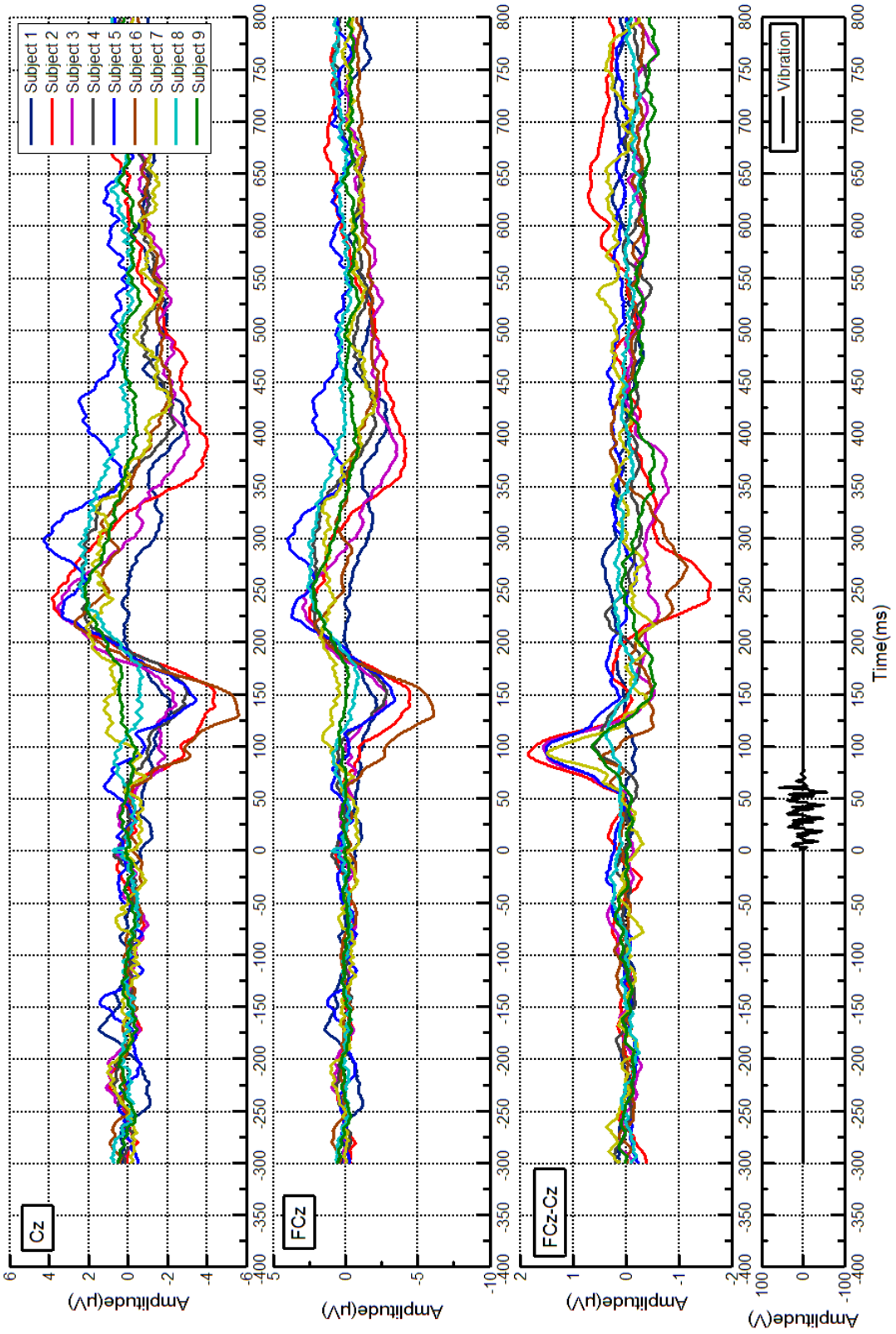


Figure 3-9. Time domain waveforms recorded after vibrotactile stimulation of the first metatarsus head in 9 subjects. The vibration stimuli pulse width was set to 75ms at 100Hz. The graphs shows SEPs recorded from Cz, FCz, FCz-Cz (linear derivation of monopolar data) and the vibration waveform from top to bottom respectively.

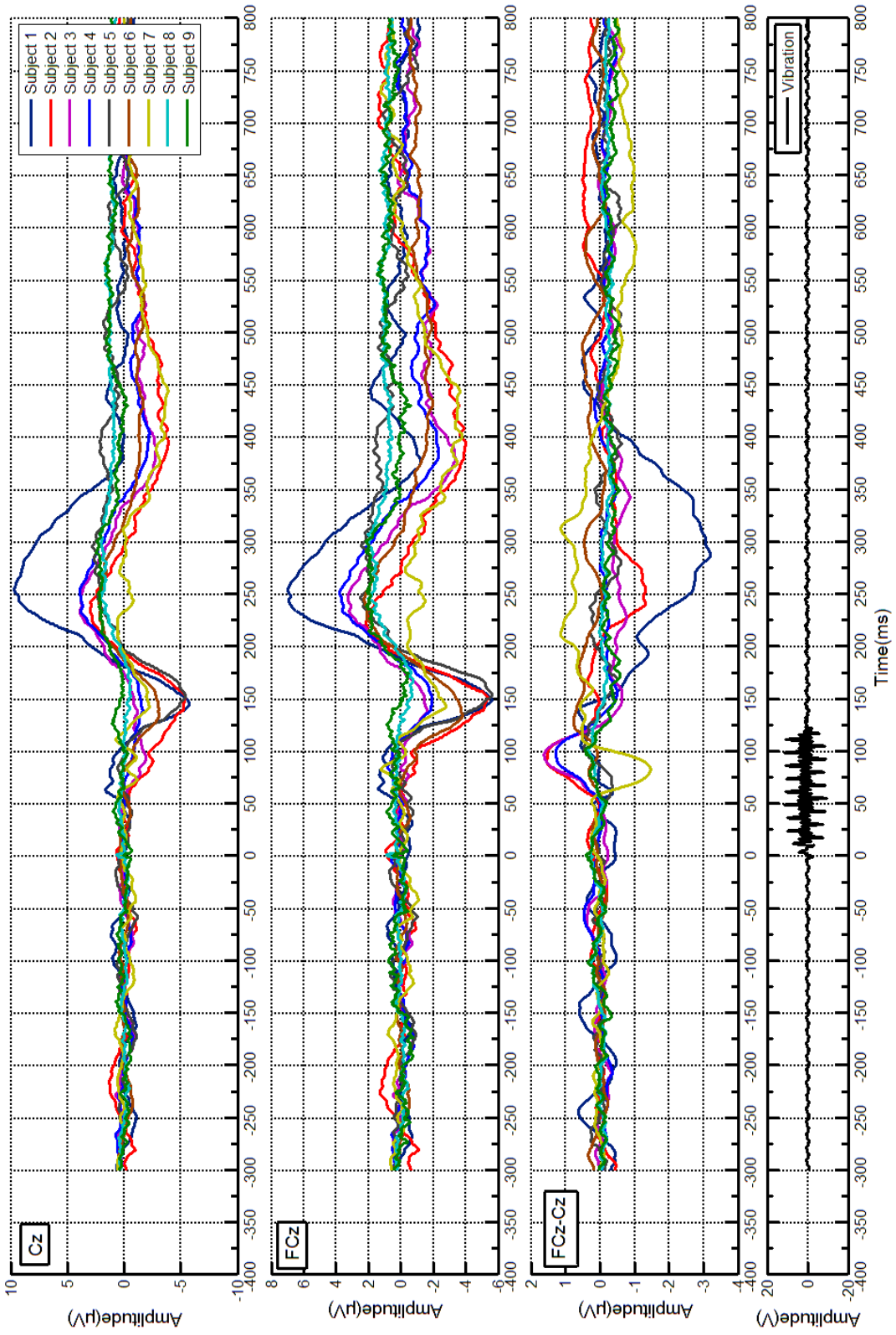


Figure 3-10. Time domain waveforms recorded after vibrotactile stimulation of the first metatarsus head in 9 subjects. The vibration stimulation pulse width was set to 110ms at 100Hz. The graphs shows SEPs recorded from Cz, FCz, FCz-Cz (linear derivation of monopolar data) and the vibration waveform from top to bottom respectively.

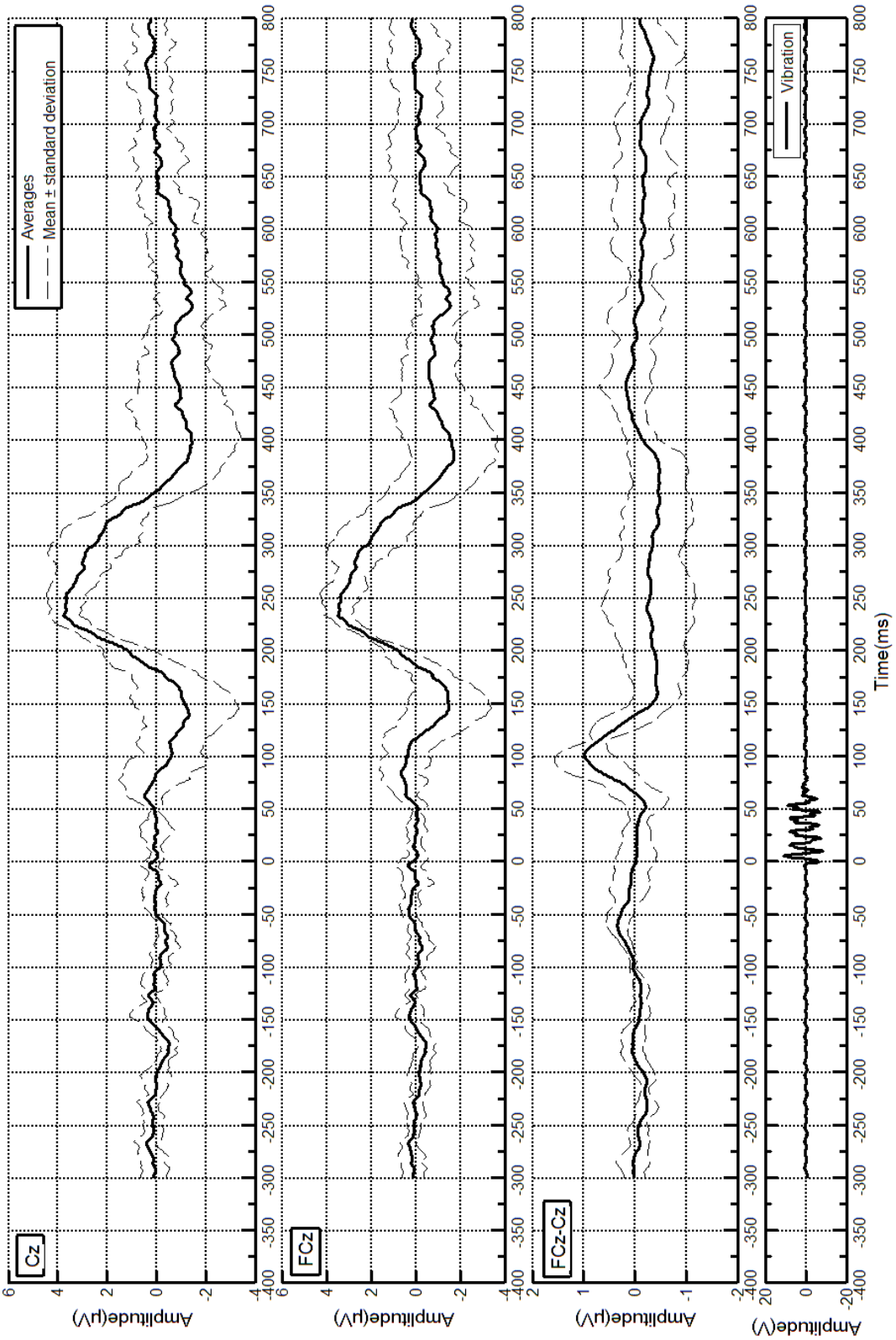


Figure 3-11. The averaged responses averaged across 9 subjects after stimulating the first metatarsal head with vibrotactile stimuli at 100Hz of 50ms in width. The graph shows the averaged SEPs recorded from Cz, FCz, FCz-Cz (bipolar configuration) and the vibration waveform from top to bottom respectively.

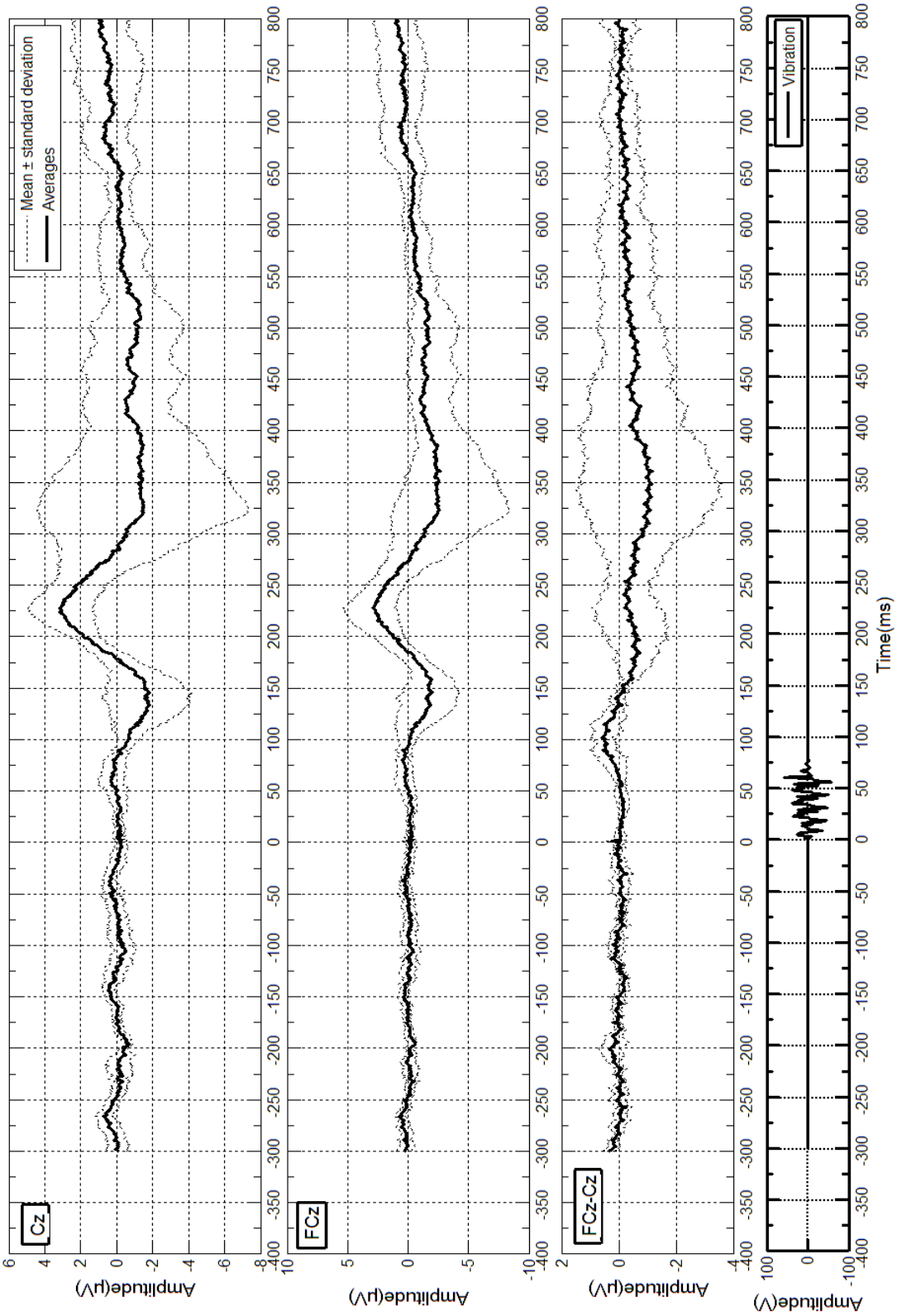


Figure 3-12. The grand averaged responses averaged across 9 subjects after stimulating the first metatarsal head with vibrotactile stimuli at 100Hz of 75ms in width. The graphs shows the averaged SEPs recorded from Cz, FCz, FCz-Cz (bipolar configuration) and the vibration waveform from top to bottom respectively.

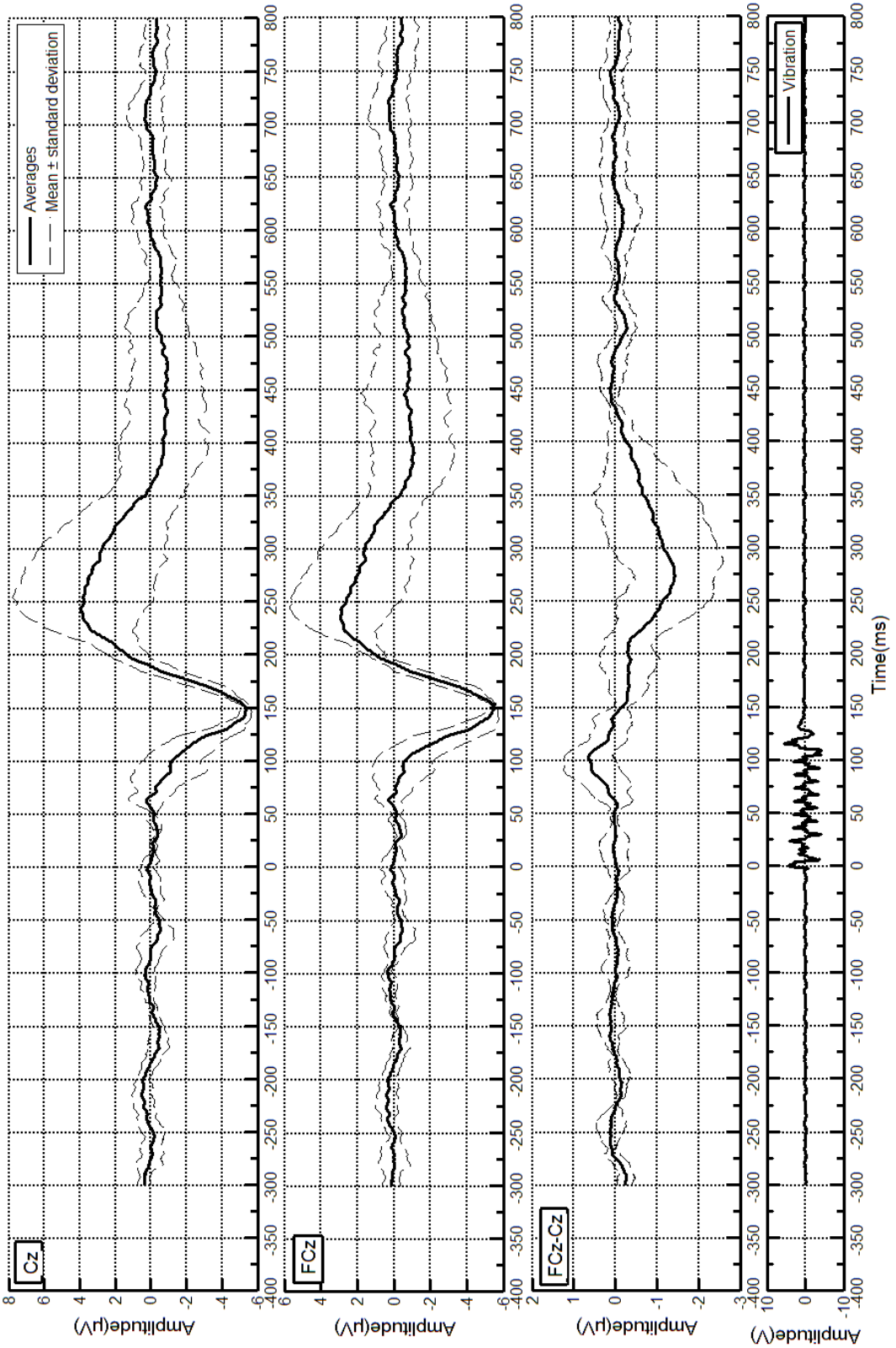


Figure 3-13. The grand averaged responses averaged across 9 subjects after stimulating the first metatarsal head with vibrotactile stimuli at 100Hz of 110ms in width. The graphs shows the averaged SEPs recorded from Cz, FCz, FCz-Cz (bipolar configuration) and the vibration waveform from top to bottom respectively.

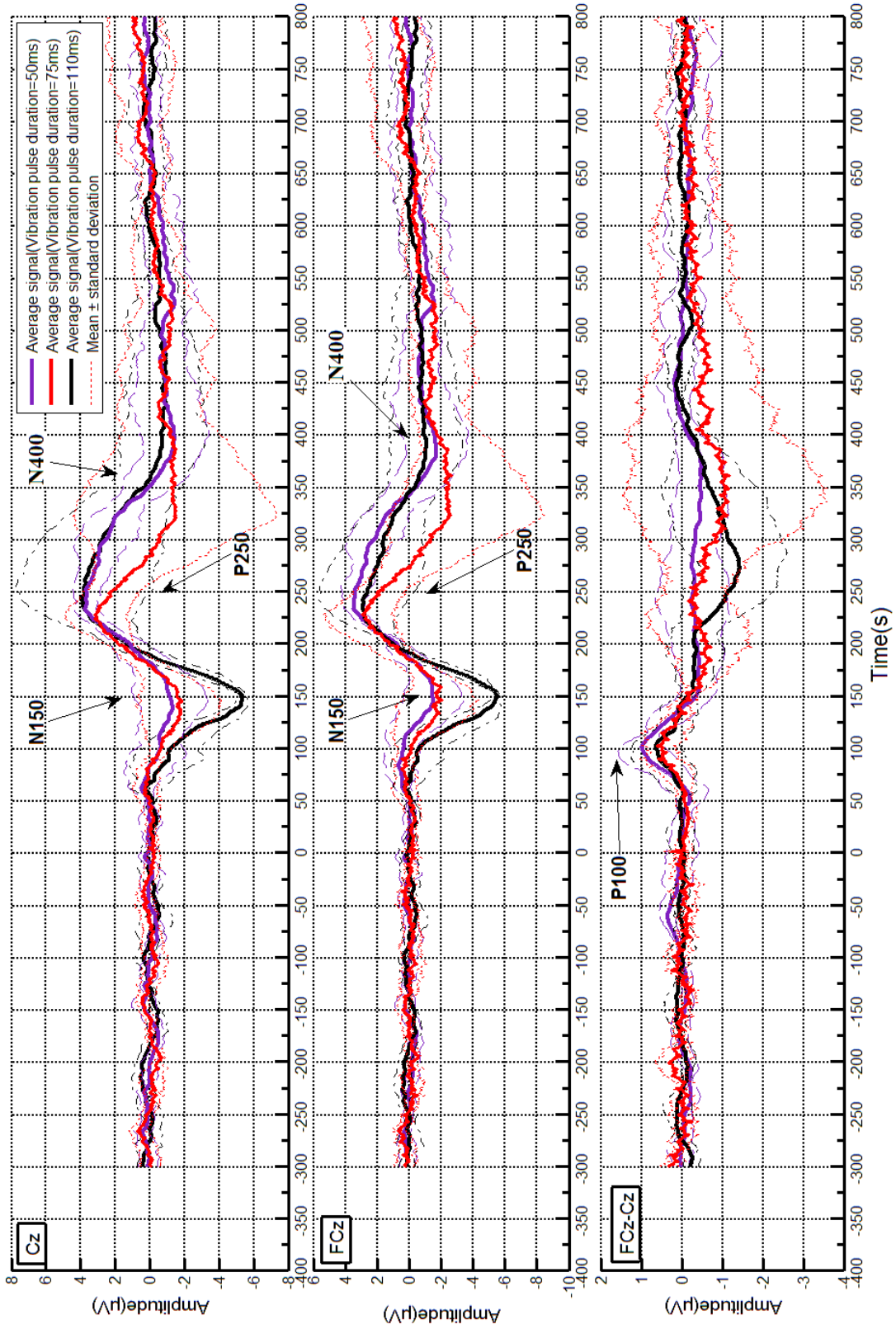


Figure 3-14. The grant averaged evoked potentials across 9 subjects recorded by vibrotactile stimulation at different pulse widths applied to the first metatarsal head. The graphs shows SEPs recorded from Cz, FCz, FCz-Cz (bipolar configuration) from top to bottom respectively.

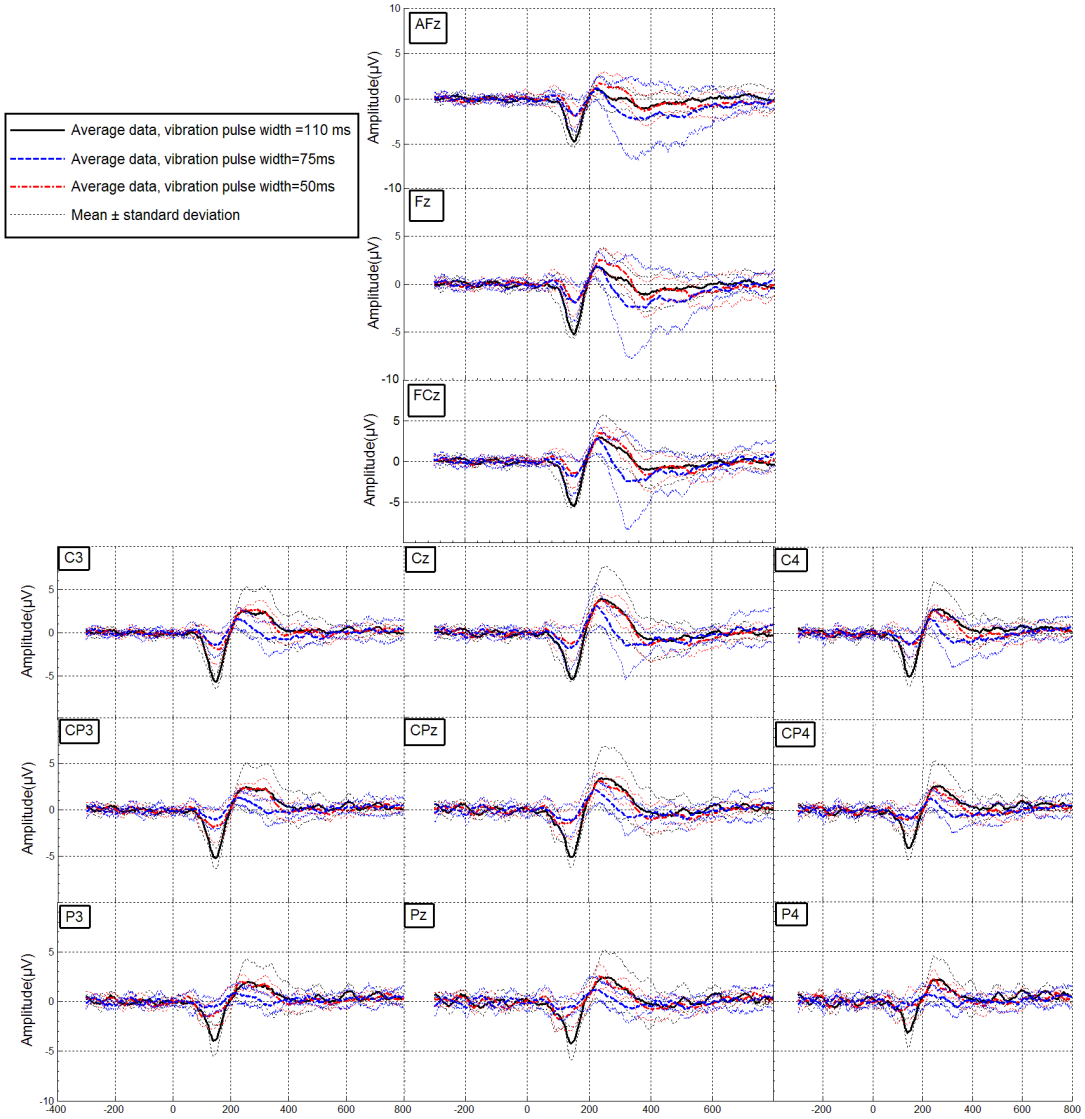


Figure 3-15. Distribution of the grand averaged SEPs at 12 different anatomical locations. Large comments (N150 and P250) are bilaterally distributed over the whole scalp.

Figure 3-16. The peak to peak amplitude of the grand averaged SEPs. This graph shows the modulation of P100-N150 across 13 anatomical locations. This graph shows that longer vibratin pusle wedith slightely enhances the peak to peak amplitude of P100-N150 but this increase is not significant.

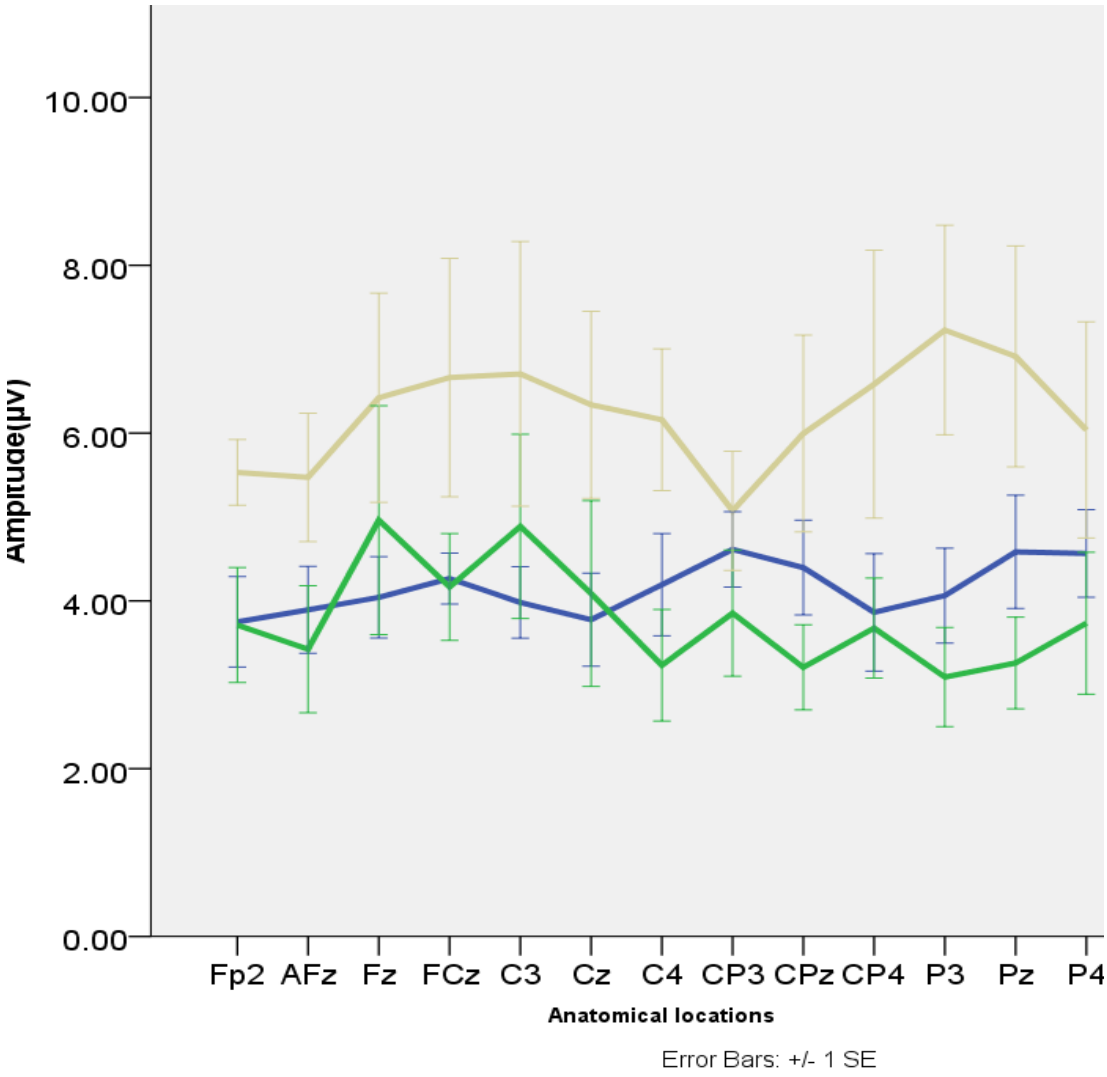


Figure 3-17. the peak to peak amplitude of the grand averaged SEPs across all subjects. This graph shows the modulation of N150-P250 across 13 anatomical locations. This graph shows that longer vibratin pusle wedith enhances the peak to peak amplitude of N150-P250 but this increase is not significant.

3.6 Experiment 2: Modulation of SEP Components by Changing the Site of Stimulation

3.6.1 Method

In this part of the study the aim was to investigate the effect of changing the stimulation targets (heel, lateral and medial metatarsal heads) on the evoked vibrotactile SEP waveform. 8 right handed healthy volunteers (21-36 years old) were recruited for this experiment and all signed the written contest form. The SEPs were obtained by applying vibration stimulation to the plantar surface of the right foot at different anatomical locations (heel, lateral and medial metatarsal heads) using the wooden platform described previously.

The experiment setup was similar to the previous experiment. The vibration pulse width was set to 50ms at 100Hz which was repeated every 3s. The vibration stimuli were adjusted to the sensation level using the method explained before. The experiment consisted of 3 different scenarios all tested in single test section. An anatomical location (heel or the right or left metatarsus heads) was selected randomly and was stimulated for 30 minutes. After finishing the test subject had a break and another anatomical location was selected randomly and stimulated for another 30 minutes. The whole experiment took about 1.45 hours. Data analysis was similar to the previous experiment.

3.6.2 Results

The recorded data was checked visually and epochs containing artefacts were rejected. The epoch length was set to -300ms to 800ms relative to time of stimulus onset. The epochs were averaged and baseline corrected. Data was averaged across 8 subjects and results are plotted in Figure **3-18**. The grand averaged data suggest that stimulating metatarsus heads evoked a larger SEP wave than stimulating the heel. The peak to peak amplitude of P100-N150 and N150-P250 is also larger when metatarsus heads are stimulated. Figure **3-19** and Figure **3-20** show the peak to peak

amplitude of the averaged data recorded at 13 different scalp landmarks. Based on the data presented in these figures, different stimulation site on the foot results in waveforms of differing amplitudes. Paired sample T-test shows that stimulating metatarsus heads elicited an increase in peak to peak amplitude of the recorded SEPs but this increase was not significant.

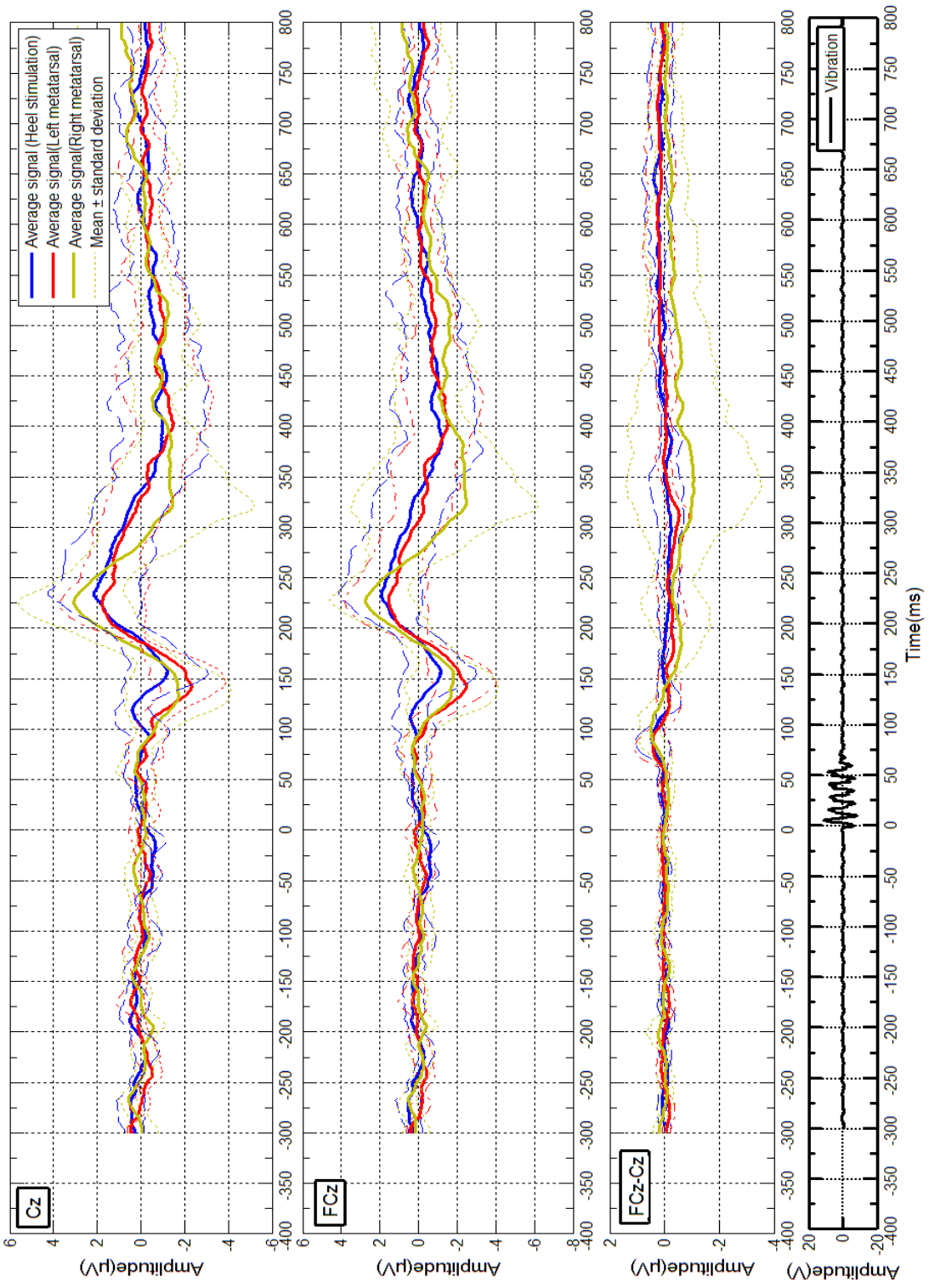


Figure 3-18. The grand averaged evoked potentials across 8 subjects. The graphs shows SEPs recorded from Cz , FCz, FCz-Cz from top to bottom respectively. Comparing the site of vibratory stimulation reveals small amplitude differences in SEP features. The stimulus applied to the medial metatarsal heads generates the largest responses and those applied to the heel generating the smallest SEP.

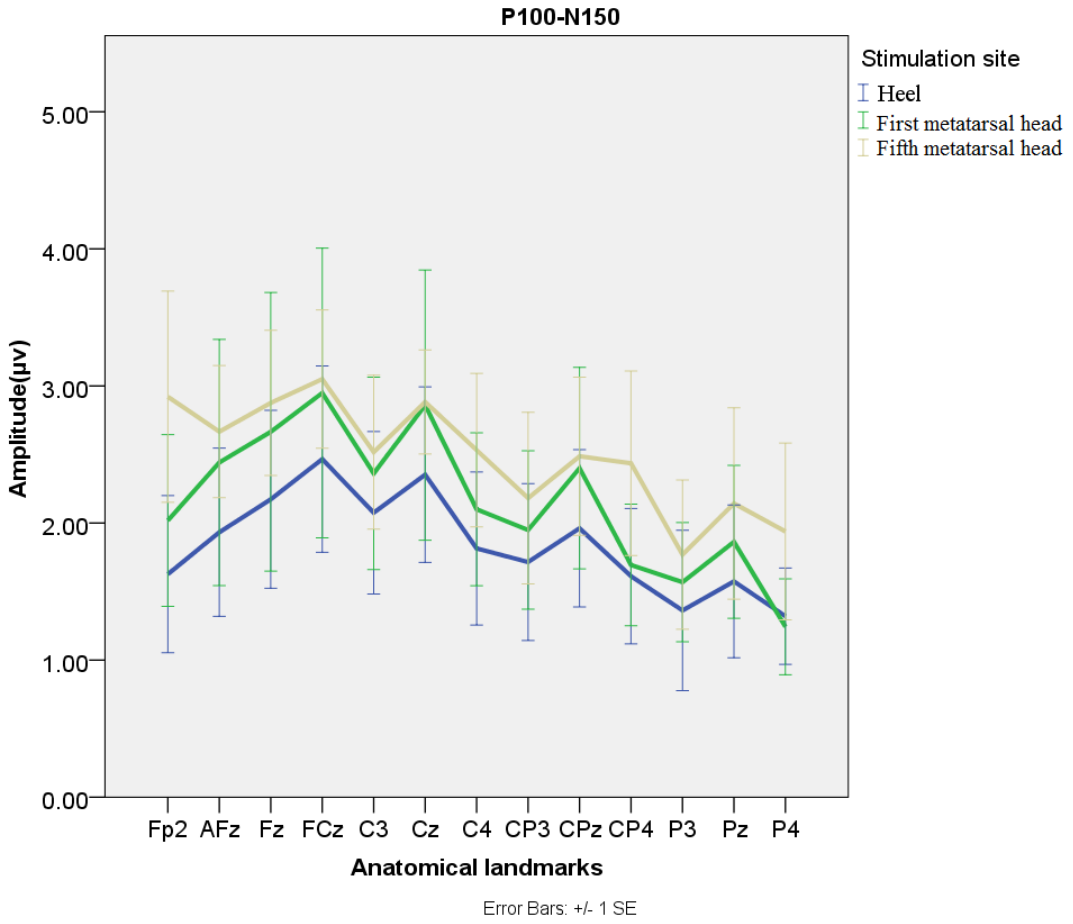


Figure 3-19. Distribution of P100-N150 peak to peak amplitude across the 13 anatomical locations. The stimulus applied to the medial metatarsal heads generates the largest responses and those applied to the heel generating the smallest SEP.

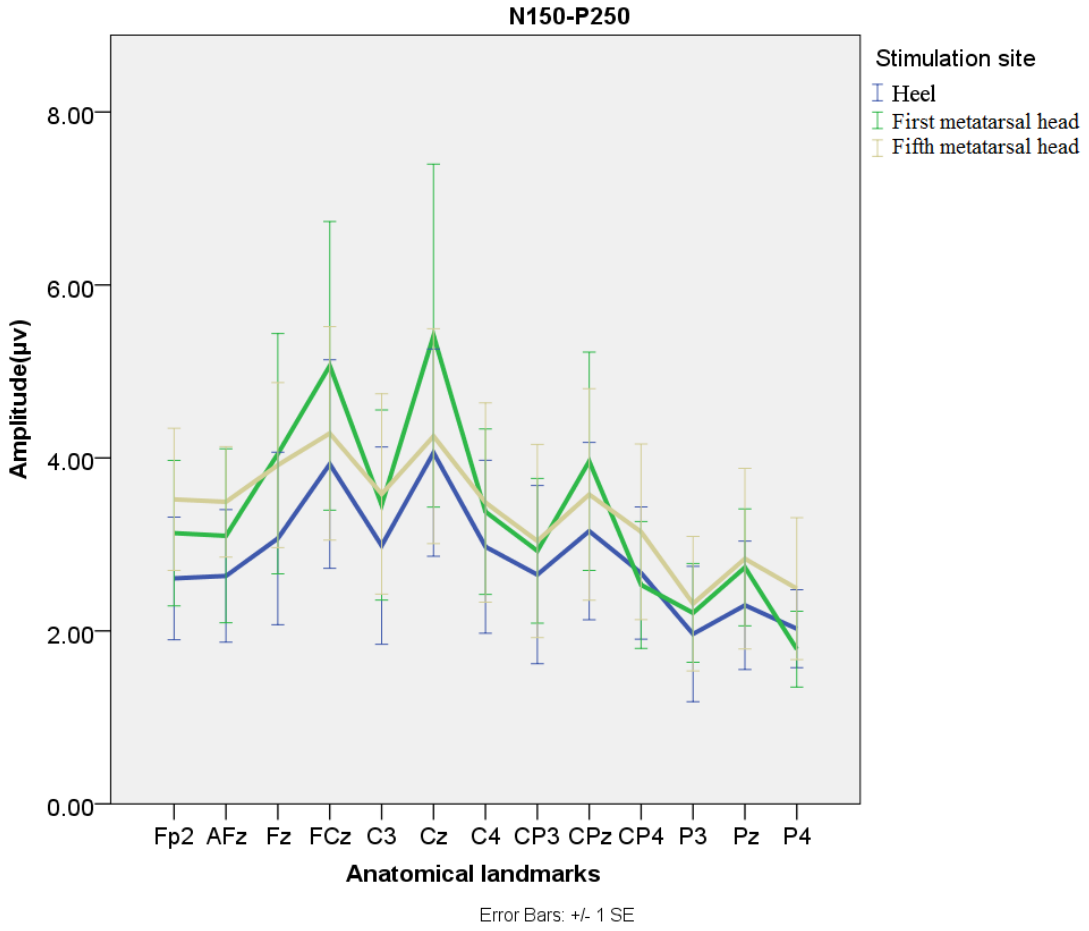


Figure 3-20. Distribution of N150-P250 peak to peak amplitude across the 13 anatomical locations. The stimulus applied to the medial metatarsal heads generates the largest responses and those applied to the heel generating the smallest SEP.

3.7 Experiment 3: Comparing Dermatomal and Vibrotactile Somatosensory Evoked Potentials

3.7.1 Introduction

Dermatomal somatosensory evoked potentials (DSEPs) are recording of the cortical evoked responses from cutaneous stimulation of specific dermatomal innervation. DSEPs are recorded in a similar way to standard SEP recordings. The only difference is that the stimulation electrodes are placed over the skin rather than underlying peripheral nerve (American Academy of Neurology's Therapeutics and Technology Assessments, 1997). DSPEs are useful in evaluation of patients with spinal lesion and establishing the functional correlates with radiographic abnormalities (American Academy of Neurology's Therapeutics and Technology Assessments, 1997). In this study the aim was to determine if the DSPEs from the foot sole display significant difference to the SEP evoked by vibration.

3.7.2 Method

5 healthy subjects were recruited for this experiment. A pair of electrodes was attached to the foot sole at the first metatarsus head (Pop et al., 1988). Usually the stimulation intensity was set to 4 times the sensation level (Schmid et al., 1988) (Pop et al., 1988) but in this experiment we set the stimulation intensity to the sensation threshold and ~2x the sensation threshold in order to activated only low threshold skin afferents and to compare these results with the results obtained by vibrotactile stimulation of the foot. Some subjects were not happy with the stimulation intensities at the 2x the sensation threshold so the stimulation intensity was slightly reduced so they could tolerate it. The pulse duration was set to 0.2ms and the stimulation rate was 1/s (Pop et al., 1988) (Schmid et al., 1988). Data recording setup was similar to the previous experiments. Experiment consisted of 2 different scenarios all tested in single test session. For about 15 minutes DSEPs were recorded at the sensation level. After finishing test subjects had a break and for the next 15 min DSEPs were

recorded at ~2x the sensation threshold. This was the highest strength subjects could tolerate in our study. All the recoding setups and data analysis procedure were similar to the previous experiments.

3.7.3 Results

Dermoatomal cortical SEPs recorded by stimulating the first metatarsus head of the right foot at sensation level and ~2x the sensation threshold recorded from the 5 subjects were averaged and the grand averaged waveform is shown in Figure **3-21** and Figure **3-22**. It is not easy to distinguish any discernible components at 1x the sensation threshold. By increasing the stimulation intensity to ~2x the sensation threshold (Figure **3-22**) some SEP components appear. Figure **3-23** compares the grand averaged dermoatomal cortical SEPs recorded at 1x and 2x the sensation threshold with the averaged vibrotactile SEPs record from previous experiments. This graph suggest that vibrotactile SEP at sensation level generate bigger waveform with distinguishable components compared to the dermoatomal cortical SEPs recorded at 1x the sensation level. No clearly distinguishable SPE components appear to exist in each set of vibrotactile SEP compared with DSEPs. This is most likely due to the difference in the synchronisation and population of sensory afferents recruited. The results also highlight how electrical stimulation is not comparable to vibrotactile in respect to the evoked cortical responses.

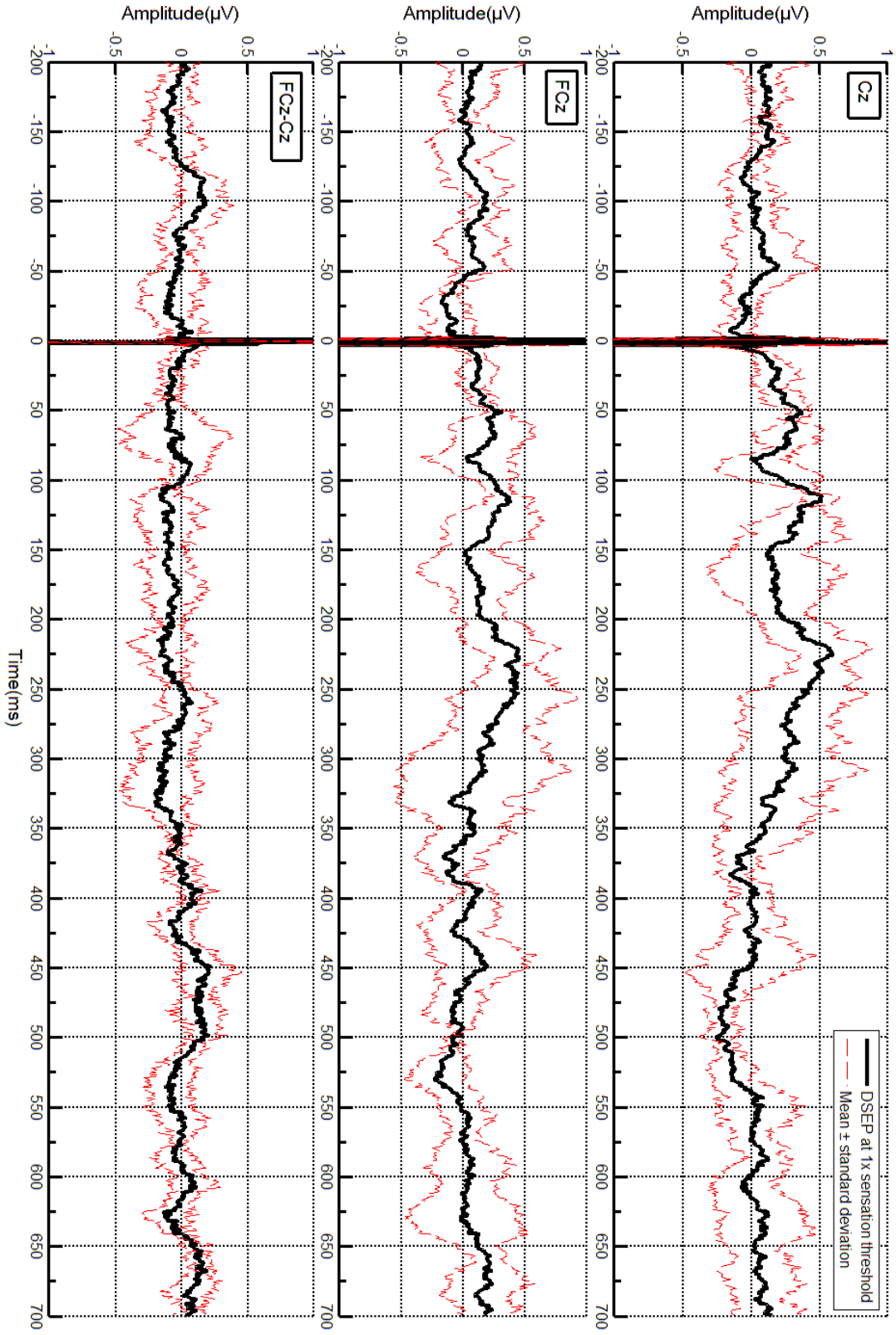


Figure 3-21. The grand averaged evoked potentials averaged across 5 subjects. The graphs shows SEPs recorded from Cz , FCz, FCz-Cz from top to bottom respectively. The stimulation site was the lateral side of the first metatarsus bone and stimuli were applied at the sensation level. The stimuli artefact can be observed at 0s.

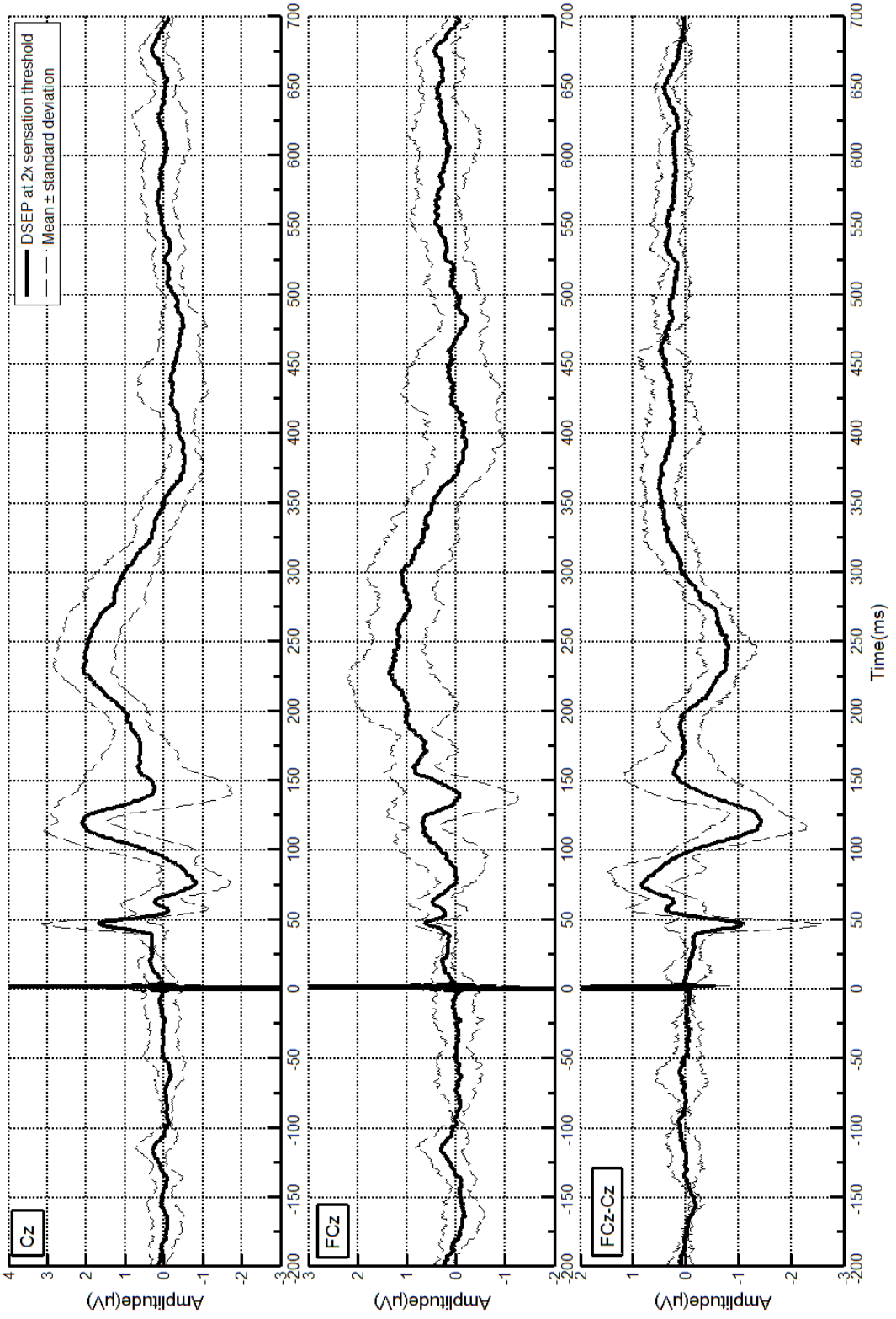


Figure 3-22. The grand averaged evoked potentials averaged across 5 subjects. The graphs shows SEPs recorded from Cz, FCz, FCz-Cz from top to bottom respectively. The stimulation site was the lateral side of the first metatarsus bone and stimuli were applied at ~2x the sensation level. The stimuli artefact can be observed at 0s.

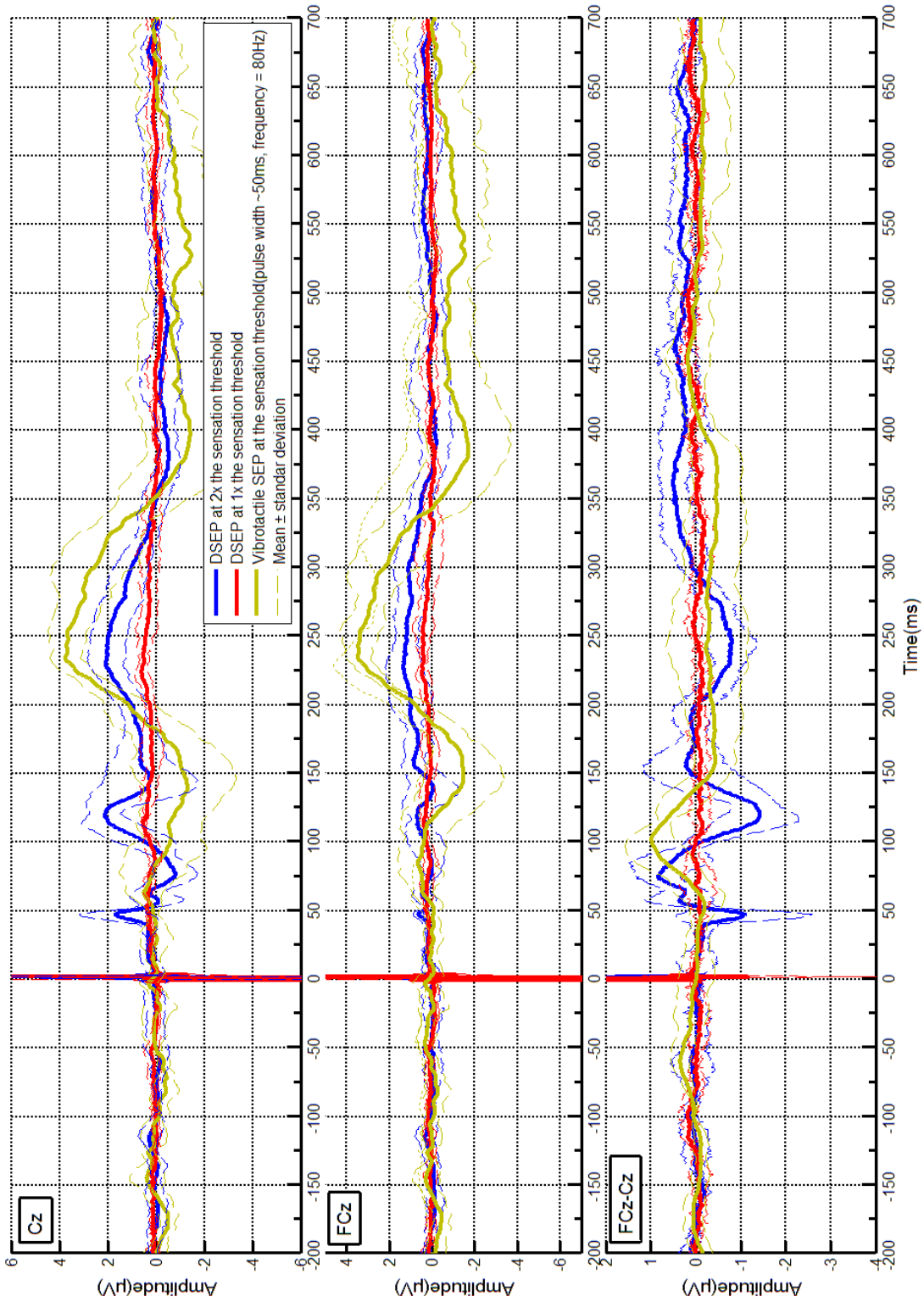


Figure 3-23. The grand averaged evoked potentials recorded from vibrotactile stimulation and electrical skin stimulation. The graphs shows SEPs recorded from Cz, FCz, FCz-Cz from top to bottom respectively. It is clear that vibrotactile stimulation at the sensation level generated an enhanced waveform compare to the electrical skin stimulation at the sensation threshold.

3.8 Source Localization

3.8.1 Introduction

With main components of the vibrotactile SEP being identified it is also important to know if the signal relates to activation of brain regions corresponding to known sensory areas. The equivalent current dipole (ECD) model is one of simple source localization methods and assumes that scalp evoked potentials are generated by one or few focal sources. The identified dipoles reflect a mathematical representation of the synchronized neural activity of a big group of cells inside the brain (Pizzagalli, 2006). Estimating the sources of scalp-recorded activity will help to understand the activation mechanisms used in sensory information processing and utilising the responsible pathways.

3.8.2 Method

6 normal healthy subjects participated in this study. The experiment protocol was similar to the previous studies but 128 electrode recording setup was used to collect EEG signals. A digitizer was used for digitizing of electrode positions in 3D and anatomical landmarks for each subject. The position of each electrode and fiduciary points including nose, nasion and preauricular points were also digitized. The plan was to use these coordinates to create the 3D head model for source localisation. Despite attempting to digitize the electrodes positions we didn't use them due to issues with software compatibility.

Data were sampled at 2000Hz and the amplification and filtering setups were the same as the previous experiments. The whole experimental session was about 4 hours for each subject. The first metatarsus head of the left foot was stimulated with vibrotactile stimulation delivered at the sensation level. The pulse duration was 50ms at 100Hz and the stimulation rate was 0.3/s.

3.8.3 Data Analysis

The raw data was epoched using SCAN software. The epoch length was set to [-300ms 800ms]. The epoch data were averaged and baseline corrected. The averaged data was exported to Curry 6 software for further analysis and dipole localization. After importing data to Curry we realised some compatibility issues with digitizer data so the predefined sensor locations labelling system provided by the software was used instead (NeuroScan).

Some pre-processing was performed on the data before running the dipole analysis. The signal noise level was estimated using a specified time interval method. The classical spherical head model was used for source reconstruction because it is used in the majority of the source reconstruction community and is numerically stable. Principle component analysis was used to decompose the data into orthogonal components and to reduce the number of variables. Only those components with signal to noise ratio greater than 1 were selected (typically 2 components were reviled).

The inverse methods using dipoles assume that only a discrete number of generators are active for a given time interval so source localization was performed in specific time intervals to find the corresponding dipoles of each most prominent SEP components (P100, N150, and P250). The rotating dipole model was chosen because it has been well established that several sources in the foot region of the motor cortex have tangential components (Baumgärtner et al., 1998) (Valeriani et al., 2001). By changing the time range interval, independent dipole components will be determined.

Source localization was performed on the data obtained from each subject individually and also on the grand averaged data across the subjects. Averaged MRI pictures and predefined electrode positions and anatomical landmarks were employed as provided in the Curry 6 package.

3.8.4 Results

3.8.4.1 Dipole Localization for P100

The P100 appears in the bipolar configuration which suggests that the source generator for this component should be close to the cortex surface. Due to small amplitude (low S/N ratio) of this component in the data obtained from each individual subjects, source localization failed to locate the source generator corresponding to P100 for each subject individually.

The S/N ratio of P100 was increased after averaging the data across subjects and we could localise it. The selected time range for dipole localization was considered as [78ms 117ms] and all channels where referenced to Cz. The identified source is projected into the reconstructed cortex model and an averaged MRI picture for better understanding of the source location (Figure **3-24** and Figure **3-25**). The resulted dipole is located near the somatosensory region of the brain.

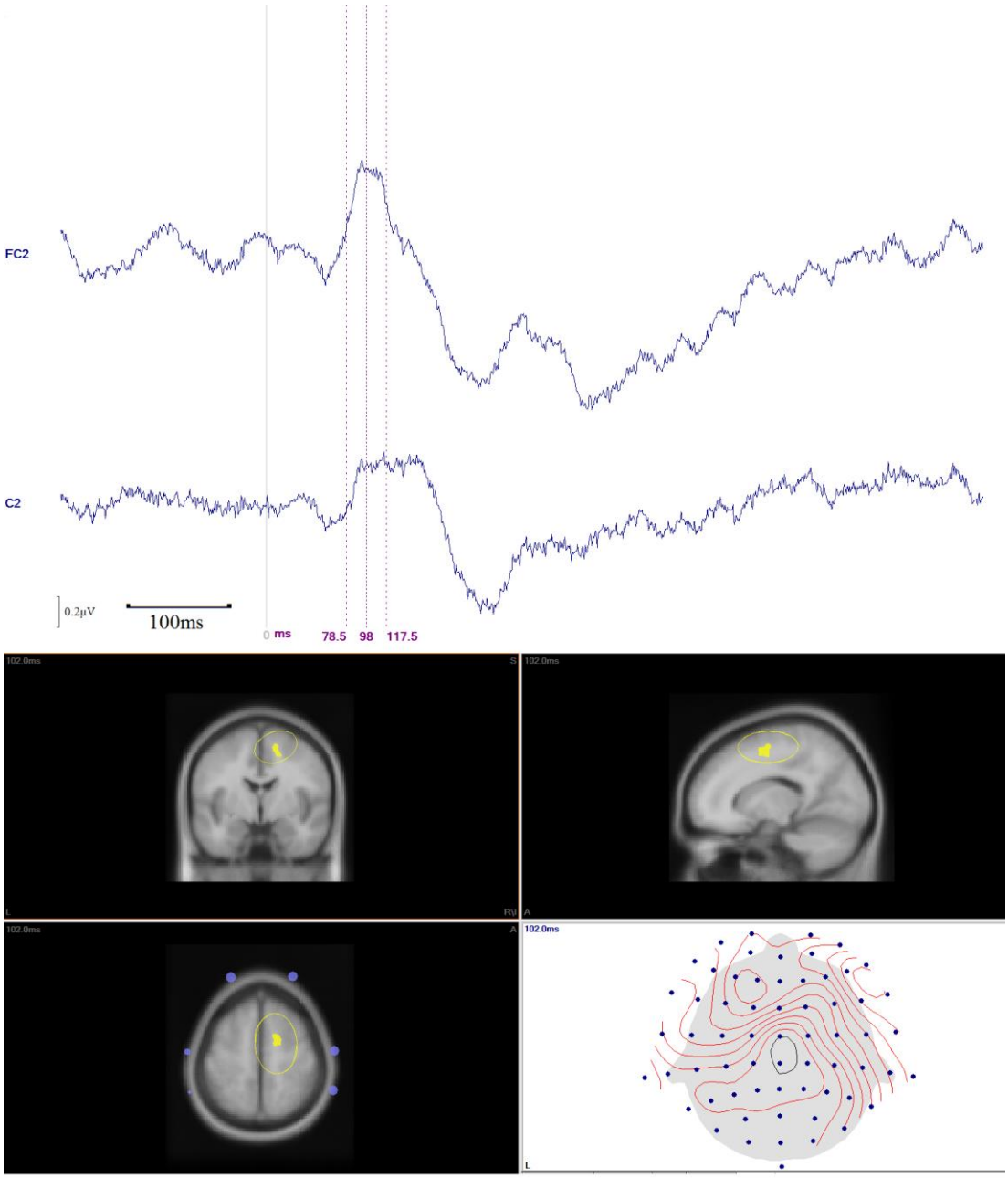


Figure 3-24. Anatomical position of the dipole source explaining the P100 peack. This component usually apprears at 80-100ms realative to the stimulation onset. the identified dipole is projected onto a averagd MRI picture. The top plot shows the selected time range for dipole localization ([78ms 117ms]). The picture on the bottom right shows topographical distribution of primary cortical component(P100) (view from above). The identified dipole is located near the somatosensory region of the brain.

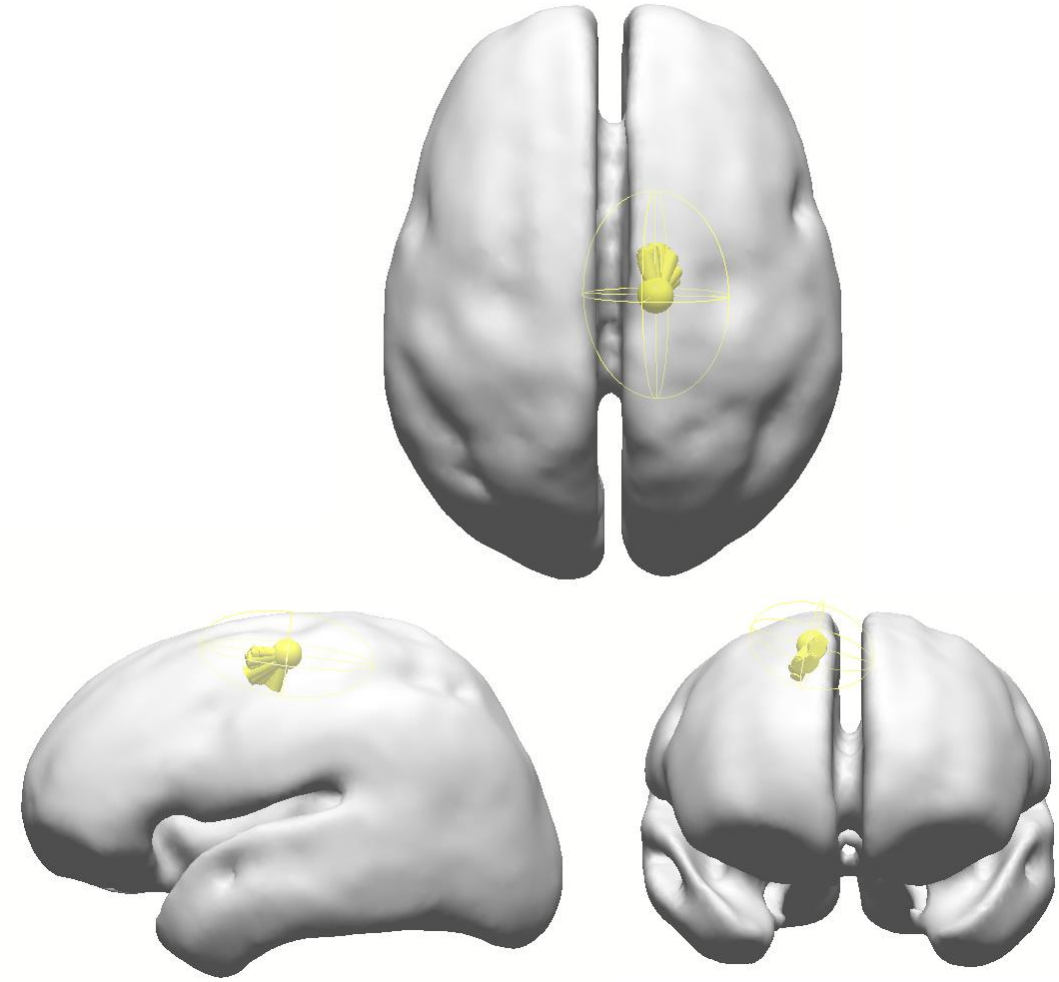


Figure 3-25. Anatomical position of the dipole source explaining the P100 peack. Thw dipole is projected onto a reconstructed cortex surface. The picture shows the top, side and the front view on the cortex. The resulting dipole is located near somatosensory region of the brain.

3.8.4.2 Dipole Localization for N150 and P250

All subjects showed SEPs components occurring 150ms and 220-250ms after tactile stimulation. Figure **3-28** and Figure **3-29** show the estimated dipoles location for N150 and P250. The selected time range for dipole localization was considered as [119ms to 182ms] and [202ms to 247ms] for N150 and P250 respectively (Figure **3-26** and Figure **3-27**). The identified sources are project into the reconstructed cortex model for better visualisation of the source location (Figure **3-28** and Figure **3-29**). Dipole localization shows that long latency components (N150 and P250) are located near cingulated cortices and bilateral S2. Figure **3-30** shows all the

identified dipoles projected into an averaged MIR picture which was provided by the Curry software. This picture shows the movement of the dipoles inside the brain over time. Dipole localization for P100, N150 and P250 in this study shows neural activity in areas near the somatosensory region of the brain, cingulate cortex and S2.

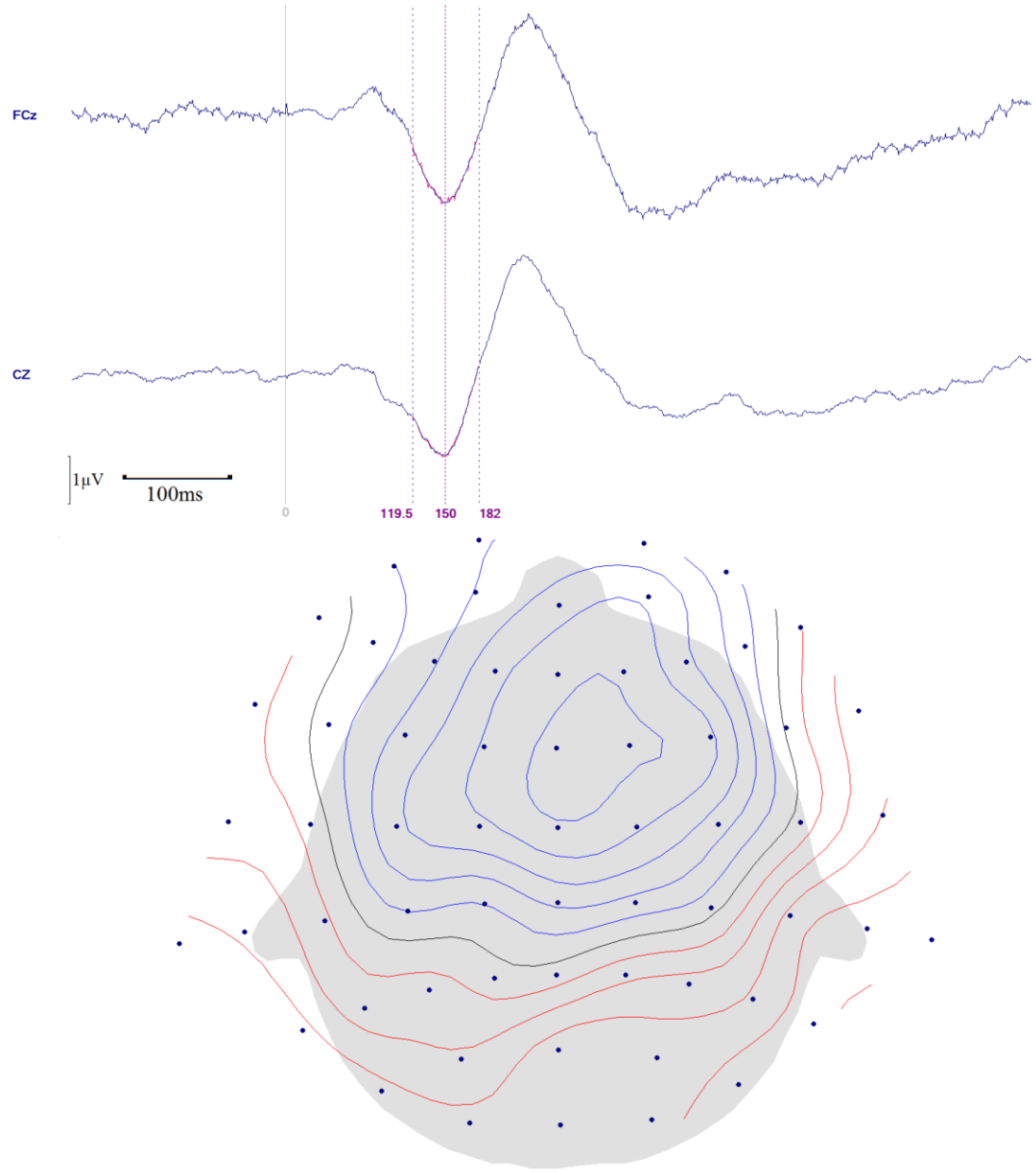


Figure 3-26. The selected time range for dipole localization of the negative components appearing at 150ms poststimulation ([78ms 117ms]) and the corresponding iso-voltage map at ~150ms.

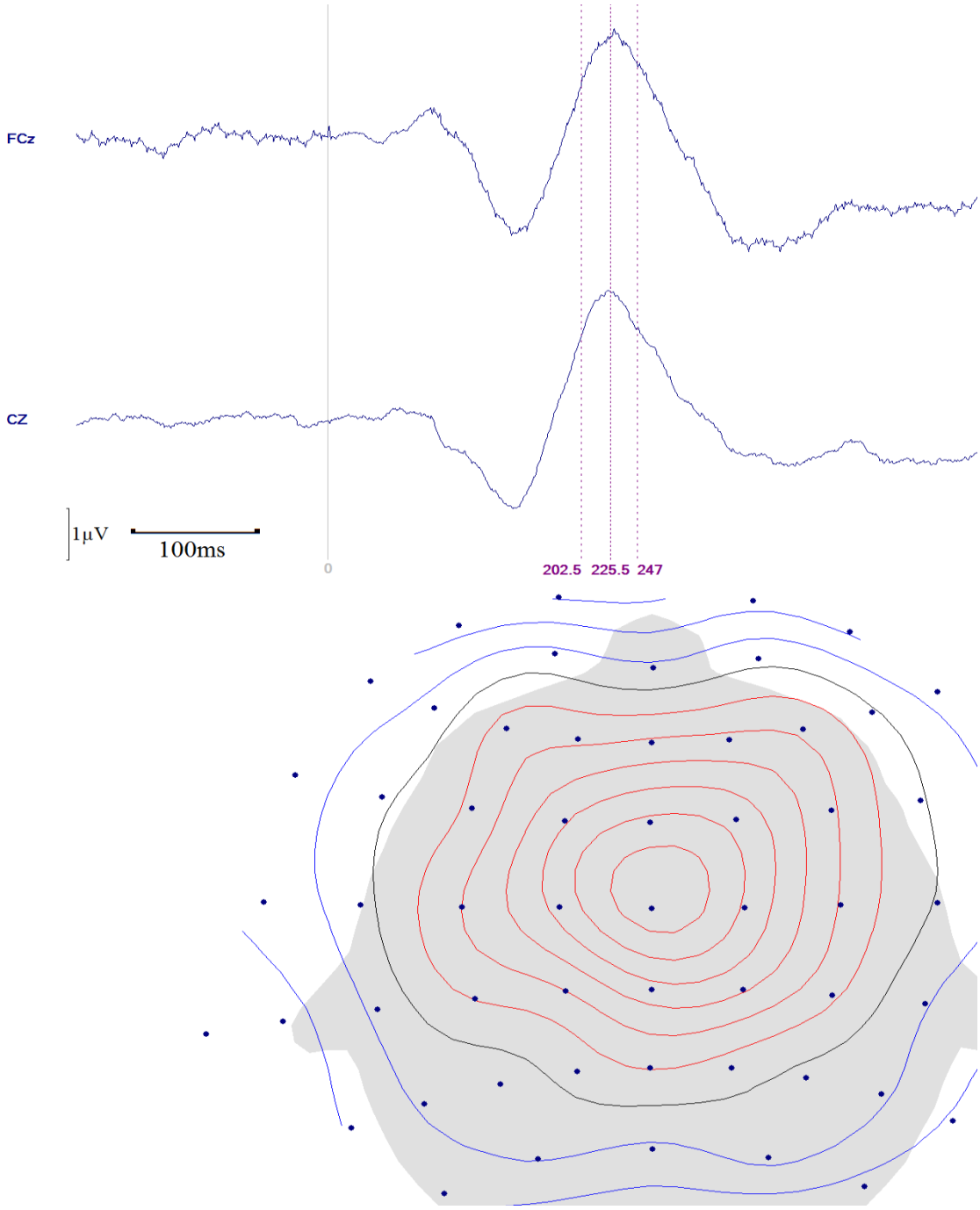


Figure 3-27. The selected time range for dipole localization of the postive components appearing at 250ms poststimulation ([78ms 117ms]) and the corresponding iso-voltage map at ~250ms.

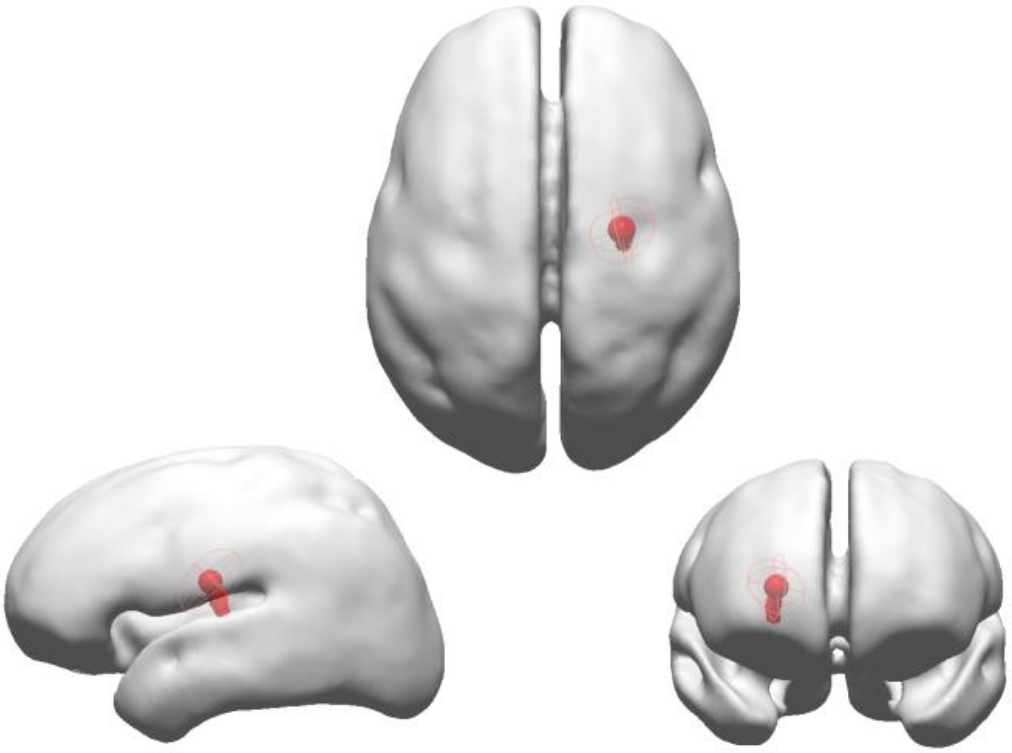


Figure 3-28. Anatomical position of the dipole source explaining the N150 peack. Dipole have been projected onto a braine model. The picture reprensent the top, side and the front view on the brain.

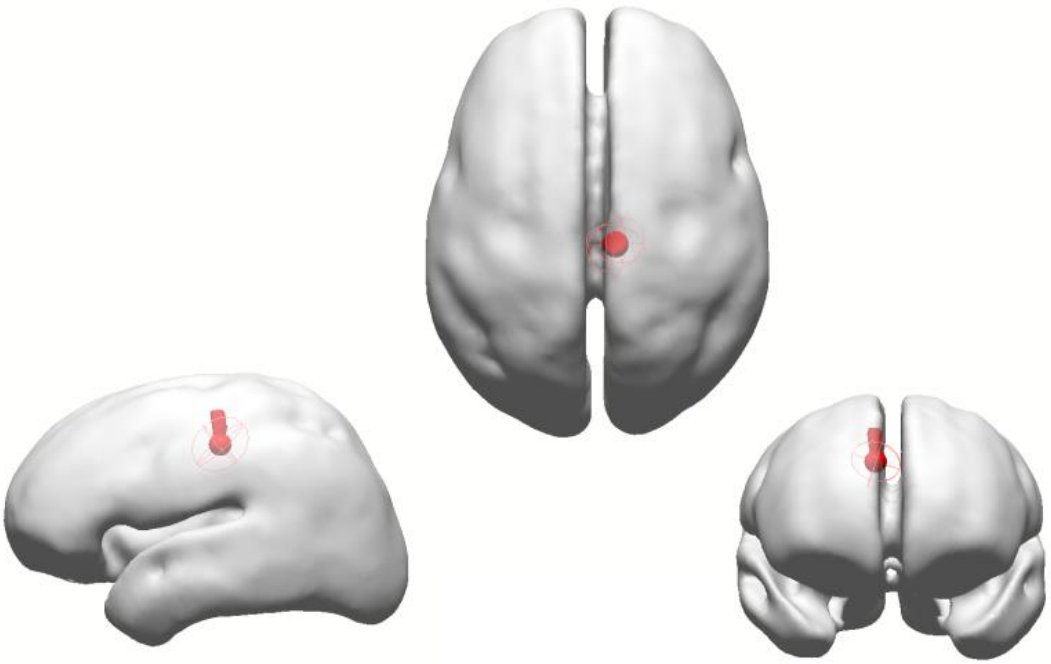


Figure 3-29. Anatomical position of the dipole source explaining the P250 peack of the averaged data. Dipole have been projected onto a brain model. The picture reprensent the top, side and the front view on the brain.

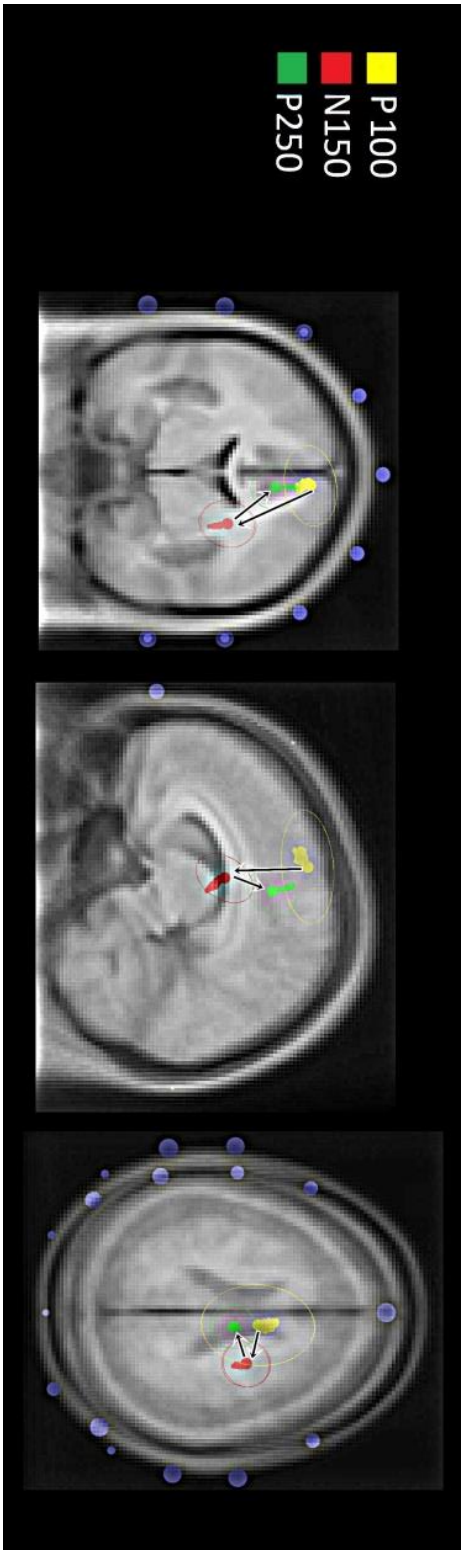


Figure 3-30. Arrows show movements of the idetified dipoles insided the braine over time. Dipole have been Projected Onto an averagd MRI Picture. Dipole localization for P100, N150 and P250 in this study shows neural activity in areas near the somatosensory region of the brain, cingulate cortex and S2.

3.9 Frequency Analysis

3.9.1 Introduction

Currently SEP monitoring techniques are mostly based on time domain measurements of amplitude and latency to provide information on the conduction of signals along the afferent pathway (Hu et al., 2008). The weak point of time domain analysis is that only highly synchronised activities will emerge in the analysis and any non-phased locked activation will be lost. This may be particularly significant in cases of CNS injury or when natural stimulation methods are used instead of electrical stimulation. In spinal cord injured patients partially functioning pathways may also show high dispersal of signal as action potentials propagate through damaged regions.

Frequency analysis can add to the time domain measures and simplifies the understanding of the recorded signals. Usually Fast Fourier Transform (FFT) is used to analysis SEP signals. It has been shown that lesion in the spinal cord changes the spectrum of the SEP waveform. Frequency changes in the SEP signal can provide important indicator of spinal cord injury (Hu et al., 2011). Time frequency analysis of SEP signals can provide important information not evident in the standard averaged SEPs.

3.9.2 Results

The data obtained from previous experiments were analysed using EEGLAB toolbox. The time-frequency analysis was performed on the grand averaged data. Figure **3-31** and Figure **3-32** shows the time-frequency analysis of grand averaged SEPs recorded from previous experiments when the vibration duration is 50ms and 110ms. The results are presented as a two dimensional plot with X axis as time, the Y axis as frequency and the intensity of the frequency in relative colour. The scale of the intensity index is plotted on the right side of each time-frequency plot. The areas of desynchronization are shown in cold colours and areas of synchronization in hot colours. All stimuli were applied at 0s. For 50ms vibration duration not any significant synchronisation cortical activity could be observed which could be due to

the low S/N ratio. For 110ms vibration duration a prominent peak at ~60 Hz between 50ms to 100ms and one at ~20Hz between 100ms to 200ms could be observed. The observed peaks between 50ms to 100ms could be due to the hidden early components (<100ms) which were not easily quantifiable in time domain analysis.

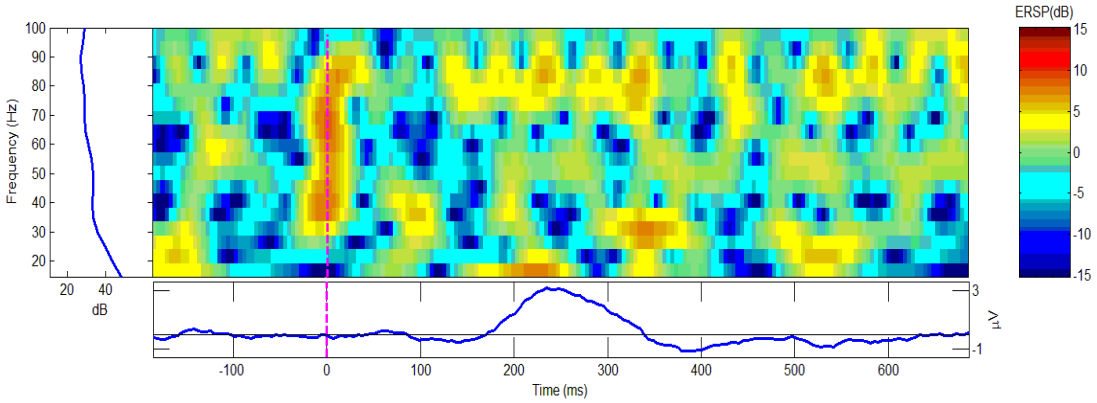


Figure 3-31. Time-frequancy frequancy analysis of the averaged vibrotactile SEP recorded from previous experimtns. The waveform recorded from Cz is presented here. The vibration stimulation pulse width was 50ms at 100Hz applied to the first metatarsus head of the right foot.

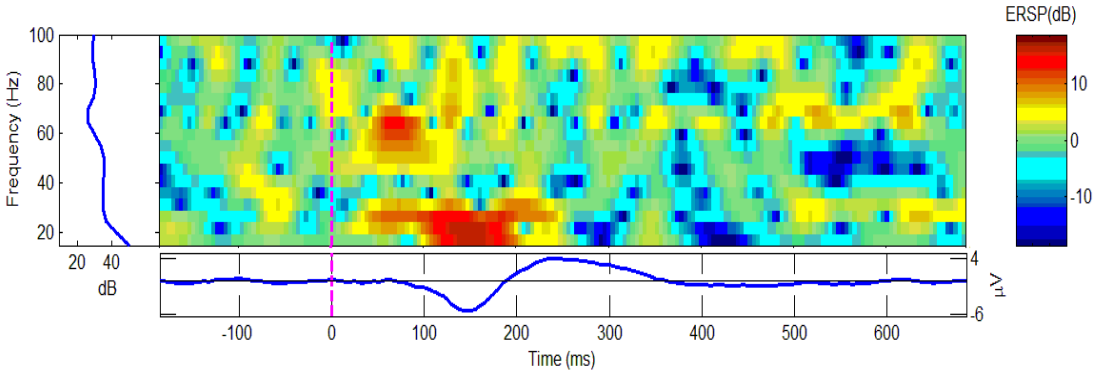


Figure 3-32. Time-frequancy analysis of the averaged vibrotactile SEP recorded from previous experimtns. The waveform recorded from Cz is presented here. The vibration stimulation pulse width was 110ms at 100Hz applid to the first metatarsus head of the right foot.

3.10 Discussion

3.10.1 Introduction

Stimulation of the somatosensory system stimulation using vibration or electrical stimulation can be used to test the intactness of the afferent pathways in patients. It can also be used as a means of conditioning ascending and spinal pathways for rehabilitation purposes. In this part of the thesis the responsiveness of the cortex to vibrotactile stimulations were studied in order to determine what level of stimulation is effective at generating a recognisable cortical event and therefore to correlate with meaningful stimulation. There is limited information on the projection of the foot sole afferents to cortex and most of studies of this type are related to the upper limb function (Maldjian et al., 1999) (Pihko et al., 2004) (Hegner et al., 2007). Only a few studies have investigated cortical activity after lower limb stimulation and the majority of these studies have used fMRI techniques to study the cortical activity (Gallasch et al., 2006) (Siedentopf et al., 2008) (Golaszewski et al., 2005) (Naka et al., 1998). fMRI has good spatial but very limited temporal resolution. Using fMRI it will not be possible to study the detailed information about the timing of the cortical activity after tactile stimulation.

We use somatosensory evoked potentials which can provide a good temporal resolution. We studied vibrotactile SEPs evoked by tactile stimulation of the foot sole in the time range up to 400ms from the onset of stimuli and their respective dipoles. No previous study has addressed these achievements. To examine the lower limb vibrotactile SEPs, we used dipole source reconstruction with applied vibrotactile stimuli at the sensation level. In this study we wanted to address several questions:

- Does vibrotactile stimulation generate an evoked potential that can serve as marker for interpreting ascending pathways?
- What are the main quantifiable components of the vibrotactile SEP recorded from lower limb?
- Is there any somatotopic differentiation between heel, first and fifth metatarsus heads that could be detected using vibrotactile evoked SEPs?

- Is the SEP induced by vibrotactile stimulation enhanced by increasing stimuli duration?
- Is it possible to model the SEPs components by simple dipoles?

Vibrotactile stimuli were delivered via a magnetic actuator system installed on a platform compatible with recording devices available in our lab. Choose of actuator was made to provide maximum flexibility in controlling the vibratory stimuli while minimising the interference between the mechanical transducer and the recording system. The designed platform ensures the effective transmission of vibratory stimuli by allowing independent adjustment of the contact force. The platform height was adjusted to bring the tip of the vibrator into contact with the subject's foot sole, at a level that subjects could just feel the vibration pulses (sensation level). This force was kept constant by fixing the subjects foot on the platform and locking the device height. The contact area between the tip of vibrator and the subjects' skin was around ~0.3cm^2 (1.5cm×0.2cm). In similar studies on evaluating cortical responses of vibrotactile stimulation of foot or hand a much wider area (19.63cm^2 (Siedentopf et al., 2008), 63.5cm^2 (Tobimatsu et al., 2000) and 20cm^2 (Golaszewski et al., 2005)) has been stimulated. A small stimulation area was chosen for this study to enable localised effect of vibrotactile stimulation to be investigated. The 100Hz for tactile stimulation was selected because this frequency is the normal activation range of pacinian corpuscles (50-400Hz). It has also been shown that a frequency range of 100-150Hz is suitable to evoke robust steady somatosensory evoked responses (Siedentopf et al., 2008) (Tobimatsu et al., 2000) (Snyder & Abraham, 1992). Short tactile stimuli with 3s time delay between pulses was used in this study to avoid adaptation and vibratory sense fatigue. Vibrotactile stimuli above the sensation threshold can elicit a continuous afferent impulse volley without adaptation just for few seconds (Hari, 1980). This form of discontinuous stimulation would be most like that employed during walking trainings. Studies also show that the sensitivity to vibratory stimuli is reduced 5-15 times when continuous vibration stimuli are applied to the palm for 3 minutes. The loss is enhanced by increasing the frequency and the intensity (Wedell & Cummings, 1938).

Stimulating sole using vibration could potentially stimulate skin mechanoreceptors as well as underlying muscles and bone structures. By keeping the vibration amplitude at the sensation level it was tried to minimize muscle and bone vibration effects. Activating underlying muscles and bones using vibration could produce other afferent stimulation which might affect SEP waveform.

In this study two experiments looked at identification and modulation of the vibrotactile SEP components generated by stimulating different anatomical locations of the foot sole in healthy subjects using vibratory stimuli at different pulse widths (50ms, 75ms and 110ms). Comparison was then made between the vibrotactile SEP wave with dermoatomal cortical SEPs recorded at sensation level and ~2x the sensation level. Source reconstruction method was also used for better understanding of the generation and propagation of the identified vibrotactile SEP. in total 33 healthy subjects were recruited and 28 completed the study. In 5 subjects the recorded data had a very large S/N ratio which was not included in further analysis. The observations in this study can be summarized as:

- Localized vibrotactile stimulation at sensation level generates a clear waveform which contains 3 main distinguishable components. Two of them are long-latency components and one is a mid-latency component
    - The mid-latency component appears as a positive peak with a deflection at 80-100ms relative to the stimulation onset. P100 was the first actively recorded wave and has small amplitude
    - The far field components (long-latency) are a series of negative and a positive peaks appearing at 150ms (N150), 220-250ms (P220) and 350-400ms (N400) relative to the stimulation onset
- The size of the recorded vibrotactile SEP is highly variable when recorded from different subjects. This could be due to the number of afferents being recruited to a response or changes in the sensibility of the different feet
- Increasing the vibration pulse width dose not significantly enhances the SEP waveform although longer stimuli duration evokes a greater SEP waveform

- Stimulating lateral and medial metatarsal heads seems to evokes a greater SEP waveform compared to heel region but this not a statistically significant increase
- Dermatomal cortical SEPs generated by electrical stimulation of the skin evoked at sensation level does not generate a clear waveform compared to the vibrotactile SEP at sensation level. This highlights the difficultly in using electrical stimulation of the plantar region within a rehabilitation context as the stimulation was also considered uncomfortable
- Source reconstruction suggests that the identified sources corresponding to P100, N150 and P220 are located near the somatosensory region of the brain, secondary somatosensory cortex and cingulated cortices
- Frequency analysis of the vibrotactile SEP shows peaks in the time-frequency domain around 60Hz and 20Hz for synchronized cortical activities around [50ms-100ms] and [100ms-200ms] respectively.

In following the findings in this thesis will be compared with similar studies in literate to see if the present findings are consistent with other researches.

3.10.2 Vibrotactile Components

In this study non-invasive recorded evoked potentials revealed a mid and late synchronization activity in human motor cortex. A noticeable deflection at 80-100ms, 150ms, 220-250ms and to 350-400ms relative to the stimulation onset was observed. The initial prominent activity starts at 80-100ms. This mid-latency activity is week and appears when differentiating channels. The earlier SEP components (<80ms) typically seen in tactile sensation using electrical nerve stimulation were not easily quantifiable due to their small S/N ratio.

3.10.2.1 Mid and Long Latency Components

Use of mechanical transducers to evoke sensory evoked potentials in the majority of works has been related to hand and upper body studies. In a study by Johnson

(Johnson et al., 1980) he applied vibrotactile stimuli at 250Hz to the dorsal bony prominence at the base of the middle finger and the cerebral evoked potentials were recorded using monopolar configuration (Johnson et al., 1980). He reported an interindividual variability in the early components. Siedentopf (Siedentopf et al., 2008) also reported a high inter subjects variability in his data after vibrotactile stimulation of the foot. (Siedentopf et al., 2008). Components up to a latency of 120ms showed a lateral localisation in the foot area and the large comments after 120ms were found bilaterally over the whole scalp. He also reported that late components show a regular rhythm at 5-10Hz (Johnson et al., 1980). Hämäläinen also measured SEPs to short vibrotactile stimuli applied to the fingertip (Hämäläinen et al., 1990). The first observed early response was a positive component at 50ms (P50) followed by a negative peak at 70ms (N70). Early responses were followed by a bilateral positive peak at 100ms (P100) and a large negative peak at 140ms. Kekoni (Kekoni et al., 1997) also reported positive peaks at 50ms, 100ms (P50, P100) and a negative deflection at 140ms (N140) after vibrotactile stimulation of the left middle finger. Hari also studied sustained potentials elicited by long (60Hz, 600ms) vibrotactile stimuli (Hari, 1980). She suggested that the recorded vibrotactile SEP is in many respects similar to the auditory and visually evoked potentials and the time course of his recorded EP were similar to those other slow potentials which are associated with the orienting reflex (Hari, 1980). Her recordings showed a long-latency deflection at 300-400ms (see Figure **3-33**).

The findings in this thesis are in agreement with those authors who show the presence of mid and long latency components around 100ms, 140-150ms and 220-250ms and >300ms (Figure **3-14**) (Baba et al., 2001) (Tobimatsu et al., 2000) (Kekoni et al., 1997) (Johnson et al., 1980) (Hämäläinen et al., 1990) (Hari, 1980) (Hoshiyama & Kakigi, 2000). A late deflection around 350-400ms in some subjects similar to that reported by Hari (Hari, 1980) is also seen in the results presented here. The findings of the current study are consistent with those who found that large late comments after 120ms were bilaterally distributed over the whole scalp (see Figure **3-15**) (Kekoni et al., 1997) (Johnson et al., 1980). A regular rhythm activity at 5Hz was not observed in our data as reported by Johnson reported (see Figure **3-31** and Figure **3-32**) (Johnson et al., 1980).

The mid and long-latency components are assumed to be related to the perception of the stimulation. It has been also found that electrical stimulation of the skin is perceived only if they give rise to the long-latency large amplitude cortical evoked potentials (Libet et al., 1967). Our result presented in Figure **3-23** is consistent with those of Libet (Libetet al., 1967). Our findings indicate that localised vibrotactile stimulation of the foot sole at the sensation level generates a naturally synchronous input that is sufficient to activate the neural mechanisms in the brain. This activation was detectable in conventional SEP recordings something which was not observed after stimulating skin using electrical stimulation at sensation level (see Figure **3-23**).

High intensity stimulation of the peripheral nerve generates long-latency components similar to vibrotactile ones. It has been shown that vibrotactile stimulation and high intensity peripheral nerve stimulation produce activation in similar regions of the brain (Coghill et al., 1994). High intensity stimulation of median and sural nerve also evokes predominately middle-latency potential at 150ms (N150) and 220-250ms (P250) (Hoshiyama & Kakigi, 2000) (Dowman, 2007). These components are not clear when stimulus is delivered at lower intensities (Hoshiyama & Kakigi, 2000). These components are also similar to those components observed in this study .This will be referred to later when discussing dipole localisation section (see page 99).

Figure **3-33** shows 3 typical evoked potentials recorded from 3 different experimental subjects at 3 different studies conducted by Dowman, Kekoni and Hari (Dowman, 2007) (Kekoni et al., 1997) (Hari, 1980). Their obtained data is compared with the recorded evoked potential from one of our experimental subjects in Figure **3-33**. A clear similarity exists between the SEP waves recorded by them and the SEP recorded from one of our subjects.

3.10.2.2 Early SEP Components

According to Allison et al., the early components are those that appear up to 60ms after stimulation of lower or upper limbs (Truett et al., 1992). Studies of the bipolar scalp topography of the somatosensory evoked potentials (SEPs) following sensory nerve stimulation gives a clear view about cortical areas that generate the early

components (Hari, 1996) (Kany & Treede, 1997). Stimulating the tibial nerve usually generates an early component (P40) which is due to activation of area 3b in the cortex area (Kakigi et al., 1995). Figure **3-34** shows an example of evoked potentials elicited after tibial stimulation. The plotted data show SEPs recorded from one of the subjects in this study and the study conducted Hauck (Hauck et al., 2006). Similar to Hauck (Hauck et al., 2006) we also observed a clear synchronization in early-latency SEP components after electrical stimulation of the afferent nerve. These early components are not easily quantifiable after vibrotactile stimulation. The amplitude of a clearly defined early component will relate to the degree of synchronisation in the afferent volley. In the case of electrical stimulation a single shock produces a single highly synchronised volley. With 100HZ vibration the volley is not discrete and will not be as synchronised as seen with electrical stimulation. The long duration of the vibrotactile stimuli also act against any meaningful analysis of an early wave for the same reason. In standard SEP the early wave indicates the afferent volley conduction time clearly this would not be a distinct feature following vibrotactile stimulation.

It has been reported that the amplitude of the early vibrotactile components are far smaller than those evoked by electrical stimulation (Baba et al., 2001) (Tobimatsu et al., 2000) (Kekoni et al., 1997) (Johnson et al., 1980) (Hämäläinen et al., 1990). Johnson also reported an interindividual variability in the early components (Johnson et al., 1980).

Smaller number of quantifiable components observed after vibrotactile stimulation compare to the electrical stimulation could be related to recruitment of much lower number of fibres after vibrotactile stimuli. Electrical stimulation of the sensory nerve recruits fibres of different thickness to transmit the electrical stimulation to the brain (Delwaide, 1981a). In this study small area of the foot sole was stimulated resulting in recruitment of a much smaller number of afferents. It has been shown that the short-latency components of the evoked potentials elicited by tactile stimulation are correlated with the magnitude of stimuli (Hashimoto, 1987). Stimuli in this study were applied at sensation level to small regions of the foot sole (~0.3cm^2). This can explain the small amplitude of the short-latency components

observed in our study but more likely the problem is the lack of a synchronous volley.

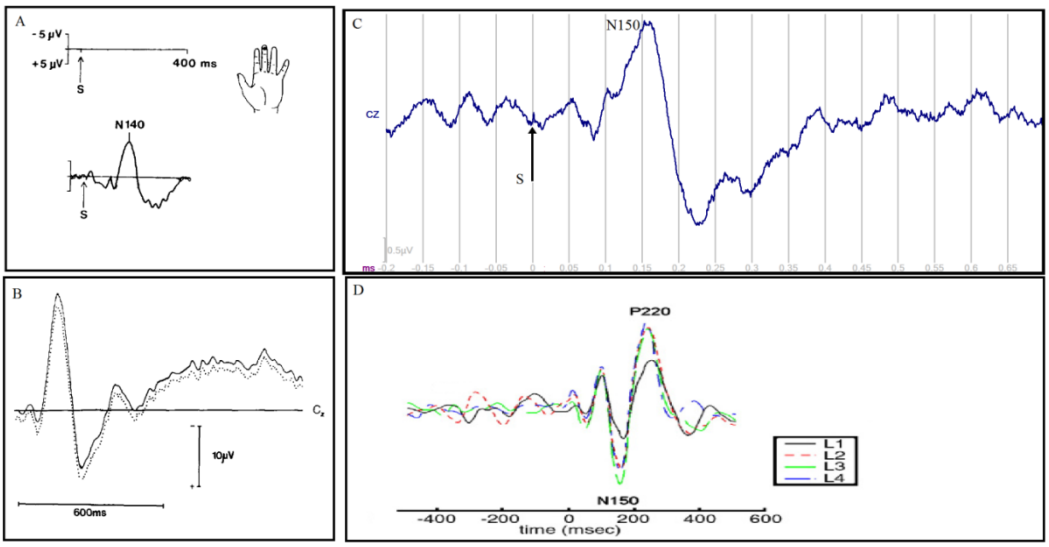


Figure 3-33.A) somatosensory evoked related potential recorded from Cz from one experimental subject (Kekoni et al., 1997). Stimuli were delivered to the tip of the left middle finger (Image Taken from (Kekoni et al., 1997)). B) Evoked potential elicited by a long (600ms) vibratory stimuli delivered to the back of the hand between thumb and index finger. The dotted lines show the standard errors of the mean (Image Taken from (Hari, 1980))). C) Vibrotactile SEP recorded from one of our subjects. Stimuli were applied to the first metatarsus head of the right foot. D) Somatosensory evoked related potential recorded from Cz after high intensity stimulation of the sural nerve (Image Taken from (Dowman, 2007)). L1-L4 represents different stimulation intensities. Similarities exist between the SEP recorded by Kekoni, Hari and Dowman and our data (Kekoni et al., 1997) (Hari, 1980) (Dowman, 2007). Note that in these pictures negative is assumed to be upwards except picture D where negative is downward.

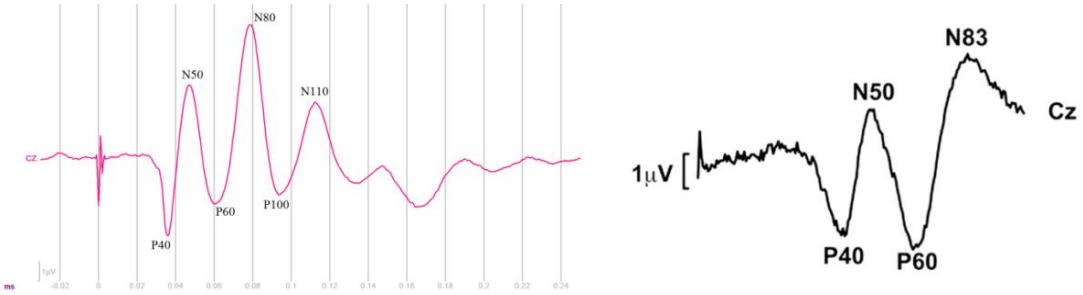


Figure 3-34. Right) Single subject SEP wave recorded after left distal tibial nerve stimulation. The figure shows SEP recorded at Cz with clear synchronization in early components (Image Taken from (Hauck, et al., 2006)). Left) the SEP we recorded from one of our experiments subjects using tibial nerve stimulation. The early components are clearly observable. Note that in these pictures negative is assumed to be upwards.

3.10.2.3 Modulation of SEP Components after Stimulating Different Regions of Foot

Perception of the mechanical stimuli is the result of activation of skin mechanoreceptors. Skin receptors are classified in different categories bases on their adaptation characteristics like their size and the receptive fields as: Merkel-disks, Ruffini-corpuscles, Meissner corpuscles, and Pacinian corpuscles (Zimmerman et al., 2014).

Pacinian corpuscles are rapid adapting receptors with large receptive fields located in the dermis. They usually respond to the acceleration of the skin deformation caused by mechanical stimulation (vibration stimuli >50Hz). Pacinian corpuscles react to the changes of velocity and firing intensity at the onset and offset of the vibration signals while Meissner corpuscles react as long as the velocity of the stimuli remains constant. The distribution of these receptors also varies in the foot sole according to the anatomical location. Distribution of the foot sole mechanoreceptors has been widely studied by several authors (Kennedy & Inglis, 2002) (Schneider, 2006) (Schlee & Günther, 2010). Meissner corpuscles have their highest density in the third and fifth metatarsal heads and the Pacinian corpuscles are mostly concentrated in the first, second, third and fifth metatarsus heads. Both receptors have low concentration at heel region (see Figure **3-35**). The provided information about the general properties of the mechanoreceptor and their distribution in the foot sole is highly compatible with our finding. The enhanced SEP waveform generated by stimulation the metatarsus heads is possibly due to higher concentration of mechanoreceptors at the metatarsus heads (see Figure **3-18**, Figure **3-19** and Figure **3-20**).

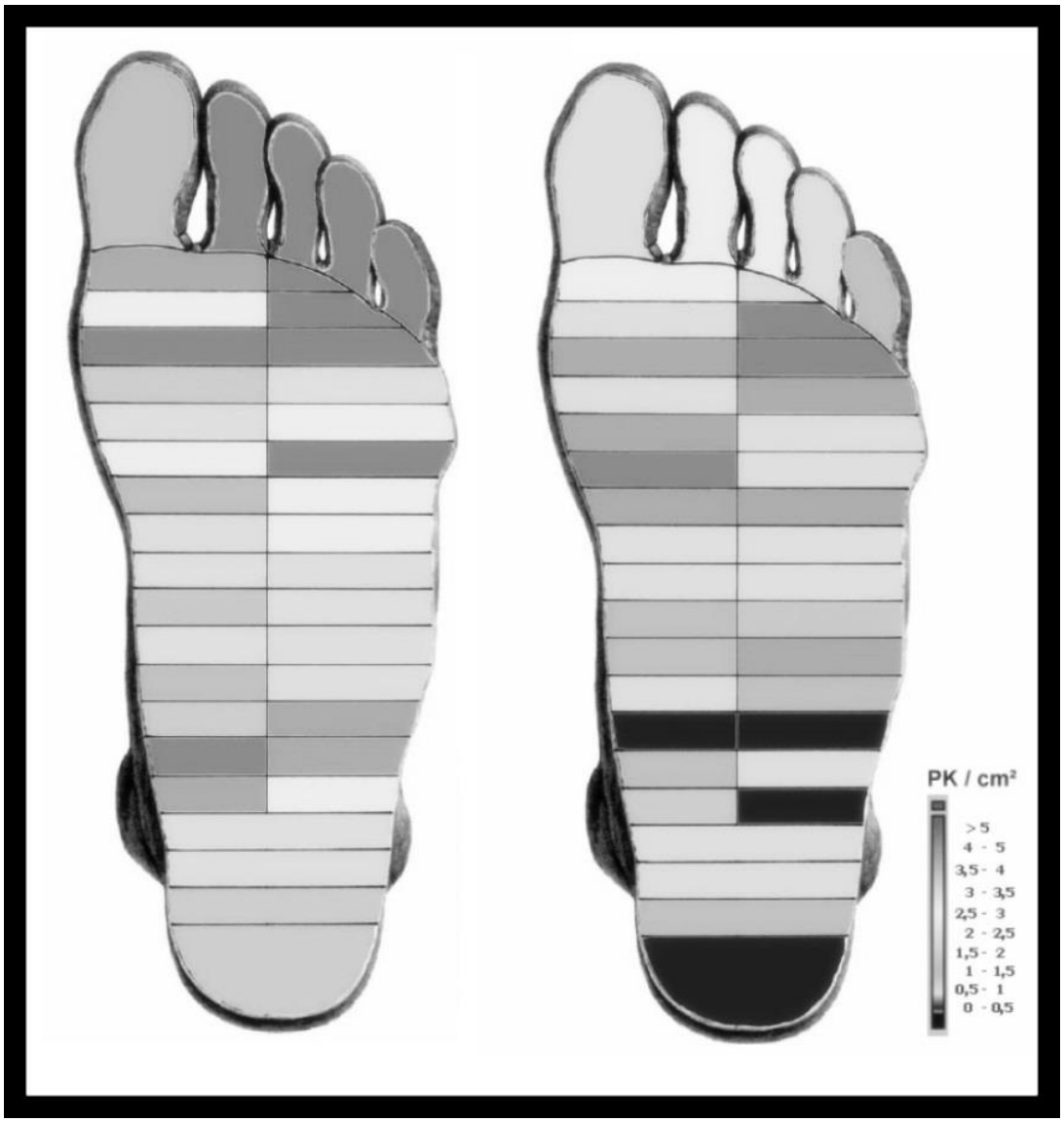


Figure 3-35. Distribution of the Meissner corpuscles (left picture) and Pacinian corpuscles (right picture) at the foot sole. These receptors have low concentration at heel region and high concentration at metatarsus heads (Image taken from (Schlee & Günther, 2010) (Schneider, 2006)).

3.10.2.4 Modulation of the SEP Wave due to Changing the Stimuli Duration

The modulation of the SEP wave by increasing signal duration has not been studied previously for tactile stimulation but it is studied for auditory stimulations. Davis observed no consistent change in the averaged SEP response with changes in duration of auditory stimuli (Davis & Zerlin, 1966). Skinner also did not observed any clear and significant trends in peak to peak amplitude of the auditory EP with an increase in stimuli duration (Skinner & Antinoro, 1971) (Skinner & Jones, 1968).

Referring to Figure **3-14**, Figure **3-16** and Figure **3-17** this study shows a clear (but not significant) trend in peak to peak amplitude of the vibratory EP with increasing the stimuli duration. The data trend suggests that stimuli with longer duration will more strongly (but not significantly) activate the neural mechanism responsible for processing tactile information.

The dependency between the stimulation pulse width and peak to peak amplitude of the SEP components observed in data present in this study could be related to exceptional and attentional functions. With longer vibration duration subjects may pay greater attention to the stimuli. The influence of attention in somatosensory responses has been studied in human subjects (Siedentopf et al., 2008) (Nelson et al., 2004). It has been shown that there is relation between the amplitude of the late components and the perception of the stimuli in somatosensory systems (Johnson et al., 1980). Hämäläinen also reported a good correlation between the vibrotactile evoked potentials amplitude and the magnitude of perception in the late-large components (Hämäläinen et al., 1990). Siedentopf also showed that stimulating with larger amplitude vibrotactile stimulus more strongly activates neural mechanism responsible for tactile processing (Siedentopf et al., 2008). He has also suggested that the BOLD response is modulated by the amplitude but not by the waveform of vibrotactile stimulation (Siedentopf et al., 2008). Based on his data some condition may apply to foot stimulation as to hand. For the mid-latency negative SEP components at ~150ms evoked by visual, auditory, tactile or painful tactile stimulations is also smaller when the evoking stimulus is unattended than when it is attended (Dowman, 2007). This may also be the cause in our data (Figure **3-14**). Increasing the vibration duration enhances the SEP N150 peak component and this enhancement in SEP wave due with longer vibrotactile stimulation may therefore link to attention process. Increasing the vibration pulse width could possibly increase the afferentation to the somatosensory cortex and therefore enhance perception of the stimuli and SEP waveform.

3.10.3 Dipole Localization

Activation of multiple regions of the brain in response to vibrotactile stimulation has been studied mostly for upper limbs (Harrington et al., 2000). In lower limb studies,

majority of works have used electrical stimulation to evoke cortical activity and dipole localization (Hari, 1996) (Kakigi et al., 1995). In lower limb studies many of those who have used vibrotactile stimulation have used fMRI technique to study the cortical. fMRI has limited temporal resolution (Golaszewski et al., 2005) (Siedentopf et al., 2008) (Gallasch et al., 2006). At the present time no study has evaluated cortical and subcortical neural responses evoked by vibrotactile stimulation of the foot using evoked potentials and dipole localization.

Sensory information is considered to be processed hierarchical inside the brain. It has been shown in humans using fMRI technique that rapidly adapting mechanoreceptors project the tactile information to the somatosensory cortex (S1), secondary somatosensory cortex (S2), superior temporal gyrus, postcentral gyrus, ipsilateral insula and bilateral supplementary motor area (Chung et al., 2013) (Disbrow et al., 2000) (Hegner et al., 2007). Mechanosensation of vibration travelling through afferents activates S1 and S2 regions persistently during the entire simulation (Chung et al., 2013). Kremneva (Kremneva et al., 2012) also identified activation regions in the brain during mechanical stimulation (foot compression) of the plantar support zones using fMRI. He found activation on S1, paracentral lobules, postcentral gyri, inferior parietal lobules, and upper frontal gyrus (Kremneva et al., 2012).

Vibrotactile stimuli are projected via the dorsal column pathway to the brain stem, and with thalamus to S1 and bilateral S2 (Siedentop et al., 2008). It is suggested that S2 may play an important role in the tactile object recognition and detection of high frequency vibration (Caselli, 1993) (Burton et al., 1993). Secondary somatosensory cortex receives information from all areas of primary somatosensory cortex as well as a sparse projection directly from thalamic neurons. S1 is mainly engaged in processing the type and intensity of the stimuli and S2 process higher features such as context of attention, learning and integration of painful and nonpainful inputs (Burton et al., 1999). S2 is able to respond to temporal information over a wide variety of time scales caused by vibration or flutter (Karhu & Tesche, 1999).

The dipole of a small mid-latency component around 100ms which is observed after electrical stimulation of the posterior tibial nerve is suggested to be located

around S2 (Kany & Treede, 1997) (Kakigi et al., 1995). The middle latency components of tibial nerve SEP is usually measured around 130ms (N130) and is suggested to be generated in or near the secondary cortex (S2). It is also suggested that electrical brain activity in the temporal region about 110–140ms, is originate in S2 (Truett et al., 1992).

Stimulating the peripheral nerve at lower intensities does not evoke significant long-latency components. These long-latency components usually appear at higher intensity sensory nerve stimulations (usually referred to as painful electrical stimulations) (Hoshiyama & Kakigi, 2000) (Dowman, 2007) (Dowman, 1994) (Dowman, 2007). In a study conducted by Coghill (Coghill et al., 1994) it was revealed that painful and vibrotactile (100Hz) stimulation of the left forearm produced activation in similar regions of S1 and S2. Studies on somatosensory evoked neuromagnetic fields (SEFs) following low and high intensity tibial nerve stimulation have also produced activation in similar regions of S1 and S2 (Ferretti et al., 2004) (Bentley et al., 2002). S1 activity is enhanced by increasing the stimulation intensity where S2 activity is enhanced when stimulation is at much higher levels (Ferretti et al., 2004). Electrical stimulation of the peripheral nerve at high intensities produces contralateral activation in S1 and S2 and cingulate cortex (Coghill et al., 1994).

In the current study the neural activity in the sensorimotor cortices after vibrotactile stimulation of the foot sole was characterized. Dipole localization for P100, N150 and P250 in this study shows neural activity in areas near the somatosensory region of the brain, cingulate cortex and S2 (see Figure **3-30**) which is in agreement with the studies mentioned. Figure 3-36 compares the fMRI map of cortical activation pattern evoked by vibrotactile stimulation of the foot sole recorded by Gallasch (Gallasch et al., 2006) and the identified dipoles in this study. These data must also be interpreted with caution because source localization using inverse model is not the most suitable and accurate method for addressing the neural activity in the cerebral cortices or other deep structures. Despite high inter-individual variability, the localized vibrotactile stimulation of the foot sole at sensation level yielded reliable results on group study levels. For clinical use of vibrotactile stimulation it is essential to active a quantifiable response on a single-subject level.

Findings of this study suggest that vibrotactile stimulation could evolve into a clinical tool to test the intactness of the afferent pathways in patients. For the long term ambitions of this project the results also revealed what areas of the brain might become activated by afferent responses to foot contact during walking or when cyclically driven vibration during stepping.

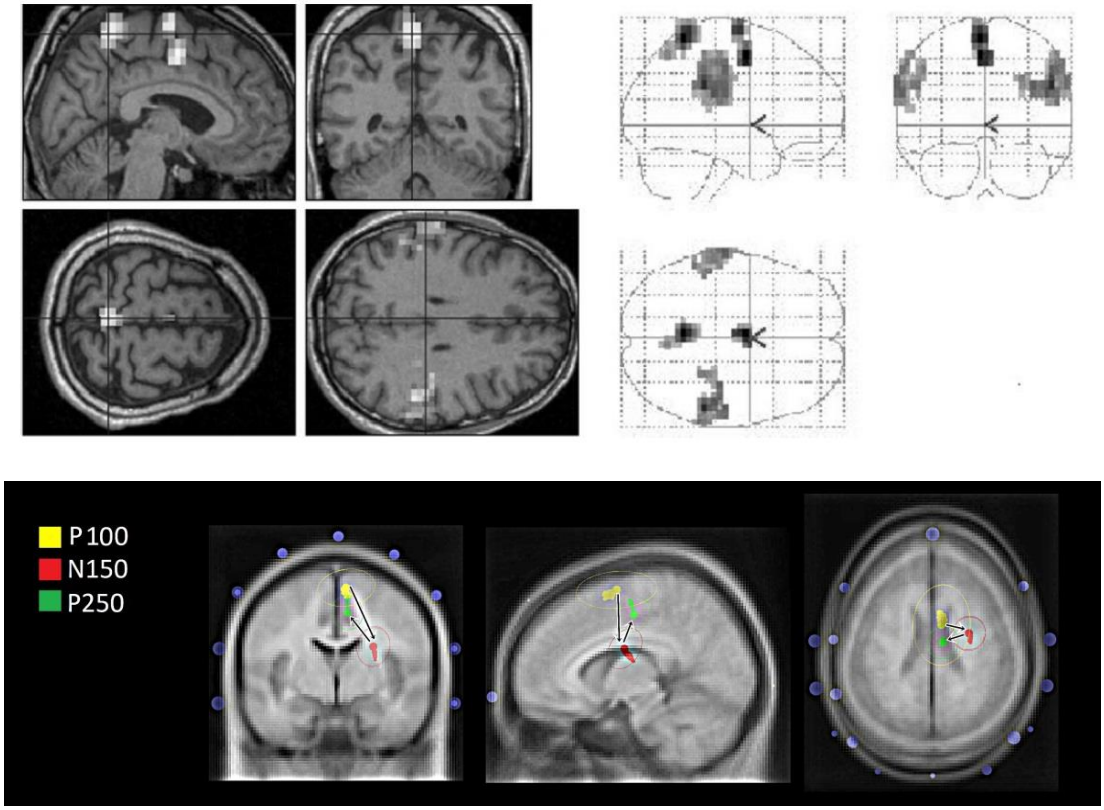


Figure 3-36. Top image) fMRI map of cortical activation pattern evoked by vibrotactile stimulation (50 Hz, 1 mm) of the foot sole(Image taken from (Gallasch et al., 2006)). Bottom image) identified dipoles in our study using dipole localization method.

CHAPTER 4
Effects of Vibrotactile Conditioning of Foot Sole on the Sol H-Reflex Modulation

4.1 Abstract

These series of studies investigates the conditioning effect of plantar vibration on SOL H-reflex excitability in healthy subjects. Localized vibration stimuli was applied to the plantar surface of the foot to test whether or not localized excitation of different sites of the foot sole modulates the soleus H-reflex in healthy subjects in order to determine if such actions in a patient population may be an effective method for altering spinal excitability. Vibration stimuli were applied to the plantar surface of the heel and below the first metatarsal head during sitting, quite standing, and walking on the treadmill at varying levels of body weight support. Stimuli were applied at 1.5-2x the sensation level. Our findings show H-reflex is depressed more when metatarsus regions are stimulated compare to heel region. Comparison between sitting and standing shows that the decrease in the conditioned H-reflex amplitude is greatest when subjects are standing. Experiments on body weight support treadmill walking suggest that H-reflex inhibition is not statistically greater when 25% body weight support is used. Studies on using vibratory stimulation at different frequencies and amplitudes suggest that H-reflex inhibition is not a simple function of the stimulation frequency or amplitude.

4.2 Vibration Insole

4.2.1 Vibrating Transducer

The aim of this work is to develop a vibrating insole which can increase the somatosensory feedback from foot mechanoreceptors during stance phase of walking. The insole was used in physiological studies reported here to investigate the conditioning effect of plantar vibration on spinal reflex excitability.

We investigated several different types of mechanical transducers to find an effective stimulator. To apply vibration stimulation to the sole of the feet, the mechanical transducer should be built in an inlay or into the shoe. A difficult challenge is the fragility associated with these devices to the forces exerted during cyclical weight bearing. The thickness of the vibrating insole should not exceed more than 15mm otherwise it will deteriorate the balance in subjects (Robbins et al., 1992). Two transducers should also be positioned near each other at the metatarsus heads so the vibrators should not cover more than half of the width of the foot at these locations (Hijmans & Juha, 2009).

After examining several different types of transducers finally two vibrators that seemed to be suitable in our experiments were selected: C-2 tactor vibrator by Engineering Acoustics Inc (Engineering Acoustics Inc) and Pico Vibe 9mm Vibration by Precision Microdrives (Precision Microdrives). These two types of vibrators were used in different sets of experiments in this study as will be discussed in the following sections.

4.2.2 C-2 Tactor Vibrator

C-2 tactor is a linear portable actuator with frequency rage suitable for tactile stimulations. This device has the widest bandwidth among all portable vibrators in the market (at the time of test). This actuator is usually used when a wide range of frequencies are needed to be delivered to the skin. The vibrator is also used extensively in military and commercial applications. It operates at 200-300Hz and uses a moving magnet linear actuator to produce vibration. If it is going to be used in a vibrating insole while subjects are walking it has to be mounted with care and requires to be housed in a way that leaves its housing flush with the surface of the sole (so the load from the foot is then spread over the shoe). Figure **4-1** shows the actuator.

4.2.3 Pico Vibe 9mm Vibration Motor

Pico Vibe 9mm Vibration Motor 307-100 vibrator motor is a 9×25 mm^2 encapsulated coreless motor designed for haptic / tactile / vibration feedback functions. This transducer is mainly used in mobile phones, and portable instruments (Precision Microdrives). The characteristic of this vibrator (amplitude and frequency) is not affected when used under pressure. It also provides vibrations both in X and Y planes. This motor has proved to be very effective in Haptic / Tactile Feedback applications (Precision Microdrives). Figure **4-2** shows this actuator.

Figure 4-1. The C-2 tactor vibrator.

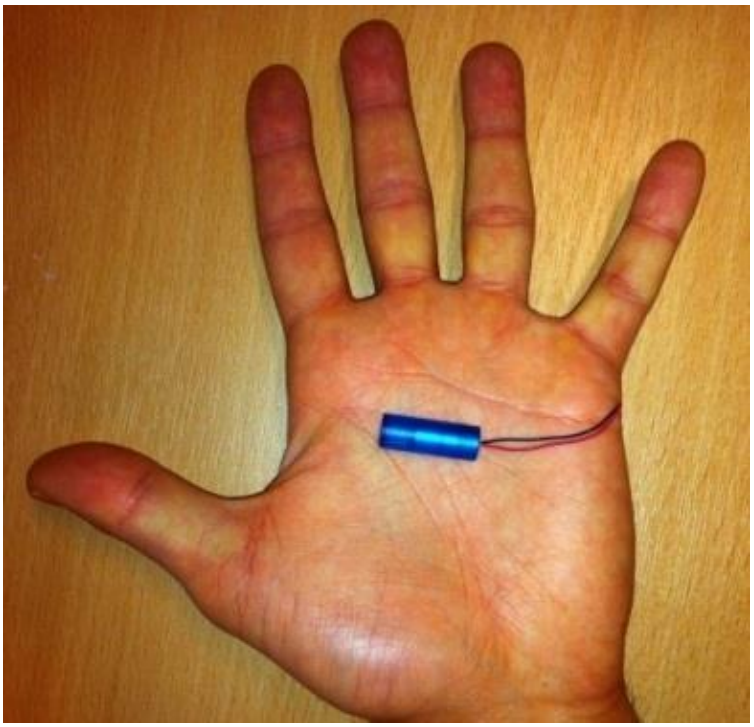


Figure 4-2. The vibrator motor (Pico Vibe 9mm vibration motor 307-100).

4.2.4 Vibrating Insole Control System

The main objective of developing a vibrating insole was to enhance somatosensory feedback by stimulating the plantar support zones (Heel and metatarsus heads (MTP)) during appropriate phases of treadmill walking. It was considered more appropriate to replace a standard insole by a vibrating insole instead of modifying the shoe itself (Hijmans et al., 2007) (Kennedy & Inglis, 2002).

Pico Vibe 9mm vibration motors were used and placed over a woollen insole. The vibrators were controlled by a custom made electric board and a Matlab/Simulink program as shown in Figure **4-3**. The foot pressure was detected using FSRs placed in the shoe. A Matlab controller program was developed in such a way that it can easily be linked to a gait training systems such as the Locomat. The insole can be synchronized with the kinematics generated by Lokomat or it can work independently based on the ground reaction force.

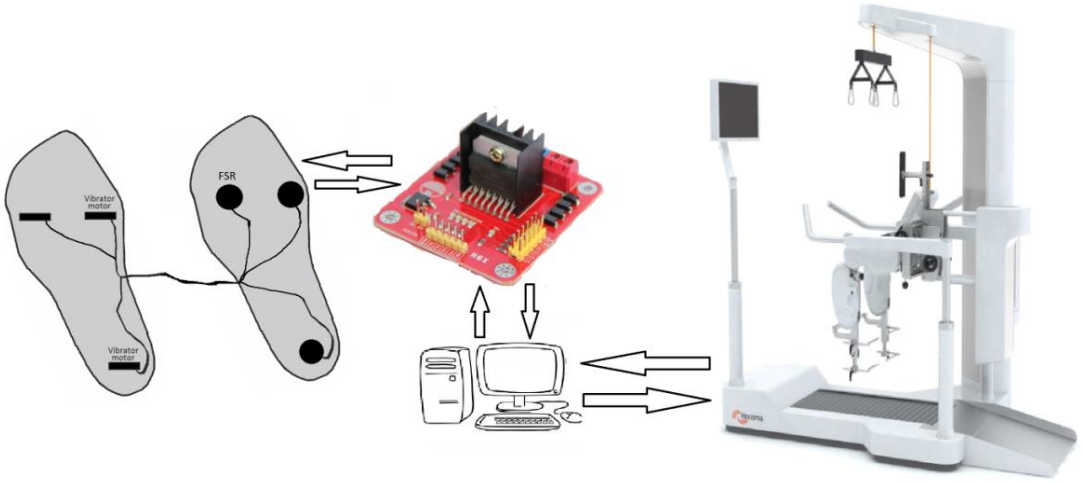


Figure 4-3. The vibrating insole was controlled using a custom control board and a Matlab program. The vibrating insole can be linked to Lokomat synchronized with the kinematics generated by Lokomat or it can work independently based on the foot ground reaction force.

4.3 Conditioning Effects of Plantar Vibration on H-Reflex during Standing and Sitting

4.3.1 Introduction

The aim of this experiment was to investigate the conditioning effect of plantar vibration on spinal reflex excitability in healthy subjects when subjects are sitting and standing. To explore this we applied vibration stimuli to the plantar surface of the foot to test whether localized excitation of the foot sole can affect the soleus H-reflex excitability in the healthy subjects. Vibratory stimuli were applied at 2 different sites on the foot sole (plantar surface of the heel and below the first metatarsal) during quiet sitting and sitting. In total of 23 healthy subjects (age 21-35 years) who had no history of neurological disorders were recruited.

According to the site of stimulation and the body postural position subjects were divided into three groups:

- Group1: Subjects sitting and stimuli applied to the heel region (8 subjects).

- Group2: Subjects sitting and stimuli applied to the first metatarsus head (9 subjects).
- Group3: Subjects standing and stimuli applied to the right metatarsus head (6 subjects).

Subjects in group 1 and group 2 were asked to sit on a reclining chair with their right leg attached and secured to a foot plate. The ankle was fixed at ~100° and the knee at ~100° (Figure **4-4**). The vibrating insole was placed underneath the right foot inside the shoe. Subjects in the third group where asked to stand in a natural and comfortable position and the vibrating insole was worn within their right shoe. The first metatarsus head of the right foot of all subjects in second and third groups was conditioned using the vibratory stimuli.

Figure 4-4. Subjects were asked to sit on a chair in a comfortable position. The right leg was attached and secured to the foot plate.

4.3.2 Subjects Recruitment

All the subjects participated in this study were recruited on voluntary basis and all subjects signed the written informed consent document. Subjects were asked to avoid having tea or coffee within 2 hours and not to undertake any strenuous exercise on the day prior to the experiment. The "Health status assessment prior to the test" form was used to consider the health situation the subjects. The main inclusion criteria were:

- Healthy subjects with no previous history of neurological problems
- 18-65 years of age
- Able to stand upright and walk for 40min
- No structure surgically implanted cardiovascular, orthopaedic or neurological device

All participants went through a familiarization session before beginning the experiments. These series of studies were covered under the general ethics policy approved by the department of bioengineering at the University of Strathclyde.

4.3.3 H-reflex Recordings

In this research the SOL H-reflex was examined because it is relatively easy to study in posture and walking and has been used as a means to measure spinal excitability in many research studies (Knikou, 2008). The H-reflex was evoked by electrical stimulation of the tibial nerve via a constant-current electrical stimulator, DS7AH (Digitimer). The electrical stimulation was a square pulse of 1ms in width. An electrode was place on the popliteal fossa as the cathode electrode and a reusable self-adhesive electrode was placed slightly above the patella as the anode electrode. The position of the cathode electrode was determined by a trial and error procedure. The electrode position that generated the greatest amplitude of H-wave to constant stimulation strength was considered the optimum site. The SOL H-reflex was measured from the right foot of all the subjects. A self-adhesive conductive disk electrode was placed over the medial condyle of the femur bone as the anode.

The SOL EMG signals were recorded using a Neurolog isolated AC-coupled amplifier and filter setup (gain range 1K-5K, filters 10-1000Hz and digitised using a CED1401 sampling at 5000Hz. The Spike program was used to record the data. Tibial nerve stimulation was triggered and controlled via a signal generated by a PC running a Matlab program. Figure 4-8 illustrates the recording system configurations. Recording sessions took at least 60 minutes and subjects were asked to relax and avoid unnecessary upper body or lower body movements during the course of the experiment.

Soleus H and M-wave were determined for each subject utilizing the procedures outlined by Hugon (Hugon, 1973). The electrical stimulation intensity was adjusted to evoke an H-wave with amplitude between 20-30% of the maximum M-wave. To achieve this, tibial nerve was stimulated by an electrical pulse and the pulse intensity was gradually increased until H-wave disappeared and there was not any significant increase in the M-wave amplitude (Mmax) (see Figure **4**-**5**). After measuring Mmax the electrical stimulation intensity was adjusted to evoke an H-wave with 20-30% of the maximum M-wave. The H-waves and M-waved were also measured by their peak-to-peak values. To generate M-wave and H-wave recruitment curves stimuli were applied several times with at least 8s delay between stimuli (Chen & Zhou, 2011b).

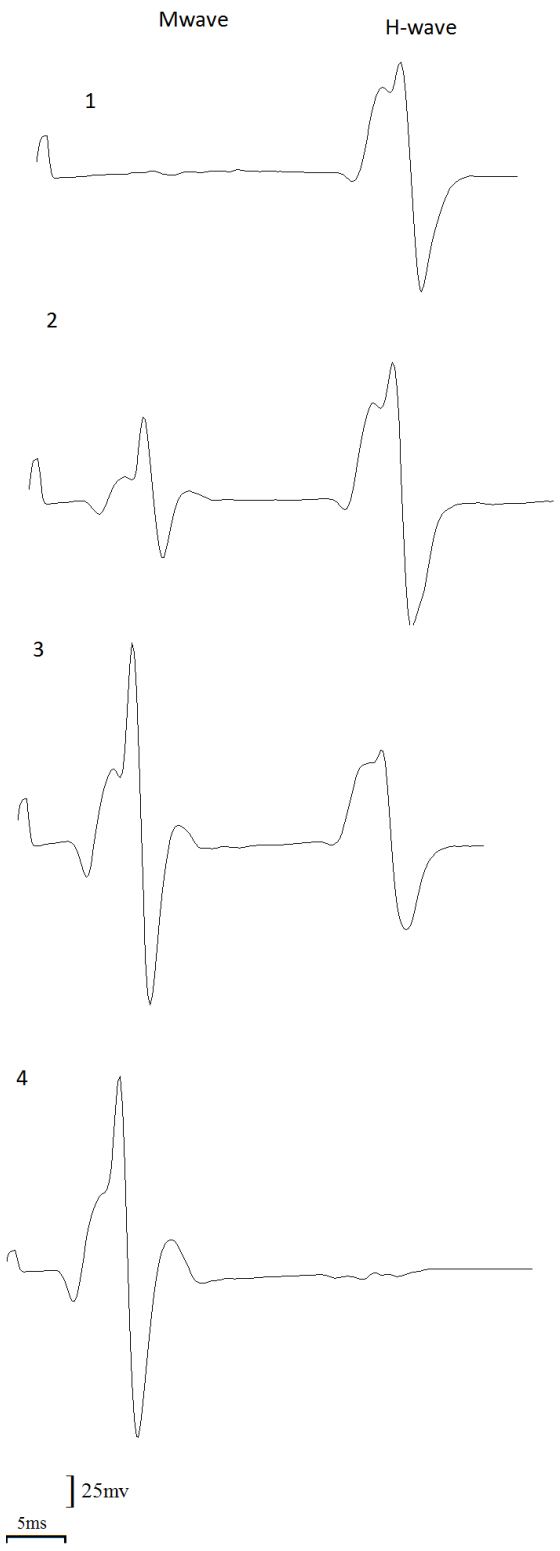


Figure 4-5. By increasing the tibial nerve stimulation the H-wave decreases and M-wave increases until it gets to its maximum amplitude (M_{max}). Four pictures show the modulation of M-wave and H-wave with increasing the stimulation intensity recorded from one subject. In picture 1 the stimulation intensity is low and it is progressively increased (picture 2 and 3) until M-wave reaches its maximum (picture 4).

4.3.4 Conditioning Vibrotactile Stimuli

When testing H-reflex modulations all the conditioning stimuli were delivered at ~100Hz[3]. A series of vibration pulses of 3s in width were used to stimulate foot regions. These conditioning vibratory stimuli were grouped as 6 conditioning stimuli surrounded by two controls H-reflex with 10s delay between them. This block (bin) was delivered 30 times to the subject's foot during this part of the experiment (~1 hour) (see Figure **4-6**). In each block, conditioned H-reflexes were measured at different latencies relative to time of stimuli onset (50ms, 200ms, 400ms, 1s and 2s) and with ~90ms delay after the end of stimulation (post stimulation) (see Figure **4-7**). These latencies are shown symbolically by "Td" (Time delay) in the rest of this thesis and were assigned randomly in each block during the experiments. It should be noted that control H-reflexes are measured at the beginning and end of each bin when there is no vibrotactile stimulation. 10s rest intervals between stimuli was considered to avoid repetitive reflex depression. Using this method it will be possible to study the modulation of H-reflex at different latencies relative to time of stimulation onset which can cover a set of times that would be both shorter and longer than the likely stance duration times observed during Lokomat® gait training sessions.

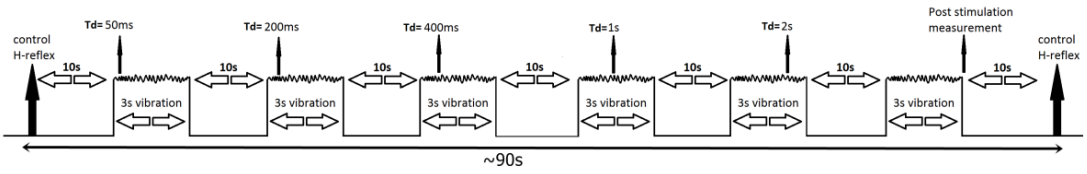


Figure 4-6. A series of vibration pulses of 3s in width was used to stimulate the foot. These conditioning vibratory stimuli were grouped as block of 6 conditioning stimuli surrounded by two controls H-reflexes. The duration of the constructed bin is about 90s and was applied 30 times to the subject's foot in about 1 hour. Conditioned H-reflexes were measured at different latencies relative to time of stimulation onset (T_d=50ms, 200ms, 400ms, 1s and 2s) and with 90ms delay relative to the end of stimuli (post stimulation). A 10s rest intervals between stimuli was also considered.

[3] The direct effect of vibration stimulation on SOL background EMG activity was examined on 3 subjects but it was never observed to induce a change in EMG activity or result in painful sensations.

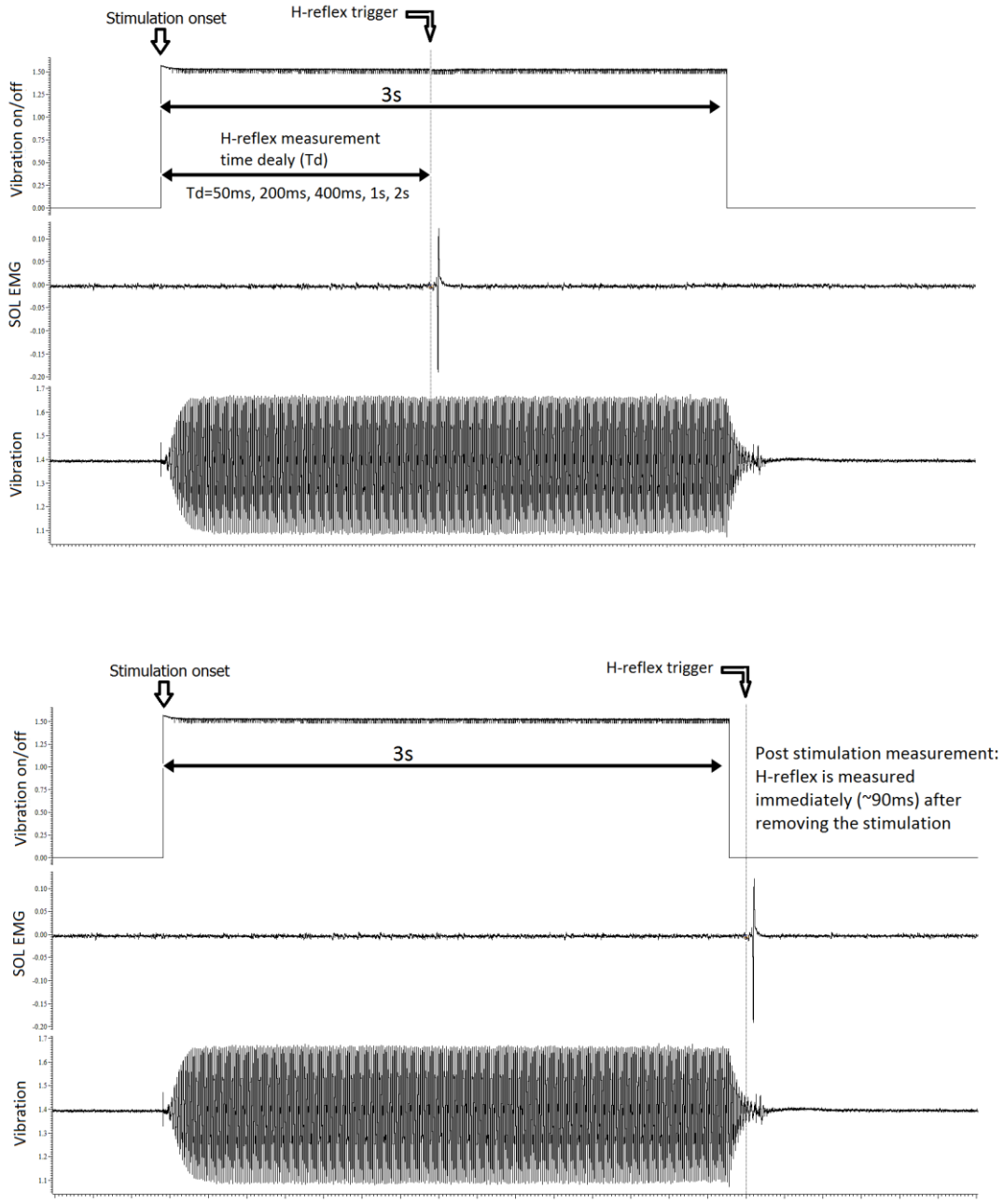


Figure 4-7. The conditioning stimulation is a vibration pulses of 3s in width at 100Hz. Conditioned H-reflexes were measured with T_d second delay relative to time of stimulation onset. T_d values were selected as 50ms, 200ms, 400ms, 1s, 2s relative to the stimuli onset and ~90ms after the end of stimuli (post stimulation). The top plot shows the conditioned H-reflex measurement at T_d =50ms, 200ms, 400ms, 1s, 2s and the bottom plot shows the conditioned H-reflex measurement with 90ms delay relative to the end of stimuli (post stimulation).

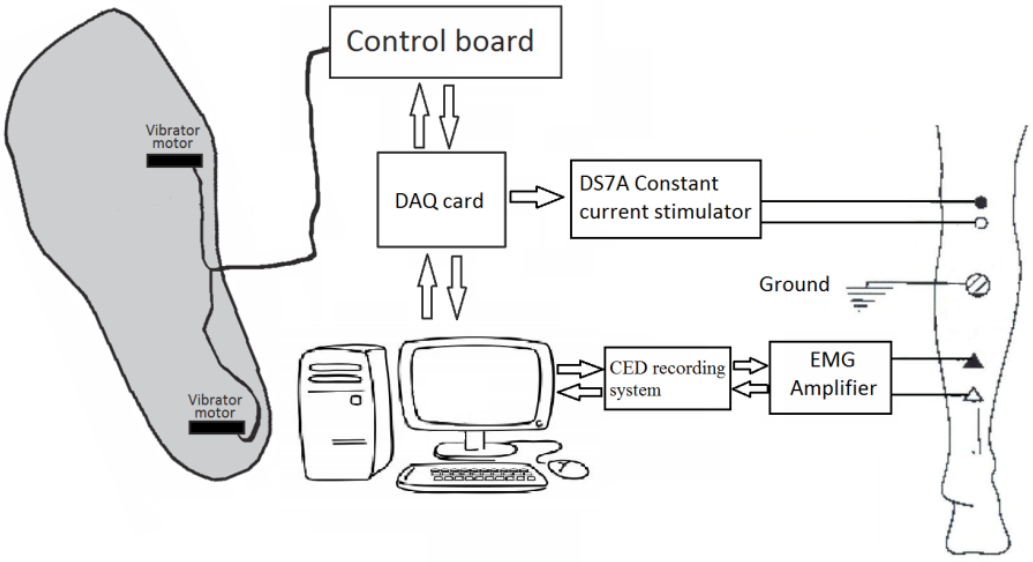


Figure 4-8. Schematic representation of the recording system. The vibrators were controlled with a custom Matlab program and a control board. H-reflex was also evoked by triggering DS7A stimulator which was also controlled by a Matlab program. EMG signals are amplified using NL824 EMG amplifier. The amplified EMG signals were then sampled by CED data acquisition card and data are recorded by spike2 program (Cambridge Electronic Design).

4.3.4 Data Analysis

The H-reflexes and M-waves were measured by their peak-to-peak values. The conditioned H-reflexes were averaged according to their conditioning time delay (T_d) and normalized to the averaged control H-reflex. Some of the conditioned H-waves with much bigger or smaller M-waves compared to the corresponding control H-waves in each bin were rejected.

All statistical analyses were performed in SPSS software. The paired sample t-test and ANOVA test were used to analysis the data with $p < 0.05$ as the criteria of the significant difference. The hypothesis we are going to examine is:

1. In within subject study is there any statistically significant change in the average size of the conditioned H-reflexes compared to the control H-reflex or not?
2. Is there any statistically significant change in the average size of the conditioned H-reflexes compared to the control H-reflex when data is grand averaged across all subjects in each group?

3. Are there any statistically significant differences between mean values of the conditioned grand averaged H-reflexes when data are compared across different groups?

For T-tests to be able to provide a valid result, some assumptions must hold. Data should be checked for normality, homogeneity of variances and existence of any outliers. The normality of the data was also checked using Shapiro-Wilks test and homogeneity of variances was checked using Levene-Test.

4.4 Results

4.4.1 Recruitment Curves

Figure 4-9 shows examples of the H-reflex recruitment curves obtained from 5 different subjects. In most subjects the H-wave threshold was lower than the M-wave threshold as expected from the literature. The size of the H-waves grew gently with increasing stimulation intensity. In most cases the H-reflex maximum amplitude coincided with the appearance of the M-wave, after which it decreased with the progressive increase in the size of the M-wave.

4.4.2 H-reflex Variability

A significant problem in H-reflex studies is its variability from one trial to the next (Brinkworth et al., 2007) (Funase & Miles, 1999). Averaging over a very large number of trials is a way to estimate the variance and produce a valid average (Funase & Miles, 1999). There is a strong positive relationship between the amplitude of the H-reflex and the level of background muscle activity (Funase & Miles, 1999). The H-reflex variability is directly related to the mean level of excitation of the SOL motoneuronal (Funase & Miles, 1999). The variation of H-reflex from trial to trial was observed while testing subjects and some examples are also shown in Figure **4-18**, Figure **4-19** and Figure **4-20**. The H-reflex variably was significantly enhanced when subjects were standing or walking on the treadmill.

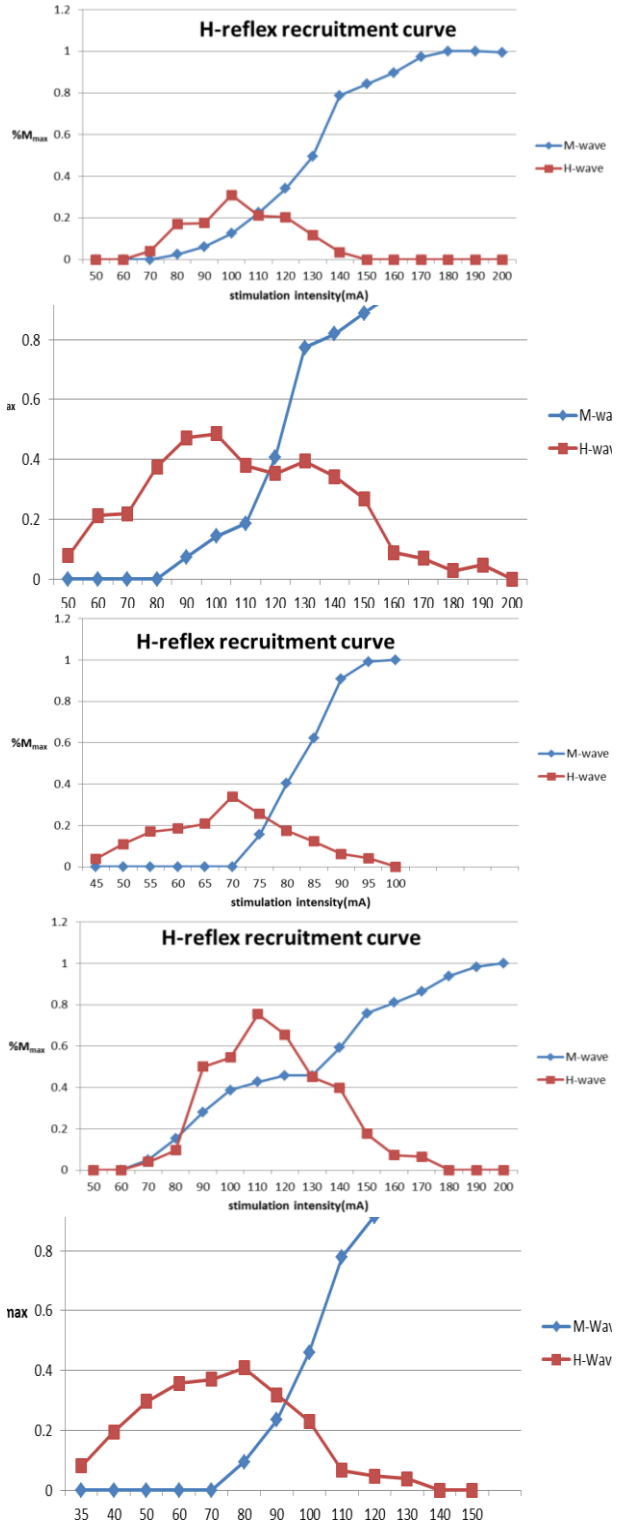


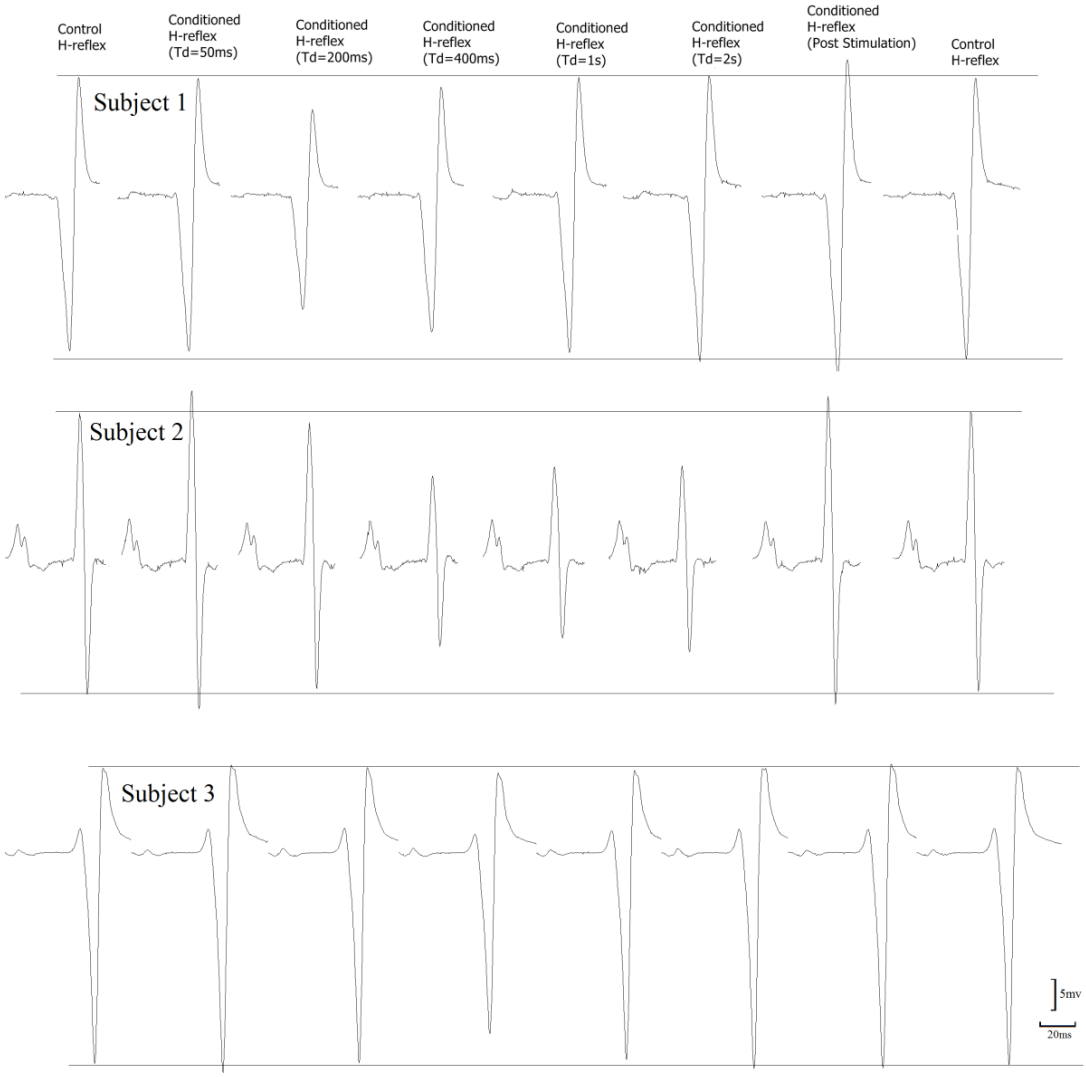
Figure 4-9. Examples of the control H-reflex recruitment curves obtained from 5 different healthy subjects. The amplitude of H- and M-waves, both expressed as a percentage of the M_{max}, are plotted as a function of the stimulus intensity.

4.4.3 Group1: Subjects siting and Heel is Stimulated

8 subjects were randomly assigned to this group. Group 1 participants were asked to seat on a chair in a comfortable position and the heel region of their right foot was stimulated by vibratory stimuli using the protocol explained before (see Figure **4-6**). Figure **4-10** show a 90s sample of raw EMG data recorded from 6 different subjects. The H-waves are plotted alongside each other in each figure for better comparison. Two parallel lines also show the peak to peak amplitude of the control H-waves at the beginning and the end of the selected bins. Controls H-waves at the beginning and the end of the selected bins have consistent amplitudes and all the H-waves also have similar M-wave size.

A clear inhibition or depression of the H-reflexes can be observed from the raw data when vibrotactile stimulation is applied to the subjects' foot (heel region). In the majority of cases the observed inhibition seems to be greatest when the H-reflex is evoked between 200ms-1000ms relative to stimuli onset (T_d=200ms, 400ms and 1s). More information will be presented in the discussion section (see page 162).

Figure 4-11 and Figure 4-12 show the averaged SOL H-waves normalized to the control H-reflex amplitude evoked at different latencies relative to the stimulus onset (Td) following excitation of the heel region in the test group. This graph presents the Mean±95%CI of the normalized averaged H-reflexes. A considerable variation in H-reflex amplitude and variance is observed across the subject group. However the mean difference between the corresponding control H-reflex and the conditioned H-reflex is observed to be significant between Td=200-400ms for most of the subjects as assessed by paired sample T-test. Data were grand averaged across all subjects and the result is shown in Figure 4-13. The paired sample T-test at a 95% confidence limit was used to test whether or not there is any statistically significant difference between the grand mean values of the control H-reflex and conditioned H-reflexes. T-test results suggest that the maximum inhibition occurs at Td=200-400ms and provokes a ~6% depression of the control H-reflex. The results of paired sample T-test analysis are presented Table 4.1.


Control H-reflex
Conditioned H-reflex (Td=50ms)
Conditioned H-reflex (Td=200ms)
Conditioned H-reflex (Td=400ms)
Conditioned H-reflex (Td=1s)
Conditioned H-reflex (Td=2s)
Conditioned H-reflex (Post Stimulation)
Control H-reflex
Subject 1
Subject 2
Subject 3
5mv
20ms

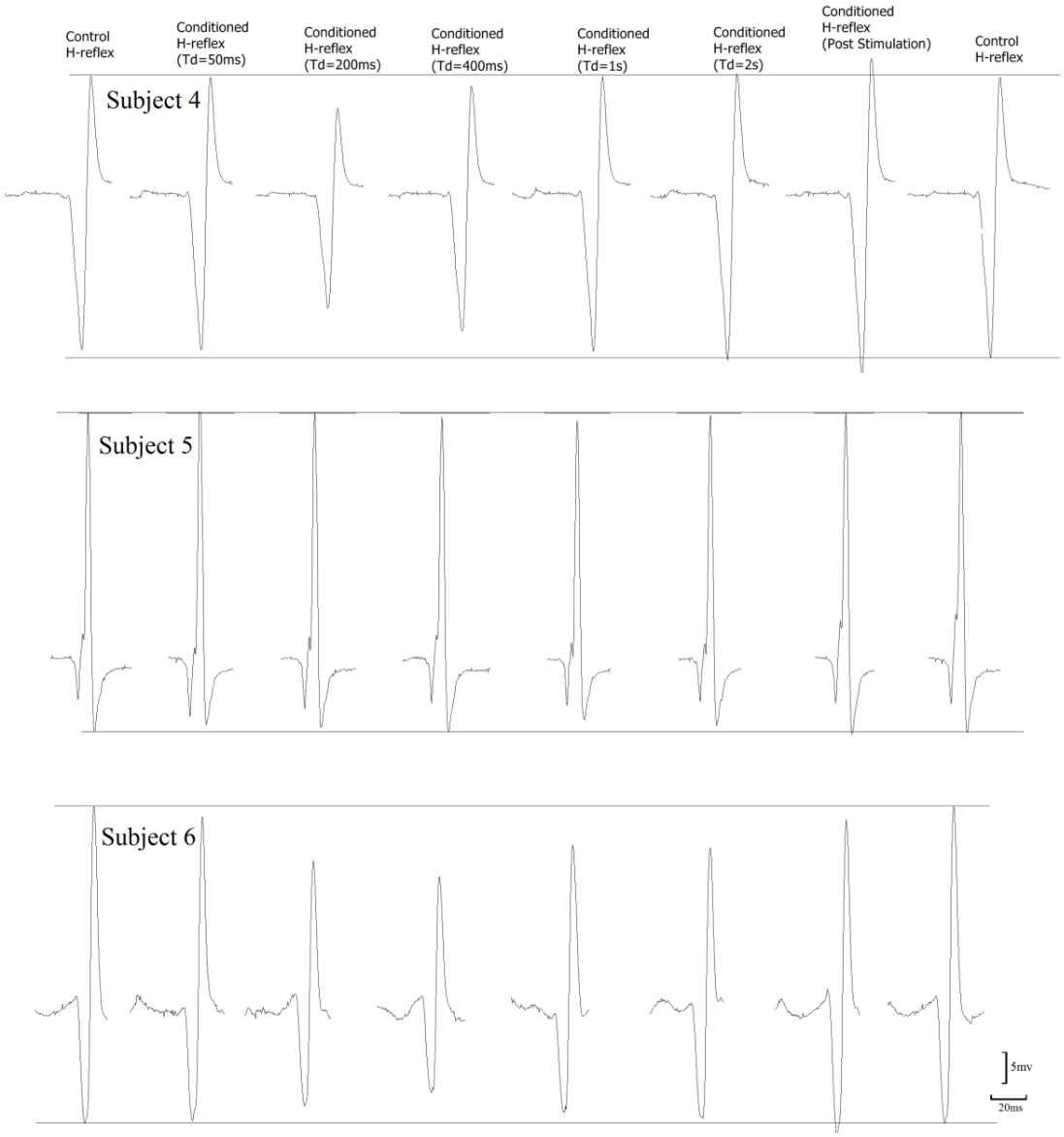


Figure 4-10. Raw EMG data recorded from 6 different subjects. This figure shows examples of the un-averaged conditioned soleus H-waves evoked at different latencies relative to the stimulus onset (Td). The plotted data show H-waves recorded from one out of 30 applied bins (see Figure 4-6) to the heel region of a subject. The first and the last H-waves shows the control (unconditioned H-wave) H-waves in the selected bin. Two parallel horizontal lines show the peak to peak amplitude of the control H-waves at the beginning and the end of the selected bin and show consistent control H-reflex amplitude.

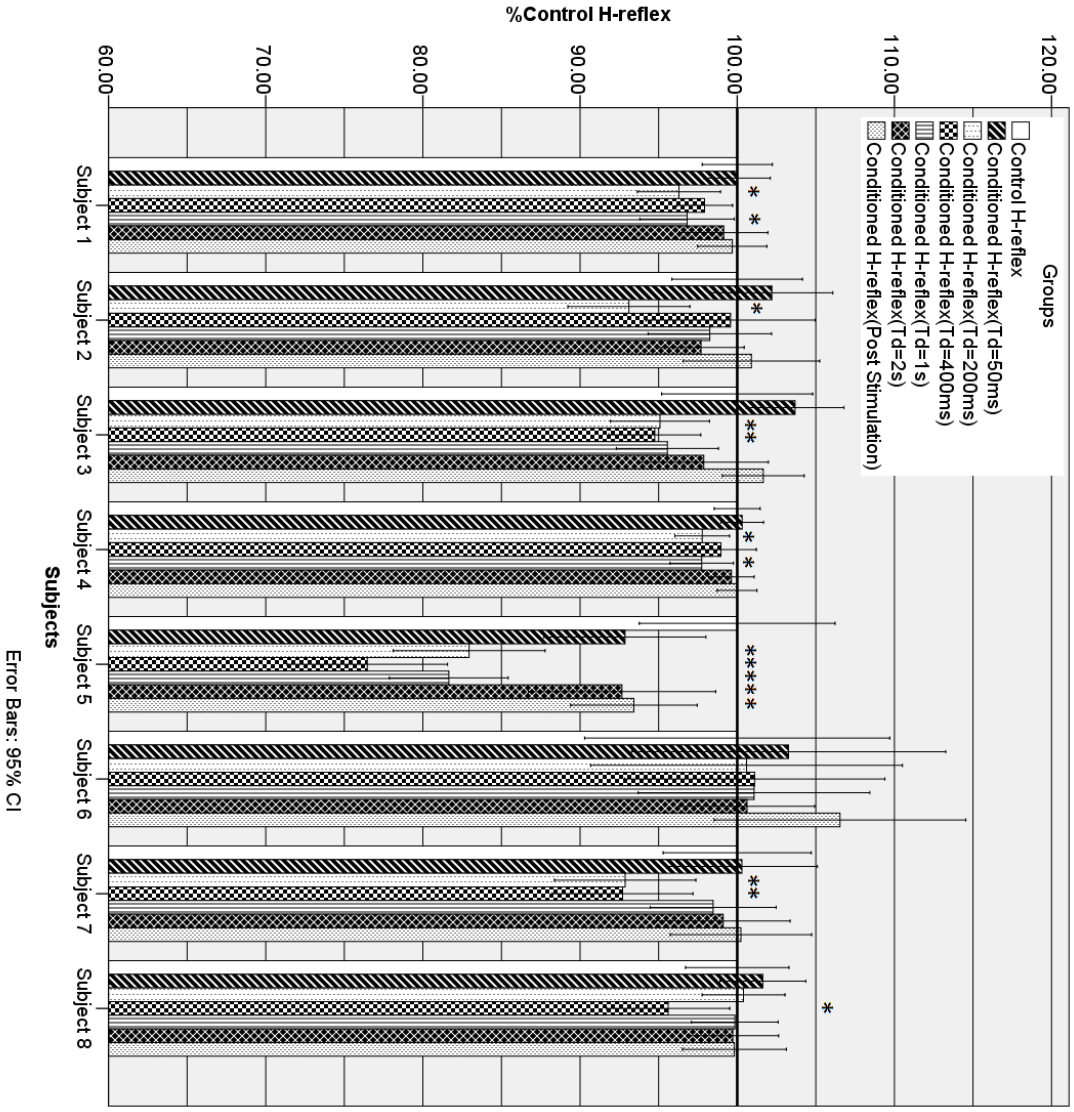


Figure 4-11. Bars showing the effect of plantar vibrotactile cutaneous stimulation delivered to the heel region at different T_d intervals. For each T_d interval tested, the overall average size of the conditioned SOL H-reflex is presented as a percentage of the overall average control size (mean ±95%CI). Asterisks indicate statistically significant differences between the corresponding control H-reflex and the conditioned H-reflex sizes (*$p < 0.05$).

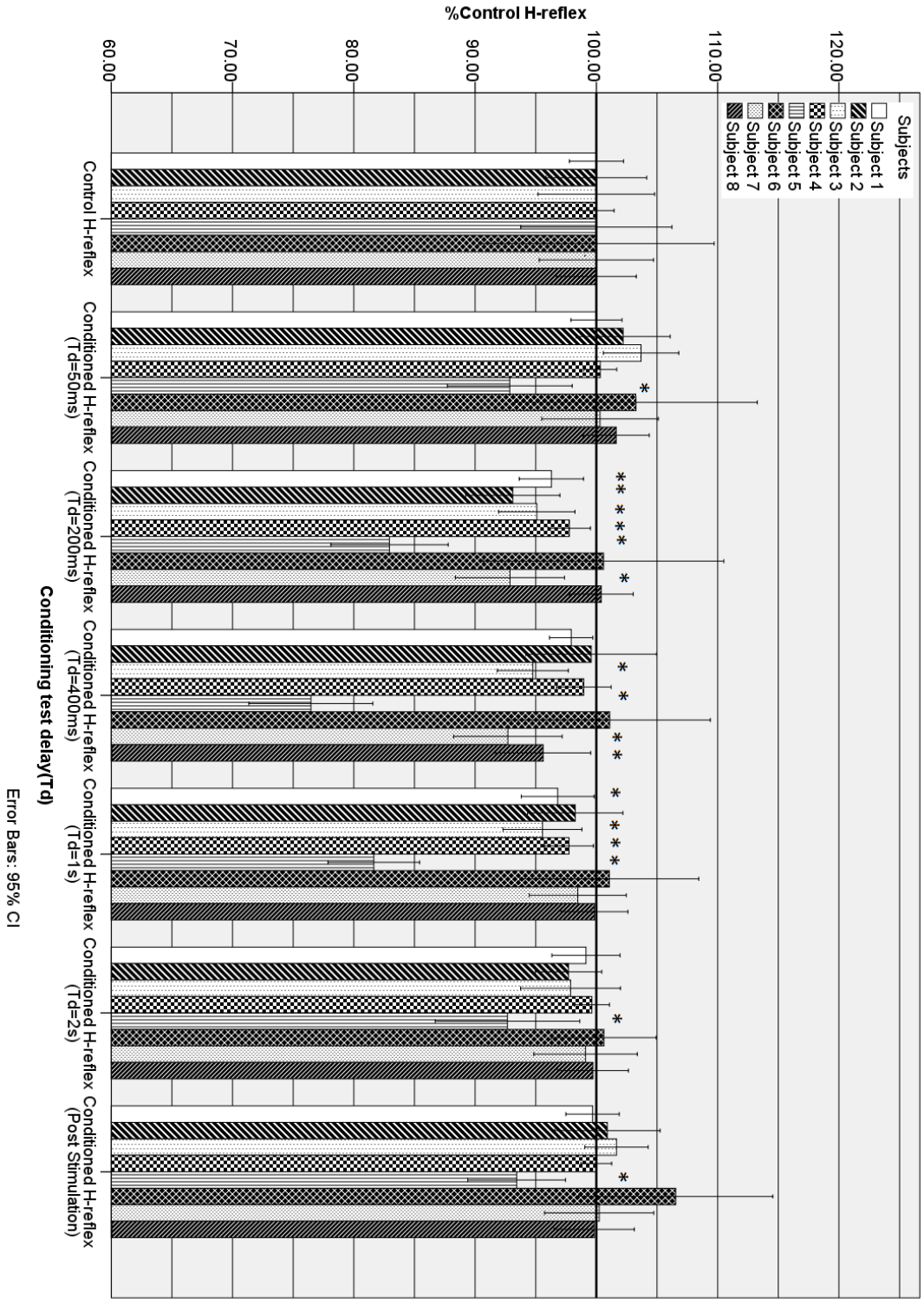


Figure 4-12. The magnitude of the conditioned and control H-waves recorded from 8 subjects grouped based on subjects. Data are normalized to the averaged control H-reflex size. Asterisks indicate statistically significant differences between the control H-reflex and the conditioned H-reflex sizes (*$p < 0.05$).

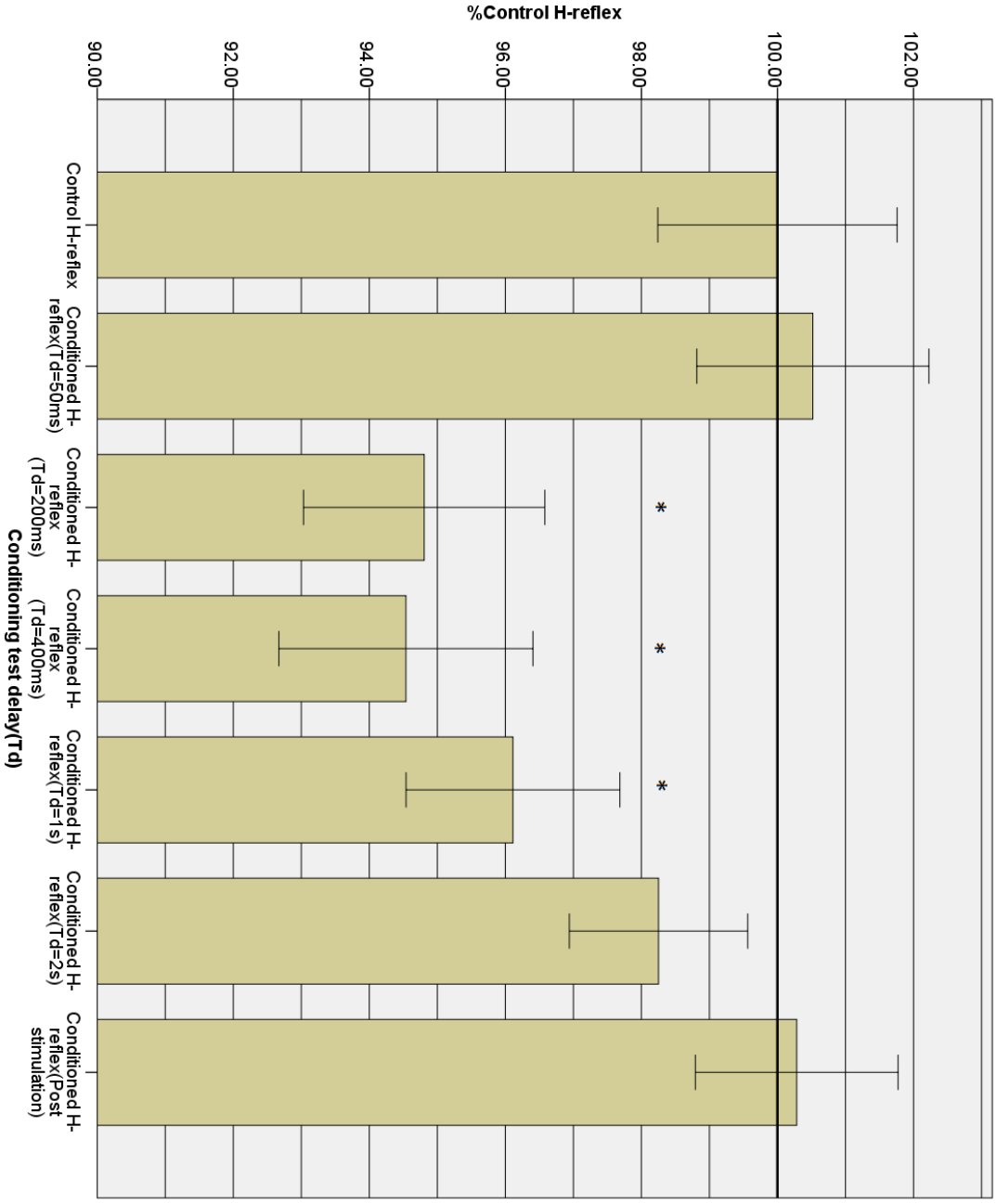


Figure 4-13. Mean ±95%CI of the normalized H-waves grand averaged across 8 subjects. A significant (*p<0.05) reduction in the H-reflex size exist between the unconditioned H-reflex (control H-reflex) and the conditioned H-reflexes at T_d=200ms, 400ms and 1s when data grand averaged across all subjects. A small facilitation is also observed at T_d=50ms and post stimulation which is not significant. Asterisks indicate statistically significant differences between the control H-reflex and the conditioned H-reflex sizes when data averaged across subjects (*p < 0.05).

Table 4.1. Paired sample T-test conducted on the grand averaged data across all subjects to determine whether there were statistically significant differences between the conditioned H-reflexes and the unconditioned H-reflex. The T-test reveals that conditioned H-reflexes are statistically significantly different in mean from the unconditioned H-reflex (control H–reflex) at T_d= 200ms, 40ms, and 1s when data averaged across all subjects. The significant parries are **bolded** in this table.

Pairwise Comparisons						
pairs		Mean Difference	Std. Error	Sig.	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
Control H-reflex	Conditioned H-reflex (Td=50ms)	-.290	.932	1.000	-3.155	2.575
	Conditioned H-reflex (Td=200ms)	**5.224***	**1.173**	**0.000**	**1.615**	**8.832**
	Conditioned H-reflex (Td=400ms)	**5.398***	**1.136**	**0.000**	**1.904**	**8.892**
	Conditioned H-reflex (Td=1s)	**4.122***	**1.040**	**0.002**	**.923**	**7.321**
	Conditioned H-reflex (Td=2s)	1.277	1.037	1.000	-1.913	4.467
	Conditioned H-reflex (Post Stimulation)	-.522	1.126	1.000	-3.984	2.940
*. The mean difference is significant at the .05 level.						

4.4.4 Group2: Subjects siting and First Metatarsus Head is Stimulated

Figure **4-14** shows a 90s interval selected from the raw EMG data recorded from 4 different subjects. The H-waves are plotted side by side in each figure for better comparison. Two parallel dashed lines also show the peak to peak amplitude of the control H-waves at the beginning and the end of the selected bin which have consistent amplitudes. All the plotted H-waves also have similar M-wave size. This suggests that the inhibition of the conditioned H-wave in the selected bins is due to the conditioning effect of the vibratory stimuli. Similar to the previous experiment some small facilitation was observed in few cases which were not significant.

Mean±95%CI of the normalized averaged H-reflexes grouped based on the conditioning time delay intervals (Td) from each volunteer are shown in Figure **4-15**. Figure **4-16** presents the averaged data grouped based on subjects. A considerable variation in H-reflex amplitude is observed within the subject groups. However the variation between the corresponding control H-reflex and the conditioned H-reflex is significant at intervals ranging from Td=200, 400ms and 1s for most of the subjects, as assessed by paired sample T-test. Grand averages across all subjects are shown in Figure **4-17**. The paired sample T-test was used to test whether or not there is any statistically significant difference between the mean values of the averaged control H-reflex and the averaged conditioned H-reflexes when data was grand averaged across all subjects. T-test suggests that the maximum inhibition of 9% of the control

reflex is seen at T_d=400ms when data is averaged across all subjects. The results of paired sample T-test analysis are presented Table 4.2.

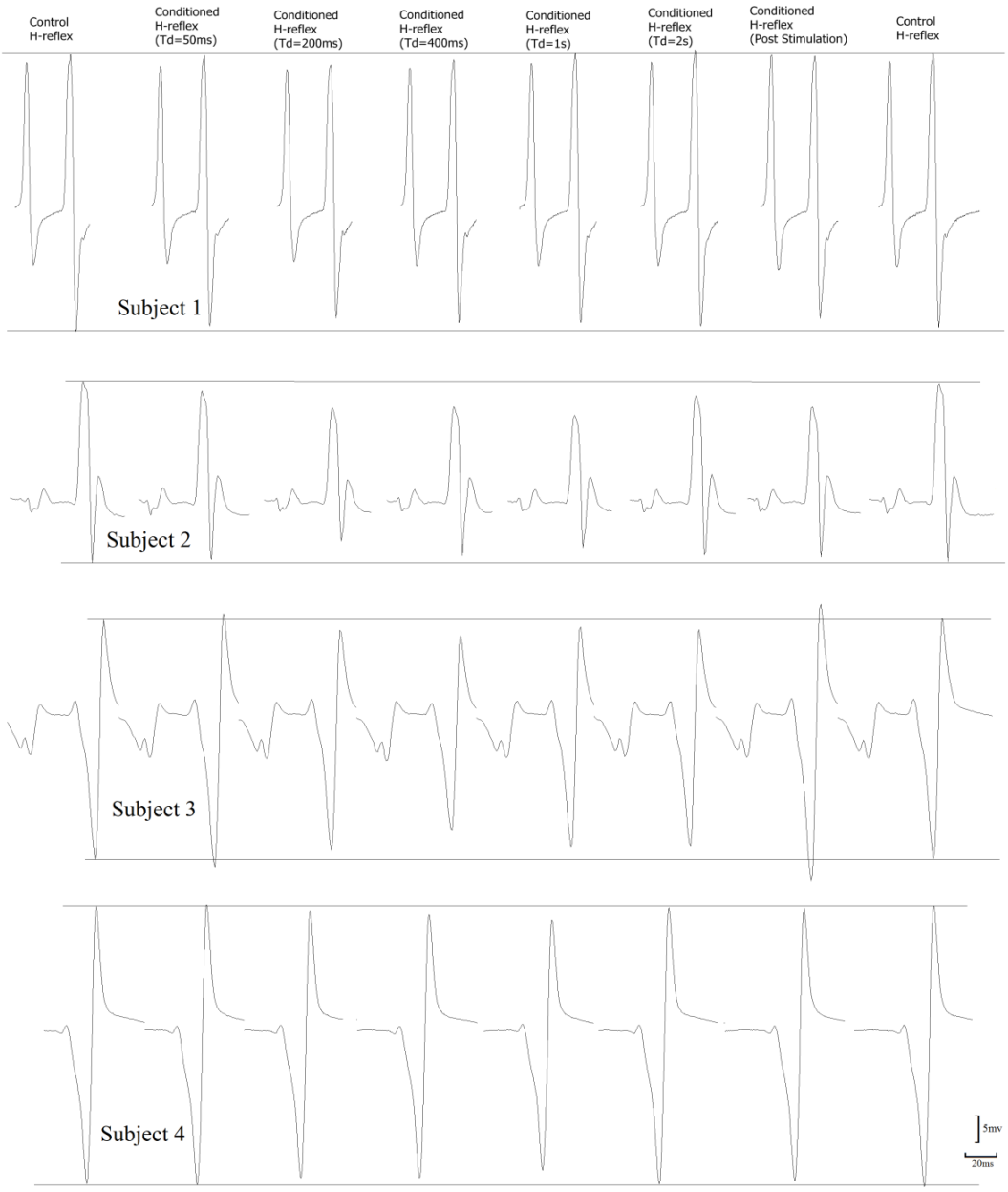


Figure 4-14. Raw EMG data recorded from 4 different subjects. This figure shows examples of the un-averaged conditioned soleus M and H-waves evoked at different latencies relative to the stimulus onset (Td). The plotted data show H-waves recorded from one out of 30 applied bins (see Figure 4-6). The first and the last H-waves shows the control (unconditioned H-wave) H-waves in the selected bin. Two parallel horizontal lines show the peak to peak amplitude of the control H-waves at the beginning and the end of the selected bin and show consistent control H-reflex amplitude. All the recorded H-waves also have consistent M-wave size.

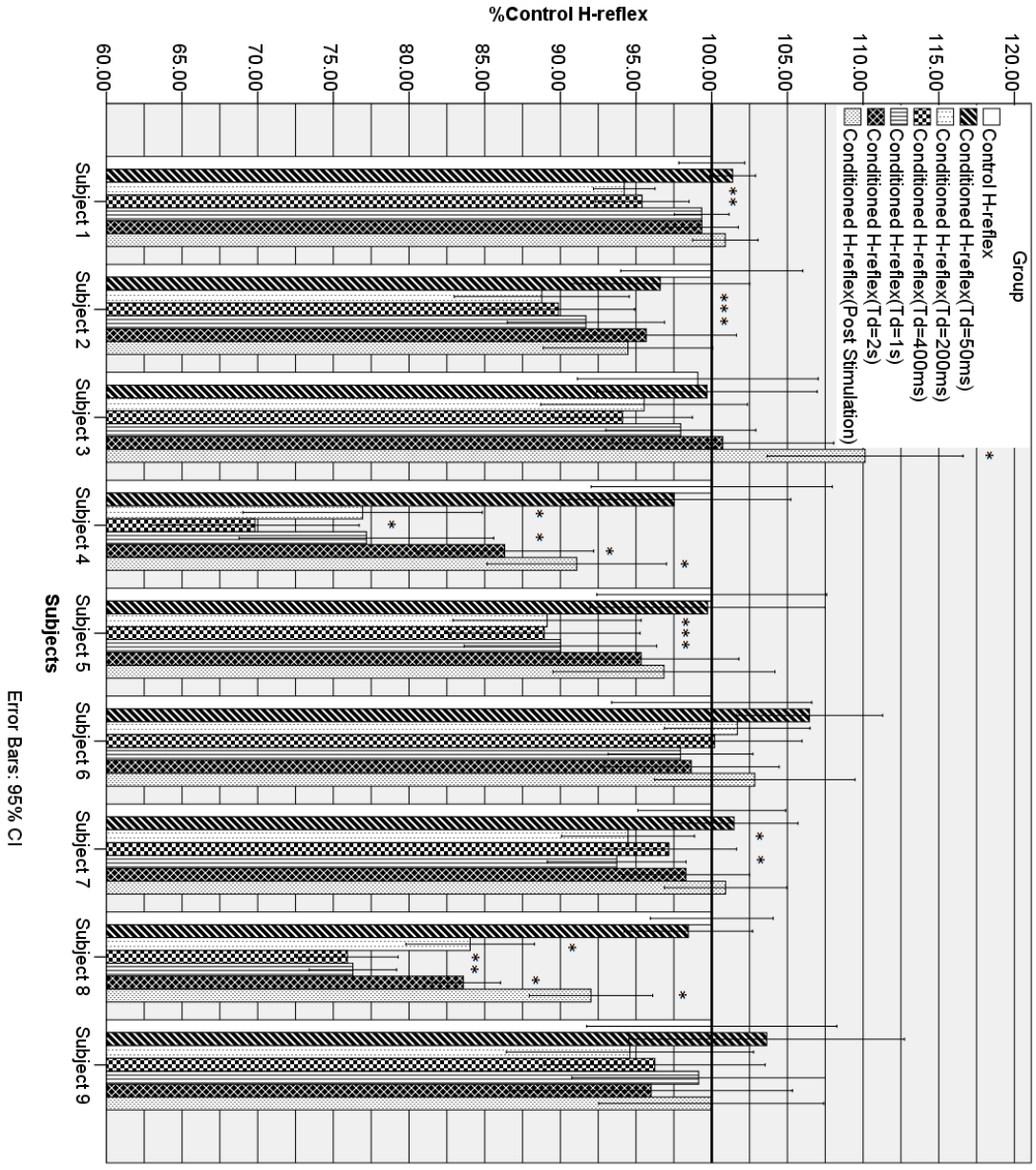


Figure 4-15. Bars showing the effect of plantar vibrotactile cutaneous stimulation delivered to the first metatarsus region (subject are sitting) at different Td intervals. For each Td interval tested, the overall average size of the conditioned SOL H-reflex is presented as a percentage of the overall average control size (mean ±95%CI). Asterisks indicate statistically significant differences between the control H-reflex and the conditioned H-reflex sizes (*$p < 0.05$).

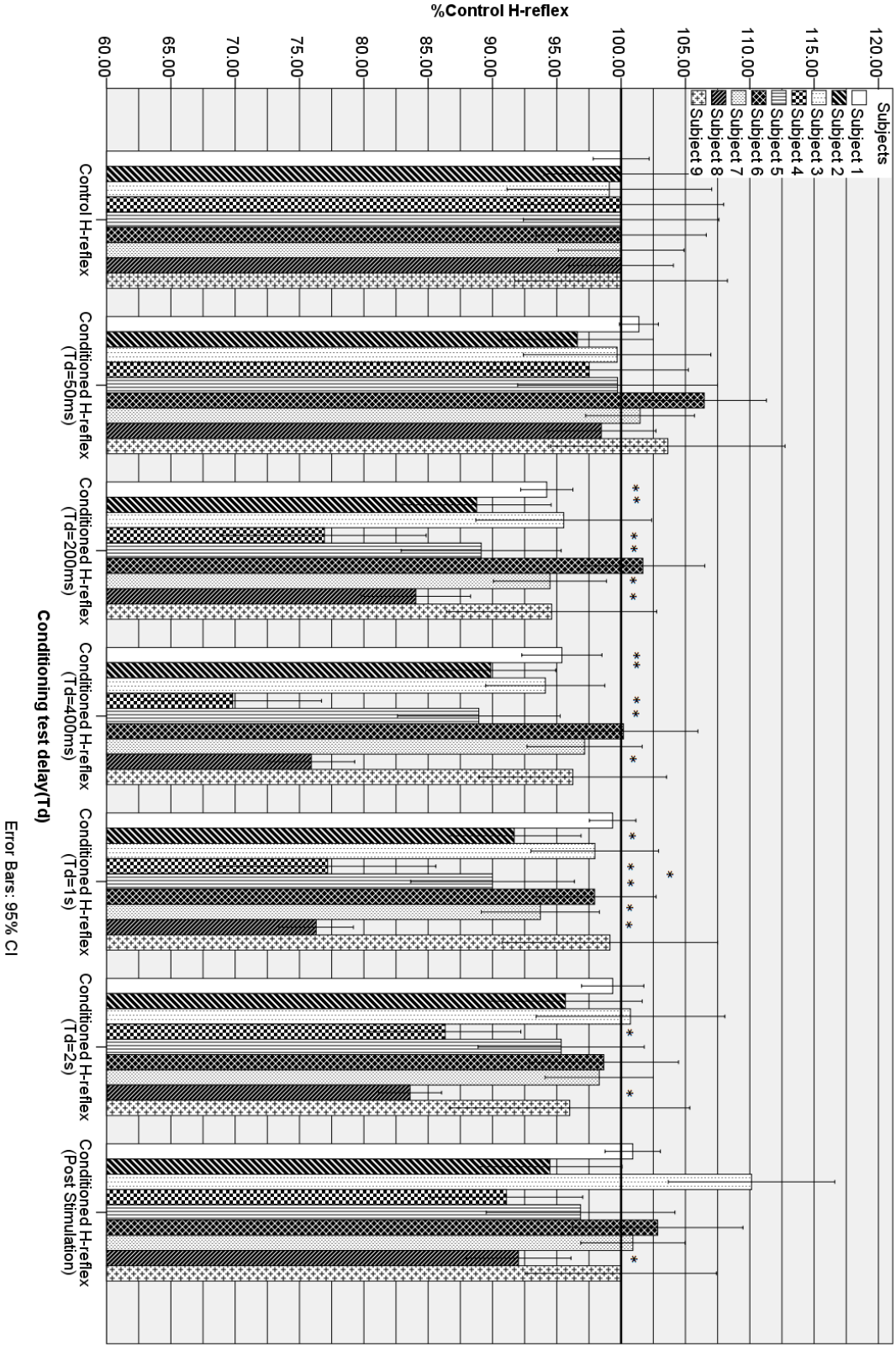


Figure 4-16. The magnitude of the conditioned and control H-waves recorded from 8 subjects grouped based on subjects. Data are normalized to the averaged control H-reflex size. Asterisks indicate statistically significant differences between the control H-reflex and the conditioned H-reflex sizes (*$p < 0.05$).

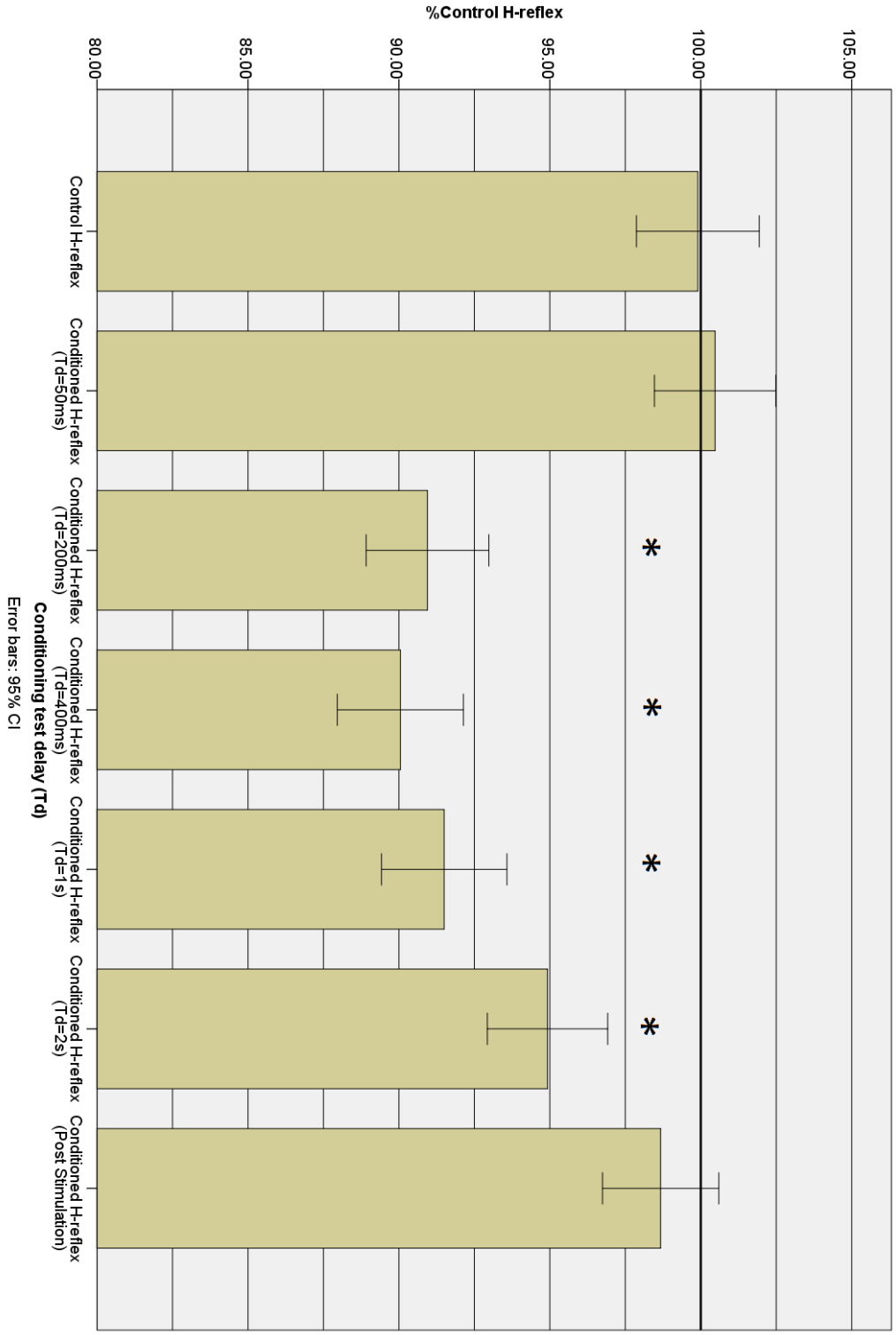


Figure 4-17. Mean ±95%CI of the normalized H-waves averaged across 8 subjects. A significant (*p<0.05) reduction in the H-reflex size exist between the unconditioned H-reflex (control H-reflex) and the conditioned H-reflexes at T_d=200ms, 400ms, 1s and 2s when data averaged across all subjects. A small facilitation is also observed at T_d=50 which is not significant. Asterisks indicate statistically significant differences between the control H-reflex and the conditioned H-reflex sizes when data averaged across subjects (*p < 0.05).

Table 4.2. Paired sample T-test shows that conditioned H-reflexes are statistically significantly different in mean from the unconditioned H-reflex (control H–reflex) at T_d= 200ms, 40ms, 1s and 2s. The significant parries are **bolded** in the table.

Pairwise Comparisons						
pairs					95% Confidence Interval for Difference	
		Mean Difference	Std. Error	Sig	Lower Bound	Upper Bound
Control H-reflex	Conditioned H-reflex (Td=50ms)	-1.198	.988	1.000	-4.233	1.837
	Conditioned H-reflex (Td=200ms)	**8.793***	**1.122**	**0.000**	**5.346**	**12.241**
	Conditioned H-reflex (Td=400ms)	**9.326***	**1.283**	**0.000**	**5.383**	**13.269**
	Conditioned H-reflex (Td=1s)	**7.748***	**1.244**	**0.000**	**3.925**	**11.571**
	Conditioned H-reflex (Td=2s)	**4.122***	**1.301**	**0.037**	**.125**	**8.120**
	Conditioned H-reflex (Post Stimulation)	.644	1.266	1.000	-3.246	4.535
*. The mean difference is significant at the .05 level.						

4.4.5 Group2: Subjects standing and First Metatarsus Head is Stimulated

Figure **4-18**, Figure **4-19** and Figure **4-20** show a 180s interval (2 Bins4) selected from the raw EMG data recorded from 3 different subjects. 2 different bins from each subject are selected and the H-waves are plotted side by side for better comparison. Two parallel dashed lines also show the peak to peak amplitude of the control H-waves at the beginning and the end of the each bin.

Inspection of the raw EMG data suggests that the amplitude of the conditioned H-reflex is highly variable during the experiment. For example in Figure **4-19** the amount of inhibition at Td=400ms considerably varies in Bin1 and Bin2. In the first set of records show (bin1) the peak to peak amplitude of the conditioned H-wave at Td=400ms is 87% of the corresponding control H-wave while in the second data segment (bin2) the peak to peak amplitude of the conditioned H-wave at T_d=400ms is 56% of the corresponding control H-waves. Similar patterns of high variance were observed in all the subjects during standing experiments and suggest a further factor may be influencing the H-reflex size; this may be background excitability changes associated with postural adjustments.

[4] As mention before each during the experiment a series of vibration pulses of 3s in width was used to stimulate the foot. These conditioning vibratory stimuli were grouped as block of 6 conditioning stimuli surrounded by two controls H-reflex. Each block is referred to as Bin and in total 30 bins was applied to the subjects' foot. The length of each Bin is 90s.

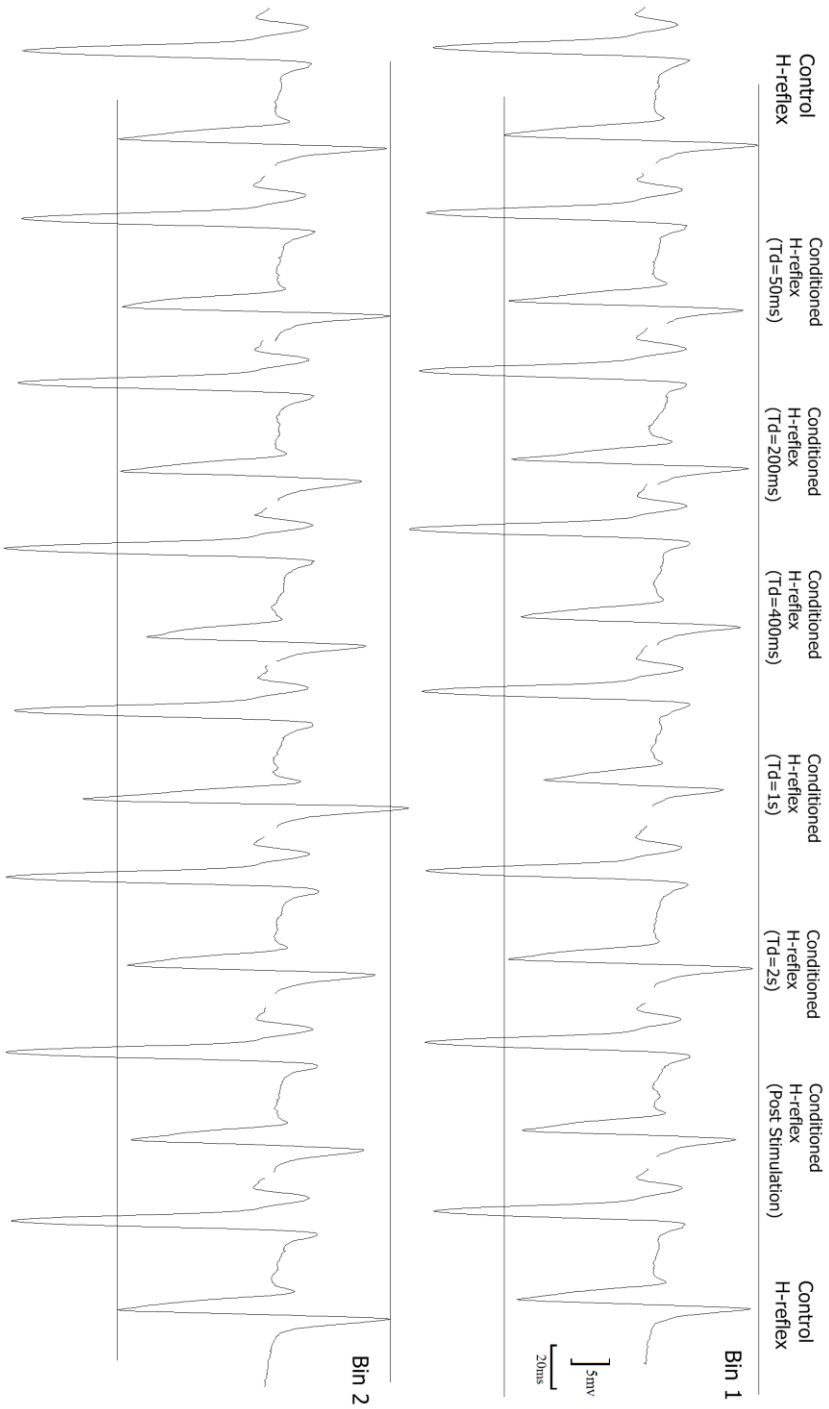


Figure 4-18. Raw EMG data recorded from one subject. This figure shows examples of the un-averaged conditioned soleus M and H-waves evoked at different latencies relative to the stimulus onset (Td). The plotted data show H-waves recorded from 2 out of 30 applied bins (see Figure 4-6). The first and the last H-waves at each bin shows the control (unconditioned H-wave) H-waves in the selected bin. Two parallel horizontal lines show the peak to peak amplitude of the control H-waves at the beginning and the end of the selected bins and show consistent control H-reflex amplitude. All the recorded H-waves also have consistent M-wave size.

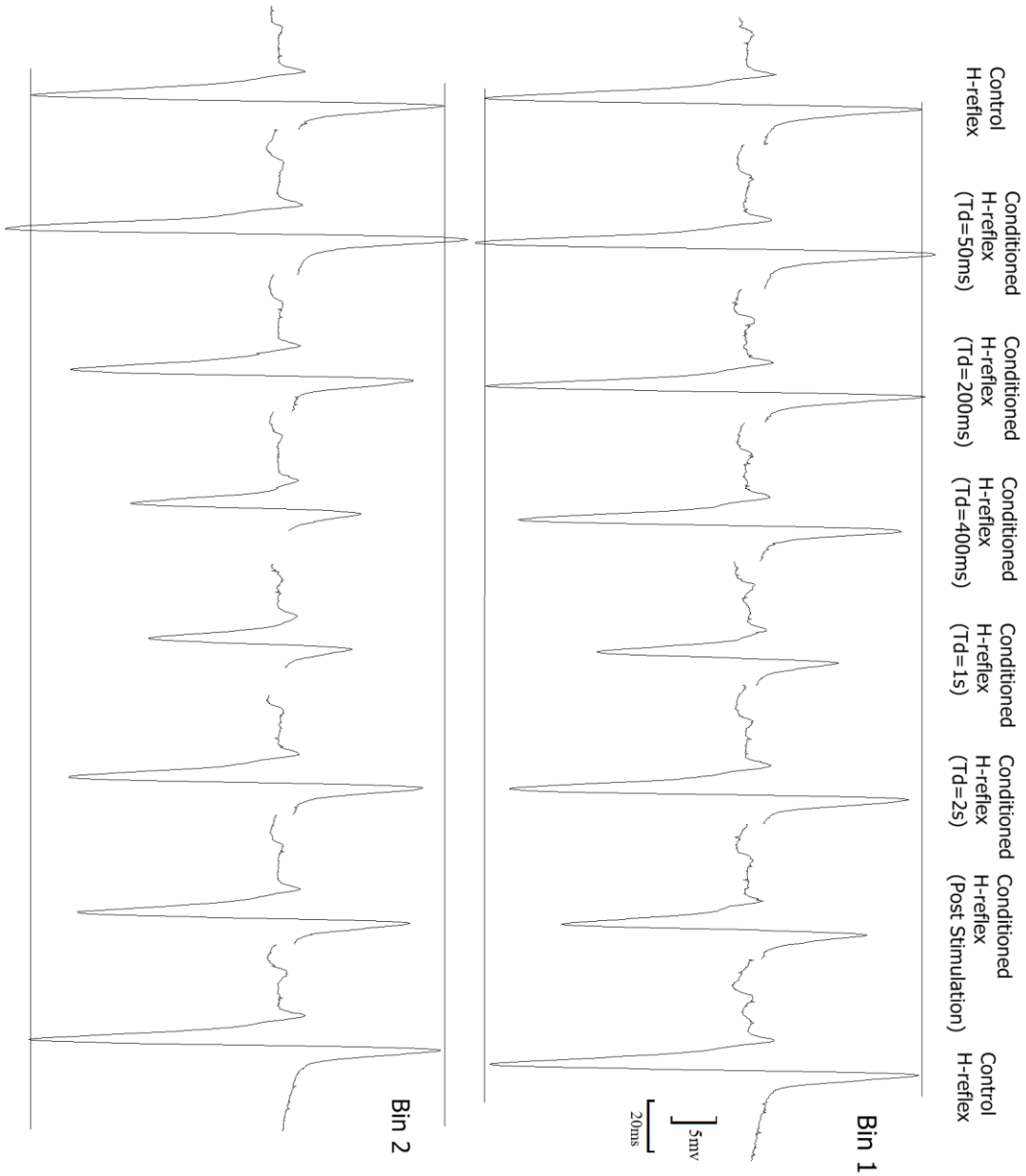


Figure 4-19. Raw EMG data recorded from one subject. This figure shows examples of the un-averaged conditioned soleus M and H-waves evoked at different latencies relative to the stimulus onset (Td). The plotted data show H-waves recorded from 2 out of 30 applied bins (see Figure 4-6). The first and the last H-waves at each bin shows the control (unconditioned H-wave) H-waves in the selected bin. Two parallel horizontal lines show the peak to peak amplitude of the control H-waves at the beginning and the end of the selected bins and show consistent control H-reflex amplitude. All the recorded H-waves also have consistent M-wave size.

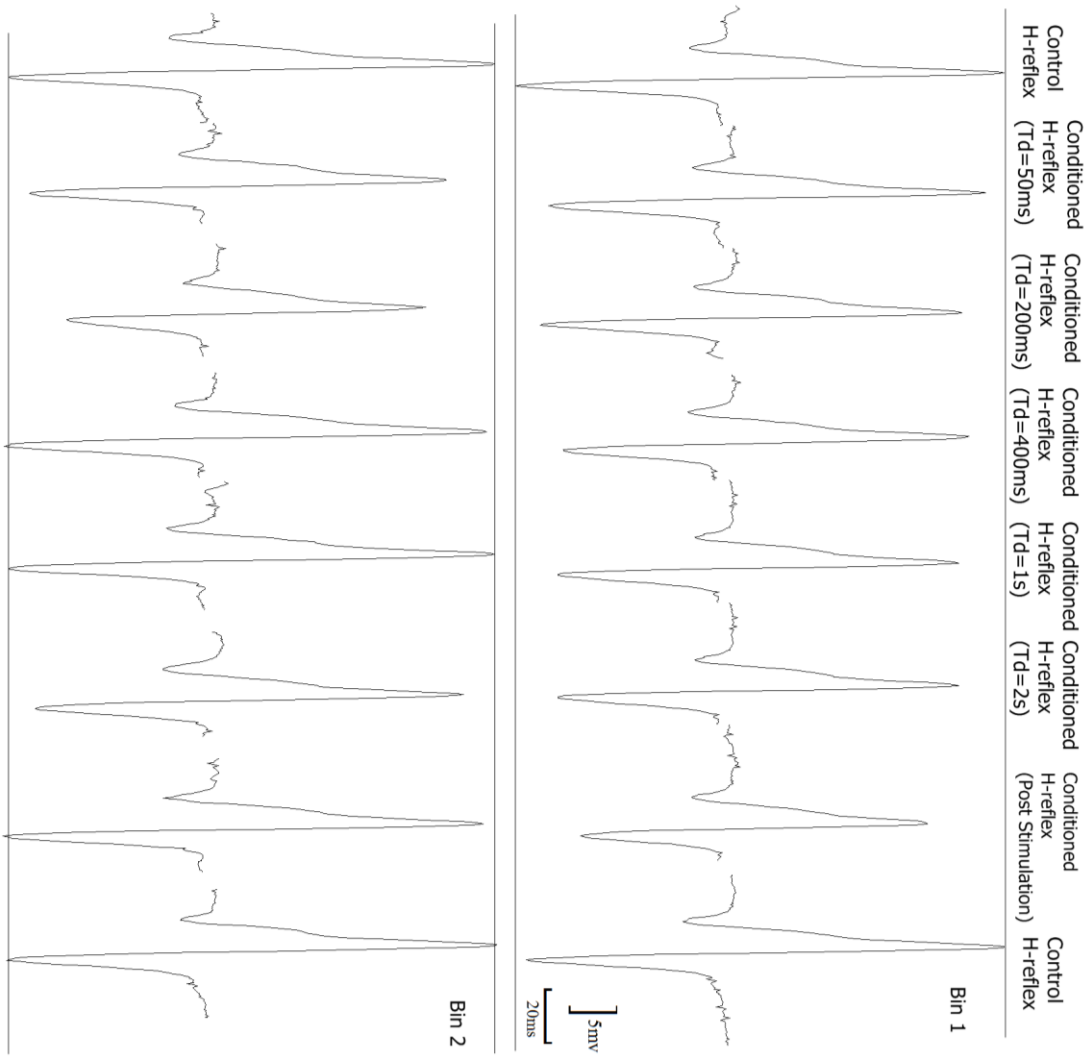


Figure 4-20. Raw EMG data recorded from one subject. This figure shows examples of the un-averaged conditioned soleus M and H-waves evoked at different latencies relative to the stimulus onset (T_d). The plotted data show H-waves recorded from 2 out of 30 applied bins (see Figure 4-6). The first and the last H-waves at each bin shows the control (unconditioned H-wave) H-waves in the selected bin. Two parallel horizontal lines show the peak to peak amplitude of the control H-waves at the beginning and the end of the selected bins and show consistent control H-reflex amplitude. All the recorded H-waves also have consistent M-wave size.

Mean±95%CI of the normalized averaged conditioned H-reflexes of each volunteer grouped based on the conditioning time delay intervals (Td) are shown in Figure **4-21**. Figure **4-22** presents the averaged data grouped based on subjects. A considerable variation in H-reflex amplitude is observed across each subject however, despite this variability significant depression of the H-reflex is observed for at least one stimulation conditioning interval between 200ms and 1000ms for all subjects as assessed by paired T-test.

Data were grand averaged across all subjects and the grand averaged result is presented in Figure **4-23**. The paired sample T-test was used to test whether or not there is any statistically significant difference between the mean value of the grand averaged control H-reflex and the averaged conditioned H-reflexes when data was averaged across all subjects. T-test suggests that the maximum inhibition, equivalent to a 15% reduction in H-reflex size occurs at Td=400ms. The results of paired sample T-test analysis are presented Table 4.3.

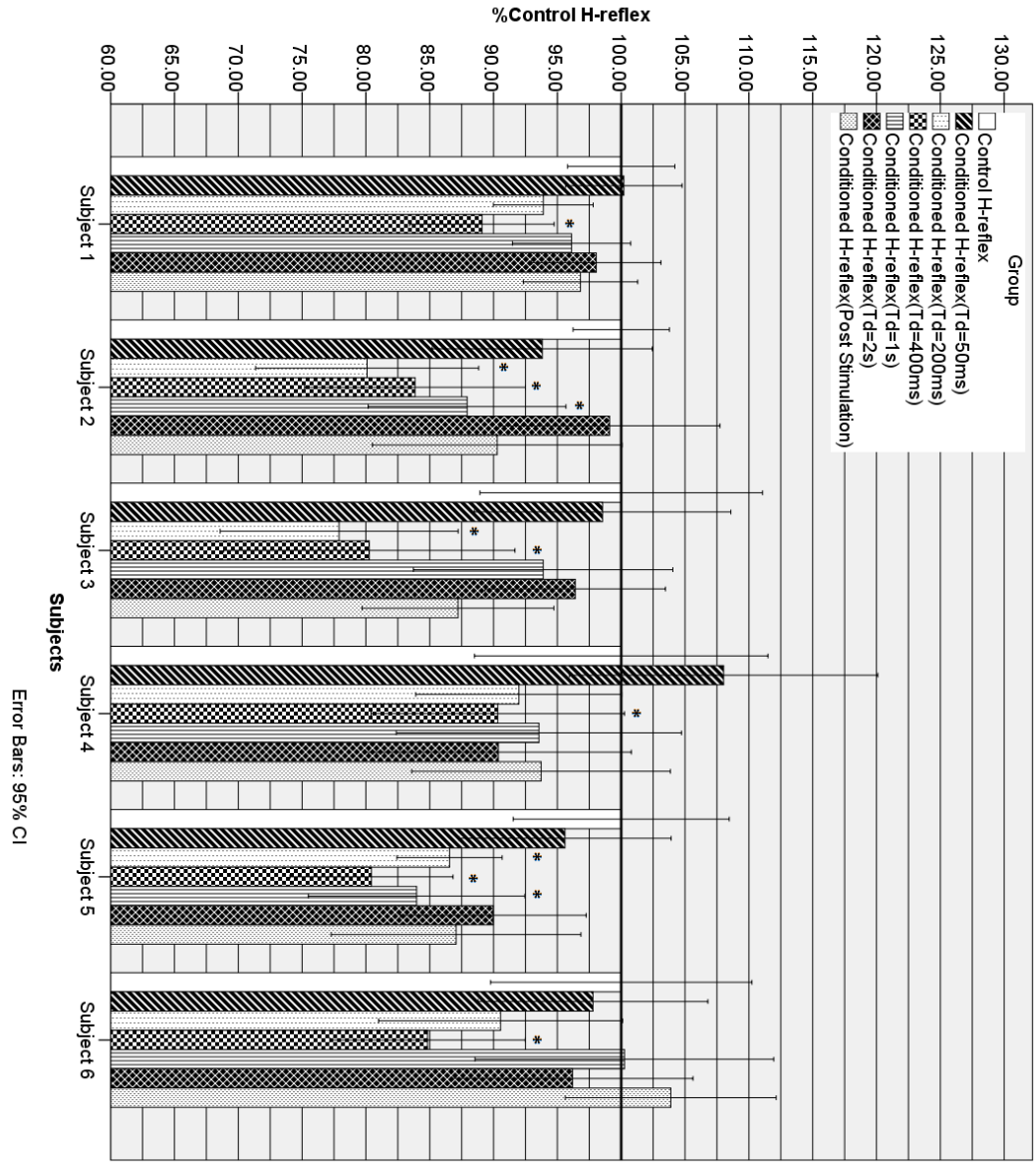


Figure 4-21. Bars showing the effect of plantar vibrotactile cutaneous stimulation delivered to the first metatarsus region (subject are standing) at different Td intervals. For each Td interval tested, the overall average size of the conditioned SOL H-reflex is presented as a percentage of the overall average control size (mean ±95%CI). Asterisks indicate statistically significant differences between the control H-reflex and the conditioned H-reflex sizes (*$p < 0.05$).

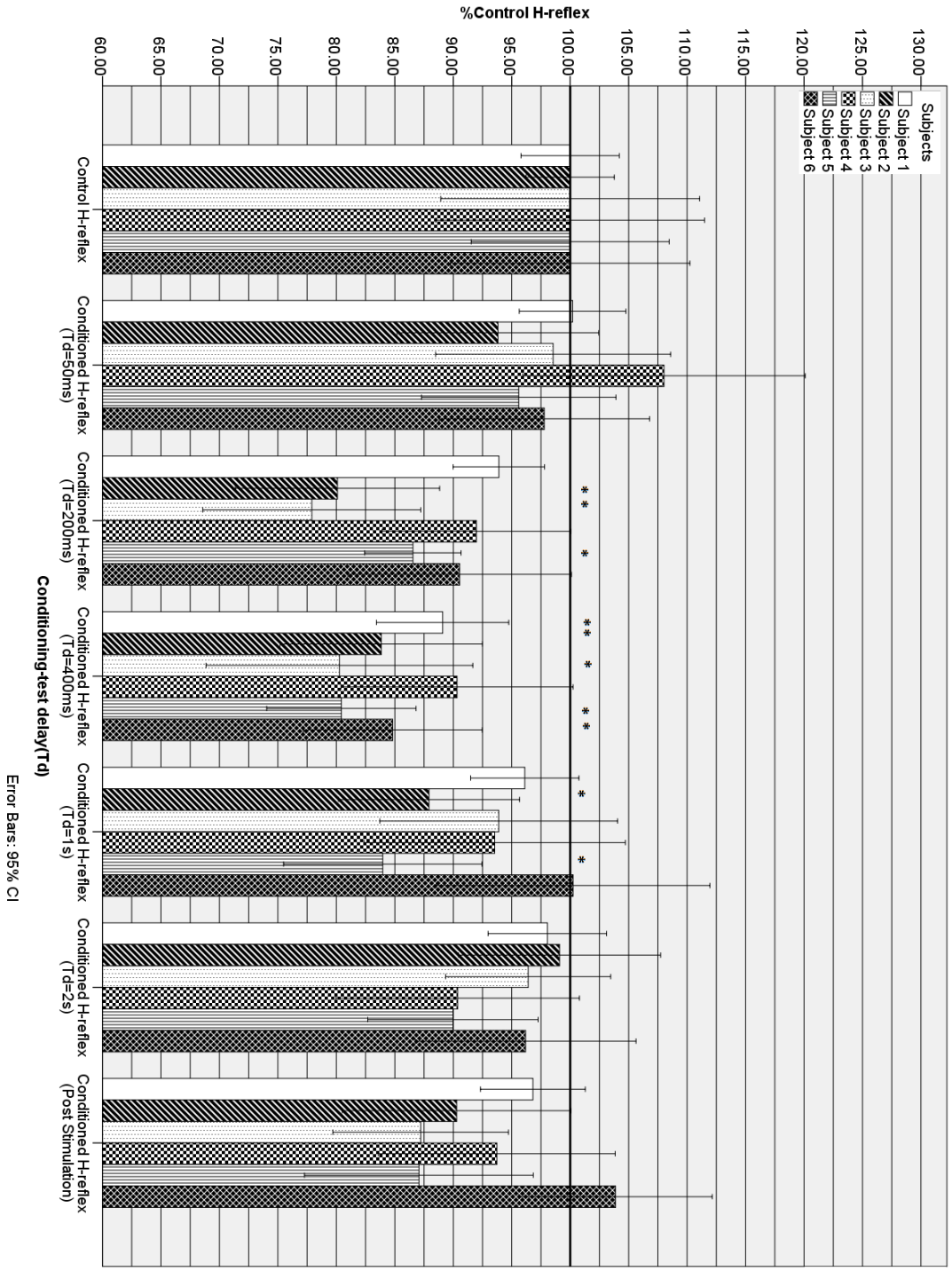


Figure 4-22. The magnitude of the conditioned and control H-waves recorded from 8 subjects grouped based on subjects. Data are normalized to the averaged control H-reflex size.

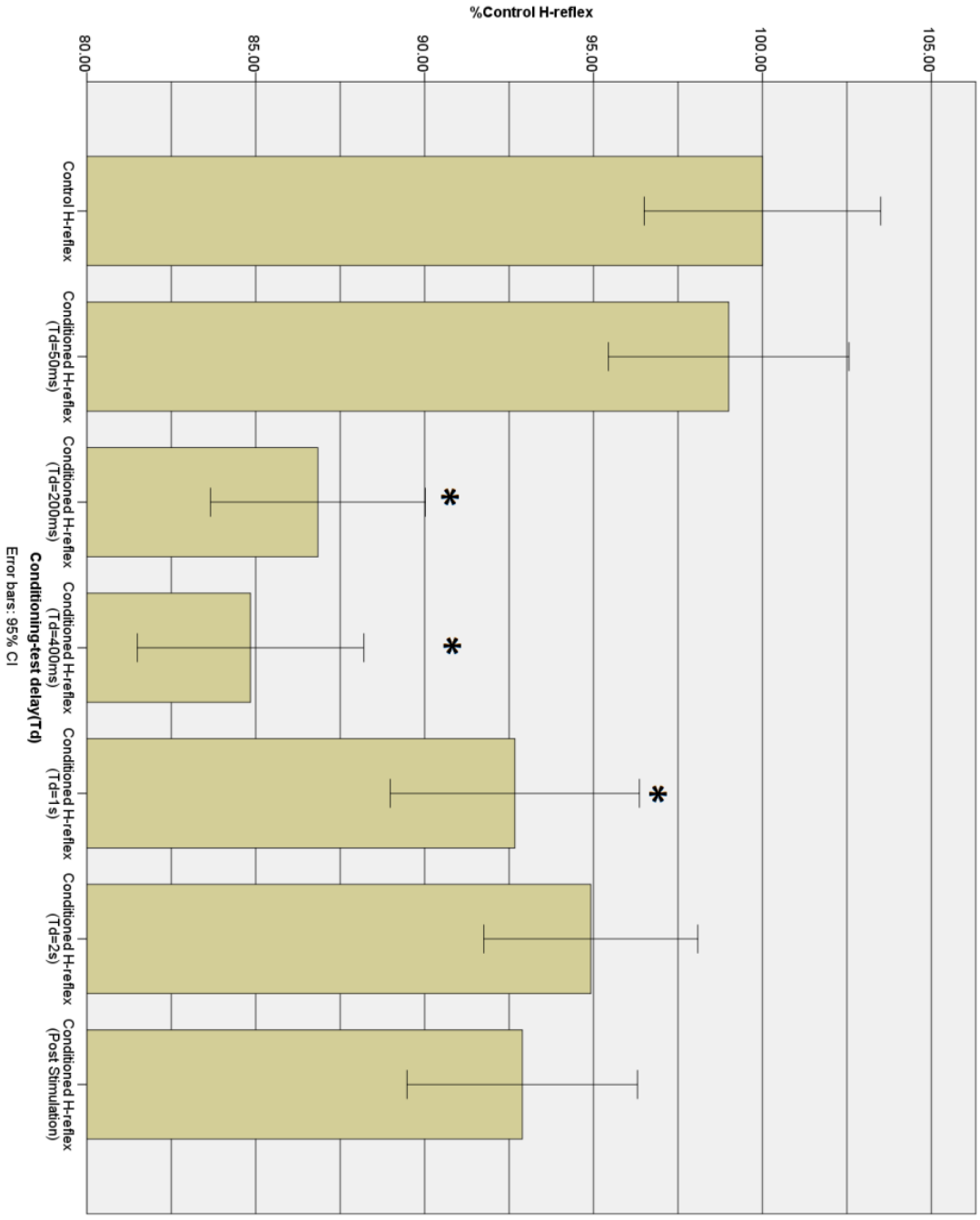


Figure 4-23. Mean ±95%CI of the normalized H-waves averaged across 8 subjects. A significant (*p<0.05) reduction in the H-reflex size exist between the unconditioned H-reflex (control H-reflex) and the conditioned H-reflexes at Td=200ms, 400ms, 1s and 2s when data averaged across all subjects. A small facilitation is also observed at T_d=50 which is not significant. Asterisks indicate statistically significant differences between the control H-reflex and the conditioned H-reflex sizes when data averaged across subjects (*p < 0.05).

Table 4.3. Paired sample T-test reveals that conditioned H-reflexes are statistically significantly different in mean from the unconditioned H-reflex (control H–reflex) at T_d= 200ms, 40ms, and 1s. The significant pairs are **bolded** in this table.

Pairwise Comparisons						
pairs		Mean Difference	Std. Error	Sig.	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
Control H-reflex	Conditioned H-reflex (Td=50ms)	-.698	2.510	1.000	-8.458	7.062
	Conditioned H-reflex (Td=200ms)	**11.983***	**2.535**	**0.000**	**4.146**	**19.821**
	Conditioned H-reflex (Td=400ms)	**14.837***	**2.385**	**0.000**	**7.464**	**22.211**
	Conditioned H-reflex (Td=1s)	**8.022***	**2.562**	**0.044**	**.101**	**15.943**
	Conditioned H-reflex (Td=2s)	5.010	2.293	0.640	-2.079	12.100
	Conditioned H-reflex (Post Stimulation)	7.188	2.403	0.068	-.242	14.618
*. The mean difference is significant at the .05 level.						

4.5.6 Group Comparison

The one-way analysis of variance (ANOVA) with interaction of postural position (sitting and quite standing) × conditioned H-reflex measurement delay (Td=50ms, 200ms, 400ms, 1s, 2s and post stimulation) was used to determine whether the conditioned H-reflex values are significantly different when the grand averaged data are compared across all groups. Data were normally distributed as assessed by Shapiro-Wilk's test of normality and the assumption of homogeneity of variances was violated in all cases, as assessed by Levene's Test of homogeneity of variance so we use Welch ANOVA to analysis the data. Based on Welch's ANOVA table (Table 4.4) there is a significant change in the mean values of the conditioned H-waves at some conditioning time delay intervals (Td) when data are compared across different groups. These results are presented in Figure **4-24** and summarized in Table 4.4.4.

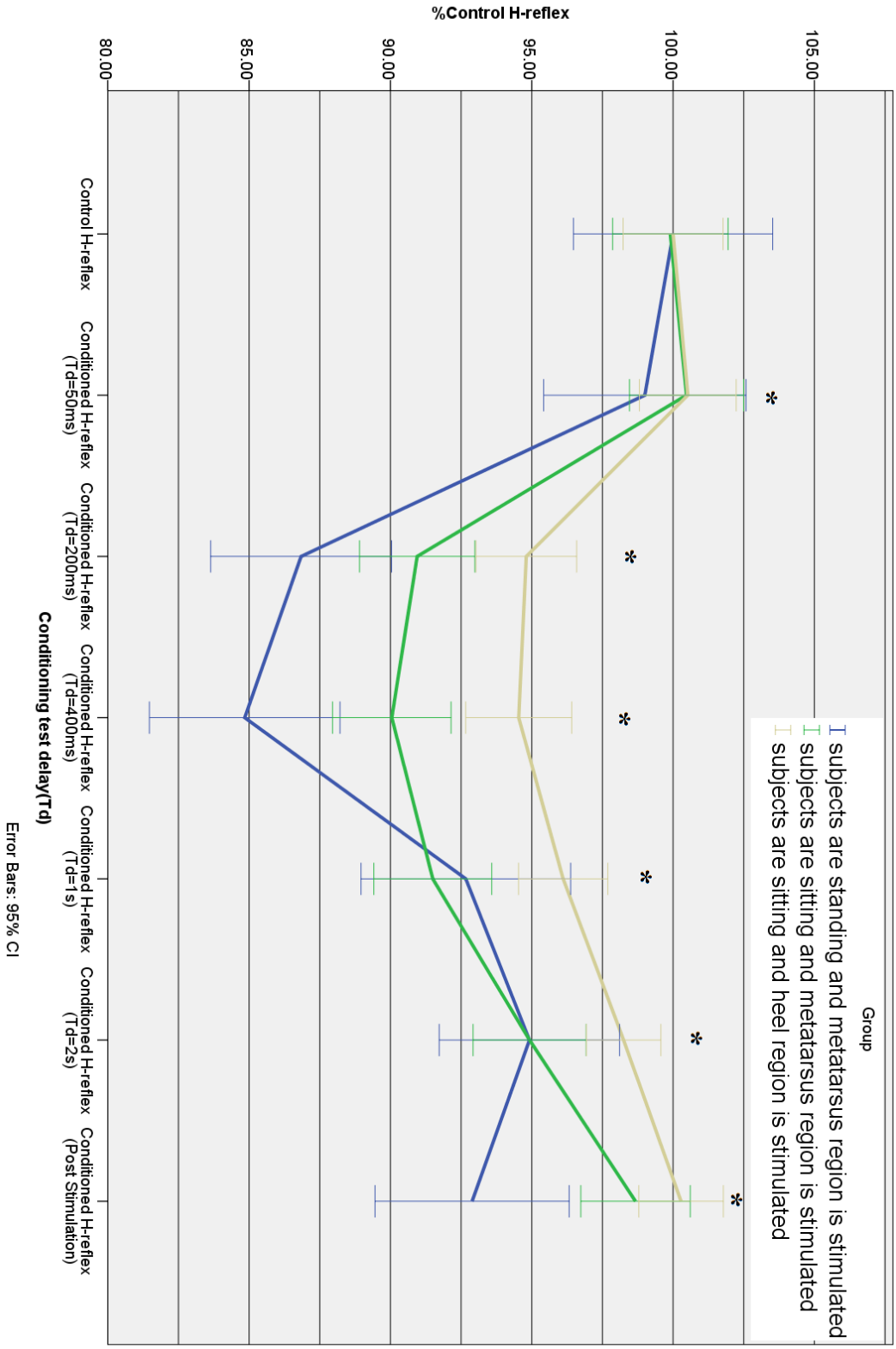


Figure 4-24. Mean ±95%CI of the grand averaged normalized H-waves in all groups.

Table 4.4. The results of the one-way ANOVA test. The mean values of the grand averaged conditioned H-waves are compared according to the T_d measurement time in each group. The significant pairs are **bolded**. "SM" means subjects are standing and the first metatarsus head is stimulated. "M" means subjects are sitting and the first metatarsus head is stimulated and "H" means subjects are siting and heel region is stimulated.

Multiple Comparisons							
Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Conditioned H-reflex (Td=50ms)	SM	M	-2.42543	2.08271	.475	-7.3354	2.4845
		H	**-6.59137***	**2.01080**	**.003**	**-11.3350**	**-1.8478**
	M	SM	2.42543	2.08271	.475	-2.4845	7.3354
		H	**-4.16595***	**1.43876**	**.011**	**-7.5495**	**-.7824**
	H	**SM**	**6.59137***	**2.01080**	**.003**	**1.8478**	**11.3350**
		M	**4.16595***	**1.43876**	**.011**	**.7824**	**7.5495**
Conditioned H-reflex (Td=200ms)	SM	M	-2.42543	2.08271	.475	-7.3354	2.4845
		H	**-6.59137***	**2.01080**	**.003**	**-11.3350**	**-1.8478**
	M	SM	2.42543	2.08271	.475	-2.4845	7.3354
		H	**-4.16595***	**1.43876**	**.011**	**-7.5495**	**-.7824**
	H	**SM**	**6.59137***	**2.01080**	**.003**	**1.8478**	**11.3350**
		M	**4.16595***	**1.43876**	**.011**	**.7824**	**7.5495**
Conditioned H-reflex (Td=400ms)	SM	M	-4.74669	2.14893	.072	-9.8127	.3193
		H	**-9.27103***	**2.07643**	**.000**	**-14.1693**	**-4.3728**
	M	SM	4.74669	2.14893	.072	-.3193	9.8127
		H	**-4.52434***	**1.49084**	**.007**	**-8.0304**	**-1.0183**
	H	**SM**	**9.27103***	**2.07643**	**.000**	**4.3728**	**14.1693**
		M	**4.52434***	**1.49084**	**.007**	**1.0183**	**8.0304**
Conditioned H-reflex (Td=1s)	SM	M	.49112	2.32159	.976	-4.9844	5.9667
		H	-3.73100	2.17719	.203	-8.8737	1.4117
	M	SM	-.49112	2.32159	.976	-5.9667	4.9844
		H	**-4.22212***	**1.37322**	**.006**	**-7.4524**	**-.9918**
	H	SM	3.73100	2.17719	.203	-1.4117	8.8737
		M	**4.22212***	**1.37322**	**.006**	**.9918**	**7.4524**
Conditioned H-reflex (Td=2s)2	SM	M	-.12339	2.00903	.998	-4.8594	4.6126
		H	-3.56464	1.84535	.133	-7.9227	.7934
	M	SM	.12339	2.00903	.998	-4.6126	4.8594
		H	**-3.44125***	**1.26680**	**.019**	**-6.4216**	**-.4609**
	H	SM	3.56464	1.84535	.133	-.7934	7.9227
		M	**3.44125***	**1.26680**	**.019**	**.4609**	**6.4216**
Conditioned H-reflex (Post Stimulation)	SM	**M**	**-5.77888***	**2.10822**	**.018**	**-10.7501**	**-.8076**
		H	**-7.54143***	**1.97025**	**.001**	**-12.1943**	**-2.8885**
	M	**SM**	**5.77888***	**2.10822**	**.018**	**.8076**	**10.7501**
		H	-1.76255	1.29806	.364	-4.8160	1.2909
	H	**SM**	**7.54143***	**1.97025**	**.001**	**2.8885**	**12.1943**
		M	1.76255	1.29806	.364	-1.2909	4.8160

*. The mean difference is significant at the 0.05 level.

4.5.7 Summary

In these experiments the effects of localised vibrotactile stimulation on SOL H-reflex was measured on 23 healthy subjects. The H-reflex modulation was measured when subjects were sitting and standing and vibrotactile stimuli at different duration was applied to heel and right metatarsus regions of the sole. The finding show that vibrotactile stimulation of the metatarsus heads generates greater H-reflex inhibition

compare to heel stimulation. This could be due to greater number of cutaneous receptors located at metatarsus heads. The H-reflex inhibition is also enhanced when subjects are standing compare to sitting. This suggests that there are other factors that may be influencing the H-reflex size during standing. Applying vibrotactile stimuli at varying duration also suggest that H-reflex is more depressed when stimuli duration is between 200ms and 1s. This could also be due to adaptation for longer vibration durations (>1s). Probably continues stimulation of the foot mechanoreceptors for more than 1s generates some adaptation in the spinal or supra spinal mechanism which will then change the sensitivity of the ankle reflex pathway to the vibrotactile stimulation.

4.6 Conditioning Effects of Plantar Vibration on H-Reflex during Body Weight Support Treadmill Walking

4.6.1 Introduction

The aim of this experiment was to investigate the modulation of the soleus H-reflex caused by phase dependent localized vibratory conditioning stimuli applied during treadmill walking in 12 healthy subjects. The modulation of SOL H-reflex during treadmill walking with 0% and 25% unloading using a harness system was studied to understand if vibration stimulation can more profoundly inhibit soleus H-reflex when higher percentage of body weight support is used.

4.6.2 Method

The test soleus H-reflex was obtained by tibial nerve stimulation in the popliteal fossa via a constant-current electrical stimulator (DS7AH). The entire recording setup and electrode placement was similar to previous experiments.

Subjects were asked to stand and the H-reflex recruitment curve was determined for each subject. The stimulation intensity was then adjusted to yield a minimally detectable M-wave or M-wave response of 10%±3% M_{max} (Phadke et al., 2007) (Fung & Barbeau, 1994). During the experiments, M-waves were measured

online during the experiment and the stimulation intensity was adjusted if necessary to obtain the same and constant M-wave size (Phadke et al., 2007).

FSR were place in the shoe to monitor the cycle duration, defined as the averaged time interval from one heel contact to the next. H-reflexes were measured at two discrete phases of the gait cycle: early midstance (just after foot flat) and late midstance (just before heel off).

Experiment consisted of 4 different scenarios all tested in single test section. Subjects step continuously over treadmill for ~40 minutes and experience exposure to different conditioned H-reflex measurement and body weight support. Each scenario tested for 10-12 minutes with >2 minutes break (normal unperturbed walking) between tests. The scenarios were randomized to minimise the history effect (Cotey D, 2009). The 4 scenarios including:

1. Subjects were asked to walk on the treadmill without any body weight support and the conditioned and control H-reflexes was measure in early midstance.
2. Subjects were asked to walk on the treadmill with 25% body weight support and the H-reflex was measured during early midstance.
3. Subjects were asked to walk on the treadmill without any body weight support and the H-reflex was measure at late midstance.
4. Subjects were asked to walk on the treadmill with 25% body weight support and the H-reflex measure at late midstance.

The experiments were performed on a manual treadmill with a harness support system. Subjects were fitted in to the harness support system using adjustable straps at the trunk, pelvis and lower limbs. An independent pulley system provided weight support through the harness over the treadmill. All subjects were support approximately by 25% and 0% of their body weight with treadmill speed set at ~1mph. subjects were asked not to use their arms to support their weight. All subjects were instructed to walk on treadmill at low speed but majority of them found low speed walking uncomfortable. Subjects were asked to walk as naturally as possible without dragging their feet.

The conditioning vibrotactile stimuli were generated and delivered using the vibrating insole which was placed in the subjects' right shoe. The vibrating insole can generate phase dependent vibratory stimulation to the sole as described before. Conditioning stimuli were generated using 3 vibrators placed at heel and the two metatarsus heads. The vibrotactile stimuli were applied to the sole during the stand phase of walking. The duration of the vibration stimuli depended on the duration of foot ground contact. The vibrator which was placed at heel was activated from the heel strike to heel off. Two vibrators placed at metatarsus heads were activated from foot flat to toe off. Note that small differences in measuring heel contact time and the actual heel contact could occur due to changes in the walking pattern and motion of subjects on the treadmill. This is enhanced when body weight support is used. On average every subjects received 2.4±0.3s heel stimulation and 0.9±0.2s metatarsus head stimulation when H-reflex was measure at late-midstance. The subjects' heel region was also stimulated for 1±0.3s and the metatarsus heads were stimulated for 650±200ms when H-reflex is measured at early-midstance.

Figure **4-25** shows the way vibrators are switched on and off during treadmill walking. The vibrotactile stimuli were applied to the subjects' foot every 4 cycles. The control H-waves (unconditioned H-reflex) were measured 2 gait cycles after measuring the conditioned H-reflex. One gait cycle was delayed between measuring the conditioned H-reflex and the control H-reflex to avoid repetitive reflex activation. Using this method there will be at least 8 second delays between consecutive H-reflex measurements. This procedure is shown in Figure **4-26**. The treadmill speed was set to 1.6km/h during all 4 experiments.

Some of the subjects couldn't finish all the 4 scenarios due to some technical issues or difficulty with maintenance of walking with body weight support.

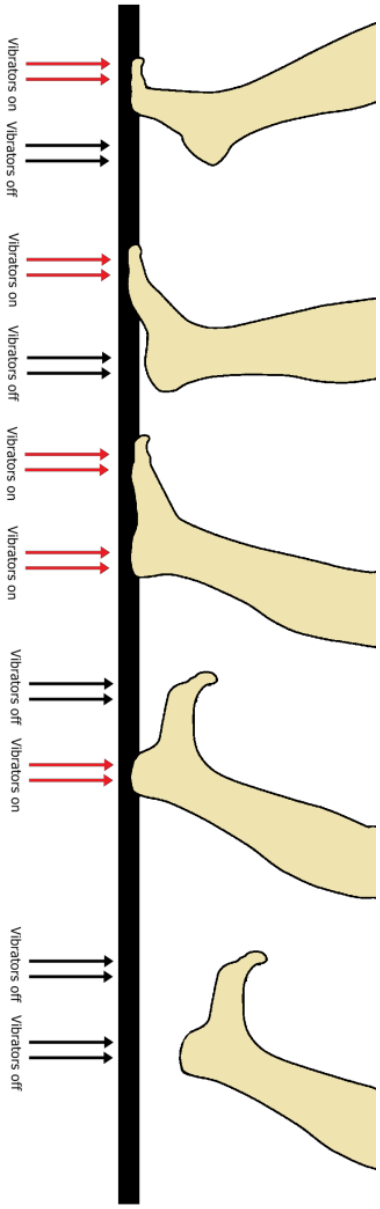


Figure 4-25. The conditioning vibrotactile stimuli was generated and delivered using the vibrating insole which was placed in the subjects' right shoe. The vibrating insole can generate phase dependent vibratory stimulation to the sole. One vibrator was placed at heel and two vibrators were placed at first and fith metatarsus heads. Vibrators switched on and off depending on the gait phase.

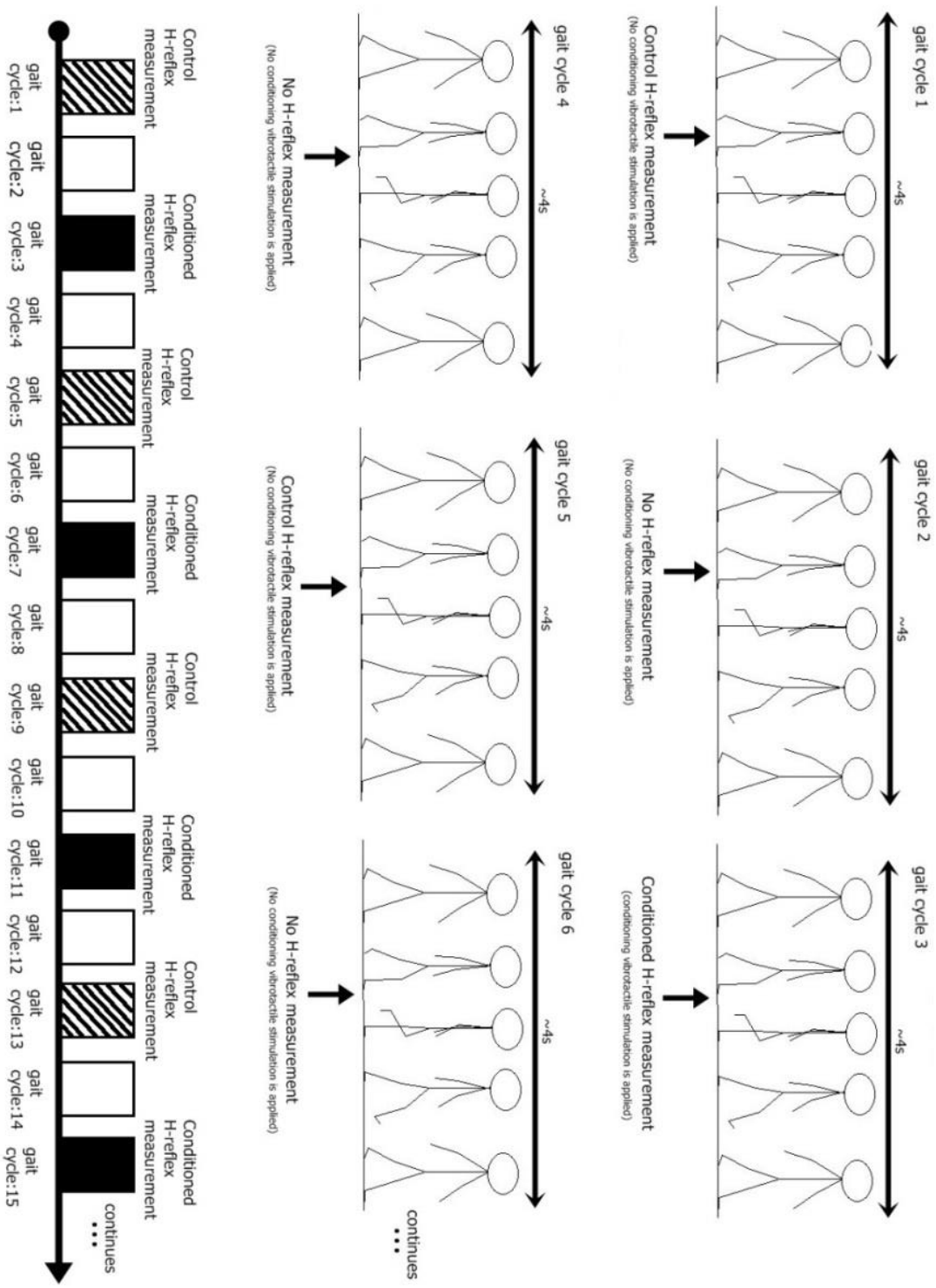


Figure 4-26. During treadmill walking, the H-reflex was elicited every 2 gate cycles and the conditioning vibrotactile stimuli were applied every 4 gait cycles. H-reflex was measure at late-midstance or early-midstance phases depending on the examined scenarios.

4.6.3 Results

Figure **4-27**, show 70s intervals selected from the raw EMG data recorded from 3 different subjects. Control and conditioned H-waves are plotted side by side in each figure for better comparison. A clear inhibition can be observed when the conditioned H-waves are compared with the adjacent control H-reflexes. Similar patterns of high variance were also observed in all the subjects during this experiment which can also be observed in Figure **4-27**.

Mean±95%CI of the normalized H-reflexes averaged across individual subjects are shown in Figure **4-28** and Figure **4-29**. A clear inhibition can be observed from the averaged data when H-reflex is conditioned with vibratory stimuli during treadmill walking. The grand averaged data also suggests that 25% body weights support evokes greater (but not significant) inhibition of the conditioned H-wave in both mid-stance and late-midstance. Paired sample T-test shows that there is a statistically significant change in the mean values of the conditioned H-reflex compared to the corresponding control H-reflex in some subjects which is shown by asterisk in Figure **4-28**. Figure **4-29** present the results when data are grouped based on subjects.

Data were also averaged across all subjects and the grand averaged results are shown in Figure **4-30**. A significant (*$p<0.05$) reduction in the H-reflex size exist between the corresponding unconditioned H-reflex (control H-reflex) and the conditioned H-reflexes in each scenario tested when data averaged across subjects. The grand averaged data suggests that vibratory stimulation has inhibitory effect in the early midstance and late midstance phases of walking. When 25% body weight support is used the level of inhibition is increased slightly (but not significantly), a result which is more prominent in late midstance. These results are summarized in Table 4.5.

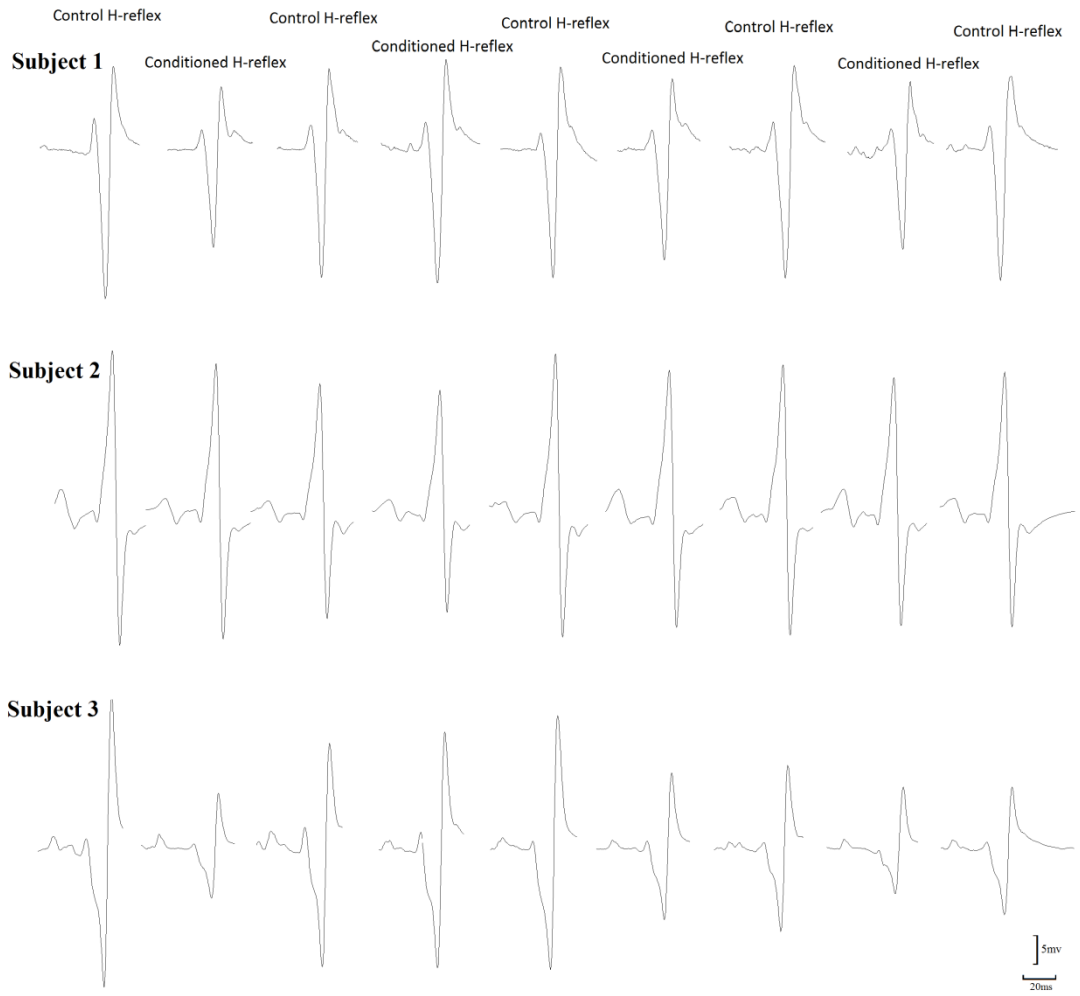


Figure 4-27. Raw EMG data recorded from 3 different subjects. This figure shows examples of the conditioned and control soleus H-waves and M-waves evoked during treadmill walking. The plotted data shows a 70s continues recoded EMG data.

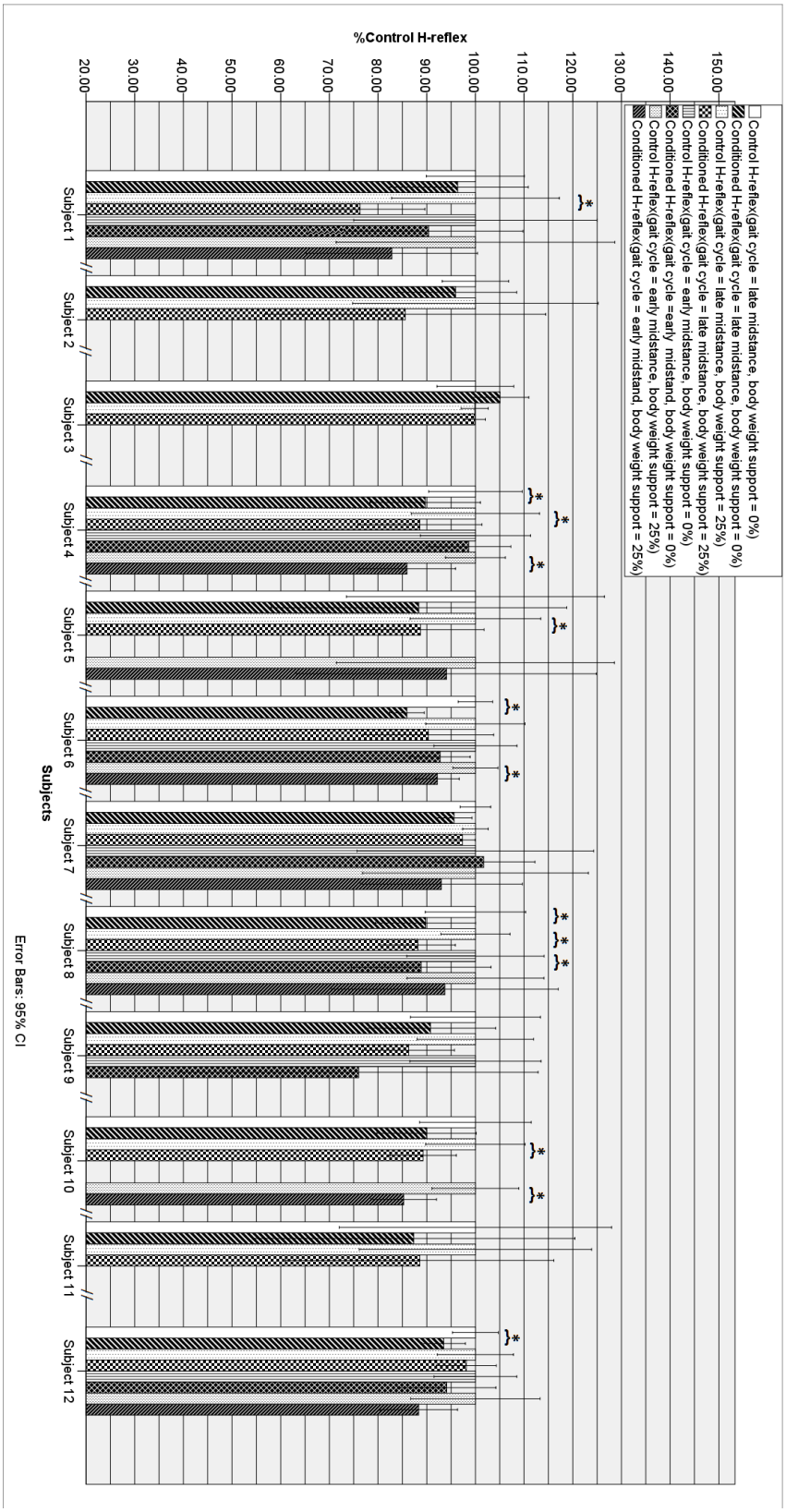


Figure 4-28. Bars showing the effect of plantar vibrotactile cutaneous stimulation delivered to foot sole when subjects walking at treadmill. SOL H-reflex is presented as a percentage of the overall average control size (mean ±95%CI). Asterisks indicate statistically significant differences between the control H-reflex and the conditioned H-reflex sizes (*$p < 0.05$).

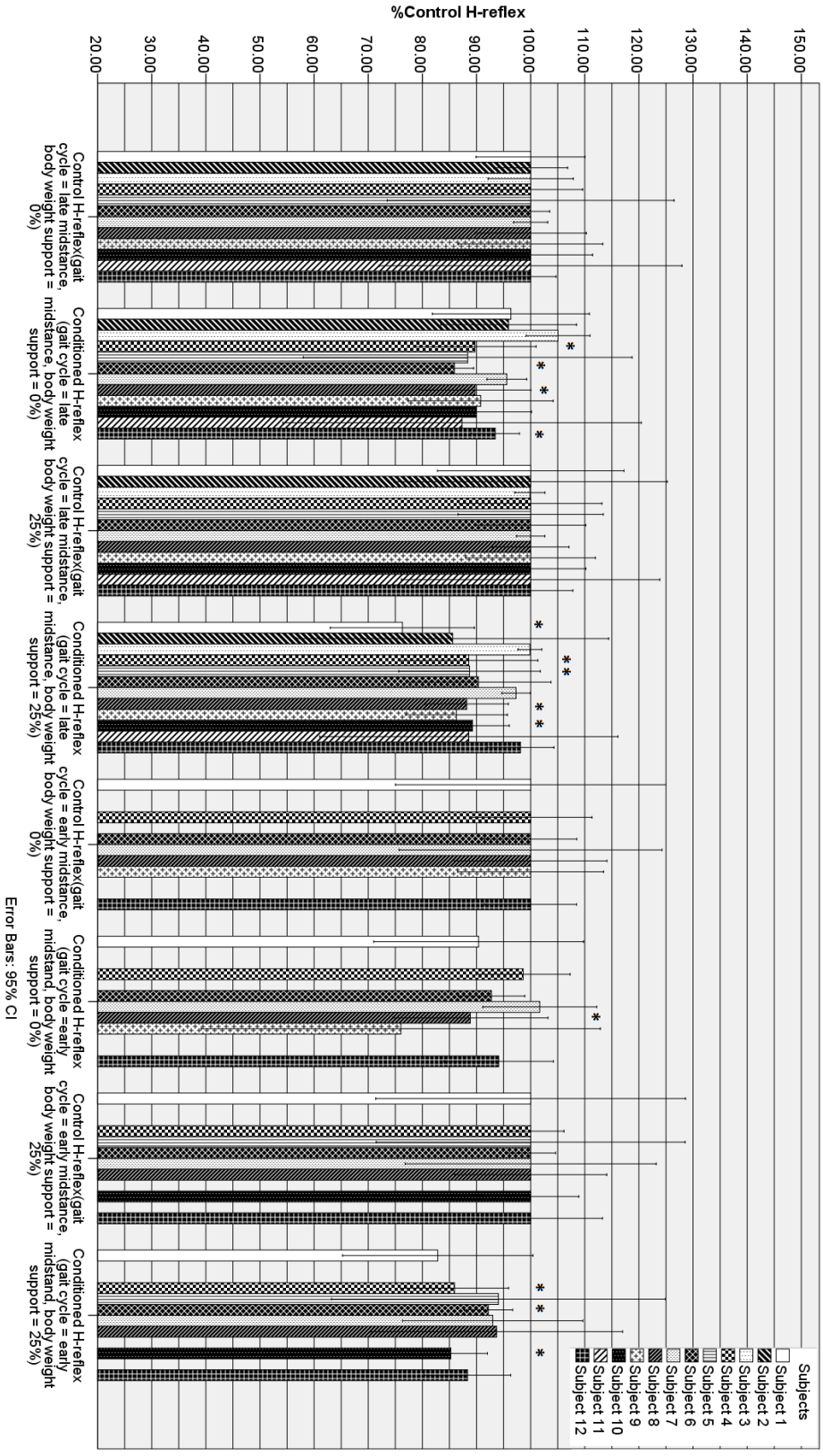


Figure 4-29. Bars showing the effect of plantar vibrotactile cutaneous stimulation delivered to foot sole when subjects walking at treadmill. SOL H-reflex is presented as a percentage of the overall average control size (mean ±95%CI).

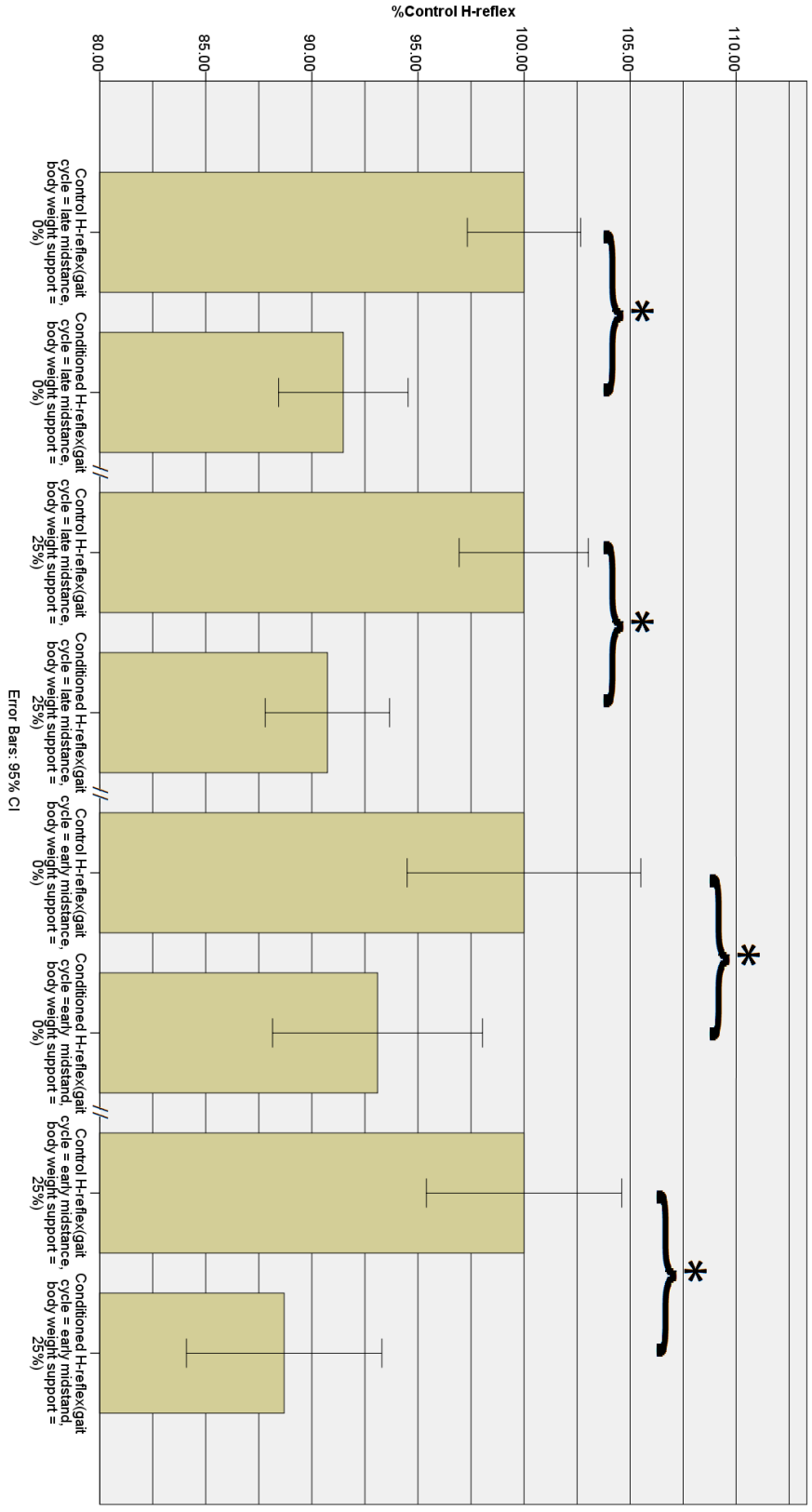


Figure 4-30. Mean ±95%CI of the normalized H-waves averaged across all subjects. Bars present the grand averaged data in 4 different tested scenarios. A significant (*p<0.05) reduction in the H-reflex size exist between the unconditioned H-reflex (control H-reflex) and the conditioned H-reflexes in all cases.

Table 4.5. Paired sample T-test reveals that grand averaged conditioned H-reflexes are statistically significantly different in mean from the corresponding unconditioned H-reflex (control H–reflex) in all tested scenarios.

Paired Samples Test

Pairs		Paired Differences			Sig. (2-tailed)
		Mean	95% Confidence Interval of the Difference		
			Lower	Upper	
Pair 1	Control H-reflex - Conditioned H-reflex (measurement phase: late midstance, bodyweight support = 0%)	7.29828	3.54176	11.05480	.000
Pair 2	Control H-reflex - Conditioned H-reflex (measurement phase: late midstance, bodyweight support = 25%)	12.13617	7.12713	17.14520	.000
Pair 3	Control H-reflex - Conditioned H-reflex (measurement phase: early midstance, bodyweight support = 0%)	8.20521	1.38587	15.02455	.019
Pair 4	Control H-reflex - Conditioned H-reflex (measurement phase: early midstance, bodyweight support = 25%)	10.25771	4.23598	16.27944	.001

4.6.4 Summary

The modulation of the soleus H-reflex caused by phase dependent localized vibratory conditioning stimuli applied during treadmill walking with 0% and 25% unloading using a harness system was studied. Most subjects showed a significant H-reflex inhibition during foot stimulation at late and mid stance phase of the gait with both 0% and 25% weight loading. This suggests that stimulating foot using vibration is more effective during the late-midstance phase than the early-midstance phase. The cause for this could be related to longer vibration stimulation duration applied to the subject foot during late-midstance H-reflex measurements. The grand average data suggests that H-reflex is more depressed when 25% of the subjects' body weight is unloaded but this different is not statistically significant.

4.7 Conditioning Effects of Plantar Vibration at Different Frequencies and Amplitudes on H-Reflex Modulation

4.71 Aims and Objectives

In previous studies we demonstrated that vibrotactile stimuli applied to the localized sites on the foot sole produce a clear inhibitory actions on the segmental H-reflex in healthy subjects. Vibration to the plantar surface beneath the first metatarsal head

evokes a greater depression of the soleus H-reflex than seen when the vibration is applied to the heel region. The maximum depression of the conditioned H-reflex can be seen to occur when the conditioned H-reflex is measured 200-400ms relative to time of stimulation onset. The depression magnitude is also enhanced when subjects are standing. In this study we wanted to investigate whether changing the amplitude and frequency of the localized vibrotactile stimuli can affect the soleus H-reflex excitability in the healthy subjects. We applied vibration stimuli to the plantar surface of the foot (first metatarsus head) in 7 healthy subjects. Vibration pulses of 1s in width at 2x, 3x and 4x the sensation level at different frequencies (150Hz, 220Hz and 320Hz) were applied randomly to the subjects' foot. The conditioned H-reflexes were measured at 400ms relative to time of stimulation onset.

4.7.2 Method

The C-2 tactor vibrators were used in this experiment. This transducer uses a moving magnet linear actuator to produce stimuli to the foot. Using C-2 tactor it is possible to change both amplitude and frequency simultaneously and independently. The C-2 tactor was installed on an insole. Subjects were asked to stand in a relax position and the vibrating insole was inserted beneath their right foot. The experiment took 60 minutes and subjects were asked to avoid doing any unnecessary upper body or lower body movement during the experiment. H-reflex measurement and EMG data recording were similar to the previously described experiments. All the statistical analysis was performed in SPSS similar to the previous experiments.

4.7.3 Conditioning Vibratory Stimulation

A series of vibration pulses of 1s in width were used to stimulate the first metatarsus head while subjects were standing. These conditioning vibratory stimuli were grouped as 9 conditioning stimuli surrounded by two controls H-reflex with 8s delay between them. This block (bin) was delivered to the subjects' foot 30 times during an hour (see Figure **4-31**). In each block, the conditioned H-reflexes were measured at 400ms relative to time of stimulation onset (Td=400ms). The frequency and the

amplitude of the vibrotactile stimuli were assigned randomly in each block. Vibration stimuli were applied at 2x, 3x and 4x the sensation level at 150Hz, 220Hz and 320 Hz.

4.7.4 Results

Figure **4-32** shows a data segment of 90s selected from the raw EMG data recorded from 3 different subjects. The H-waves are plotted side by side in each figure for better comparison. Inhibitory effects can be observed when vibrotactile stimulation at different frequencies/amplitudes is applied to the subjects' feet. Two parallel dashed lines also show the peak to peak amplitude of the control H-waves at the beginning and end of the select bin. All the H-waves also have similar M-wave size.

Data were averaged across individual subject and the mean±95%CI of the normalized averaged conditioned and control H-reflexes grouped based on the conditioning vibrotactile stimulation and subjects are shown in respectively in Figure **4-33** and Figure **4-34**. A clear inhibition can be observed when H-reflex is conditioned with vibratory stimuli but the inhibition seems not to be a simple function of the frequency and the amplitude of the vibration. After inspecting and comparing the raw EMG data with the average data across individual subjects I could not find any relationship between the level of inhibition and the frequency/amplitude of the vibratory stimulation.

Data were averaged across all subjects and the results are plotted in Figure **4-35**. The grand averaged data suggest that all the conditioned H-reflexes are significantly inhibited compared to the averaged control H-reflex but there is no significant difference between the mean values of the conditioned grand averaged H-waves evoked using vibrotactile stimuli at different frequency and amplitudes. These results are also summarized in Table 4.6.

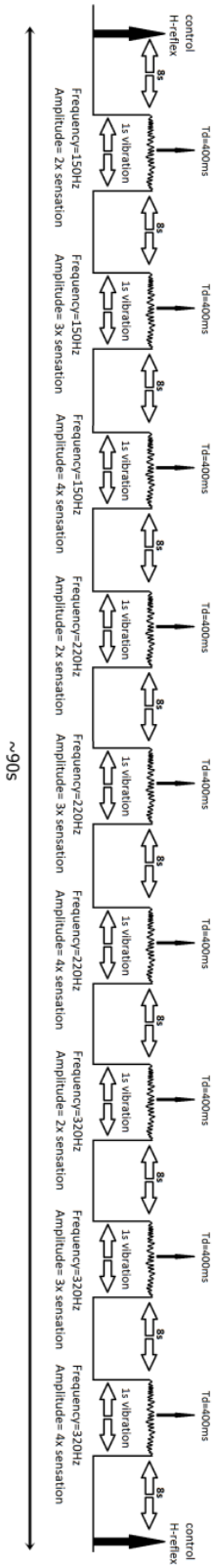


Figure 4-31. All the conditioning stimuli were vibration pulses of 1s in width at different frequencies and different amplitudes. These conditioning vibratory stimuli were grouped as a group of 9 conditioning stimuli surrounded by two controls H-reflex and was applied 30 times to the subject's foot. Conditioned H-reflexes were measure 400ms relative to time of stimulation onset (T_d=400ms).

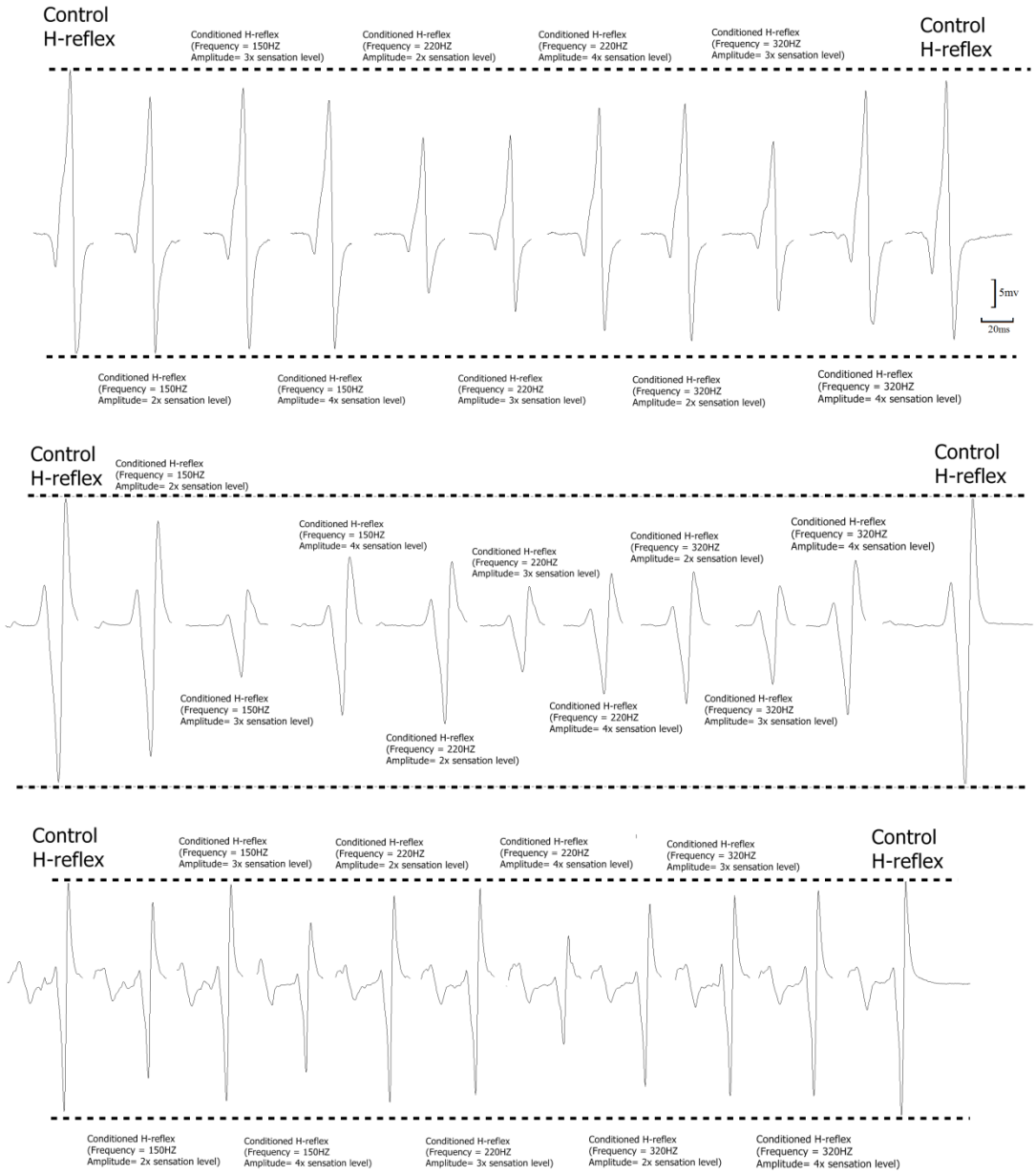


Figure 4-32. Raw EMG data recorded from 3 different subjects. This figure shows examples of the un-averaged conditioned soleus H-waves evoked by vibrotactile stimuli at different frequency and amplitudes. The plotted data show H-waves recorded from one out of 30 applied bins (see Figure 4-31). The first and the last H-waves shows the control (unconditioned H-wave) H-waves in the selected bin. Two parallel horizontal lines show the peak to peak amplitude of the control H-waves at the beginning and the end of the selected bin and show consistent control H-reflex amplitude.

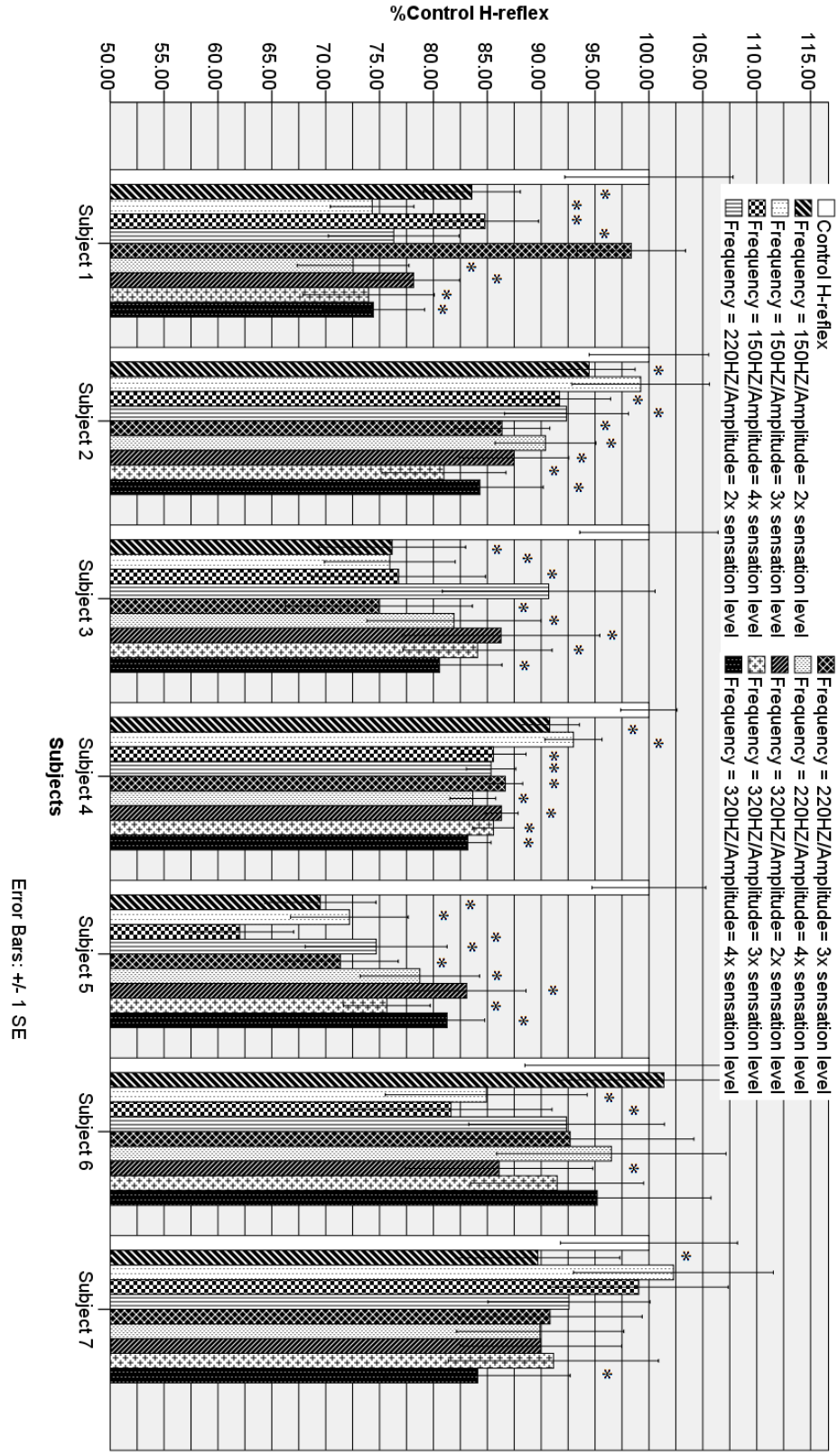


Figure 4-33. Bars showing the effect of plantar vibrotactile cutaneous stimulation delivered to the first metatarsus region at different frequencies and amplitudes. The overall average sizes of the conditioned SOL H-reflexes are presented as a percentage of the overall average control size (mean ±95%CI).

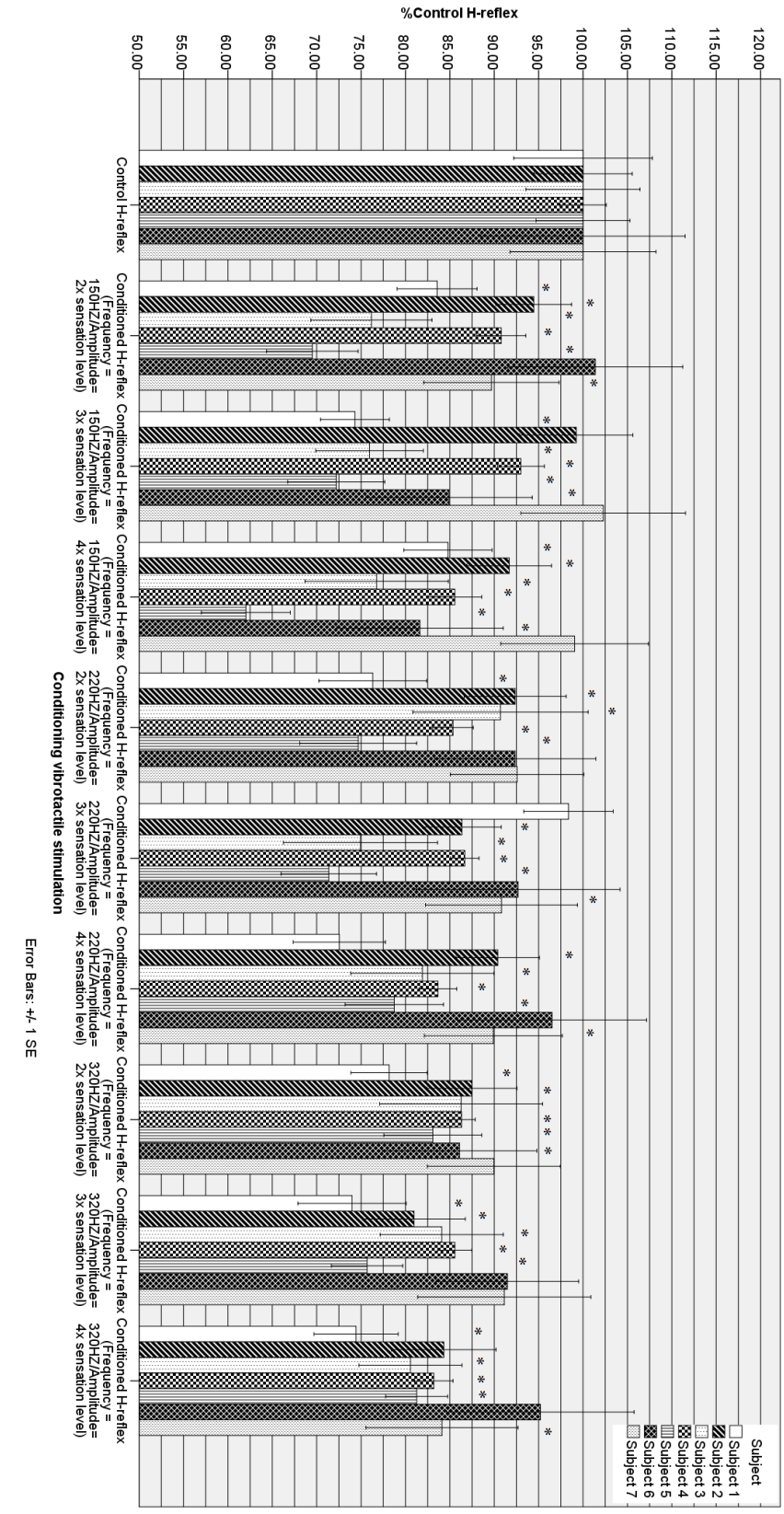


Figure 4-34. Bars showing the effect of plantar vibrotactile cutaneous stimulation delivered to the first metatarsus region at different frequencies and amplitudes. The overall average sizes of the conditioned SOL H-reflexes are presented as a percentage of the overall average control size (mean ±95%CI).

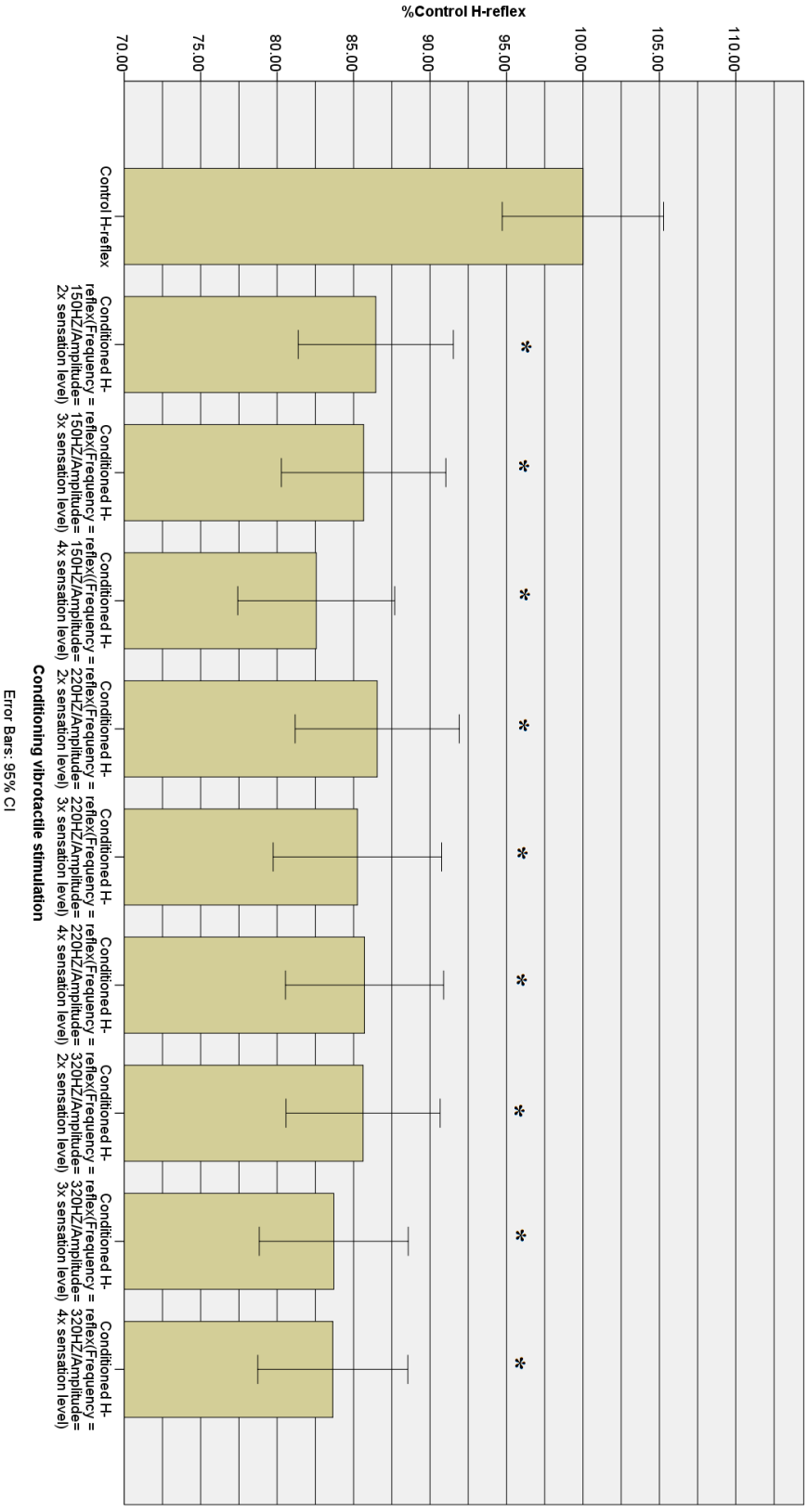


Figure 4-35. Mean ±95%CI of the normalized H-waves averaged across all subjects. A significant (*p<0.05) reduction in the H-reflex size exist between the unconditioned grand averaged H-reflex (control H-reflex) and the conditioned H-reflexes in all cases.

Table 4.6. Paired sample T-test conducted on the grand averaged data to determine whether there are any statistically significant differences between the conditioned H-reflexes and the unconditioned H-reflex. The significant parries are **bolded** in this table.

Paired Samples Test

Pair		Paired Differences			Sig. (2-tailed)
		Mean	95% Confidence Interval of the Difference		
			Lower	Upper	
Pair 1	**Control H-reflex - Conditioned H-reflex (Frequency = 150HZ/Amplitude= 2x sensation level)**	**13.11880**	**8.06647**	**18.17114**	**.000**
Pair 2	**Control H-reflex - Conditioned H-reflex (Frequency = 150HZ/Amplitude= 3x sensation level)**	**12.15042**	**6.95179**	**17.34904**	**.000**
Pair 3	**Control H-reflex - Conditioned H-reflex (Frequency = 150HZ/Amplitude= 4x sensation level)**	**15.50047**	**9.81524**	**21.18570**	**.000**
Pair 4	**Control H-reflex - Conditioned H-reflex (Frequency = 220HZ/Amplitude= 2x sensation level)**	**13.34746**	**8.34177**	**18.35316**	**.000**
Pair 5	**Control H-reflex - Conditioned H-reflex (Frequency = 220HZ/Amplitude= 3x sensation level)**	**16.45705**	**11.34099**	**21.57310**	**.000**
Pair 6	**Control H-reflex - Conditioned H-reflex (Frequency = 220HZ/Amplitude= 4x sensation level)**	**13.85568**	**9.69792**	**18.01344**	**.000**
Pair 7	**Control H-reflex - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 2x sensation level)**	**14.53227**	**9.55817**	**19.50637**	**.000**
Pair 8	**Control H-reflex - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 3x sensation level)**	**13.22204**	**7.96900**	**18.47508**	**.000**
Pair 9	**Control H-reflex - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 4x sensation level)**	**12.83871**	**7.41151**	**18.26591**	**.000**
Pair 10	Conditioned H-reflex (Frequency = 150HZ/Amplitude= 2x sensation level) - Conditioned H-reflex (Frequency = 150HZ/Amplitude= 3x sensation level)	-.96838	-5.10006	3.16330	.644
Pair 11	Conditioned H-reflex (Frequency = 150HZ/Amplitude= 2x sensation level) - Conditioned H-reflex (Frequency = 150HZ/Amplitude= 4x sensation level)	2.38167	-1.17872	5.94205	.188
Pair 12	Conditioned H-reflex (Frequency = 150HZ/Amplitude= 2x sensation level) - Conditioned H-reflex (Frequency = 220HZ/Amplitude= 2x sensation level)	.22866	-3.79859	4.25591	.911
Pair 13	Conditioned H-reflex (Frequency = 150HZ/Amplitude= 2x sensation level) - Conditioned H-reflex (Frequency = 220HZ/Amplitude= 3x sensation level)	3.33825	-1.07453	7.75102	.137
Pair 14	Conditioned H-reflex (Frequency = 150HZ/Amplitude= 2x sensation level) - Conditioned H-reflex (Frequency = 220HZ/Amplitude= 4x sensation level)	.73688	-3.60924	5.08300	.738
Pair 15	Conditioned H-reflex (Frequency = 150HZ/Amplitude= 2x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 2x sensation level)	1.41347	-2.02171	4.84864	.418

Pair 16	Conditioned H-reflex (Frequency = 150HZ/Amplitude= 2x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 3x sensation level)	.10324	-4.09844	4.30492	.961
Pair 17	Conditioned H-reflex (Frequency = 150HZ/Amplitude= 2x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 4x sensation level)	-.28009	-5.02525	4.46507	.907
Pair 18	Conditioned H-reflex (Frequency = 150HZ/Amplitude= 4x sensation level) - Conditioned H-reflex (Frequency = 220HZ/Amplitude= 2x sensation level)	-2.15301	-6.61219	2.30617	.342
Pair 19	Conditioned H-reflex (Frequency = 150HZ/Amplitude= 4x sensation level) - Conditioned H-reflex (Frequency = 220HZ/Amplitude= 3x sensation level)	.95658	-3.46389	5.37704	.670
Pair 20	Conditioned H-reflex (Frequency = 150HZ/Amplitude= 4x sensation level) - Conditioned H-reflex (Frequency = 220HZ/Amplitude= 4x sensation level)	-1.64479	-5.91651	2.62693	.448
Pair 21	Conditioned H-reflex (Frequency = 150HZ/Amplitude= 4x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 2x sensation level)	-.96820	-5.10956	3.17316	.645
Pair 22	Conditioned H-reflex (Frequency = 150HZ/Amplitude= 4x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 3x sensation level)	-2.27843	-7.36388	2.80702	.378
Pair 23	Conditioned H-reflex (Frequency = 150HZ/Amplitude= 4x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 4x sensation level)	-2.66176	-7.86701	2.54350	.314
Pair 24	Conditioned H-reflex (Frequency = 220HZ/Amplitude= 2x sensation level) - Conditioned H-reflex (Frequency = 220HZ/Amplitude= 3x sensation level)	3.10958	-1.59605	7.81522	.194
Pair 25	Conditioned H-reflex (Frequency = 220HZ/Amplitude= 2x sensation level) - Conditioned H-reflex (Frequency = 220HZ/Amplitude= 4x sensation level)	.50822	-3.92001	4.93645	.821
Pair 26	Conditioned H-reflex (Frequency = 220HZ/Amplitude= 2x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 2x sensation level)	1.18481	-2.78554	5.15515	.557
Pair 27	Conditioned H-reflex (Frequency = 220HZ/Amplitude= 2x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 3x sensation level)	-.12542	-5.01993	4.76909	.960
Pair 28	Conditioned H-reflex (Frequency = 220HZ/Amplitude= 2x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 4x sensation level)	-.50875	-5.71782	4.70032	.847
Pair 29	Conditioned H-reflex (Frequency = 220HZ/Amplitude= 3x sensation level) - Conditioned H-reflex (Frequency = 220HZ/Amplitude= 4x sensation level)	-2.60137	-6.60599	1.40325	.201
Pair 30	Conditioned H-reflex (Frequency = 220HZ/Amplitude= 3x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 2x sensation level)	-1.92478	-6.21817	2.36861	.377
Pair 31	Conditioned H-reflex (Frequency = 220HZ/Amplitude= 3x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 3x sensation level)	-3.23500	-7.29799	.82799	.118
Pair 32	Conditioned H-reflex (Frequency = 220HZ/Amplitude= 3x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 4x sensation level)	-3.61833	-8.02586	.78919	.107
Pair 33	Conditioned H-reflex (Frequency = 220HZ/Amplitude= 4x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 2x sensation level)	.67659	-3.85785	5.21103	.769

Pair 34	Conditioned H-reflex (Frequency = 220HZ/Amplitude= 4x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 3x sensation level)	-.63364	-4.89181	3.62454	.769
Pair 35	Conditioned H-reflex (Frequency = 220HZ/Amplitude= 4x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 4x sensation level)	-1.01697	-5.93830	3.90437	.684
Pair 36	Conditioned H-reflex (Frequency = 320HZ/Amplitude= 2x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 3x sensation level)	-1.31022	-5.10846	2.48801	.497
Pair 37	Conditioned H-reflex (Frequency = 320HZ/Amplitude= 2x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 4x sensation level)	-1.69356	-6.39641	3.00930	.478
Pair 38	Conditioned H-reflex (Frequency = 320HZ/Amplitude= 3x sensation level) - Conditioned H-reflex (Frequency = 320HZ/Amplitude= 4x sensation level)	-.38333	-5.27723	4.51057	.877

4.7.5 Summary

In this experiment the effects of changing the vibration frequency and the amplitude on SOL H-reflex was studied. Vibration stimuli were applied to the right metatarsus head of the subjects in standing. Vibration pulses of 1s in width at 2x, 3x and 4x the sensation level at different frequencies (150Hz, 220Hz and 320Hz) were applied to the subjects' foot. The conditioned H-reflexes were measured at 400ms relative to time of stimulation onset. Our finding shows that H-reflex modulation is not a simple function of vibration frequency or amplitude and probably other mechanism are involved in H-reflex modulation.

4.8 Discussion

4.8.1 Introduction

Locomotion patterns are generated and controlled via interacting supraspinal signals, the action linked to afferent feedback and the activity of spinal networks. Ankle monosynaptic reflexes pathways contribute to locomotion by direct acting on spinal motoneurons and are themselves controlled by spinal and supraspinal networks. This presynaptic action of these pathways results in their modulation during the step cycle in normal subjects (Conway & Knikou, 2008) (Knikou, 2007) (Knikou et al., 2009).

A currently available technique to promote recovery of walking in spinal cord injured patients is focused on the use of body weight support treadmill training. This training can be provided through therapist intervention or via robotic devices. Sensory feedback linked to stepping is promoted and maximized during treadmill walking and with intensity of training this is thought to help promote the reorganization and recovery of activity within locomotor control networks within the nervous system. During the early stage of the treadmill training due to high percentage of weight bearing support the sensory feedback from the foot soul is lacking when compared with normal walking. The loss of this key sensory signal may impact on the speed of a person's rate of gait recovery. In this project a long term goal is to determine if vibrotactile stimulation can be a surrogate for the loss of this activation of the foot sole during treadmill training.

It has been shown that cutaneous afferent can influence motoneuron excitability but the role of cutaneous afferents with respect to their anatomical location was not been studied extensively (Sayenko et al., 2007). In addition, the majority of past studies have used electrical stimulation of the cutaneous afferent innervating foot regions to study the excitatory and inhibitory reflex effects on ankle muscles. For example, it has been shown that electrical stimulation of different regions of the foot sole results in different effects on motoneuron excitability of ankle muscles (Sayenko et al., 2007) (Morita et al., 1998) (Sonnenborg 2000) (Sonnenborg & Andersen, 2001). Based on these findings it was proposed that contribution of the foot sole mechanoreceptors to the lower limb muscle is highly

location–specific. Previous work has also demonstrated that pressure applied to the foot sole also produces a long lasting depression of SOL H-reflex pathways in both normal and SCI patients but it is also recognised that this modulation is largely absent in complete SCI patients (Conway & Knikou, 2008). A key hypothesis to be explored is therefore whether foot afferents stimulation can be used to help re-establish patterns of reflex modulation in SCI patients during walking.

The objective of this study was to investigate whether the idea of using localized vibrotactile stimulation of the foot sole during the early stages of body weight support treadmill training could potentially be use to compensate for the diminished afferent feedback that results from unloading the foot sole and assist in restoring the type of reflex modulation normally seen during walking. For this reason we studied effects on SOL H-reflex modulation using localized vibrotactile stimulation of the foot sole in healthy subjects. Subjects were examined in different postural states and during walking on treadmill. The findings suggest that location–specific vibrotactile stimulation of the low threshold mechanoreceptors of the foot can influence spinal reflex pathways in healthy subjects. In this study the aim was to address several questions:

1. What is the conditioning action of localized vibrotactile stimuli on the SOL H-reflex pathway in healthy subjects?
2. Is the conditioning effects altered by changing in posture?
3. Can the vibrotactile stimulation be delivered during gait and what modulatory action can be seen?
4. What conditioning effects occur when vibrotactile stimulation is combined with partial body weight support?
5. Are the conditioning actions of vibration on the SOL-H reflex affected by vibration intensity or frequency?

Vibrotactile stimuli delivered through the vibrating insole was designed and controlled using a custom written Matlab program and a control board. The vibration stimuli were adjusted to ~1.5-2x the sensation level at 100Hz in 4 experiments and studied at different amplitude/frequencies in one experiment. Conditioning of the H-reflexes was measured at different latencies relative to the stimuli onset shown

symbolically by "T_d" (T_d = 50ms, 200ms, 400ms, 1s, 2s and post stimulation). The inter stimuli intervals long 8-10s in order to avoid carry over effects. In total 51 subjects were recruited and 42 finished the experiments. 1 subject withdraw during the test due to feeling ill, 2 subjects reported discomfort during H-reflex stimulation and withdraw from experiment, 2 subjects did not demonstrate standard reflex signal and in 4 subjects it was not possible to establish any stable control H-reflex . Data for each individual subject was averaged and the averaged results were also compared to the raw EMG recorded data to check if the same modulation pattern is observed in the raw data as well. In summery the observation in this study can be summarized as:

- The time courses of soleus H-reflex modulation evoked by localized vibrotactile stimulation of the plantar support zones of the foot in different postural positions is a curve with a minimum at T_d=200-400ms(Figure **4-24**).
- In sitting or standing, vibration to the plantar surface beneath the metatarsal heads evokes a greater depression of the soleus H-reflex than seen when the vibration is applied to the heel region (Figure **4-24**).
- Experiments on H-reflex modulation studies during walking on the treadmill show that regional phase dependent foot sole vibration evokes a clear inhibition of the soleus H-reflex (Figure **4-30**).
    - If walking was assisted through 25% body weight support, phase dependent vibration of the plantar surface dose not evoked a significantly greater depression of the soleus H-reflex than seen when no body weight support was used (Figure **4-30**).
- The H-reflex was inhibited significantly compare to the control H-reflex after changing the amplitude/frequency of the localized vibrotactile stimuli but there was not any significant difference in mean difference of the conditioned H-reflexes at different amplitude/frequencies when compared to each other. (Figure **4-35**).

In the following sections a comparison of the findings associated with the above questions will be compared to the literature.

4.8.2 Inhibition and Facilitation

Comparing studies that address the conditioning effect of foot afferents on SOL H-reflex excitability reveals a contradiction in literature. Some groups have reported inhibitory actions of plantar cutaneous afferents, some have report the opposite and some have reported both (Delwaide, 1981a) (Knikou, 2007) (Sayenko et al., 2007) (Pierrot-Deseilligny et al., 1973).

In a study by Delwaide et al. (Delwaide et al., 1981a) conditioning electrical stimuli were applied to ipsilateral sural nerve using a train of 1ms pules at 300Hz. Stimulation was applied at the sensation threshold and 2-3 times the sensation threshold value (painful stimulation). With sural nerve stimulation the amplitude of the conditioned H-reflex was reported to remain similar to control values up to 40ms relative to the conditioning stimulation onset. A significant facilitation was there after observed at 60-70ms relative to the conditioning stimulation onset (maximum facilitation was report as 33% of the control H-reflex). Conditioned H-reflex measurement at 170-500ms relative to the stimulation onset showed that H-reflex recovered to 95% of the control H-reflex (%5 inhibition). This modulation was observed when conditioning electrical stimulation was applied at up to 3x the sensation level. Further increases in the conditioning stimulation (painful stimulation) resulted in facilitation around 120ms relative to the stimulation onset and inhibition up to 1s after applying the condition stimulation. In summary, sural stimulation via flexion reflex pathways elicits some facilitation of H-reflex amplitude up to 150ms relative post stimulation onset and then the H-reflex is recovered to its normal value (Delwaide et al., 1981a). The sural nerve innervates the lateral aspect of the foot as therefore the work of Delwaide is testing skin areas that are different to those studied here and therefore the cutaneous afferent activated by Delwaide may subserve different actions on spinal reflexes than those seen in this study.

In a series of experiments by Knikou et al. sural stimulation (30ms train of 1-ms pulses delivered at 300 Hz) was used to generate flexion reflexes which produce a long lasting inhibitory effect on the SOL H Reflex H-reflex inhibition up to 90ms in healthy subjects and facilitation in SCI subjects (Knikou, 2007).

Sayenko (Sayenko et al., 2007) studied the effect of stimulating plantar cutaneous afferents located at the heel on SOL stretch reflex excitability. He

conditioned the plantar skin using an electrical stimulation delivered to the heel while subjects were seated. The stimuli intensity was set to 3x the sensation threshold. He stimulated the foot using 5 electrical pulses of 1ms in width and 3ms inter stimulus interval (in total 17ms). Measurements of SOL stretch reflex amplitude at different conditioning test intervals (C-T) up to 100ms post stimulation were made. In this work he observed a strong facilitation after plantar cutaneous afferent excitation of the heel delivered at intermediate C-T interval (20-70ms) for the amount of 154% of control H-reflex. They also studied the SOL H-reflex modulation using a similar method and they observed the soleus H-reflexes occurring at CT intervals of 40 and 50ms are highly facilitated (Sayenkoet al., 2009). Similarly Philippe (Marque et al., 2001) conditioned lateral and medial parts of the heel using an electrical stimulation at sensation level. In contrast to Sayenko they reported an inhibition in SOL H-reflex (Marque et al., 2001).

SAYENKO, (Sayenkoet al., 2009) studied the modulation of spinal excitability after electrical stimulation of plantar cutaneous afferents located at metatarsus heads. They observe a clear inhibition in the SOL H-reflex amplitude lasting for C-T intervals up to 75ms most of times. The maximum depression occurring at C-T=25ms and producing a reflex of 65% of the control H-reflex size (Sayenkoet al., 2009). A clear inhibition of SOL H-reflex is also seen after cutaneous stimulation of the small and great toe by Pierrot (Pierrot-Deseilligny et al., 1973). Figure 4-36 compares the obtained results from some of the mentioned studies.

In the majority of the studies mentioned, the electrical conditioning test pulses proceeded the test reflex at different condition test intervals(C-T) measured as the time between the end of conditioning pulse train delivered to the skin or nerve and the beginning of the pulse delivered to tibial to evoke the conditioned H-reflex (Knikou, 2007). These studies basically studied the recovery of H-reflex or stretch reflex after applying electrical stimulation conditioning signals and most of the authors considered C-T intervals from 3ms to 100ms. On the other hand, some other groups studied the modulation of H-reflex after applying mechanical conditioning stimulation which will be discussed in detail in the following (Morita et al., 1998) (Knikou & Conway, 2007) (Conway & Knikou, 2008).

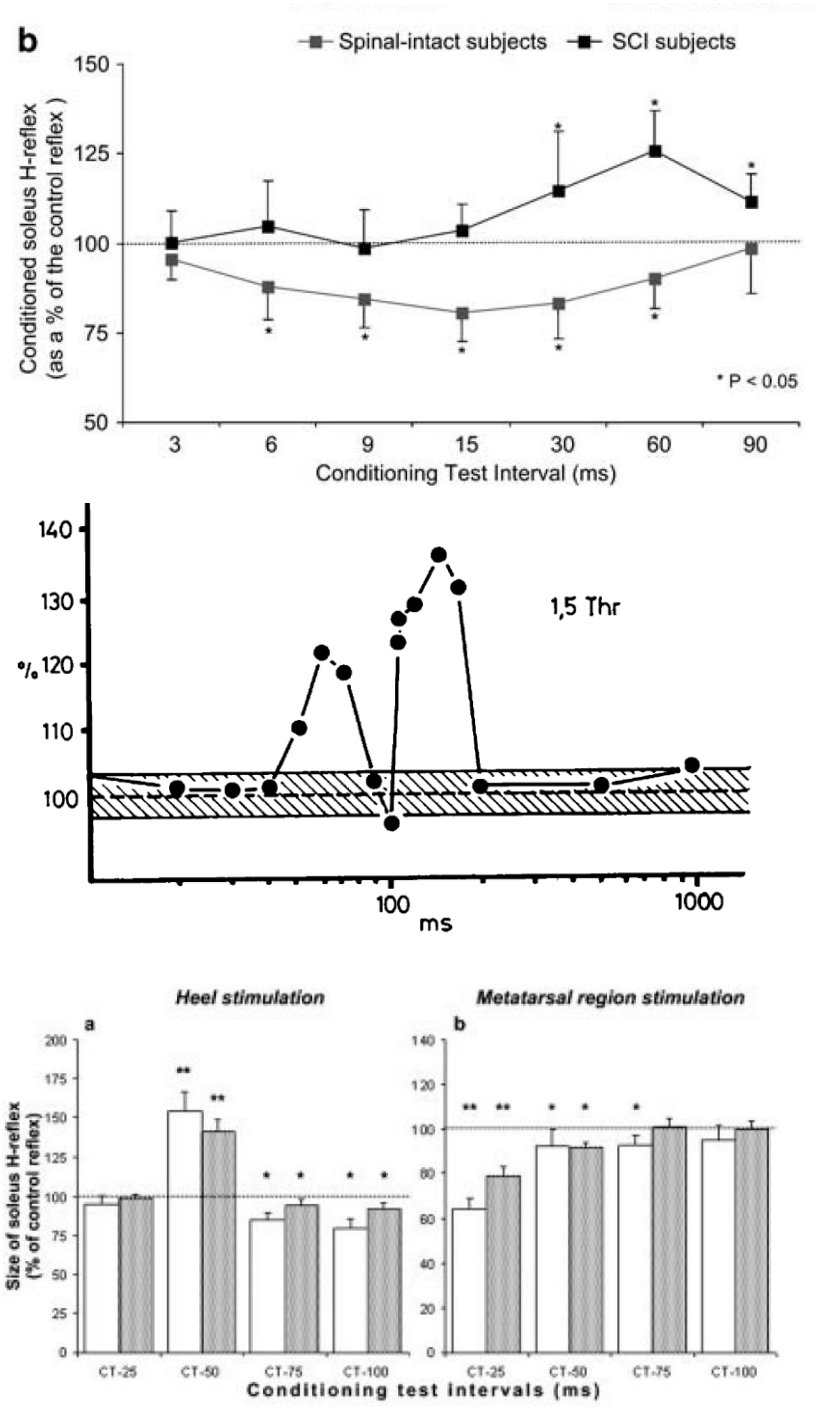


Figure 4-36. A) Effects of plantar cutaneous afferents excitation on the soleus H-reflex in normal and SCI subjects. For each C-T interval tested (Knikou, 2007). The Conditioned H-reflex was measured at different time intervals relative to the conditioning stimulation onset (image taken from (Knikou, 2007)). B) Recovery of sol H-reflex after electrical stimulation of the ipsilateral sural nerve using a 1ms pules at 300Hz at 1.5x the sensation level (Delwaide et al., 1981a). The x axis shows the delay between measuring the conditioned H-reflex and sural nerve stimulation (conditioning signal) (Image taken from (Delwaide et al., 1981a)). C) Effect of plantar cutaneous afferent conditioning delivered to (Right) the heel and (Left) the metatarsal region at different CT intervals (Sayenkoet al., 2009). White bars show the trials when the amplitude of the control H-reflex was matched to that of the control stretch (Image taken from (Sayenkoet al., 2009)).

Conway and Knikou showed that conditioning the foot afferents using electrical or mechanical stimulation inhibits the SOL H-reflex significantly in normal subjects and those with complete spinal cord injury (Conway & Knikou, 2008) (Knikou & Conway, 2007) (Knikou, 2007). Mortia et al. (Morita et al., 1998) studied soleus H-reflexes modulation when conditioned using electrical stimulation of common peroneal nerve and biceps femoris tendon tap. They reported that H-reflex was strongly depressed for a period lasting up to 300-400ms when H-reflex was conditioned by biceps femoris tendon tap (mechanical stimuli). A similar inhibition was also observed when electrical stimulation of the peroneal nerve was used as the conditioning signal but for much shorter period of time (up to 100ms). They explained that the difference in the depression of the electrically and mechanically evoked reflexes after 100ms is probably due to different afferent volleys evoked by mechanical and electrical stimuli. Electrical stimulation simultaneously activates Ia afferents from muscles and muscle nerves and generates a volley that is less spread over time on its arrival at the spinal networks but mechanical stimuli generates a volley which is more dispersed over time on their arrival to the spinal networks (Morita et al., 1998) (Burke et al., 1983).

In the experimental setup described in this thesis the conditioned H-reflexes were measured at points between the onset and end of the conditioning stimuli (Figure **4-7**). We measured conditioned H-reflexes at Td=50ms, 200ms, 400ms, 1s and 2s relative to the stimuli onset and also we also measure the recovery of the conditioned H-reflexes after ~90ms relative to the end of conditioning vibrotactile stimulation which was referred to post stimulation measurement in this thesis.

A clear inhibition is observed in the data in response to vibrotactile stimulation of heel and metatarsus region in sitting and standing. The observed inhibitions were maximised when H-reflex was measured 200ms-400ms in relation to the stimuli onset (Td=200ms, 400ms) (Figure **4-24**). The H-reflex inhibition observed in our data at longer time intervals (Td=200-400ms) when compared to electrical stimulation reported by others could possibly be related to a small number of afferents activated, the dispersion of the sensory volley and recruitment of relatively slow conducting afferents by the vibrotactile stimulation. Further investigation is needed to explore

the possible underlying mechanisms in relation to what afferents are recruited by the stimulation used here.

We also observed that SOL H-reflex inhibition lasts up to 1s relative to the onset of vibrotactile stimulation and recovers to its normal value after 1s (Figure **4-24**). The main reason for this recovery could be adaptation of the receptors induced. Vibrotactile stimuli above the sensation threshold elicits continuous afferent impulse volley without adaptation only for some second (Hari, 1980) (Konietzn & Hensel, 1977). Long lasting stimulation of the foot mechanoreceptors lasting more than 1s may lead both to receptor adaptation and also to adaptation in the spinal and supraspinal pathways.

Based on the results present in Figure **4-24**, stimulating the first metatarsus head generated a greater depression in H-reflex amplitude comparing to heel region. This could be related to the density of Pacinian corpuscles at metatarsal heads which are the most likely class receptors to be recruited by the vibrotactile stimulation. Pacinian corpuscles are mostly concentrated in the first; second, third and fifth metatarsus heads and have low concentration in heel. This issue was discussed in details in the discussion section of the previous chapter.

4.8.3 Greater H-reflex Inhibition in Standing

The conditioning stimuli were applied to the first metatarsus head while subjects were sitting and standing. Based on the data presented in Figure **4-23** and Figure **4-24** the time-course of H-reflex modulation during standing is similar to sitting but the conditioned SOL H-reflex inhibition was reduced by 15% of the control H-reflex size at Td = 400ms. Also there was a significant difference between conditioned H-reflexes mean values at Td=400ms when subjects were standing compare to sitting. Potential mechanism involved in greater inhibition of the conditioned H-reflex during standing compared to sitting might be:

- The general increase in SOL excitability associated with standing may itself unmask the strength of inhibitory actions when compared to relax state such a sitting

- Increase in the number of receptors recruited due to increase in background loading of the foot tissue
- Convergence of effects from vibration interacting with tonic load sensitive afferents feedback and hip angle producing potentiation of inhibition (Nakazawa et al., 2004b) (Knikou & Conway, 2007) (Knikou & Rymer, 2002)
- Small active postural response try to reduce pressure (vibration) under the stimulated site after vibrotactile stimulation of the first metatarsus head (Maurer et al., 2001) (Kavounoudias et al., 1998)

Knikou studied the amplitude modulation of SOL H-reflex during static variations of hip angle in combination with plantar skin stimulation or electrical activation of muscle afferents with subjects seated and supine (Knikou & Rymer, 2002). She suggests that hip flexion and extension significantly inhibits and facilitates the Sol H-reflex excitability respectively. Plantar cutaneous afferent activation inhibits H-reflex in both seating and supine where hip is flexed and facilitates when subjects are supine with hip extended. She concluded that afferent actions from the lower limb muscles during standing might contribute to the inhibitory mechanism with additional dependency on the hip angle (Knikou & Rymer, 2002).

Nakazawa (Nakazawa et al., 2004b) studied the effects of loading and unloading of lower limb joints on the soleus H-reflex in standing position. He found that reduction of limb loading will enhance the H-reflex and increase in loading will decreases H-reflex. Based on these finding it is suggested that joint afferents might mediate the suppression of SOL reflex pathway in standing.

From these studies it can be concluded that hip angle and loading of the lower limb muscles alter the level of SOL H-reflex excitability. If we take the premise that the greater depression of SOL H-reflex observed in our data when subjects were standing is related to hip angle and lower limb loading then we should conclude that extending the hip and loading of lower limb muscles alters the effective action of the projection pacinian afferent fibres onto spinal interneurons. Additional work would be needed to explore this.

Decreases in SOL H-reflex in standing could also be related to postural stability and reduction in body oscillation around the ankle joint (Nakazawa et al., 2004a). Presynaptic inhibition of SOL Ia afferents is suggested to play an important role during standing and balance control (Koceja et al., 1993). It is shown that spinal stretch reflex activity is also an essential factor in balancing movements (Dietz et al., 1980). It has been shown that people who have been trained to keep balance on a tightened ribbon have much lower H-reflexes amplitude compare to pre-training measures. This led to suggestion that reflex inhibition may serve to suppress uncontrollable reflex mediated joint oscillations (Keller et al., 2012).

Human balance control depends on feedback from plantar skin receptors (Priplata et al., 2006). Low amplitude vibratory stimulation applied to the different regions of the foot sole in quite standing results in movement of the centre of pressure in healthy subjects (Hijmans & Juha, 2009). Stimulating plantar cutaneous mechanoreceptors in standing using low amplitude vibration could lead to postural responses (Maurer et al., 2001). Foot sole stimulation produces a clear sensation of changing pressure under the stimulated site demonstrating its powerful effect on motor outflow. The small active postural response observed after localized foot stimulation have been argued to be part of a protection responses to reduce pressure under the stimulated site (Maurer et al., 2001). The movement of the subjects' centre of the mass also depends on the foot regions being stimulated and is always opposite to the vibration stimulated pressure increase (Kavounoudias et al., 1998). The increase of SOL H-reflex inhibition observed in our data when subjects were standing could probably be related to small active postural response to reduce pressure (vibration) under the stimulated site which influence the background muscle activity (Maurer et al., 2001).

4.8.4 Changes in the Conditioned SOL H-reflex Inhibition due to Body Weight Support

Ashraf et al. (Ashraf & Sabbahi, 2000) compared the modulation of SOL H-reflex in quite standing with 0% and 25% unloading using a harness system. Based on their findings 25% unloading did not significantly change the amplitude to H-reflex compare to 0% unloading. However they reported a very mild inhibition at 25%

unloading compare to 0% unloading. The main reason for such small change could be withdrawal of the excitatory effect of the calf muscles due to unloading. Knikou et al studied the phase-dependent modulation of the soleus H-reflex on Lokomat walking at different levels of body weight support in healthy subjects (Knikou et al., 2011). She founded that increasing the level of body weight support during treadmill walking slightly enhances the level of SOL-H-reflex inhibition in the stand phase of walking.

Our experiments on body weight support treadmill walking shows a clear inhibition of SOL H-reflex when the conditioned H-reflexes were measure in early and late midstance. Our finding is consistent with similar studies that showed foot sole afferents inhibit Sol H-reflex during walking. Our data suggest that vibrotactile stimulation of the foot during treadmill walking with 25% body weight support does not significantly enhance the SOL H-reflex inhibition (see Figure **4-30**).

4.8.5 Amplitude/Frequency Modulation

The purpose of this experiment was to determine the effects of changing the amplitude and the frequency of the localized vibrotactile stimulation applied to the first metatarsus head on the SOL H-reflex modulation pattern. We also tried to find the optimum amplitude and frequency for plantar stimulation.

Inhibition of the H-reflex of triceps surae muscles has also reported in healthy subjects when the skin overlying the muscle was stimulated by brushing or scratching (Wood et al., 1998). Increasing the frequency of brushing slightly increased the amount of inhibition which was suggested to be related to the intense stimulation of the receptors (Wood et al., 1998). It has been also shown that at higher vibration frequencies (>150Hz), the frequency discrimination is poor and with lowering the frequency more RA and PC fibres will be recruited (Morley & Rowe, 1990).

Our result shows that the mean difference between the conditioned SOL H-reflexes evoked by conditioning the foot mechanoreceptors using vibrotactile stimuli at different frequencies and amplitudes is not significant. Based on our data it can be concluded that changing the frequency or the amplitude of the localized vibrotactile

stimulation does not have a significant effect on the amount of SOL H-reflex inhibition.

CHAPTER 5
Conclusion

It is believed that cutaneous afferents from the foot sole influence human locomotion. These afferents adjust motoneuron excitability by influencing the reflex circuits that operate and act on ankle muscles. It has been also suggested that the expression of this type of sensory feedback following spinal cord lesion can be changed and used in rehabilitation context (Knikou, 2007).

Tactile cutaneous afferents from the foot during the stance phase of walking inhibits the actions of Ib reflex pathways to MNs supplying muscles operating at ankle. These afferent pathways are also believed to interact with hip proprioceptors and to flexor reflex pathways during walking (Knikou et al., 2006). The foot sole afferents have oligosynaptic connections with neural circuitry involved in reflexes that participate in the control of posture and locomotion and can influence motoneuron excitability by modifying the level of presynaptic and postsynaptic inhibition. The loss of modulation of these reflexes in SCI patients could be significant for the patient rehabilitation and artificially activating plantar afferents could aid in restablishing and modulating of pathways that help to normalise walking behaviour. Any disruption to the plantar cutaneous afferents cannot be compensated using any other types of sensory stimulation or mechanism (Meyer et al., 2004). Stimulation of the patients' foot cutaneous afferents during treadmill training modulates the SOL H-reflex excitability to a level similar to what is observed in healthy people (Fung & Barbeau, 1994). Facilitating this cutaneous feedback therefore might increase the chance of recovery in SCI patients being trained on treadmill.

The principal experimental findings demonstrate that the vibratory stimulation generates localized afferent stimulation that results in demonstrable activations of both cortical and spinal neural circuits. These effects can be demonstrated using commonly available electrophysiological methods meaning that in clinical studies the effects of the stimulations can be readily monitored.

Our experimental findings demonstrate that short periods (~50ms) of foot vibration in normal subjects evoke clear SEPs that can be localized to the appropriate sensorimotor areas of the cortex. This provides an important baseline dataset on how stimulation parameters and site of foot stimulation alter the magnitude of the activation and SEP topography thereby facilitating later studies investigating post-training cortical plasticity.

In relation to spinal activation, our findings suggest that activation of foot mechanoreceptors using localized vibrotactile stimulation interact with spinal inhibitory control mechanism contributing to the control of locomotion in humans and induce presynaptic inhibition of Ia afferents terminals. Most likely this can have practical benefits for normalising gait and restoring reflex modulation during gait training. Findings in this study showed that an insole device can make this happen and can be used in gait training of SCI subjects. The designed device can be controlled by measuring the ground contact force using FSR sensors or can be linked to robotic devices like Lokomat which provides additional information about the gait kinematic.

The reduction in the body loading sensory feedback during the early stages of treadmill walking might therefore be compensated by augmented sensory stimulation of the foot provided by localized vibrotactile stimulation. Vibrotactile stimulation activates both load mechanoreceptors and skin afferents that both inhibit the SOL H-reflex excitability in injured people. Further investigations are needed to express the vibration sensory afferent changes following a lesion to the spinal cord soleus H-reflex.

5.1 Suggestions and Future Work

The work presented in this thesis has several strengths and weaknesses that I will mention in the following. I will also point out some of my personal experiences during this research which could be useful in future for anyone who is interested to follow this work.

In SEP recording I didn't monitor if the vibration stimulation is transferred to the sole muscles and bone structures. This can be tested by attaching an

accelerometer to the toes to monitor if vibration stimuli are transferred to sole muscles and bone structures. In these experiments I set the vibration amplitude just at the sensation level so probably not much vibration is transferred to the underlying muscles. The vibration amplitude was set based on subject's oral response. As different subjects have different perception threshold and feeling, some other methods should be investigated to set the vibration amplitude. The effect of changing the vibration frequency on SEP components in one subject was also investigated. I observed that the higher vibration frequency slightly reduces the N150 and P250 latencies.

Vibrotactile SEPs usually appear after averaging 300 epochs. But at least 600 stimuli are needed to get a good S/N ratio after averaging. I considered 3s delay between stimuli to avoid adaptions. This increases the experiment session duration and will cause subjects to feel uncomfortable. I also tried to consider 1s delay between stimuli to get more evoked responses in an experimental session. Reducing the time delay didn't affect the data so shorter time delay between stimuli can also be considered. One of the major problems I faced while recording SEPs was electromagnetic noise induced by vibrator motors. If possible it is recommended to use non-electric vibrator devices to avoid electromagnetic signal interference while recording.

Vibrotactile stimuli usually have a very week inhibitory effect on SOL H-reflex but in one subject I observed facilitation in the conditioned H-wave amplitude in the first 3 minutes of the experiment. The observed facilitation was then removed during the experiment session. To measures the effect of skin vibrotactile stimulation of SOL H-reflex it is very important to demonstrate a stable control H-wave otherwise it will not be possible to observe the effect. One of the main difficulties in H-reflex experiments is adjusting the stimulation amplitude. In the literature people usually consider H-wave amplitude at 20%-30% of M-max for the control H-reflex. They usually use their own experience to adjust the intensity. While adjusting the stimulation intensity always try to get a stable H-wave response. If possible use more control H-waves to make sure that the control H-wave amplitude in not changing too much during the experiments sessions. Usually H-wave amplitude drops after some minutes in that case stop the experiment, ask the subject to move his ankle several

times, readjust the stimulation intensity to get a stable H-wave and continue the experiment. In some subjects I was not able to get any stable H-wave. Usually subject with lower body fat have much better H-wave signal. I also got different H-wave responses when the vibrator was just touching the sole skin and when vibrator was pushed to the sole. This could be due to induced vibration of the underlying muscles.

Sociological effects could also affect the H-reflex experiments. I measured H-reflex while the vibration stimulation was applied to the foot. Some subjects reported that they were expecting their nerve to be stimulated at some points every time the vibration was on.

For future work I recommend to repeat these experiments on spinal injured patients. Based on level and type of injury different responses are expected to be observed.

References

Aiello I, Rosati G, Serra G, Tugnoli V, Manca M. (1983) “Static vestibulospinal influences in relation to different body tilts in man.” *Experimental neurology*, 79.1, 18-26.

Ashraf AA, Sabbahi MA. (2000) “H-reflex changes under spinal loading and unloading conditions in normal subjects.” *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*, 111: 664-670.

Alrowayeh HN, Sabbahi MA. (2011a) “H-reflex amplitude asymmetry is an earlier sign of nerve root involvement than latency in patients with S1 radiculopathy.” *BMC research notes*, 5;4:102. doi: 10.1186/1756-0500-4-102.

Alrowayeh HN, Sabbahi MA, Etnyre B. (2011b) “Similarities and differences of the soleus and gastrocnemius H-reflexes during varied body postures, foot positions, and muscle function: multifactor designs for repeated measures.”, *BMC neurology, 11:65, doi:10.1186/1471-2377-11-65*

Alrowayeh HN, Sabbahi MA. (2009) “Medial and lateral gastrocnemius H-reflex intersession reliability during standing and lying postures at varied foot positions in healthy participants.” *Electromyography and clinical neurophysiology*, 49: 143-148.

American Academy of Neurology's Therapeutics and Technology Assessments. (1997) “Assessment: Dermatomal somatosensory evoked potentials.” *Neurology*, doi: 10.1212/WNL.49.4.1127

Andersen JB, Sinkjaer T. (1999) “The stretch reflex and H-reflex of the human soleus muscle during walking.” *Motor control*, 3:151-157.

Apparelyzed. (2014) <http://www.apparelyzed.com/index.html>.

Arcangel CS, Johnston R, Bishop B. (1971) “The achilles tendon reflex and the H-response during and after tendon vibration.” *Physical therapy*, 51: 889-905.

Armstrong WJ, Nestle HN, Grinnell DC, Cole LD, Van Gilder EL, Warren GS, Capizzi EA. (2008) “The acute effect of whole-body vibration on the hoffmann reflex.” *Journal of strength and conditioning research / National Strength & Conditioning Association* ,22: 471-476.

Baba M, Simonetti S, Krarup C. (2001) “Sensory potentials evoked by tactile stimulation of different indentation velocities at the finger and palm.” *Muscle & nerve* 24: 1213-1218.

Baken BC, Dietz V, Duysens J. (2005) “Phase-dependent modulation of short latency cutaneous reflexes during walking in man.” *Brain research* , 1031: 268-275.

Barbeau H, Rossignol S. (1987) “Recovery of locomotion after chronic spinalization in the adult cat.” *Brain research,* 412: 84-95.

Barthélemy D, Willerslev-Olsen M, Lundell H, Conway BA, Knudsen H, Biering-Sorensen F, Nielsen JB. (2010) “Impaired transmission in the corticospinal tract and gait disability in spinal cord injured persons.” *Journal of neurophysiology*, 104: 1167-1176.

Bastiaanse CM, Duysens J, Dietz V. (2000) “Modulation of cutaneous reflexes by load receptor input during human walking.” *Experimental brain research,* 135: 189-198.

Baumgärtner U, Vogel H, Ellrich J, Gawehn J, Stoeter P, Treede RD. (1998) “Brain electrical source analysis of primary cortical components of the tibial nerve somatosensory evoked potential using regional sources.” *Electroencephalography and clinical neurophysiology,* 108: 588-599.

Behrman AL, Harkema SJ. (2007) “Physical rehabilitation as an agent for recovery after spinal cord injury.” *Physical medicine and rehabilitation clinics of North America,* 18: 183-202.

Behrman AL, Mark G Bowden and Preeti M Nair.(2014) “Neuroplasticity After Spinal Cord Injury and Training: An Emerging Paradigm Shift in Rehabilitation and Walking Recovery.” *Physical therapy*, 86: 1406-25.

Bentley DE, Youell PD, Jones AK. (2002) “Anatomical localization and intra-subject reproducibility of laser evoked potential source in cingulate cortex, using a realistic head model.” *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*, 113: 1351-1356 .

Bolton DA, Misiaszek JE. (2009) “Contribution of hindpaw cutaneous inputs to the control of lateral stability during walking in the cat.” *Journal of neurophysiology*, 102: 1711-1724.

Bouyer LJ, Rossignol S. (2003) “Contribution of cutaneous inputs from the hindpaw to the control of locomotion. I. Intact cats.” *Journal of neurophysiology*, 90: 3625-3639.

Braddom RI, Johnson EW. (1974) “Standardization of H reflex and diagnostic use in Sl radiculopathy.” *Archives of physical medicine and rehabilitation,* 55: 161-6.

Branco F, Cardenas DD, Svircev JN. (2007) “Spinal cord injury: a comprehensive review.” *Physical medicine and rehabilitation clinics of North America,* 18: 651-679.

Brinkworth RS, Tuncer M, Tucker KJ, Jaberzadeh S, Türker KS. (2007) “Standardization of H-reflex analyses.” *Journal of neuroscience methods,* 162: 1-7.

Brown, Graham. (1911) “the intrinsic factors in the act of progression in the mammal.” *Proc. R. Soc. Lond,* 309–319.

Brüel & Kjær.(2015) <http://www.bksv.com/>.

Buford JA, Smith JL. (1990) “Buford JA, Smith JL. Adaptive control of backward quadriped walking II. Hindlimb muscle synergies.” *The Journal of physiology* , 64:756-766.

Burke D, Gandevia SC, McKeon B. (1983) “The afferent volleys responsible for spinal proprioceptive reflexes in man.” *The Journal of physiology,* 339:535-552.

Burke D, K E Hagbarth, L Löfstedt, and B G Wallin. (1976) “The responses of human muscle spindle endings to vibration during isometric contraction.” *The Journal of Physiology,* 261: 695–711.

Burton H, Abend NS, MacLeod AM, Sinclair RJ, Snyder AZ, Raichle ME. (1999) “Tactile attention tasks enhance activation in somatosensory regions of parietal cortex: a positron emission tomography study.” *Cerebral cortex* 9: 662-674.

Burton H, Videen TO, Raichle ME. (1993) “Tactile-vibration-activated foci in insular and parietal-opercular cortex studied with positron emission tomography: mapping the second somatosensory area in humans.” *Somatosensory & motor research,* 10: 297-308.

Bus SA, Waaijman R, Arts M, Manning H. (2009) “The efficacy of a removable vacuum-cushioned cast replacement system in reducing plantar forefoot pressures in diabetic patients.” *Clinical biomechanics,* 24: 459-464.

Cambridge Electronic Design. (2015). <http://www.ced.co.uk/indexu.shtml>.

Capaday C, Lavoie BA, Barbeau H, Schneider C, Bonnard M. (1999) "Studies on the corticospinal control of human walking. I. Responses to focal transcranial magnetic stimulation of the motor cortex." *Journal of neurophysiology,* 81: 129-139.

Carmen, Edelle. (2003) "Quantification of functional behavior in humans and animals: Time for a paradigm shift." *Journal of Rehabilitation Research & Development,* 40: 19-24.

Caselli, Richard J. (1993) "Ventrolateral and dorsomedial somatosensory association cortex damage produces distinct somesthetic syndromes in humans." *Neurology,* 43: 762-771.

Catz Amiram, Malka Itzkovich, MA. (2007) "Spinal Cord Independence Measure: Comprehensive ability rating scale for the spinal cord lesion patient." *Journal of Rehabilitation Research & Development,* 44 : 65 - 68.

Chen YS, Zhou S. (2011a) "Soleus H-reflex and its relation to static postural control." *Gait & posture,* 33: 169-178.

Chen, Yung-Sheng. (2011b) *Effects of ageing and Tai Chi training on soleus H-reflex in older adults*. PhD thesis, Southern Cross University, Lismore, NSW.

Chernikova L, R. Umarova, I. Saenko and I. Kozlovskaya. (2007) "Effects of mechanical support stimulation on the recovery of poststroke movement disorders and brain activity in healthy subjects." *International Society for Posture and Gait Research (ISPGR),* 30: 352-367.

Cheyne, D., Roberts, L.E., Gaetz, W., Bosnyak, D.,Weinberg, H., Johnson, B., Nahmias, C. and Deecke, L. (2000). "EEG and MEG source analysis of somatosensory evoked responses to mechanical stimulation of the fingers." *Advances in Biomagnetism Research, 96:1130-1133*

Chung YG, Kim J, Han SW, Kim HS, Choi MH, Chung SC, Park JY, Kim SP. (2013) "Frequency-dependent patterns of somatosensory cortical responses to vibrotactile stimulation in humans: a fMRI study." *Brain research,* 1504:47-57.

Clarac, F. "The History of Reflexes Part 1: From Descartes to Pavlov." *IBRO History of Neuroscience,* 2012.

Claus D, Jakob S. (1986) "The relationship between long latency responses and height." *Journal of neurology,* 233: 271-273.

Coghill RC, Talbot JD, Evans AC, Meyer E, Gjedde A, Bushnell MC, Duncan GH. "Distributed processing of pain and vibration by the human brain. (1994)"

The Journal of neuroscience : the official journal of the Society for Neuroscience, 14: 4095-4108.

Collins JJ, Imhoff TT, Grigg P. (1996) "Noise-enhanced tactile sensation." *Nature,* 383: doi:10.1038/383770a0.

Conway BA, Hultborn H, Kiehn O. (1987) "Proprioceptive input resets central locomotor rhythm in the spinal cat." *Experimental brain research,* 68: 643-656.

Conway BA, Knikou M. (2008) "The action of plantar pressure on flexion reflex pathways in the isolated human spinal cord." *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* 119: 892-896.

Corden DM, Lippold OC, Buchanan K, Norrington C. (2000) "Long-latency component of the stretch reflex in human muscle is not mediated by intramuscular stretch receptors." *Journal of neurophysiology,* 84: 184-188.

Côté MP, Gossard JP. (2004) "Step training-dependent plasticity in spinal cutaneous pathways." *The Journal of neuroscience : the official journal of the Society for Neuroscience,* 24: 11317-11327.

Cotey D, Hornby TG, Gordon KE, Schmit BD. (2009) "Increases in muscle activity produced by vibration of the thigh muscles during locomotion in chronic human spinal cord injury." *Experimental brain research,* 196: 361-374.

Davey, N. J., Ellaway, P. H. & Maskill, D. W. (1991) "Facilitation by mechanical cutaneous stimulation of muscle responses to transcranial magnetic stimulation in man." *Journal of Physiology,* 71: 273-278.

Davis H, Zerlin S. (1966) "Acoustic relations of the human vertex potential." *The Journal of the Acoustical Society of America,* 39: 109-116.

Duysensa Jacques, Henry W.A.A Van de Crommert. (1998) "Neural control of locomotion; Part 1: The central pattern generator from cats to humans." *Gait & posture* 7: 131-141.

De Leon RD, Hodgson JA, Roy RR, Edgerton VR. (1998) "Locomotor Capacity Attributable to Step Training Versus Spontaneous Recovery After Spinalization in Adult Cats." *Journal of Neurophysiology,* 79:1329-1340.

Delwaide P J, Crenna P, and Fleron M H. (1981b) "Cutaneous nerve stimulation and motoneuronal excitability: I, soleus and tibialis anterior excitability after ipsilateral and contralateral sural nerve stimulation." *Journal of neurology, neurosurgery, and psychiatry,* 44: 699–707.

Delwaide PJ, Toulouse P, Crenna P. (1981b) “Hypothetical role of long-loop reflex pathways.” *Applied neurophysiology,* 44:171-176.

Deo AA, Grill RJ, Hasan KM, Narayana PA. (2006) “In vivo serial diffusion tensor imaging of experimental spinal cord injury.” *Journal of neuroscience research,* 83: 801-810.

Diaped. (2015) <http://diaped.co.uk/product/neurothesiometer/>.

Dietz V, Colombo G. (1998a) “Influence of body load on the gait pattern in Parkinson's disease.” *Movement disorders : official journal of the Movement Disorder Society,* 13: 255-261.

Dietz V, Wirz M, Curt A, Colombo G. (1998b) “Locomotor pattern in paraplegic patients: training effects and recovery of spinal cord function.” *Spinal Cord,* 36: 380-390.

Dietz V, Mauritz KH, Dichgans J. (1980) “Body oscillations in balancing due to segmental stretch reflex activity.” *Experimental brain research,* 40: 89-95.

Dietz V, Müller R, Colombo G. (2002) “Locomotor activity in spinal man: significance of afferent input from joint and load receptors.” *Brain : a journal of neurology,* 12:2626-2634.

Dietz V, Nakazawa K, Wirz M, Erni T. (1999) “Level of spinal cord lesion determines locomotor activity in spinal man.” *Experimental brain research,* 128: 405-409.

Dietz V, G. Colombo, L. Jensen, L. Baumgartner. (1995). “Locomotor capacity of spinal cord in paraplegic patients.” Annals of Neurology, 37:574-82.

Dietz, Michèle Hubli and Volker. (2013) “The physiological basis of neurorehabilitation - locomotor training after spinal cord injury.” *Journal of neuroengineering and rehabilitation,* 10: doi: 10.1186/1743-0003-10-5.

Dietz, S. Grillner, A. Trepp, M. Hubli1 and M. Bolliger. (2009) “Changes in spinal reflex and locomotor activity after a complete spinal cord injury: a common mechanism?” *Brain,* 123: 2196-2205.

Digitimer.(2015) <http://www.digitimer.com/>.

Disbrow E, Roberts T, Krubitzer L. (2000) “Somatotopic organization of cortical fields in the lateral sulcus of Homo sapiens: evidence for SII and PV.” *The Journal of comparative neurology,* 418.1, 1-21.

Dobkin BH, Firestine A, West M, Saremi K, Woods R. (2004) “Ankle dorsiflexion as an fMRI paradigm to assay motor control for walking during rehabilitation.” *NeuroImage,* 23: 370-381.

Dobkin BH, Harkema S, Requejo P, Edgerton R. (1995) “Modulation of locomotor-like EMG activity in subjects with complete and incomplete spinal cord injury.” *Journal of neurologic rehabilitation,* 9:183-190.

Doeringer JR, Hoch MC, Krause BA. (2010) “Ice application effects on peroneus longus and tibialis anterior motoneuron excitability in subjects with functional ankle instability.” *The International journal of neuroscience,* 120: 17-22.

Dowman R, Darcey T, Barkan H, Thadani V, Roberts D. (2007) “Human intracranially-recorded cortical responses evoked by painful electrical stimulation of the sural nerve.” *NeuroImage,* 34: 743-763.

Dowman. (1994) “SEP topographies elicited by innocuous and noxious sural nerve stimulation. II. Effects of stimulus intensity on topographic pattern and amplitude.” *Electroencephalography and clinical neurophysiology,* 92: 303-315.

Dowman. (2007) “Neural mechanisms of detecting and orienting attention toward unattended threatening somatosensory targets. I. Intermodal effects.” *Psychophysiology,* 44: 407-419.

Drew T, Jiang W, Kably B, Lavoie S. (1996) “Role of the motor cortex in the control of visually triggered gait modifications.” *Canadian journal of physiology and pharmacology*, 74: 426-442.

Dromerick AW, Lum PS, Hidler J. “Activity-based therapies. (2006) ” *The journal of the American Society for Experimental NeuroTherapeutics*, 3:428-438.

Duysens J, Baken BC, Burgers L, Plat FM, den Otter AR, Kremer HP. (2004) “Cutaneous reflexes from the foot during gait in hereditary spastic paraparesis.” *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* 115: 1057-1062.

Edamura M, Yang JF, Stein RB. (1991) “Factors that determine the magnitude and time course of human H-reflexes in locomotion.” *The Journal of neuroscience : the official journal of the Society for Neuroscience,* 11: 420-427.

Edgerton VR, Tillakaratne NJ, Bigbee AJ, de Leon RD, Roy RR. (2004) "Plasticity of the spinal neural circuitry after injury." *Annual review of neuroscience,* 27: 145-167.

Edgerton, V. Reggie, et al. (2008) "Training locomotor networks." *Brain Res Rev,* 57:241-254.

Edin BB, Essick GK, Trulsson M, Olsson KA. (1995) "Receptor encoding of moving tactile stimuli in humans. I. Temporal pattern of discharge of individual low-threshold mechanoreceptors." *The Journal of neuroscience : the official journal of the Society for Neuroscience,* 15:830-847.

Eidelberg E, Walden JG, Nguyen LH. (1981) "Locomotor control in macaque monkeys.", *Brain,* 104: 647-663.

Ellaway PH, Catley M, Davey NJ, Kuppuswamy A, Strutton P, Frankel HL, Jamous A, Savic G. (2007) "Review of physiological motor outcome measures in spinal cord injury using transcranial magnetic stimulation and spinal reflexes." *Journal of rehabilitation research and development,* 44: 69-76.

Engineering Acoustics Inc. (2015) <http://www.atactech.com>.

Faist M, Hoefer C, Hodapp M, Dietz V, Berger W, Duysens J. (2006) "In humans Ib facilitation depends on locomotion while suppression of Ib inhibition requires loading." *Brain research,* 1076: 87-92.

Fehlings MG, Tator CH, Linden RD. (1989) "The relationships among the severity of spinal cord injury, motor and somatosensory evoked potentials and spinal cord blood flow." *Electroencephalography and clinical neurophysiology,* 74: 241-259.

Ferretti A, Del Gratta C, Babiloni C, Caulo M, Arienzo D, Tartaro A, Rossini PM, Romani GL. (2004) "Functional topography of the secondary somatosensory cortex for nonpainful and painful stimulation of median and tibial nerve: an fMRI study." *NeuroImage,* 23: 1217-1225.

Feuerbach JW, Grabiner MD, Koh TJ, Weiker GG. (1994) "Effect of an ankle orthosis and ankle ligament anesthesia on ankle joint proprioception." *The American journal of sports medicine,* 22: 223-229.

Field-Fote EC, Lindley SD, Sherman AL. (2005) "Locomotor training approaches for individuals with spinal cord injury: a preliminary report of walking-related outcomes." *Journal of neurologic physical therapy : JNPT,* 29: 127-127.

Forssberg H, Svartengren G. Hardwired. (1983) “locomotor network in cat revealed by a retained motor pattern to gastrocnemius after muscle transposition.” *Neurosci Lett*, 42:283-28.

Forssberg H. (1985) “Ontogeny of human locomotor control. I. Infant stepping, supported locomotion and transition to independent locomotion.” *Experimental brain research*, 57: 480-493.

Fouad K, Pearson K. (2004) “Restoring walking after spinal cord injury.” *Progress in neurobiology*, 73: 107-126.

Fukuyama H, Ouchi Y, Matsuzaki S, Nagahama Y, Yamauchi H, Ogawa M, Kimura J, Shibasaki H. (1997) “Brain functional activity during gait in normal subjects: a SPECT study.” *Neuroscience letters*, 228: 183-186.

Funase K, Miles TS. (1999) “Observations on the variability of the H reflex in human soleus.” *Muscle & nerve*, 22: 341-346.

Fung J, Barbeau H. (1994) “Effects of conditioning cutaneomuscular stimulation on the soleus H-reflex in normal and spastic paretic subjects during walking and standing.” *Journal of neurophysiology*, 72: 2090-2104.

Galen SS, Clarke CJ, McLean AN, Allan DB, Conway BA. (2014) “Isometric hip and knee torque measurements as an outcome measure in robot assisted gait training.” *NeuroRehabilitation*, 34: 287-295.

Gallasch E, Golaszewski SM, Fend M, Siedentopf CM, Koppelstaetter F, Eisner W, Gerstenbrand F, Felber SR. (2006) “Contact force- and amplitude-controllable vibrating probe for somatosensory mapping of plantar afferences with fMRI.” *Journal of magnetic resonance imaging : JMRI*, 24: 1177-1182.

Garland, S. J. & Hayes, K. C. (1987) “Effects of brushing on electromyographic activity and ankle dorsiflexion in hemiplegic subjects with foot drop.” *Physiotherapy Canada*, 39:239-247.

Geisler FH, Coleman WP, Grieco G, Poonian D and Sygen Study Group. (2001) “Measurements and recovery patterns in a multicenter study of acute spinal cord injury.” *Spine*,26: S68-86.

Golaszewski SM, Siedentopf CM, Koppelstaetter F, Fend M, Ischebeck A, Gonzalez-Felipe V, Haala I, Struhal W, Mottaghy FM, Gallasch E, Felber SR, Gerstenbrand F. (2005) “Human brain structures related to plantar vibrotactile stimulation: a functional magnetic resonance imaging study.” *NeuroImage*, 29: 923-929.

Goldshmit Y, Lythgo N, Galea MP, Turnley AM. (2008) “Treadmill training after spinal cord hemisection in mice promotes axonal sprouting and synapse formation and improves motor recovery.” *Journal of neurotrauma,* 25: 449-465.

Gordon KE, Wu M, Kahn JH, Dhaher YY, Schmit BD. (2009) “Ankle Load Modulates Hip Kinetics and EMG During Human Locomotion.” *Journal of neurophysiology,* 101: 2062-2076.

Gordon T, Stein RB, Thomas CK. (1986) “Innervation and function of hind-limb muscles in the cat after cross-union of the tibial and peroneal nerves.” *Physiol Lond,* 374:429-441.

Gossard JP, Cabelguen JM, Rossignol S. (1990) “Phase-dependent modulation of primary afferent depolarization in single cutaneous primary afferents evoked by peripheral stimulation during fictive locomotion in the cat.” *Brain research,* 537:14-23.

Goulart F, Valls-Solé J, Alvarez R. (2000) “Posture-related changes of soleus H-reflex excitability.” *Muscle & nerve,* 23: 925-932.

Gravano S, Ivanenko YP, Maccioni G, Macellari V, Poppele RE, Lacquaniti F. (2011) “A novel approach to mechanical foot stimulation during human locomotion under body weight support.” *Human movement science,* 30: 352-367.

Grillner. “Locomotion in the Spinal Cat. (1973) ” *Advances in Behavioral Biology*, 7:515-535.

Grillner S, Rossignol S. (1978) “On the initiation of the swing phase of locomotion in chronic spinal cats.” *Brain research,* 146: 269-277.

Grillner S, Wallen P. (1985) “Central pattern generators for locomotion, with special reference to vertebrates.” *Ann. Rev Neurosci,* 8:233-61.

Grillner S, Zangger P. (1979) “On the central generation of locomotion in the low spinal cat.” *Experimental brain research,* 34:241-261.

Guertin, Pierre A. (2009) “The mammalian central pattern generator for locomotion.” *Brain research reviews,* 62: 45-56.

Guertin, Pierre A. (2012). “Central Pattern Generator for Locomotion: Anatomical, Physiological, and Pathophysiological Considerations.” *Frontiers in Neurology,* 3:183. doi: 10.3389/fneur.2012.00183

Hämäläinen H, Kekoni J, Sams M, Reinikainen K, Näätänen R. (1990) "Human somatosensory evoked potentials to mechanical pulses and vibration: contributions of SI and SII somatosensory cortices to P50 and P100 components." *Electroencephalography and clinical neurophysiology,* 75: 13-21.

Han SW, Chung YG, Kim HS, Chung SC, Park JY, Kim SP. (2013) "Evaluation of somatosensory cortical differences between flutter and vibration tactile stimuli." *Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society*. Piscataway, NJ : IEEE Service Center, 2013:4402-5. doi: 10.1109/EMBC.2013.6610522.

Hanna JP, Frank JI. (1995) "Automatic stepping in the pontomedullary stage of central herniation." *Neurology,* 45:985-986.

Hari R, Nagamine T, Nishitani N, Mikuni N, Sato T, Tarkiainen A, Shibasaki H. (1996) "Time-varying activation of different cytoarchitectonic areas of the human SI cortex after tibial nerve stimulation." *NeuroImage,* 4: 111-118.

Hari, Riitta. (1980) "Evoked potentials elicited by long vibrotactile stimuli in the human EEG." *Pflügers Archiv : European journal of physiology,* 384: 167-70.

HarkemaSJ, Hurley SL, Patel UK, Requejo PS, Dobkin BH, Edgerton VR. (1997) "Human Lumbosacral Spinal Cord Interprets Loading During Stepping." *Journal of neurophysiology,* 77: 797-811.

Harkema, Susan J. (2007) "Plasticity of interneuronal networks of the functionally isolated human spinal cord." *Brain Research Reviews,* 57: 255–264.

Harkema, Susan J. (2001) "Neural Plasticity after Human Spinal Cord Injury:Application of Locomotor Training to the Rehabilitation of Walking." *The Neuroscientist : a review journal bringing neurobiology,* 7: 455-468.

Harrington GS, Hunter Downs J 3rd. (2001) "FMRI mapping of the somatosensory cortex with vibratory stimuli. Is there a dependency on stimulus frequency?" *Brain research,* 897: 188-192.

Harrington GS, Wright CT, Downs JH 3rd. (2000) "A new vibrotactile stimulator for functional MRI." *Human brain mapping,* 10: 140-145.

Hashimoto. (1987) "Somatosensory evoked potentials elicited by air-puff stimuli generated by a new high-speed air control system." *Electroencephalography and clinical neurophysiology,* 67: 231-237.

Hauck M, Baumgärtner U, Hille E, Hille S, Lorenz J, Quante M. (2006) "Evidence for early activation of primary motor cortex and SMA after electrical lower limb stimulation using EEG source reconstruction." *Brain research,* 1125: 17-25.

Hayashi R, Tako K, Tokuda T, Yanagisawa N. (1992) "Comparison of amplitude of human soleus H-reflex during sitting and standing." *Neuroscience research,* 13: 227-233.

Hayward LF, Nielsen RP, Heckman CJ, Hutton RS. (1986) "Tendon vibration-induced inhibition of human and cat triceps surae group I reflexes: evidence of selective Ib afferent fiber activation." *Experimental neurology,* 94: 333-47.

Hegner Li Y, Saur R, Veit R, Butts R, Leiberg S, Grodd W, Braun C. (2007) "BOLD adaptation in vibrotactile stimulation: neuronal networks involved in frequency discrimination." *Journal of neurophysiology*, 97: 264-271.

Hiebert GW, Whelan PJ, Prochazka A, Pearson KG. (1996) "Contribution of hind limb flexor muscle afferents to the timing of phase transitions in the cat step cycle." *Journal of neurophysiology*, 75: 1126-1137.

Hijmans JM, Geertzen JH, Schokker B, Postema K. (2007) "Development of vibrating insoles." *International journal of rehabilitation research,* 30: 343-345.

Hijmans, Juha M. (2009) *Orthotic Interventions to Improve Standing Balance in Somatosensory Loss*. PhD thesis; Centrum voor Revalidatie, Universitair Medisch Centrum Groningen.

Hodgson JA, Roy RR, Leon de R, Dobkin B, Reggie Edgerton V. (1994) "Can the mammalian lumbar spinal cord learn a motor task?" *Medicine and science in sports and exercise,* 26:1491-1497.

Hoffmann, Paul. (1910) "Beitrag zur Kenntnis der menschlichen Reflexe mit besonderer Berucksichtigung der elektrischen Erscheinungen." *Arch Anat Physiol*, 223–246.

Hornby TG, Zemon DH, Campbell D. (2005) "Robotic-assisted, body-weight-supported treadmill training in individuals following motor incomplete spinal cord injury." *Physical therapy,* 85: 52-66.

Hoshiyama M, Kakigi R. (2000) "After-effect of transcutaneous electrical nerve stimulation (TENS) on pain-related evoked potentials and magnetic fields in normal subjects." *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*, 111: 717-724.

Hu L, Zhang ZG, Hu Y. (2012) “A time-varying source connectivity approach to reveal human somatosensory information processing.” *NeuroImage,* 62: 217-228.

Hu Y, Liu H, Luk KD. (2011) “Time-frequency analysis of somatosensory evoked potentials for intraoperative spinal cord monitoring.” *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society,* 28: 504-511.

Hu Y, Luk KD, Lu WW, Leong JC. (2002) “Comparison of time-frequency analysis techniques in intraoperative somatosensory evoked potential (SEP) monitoring.” *Computers in biology and medicine,* 32: 13-23.

Hu. Y, Zhang, Z.G, Chan.S.C., Luk. K. (2008) “High-resolution Time-frequency Analysis of Somatosensory Evoked Potential Components by Means of Matching Pursuit.” *Signal Processing, 2008. ICSP 2008. 9th International Conference on,* 153 - 156.

Hubli M, Dietz V. (2013) “The physiological basis of neurorehabilitation--locomotor training after spinal cord injury.” *Journal of neuroengineering and rehabilitation,* 10:5. doi: 10.1186/1743-0003-10-5.

Hugon. (1973) “Methodology of the Hoffmann reflex in man.” *New Developments in Electromyography and Clinical Neurophysiology,* 3:277–293.

Hultborn H, Illert M, Nielsen J, Paul A, Ballegaard M, Wiese H. (1996) “On the mechanism of the post-activation depression of the H-reflex in human subjects.” *Experimental brain research,* 108: 450-62.

Hultborn H, Petersen N, Brownstone P, Nielsen J. (1993) “Evidence of fictive spinal locomotion in the marmoset.” Soc Neurosci Abstr, 19: 539

Jeka JJ, Schöner G, Dijkstra T, Ribeiro P, Lackner JR. (1997) “Coupling of fingertip somatosensory information to head and body sway.” *Experimental brain research,* 113: 475-783.

Johnson D, Jürgens R, Kongehl G, Kornhuber HH. (1975) “Somatosensory evoked potentials and magnitude of perception.” *Experimental brain research,* 22: 331-334.

Johnson D, Jürgens R, Kornhuber HH. (1980) “Somatosensory-evoked potentials and vibration.” *Archiv für Psychiatrie und Nervenkrankheiten,* 228: 101-107.

Jonathan Shemmell, Je Hi An, Eric J. Perreault. (2009) “The Differential Role of Motor Cortex in Stretch Reflex Modulation Induced by Changes in

Environmental Mechanics and Verbal Instruction." *The Journal of Neuroscience*, 29: 13255-13263

Jordan LM. (1998) "Initiation of locomotion in mammals." *Annals of the New York Academy of Sciences*, 860:83-93.

Jousmäki V, Hari R. (1999) "Somatosensory evoked fields to large-area vibrotactile stimuli." *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*, 110: 905-909.

Kaas JH, Qi HX, Burish MJ, Gharbawie OA, Onifer SM, Massey JM. (2007) "Cortical and subcortical plasticity in the brains of humans, primates, and rats after damage to sensory afferents in the dorsal columns of the spinal cord." *Experimental neurology*, 209: 407-416.

Kakigi R, Koyama S, Hoshiyama M, Shimojo M, Kitamura Y, Watanabe S. (1995) "Topography of somatosensory evoked magnetic fields following posterior tibial nerve stimulation." *Electroencephalography and clinical neurophysiology*, 95: 127-134.

Kany C, Treede RD. (1997) "Median and tibial nerve somatosensory evoked potentials: middle-latency components from the vicinity of the secondary somatosensory cortex in humans." *Electroencephalography and clinical neurophysiology*, 104: 402-410.

Karhu J, Tesche CD. (1999) "Simultaneous early processing of sensory input in human primary (SI) and secondary (SII) somatosensory cortices." *Journal of neurophysiology*, 81: 2017-2025.

Kavounoudias A, Roll R, Roll JP. (1998) "The plantar sole is a 'dynamometric map' for human balance control." *Neuroreport*, 9: 3247-3252.

Kekoni J, Hämäläinen H, Saarinen M, Gröhn J, Reinikainen K, Lehtokoski A, Näätänen R. (1997) "Rate effect and mismatch responses in the somatosensory system: ERP-recordings in humans." *Biological psychology*, 46: 125-142.

Keller M, Pfusterschmied J, Buchecker M, Müller E, Taube W. (2012) "Improved postural control after slackline training is accompanied by reduced H-reflexes." *Scandinavian journal of medicine & science in sports*, 22: 471-477.

Kennedy PM, Inglis JT. (2002) "Distribution and behaviour of glabrous cutaneous receptors in the human foot sole." *The Journal of physiology*, 538: 995–1002.

Knikou Maria. (2010a) “Plantar cutaneous afferents normalize the reflex modulation patterns during stepping in chronic human spinal cord injury.” *Journal of neurophysiology,* 103: 1304-1314.

Knikou, Maria. (2010b) “Neural control of locomotion and training-induced plasticity after spinal and cerebral lesions.” *Clinical neurophysiology,* 121: 1655-1668.

Knikou M, Angeli CA, Ferreira CK, HarkemaSJ. (2009) “Flexion reflex modulation during stepping in human spinal cord injury.” *Experimental brain research,* 196: 341-351.

Knikou M, Conway BA. (2001) “Modulation of soleus H-reflex following ipsilateral mechanical loading of the sole of the foot in normal and complete spinal cord injured humans.” *Neuroscience letters,* 303:107-110.

Knikou M, Conway BA. (2005) “Effects of electrically induced muscle contraction on flexion reflex in human spinal cord injury.” *Spinal cord,* 43: 640-648.

Knikou M, Hajela N, Mummidisetty CK, Xiao M, Smith AC. (2011) “Soleus H-reflex phase-dependent modulation is preserved during stepping within a robotic exoskeleton.” *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* 122: 1396-1404.

Knikou M, Kay E, Rymer WZ. (2006) “Modulation of flexion reflex induced by hip angle changes in human spinal cord injury.” *Experimental brain research,* 168: 577-586.

Knikou M, Rymer Z. (2002) “Effects of changes in hip joint angle on H-reflex excitability in humans.” *Experimental brain research,* 143: 149-159.

Knikou, M. (2007) “Plantar cutaneous input modulates differently spinal reflexes in subjects with intact and injured spinal cord.” *Spinal cord,* 45: 69-77.

Knikou, Maria. (2008) “The H-reflex as a probe: pathways and pitfalls.” *Journal of neuroscience methods,* 171: 1-12.

Knikou, Maria. (2012) “Plasticity of corticospinal neural control after locomotor training in human spinal cord injury.” *Neural plasticity,* 2012: 254948, doi: 10.1155/2012/254948

Knutsson E, Richards C. (1979) “Different types of disturbed motor control in gait of hemiparetic patients.” *Brain : a journal of neurology,* 102: 405-430.

Koceja DM, Trimble MH, Earles DR. (1993) “Inhibition of the soleus H-reflex in standing man.” *Brain research,* 629: 155-158.

Konietzny F, Hensel H. (1977) “Response of rapidly and slowly adapting mechanoreceptors and vibratory sensitivity in human hairy skin.” *Pflügers Archiv : European journal of physiology,* 368: 39-44.

Kremneva EI, Chernikova LA, Konovalov RN, Krotenkova MV, Saenko IV, Kozlovskaia IB. (2012) “Activation of the sensorimotor cortex with the use of a device for the mechanical stimulation of the plantar support zones.” *Fiziologiia cheloveka,* 38: 61-68.

Lammertse D, Dungan D, Dreisbach J, Falci S, Flanders A, Marino R, Schwartz E and National Institute on Disability and Rehabilitation. (2007) “Neuroimaging in traumatic spinal cord injury: an evidence-based review for clinical practice and research.” *The journal of spinal cord medicine,* 30: 205-214.

Lavrov Igor, Grégoire Courtine, Christine J. Dy, Rubia van den Brand, Andy J. Fong, Yuri Gerasimenko, Hui Zhong, Roland R. Roy and V. Reggie Edgerton. (2010) “Facilitation of Stepping with Epidural Stimulation in Spinal Rats: Role of Sensory Input.” *The Journal of Neuroscience,* 28: 7774–7780.

Lau RW, Yip SP, Pang MY. (2012) “Whole-body vibration has no effect on neuromotor function and falls in chronic stroke.” *Medicine and science in sports and exercise,* 44: 1409-1418.

Li C, Houlden DA, Rowed DW. (1990) “Somatosensory evoked potentials and neurological grades as predictors of outcome in acute spinal cord injury.” *Journal of neurosurgery,* 72: 600-609.

Libet B, Alberts WW, Wright EW Jr, Feinstein B. (1967) “Responses of human somatosensory cortex to stimuli below threshold for conscious sensation.” *Science,* 158: 1597-600.

Lovely RG, Gregor RJ, Edgerton VR. (1986a) “Weight-bearing hindlimb stepping in treadmill-exercised adult spinal cat.” *Brain research,* 514:206-218.

Lovely RG, Gregor RJ, Roy RR, Edgerton VR. (1986b) “Effects of training on the recovery of full-weight-bearing stepping in the adult spinal cat.” *Experimental neurology,* 92: 421-435.

MacKay-Lyons & Marilyn, Marilyn. (2002) “Central pattern generation of locomotion: a review of the evidence.” *Physical therapy,* 82: 69-83.

Makihara, Yukiko. (2011) *Functional Implications of H-reflex Modulation and Modification in Human Soleus, Medial Gastrocnemius, and Lateral*

Gastrocnemius Muscles. Ph.D Theses, The University of North Carolina at Chapel Hill.

Maldjian JA, Gottschalk A, Patel RS, Pincus D, Detre JA, Alsop DC. (1999) "Mapping of secondary somatosensory cortex activation induced by vibrational stimulation: an fMRI study." *Brain research*, 824: 291-295.

Manella, Kathleen J. (2011) *Operant Conditioning of Tibialis Anterior and Soleus H-reflex Improves Spinal Reflex Modulation and Walking Function in Individuals with Motor Incomplete Spinal Cord Injury*. University of Miami, <http://scholarlyrepository.miami.edu/cgi/viewcontent.cgi?article=1681&context=oa_dissertations>.

Manjarrez E, Diez-Martínez O, Méndez I, Flores A. (2002) "Stochastic resonance in human electroencephalographic activity elicited by mechanical tactile stimuli." *Neuroscience letters*, 324: 213-216.

Marque P, Nicolas G, Marchand-Pauvert V, Gautier J, Simonetta-Moreau M, Pierrot-Deseilligny E. (2001) "Group I projections from intrinsic foot muscles to motoneurones of leg and thigh muscles in humans." *The Journal of physiology*, 536: 313-327.

Martínez L, Pérez T, Mirasso CR, Manjarrez E. (2007) "Stochastic resonance in the motor system: effects of noise on the monosynaptic reflex pathway of the cat spinal cord." *Journal of neurophysiology*, 97: 4007-4016.

Matyas TA, Spicer SD. (1980) "Facilitation of the tonic vibration reflex (TVR) by cutaneous stimulation in hemiplegics." *American journal of physical medicine*, 59: 280-287.

Mauguiere F, Allison T, Babiloni C, Buchner H, Eisen AA,Goodin DS, Jones SJ, Kakigi R, Matsuoka S, Nuwer M,Rossini PM & Shibasaki H. (1999) "Somatosensory evoked potentials. The International Federation of Clinical Neurophysiology." *Electroencephalography and clinical neurophysiology. Supplement*,52:79-90.

Maurer C, Mergner T, Bolha B, Hlavacka F. (2001) "Human balance control during cutaneous stimulation of the plantar soles." *Neuroscience letters*, 302: 45-48.

McBride JM, Nuzzo JL, Dayne AM, Israetel MA, Nieman DC, Triplett NT. (2010) "Effect of an acute bout of whole body vibration exercise on muscle force output and motor neuron excitability." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 24: 184-189.

McCrea., David A. (2001) “Spinal circuitry of sensorimotor control of locomotion.” *The Journal of physiology,* 533: 41-50.

McGowan CP, Neptune RR, Kram R. (2008) “Independent effects of weight and mass on plantar flexor activity during walking: implications for their contributions to body support and forward propulsion.” *Journal of applied physiology (Bethesda, Md. : 1985),* 105: 486–494.

McDonnell Mark D, Derek Abbott. (2009) “What Is Stochastic Resonance? Definitions, Misconceptions, Debates, and Its Relevance to Biology.” *PLOS Computational Biology,* 5: e1000348. doi:10.1371/journal.pcbi.1000348.

McKay WB, Lee DC, Lim HK, Holmes SA, Sherwood AM. (2005) “Neurophysiological examination of the corticospinal system and voluntary motor control in motor-incomplete human spinal cord injury.” *Experimental brain research,* 163: 379-387.

Melnyk M, Kofler B, Faist M, Hodapp M, Gollhofer A. (2008) “Effect of a whole-body vibration session on knee stability.” *International journal of sports medicine,* 29:839-44. doi: 10.1055/s-2008-1038405

Meyer PF, Oddsson LI, De Luca CJ. (2004) “The role of plantar cutaneous sensation in unperturbed stance.” *Experimental brain research,* 156: 505-512.

Meyer-Heim A, Borggraefe I, Ammann-Reiffer C, Berweck S, Sennhauser FH, Colombo G, Knecht B, Heinen F. (2007) “Feasibility of robotic-assisted locomotor training in children with central gait impairment.” *Developmental medicine and child neurology,* 49: 900-906.

Miles TS, Flavel SC, Nordstrom MA. (2004) “Stretch reflexes in the human masticatory muscles: a brief review and a new functional role.” *Human movement science,* 23: 337-349.

Misiaszek, John. (2003) “The H-reflex as a tool in neurophysiology: its limitations and uses in understanding nervous system function.” *Muscle & nerve,* 28: 144-160.

Mohr T, J. Podenphant,F. Biering–Sorensen,H. Galbo,G. Thamsborg,M. Kjaer. (1997) “Increased Bone Mineral Density after Prolonged Electrically Induced.” *Calcified tissue international,* 61:22-25.

Mori S, Nishimura H, Kurakami C, Yamamura T, Aoki M. (1978) “Controlled locomotion in the mesencephalic cat: distribution of facilitatory and inhibitory regions within pontine tegmentum.” *Journal of neurophysiology,* 41: 1580-1591.

Morin C, Pierrot-Deseilligny E. (1977) “Role of Ia afferents in the soleus motoneurones. Inhibition during a tibialis anterior voluntary contraction in man.” *Experimental brain research,* 27: 509-522.

Morita H, Petersen N, Christensen LO, Sinkjaer T, Nielsen J. (1998) “Sensitivity of H-reflexes and stretch reflexes to presynaptic inhibition in humans.” *Journal of neurophysiology,* 80: 610-620.

Morley JW, Rowe MJ. (1990) “Perceived pitch of vibrotactile stimuli: effects of vibration amplitude, and implications for vibration frequency coding.” *The Journal of physiology,* 431:403-416.

Morton SM, Bastian AJ. (2004) “Cerebellar Control of Balance and Locomotion.” *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry,* 10: 247-259.

Naka D, Kakigi R, Koyama S, Xiang J, Suzuki H. (1998) “Effects of tactile interference stimulation on somatosensory evoked magnetic fields following tibial nerve stimulation.” *Electroencephalography and clinical neurophysiology*, 109: 168-177.

Nakajima T, Sakamoto M, Tazoe T, Endoh T, Komiyama T. (2009) “Location-specific modulations of plantar cutaneous reflexes in human (peroneus longus muscle) are dependent on co-activation of ankle muscles.” *Experimental brain research,* 195: 403-412.

Nakajima T, Sakamoto M, Tazoe T, Endoh T, Komiyama T. (2006) “Location specificity of plantar cutaneous reflexes involving lower limb muscles in humans.” *Experimental brain research,* 175: 514-525.

Nakazawa K, Kawashima N, Akai M, Yano H. (2004a) “On the reflex coactivation of ankle flexor and extensor muscles induced by a sudden drop of support surface during walking in humans.” *Journal of applied physiology*, 96: 604-611.

Nakazawa K, Miyoshi T, Sekiguchi H, Nozaki D, Akai M, Yano H. (2004b) “Effects of loading and unloading of lower limb joints on the soleus H-reflex in standing humans.” *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*, 115: 1296-1304.

Naatanen R, P. T. Michie. (1979) “Different Variants of Endogenous Negative Brain Potentials in Performance Situations: A Review and Classification.” *Human Evoked Potentials,* 9:251-267.

Nelson AJ, Staines WR, Graham SJ, McIlroy WE. (2004) “Activation in SI and SII: the influence of vibrotactile amplitude during passive and task-relevant stimulation.” *Brain research. Cognitive brain research,* 19: 174-184.

Ness LL, Field-Fote EC. (2009) “Effect of whole-body vibration on quadriceps spasticity in individuals with spastic hypertonia due to spinal cord injury.” *Restorative neurology and neuroscience* 27: 621-631.

NeuroScan. 2015. < http://compumedicsneuroscan.com//>.

Nielsen JB, Sinkjaer T. (2002) “Afferent feedback in the control of human gait.” *Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology,* 12: 213-217.

Nielsen., Jens Bo. (2003) “How we walk: central control of muscle activity during human walking.” *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry,* 9: 195-204.

Noga BR, Kriellaars DJ, Brownstone RM, Jordan LM. (2003) “Mechanism for activation of locomotor centers in the spinal cord by stimulation of the mesencephalic locomotor region.” *Journal of neurophysiology*, 90: 1464-1478.

Norton JA, Bennett DJ, Knash ME, Murray KC, Gorassini MA. (2008) “Changes in sensory-evoked synaptic activation of motoneurons after spinal cord injury in man.” *Brain : a journal of neurology* Brain, 131:1478-1491.

Novak P, Novak V. (2006) “Effect of step-synchronized vibration stimulation of soles on gait in Parkinson's disease: a pilot study.” *Journal of neuroengineering and rehabilitation*, 4:3-9.

Nuwer, M.R. (1998) “Fundamentals of evoked potentials and common clinical applications today.” *Electroencephalography and clinical neurophysiology,* 106: 142-148.

Pang MY, Yang JF. (2002) “Sensory Gating for the Initiation of the Swing Phase in Different directions of human infant stepping.” *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 22: 5734-5740.

Petersen, L O D Christensen, H Morita, T Sinkjær, and J Nielsen. (1998) “Evidence that a transcortical pathway contributes to stretch reflexes in the tibialis anterior muscle in man.” *The Journal of Physiology*, 512:267–276.

Pearson KG, Rossignol S. (1991) “Fictive motor patterns in chronic spinal cats.” *Journal of neurophysiology,* 66: 1874-1887.

Pearson, Keir G. (1993) “Common principles of motor control in vertebrates and invertebrates.” *Annual review of neuroscience,* 16: 265-297.

Petersen NT, Pyndt HS, Nielsen JB. (2003) “Investigating human motor control by transcranial magnetic stimulation.” *Experimental brain research,* 152: 1-16.

Petersen TH, Willerslev-Olsen M, Conway BA, Nielsen JB. (2012) “The motor cortex drives the muscles during walking in human subjects.” *The Journal of physiology,* 590: 2443-52

Phadke CP, Wu SS, Thompson FJ, Behrman AL. (2007) “Comparison of soleus H-reflex modulation after incomplete spinal cord injury in 2 walking environments: treadmill with body weight support and overground.” *Archives of physical medicine and rehabilitation,* 88: 1606-1613.

Pierrot-Deseilligny E, Bussel B, Sideri G, Cathala HP, Castaigne P. (1973) “Effect of voluntary contraction on H reflex changes induced by cutaneous stimulation in normal man.” *Electroencephalography and clinical neurophysiology,* 34: 185-192.

Pihko E, Lauronen L, Wikström H, Taulu S, Nurminen J, Kivitie-Kallio S, Okada Y. (2004) “Somatosensory evoked potentials and magnetic fields elicited by tactile stimulation of the hand during active and quiet sleep in newborns.” *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* 115: 448-455.

Pizzagalli, DA.(2006) “Electroencephalography and High-Density Electrophysiological Source Localization.” *Progress in neurobiology,* 3:56-84.

Pop PH, Oepkes CT, Notermans SL, Vlek NM, Stegeman DF. (1988) “Dermatomal somatosensory evoked potentials of the lumbar and cervical roots. Method and normal values.” *European archives of psychiatry and neurological sciences,* 238: 22-27.

Precision Microdrives. 2015. <http://www.precisionmicrodrives.com/>.

Priplata AA, Niemi JB, Harry JD, Lipsitz LA, Collins JJ. (2003) “Vibrating insoles and balance control in elderly people.” *Lancet,* 362: 1123-1124.

Priplata AA, Patritti BL, Niemi JB, Hughes R, Gravelle DC, Lipsitz LA, Veves A, Stein J, Bonato P, Collins JJ. (2006) “Noise-enhanced balance control in patients with diabetes and patients with stroke.” *Annals of neurology,* 59: 4-12.

Reaz MB, Hussain MS, Mohd-Yasin F. (2006) “Techniques of EMG signal analysis: detection, processing, classification and applications (Correction).” *Biological procedures online,* 8:163. doi: 10.1251/bpo124.

Ritzmann R, Kramer A, Gollhofer A, Taube W. (2011) “The effect of whole body vibration on the H-reflex, the stretch reflex, and the short-latency response during hopping.” *Scandinavian journal of medicine & science in sports*, doi: 10.1111/j.1600-0838.2011.01388.x.

Robbins S, Gouw GJ, McClaran J. (1992) “Shoe sole thickness and hardness influence balance in older men.” *Journal of the American Geriatrics Society,* 40: 1089-1094.

Roby-Brami A, Bussel B. (1990) “Effects of flexor reflex afferent stimulation on the soleus H reflex in patients with a complete spinal cord lesion: evidence for presynaptic inhibition of Ia transmission.” *Experimental brain research* 81: 593-601.

Rood, M. (1954) “Neurophysiological reactions as a basis for physical therapy.” *The Physical therapy review,* 34: 444-449.

Rossi A, Decchi B. (1994) “Flexibility of lower limb reflex responses to painful cutaneous stimulation in standing humans: evidence of load-dependent modulation.” *The Journal of physiology,* 481: 521-532.

Sadowsky CL, McDonald JW. (2009) “Activity-based restorative therapies: concepts and applications in spinal cord injury-related neurorehabilitation.” *Developmental disabilities research reviews,* 15: 112-116.

Sai K. Banala, Seok Hun Kim, Sunil K. Agrawal, and John P. Scholz. (2009) “Robot Assisted Gait Training With Active Leg Exoskeleton (ALEX).” *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 17:2-8

Satoshi Kudoh, Ming Ding, Hirohsi Takemura, Hiroshi Mizoguchi. (2011) “Improvement of Plantar Tactile Sensitivity by Stochastic Resonance for Prevention of Falling.” *4th International Congress on Image and Signal Processing*, 182 - 185.

Sayenko DG, Masani K, Alizadeh-Meghrazi M, Popovic MR, Craven BC. (2010) “Acute effects of whole body vibration during passive standing on soleus H-reflex in subjects with and without spinal cord injury.” *Neuroscience letters,* 482: 66-70.

Sayenko DG, Vette AH, Kamibayashi K, Nakajima T, Akai M, Nakazawa K. (2007) “Facilitation of the soleus stretch reflex induced by electrical excitation of

plantar cutaneous afferents located around the heel." *Neuroscience letters*, 415: 294-298.

Sayenko DG, Vette AH, Obata H, Alekhina MI, Akai M, Nakazawa K. (2009) "Differential effects of plantar cutaneous afferent excitation on soleus stretch and H-reflex." *Muscle & nerve*, 39: 761-9

Schlee, M.A. Günther. (2010) *Quantitative assessment of foot sensitivity: The effects of foot sole skin temperature, blood flow at the foot area and footwear*. Faculty of Behavioral and Social Sciences of the Chemnitz University of Technolog.

Schmid UD, Hess CW, Ludin HP. (1988) "Somatosensory evoked potentials following nerve and segmental stimulation do not confirm cervical radiculopathy with sensory deficit." *Journal of neurology, neurosurgery, and psychiatry*, 51: 182–187.

Schneider, F. (2006) *Korpuskuläre und enkapsulierten Nervenendigugen im Bereich der Fußsohle des Menschen.* Doctoral dissertation, Orthopädische Klinik und Polyklinik der.

Sherrington, C. S. (1910) "Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing." *The Journal of physiology*, 40:28-121.

Siedentopf CM, Heubach K, Ischebeck A, Gallasch E, Fend M, Mottaghy FM, Koppelstaetter F, Haala IA, Krause BJ and others. (2008) "Variability of BOLD response evoked by foot vibrotactile stimulation: influence of vibration amplitude and stimulus waveform." *NeuroImage*, 41: 504-510.

Skinner PH, Antinoro F. (1971) "The effects of signal rise time and duration on the early components of the auditory evoked cortical response." *Journal of speech and hearing research*, 14: 552-558.

Skinner PH, Jones HC. (1968) "Effects of signal duration and rise time on the auditory evoked potential." *Journal of speech and hearing research*, 11: 301-306.

Snyder, Abraham Z. (1992) "Steady-state vibration evoked potentials: description of technique and characterization of responses." *Electroencephalography and clinical neurophysiology*, 84: 257-268.

Sonnenborg FA, Andersen OK, Arendt-Nielsen L, Treede RD. (2001) "Withdrawal reflex organisation to electrical stimulation of the dorsal foot in humans." *Experimental brain research*, 136: 303-312..

Spackman L, Boyd S, Towell T. (2006) “Identification and characterization of somatosensory off responses.” *Brain research,* 1114: 53-62.

Stacey Apple, Kelly Ehlert, Pam Hysinger, Cara Nash, Michael Voight, Pat Sells. “The Effect of Whole Body Vibration on Ankle Range of Motion and the H-reflex.” *North American Journal of Sports Physical Therapy : NAJSPT*, 5: 33–39.

Stewart JE, Barbeau H, Gauthier S. (1991) “Modulation of locomotor patterns and spasticity with clonidine in spinal cord injured patients.” *The Canadian journal of neurological sciences,* 18: 321-332.

Sundberg LM, Herrera JJ, Narayana PA. (2010) “In vivo longitudinal MRI and behavioral studies in experimental spinal cord injury.” *Journal of neurotrauma,* 27: 1753-1767.

Tabakow P, Raisman G, Fortuna W, Czyz M, Huber J, Li D, Szewczyk P, Okurowski S, Miedzybrodzki R, Czapiga B, Salomon B, Halon A, Li Y, Lipiec J, Kulczyk A, Jarmundowicz W. (2014) “Functional regeneration of supraspinal connections in a patient with transected spinal cord following transplantation of bulbar olfactory ensheathing cells with peripheral nerve bridging.” *Cell transplantation*, doi: 10.3727/096368914X685131

Tannan V, Dennis R, Tommerdahl M. (2005) “A novel device for delivering two-site vibrotactile stimuli to the skin.” *Journal of neuroscience methods*, 147: 75-81.

Taylor S, P Ashby, and M Verrier. (1984) “Neurophysiological changes following traumatic spinal lesions in man.” *Journal of Neurology, Neurosurgery & Psychiatry,* 47: 1102–1108.

Thilmann AF, Schwarz M, Töpper R, Fellows SJ, Noth J. (1991) “Different mechanisms underlie the long-latency stretch reflex response of active human muscle at different joints.” *The Journal of Physiology*, 444: 631–643.

Thomas SL, Gorassini MA. (2005) “Increases in corticospinal tract function by treadmill training after incomplete spinal cord injury.” *Journal of neurophysiology*, 94: 2844-2855.

Tobimatsu S, Zhang YM, Suga R, Kato M. (2000) “Differential temporal coding of the vibratory sense in the hand and foot in man.” *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* 111: 398-404.

Troni W. (1983) “The value and limits of the H reflex as a diagnostic tool in S1 root compression.” *Electromyography and clinical neurophysiology,* 23: 471-480.

Truett Allison, McCarthy G, Wood CC. (1992) “The relationship between human long-latency somatosensory evoked potentials recorded from the cortical surface and from the scalp.” *Electroencephalography and clinical neurophysiology,* 84.4:301-314.

Tzvetanov P, Rousseff RT. (2005) “Predictive value of median-SSEP in early phase of stroke: a comparison in supratentorial infarction and hemorrhage.” *Clinical neurology and neurosurgery,* 107: 475-481.

Tzvetanov P, Rousseff RT, Milanov I. (2003) “Lower limb SSEP changes in stroke-predictive values regarding functional recovery.” *Clinical neurology and neurosurgery,* 105: 121-127.

Valeriani M, Le Pera D, Tonali P. (2001) “Characterizing somatosensory evoked potential sources with dipole models: advantages and limitations.” *Muscle & nerve,* 24: 325-339.

Van Nes IJ, Geurts AC, Hendricks HT, Duysens J. (2004) “Short-term effects of whole-body vibration on postural control in unilateral chronic stroke patients: preliminary evidence.” *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists,* 83: 867-873.

Van Wezel BM, Ottenhoff FA, Duysens J. (1997) “Dynamic control of location-specific information in tactile cutaneous reflexes from the foot during human walking.” *The Journal of neuroscience : the official journal of the Society for Neuroscience,* 17: 3804-3814.

Van Wezel BM, van Engelen BG, Gabreëls FJ, Gabreëls-Festen AA, Duysens J. (2000) “Abeta fibers mediate cutaneous reflexes during human walking.” *Journal of neurophysiology,* 83: 2980-2986.

Vilensky JA, Moore AM, Eidelberg E, Walden JG. (1992) “Recovery of locomotion in monkeys with spinal cord lesions.” *Journal of motor behavior,* 24: 288-296.

Vilensky JA, O'Connor BL. (1997) “Stepping in humans with complete spinal cord transection: a phylogenetic evaluation.” *Brain Res Rev,* 1: 284-292.

Visintin M, Barbeau H. (1989) “The effects of body weight support on the locomotor pattern of spastic paretic patients.” *The Canadian journal of neurological sciences* 16: 315-325.

Wang G, Grone B, Colas D, Appelbaum L, Mourrain P. (2011) “Synaptic plasticity in sleep: learning, homeostasis and disease.” *Trends in neurosciences,* 34: 452-463.

Wenger Nikolaus, Eduardo Martin Moraud, Stanisa Raspopovic. (2014). “Closed-loop neuromodulation of spinal sensorimotor circuits controls refined locomotion after complete spinal cord injury.” *Science translational medicine,* 6: 255ra133: dio: 10.1126/scitranslmed.3008325

Wedell, C. H. and S. B. Cummings Jr. (1938) “Fatigue of the vibratory sense.” *Journal of Experimental Psychology,* 22: 429-438.

Wernig A, Müller S. (1992) “Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries.” *Paraplegia,* 30: 229-238.

Wernig A, Müller S, Nanassy A, Cagol E. (1995) “Laufband therapy based on 'rules of spinal locomotion' is effective in spinal cord injured persons.” *The European journal of neuroscience,* 7: 823-829.

Whelan PJ, Hiebert GW, Pearson KG. (1995) “Stimulation of the group I extensor afferents prolongs the stance phase in walking cats.” *Experimental brain research,* 103: 20-30.

Whelan PJ. (1996) “Control of locomotion in the decerebrate cat.” *Progress in neurobiology,* 49:481-515.

Winchester Patricia, Smith Patricia, Nathan Foreman, James M Mosby, Fides Pacheco, Ross Querry, and Keith Tansey. (2009) “A Prediction Model for Determining Over Ground Walking Speed After Locomotor Training in Persons With Motor Incomplete Spinal Cord Injury.” *The Journal of Spinal Cord Medicine,* 32: 63-71.

Wirz M, Bastiaenen C, de Bie R, Dietz V. (2011) “Effectiveness of automated locomotor training in patients with acute incomplete spinal cord injury: a randomized controlled multicenter trial.” *BMC neurology,* doi: 10.1186/1471-2377-11-60.

Wood L, Nicol DJ, Thulin CE. (1998) “The effects of skin brushing on H reflex amplitude in normal human subjects.” *Experimental physiology,* 83: 175-183.

Woodman, Geoffrey F. (2010) “A brief introduction to the use of event-related potentials in studies of perception and attention.” *Attention, perception & psychophysics,* 72: 2031-2046.

Yamauchi N, Fujitani Y, Oikawa T. (1981) “Somatosensory evoked potentials elicited by mechanical and electrical stimulation of each single pain or tactile spot of the skin.” *The Tohoku journal of experimental medicine,* 133: 81-92.

Yang JF, Stein RB, James KB. (1991) “Contribution of peripheral afferents to the activation of the soleus muscle during walking in humans.” *Experimental brain research,* 87: 679-687.

Zehr EP, Stein RB. (1999) “What functions do reflexes serve during human locomotion?” *Progress in neurobiology,* 58: 185-205.

Zhang S, Li L. (2013) “The differential effects of foot sole sensory on plantar pressure distribution between balance and gait.” *Gait & posture,* 37: 532-535.

Zimmerman A, Bai L, Ginty DD. (2014) “The gentle touch receptors of mammalian skin.” *Science,* 346: 950-954.