Evoked Human Cutaneous Reflexes During

Standing and Step Initiation

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Abstract

Cutaneous reflexes have been shown to be task dependent, phase dependent and stimulus intensity dependent in movement tasks (e.g. walking and obstacle avoidance). We have demonstrated previously that cutaneous input can reduce reaction times and alter anticipatory postural adjustments that precede a step. It is not known how cutaneous input produces these changes. The influence of cutaneous reflexes during step initiation and standing was assessed in young, healthy subjects (n=15). Two sets of experiments were conducted. In the first experiment subjects stood on a force platform, then initiated three steps as fast as possible, to either a visual or sural go cue. For each "go" cue, a sural stimulation (2 Radiating Threshold) was delivered at two phases, loading and unloading phase of step initiation. Fifteen trials were acquired for each go cue during each of the two phases. Average reflex responses were determined from tibialis anterior (TA) muscle. This task was again repeated after the second experiment. In the second experiment subjects stood for 40 sec on a wooden platform and reflexes were evoked for varying stimulus intensities. Average evoked responses from TA were obtained. During step initiation, the primary effect in TA was a long latency excitation (70 - 90 ms). The results obtained demonstrate (1) *Effect of cueing*- reflexes were modulated during visual cueing vs. reversed signs during sural cueing**.** (2*) Effect of phase of step initiation*- greater amplitude for the loading than the unloading phase for both go cues. (3) *Effect of task*- net reflex response was primarily excitatory during step initiation but primarily inhibitory during standing. The cutaneous reflex responses for step initiation suggest behaviorally appropriate modulation of the reflexes which may play a role in the earlier release of the step and enhancement of APAs that we have previously reported (Kukulka et al, 2009).

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CHAPTER 1: Introduction

This study investigated for the first time the influence of cutaneous reflexes in anticipatory postural adjustments (APAs) that precede a step in healthy human subjects. In addition, we compared the reflex responses during step initiation to those evoked while standing. By comparing cutaneous reflexes under different conditions we were able to assess how these pathways are modulated in a functional task. In so doing, these findings help explain our earlier observation (C. G. Kukulka et al., 2009) that sural cueing has a positive influence on APAs in step initiation as compared to visual cueing.

Several reflex studies in humans (Aniss, Gandevia, & Burke, 1992; Burke, D., Dickson, H. G. and Skuse, N. F., 1991; Nielsen & Kagamihara, 1993) have shown sural nerve stimulation to produce an initial inhibition (~40 ms) followed by a significant later excitation (~80 ms) in tibialis anterior (TA) muscle, a major contributor to the posterior center of pressure displacement during step initiation. It has been proposed that short latency inhibition has a spinal origin (Burke, D., Dickson, H. G. and Skuse, N. F., 1991) and the later excitation may be mediated at least partly by a transcortical pathway (Christensen, Morita, Petersen, & Nielsen, 1999; Christensen, Petersen, Andersen, Sinkjaer, & Nielsen, 2000; Nielsen, Petersen, & Fedirchuk, 1997) . The study of cutaneous reflexes in TA therefore offered a unique opportunity to evaluate both potential spinal and cortical influence on the APAs.

Stimulation of the sural nerve has been shown to produce complex inhibitory and excitatory reflex effects (Christensen et al., 1999; Li, Kukulka, Rogers, Brunt, & Bishop, 2004) in lower limb muscles that are *task dependent*: sitting, standing, walking (Burke,

D., Dickson, H. G. and Skuse, N. F., 1991; Gibbs, Harrison, & Stephens, 1995) *phase dependent* : swing vs. stance phase of walking (J. Duysens, Trippel, Horstmann, & Dietz, 1990; J. Duysens, Tax, Trippel, & Dietz, 1992; Yang & Stein, 1990; Zehr EP, Komiyama T, Stein RB, 1997) and *stimulus intensity dependent*: i.e. during non-noxious vs. noxious (Crenna P, 1984 Aug; J. Duysens et al., 1990). These studies suggested that cutaneous reflexes can be modulated to affect activity in both short latency and long latency pathways.

Previous studies on step initiation (Brown S, Gregory A, Kukulka CG, Pommier M, Simone, A, 2007; Hajela N, Kukulka CG, Olson E, Peters A, Podratz K, Quade C, 2006; C. G. Kukulka et al., 2009) have reported that sural cuing produced (1) earlier onsets of TA and gluteus medius (GM) and greater mean EMG amplitudes in these muscles (2) earlier onset of force, greater vertical ground reaction forces and a greater rate of rise of force, and (3) greater center of pressure (COP) displacements in both the posterior and lateral direction. These studies demonstrated that step release is earlier with a sural stimulus “go” cue in comparison to visual “go” cue and also that APAs may be enhanced with sural cueing. We have demonstrated that sural stimulation can have positive effects on APAs but we do not know the underlying factors that may contribute to these enhanced APAs. Previous studies that have addressed the functional role of cutaneous afferent input and modulation of cutaneous reflexes have focused primarily on walking and obstacle avoidance (Van Wezel, Ottenhoff, & Duysens, 1997; Zehr EP, Komiyama T, Stein RB, 1997) but little attention has been given to the influence of cutaneous reflexes during step initiation.

It is essential to address this gap in knowledge because it has potential relevance to applications in the rehabilitation of patients with neurological disorders such as stroke and Parkinson's as well as elderly individuals who have frequent history of falls. APAs are diminished in both elderly subjects (Patla AE, Frank JS, Winter DA, Rietdyk S, Prasad S, 1993) and patients with neurologic disorders such as Parkinson's (Burleigh-Jacobs, Horak, Nutt, & Obeso, 1997; Fukson, Berkinblit, & Feldman, 1980; Mancini , Zampieri , Carlson-Kuhta, Chiari, & Horak FB., 2009) and stroke (Rogers, Hedman, & Pai, 1993). Additionally, the ability to react to a visual cue to step is markedly diminished in the elderly (Patla AE, Frank JS, Winter DA, Rietdyk S, Prasad S, 1993) which has been shown to be a strong predictor of falls (Lord & Fitzpatrick, 2001). The use of a sural cue to trigger activation of a step might be used to alter the diminished APAs and slower reaction times seen in the elderly and patients with neurological disturbances. In neuro-rehabilitation, there is still an emphasis on treating gait initiation deficits by giving visual cues. Step training using sural cues may have the potential to provide a more effective imperative cue than visual and other cutaneous cues (e.g. stimulation on hand and ear lobe) for influencing the APAs. Learning the importance of sural cueing along with the potential mechanisms involved may offer an alternative to treatment of patients with impaired APAs.

Our long term goal is to improve postural control in patient populations that include elderly people who have a tendency to fall and people with neurological disorders such as Parkinson's and stroke. The immediate objective was to demonstrate the effects of different tasks, phases of loading force, triggering cues and stimulus intensity on the

evoked cutaneous reflex responses in TA, one of the muscles responsible for generating an APA and also to identify factors underlying these responses. The general hypothesis of this study was that evoked responses in the TA muscle would demonstrate both short and long latency effects. These reflex responses would be influenced by the level of stimulus intensity and type of “go” cue, and would be modulated according to the task required (i.e. standing and step initiation) and phases of the loading force.

CHAPTER 2: Background

2.1 Influence of cutaneous input on spinal motor neurons

(Sherrington, 1910) established the foundations of our earliest knowledge of cutaneous reflexes in mammals through the study of the nociceptive flexion reflex in the hind limb of the decerebrate cat. He demonstrated that electrical stimulation of a peripheral nerve trunk resulted in the flexion of the stimulated limb and extension of the contra lateral limb. In the ipsilateral limb the excitation of alpha motoneurons to flexor muscles was associated with inhibition of those to extensors. He stated that whichever cutaneous nerve trunk was stimulated in the limb, the reflex in the limb muscles was essentially the same, which means that the general effect throughout was excitation of the motoneurons of flexors and inhibition of the motoneurons of extensors. The receptive field of the flexor reflex was found to include “the skin of the whole limb as far as the groin in the front, the perineum medially and the ischial region behind”. It was also stated that noxious stimuli within the receptive field caused not only a contraction of the flexors of hip and knee and the dorsiflexors of foot and digits but also a relaxation of antagonistic extensors and plantar flexors. Cutaneous stimulation of different skin areas caused reflex contraction of muscles mainly underlying the areas of stimulation. For example, contraction of upper abdominal muscle was caused by stroking the upper abdomen and contraction of lower abdominal muscles was a result of stroking of lower abdomen. This phenomenon, in which the location of the stimulus affects the particular muscles that was activated in the response, was later termed local sign. (Hagbarth, 1952) observed that cutaneous stimuli have a sub threshold effect on motoneuron excitability. He used low intensity electrical

stimulation to selectively activate large spindle afferents of motor nerve in cats thereby producing a contraction of the muscle through the monosynaptic stretch reflex pathway. It was demonstrated that mild pinching of wide areas of the skin overlying the contracting muscle increased the strength of the electrically evoked reflex contraction indicating that the motor neurons had been facilitated; while pinching the skin over the antagonist muscle diminished muscle contraction indicating that the motor neurons had been reciprocally inhibited (Fig. 1). Thus, it was shown that the effects of cutaneous stimuli on motor neuron excitability are both spatially specific and reciprocal causing excitation of specific motoneurons and inhibition of motoneurons of the corresponding antagonist muscles. He also found that extensor muscles in the cat could be excited by ipsilateral stimulation provided the stimuli were applied to the skin overlying the muscle belly and stimuli anywhere else in the limb produced inhibition. The flexor muscle was in contrast with this situation, as the inhibitory field was small and centered over the antagonist extensor muscle and the excitatory field was extensive and covered the reminder of the limb. The organization of these responses made it possible for the limb to be automatically withdrawn from a noxious stimulus whenever the latter was applied.

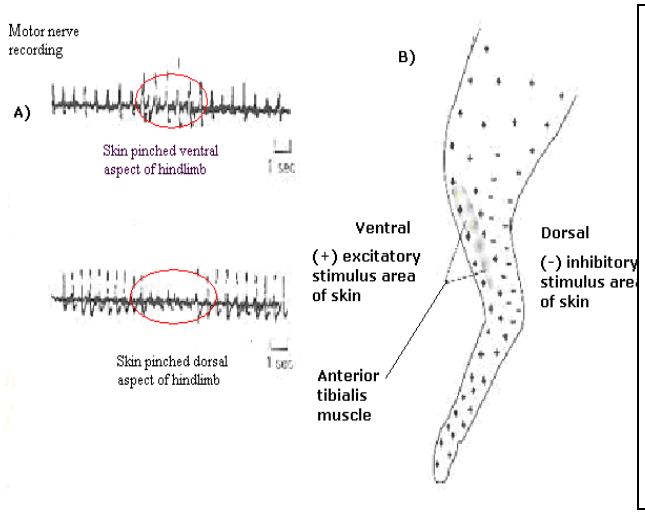


FIG.1. Adapted and modified from Hagbarth 1952: effect of cutaneous stimuli in modifying the excitability of specific motor neurons in a reciprocal fashion. A) Tonic stimulation of 1a afferents from the tibialis anterior muscle in a spinal cat elicits a monosynaptic reflex contraction of the muscle. The strength of this contraction is then used experimentally to monitor the effects of cutaneous stimuli on different areas of skin on the excitability of the motor neurons.
B) Diagram of cat hind limb shows the excitatory (+) and inhibitory (-) stimulus areas of skin for tibialis anterior.

Later, (Hagbarth, 1960) found evidence for similar reciprocal relationships for excitatory and inhibitory influences on flexor and extensor motoneurons in man. He observed that for both flexor and extensor muscles, there are specific excitatory and inhibitory skin areas. It was concluded that the reflex patterns in the human lower limb vary considerably according to the localization of the ipsilateral skin stimulus.

(Gassel & Ott, 1970a) investigated the excitability changes in the population of tricep surae motoneurons in man, on stimulation of the dorsal and plantar surfaces of the distal foot in humans. They showed that there were early excitatory changes at 40 to 90 msec with local sign in the triceps surae motoneurons. There was facilitation on stimulation of the dorsum and inhibition on plantar stimulation of the distal foot. A significant late increase in excitability occurred at 110 to 250 msec without local sign. It was suggested that changes in motoneuron excitability with serial alterations in electrode placement supported the concept of an intricate organization of the receptor fields of flexion and extension reflexes with considerable overlapping and interactions. Early investigations have demonstrated (Bathien & Hugon, 1964; Gassel & Ott, 1970b) that afferences from the skin affect the excitability of the soleus motoneurons as tested by the H reflex (Hugon, 1973; Pierrot-Deseilligny E, Bussel B, Sideri G, Cathala HP, Castaigne P, 1973 Feb).

Evidence from studies on human subjects (Delwaide, Crenna, & Fleron, 1981; Delwaide & Crenna, 1983) have shown that non-noxious sural stimulation induces significant periods of excitation in both soleus and TA muscles as measured by H-reflex modulation. **(**Delwaide, Crenna, & Fleron, 1981) investigated the excitability of the antagonistic

soleus and tibialis anterior motor nuclei following sural stimulation (2.5*Perception threshold). The excitability of the soleus and tibialis anterior motoneuron pools was tested by means of the Hoffmann (H) reflex. This stimulus intensity which elicited tactile sensation increased the amplitude of the test monosynaptic soleus reflexes over two time periods i.e. from 55 to 90ms and also from 130 to 170 ms. They also suggested that both peaks of facilitation after either ipsilateral or contralateral stimulation are related to Group II afferents and that there may be an involvement of the suprasegmentary neuronal mechanisms. Later, (Delwaide & Crenna, 1983) expanded on the previous work and investigated the effect of stimulation of various sensory nerves (lateral femoral cutaneous, iliohyogastric, median, trigeminal and saphenous) on the soleus motor nucleus and also the effect of sural nerve stimulation on various motor nuclei located along the length of the neuraxis: soleus, quadriceps, short biceps, biceps brachii and masseter. They concluded that stimulation of a particular nerve gives rise to two phases of facilitation in lower limb nuclei and two or more and often three phases of facilitation in upper limb nuclei. They also suggested that apart from segmental spinal mechanisms there seems to be the existence of a supraspinal center which is activated by medium – low- threshold exteroceptive afferents, facilitates all motor nuclei in a rostro-caudal sequence and is responsible for certain features of first and second peaks. The facilitation latencies reported in their study were also compatible with a supraspinal mechanism. More painful ipsilateral stimulation depresses soleus concomitant with facilitation of TA, as in the generation of a flexor reflex. Studies (Gibbs et al., 1995; Jenner & Stephens, 1982) have also shown cutaneous stimulation to induce a triphasic

response involving excitation, inhibition, and a later excitation. (Kukulka, 1994) showed that non-noxious sural stimulation evokes very complex responses in human triceps surae motoneurones. The most common responses observed were a short latency (onset ~ 40 msec) inhibition (decrease in firing rate) and a longer latency (onset~ 70 msec) excitation. In the cat, motor unit type specificity has been shown subsequent to sural stimulation, such that type I motor units are inhibited and type II excited (Burke, R. E., Jankowska, E. and Ten Bruggencate, G., 1970). Interestingly, this has also been reported for the TA muscle in human subjects (Nielsen & Kagamihara, 1993). (Rossi, A., Zala, A. and Decchi, B., 1996) reported that non-nociceptive and nociceptive afferents from the medial plantar nerve (distal branch of the posterior tibial nerve) of the foot share spinal pathways and converge on motoneurones of TA muscle in intact humans. They demonstrated that the level of descending activation of the motor pool can markedly influence which responses predominate, such that faster conducting (non-nociceptive) afferents can more easily elicit reflex discharge of the motor pool during contraction. To summarize, these studies indicated that stimulation of cutaneous afferents in the human subject during sitting induce complex excitatory and inhibitory effects on lower leg muscles. However, the exact extent to which these reflexes can be extrapolated to more functional activities such as standing and walking is not clear. This issue is discussed in the following section.

2.2 Influence of cutaneous input during posture and gait

2.2.1 Animals studies

(H. Forssberg, 1979) provided the first systematic attempt to evaluate the functional role of cutaneous reflexes by measuring both kinematics and neural responses. The experiment included both electrical and mechanical stimulation of the dorsal surface of the paw in the cat distal hind limb during locomotion. A coordinated reflex forming a functionally-relevant ``stumbling corrective response'' was documented (H. Forssberg, 1979). This response consisted of a sequential neural activation of the hind-limb musculature to allow the perturbed swing limb to continue past the encountered obstacle and maintain stability of ongoing locomotion. Similar responses were also observed by (Wand, Prochazka, & Sontag, 1980) and (Prochazka, A., Sontag, K.-H. and Wand, P., 1978) who, in a series of experiments, systematically revealed that the origin of the corrective response lay in the cutaneous afferents arising from the paw dorsum. Neuro-mechanical linkage was also showed in the cat forelimb by (Drew & Rossignol, 1987). (Buford, J. A. and Smith, J. L., 1993) demonstrated that reflex responses elicited by mechanical and electrical stimulation during both forward and backward walking have relevant neuromechanical correlates. A corrective response which was suitable for maintaining ongoing locomotion was elicited by stimulating the dorsal surface of the foot during forward walking and the ventral surface during backward walking. In both instances the swing limb was moved over and past the mechanical or electrically-simulated perturbation. These results demonstrate that cutaneous afferents have strong reflex responses which serve to functionally modify ongoing quadrupedal locomotion, particularly in the swing limb. What remained unclear, though, is to what extent the

results obtained in the experiments on the cat apply to the bipedal human in whom balance and postural concerns are quite different.

2.2.2 Human Cutaneous reflex modulation: task dependence

Reflexes are "task dependent" which means that they are influenced by the motor task that is being performed at the time they are evoked. Task dependency has been described as the phenomenon of reflexes changing amplitude or signs between motor tasks (Zehr & Stein, 1999). Cutaneous reflexes evoked during active movement such as *walking* are different from those evoked while quiet or static contraction such as *standing and sitting* (Christensen et al., 1999; Duysens, J., Tax, A. A. M., Trippel, M. and Dietz, V., 1993; Kanda, K. & Sato, H., 1983; Komiyama, Zehr, & Stein, 2000). (Aniss et al., 1992) investigated the effects of sural and posterior tibial stimulation on ongoing EMG of the soleus, TA, medial gastrocnemius (MG) and lateral gastrocnemius (LG) muscles. A short latency inhibition (onset ~ 45±50 msec) was observed in soleus after stimulation of both nerves. This effect was observed both while recumbent and during standing**.** (Burke, D., Dickson, H. G. and Skuse, N. F., 1991) examined in detail the task- dependent changes of the effect of cutaneous afferent input on several muscles of the human lower limb. They demonstrated that following sural stimulation, inhibition within 100 msec was recorded in TA, soleus, biceps femoris (BF) and vastus lateralis (VL). There was no reflex effect when the muscles were not active. Reflexes in TA that occurred between 60 and 80 msec post-stimulus were different when examined while sitting, standing normally or standing on an unstable base; the pattern (both excitation and inhibition) became more pronounced the more unstable the posture. It was concluded that the reflex pattern within a given

muscle as well as between other muscles is task-dependent and that the responses may be quite modifiable. (Gibbs et al., 1995) showed that a triphasic (excitation -inhibition - excitation) pattern that may occur subsequent to digital nerve stimulation at the toes while recumbent persists during standing. (Abbruzzese, M., Rubino, V. and Schieppati, M., 1996) also observed task-dependent modulation of reflexes after stimulation of afferents from the foot surface. They showed that low intensity electrical stimulation of the posterior tibial nerve at the ankle produced facilitation of soleus while prone lying, but inhibition during standing. If the foot were pressed against a firm surface while prone, they found a similar modulation to standing. They suggested that afferent transmission from the foot surface and intrinsic foot muscles is modulated by cutaneous input to the foot sole. This suggests that the afferent input to the spinal cord delivered via the stimulation of peripheral nerves (e.g. activation of cutaneous afferents) can elicit prominent reflexes in various muscles of the human lower leg under static and dynamic conditions. This characteristic is suggestive of the useful function of reflexes during different behaviors.

Tasks with obvious differences in motor output and peripheral feedback (e.g. sitting, standing and walking) have different reflex modulation patterns. Reflex modulation patterns are described as being different and indicative of differences in neural control, if there were significant differences in the sign of reflexes. (Komiyama et al., 2000) compared cutaneous reflexes responses in two different tasks conditions i.e. *standing and walking*. They suggested that during standing net reflexes are predominantly suppressive and graded with background EMG. In contrast, during walking net reflexes are mostly

facilitatory and uncorrelated with background EMG. Thus, opposite signs such as negative during standing and positive during walking have been observed. They suggested that during standing, where maintenance of posture is of primary importance, there is a global suppressive response, while during walking there is a modulation of reflexes which is independent of muscle activation level and closely coupled with events occurring in the step cycle. (Duysens, J., Tax, A. A. M., Trippel, M. and Dietz, V., 1993) compared the amplitude of the cutaneous reflex responses in TA and biceps femoris (BF) muscle during *standing and running*, at equivalent background contractions. They found that the mean latency of the main response to sural nerve stimulation in BF and TA was 76ms and 79 ms respectively. This response is preceded by a small and inconsistent short latency excitatory response (~50 to 55 ms).The early response was labeled as P1 while the later and larger response was termed as P2. Their results were focused around P2 response. Thus, the amplitude of the P2 response was on average higher during running than during standing, even when the background EMG levels were matched. All these studies imply that specific reflex differences may emerge during different tasks due to changes in descending drive or afferent feedback which may be important in specifically determining the motor output to the demands of ongoing task. Thus, reflex modulation may occur across different tasks that involve differences in joint kinematics and stability demands. Since responses to electrical stimulation of cutaneous nerves may reveal functional strategies to overcome an obstacle or recover stability (Zehr & Stein, 1999) , these reflexes may be enhanced during less stable tasks because of the increased probability of one's fall. Amplification of reflexes has been shown during unstable forms

of standing (D. Burke, Gandevia, & McKeon, 1984) and walking (Haridas, Zehr, & Misiaszek, 2005). Though task dependency has been demonstrated in various studies that looked at evoked cutaneous reflexes during various tasks (sitting, standing, walking, running) none of these studies so far has explored its role in step initiation and have not compared these evoked cutaneous reflex responses during step initiation to more stable tasks like sitting and standing. Through this study, we will explore the role of cutaneous reflexes in step initiation for the first time and will try to demonstrate the task dependency of the reflex responses as we compare them in ~~sitting,~~ standing and step initiation.

2.2.3 Human Cutaneous reflex modulation: phase dependence

During gait, electrical stimulation of the foot elicits facilitatory responses in leg muscles at the onset of the swing phase and suppressive responses at the end of swing phase along with facilitatory responses in antagonists. This phenomenon is called *phase dependent reflex reversal*. Complete reversals in the sign of a cutaneous reflex, originally shown in the cat (Forssberg, H., Grillner, S. and Rossignol, S., 1975) have been reported during human walking (DeSerres, S. J., Yang, J. F. and Patrick, S. K., 1995; J. Duysens et al., 1990; J. Duysens et al., 1992; Van Wezel et al., 1997; Yang & Stein, 1990). (J. Duysens et al., 1990; Yang & Stein, 1990) carried out the first systematic analysis of non-noxious cutaneous reflexes during human walking. Previously, most studies involving cutaneous stimulation during human walking involved painful stimulation (BeÂlanger, M. and Patla, A. E., 1987; Crenna P, 1984 Aug). (Yang & Stein, 1990) demonstrated reflex responses in three muscles (ipsilateral TA, soleus and biceps femoris) that were evoked

by stimulation of the tibial nerve (mixed nerve, not purely cutaneous) and sural nerve at the ankle. The most reproducible response was observed at a latency of 50 - 90 ms, which they called a middle latency response or P2 response. For the first time, the reversal in the direction of this middle latency response from excitation to inhibition was observed within a single muscle. The reflex reversal is showed in Fig. 2 in which the reflexes in TA muscle are shown subsequent to tibial nerve stimulation at the ankle of a walking subject. During stance (top) there is no reflex activity in the TA muscle. During early swing phase (middle trace), there is a prominent middle-latency facilitation which changed to a suppressive response at the swing to stance transition (bottom trace). They concluded that cutaneous reflexes likely are important in withdrawal responses to stimuli and responses which would preserve balance during the step cycle.

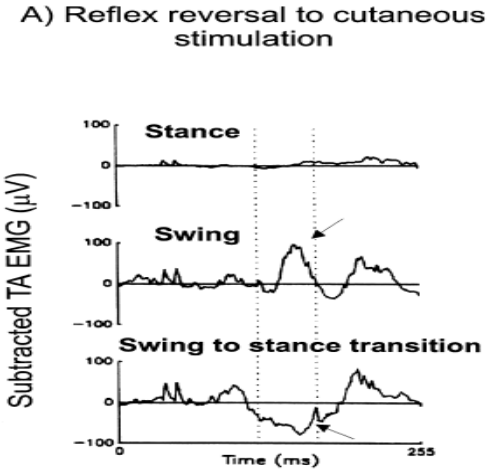


FIG. 2.Adapted and modified from Yang and Stein (1990). Phase-dependent modulation and reversal of cutaneous reflexes during locomotion. The EMG traces in (A) are from TA muscle and are the reflexes to tibial nerve stimulation once the background loco motor related EMG has been subtracted. The arrowhead marks the excitatory reflex during swing which becomes an inhibitory one at the swing to stance transition.

Later, Duysens et al, 1992 illustrated the reflex reversal in TA muscle to low (<2.5 RT) and high intensity (> 2.5 RT) stimulation induced by sural nerve stimulation during the human step cycle. They reported that at lower intensity stimulation (< 2.5 RT) of the sural nerve the reversal is from ankle dorsiflexion in early swing to ankle plantar flexion

at end swing. At high intensity stimulation (>2.5 RT), the reversal is from dorsiflexion during early and middle stance to plantar flexion at end stance and early swing. They provided an initial *quantification of the reflexes* by showing relatively strong correlation between movement responses at the ankle and EMG responses in TA. However, contrary to the conclusions on the potential functional role of cutaneous reflexes during human gait (e.g. stumbling corrective response), (J. Duysens et al., 1992) concluded that cutaneous reflexes “do not correspond directly to corrections for stumbling following mechanical perturbations during the step cycle" but are related more to the opening and closing of reflex pathways by a central pattern generator for locomotion.(Van Wezel et al., 1997; Zehr EP, Komiyama T, Stein RB, 1997) addressed the issue of local sign of cutaneous reflexes in humans that was already demonstrated in experiments involving cats (Buford, J. A. and Smith, J. L., 1993). They conducted experiments in which the three major lower limb cutaneous nerves, sural, tibial and superficial peroneal (SP) nerve innervating the foot dorsum were electrically stimulated at non-noxious intensities during tread-mill walking. Reflex EMG responses from the upper and lower leg muscles were measured and changes in joint kinematics were also recorded. Thus, by evaluating reflex function, it was feasible to directly compare the net neural command (i.e. the net reflex response) to the net mechanical outcome (i.e. kinematics). It was suggested that to contribute functionally, reflexes should not only be associated with mechanical change but also the association should be one in which the response modifies the gait pattern in a behaviorally relevant manner. Reflexes to stimulation of these nerves were shown to have functional effects particularly during swing or the swing to stance transition. As

demonstrated by (Zehr EP, Komiyama T, Stein RB, 1997) after SP nerve stimulation, TA muscle exhibited a significant suppression during swing phase which is highly correlated with ankle plantar flexion. The tibial nerve stimulation produced a reversal with dorsiflexion during the transition from stance to swing and a plantar flexion during late swing. They argued that these responses to non-noxious electrical stimulation in humans are functional in nature as SP nerve reflex responses suggest a stumbling corrective response (H. Forssberg, 1979) involving ankle plantar flexion and knee flexion. The tibial nerve reflexes allow for smooth transition movement of the swing leg so as to avoid tripping during swing and to help in placing and weight acceptance at the beginning of stance. Thus, this study very well explained the functional significance of local sign where stimulation of the foot dorsum produces plantar flexion (e.g. SP at early swing) and stimulation of the foot sole produces dorsiflexion (e.g. Tibial nerve at stance to swing transition). It is important to note that this reflex reversal has usually been observed in muscles which display a two-burst pattern in the step cycle (i.e. TA and BF) and only subsequent to stimulating nerves which are purely or mostly cutaneous (Stein, 1991). In the case of TA muscle in humans, it is active in two parts of the walking cycle. Part one starts from late stance and extends through most of the swing phase to dorsiflex the ankle to clear the foot from the ground, Part two involves the transition from the swing to stance to control the lowering of the foot after heel contact. The reversal in sign of the response suggests possible organization of the reflex pathways and a possible neural mechanism for phase dependent reflex reversal was postulated by (Yang & Stein, 1990). They hypothesized parallel excitatory and inhibitory cutaneous pathways to single alpha

motoneurons and a mechanism that would allow switching between these pathways during walking and that a switching occurs between these two reflex pathways depending when the stimulus was delivered in the step cycle. This hypothesis was tested in more detail when (DeSerres, S. J., Yang, J. F. and Patrick, S. K., 1995) studied single motor units that were recorded from the TA muscle of healthy human subjects walking on the treadmill with a splint that limited motion on the ankle joint. They concluded that reflex reversal is likely due to the presence of parallel inhibitory and excitatory pathways from cutaneous afferents to single motoneurons of the TA muscle. Thus, these parallel pathways seem to be alternately recruited as a function of the walking cycle.

2.2.4 Human Cutaneous reflex modulation: stimulus intensity dependence

(J. Duysens et al., 1990) demonstrated that the stimulation of tibial and sural nerve at the ankle during the swing phase induced a long latency (67- 118 ms) suppression of the ankle flexor, TA when 1.6 RT was used and short latency (56-74 ms) facilitation when stronger stimuli (2.8 RT) were given. The latter facilitatory response was identified as a flexor reflex, producing additional ankle dorsiflexion if elicited in the middle of the swing phase, when these TA facilitatory responses were strongly enhanced. Later, (J. Duysens et al., 1992) suggested that reflex induced ankle movements illustrate a phase dependent reversal which depends on stimulus intensity. At lower intensity stimulation (< 2.5 RT) of the sural nerve the reversal is from ankle dorsiflexion in early swing to ankle plantar flexion at end swing. At high intensity stimulation (>2.5 RT), the reversal is from dorsiflexion during early and middle stance to plantar flexion at end stance and early

swing. Thus stimulus intensity seems to play a role in modulating cutaneous reflex responses.

2.3 Neural mechanisms underlying short and long latency reflex responses

This section is dedicated to the possible mechanisms underlying short and long latency responses that are evoked from cutaneous input.

2.3.1 Short latency responses

Support in favor of a *segmental influence* mainly comes from the study by (Kukulka, 1994) in which he showed sural afferent input onto tricep surae motor neurons indicative of a spinal influence of sural nerve stimulation. He demonstrated that the stimulation of the sural nerve at intensities sufficient for activating low threshold cutaneous afferents produced both enhancement and depression in the firing of human tricep surae motor units at latencies between 30 – 120 ms. The 2 most common response seen in the muscles studied were a short latency depression (D1) in firing (mean onset latency = 40 ms) and a secondary enhancement (E2) in firing (mean onset latency = 72 ms) as shown in Fig.3. Another study by (Kukulka & Halle, 1991) demonstrated that early inhibitory effects similar to the (D1) response (Kukulka, 1994) were produced by peroneal nerve stimulation. The results of each of these studies raise the issue whether cutaneous and muscle afferents share common interneurons. Such a possibility would provide the ability for cutaneous input to influence control over the important reciprocal inhibitory pathway.

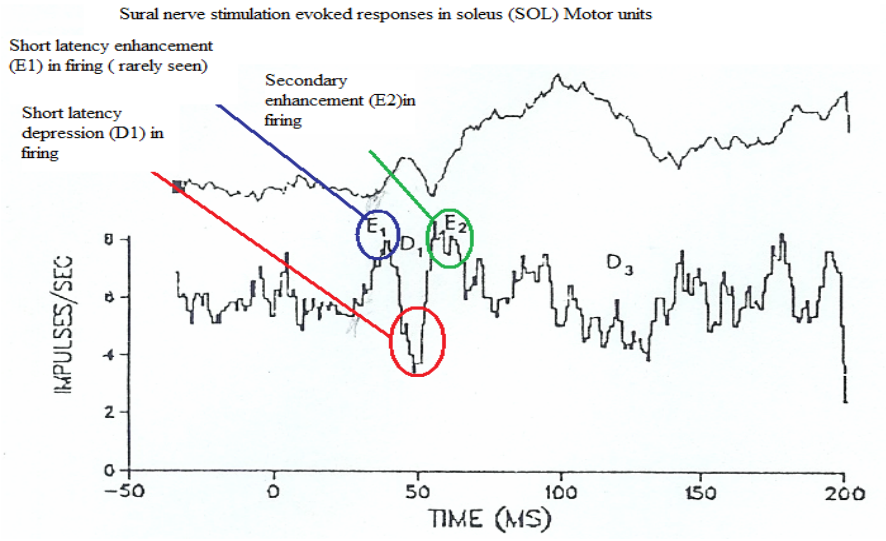


FIG. 3. Adapted and modified from Kukulka 1994. Shows firing response in soleus (SOL) motor units to low intensity sural nerve stimulation.

Based on estimates of conduction times for activation of low-threshold cutaneous afferents, the short-latency D 1 response seems to represents an oligosynaptic spinal reflex with conduction times similar to the Ia reciprocal inhibitory pathway. These findings suggest a possibility that low-threshold cutaneous afferents may share common interneurons with low-threshold muscle afferent reflexes that have similar onset latencies. The complex reflex effects associated with low-level stimulation of a cutaneous nerve indicate a large variation of peripheral responses that may influence a given movement. Non-nociceptive stimulation of the sural, posterior tibial, and superficial peroneal nerves was shown to evoke significant reflex responses, which indicate the presence of location-specific information from the skin of the foot in cutaneous reflexes during human walking (Van Wezel et al, 1997). The nerve-specific phase-dependent reflex modulation patterns point to the dynamic control of this information during the course of a step cycle. Afferents from mechanoreceptors (Aniss et al, 1992) in the sole of the foot have multisynaptic reflex connections with the motoneuron pools innervating the muscles that

act at the ankle and the onset latencies suggested a spinal pathway for the early components of the response. In an oligosynaptic spinal reflex the latency at which EMG would occur is 40-50 ms.

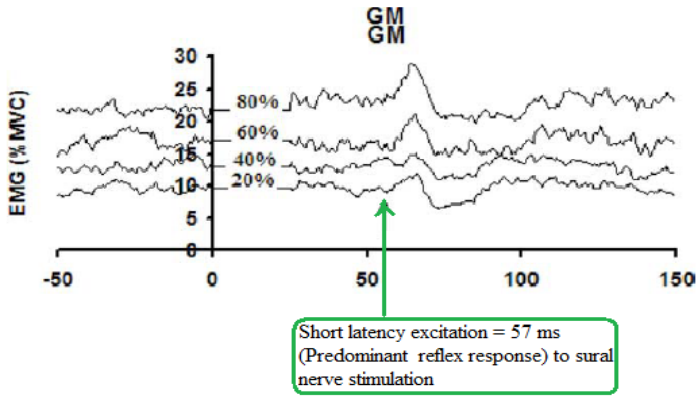


FIG. 4. Adapted and modified from Li et al, 2004. Shows evoked reflex response in (GM) Gluteus medius (short latency excitation) to sural nerve stimulation for 4 levels of body loading (20, 40, 60, and 80%).

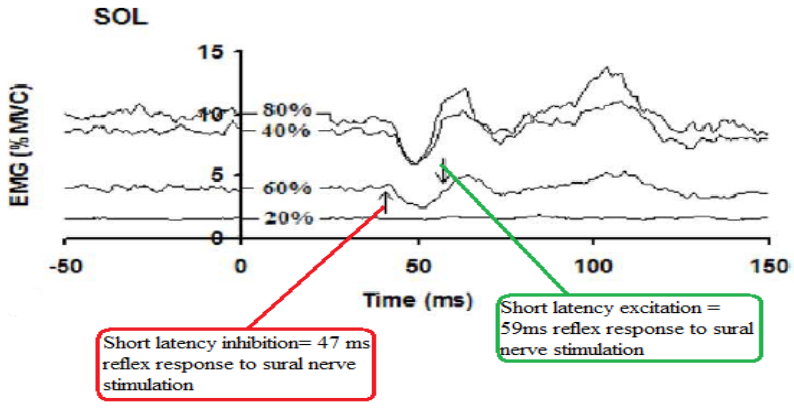


FIG.5. Adapted and modified from Li et al, 2004. Shows evoked reflex response in soleus (SOL): short latency inhibition-excitation to sural nerve stimulation for 4 levels of body loading (20, 40, 60 and 80 %).

(Li et al, 2004) showed significant effects of sural nerve on the reflex responses in the ipsilateral soleus (SOL) and gluteus medius (GM) motor neuron pool. In GM (Fig.4) the most frequent response was the early excitation at the latency of 57 ms and for soleus (SOL) the most frequent response was the short latency inhibition and excitation at latencies of 47 and 59 ms respectively (Fig.5). Thus cutaneous input from activation of

the sural nerve afferent, influence both proximal and distal motor neuron pool (Li et al., 2004) which are engaged by central commands.

2.3.2 Long latency responses

In recent years there has been a considerable debate over the mechanism behind long latency reflex responses elicited by cutaneous input in muscles of the lower limb. We provide evidence which suggests that long-latency cutaneous reflex responses may be mediated by a transcortical pathway.

A transcortical pathway is a pathway through which somatosensory input reach M1 via projections from the thalamus through primary sensory cortex (Evarts & Fromm, 1981). Like neurons in somatosensory cortex, neurons in the motor cortex have receptive fields in the periphery. The advantage of these reflexes is that it provides a degree of flexibility to rapid responses that are unavailable in spinal reflexes. (Evarts & Fromm, 1981) suggested that within the motor cortex (M1) there is a caudal region (M1/c) that receives exteroceptive cutaneous input and a rostral region (M1/r) which receives proprioceptive inputs. They speculated that cutaneous reflexes via M1/c might be functionally similar to the segmental cutaneous reflexes. (Nielsen et al., 1997) investigated whether stimulation of cutaneous afferents from the foot can modulate the motor cortex output evoked by transcranial magnetic stimulation. They wanted to explore whether the excitation of TA motoneurons seen during tonic voluntary dorsiflexion at a latency of approximately 70-95 ms following stimulation of the sural nerve and superficial peroneal nerve is, at least partly, mediated by a transcortical reflex pathway. The experiment was done with healthy subjects seated in a chair. Stimulation of the superficial peroneal or the sural nerve (3

shocks, 3 ms interval, 1 ms duration,) evoked a reflex activation of the tibialis anterior muscle at a latency of approximately 70-95 *ms*. They combined the cutaneous stimulations and a transcranial magnetic stimulation of the contralateral motor cortex to test the possibility that transcortical pathway contributes to these late reflex responses. They observed a significant facilitation of short-latency peaks in the post-stimulus time histogram of single tibialis anterior motor units evoked by the transcortical magnetic stimulation. With the same timing for the stimuli, the superficial peroneal and sural nerve stimulations produced a significant increase in the short-latency, presumed monosynaptic, facilitation of the tibialis anterior H reflex produced by the brain stimulation. Similar facilitatory effects of the cutaneous stimuli could not be demonstrated when the magnetic stimulation of the cortex was replaced with electrical stimulation, implying that cortical excitability is affected by a conditioning cutaneous stimulation.

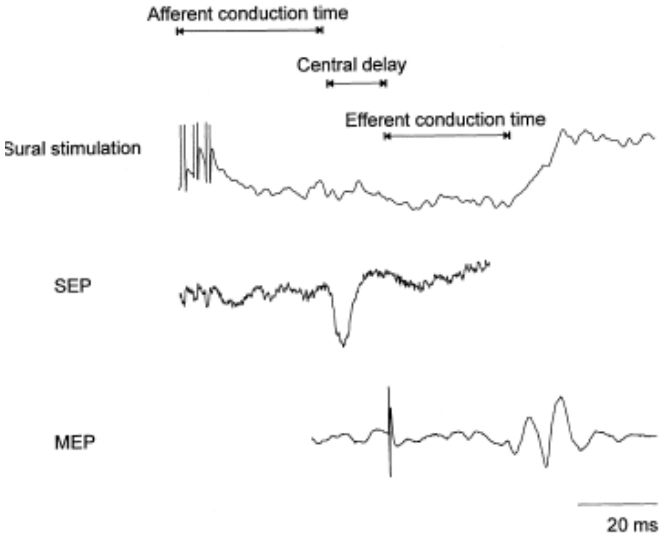


FIG.6. Modified from Nielsen et al.1997: Conduction time for possible transcortical cutaneous reflexes in TA. An estimate of the efferent conduction time for a possible transcortical reflex pathway is given by the latency of an MEP in the TA muscle following TMS (lowermost trace). An estimate of the time that an afferent volley takes to reach the cortex is given by the latency of the somatosensory evoked potentials (SEPs) following sural nerve stimulation (middle trace). When allowing a short central delay of around 10 ms for processing of the signals in the cortex, it is seen that the total conduction time for a transcortical reflex pathway fits quite well with the late facilitation in the TA EMG following sural nerve stimulation (uppermost trace).

They also calculated (Fig. 6) afferent conduction time (38ms), central delay (10ms) and efferent conduction time (35ms) to demonstrate that the stimulation of the sural nerve in the subject that evoked a facilitation of TA EMG at a latency of 83 ms is mediated by a transcortical reflex pathway. These findings suggested that the long-latency reflexes in the tibialis anterior muscle evoked by activation of cutaneous afferents from the human foot are, at least partly, mediated by a transcortical pathway.

(Pijnappels M, Van Wezel BM, Colombo G, Dietz V, Duysens J., 1998 Mar 16) found that compound motor action potential in the tibialis anterior muscle evoked by magnetic stimulation of the motor cortex in the early swing phase were facilitated by stimulation of the sural nerve at the same interval as the facilitation investigated by (Nielsen et al., 1997). However this study, only provided evidence for an interaction between the corticospinal activation and the cutaneous stimulation but not for the level at which this interaction took place. (Christensen et al., 1999) conducted a study to investigate the underlying mechanism behind this long latency facilitation. They evoked reflex responses while maintaining tonic dorsiflexion in sitting and also during different phases of walking and observed a large facilitation during mid swing that disappeared during late swing. The facilitation observed during tonic dorsiflexion (smaller facilitation than walking) has been already suggested to be at least partly mediated by transcortical pathway (Nielsen et al., 1997). They reported that the average latency of facilitation during tonic dorsiflexion was 78 ± 4 ms as compared with 79 ±4 ms during walking, whereas the time from the onset to the peak of the facilitation was 12 ±7 ms and 13 ± 7 ms respectively. They also investigated whether a similar mechanism contributes to the

facilitation observed during walking. Magnetic stimulation of the motor cortex (1.2x motor threshold) was applied in the early swing phase at different times in relation to the cutaneous stimulation. They concluded that a transcortical pathway may also contribute to long latency cutaneous reflexes during walking. The study by (Christensen et al., 1999) only provided comparison of cutaneous reflex responses in sitting and walking. (Christensen et al., 2000) suggested that responses to cutaneous stimulation in lower limb muscles are generally complex (Fig.7) because they are a mixture of inhibitory and facilitatory responses. They focused on the late latency responses that typically show the most interesting patterns of modulation (Christensen et al., 1999; Nielsen et al., 1997).

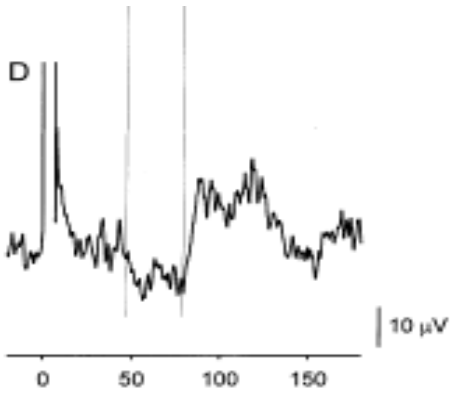


FIG.7. Adapted from Christensen 2000. Example of cutaneous reflexes in the tibialis anterior muscle: Responses in TA EMG to stimulation of the sural nerve (3 shocks, 3 ms inter stimulus interval, 2.5 x perception threshold). The traces are averages of 100 stimuli each. Note that the stimulation evoked an ***inhibition*** at short latency in the TA EMG followed by facilitation at latency of 77ms. The background Torque level was 5-6 N m in all cases. All signals were rectified before averaging.

2.4 Step Initiation

When a standing person initiates a step, there are reproducible mechanical events preceding the lift off of the foot of the stepping leg. In particular, the voluntary step initiation is preceded by a sequence of trunk and lower limb muscle activations (Brunt, Liu, Trimble, Bauer, & Short, 1999) leading to kinetic and kinematic changes (Breniere

Y, Do MC, Bouisset S., 1987) that promote the successful execution of the step. These anticipatory postural adjustments (APAs), from a mechanical perspective, consist of a brief increase in the stepping limb vertical ground reaction force together with a lateral and posterior displacement of the body's center of pressure (*COP- the point of application of the vertical force acting from the support of the body*). The net result of these APAs is a reactive propulsion of the body's center of mass (*COM- The point in a system of bodies or an extended body at which the mass of the system may be considered to be concentrated and at which external forces may be considered to be applied*) forward and towards the impending stance limb.

2.4.1 APAs during step initiation

An inverted pendulum model (Winter D. A., 1995) is the common model that allows us to analyze the dynamics of balance**.** It assumes that the whole body acts like an inverted pendulum that is pivoting about the ankle joint. Initially based on the inverted pendulum model in the A/P direction, (Winter D. A., 1995) showed that the COP and COM are tightly coupled during quiet standing and sway back and forth to maintain equilibrium. It was suggested that when the COP is ahead of COM the acceleration is backward and when the COP is behind COM the acceleration is forward. Thus in order to take a step following events (Breniere Y, Do MC, Bouisset S., 1987; Crenna & Frigo, 1991) occurs:

1) Soleus muscle is inhibited and TA is activated. There is also activation of the Gluteus medius (GM) muscle.
2) The activation of TA contributes to the backward displacement of the COP towards the swing leg side. Crenna 1990 demonstrated a strong correlation

between the amplitude of the TA burst and the amount of backward displacement of COP.

3) There is also GM activation which contributes to an increase of the vertical GRF on the swing limb side (limb loading) and a lateral COP displacement to the swing limb side. Both TA activation and Gluteus medius activation occur in close sequence. Thus, loading of the limb leads to posterior lateral COP displacement (Fig.8).This causes a decoupling between the COP and COM, propelling the COM forward, leading to a forward lean to take the step.

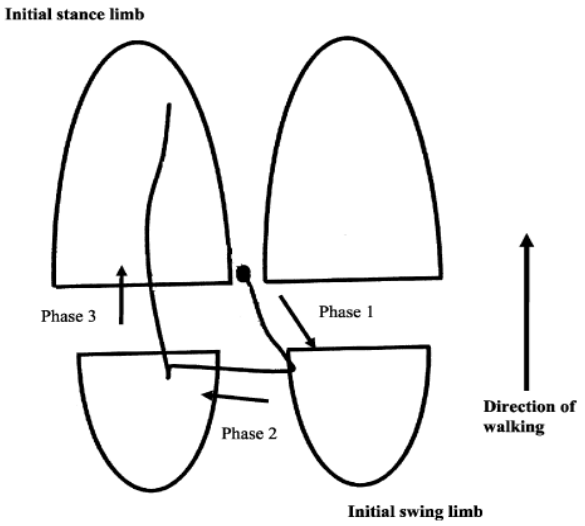


FIG. 8. Adapted from Dibble et al, 2004
Phase 1: During the Double Limb support portion of gait initiation, the COP begins at a position between the feet. It then moves posterior and lateral towards the initial swing limb.
Phase 2: The COP then moves medially towards the initial stance limb.
Phase 3: Finally COP moves anteriorly under the impending stance limb.

2.4.2 Cueing effects on step initiation: Related work

We previously reported (Hajela et al., 2006; Kukulka et al., 2009) that a sural cue has the potential to positively influence the APAs during step initiation when used as a reaction time cue. We compared the effects of sural nerve stimulation to visual cuing on step initiation in young healthy individuals.

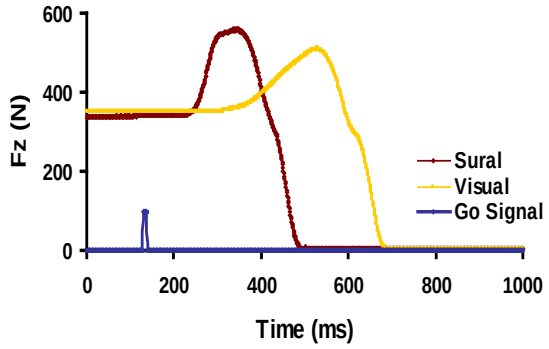


FIG.9. Adapted from Hajela et al, 2006. Loading responses (Fz) for a sural versus a light go cue. Sural cue induced a faster reaction time, higher load amplitude, and faster speed of load onset then a visual cue.

In one group, vertical ground reaction force and EMG in tibialis anterior and gluteus medius were recorded and in a second group vertical ground reaction force and center of pressure were recorded. Subjects stood with one foot on a force platform with weight equally distributed and were asked to take three steps as quickly as possible. A visual ready signal was followed at random times (0.5 – 2 s) by either a second visual go cue or stimulation of the sural nerve. We demonstrated that sural cueing is better than visual cueing in releasing the step faster (Fig. 9) as sural cueing produced: (1) Earlier onset times, greater vertical ground reaction forces and a greater rate of rise of force, (2) Earlier onsets of TA and GM and greater mean EMG amplitudes in these muscles and (3) Greater COP displacements in both the posterior and lateral direction. Thus, sural cueing enhances these kinetic, kinematic and EMG responses that comprise the anticipatory postural adjustments (APA) for the step. This study raised two key questions: 1) are the effects produced by sural nerve stimulation specific to sural nerve or could a generalized cutaneous cue produce similar effect? and 2) could the effects produced by the sural cue be similar to those of loud auditory cue? A recent study in our laboratory (Brown S, Gregory A, Kukulka CG, Pommier M, Simone, A, 2007) showed that there is no statistically

significant difference in reaction times between sural or arm cuing but that sural cuing produced greater load amplitude and faster speed of load onset than an arm cue. Therefore we cannot generalize the effects seen with sural to other forms of cutaneous cue with respect to kinematic and kinetic changes. On the other hand, the difference in loading responses and speed of load onsets for sural cueing versus the three other types of cueing indicate that sural input may influence the motor neuron pools to facilitate greater anticipatory postural adjustments during step initiation. Another fascinating finding based on the reaction time is that loud auditory cue produces faster reaction times than cutaneous cue but greater ground reaction force is produced by sural cue than loud auditory cue. If both cues were sharing the same pathway then we should not see these significant differences in their effect on reaction times and ground reaction forces. The loud auditory cue is hypothesized to produce a stepping response via a sub-cortical releasing mechanism (Mackinnon et al, 2007). This possibly suggests that a sural cue is not going through a reticulospinal pathway to release the step. Thus there is need to further explore the potential pathways taken by sural cue during step initiation. There have been studies that that have explored the function of sural nerve reflexes in walking (Zehr & Stein, 1999) but no study so far has explored the role of these reflexes in step initiation. Therefore, in this study we will explore the role of sural nerve reflexes during step initiation and also the factors that affect APAs.

2.5 Clinical implications in target patient population

Disturbance of the APA is considered to be a major pathophysiological mechanism that hinders gait initiation in PD subjects and elderly who fall. APAs are diminished in elderly subjects (Patla AE, Frank JS, Winter DA, Rietdyk S, Prasad S, 1993) and patients with

neurologic disorders such as Parkinson's (Mancini et al., 2009) and stroke (Rogers et al., 1993). Fig.10, illustrates the COP displacement trajectories for young, elderly and (Parkinsonism) PD subjects and shows the posterior- lateral COP displacement for the three groups (PD < Elderly < Young). This finding indicates that PD subjects have the ability to generate COP displacement though not to the same extent as other groups.

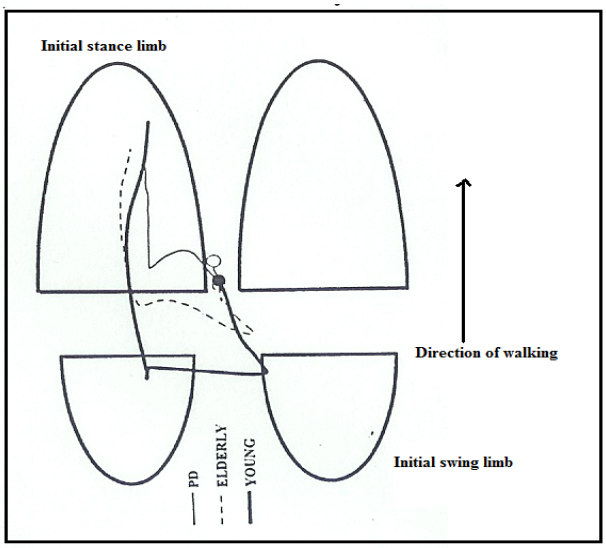


FIG.10. Adapted and modified from Halliday et al, 1998 shows CoP trajectories in Young, Elderly and Patients with Parkinsonism.

In stroke, APAs have been shown to be decreased and/or delayed with respect to those seen in healthy individuals. Individuals with hemiparesis due to stroke also show impaired acquisition of APAs associated with a newly learned task. In a recent study it was found that APAs were reduced in individuals with hemiparesis, especially on the paretic side.

2.6 Summary of the Background

Evidence from studies on cutaneous reflexes suggests that the reflexes that are elicited by a non noxious cutaneous stimulation are task dependent, phase dependent and stimulus intensity dependent and are modulated in a behaviorally appropriate manner during a functional task like walking. Though these studies emphasized the effect of various factors affecting cutaneous reflexes during walking, they did not address whether same modulation is seen during anticipatory postural adjustments prior to step initiation. Studies on step initiation suggest that a sural cue has the potential to positively influence kinetic, kinematic and EMG changes that precede the step (Hajela N, Kukulka CG, Olson E, Peters A, Podratz K, Quade C, 2006; C. G. Kukulka et al., 2009). Yet we still do not know the underlying factors that may contribute to these enhanced APAs.

CHAPTER 3: Purpose

A large body of evidence reviewed in the background section indicates the importance of cutaneous reflexes in modulating movement (e.g. walking, obstacle avoidance and running). We have demonstrated in a previous study that cutaneous input, when used as an imperative cue can alter anticipatory postural adjustments (APAs) that precede a step (Kukulka et al, 2009). Little evidence exits for how cutaneous reflexes may modulate the APA. It was therefore important to evaluate the underlying reflex influences that could be modulating APAs when sural stimulation is used as an imperative cue. The *purpose* of this study was to assess the influence of cutaneous reflexes in anticipatory postural adjustments (APAs) that precede a step in healthy human subjects. In addition, we compared the reflex responses during step initiation to those evoked while standing. By comparing cutaneous reflexes under different conditions we were able to assess how these pathways are modulated in a functional task such as step initiation.

3.1 Aims

Aim 1: To *investigate* the reflex responses in healthy human TA muscle during dynamic task (step initiation) and to determine the influence of "go" cues (visual vs. sural), phases of step initiation (positive and negative slope of the loading force) on the modulation of reflex responses.

Aim2: To *establish* baseline reflex responses in healthy human TA muscle during static task (standing) and to determine the influence of electrical stimulus intensity (0, 1.5, 2 and 2.5RT) on the sural nerve evoked EMG responses.

Aim 3: To *compare* the effect of different tasks (standing and step initiation) on the sural nerve evoked EMG responses

3.2 Hypotheses

Hypothesis 1: The net reflex EMG response during step initiation will be primarily excitatory and will be influenced by the –

a) "Go" cues: *reflex modulation* to visual cue (more excitatory during loading phase then unloading phase) and *reflex reversal* to sural cue (excitatory during loading phase and inhibitory during unloading phase)

b) Phase of the loading force: larger amplitude for loading phase then unloading phase.

Hypothesis 2: The net reflex EMG response during standing will be inhibitory. The strength (% baseline) of the inhibitory reflex response will increase with increasing stimulus intensity.

Hypothesis 3: The net reflex EMG response will differ in standing and step initiation. Net reflex EMG responses will be inhibitory during standing and primarily *excitatory* during step initiation.

CHAPTER 4: Methods

4.1 Subjects

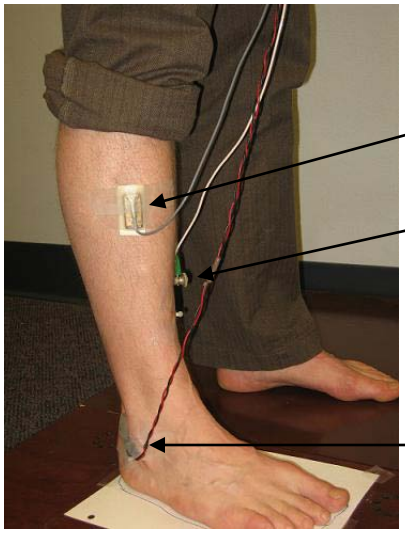
A convenience sample of 21 college students was recruited for the study. We were able to evoke out reflex responses in 15 subjects. The final data set therefore consisted of 15 subjects (mean age = 27.8 years) who produced a complete set of data for the variables measured. The inclusion criteria included male and female healthy subjects between the ages of 22 to 40 years. Exclusion criteria included subjects with any orthopedic injury, neurological deficit, sight, hearing or sensory impairment that interferes with taking a step. The subjects were recruited as volunteers through advertisements around the university campus. All subjects were required to sign a written consent which was approved by the University of Minnesota Institutional Review Board. Sensory testing was also done as impaired sensation was one of the exclusion criteria. In addition they were asked to fill out the survey footedness screen (Coren. S, 1993) that projected their foot dominance.

4.2 Instrumentation

4.2.1 Nerve Stimulation

The electrical stimulus was applied with a bipolar electrode at the subject's right ankle on the sural nerve (Fig.11) just below the lateral malleolus, where the nerve is closest to the skin surface (approximately halfway between the lateral malleolus and the Achilles tendon). A Grass S88 stimulator was used to deliver constant current stimulation (Grass CCU Constant current unit) through a stimulus isolation unit (Grass SIU Isolation unit).

The stimulus consisted of a 10 ms train of 0.1 ms pulse at 300/sec and was delivered at 3 times/ sec (Fig.12) for all the trials.



EMG electrode on the right tibialis anterior

Reference electrode over the crest of tibia (shin bone) of the right limb below the EMG electrode

Stimulation electrode positioned over right sural nerve (approximately halfway between the lateral malleolus and the achilles tendon).

FIG.11.Set up for electrode placement for EMG recording and sural nerve stimulation

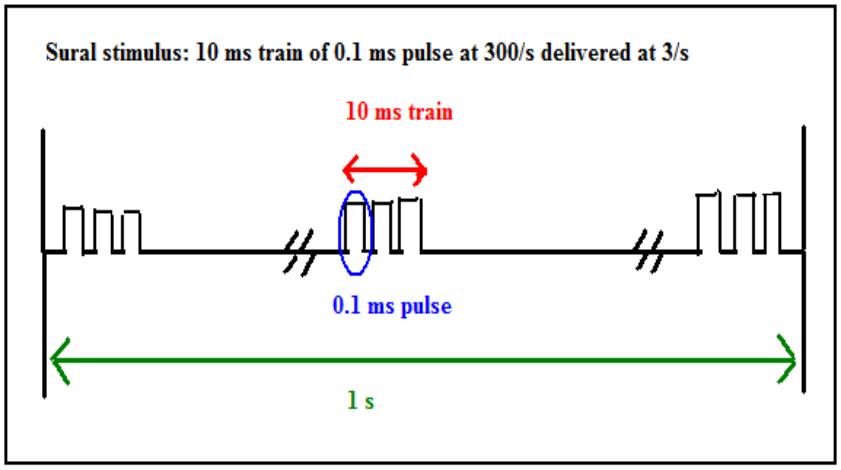


FIG.12. Shows the delivery of train of sural nerve stimulation.

This stimulation protocol is similar to that used to evoke cutaneous reflexes in previous studies (C. G. Kukulka, 1994; Li et al, 2004). Stimulus intensity was adjusted until the subject reports radiation of the stimulus into the lateral aspect of the foot. The intensity is then reduced to where the subject reports a lack of radiation. The intensity is then again

increased to where the subject reports radiation. This intensity was designated as 1 radiation threshold (RT); radiating threshold is defined as the clear radiating paresthesia into the area of skin innervated by the sural nerve at the lowest stimulation intensity. The intensity was increased to 1.5 and 2 and 2.5 RT for the standing experiment. For the stepping experiment, the intensity of the stimulus was 2 RT. During step initiation, sural input was used to serve two purposes: 1) ***Sural "go" cue*** - It was provided prior to step initiation as a reaction time cue. ***2) Sural stimulation*** - It was provided during loading and unloading phase of step initiation, to probe the state of cutaneous reflex pathways. To maintain a constant stimulus throughout the whole stepping trial, the electrode was firmly attached to the skin with a surgical tape.

4.2.2 Electromyography (EMG)

All recordings were done on the right lower limb. To prepare the skin for EMG recordings, the site over the selected muscle, i.e. TA, was cleaned with rubbing alcohol towelettes. EMG was recorded from the ipsilateral (right) TA muscle using surface electrodes (Fig.11) applied in bipolar configuration, midpoint between lateral malleolus and fibular head using a Therapeutics unlimited amplifier (Iowa City). Electrodes consisted of 5mm diameter Ag/AgCl surface electrodes embedded with a pre-amplifier into an epoxy mount. EMG was amplified by a factor of 10 K and was full wave rectified and low pass filtered with a time constant of 2.5ms. A reference electrode (Fig.11) was placed over the crest of tibia (shin bone) below the EMG electrode. Accurate placement of the EMG electrode over the TA muscle to be able to capture its muscle activity was

verified by asking the subject to dorsiflex the right foot and monitoring the activity on an oscilloscope.

4.3 Experimental set up

The two experiments were carried out in one session over the duration of 3 hrs. The experimental set up is shown in Fig. 13.

Step 0: Setting up time – 30 minutes

Step 1: Practice session- 15 minutes

Step 2: Experiment 1 (step initiation series 1) - 45 minutes

Step 3: Rest period- 5 minutes

Step 4: Experiment 2 (standing) – 20 minutes

Step 5: Rest period- 5 minutes

Step 6: Repeat Experiment 1 (step initiation series 2) – 45 minutes

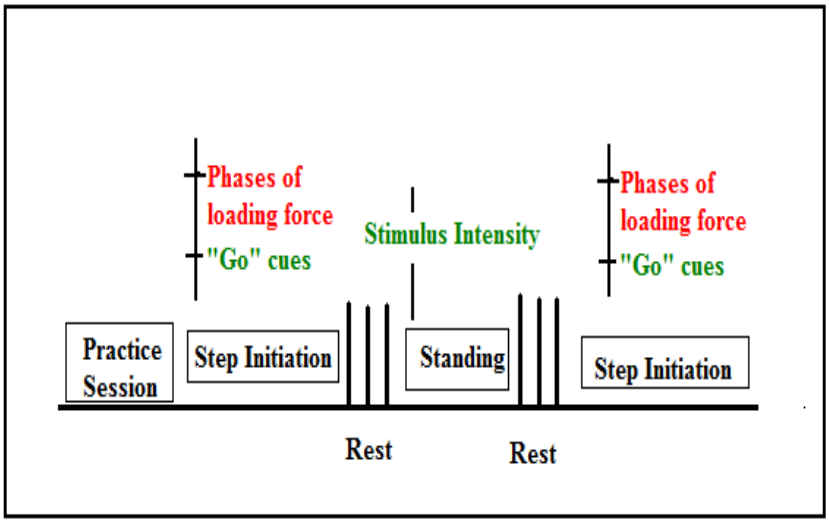


FIG.13.Shows experimental set up and the order of the tasks.

After the subject read and signed the informed consent. They underwent a practice session to get accustomed to the set up and the requirements of the experiment such as taking three steps as soon as they get the cues and standing quietly on the force platform before they take a step.

4.4 Procedure and Experimental design

4.4.1 Practice Session

Every subject was required to go through a practice session before each experiment. This helped the subjects to become accustomed to the tasks required for testing. They were given 5 practice trials for stepping on the force platform to the two cues (visual and sural cues).

4.4.2 Experiment 1 - Step Initiation

Determination of equal weight distribution:

The subjects were asked to stand with both the feet on the force platform (Bertec Corporation, Columbus OH, force platform Model 4060-NC) and their full body weight was measured by adjusting a curser on a Tektronix TDS 3014B Oscilloscope. The subjects were asked to stand with one foot on the force platform with their comfortable stance and the outline of their foot is drawn so that every time they start from the same stance. Half (½) the body weight was determined through cursor adjustment and visual feedback of the signal was provided to the subject for standing with equal support on each limb.

Determination of positive and negative slope of the loading force of step initiation:

Positive slope and negative slope of the loading force was calculated as follows:

Positive (+) slope of loading force = ½ body weight + 0.25* ½ body weight

Negative (-) slope of loading force= ½ body weight - 0.25* ½ body weight

A comparator circuit was used to set a given level in the loading force which was used to trigger the sural nerve stimulation. This was accomplished by monitoring on an oscilloscope the Fz output of the force plate together with the voltage level of the comparator. A cursor was placed on the voltage level trace and set to either positive (+) slope or negative (-) slope of the loading force of step initiation (Fig. 14).

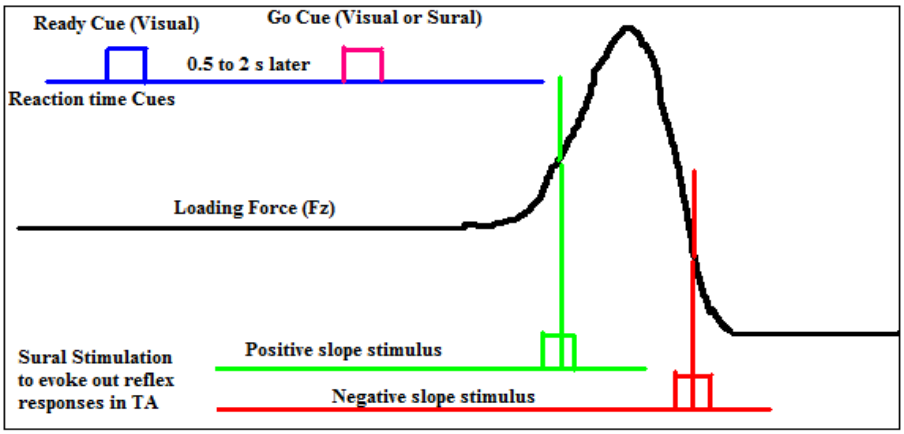


FIG.14. Schematic diagram that shows the positive and negative slope of the loading force of step initiation on which the sural stimulation was provided.

Protocol

Surface EMG electrode was placed on the right lower limb and the radiating threshold was determined. The radiating threshold was set to 2RT for this part of the experiment. This intensity of stimulation activates the low-threshold cutaneous afferents from the sole of the foot. Subjects stood with one foot on the force platform (Bertec Corporation, Columbus, OH, USA force platform Model 4060-NC) with weight equally distributed.

Equal weight distribution (Fig.15) was monitored on an oscilloscope throughout the experiment and for each trial.

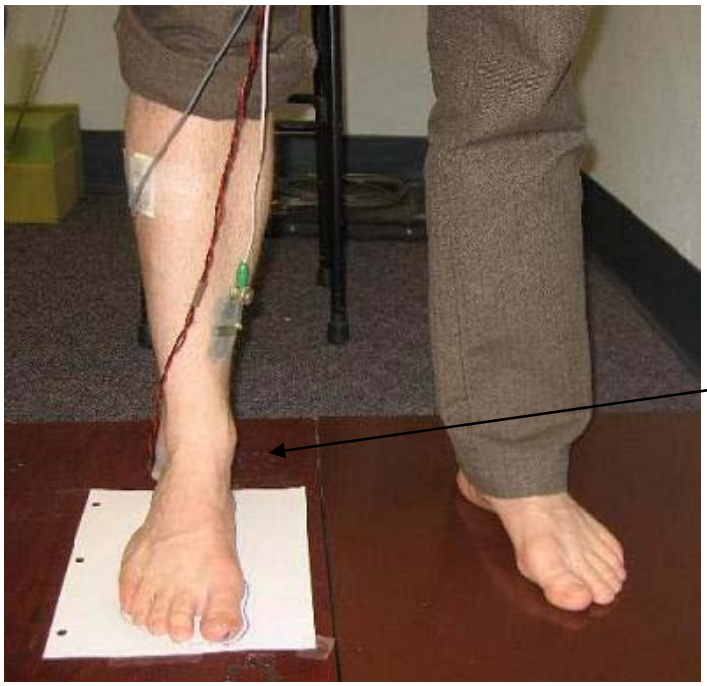


FIG.15. Set up for the step initiation task.

A visual ready cue (7 mm diameter red LED placed 2 m in front of and at subject eye level) was followed at random times (0.5–2 s) by either a second visual "go" cue (7 mm diameter red LED at same position) or stimulation of the right sural nerve. Subjects were instructed to take 3 steps as fast as possible beginning with the right leg (equivalent to 1 trial). Inter-trial time interval was approximately 10 seconds. Twenty stepping trials were acquired for each go cue (visual and sural) and for each of the two points of step initiation, (+) and (–) slope of loading force. There were also additional, five ***catch trials*** which were provided in a random manner in between other trials which included giving a ready cue and not giving the go cue. The subjects were expected to remain standing as they have not been given a "go" cue to take the step. The purpose for giving catch trials

was to make sure that subjects were always reacting to the go cue and that their steps were not self generated. To verify that the reflex responses are produced by sural stimulation ***control trials*** were also done. *Control trials* comprised of taking 3 steps as fast as possible with the right leg to visual go cue and triggering of the averaging of EMG response with the stimulus disabled for the (+) slope and (-) slope of the loading force of step initiation. The EMG data (average of 15 stimuli) was used to determine the reflex effects in TA muscle during step initiation. Although we performed 20 stepping trials, average of first 15 stimuli (good trials) was done. The rationale for doing that was, at times subjects start from an unstable baseline and these trials were regarded as bad trials and were not used for the analysis. Five extra trials were done to ensure 15 good trials for averaging.

Visual + slope	20 Real Trials	5 Catch trials
Sural + slope	20 Real Trials	5 Catch trials
Control + slope	20 Real Trials	5 Catch trials
Visual - slope	20 Real Trials	5 Catch trials
Sural - slope	20 Real Trials	5 Catch trials
Control - slope	20 Real Trials	5 Catch trials

Table 1: Represents layout of the 20 trials of step initiation.

Thus a total of 120 (20*6) trials were collected, which comprised of 6 conditions listed (Table 1). Within each condition we had 20 real trials and 5 catch trials.

Experimental Design

A **two factor repeated measure design** was used. The two factors were the stimulus cue and the phase of the loading force of step initiation (Table 2). (1) Stimulus cue had 3 levels: visual cue, sural cue and control (visual cue without sural stimulation given to the

subject). (2) Phase of loading force of step initiation had 2 levels – positive slope of the loading force and negative slope of the loading force.

Dependent variables were the individual *reflex responses (latency, duration and strength), Net Reflex EMG response (NRE), reaction time (Rn. Time), TA EMG amplitude* and *duration, vertical ground reaction force amplitude* and speed, posterior *center of pressure (COP) displacements and speed*. The ***independent variables*** were the *stimulus cue* and the *phase of loading force of step initiation* (positive slope and negative slope).

	Phase of loading Force of Step Initiation					
	Positive Slope (Loading phase)			**Negative slope(Unloading phase)**		
Stimulus cue	**Visual**	**Control**	**Sural**	**Visual**	**Control**	**Sural**
Subject one	*RR(reflex response)* *NRE*	*RR* *NRE*	*RR* *NRE*	*RR* *NRE*	*RR* *NRE*	*RR* *NRE*
	Rn. Time *-TA EMG onset* *-Load onset* *-COP onset*	*Rn.Time*	*Rn. time*	*Rn.time*	*Rn. time*	*Rn. time*
	EMG amplitude and duration	*EMG*	*EMG*	*EMG*	*EMG*	*EMG*
	Vertical (GRF) amplitude, speed	*GRF*	*GRF*	*GRF*	*GRF*	*GRF*
	COP *-Ant-post. displacement* *-speed of COP onset*	*COP*	*COP*	*COP*	*COP*	*COP*

Table 2: Schematic of design for the *step initiation* task.

4.4.3 Experiment 2- standing

In this part of the experiment, reflex changes in TA were demonstrated by standing on a wedge shaped wooden platform with 15 degree incline (Burke, D., Dickson, H. G. and Skuse, N. F., 1991) for 40 seconds. During quiet standing, TA is not active and therefore to produce a small load on that muscle, subjects stood on a 15 degree incline (Fig. 16). This produced a low level of tonic activity in the muscle (~20-25% of a maximum contraction). All subjects stood with 15 degrees of dorsiflexion at four different intensities of 0, 1.5, 2 and 2.5 RT. The EMG data was collected for 40 seconds and the sural stimulation is delivered at 3/second, which is equivalent to (40*3) 120 stimuli. Thus average of 120 stimuli was required to evoke out the reflex responses during standing.

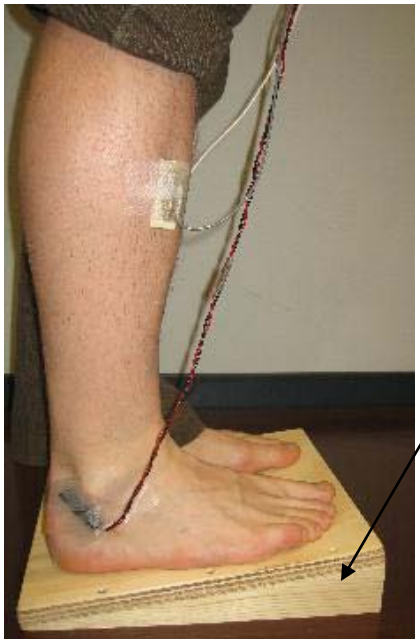


FIG.16.Set up for the standing task.

Experimental design

	Stimulus Intensity (RT)			
	0RT	1.5 RT	2RT	2.5 RT
Subject 1	***RR*** *-latency* *-duration* *-strength* *-sign* ***(NRE)***	*RR*	*RR*	*RR*

Table 3: Schematic of design for the standing task.

One factor repeated measure design was used for this part of the study. The one factor was stimulus intensity which will have 4 levels: 1.5 RT, 2 RT, 2.5 RT and 0RT as a control (Table 3). The **dependent variables** were *Reflex responses (latency, duration, strength) and Net Reflex EMG effect* and the i**ndependent variable** was the stimulus intensity.

CHAPTER 5: Data Analysis

5 dependent variables were analyzed:

For experiment 1 &2:

- Cutaneous reflexes

For experiment 1:

- TA EMG amplitude and duration
- Vertical Ground reaction force (GRF)
- Center of Pressure (COP)
- Reaction time (RT)

5.1 Cutaneous reflexes

For TA, reflexes were sorted into short (<60 ms) and long (>60 ms) latencies as reported previously by (Li et al, 2004). For each reflex response the significance of occurrence (Z score), onset latency, duration, strength and sign was determined. TA EMG was averaged online for experiment one and two using a Tektronic TDS 1002B oscilloscope for visual assessment of potential reflex effects. For, final analysis the data was fed into a computer (Dell optiplex GX 260) and was acquired by a custom built Lab View program. Eight channels of data (Table 4) were fed into the 16 bit A/D board (National instrument PCI-6034E Data Acquisition board) during step initiation and 2 channels of data during standing. EMG was amplified by a factor of 10 K and was full wave rectified and low pass filtered with a time constant of 2.5ms.The full wave rectified and filtered EMG were used for the analysis of the latency and magnitude of all significant inhibition and facilitation of reflex responses.

Channel	Experiment 1 (Step initiation)	Experiment 2 (Standing)
1	Visual ready or visual "go" cue	Sural stimulation onset pulse
2	Loading force (Fz)	
3	TA EMG	TA EMG
4	Fx	
5	Fy	
6	Mx	
7	My	
8	sural go cue and sural stimulation onset pulse	

Table 4: Represents the type of data going into the 16 bit A/D board

The sural evoked reflex response was determined by streaming the EMG data to an excel spreadsheet. A representative example of the full wave rectified and filtered EMG data is depicted (Fig.17a).

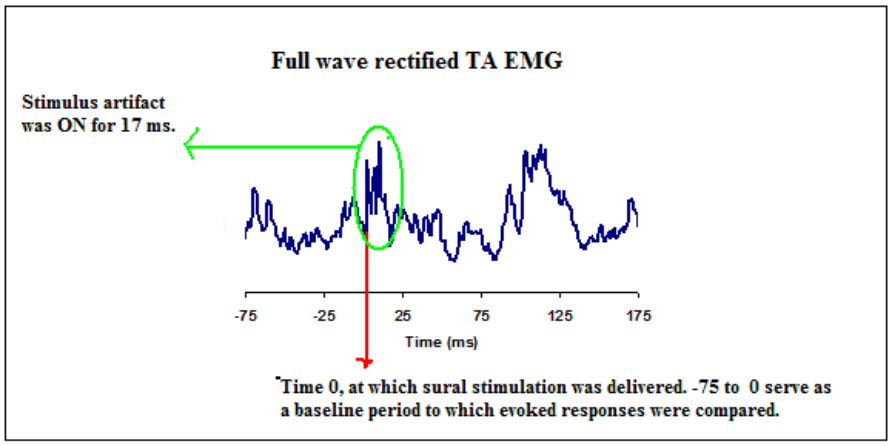


FIG.17a.Full wave rectified and filtered EMG data.

The TA EMG was averaged over a 250 ms time period, in which the first 75 ms prior to the delivery of a stimulus served as a baseline to which evoked responses were compared. The stimulus artifact was removed by finding the average of the baseline period and substituting this value for the period the artifact was on (approx. ~ 17 ms). This is depicted in Fig.17b which shows the EMG data after the artifact had been removed.

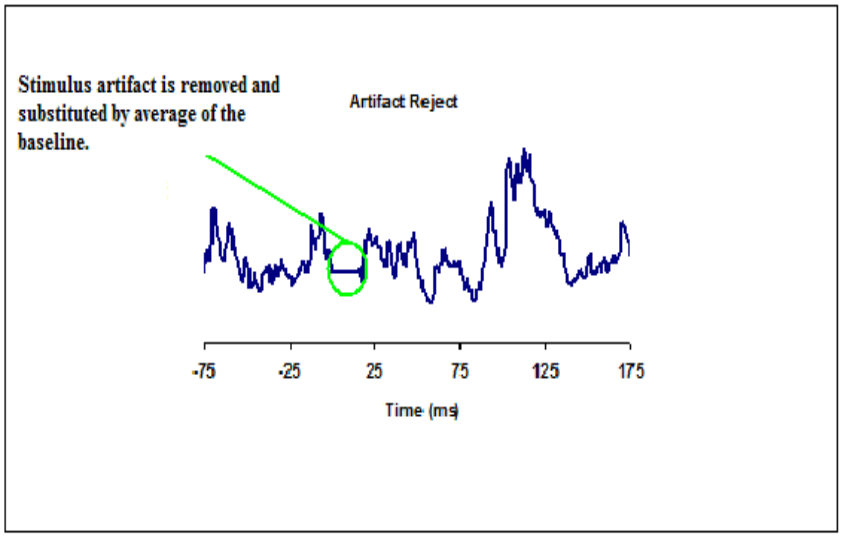


FIG. 17b.Full wave rectified EMG data after stimulus artifact removal.

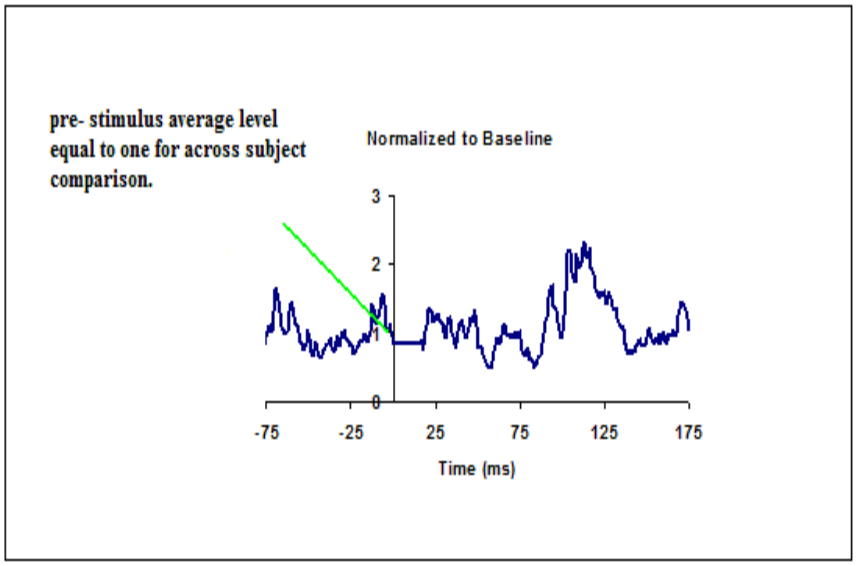


FIG.17c. Full wave rectified EMG after normalization to the baseline.

In order to make comparisons across subjects, full wave rectified EMG was normalized to the baseline (Brinkworth RS, 2003). This was achieved by dividing the averaged EMG trace by the average pre- stimulus value; this made the pre- stimulus average level equal to one (Fig17c) and allowed comparisons across subjects.

To accurately determine the onset and offset of potential reflex responses the cumulative sum (CUSUM) technique (Ellaway P.H., 1978 Aug) was used as modified by (Zehr EP,

Komiyama T, Stein RB, 1997). The CUSUM of the averaged EMG data (Fig.17d) was constructed by calculating a mean baseline count, subtracting the mean baseline count from each bin of the averaged EMG record and then sequentially summing these differences across all bins (Ellaway P.H., 1978 Aug). In the CUSUM, increases from the mean were shown as positive slopes (Fig.17d) while decreases from the mean were recognized as negative slopes. Fig. 17d is an example that demonstrates the construction of CUSUM on averaged EMG data that shows long latency excitation (E1) ~ 97 ms in TA when sural nerve stimulation was provided during loading (+) phase of step initiation.

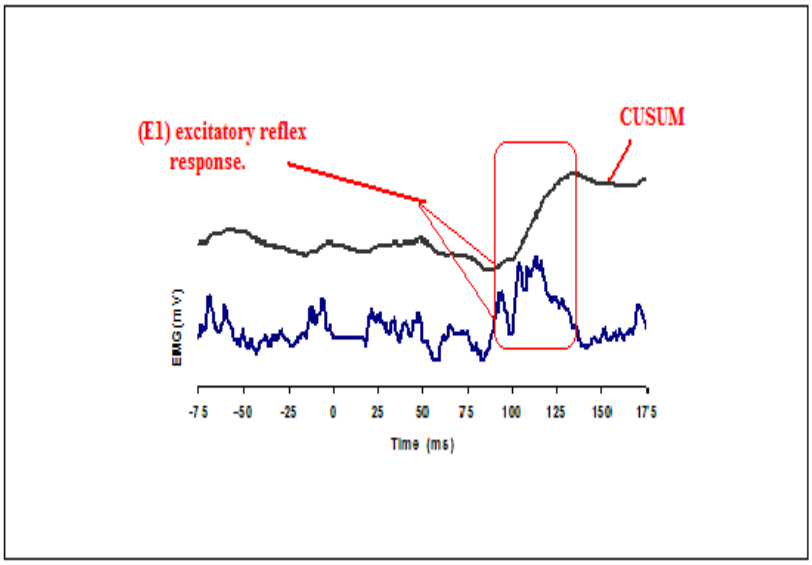


FIG.17d. Representative example of excitatory response in TA to sural nerve stimulation during step initiation .In this trial visual cue was given during loading phase (+) phase of step initiation. *Upper graph:* CUSUM showing Long latency excitatory reflex response at 97ms. .*Lower graph:* Full wave rectified EMG after artifact removal.

The following parameters of reflex response were determined:

5.1.1 Reflex occurrence

Qualitative determination of the reflex effects in the averaged EMG was done by constructing the statistical limits for the CUSUM for 3 standard deviations. The variance (V) of the Poisson distribution (Davey NJ, Ellaway PH, Stein RB., 1986 Aug) over *n* trials was given by V = (n*t/m) where t was the time and *m* was the average of the

normalized EMG. The standard deviation of the estimated variance was equal to the square root of the variance calculated using the above equation. These parabolic limits were derived from Poisson statistics (Davey NJ, Ellaway PH, Stein RB., 1986 Aug) and when they were superimposed (Fig.17e) on the CUSUM, they allowed for visual assessment of potential reflex response.

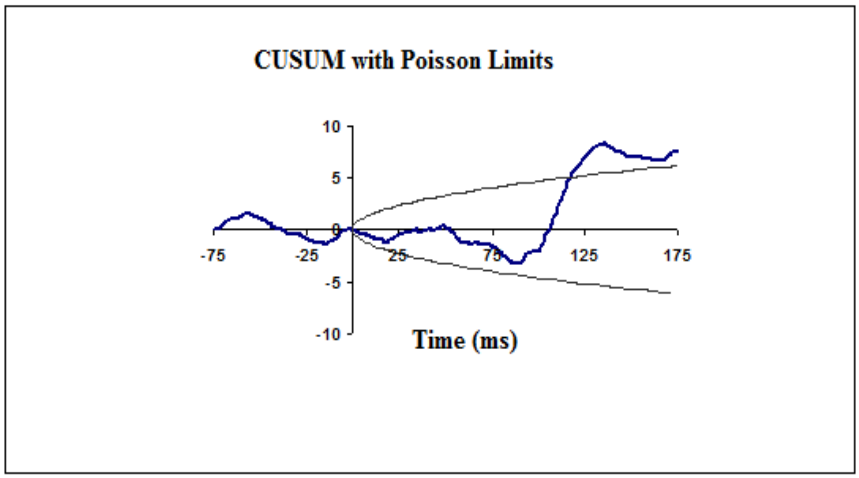


FIG.17e. Shows CUSUM with Poisson limits.

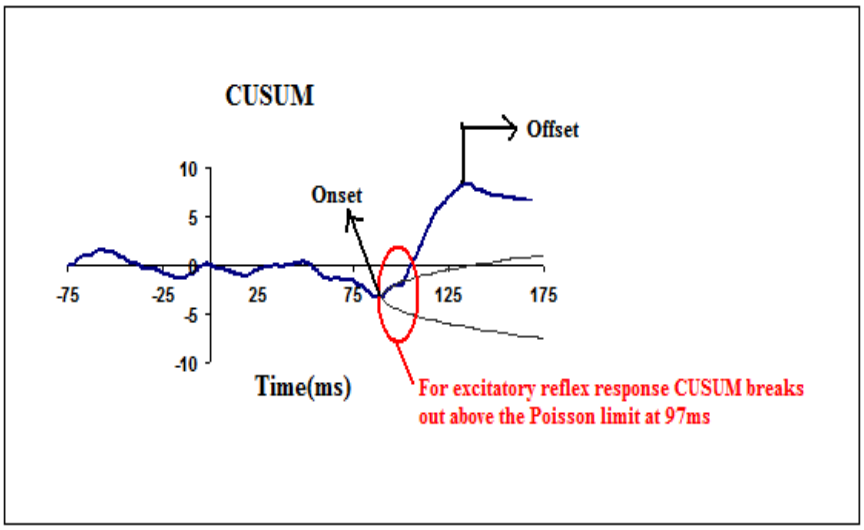


FIG.17f.Shows CUSUM with Poisson limits. The response was considered excitatory if the CUSUM breaks out *above the Poisson limit.*

To find the potential reflex period, Poisson limits was superimposed to detect changes in the CUSUM that signify the onset and offset of the response. The response was considered ***excitatory*** if the CUSUM breaks out *above the Poisson limit* (Fig.17f) and

inhibitory when the CUSUM breaks out *below the Poisson limit.* The time period of the suspected reflex response was noted and tested for significance of occurrence. Quantitative validation for a reflex effect was done by a Z score statistic for comparing the period of suspected effect to the baseline period of activity (Garnett & Stephens, 1980) according to the formula:

$$Z = \frac{n_1/t_1 - n_2/t_2}{(n_1/t_1^2 + n_2/t_2^2)^{1/2}}$$

Where n1 and n2 represented the sum of the suspected *reflex effect data points* and the *baseline data point* from the normalized EMG signal respectively, observed in time periods t1 (suspected reflex effect period) and t2 (baseline time period =75 ms before the stimulation). In as much as comparisons of the baseline period were often made to two or more potential reflex effect periods , the $P < 0.01$ level of significance was used to alleviate adjustment of a 0.05 level for multiple comparisons. To be considered significant the z score of the reflex effect should be greater than +2.13 or smaller then -2.13.

5.1.2 Reflex latency

The Poisson limits were moved along the entire CUSUM and the onset (Fig. 17f) of the response was detected when the data point of the CUSUM graph was completely out of the Poisson limits and offset of the response was identified when the data point of the CUSUM falls back within the Poisson limits.

5.1.3 Reflex duration

The CUSUM reflex duration was the horizontal distance between the start of a reflex, as defined by the CUSUM latency and the next turning point. Poisson limits were superimposed to detect change in the CUSUM that signifies the onset and offset of the response. This was equivalent to the time period between the EMG crossing the pre-stimulus mean twice.

5.1.4 Reflex strength

To quantify the reflex responses**,** reflex strength was determined according to the formula: {Average (reflex effect) - Average (baseline)/Average (baseline)}*100. This provided us with the percentage change from the baseline.

5.1.5 Net Reflex EMG Response (NRE)

Cutaneous reflexes are comprised of complex excitatory and inhibitory effects. It is the net reflex effect over the entire reflex response period that should give a more realistic assessment of the influence of the cutaneous input. We therefore, measured the net reflex response as recommended by (Zehr EP, Komiyama T, Stein RB, 1997). The NRE was obtained by summing the reflex effects of the evoked response between 40 – 125 ms and comparing it to the baseline period (-75 to 0ms).

5.1.6 Reflex Sign

The positive reflex strength signifies excitatory reflex response and negative reflex strength signifies inhibitory reflex response, and corresponds to whether the peak response was larger (+) or smaller (-) than the mean pre-stimulus EMG.

5.2 TA EMG Amplitude and Duration

During step initiation, the TA EMG burst for each trial was normalized by first determining the mean EMG for the visual go cue trials. TA EMG Amplitude was determined from TA onset to TA offset. Each individual trial for both visual and sural go cues was then expressed as a percent of the mean EMG for visual trials. TA EMG duration was determined from TA onset to TA offset. A final grand mean for visual versus sural go cue was then determined for each subject.

5.3 Vertical Ground Reaction Forces

Vertical ground reaction forces and moments were obtained from a Bertec Corp (Columbus, OH), Model 4060-NC force platform to calculate the anterior-posterior COPs (see below). The force platform data was streamed to disk using a custom-built Lab View data acquisition and analysis program that sampled each channel at 1000 Hz. *The vertical force onset times* as well as *vertical force amplitude* were determined. Vertical force amplitude was normalized to percent body weight and was calculated as additional force generated from baseline of 50% body weight. This meant that a loading force of 30% body weight corresponded to a total force of 80% body weight. Speed of force onset was also calculated and was given by vertical force amplitude divided by the time it took to reach peak force.

The vertical force onset times as well as *vertical force amplitude* were stored into an excel spreadsheet and vertical GRF measurements were calculated within the spreadsheet.

5.4 Centre of Pressure (COP)

Anterior-posterior COP was assessed in all subjects. The calculation that was used is as follows: $Yp = Mx/Fz \times 100$, where Yp is the anterior–posterior COP, Mx is the moment in the y direction, Fz is the vertical ground reaction force. The single force platform was used for the swing limb and therefore we were able to calculate the COP under a single limb and not the net COP. A similar normalization procedure as we used with the EMG amplitudes was used for normalization of the COP displacements. COP displacements during step initiation were normalized by first determining the mean COP displacements for the visual go cue trials. The time window for determining the mean COP displacements was from the onset of EMG to the peak Fz force. It is important to note that only single force platform was used for the swing limb and therefore we were able to calculate the COP under a single limb and not the net COP. Reaction forces and moments were stored into an excel spreadsheet and center of pressure measurements were calculated within the spreadsheet. The speed of COP was determined by the COP displacement divided by the time taken from the onset of COP to when the displacement was maximum.

5.5 Reaction time

Reaction time is the time from the appearance of the stimulus to the time of initiation of movement and was determined using a custom made lab view program with interactive cursor adjustments. Time to vertical force onset, time of TA onset and time of COP onset were also determined.

CHAPTER 6: Statistical Analysis

Step initiation: The dependent variables were *latency, duration and strength of individual reflex responses (D2 and E1) and NREs, reaction time (mean TA EMG onset, mean vertical force onset, mean COP onset), mean TA EMG amplitude, mean TA EMG duration, mean vertical force amplitude, mean speed of force onset* and *mean COP displacement, mean speed of COP onset*. The independent variables are the *stimulus cue* (visual and sural) and the *level of loading force,* (+) slope and (-) slope.

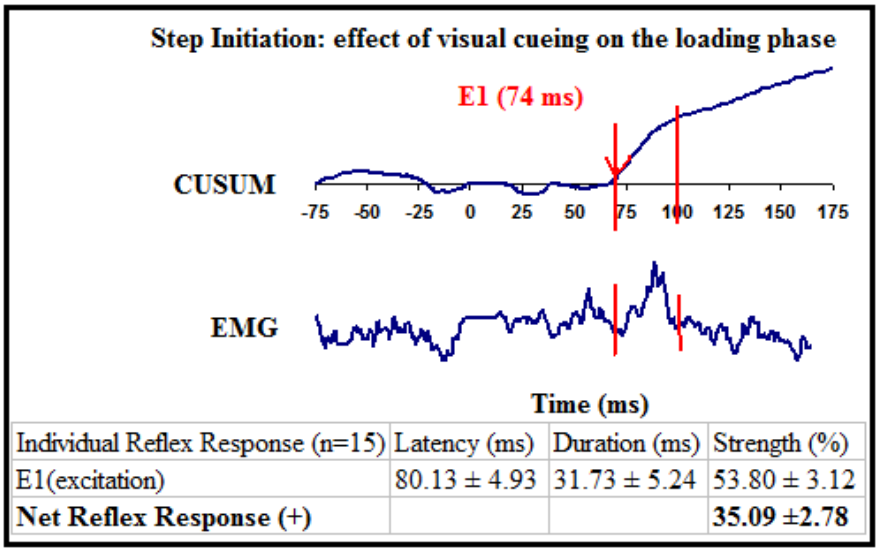
Standing: The dependent variables were *latency, duration and strength of individual reflex responses (D1 and D2) and NREs.* The independent variable was the *stimulus intensity.*

Means and standard deviations are provided for all outcomes by slope and stimulus. A general linear mixed model with a random intercept for each subject and fixed effects for slope (positive/negative), stimulus (visual cue/sural cue), their interaction, time (stepping series first/second) and order (positive slope first/negative slope first) was used to assess the effect of stimulus on the outcomes related to stepping. Contrasts were calculated to determine the effect of the stimuli for the negative and positive slopes separately. In addition, the inter-class correlation (ICC) for each outcome between stepping series 1 and 2 was calculated. A general linear mixed model was used for standing with varying stimulus intensities. Also, a general linear mixed model was used to compare the net reflex effect (NRE) at 2RT with the average stepping NRE with the visual stimulus and on the positive slope. All analyses were carried out in SAS Version 9.1 (SAS Institute,

Inc., Cary, NC) and all significance levels were set at 0.05. All the outcome measures were determined for all the subjects in which the cutaneous reflexes were evoked (n =15). The tables for the analysis are also provided (Appendix O and P).

CHAPTER 7: Results

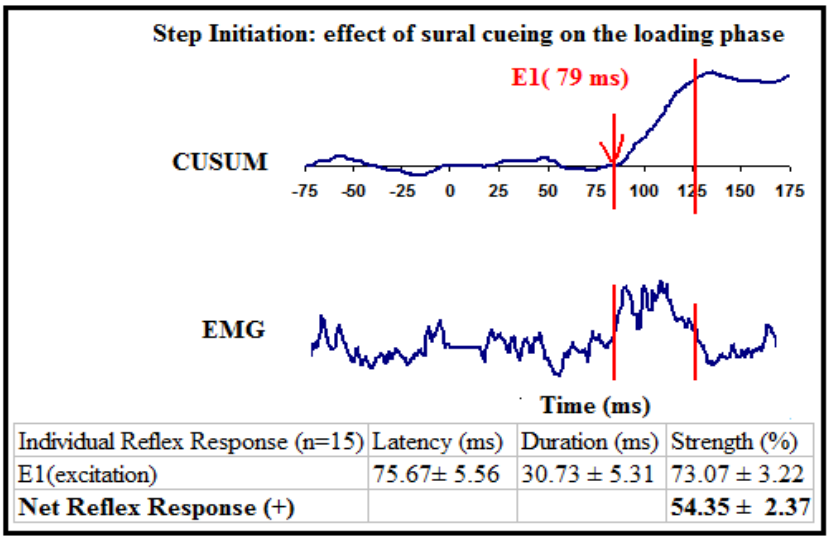
7. 1 Cutaneous Reflexes during step initiation



Individual Reflex Response (n=15)	Latency (ms)	Duration (ms)	Strength (%)
E1(excitation)	80.13 ± 4.93	31.73 ± 5.24	53.80 ± 3.12
Net Reflex Response (+)			**35.09 ±2.78**

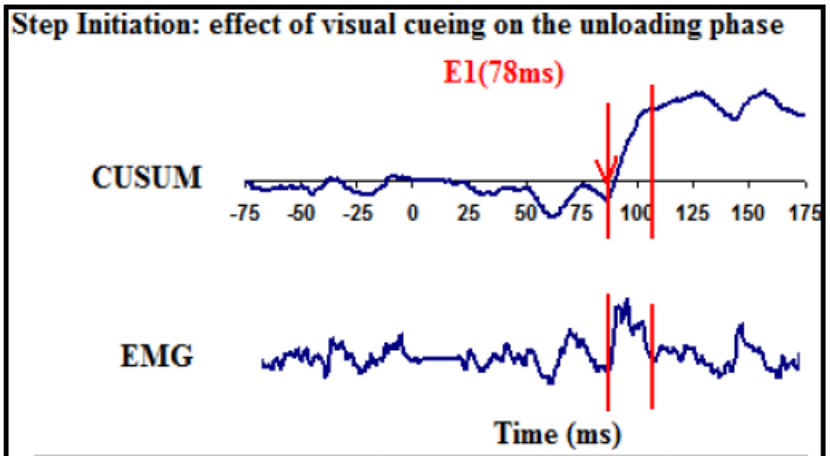
FIG.18a. CUSUM and PSTH for a typical subject showing long latency excitation (E1) ~ 74 ms. Reflex response was significantly different from baseline (52 % increase).

Fig.18a illustrates a typical reflex response for a single subject stepping to a visual go cue and evoking the reflex response in the loading phase of step initiation (+ slope). For this subject, a significant (z = 2.74) long latency excitation (E1) was observed with onset latency of 74 ms and strength of 52% above baseline levels. All subjects demonstrated this primary excitatory effect. The table below the figure depicts the mean responses for all subjects (n = 15). The ICC's for onset latency = 0.86, duration = 0.76, strength = 0.83 and net reflex strength = 0.58. For a sural go cue and evoking the reflex response during the + slope, again the typical response for a single subject (Fig. 18b) was a long latency excitation (z = 3.19) at 79 ms with a strength of 73% above baseline levels. All subjects showed this excitatory effect (means and SDs in table below Fig.18b). The ICC's for onset latency = 0.86, duration = 0.73, strength = 0.76 and net reflex strength = 0.76.



Individual Reflex Response (n=15)	Latency (ms)	Duration (ms)	Strength (%)
E1(excitation)	75.67± 5.56	30.73 ± 5.31	73.07 ± 3.22
Net Reflex Response (+)			**54.35 ± 2.37**

FIG.18b. CUSUM and PSTH for a typical subject showing long latency excitation (E1) ~79 ms. Reflex response was significantly different from baseline (73 % increase).

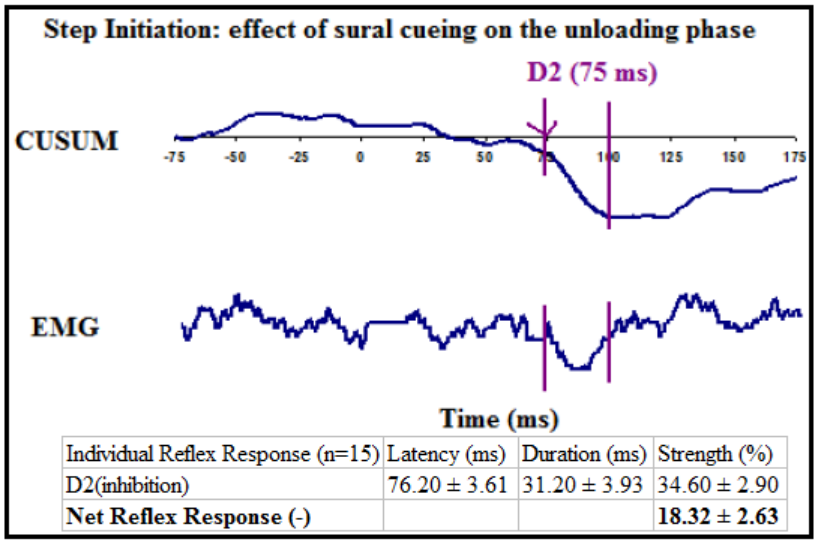


Individual Reflex Response (n=15)	Latency (ms)	Duration (ms)	Strength (%)
E1(excitation)	74.33 ± 2.66	28.20± 4.16	43.27± 2.69
Net Reflex Response (+)			**24.72 ±2.73**

FIG.18c. CUSUM and PSTH for a typical subject showing long latency excitation (E1) ~ 78 ms. Reflex response was significantly different from baseline (41 % increase).

Fig.18c illustrates a typical reflex response for a single subject stepping to a visual go cue and evoking the reflex response in the unloading phase of step initiation (- slope). For this subject, a significant (z = 2.23) long latency excitation (E1) was observed with onset latency of 78 ms and strength of 41% above baseline levels. All subjects demonstrated this primary excitatory effect. The table below the figure depicts the mean responses for all subjects (n = 15). The ICC's for onset latency = 0.70, duration = 0.71, strength = 0.66

and net reflex strength = 0.59. In contrast, for a sural go cue and evoking the reflex response during the - slope, the typical response for a single subject (Fig. 18d) was a long latency inhibition (z = -2.52) at 75 ms with a strength of 37% below baseline levels. All subjects showed this inhibitory effect (means and SDs in table below Fig. 18d). The ICC's for onset latency = 0.79, duration = 0.78, strength = 0.73 and net reflex strength = 0.84.



Individual Reflex Response (n=15)	Latency (ms)	Duration (ms)	Strength (%)
D2(inhibition)	76.20 ± 3.61	31.20 ± 3.93	34.60 ± 2.90
Net Reflex Response (-)			**18.32 ± 2.63**

FIG.18d. CUSUM and PSTH for a typical subject showing long latency inhibition (D2) ~ 75 ms. Reflex response was significantly different from baseline (37 % decrease).

7.1.1 Effect of cueing and phases of step initiation

There were no statistically significant differences between visual and sural cueing and for evoking reflexes during + and – slope for the latencies and durations of the E1 effect (Fig. 19a and 19b). All p values were > 0.07.

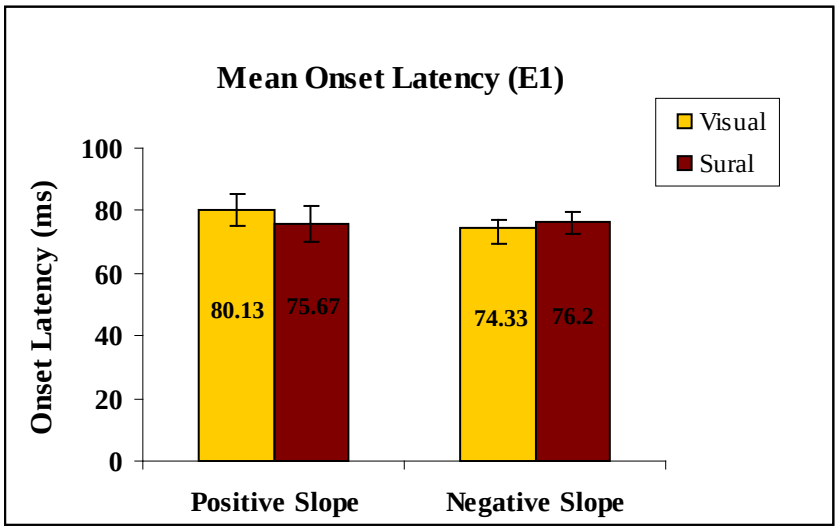


FIG.19a. Shows that the there was no effect of cues and phases of step initiation on the mean onset latency of the reflex response.

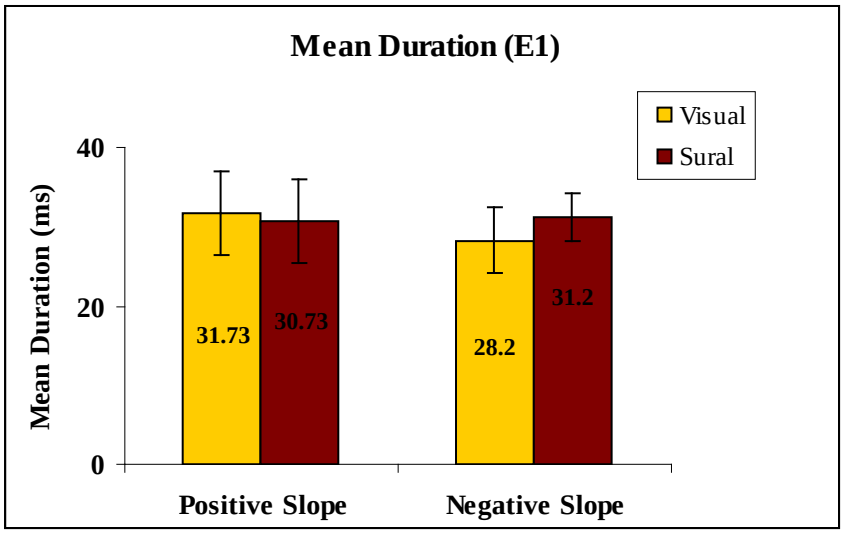


FIG.19b. Shows that the there was no effect of cues and phases of step initiation on the mean duration of the reflex response.

Strength of the reflex response (Fig.19c) was influenced by both the type of cue used (visual vs. sural) and the slope for which triggering of the reflex response was made (+ and – slope). For reflexes evoked during the + slope, the reflex was statistically greater for sural vs. visual cuing ($p = 0.0133$,*) and for reflexes evoked during the - slope, visual cuing was statistically significantly different from sural cuing ($p=0.0067$, **).

For visual cueing, the reflex was down modulated from 53.8 % during + slope triggering to 43.27% during – slope triggering (p = 0.0323, ***). For sural cueing, reflex reversal was seen with a 70.07% excitatory effect during + slope triggering to -34.6% inhibitory effect during – slope triggering (p = 0.0105,****). A significant stimulus cue * slope interaction (p< 0.0001) was found.

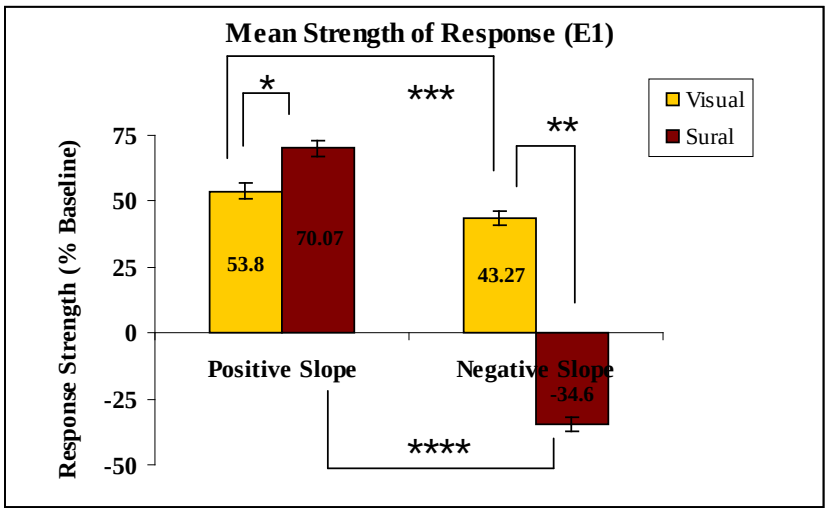


FIG.19c. Shows that mean strength of reflex response was influenced by the cue and the phases of step initiation.

7.1.2 Step Initiation: Net Reflex EMG Response

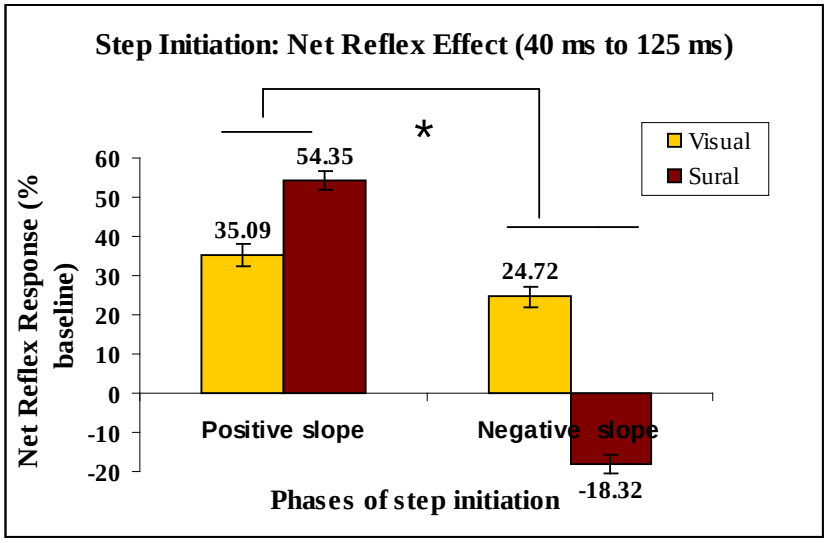
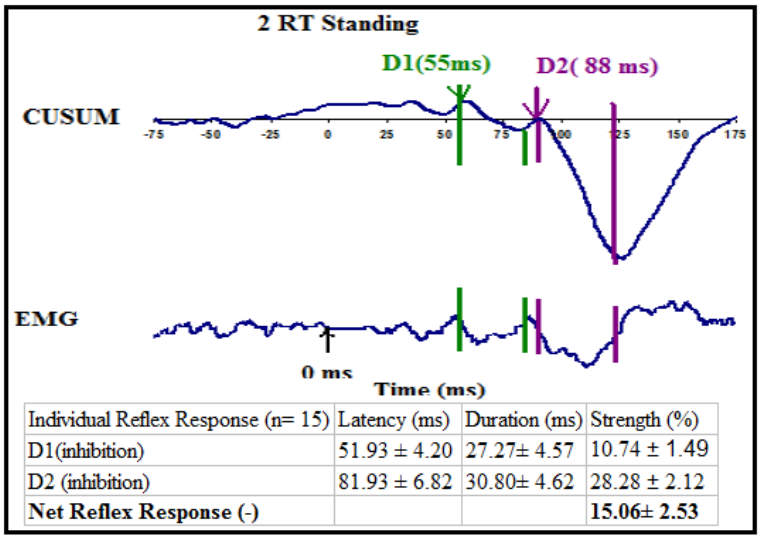


FIG.19d. Influence of phases of loading force and cue on net reflex effect. Greater amplitude for loading than unloading phase (p < 0.001).Reflex modulated during visual cue vs. reversed during sural cue (p < 0.001) .

Fig.19d depicts the net reflex effect for the time period of 40 to 125 ms. As seen in this figure, the net effects were similar but of smaller amplitude than that seen for the E1 response only (Fig. 19c). The strength of the reflex response was modulated by the phase of loading force (larger amplitude of response for loading phase, i.e. evoking reflex during + slope) then unloading phase (evoking reflex during – slope). A slope alone effect ($p<0.0001$) and stimulus cue * slope interaction ($p < 0.0001$) effect was also seen.

7.2 Cutaneous Reflexes during standing



Individual Reflex Response (n= 15)	Latency (ms)	Duration (ms)	Strength (%)
D1(inhibition)	51.93 ± 4.20	27.27± 4.57	10.74 ± 1.49
D2 (inhibition)	81.93 ± 6.82	30.80± 4.62	28.28 ± 2.12
Net Reflex Response (-)			**15.06± 2.53**

FIG.20. CUSUM and PSTH for a typical subject showing a short latency inhibition (D1) ~ 55 ms and a long latency inhibition (D2) ~ 88 ms. Both the reflex responses were significantly different from the baseline (z = -2.18 and -3.13) respectively and represented (-10.75% and 27.79% decreases respectively).

During standing the reflex responses were primarily inhibitory as depicted in Fig.20.

Both mean short latency inhibition (D1) ~ (-51.93 ± 4.20 ms) and mean long latency inhibition (D2) ~ (-81.93 ± 6.82) reflex responses were seen. The mean duration of the reflex response was (27.27 ± 4.57) for the D1 response and (30.80± 4.62) for the D2 response respectively. The mean net reflex effect (-15.06 ± 2.53) was primarily inhibitory. There was no effect ($p = 0.4311$) of varying stimulus intensity on the strength of the reflex response.

7.3 Effect of tasks: Standing vs. Step Initiation

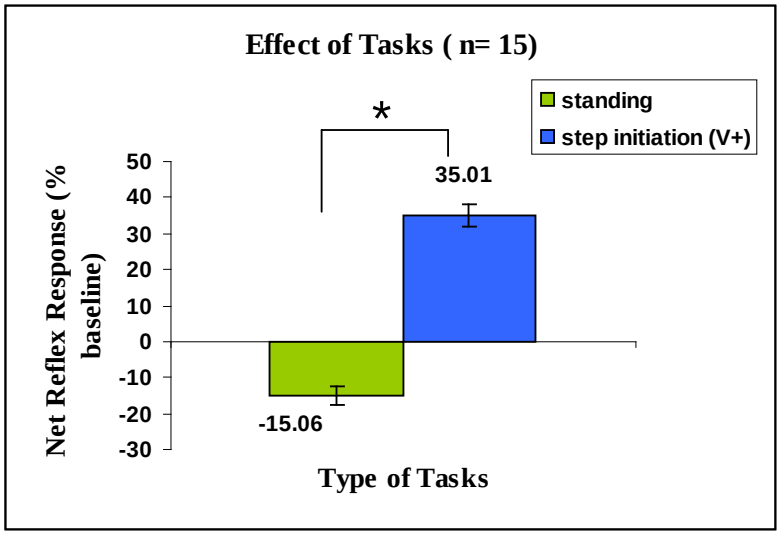


FIG.21. Net reflex response was primarily excitatory during step initiation (Visual positive slope, V+) and primarily inhibitory during standing at 2 RT ($p < 0.001$).

By comparing cutaneous reflexes under different conditions we were able to assess how these pathways are modulated in a functional task such as step initiation. To draw the comparison we used the standing data for 2 RT and the visual positive slope data for the stepping task. The rationale behind using this particular data set was that we used stimulation threshold at 2RT for the stepping task and also visual positive slope data provided effect of task without any cutaneous cue influenced. The net reflex responses were significantly different ($p < 0.0001$) for standing (-15.06 ± 2.53) at 2 RT to step initiation at visual + slope only (35.01 ± 2.72). Mean net reflex response (Fig.21) was primarily inhibitory during standing and during step initiation the primary effect in TA was a long latency excitation (70- 90 ms). The average number of averages required to evoke out reflexes during standing was 120 as compared to 12 to 15 stimuli during step initiation.

7.4 Kinetic, Kinematic and EMG data during step initiation

7.4.1 Vertical ground reaction forces

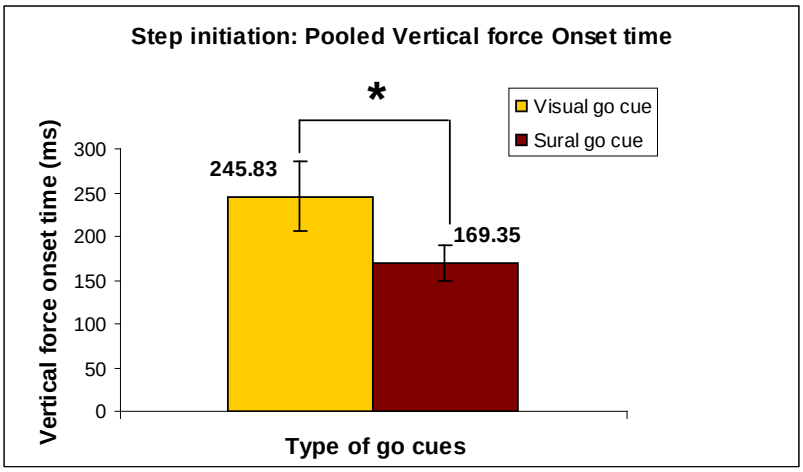


FIG.22a.Mean vertical force onset time is earlier with sural cueing than visual cueing (p = 0. 0021).

Fig. 22a, depicts the mean (n= 15) onset of the vertical force which occurred earlier with sural cueing than visual cueing. On average, sural cueing resulted in a statistically significant 76 ms earlier vertical force onset (31% decrease) than with visual cueing (p= 0.0021).

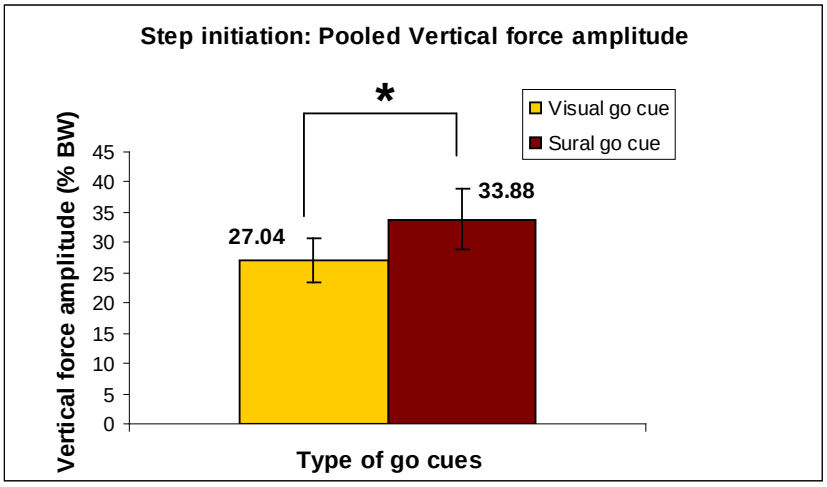


Fig.22b. Mean vertical force amplitude is larger with sural cueing then visual cueing (p= 0.0173).

Fig. 22b illustrates differences in vertical ground reaction forces found between the two cues. –The mean vertical force amplitude was larger with sural cueing then visual cueing

(p= 0.0173). On average sural cueing resulted in a statistically significant 6 % body weight increase in the vertical force than visual cueing.

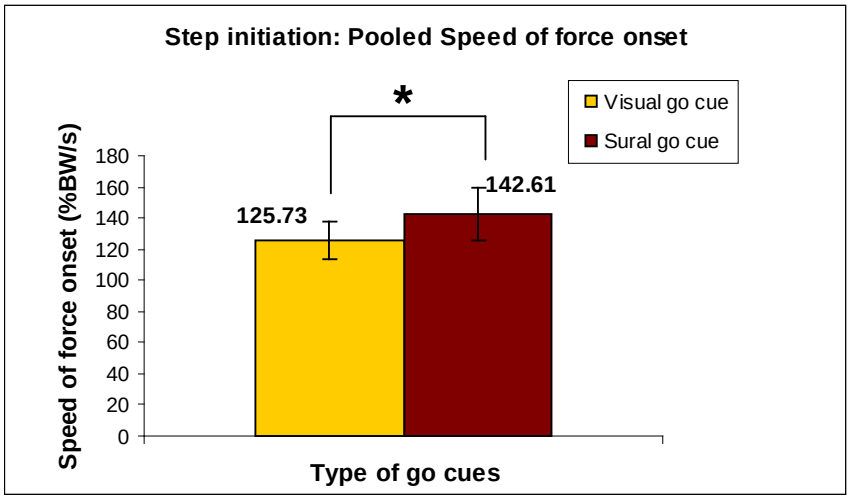


FIG.22c.Mean speed of force onset is faster with sural cueing then visual cueing (p= 0.0154).

As shown in Fig. 22c there were differences in the speed of force onset between the two cues. The mean speed of force onset was faster with sural cueing then visual cueing (p= 0.0154). On average, sural cueing produced a 17 % body weight/s faster speed of force onset than visual cueing.

7.4.2 EMG

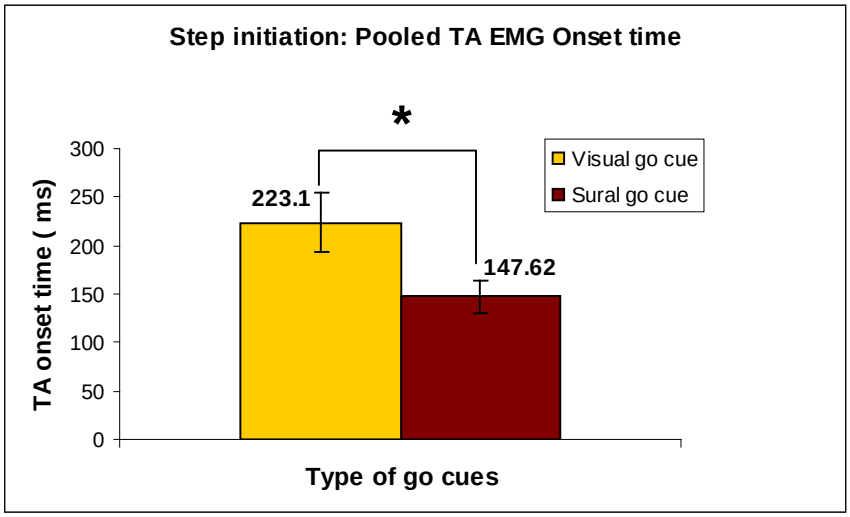


FIG.23a. Mean TA EMG onset times were statistically earlier for sural versus visual cueing (p= 0.0012).

The mean TA EMG onset times were statistically earlier for sural versus visual cueing (p= 0.0012) as shown in Fig. 23a. On average, sural cueing resulted in a 75 ms earlier onset for TA EMG than visual cueing. Secondly the average TA EMG duration was statistically shorter with sural cueing than with visual cueing (p= 0.0091). On average TA EMG duration was 50 ms shorter with sural cueing than visual cueing (Fig. 23b). Also, the average TA EMG amplitude was statistically greater with sural cueing than with visual cueing (p = 0.0205). On average TA EMG amplitude was 12% greater with sural cueing than visual cueing (Fig.23c).

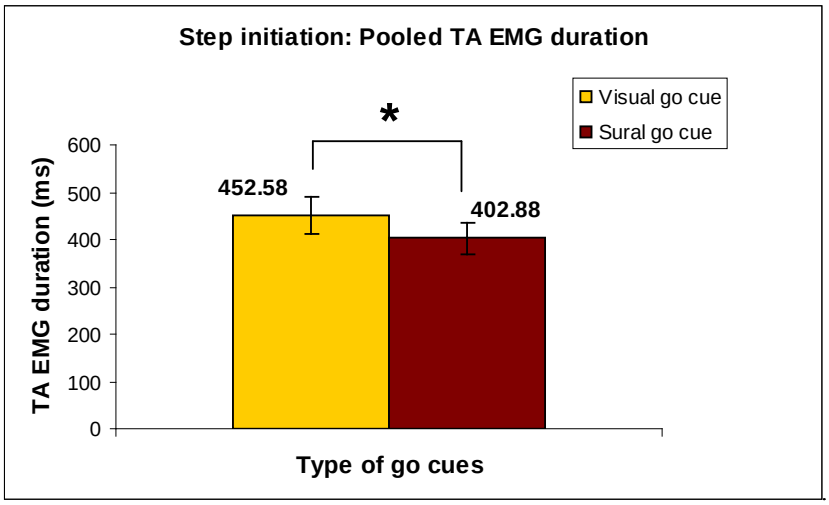


FIG.23b. Mean TA EMG duration was statistically shorter with sural cueing than with visual cueing (p= 0.0091).

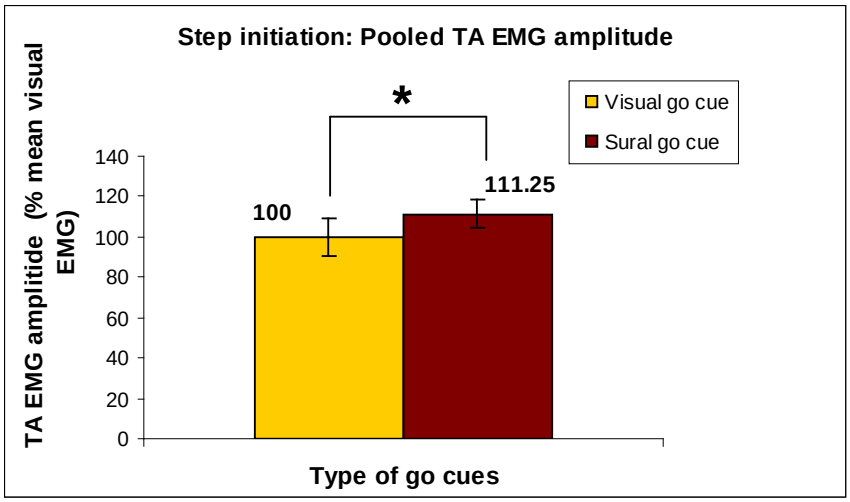


FIG.23c.Mean TA EMG amplitude was statistically greater with sural cueing than with visual cueing (p = 0.0205).

7.4.3 Posterior COP Displacements

Fig. 24a depicts the posterior COP onset produced by the two different cueing. Mean posterior COP onsets occurred earlier (p= 0.0054) and were of greater magnitude (p= 0.0220) for sural versus visual cueing. On average, sural cueing produced 77 ms earlier posterior COP onset and 23% greater posterior COP displacement than visual cueing as shown in figure 24b.

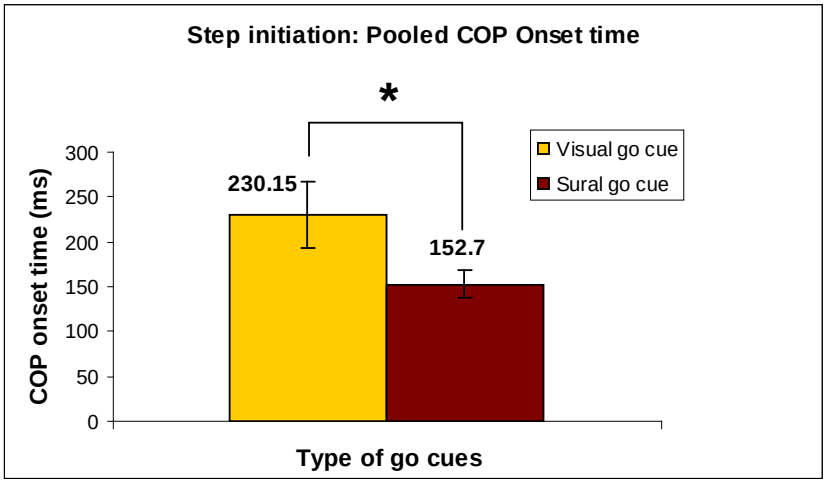


FIG.24a. Mean posterior COP onset occurred earlier with sural cueing than visual cueing (p= 0.0054).

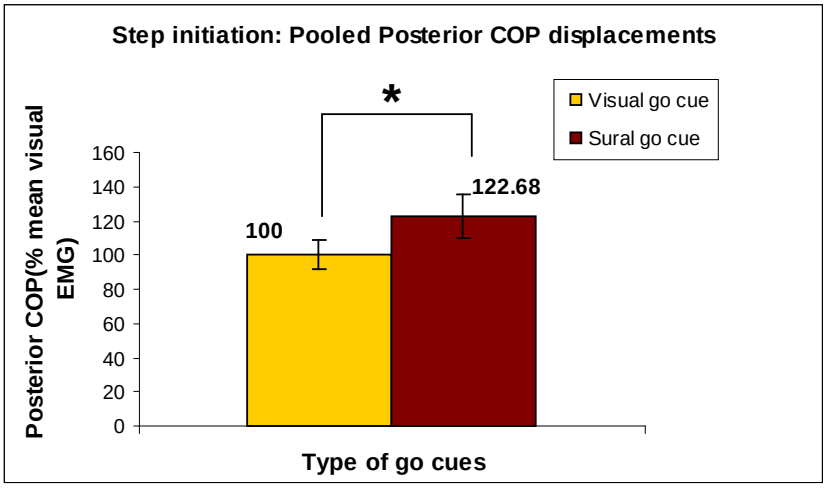


FIG.24b.Mean posterior COP displacements occurred earlier with sural cueing than visual cueing (p= 0.0220).

As shown in Fig. 24c there were differences in the speed of posterior COP onset between the two cues. The mean speed of posterior COP onset was faster with sural cueing then visual cueing (p= 0.0246). On average, sural cueing produced a 16 % faster speed of posterior COP onset than visual cueing. ICC scores for all the kinetic, kinematic and EMG data demonstrate that the results were reliable between stepping series 1 and 2 (Table 5).

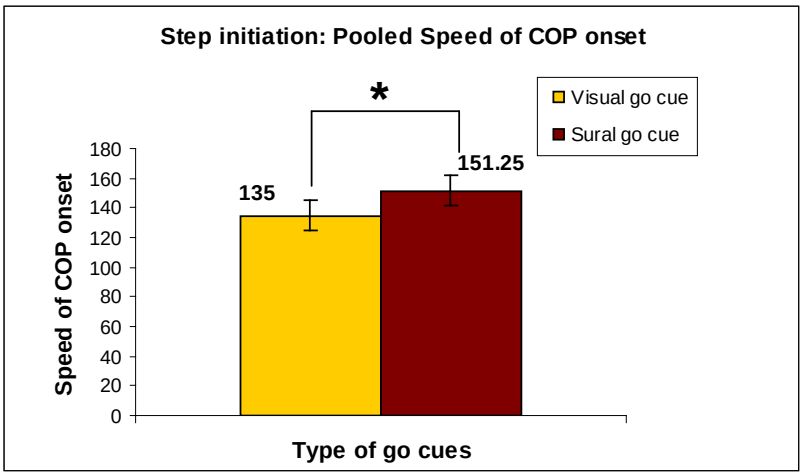


FIG.24c.Mean speed of posterior COP onset was faster with sural cueing than visual cueing (p= 0.0246).

Outcome Measure	Visual go cue (ICC)	Sural go cue (ICC)
TA EMG onset time (ms)	0.71	0.61
Posterior COP onset time (ms)	0.67	0.64
Vertical force onset time (ms)	0.56	0.61
Vertical force amplitude (% BW)	0.66	0.59
Speed of force onset (%BW/s)	0.61	0.63
TA EMG duration(ms)	0.59	0.63
TA EMG Amplitude (% mean visual EMG)	0.58	0.6
Posterior COP (% mean visual EMG)	0.61	0.62
Speed of Post COP onset (mm/s)	0.69	0.71

Table 5: ICC scores for stepping series 1 and 2.

To summarize, these results reveal significant differences in mechanical and EMG responses between sural and visual cueing during step initiation (Table 6). Thus, lending support to our earlier findings regarding the effect of sural cueing in enhancing (Kukulka et al, 2009, Hajela et al, 2006) APAs.

Outcome Measure	**Visual go cue (mean ± SD)**	**Sural go cue (mean ± SD)**	**P value**
TA EMG onset time (ms)	223.1± 30.63	147.62 ± 16.96	0.0012
Posterior COP onset time (ms)	230.15 ± 37.13	152.7 ± 15.25	0.0054
Vertical force onset time (ms)	245.83± 39.29	169.35 ± 19.89	0.0021
Vertical force amplitude (% BW)	27.04 ± 3.56	33.88 ± 4.95	0.0173
speed force onset (%BW/s)	125.73 ± 12.15	142.61±17.02	0.0154
TA EMG duration(ms)	452.58 ± 29.91	402.88 ± 34.32	0.0091
TA EMG Amplitude (% mean visual EMG)	100 ± 9.37	111.25 ± 7.1	0.0205
Posterior COP (% mean visual EMG)	100 ± 8.39	122.68 ± 12.28	0.022
Speed of Post COP onset (mm/s)	135 ± 10.49	151.25 ± 10.22	0.0246

Table 6: Descriptive statistics for kinetic, kinematic and EMG data

CHAPTER 8: Discussion

The results of this study demonstrate, for the first time the influence of cutaneous reflexes in APAs that precede a step in healthy human subjects. In addition, we confirmed the ability of sural nerve stimulation to enhance the EMG, kinetic and kinematic variables contributing to the postural adjustments that precede taking a step. The primary reflex effect in tibialis anterior muscle was a long latency excitation (70 - 90 ms) and under the experimental conditions of this experiment revealed 3 specific results: 1) *Effect of cueing*: Both visual and sural cueing produced excitatory reflex responses during the rise in limb loading with the sural cueing producing the larger response; visual cueing produced an excitatory reflex response during the decline in the loading response while sural cueing produced an inhibitory response. 2) *Effect of phases of step initiation*: amplitude of the reflex response was greater for the loading than the unloading phase for both the go cues. 3) *Effect of task:* net reflex response was primarily excitatory during step initiation, but primarily inhibitory during standing. The results suggest behaviorally appropriate modulation of the reflexes during step initiation (Hajela and Kukulka, 2009) which means that the relevant up or down regulation of the reflexes may influence earlier release of a step and enhancement of APAs. Also during step initiation there were numerous significant differences in mechanical and EMG responses between visual and sural cueing. Sural cueing produced 1) earlier mean vertical force onset times, greater mean vertical force amplitude and faster mean speed of force onset 2) earlier mean TA EMG onset times, shorter mean EMG duration and greater mean TA EMG amplitudes 3) earlier mean posterior COP onset times, greater mean posterior COP displacements and faster speed of posterior COP onset . These results confirm our earlier findings regarding

the effect of sural cueing (Kukulka et al, 2009, Hajela et al, 2006) in enhancing the APAs.

8.1 Effect of cueing and phases of step initiation on the reflex pattern

In our study, the most consistent response we observed during step initiation was a long latency excitation (70 - 90 ms). In TA, several studies (Aniss et al, 1992; Burke et al, 1991; Gibbs et al, 1993; Nielsen and Kagamihara, 1993; Nielsen et al, 1997) have shown sural nerve stimulation to produce a long latency excitation at similar latencies. From a functional perspective, this effect may be relevant to various task applications: the posterior displacement of COP prior to step initiation (Kukulka et al, 2009), mechanical events of the APA (Rogers et al, 2001), the increase in ankle joint dorsiflexion of the swing limb during gait (Duysens et al, 1992), eversion and dorsiflexion of the ipsilateral foot – this response would act to stabilize the limb if there were pressure activation on the lateral foot border caused by uneven terrain in early stance phase of locomotion (Zehr et al, 1999). The current study also verified our previous findings (Kukulka et al, 2009) that sural cueing releases the step faster and enhances APA. For visual cueing the long latency reflex responses were up modulated when comparing evoked reflexes during the rise in limb loading (53%) versus the decline in loading(43%) , while for sural cueing, the reflex reversed sign between the loading phases, +73% to -34% respectively. It further appears that the shortened duration of TA burst when sural cue was provided (50 ms shorter) may contribute to the reflex reversal. This was also supported by the current finding that the TA EMG amplitude was 12% greater and the speed of posterior COP onset was 16 % faster with sural cueing. In the previous study (Kukulka et al, 2009) we

have shown that GM EMG amplitude increased similar to the TA, which is contributing to the faster speed of COP displacement in the posterior direction. Thus, the reflex modulation and reversal are in sync with the mechanical and EMG data and suggests that reflex effects are influencing the kinetic, kinematic and EMG responses that precede step initiation, thereby influencing APAs.

The amplitude of the long latency reflex response was greater for the loading than the unloading phase for both the go cues during step initiation. The demonstration that the stimulation of sural cutaneous afferents on the side of the foot affected the reflex pattern during the loading and the unloading phase of step initiation suggests that the feedback from the side of the foot (cutaneous region of the sural nerve) provides afferent dependent motoneuron excitation gated by the phase of the step initiation in healthy individuals. Our findings suggest that the excitation of cutaneous afferents of the foot during step initiation influence the cutaneous reflex modulation pattern in a phase dependent manner in young healthy subjects. Reflex modulation originally shown in the cat (Forssberg, H., Grillner, S. and Rossignol, S., 1975) have been reported during human walking (DeSerres, S. J., Yang, J. F. and Patrick, S. K., 1995; J. Duysens et al., 1990; J. Duysens et al., 1992; Van Wezel et al., 1997; Yang & Stein, 1990). The phasic TA reflex modulation may be the result of complex interaction between segmental reflex circuits and descending control. We, thus suggest that this protocol of evoking cutaneous reflexes could be utilized as a testing measure for sensorimotor integration. Also, the findings in the young healthy individuals can be used as a baseline measure to compare it to the findings in the neurological populations.

8.2 Effect of tasks on the reflex pattern

In this study, the net reflex response was primarily excitatory during step initiation but primarily inhibitory during standing. The reflex response was primarily inhibitory during standing because where maintenance of posture is of primary importance; there is a reduction of effort that led to increased cutaneous input (i.e., a global suppressive response). The advantage for quite standing to utilize the inhibitory influence is that during standing postural perturbations might be best met with smaller, suppressive responses whereas during step initiation larger responses might be required to take a step. The finding of inhibitory response during standing also lends support from the study by (Komiyama et al., 2000) which compared cutaneous reflexes responses in two different tasks conditions i.e. standing and walking. They suggested that during standing net reflexes in TA are predominantly suppressive and graded with background EMG while during walking there is modulation of reflexes which is independent of muscle activation level and closely coupled with events occurring in the step cycle.

We did not find any effect of varying stimulus intensity on the reflex response. One of the reasons for not seeing any effect could be that the difference in the different intensities was not enough to bring out the differences. It might also suggest that the range of stimulus intensities used was not sufficient to recruit a greater number of afferents. The small influence of stimulus intensity may likely be due to the standing task used in our study which involved standing on an inclined wedge shaped wooden platform but the subjects were not asked to hold an isometric contraction. Previous studies have in general, required subjects to perform an isolated contraction of a target muscle while standing. The task constraint for consciously controlling loading the limb while standing

versus an isolated contraction, may therefore, more strongly bias the influence of neural command signals on the reflex response amplitude and mask more subtle influences due to stimulus intensity.

In our study, the excitatory reflex response during step initiation suggests that the excitatory reflex pathways are engaged during a functional task such as step initiation. These results are in general agreement with previous findings which demonstrated that reflexes are excitatory during swing phase of walking (Duysens et al, 1990).Cutaneous reflexes evoked during dynamic task such as walking have been suggested to be different from those evoked during static tasks, i.e. standing and sitting (Christensen et al., 1999; Duysens, J., Tax, A. A. M., Trippel, M. and Dietz, V., 1993). It was suggested (Burke, D., Dickson, H. G. and Skuse, N. F., 1991) that the reflexes in TA that occurred between 60 and 80 msec post-stimulus were different during sitting, standing normally or standing on an unstable base and the pattern (both excitation and inhibition) became more pronounced the more unstable the posture became . It was concluded that the reflex pattern within a given muscle as well as between other muscles is task-dependent and that the responses may be quite modifiable. Task dependent modulation (Abbruzzese, M., Rubino, V. and Schieppati, M., 1996) of reflexes was observed after stimulation of afferents from the foot surface. It was suggested that the afferent input to the spinal cord delivered via the stimulation of peripheral nerves (e.g. activation of cutaneous afferents) can elicit prominent reflexes in various muscles of the human lower leg under static and dynamic conditions. This characteristic is suggestive of the useful function of reflexes during different behaviors. These kinds of task dependent differences in response

amplitude suggest reweighing of sensory inputs to meet the demands of the task (Clair et al, 2009). Cutaneous reflexes are strongly modulated in a task and posture dependent manner. This implies that the excitability of interneurons impinging on the reflex pathway responsible for cutaneous reflexes may be controlled by the descending input from the cortex to optimize reflex action in response to sudden tactile sensation to the foot (Baken et al, 2006). The task dependent adaptation of cutaneous reflexes may be involved with the ongoing regulation of dynamic stability during walking. One of the possible mechanisms for the task dependent modulation observed involves supraspinal pathways projecting onto reflex pathways of the muscles of the lower limb. It was reported (Pijnappels et al, 1998) that the amount of cortical facilitation onto cutaneous reflex pathways varied according to the phase of the step cycle, suggesting that cortical input is able to generate the differential modulation observed. Similarly, (Bretzner and Drew et al, 2005) showed that the differential modulation of cutaneous reflexes according to the nerve and cortical site stimulated in intact cats at the onset of swing. There was facilitation in some vs. depression in other muscles, suggesting the cortical and cutaneous pathways have specific termination to various interneuronal networks residing in the spinal cord. The convergence of cortical input onto interneurons of the reflex pathways could serve to modify the magnitude of reflex responses with respect to the specified task. Thus, all these studies imply that specific reflex differences may emerge during different tasks due to changes in descending drive or afferent feedback which may be important in specifically determining the motor output to the demands of ongoing task.

Reflex modulation patterns are described as being different and indicative of differences in neural control, if there were significant differences in the sign of reflexes. Cutaneous afferents and in particular those of the foot contribute profoundly to the reflex regulation of balance and movement in mammals (Rossignol, 2006).The task related gating of cutaneous reflexes suggest a functional role of these reflexes in the maintenance of stability during walking (Zehr & Stein, 1999). It was suggested that the reflexes were altered when walking in an environment in which stability is challenged. Mechanoreceptors located along the lateral border of the foot which is the region innervated by the sural nerve have been shown to be important in maintaining upright stance and postural control (Meyer et al, 2004). During step initiation the reflexes are modulated in a phase dependent manner to further assist postural stability and better preparation in the form of anticipatory postural adjustments.

8.3 Spinal and Supraspinal Contributions

The complex reflex effects associated with low-level stimulation of a cutaneous nerve indicate a large variation of peripheral responses that may influence a specified movement. The results from these experiments demonstrate that stimulation of the sural nerve at intensities sufficient for activating low threshold cutaneous afferents produced both inhibitory and excitatory reflex responses at latencies between 40 and 120 ms.

In our study, the primary effect in TA during step initiation was a long latency excitation (70 - 90 ms). Based on measurements (Nielsen et al., 1997) of afferent conduction time (somatosensory evoked response ~ 38 ms following sural nerve stimulation), efferent conduction time (TMS cortically evoked potential in TA ~ 35 ms) and a central delay of

10 ms, these authors estimated that the earliest cortical contribution to sural reflex responses would be ~ 83ms. Thus, the minimal latency for such a pathway was estimated to be between 70 – 90 ms. The reflex responses seen in the present study therefore fall within the range of latencies for a transcortical pathway. Our current finding of a 12 % greater average EMG in TA with sural versus visual cueing therefore raises the possibility that a transcortical pathway may contribute to up modulate TA response in step initiation. Sural cueing might therefore excite cortical motor neurons through a transcortical mechanism leading to both the earlier release of the APA together with enhancement of TA EMG. In humans, stimulation of cutaneous afferents from the foot evokes complex synaptic actions on lower limb muscles (Aniss et al. 1992; Delwaide et al. 1981). Cutaneous afferents from the foot provide a neuronal population vector that encodes the direction of the ankle movement and contribute to awareness of our body in space and to upright human posture (Aimonetti et al. 2007; Kavounoudias et al. 2001; Roll et al. 2002). It was demonstrated (De Serres et al, 1995) that the existence of distinct facilitatory and suppressive reflex pathways acting upon a single motoneuron in the TA. Also, when the latency of the reflex response is taken into consideration, changes in the excitability of the transcortical reflex pathways (Nielsen et al, 1997) may be included in the reflex modulation observed in this study. At the same time segmental influence cannot be ignored. During standing we have seen both short latency inhibition (D1) and long latency inhibition (D2). Based on the estimates of conduction times for activation of low-threshold cutaneous afferents, the short-latency D1 response seems to represents an oligosynaptic spinal reflex with conduction times similar to the Ia reciprocal inhibitory

pathway. These findings suggest a possibility that low-threshold cutaneous afferents may share common interneurons with low-threshold muscle afferent reflexes that have similar onset latencies. This finding lends support from the study (C. G. Kukulka, 1994) which showed that the sural afferent input onto tricep surae motor neurons is indicative of a spinal influence of sural nerve stimulation.

8.4 Clinical implications

Extension of this research offers several potential clinical benefits. Disturbance of the APA is considered to be a major pathophysiological mechanism that hinders gait initiation in PD subjects and elderly who fall. APAs are diminished in elderly subjects (Patla AE, Frank JS, Winter DA, Rietdyk S, Prasad S, 1993) and patients with neurologic disorders such as Parkinson's disease (Mancini et al., 2009) and stroke (Rogers et al, 1993). In stroke, APAs have been shown to be decreased and/or delayed with respect to those seen in healthy individuals. Individuals with hemiparesis due to stroke also show impaired acquisition of APAs associated with a newly learned task. In a recent study it was found that APAs were reduced in individuals with hemiparesis, especially on the paretic side. Our study demonstrated that reflex responses are modifiable and can be influenced by the type of cue and the task involved (standing and step initiation). Therapist might therefore consider cueing effects to better design step training protocols for their neurologically involved patients and patients who fall. Carrying out this study on healthy subjects allowed us to establish a model for testing and training in the future. For instance, it will be very useful to see the application of sural stimulation as a portable sensory cue to assist Parkinson's patients in gait initiation. Applications of this study can

also be seen in training postural control in individuals with neurological disorders and elderly. This study warrants further research to answer two important questions that emphasize the clinical implications of this study.

1) Can these results be verified in neurologic populations?

Cutaneous reflexes are comprised of complex excitatory and inhibitory effects. Reflex modulation patterns are described as being different and indicative of differences in neural control, if there are significant differences in the sign of reflexes. It is the net reflex effect over the entire reflex response period that provides a realistic assessment of the influence of the cutaneous input (Zehr et al, 1997). Research in neurologically normal subjects reveals (Abbruzzese et al, 1996) that afferent transmission from the foot surface and intrinsic foot muscles is modulated by cutaneous input to the plantar surface of the foot. This suggests that the afferent input to the spinal cord delivered via the stimulation of peripheral nerves (e.g. activation of cutaneous afferents) can elicit prominent reflexes in various muscles of the human lower leg under static and dynamic conditions. Strong interlimb reflexes have been demonstrated (Zehr et al, 2001) in many muscles on both the ipsilateral and contralateral sides after superficial peroneal (SP) and superficial radial nerve stimulation in neurologically intact subjects. As such, interlimb reflex pathways connecting distant cutaneous receptive fields could be important in directly relaying exteroceptive information important for the reflex coordination of movement. During gait, cutaneous reflexes can be completely reversed from exciting to inhibiting a muscle during each step cycle, particularly in muscles that normally show two bursts of activity per cycle (e.g. TA).

Walking dysfunction is one of the greatest physical limitations affecting persons post-stroke. The important component of the paretic limb deficit in hemiparetic walking is due to abnormal influences of ipsilateral and contra-lateral afferent information on the control of the paretic leg, while a second component involves impaired activation of the paretic motor pools (Patten et al, 2007). In the case of stroke, (Zehr et al, 1998) demonstrated that cutaneous reflex modulation is impaired. They studied stroke patients with mild spasticity and elicited cutaneous reflexes from the SP nerve during treadmill walking. It was shown that in contrast to tibial nerve stimulation (Jones and Yang, 1994), suppressive responses seem to dominate.

There was a correspondence between net reflex responses and changes in ankle joint trajectory (compare soleus suppression during stance with a reduction in plantar flexion contrasted with increased dorsiflexion, in neurologically intact subjects). Based on our study, ipsilateral cutaneous reflex responses in the tibialis anterior (TA) muscle during the loading phase of step initiation are excitatory in healthy individuals (Hajela et al, 2009) and suggest behaviorally appropriate modulation of the reflexes, which may play a role in the earlier release of the step and enhancement (Kukulka et al, 2009) of APAs. Therefore, it will be of importance to assess the net sural reflex responses in the paretic and the non-paretic limb for ipsilateral and contralateral stimulation during step initiation in adults with chronic post-stroke hemiparesis.

2) Can step training exercises using sural cueing be used to train patient populations to react faster and enhance their APAs?

Balance, stepping and adaptability comprise the three fundamental but non-exclusive subtasks of locomotion. APAs contribute to the balance subtask. In particular, the voluntary step initiation is preceded by a sequence of trunk and lower limb muscle activations (Brunt et al, 1999) leading to kinetic and kinematic changes (Breniere et al, 1987) that promote the successful execution of the step. APAs are often delayed and diminished after stroke (Rogers et al. 1993), and these changes appear to disrupt functional performance. Recently, (Rogers et al, 2003) investigated the influence of step training on the timing characteristics of voluntary step initiation in young and older adults. Their results indicated significant improvements in initiation timing in old and young adults. The induced step training group demonstrated greater improvement in step initiation time than the voluntary practice group for the auditory transfer cue task. However it still remains unclear what effects step training will have on the contralateral limb and what mechanisms are involved. Also, the effect of step training using sural cueing on enhancing APAs in persons with stroke still needs to be explored. The result obtained from these studies can contribute to a future research in developing a combined training intervention addressing both the preparation and execution component of voluntary movement (e.g. walking) to remediate walking dysfunction in patient populations.

8.5 Summary of outcomes for hypotheses

Hypothesis 1: The net reflex EMG response during step initiation will be primarily excitatory and will be influenced by the -a) "Go" cues: *reflex modulation* to visual cue (more excitatory during loading phase then unloading phase) and *reflex reversal* to sural cue (excitatory during loading phase and inhibitory during unloading phase). b) Phase of the loading force: larger amplitude for loading phase then unloading phase.

Both the parts of the hypothesis were accepted. The principal effect in TA during step initiation was a long latency excitation (70 - 90 ms). The net reflex effect depicts the reflex effect for the time period of 40 to 125 ms. The net effects were similar but of smaller amplitude than that seen for the E1 response only. The net reflex EMG response was modulated by the phase of loading force (larger amplitude of response for loading phase, i.e. evoking reflex during + slope) then unloading phase (evoking reflex during – slope).

Hypothesis 2: The net reflex EMG response during standing will be inhibitory. The strength (% baseline) of the inhibitory reflex response will increase with increasing stimulus intensity.

The first part of the hypothesis was accepted and the second part was rejected.

During standing the net reflex EMG response was mainly inhibitory. There was no effect of varying stimulus intensity on the strength of the reflex response.

Hypothesis 3: The net reflex EMG response will differ in standing and step initiation. Net reflex EMG responses will be inhibitory during standing and be primarily *excitatory* during step initiation.

The hypothesis was accepted. The net reflex EMG response was significantly different for standing to step initiation. Mean net reflex effect was primarily inhibitory during standing and during step initiation the primary effect in TA was a long latency excitation (70- 90 ms).

8.6 Study Limitations

There was a decrease, although not statistically significant, in the strength of the reflex response from stepping series 1 to 2. This finding can be attributed to the fact that the number of stepping trials may have induced fatigue. The subjects were not asked to fill out a specific self report on their fatigue level.

We were limited to having only one force platform so the COP measurements were under the stepping limb and not the net COP under both the limbs. It would have been useful to record from multiple muscles especially gluteus medias and soleus. A technological limitation is the potential change in the radiation threshold, though we used the surgical tape to make sure that the radiating threshold didn't change during the experiment.

We only looked at ipsilateral cutaneous reflexes; it would have been useful to record from muscles on the contra-lateral limb also. This would have provided information on the ipsilateral and contralateral reflex effects.

8.7 Future Research

Carrying out this study on healthy subjects allowed us to establish baseline criteria for testing and training in the future. The outcomes of our study paved the way for future studies on step initiation in patient populations (i.e. stroke, Parkinson's and incomplete spinal cord injury). We thus suggest that in future, the step initiation protocol can be converted into a step training paradigm to see its effect in improving APAs in neurologic population and elderly people who fall. Also if sural cueing can be used in a clinical setting to improve both reaction times and APAs in the target patient populations.

To build upon these exploratory results, future investigations using step initiation paradigm can include standing on two force platforms and then measuring the net COP. We would also suggest recoding from the multiple muscles such as TA, GM, and soleus during such experiments and include motion analysis to obtain an indirect measurement of the body's center of mass displacement.

The information regarding ipsilateral and contra lateral cutaneous reflex responses would provide more information on the interlimb reflex pathways. So far, we do not have information regarding the influence of interlimb reflex pathways during step initiation. Thus further studies that would like to seek answers regarding the contralateral cutaneous reflex effects and the mechanisms involved could be undertaken.

We still do not have the direct evidence regarding the transcortical mechanism responsible for the long latency reflex responses in the TA during step initiation. We thus suggest studies involving TMS during step initiation paradigm which will provide direct support regarding the involvement of transcortical mechanisms influencing the sural reflex pathways during step initiation in healthy and neurological populations. Once we

have the direct evidence. We can use cutaneous reflexes as a testing measure to verify the integration of the transcortical pathway. The next step could be to compare cutaneous reflexes in different neurological populations. For example, comparing cutaneous reflexes in individuals with cortical vs. subcortical stroke, Parkinson's vs. stroke to study the influence of different kind of neurological insults on the effectiveness of the cutaneous reflex pathways. Such findings could help physical therapists design better mechanism based treatment interventions.

8.8 Conclusion

In summary, this study demonstrated for the first time the influence of cutaneous reflexes in anticipatory postural adjustments (APAs) that precede a step in healthy human subjects. During step initiation the primary effect in TA (Hajela & Kukulka, 2009) was a long latency excitation (70 - 90 ms) along with the effect of type of cue, task and phases of step initiation. The results suggest behaviorally appropriate modulation of the reflexes which may play a role in the earlier release of a step and enhancement of APAs. Also, the mechanical and EMG responses during step initiation confirm our earlier findings regarding the effect of sural cueing in enhancing (Kukulka et al., 2009; Hajela et al., 2006) APAs. These findings suggest that cutaneous reflexes influence APAs and invite further investigation of the modulation of cutaneous reflexes in neurologic populations and elderly people who fall. Also the effect of step training paradigm using sural cueing in enhancing APAs in neurologic populations still need to be explored.

Chapter 9: References

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Chapter 10: Appendices

Appendix A1

Data for visual cueing on the loading phase of step initiation- Series I

Step Series 1		E1			NRE	
Condition	Subject	Latency (ms)	Duration (ms)	Strength (%)	Strength (%)	Sign
Visual + slope	J21	80	23	52	34.54	Pos
	C21	75	35	56	38.13	Pos
	F21	88	27	53	31.01	Pos
	D21	78	34	55	37.45	Pos
	A11	88	37	56	38.76	Pos
	T11	78	32	52	31.55	Pos
	R11	85	39	55	35.87	Pos
	V11	75	35	55	36.99	Pos
	B11	70	23	49	38.23	Pos
	L11	84	35	50	32.11	Pos
	Z11	79	32	59	36.65	Pos
	Q31	81	32	59	34.16	Pos
	U31	79	38	50	30.22	Pos
	G31	83	25	55	35.89	Pos
	X41	79	29	51	34.79	Pos
	Mean	80.13	31.73	53.80	35.09	Pos
	SD	4.93	5.24	3.12	2.78	

Appendix A2

Data for visual cueing on the loading phase of step initiation – Series Π

Step Series 2		E1			NRE	
Condition	Subject	Latency (ms)	Duration (ms)	Strength (%)	Strength (%)	Sign
Visual + slope	J21	82	32	53	32.09	Pos
	C21	75	30	49	31.22	Pos
	F21	77	32	51	32.91	Pos
	D21	81	24	52	35.05	Pos
	A11	88	25	59	39.76	Pos
	T11	74	30	53	30.49	Pos
	R11	86	29	57	37.07	Pos
	V11	70	34	53	39.02	Pos
	B11	75	26	50	39.27	Pos
	L11	75	38	53	30.03	Pos
	Z11	81	37	50	31.65	Pos
	Q31	82	32	59	38.19	Pos
	U31	78	31	52	32.27	Pos
	G31	82	28	50	36.9	Pos
	X41	74	31	48	38.09	Pos
	Mean	78.67	30.60	52.60	34.93	Pos
	SD	4.98	3.96	3.38	3.54	

Appendix B1

Data for sural cueing on the loading phase of step initiation- Series I

Step Series 1		E1			NRE	
Condition	Subject	Latency (ms)	Duration (ms)	Strength (%)	Strength (%)	Sign
Sural + slope	J21	79	24	73	54.02	Pos
	C21	70	28	70	50.89	Pos
	F21	85	35	75	54.12	Pos
	D21	75	35	76	54.23	Pos
	A11	80	40	76	55.34	Pos
	T11	78	36	78	55.09	Pos
	R11	70	23	71	52.22	Pos
	V11	70	28	72	53.53	Pos
	B11	72	35	68	52.56	Pos
	L11	85	27	72	51.09	Pos
	Z11	73	36	71	57.44	Pos
	Q31	80	32	74	58.91	Pos
	U31	79	30	69	58.22	Pos
	G31	69	23	72	53.53	Pos
	X41	70	29	79	54.11	Pos
	Mean	75.67	30.73	73.07	54.35	Pos
	SD	5.56	5.31	3.22	2.37	

Appendix B2

Data for sural cueing on the loading phase of step initiation – Series Π

Step Series 2		E1			NRE	
Condition	Subject	Latency (ms)	Duration (ms)	Strength (%)	Strength (%)	Sign
Sural + slope	J21	78	25	72	52.03	Pos
	C21	72	29	71	51.84	Pos
	F21	87	32	70	53.17	Pos
	D21	75	33	75	55.22	Pos
	A11	80	33	77	54.34	Pos
	T11	77	35	76	56.11	Pos
	R11	72	28	69	50.45	Pos
	V11	75	29	70	54.53	Pos
	B11	70	39	65	50.51	Pos
	L11	80	28	70	50.01	Pos
	Z11	75	33	69	56.43	Pos
	Q31	78	34	76	55.81	Pos
	U31	79	32	72	55.24	Pos
	G31	71	29	72	55.99	Pos
	X41	72	28	78	52.19	Pos
	Mean	76.07	31.13	72.13	53.59	Pos
	SD	4.50	3.56	3.60	2.26	

Appendix C1

Data for visual cueing on the unloading phase of step initiation- Series I

Step Series 1		E1			NRE	
Condition	Subject	Latency (ms)	Duration (ms)	Strength (%)	Strength (%)	Sign
Visual - slope	J21	75	29	45	27.41	Pos
	C21	74	24	43	26.01	Pos
	F21	76	25	44	27.98	Pos
	D21	75	35	42	25.77	Pos
	A11	73	27	42	26.65	Pos
	T11	78	25	43	26.23	Pos
	R11	73	37	47	25.66	Pos
	V11	70	29	43	24.43	Pos
	B11	79	25	48	22.09	Pos
	L11	70	27	39	26.44	Pos
	Z11	75	29	38	20.91	Pos
	Q31	71	31	45	19.96	Pos
	U31	74	32	44	22.65	Pos
	G31	77	22	41	20.78	Pos
	X41	75	26	45	27.9	Pos
	Mean	74.33	28.20	43.27	24.72	Pos
	SD	2.66	4.16	2.69	2.73	

Appendix C2

Data for visual cueing on the unloading phase of step initiation – Series Π

Step Series 2		E1			NRE	
Condition	Subject	Latency (ms)	Duration (ms)	Strength (%)	Strength (%)	Sign
Visual - slope	J21	75	27	42	27.31	Pos
	C21	72	27	41	25.04	Pos
	F21	78	25	42	24.55	Pos
	D21	70	34	40	24.76	Pos
	A11	74	28	40	20.66	Pos
	T11	79	31	41	22.25	Pos
	R11	75	36	42	27.41	Pos
	V11	70	30	44	22.43	Pos
	B11	77	29	43	20.11	Pos
	L11	70	25	35	20.46	Pos
	Z11	71	28	39	20.87	Pos
	Q31	73	32	43	18.66	Pos
	U31	75	27	40	23.62	Pos
	G31	76	24	43	21.44	Pos
	X41	72	22	43	24.92	Pos
	Mean	73.80	28.33	41.20	22.97	Pos
	SD	2.96	3.79	2.24	2.66	

Appendix D1

Data for sural cueing on the unloading phase of step initiation – Series I

Step Series 1		D2			NRE	
Condition	Subject	Latency (ms)	Duration (ms)	Strength (%)	Strength (%)	Sign
Sural - slope	J21	78	27	-33	-15.99	Neg
	C21	74	36	-29	-19.9	Neg
	F21	78	33	-35	-17.75	Neg
	D21	78	34	-36	-16.78	Neg
	A11	82	29	-32	-17.16	Neg
	T11	78	37	-38	-19.9	Neg
	R11	75	25	-37	-23.45	Neg
	V11	78	34	-36	-18.01	Neg
	B11	70	33	-38	-20.78	Neg
	L11	78	31	-35	-17.75	Neg
	Z11	80	24	-37	-14.78	Neg
	Q31	69	29	-32	-17.08	Neg
	U31	78	35	-38	-14.56	Neg
	G31	73	29	-32	-22.95	Neg
	X41	74	32	-31	-18.01	Neg
	Mean	76.20	31.20	-34.60	-18.32	Neg
	SD	3.61	3.93	2.90	2.63	

Appendix D2

Data for sural cueing on the unloading phase of step initiation – Series Π

Step Series 2		D2			NRE	
Condition	Subject	Latency (ms)	Duration (ms)	Strength (%)	Strength (%)	Sign
Sural - slope	J21	77	26	-36	-14.78	Neg
	C21	74	28	-27	-18.91	Neg
	F21	79	33	-33	-16.71	Neg
	D21	77	36	-34	-16.78	Neg
	A11	84	29	-30	-15.09	Neg
	T11	70	35	-33	-17.91	Neg
	R11	75	25	-35	-20.44	Neg
	V11	75	36	-34	-19.09	Neg
	B11	70	32	-34	-22.66	Neg
	L11	79	33	-34	-16.73	Neg
	Z11	82	25	-35	-12.77	Neg
	Q31	70	30	-30	-16.11	Neg
	U31	79	34	-36	-15.59	Neg
	G31	75	32	-35	-20.66	Neg
	X41	70	30	-30	-19.67	Neg
	Mean	75.73	30.93	-33.07	-17.59	Neg
	SD	4.46	3.75	2.63	2.64	

Appendix E

Data for the Standing task

Standing Task	D1			D2			NRE	
Subject	Latency (ms)	Duration (ms)	Strength (%)	Latency (ms)	Duration (ms)	Strength (%)	Strength (%)	Sign
J21	58	27	-10	87	28	-30.56	-18.56	Neg
C21	55	29	-8.11	86	35	-29.75	-19.64	Neg
F21	50	20	-11.23	72	31	-25.66	-18.43	Neg
D21	55	25	-10.45	88	36	-26	-22.55	Neg
A11	47	25	-12.08	77	33	-28.11	-14.03	Neg
T11	49	24	-8.92	75	38	-27.23	-16.31	Neg
R11	50	33	-12.2	90	31	-31.42	-17.22	Neg
V11	50	28	-11.44	80	35	-29	-15.56	Neg
B11	48	31	-11.23	73	32	-28.66	-15.43	Neg
L11	52	32	-10.45	89	35	-27.78	-15.33	Neg
Z11	59	23	-12.98	75	25	-28.9	-13.92	Neg
Q31	58	24	-7.9	76	24	-26.12	-16.22	Neg
U31	49	34	-12.2	91	29	-25.43	-18.23	Neg
G31	46	21	-11.11	82	26	-32.44	-23.33	Neg
X41	53	33	-10.78	88	24	-27.14	18.89	Neg
Mean	51.93	27.27	-10.74	81.93	30.80	-28.28	-15.06	Neg
SD	4.20	4.57	1.49	6.82	4.62	2.12	2.53	

Appendix F

Data for Vertical Force Onset during step initiation

Series1	S_ ID	Visual pos	Sural pos	visual neg	sural neg
Vertical Force_Onset	J21	232	158	241	175
	C21	306	143	250	157
	F21	290	166	247	189
	D21	280	198	238	184
	A11	206	196	217	161
	T11	160	154	287	156
	R11	268	178	287	168
	V11	199	142	248	178
	B11	242	145	257	126
	L11	284	193	191	147
	Z11	206	166	246	183
	Q31	303	191	304	191
	U31	209	146	199	156
	G31	180	165	214	203
	X41	302	180	275	183
	Mean	244.467	168.07	246.73	170.47
	SD	49.07	20.194	32.61	20.04
Series 2	J21	228	161	247	166
	C21	298	149	302	162
	F21	239	156	246	197
	D21	257	208	222	164
	A11	250	189	199	165
	T11	250	155	259	156
	R11	216	170	297	168
	V11	228	157	258	178
	B11	257	126	212	145
	L11	191	147	284	193
	Z11	246	183	206	166
	Q31	304	191	303	191
	U31	198	156	209	146
	G31	214	203	180	165
	X41	277	179	305	191
	Mean	243.53	168.67	248.60	170.200
	SD	32.91	22.88	42.59	16.45

Appendix G

Data for Vertical Force Amplitude during step initiation

Series1	S_ ID	Visual pos	Sural pos	visual neg	sural neg
Vertical Force Amplitude	J21	31.2	47.2	26.7	38.9
	C21	27.3	30.9	29.7	28.6
	F21	27.5	33.1	30.6	36.5
	D21	33.4	37.2	20.3	31.5
	A11	21.7	29.3	23.1	33.7
	T11	24.5	28.7	28.2	27.4
	R11	32.6	32.8	22.3	29.3
	V11	26.4	29.3	25.6	27.8
	B11	28.6	47.6	28.5	29.6
	L11	24.9	41.1	33.8	36.5
	Z11	34.1	42.3	22.3	35.5
	Q31	29.7	36.2	22.1	37.7
	U31	23.2	39.3	25.6	35.4
	G31	28.6	30.7	26.8	33.3
	X41	29.9	32.8	25.4	37.8
	Mean	28.24	35.90	26.07	33.30
	SD	4.07	6.18	3.68	4.28
Series 2	J21	33	47.6	25.9	31.9
	C21	28.7	31.1	28.5	25.6
	F21	28.9	32.3	33.8	33.4
	D21	34.1	36.2	25.3	34.6
	A11	25.7	29.3	22.1	32.9
	T11	25.2	29.7	25.2	29.7
	R11	28.6	30.8	27.3	29.3
	V11	28.9	30.3	26.7	26.89
	B11	21.7	29.3	30.6	29.3
	L11	24.5	28.7	20.3	27.8
	Z11	32.6	32.8	23.1	29.6
	Q31	26.4	29.3	28.2	36.5
	U31	28.6	47.6	22.3	35.5
	G31	24.9	41.1	25.6	37.7
	X41	27.1	42.3	23.7	35.4
	Mean	27.93	34.56	25.91	31.74
	SD	3.10	6.13	3.38	3.21

Appendix H

Data for Speed of Force Onset during step initiation

Series1	S_ ID	Visual pos	Sural pos	visual neg	sural neg
Speed of Force Onset					
	J21	132.62	167.23	140.24	129.78
	C21	108.17	134.34	125.93	137.89
	F21	143.74	120.53	120.19	131.09
	D21	146.98	156.96	109.33	146.12
	A11	119.93	124.03	111.99	121.07
	T11	125.54	145.9	120.71	139.77
	R11	109.83	122.99	113.55	176.35
	V11	114.54	132.67	134.66	128.73
	B11	102.27	123.11	115.43	126.12
	L11	123.75	150.12	122.19	151.07
	Z11	143.98	156.56	133.15	142.77
	Q31	129.93	144.03	124.99	149.35
	U31	135.54	148.9	144.72	145.66
	G31	119.83	176.11	137.65	139.67
	X41	135	131.67	118	143.89
	Mean	126.11	142.3	124.8	140.6
	SD	14.84	17.09	10.99	17.00
Series 2	J21	122.34	145.13	136.14	124.73
	C21	102.27	124.11	115.43	158.49
	F21	123.75	150.43	120.19	129.09
	D21	143.98	156.96	113.11	149.12
	A11	129.93	144.03	122.99	121.07
	T11	135.54	145.9	140.72	142.77
	R11	119.83	176	127.65	169.35
	V11	135	132.67	116.09	120.66
	B11	108.17	120.53	139.33	146.12
	L11	143.74	156.96	134.99	139.07
	Z11	146.98	184.03	120.71	152.89
	Q31	119.93	145.9	133.53	176.35
	U31	125.54	122.99	134.66	144.73
	G31	109.83	132.67	125.43	146.12
	X41	114.54	124.11	117.19	129.07
	Mean	125.4	144.2	126.5	143.3
	SD	12.69	15.56	10.07	18.42

Appendix I

Data for TA EMG Onset during step initiation

Series1	S_ ID	Visual pos	Sural pos	visual neg	sural neg
TA EMG Onset	J21	215	125	289	149
	C21	259	140	210	145
	F21	233	143	227	138
	D21	228	142	187	145
	A11	198	167	177	166
	T11	245	156	256	171
	R11	218	106	240	163
	V11	187	145	267	145
	B11	210	131	243	174
	L11	227	167	218	124
	Z11	167	186	198	145
	Q31	278	126	245	144
	U31	206	145	197	171
	G31	240	176	206	123
	X41	237	126	214	127
	Mean	223.20	145.4	224.9	148.7
	SD	23.65	18.52	39.05	12.10
Series 2	J21	221	119	266	156
	C21	242	130	240	144
	F21	222	153	240	124
	D21	247	131	189	145
	A11	266	167	224	154
	T11	235	186	236	171
	R11	228	126	242	163
	V11	147	145	267	145
	B11	218	156	187	174
	L11	187	106	190	124
	Z11	210	145	204	135
	Q31	227	131	221	144
	U31	185	167	243	162
	G31	239	186	203	123
	X41	243	163	195	171
	Mean	221.13	147	223.1	149.0
	SD	35.18	22.95	24.64	14.26

Appendix J

Data for TA EMG Duration during step initiation

Series1	S_ ID	Visual pos	Sural pos	visual neg	sural neg
TA EMG Duration	J21	484	420	457	439
	C21	481	355	472	409
	F21	517	321	435	402
	D21	515	429	496	427
	A11	408	410	411	434
	T11	451	404	441	400
	R11	424	433	460	411
	V11	455	422	434	497
	B11	459	359	460	409
	L11	441	319	398	402
	Z11	430	398	383	427
	Q31	426	416	470	414
	U31	467	429	454	310
	G31	435	435	491	341
	X41	444	377	487	346
	Mean	455.80	395	450	405
	SD	39.68	39.98	26.26	31.68
Series 2	J21	478	414	472	456
	C21	459	359	435	445
	F21	441	319	496	478
	D21	515	417	421	417
	A11	426	411	441	467
	T11	467	409	460	410
	R11	435	416	445	418
	V11	429	440	460	417
	B11	432	329	398	427
	L11	500	329	383	404
	Z11	437	398	470	400
	Q31	448	421	474	357
	U31	423	441	491	407
	G31	512	425	444	379
	X41	446	423	431	345
	Mean	456.5	396.7	448.1	415.1
	SD	30.21	39.20	23.48	26.40

Appendix K

Data for TA EMG Amplitude during step initiation

Series1	S_ ID	Visual pos	Sural pos	visual neg	sural neg
TA EMG Amplitude	J21	100	112.69	100	102.83
	C21	100	127.46	100	97.36
	F21	100	112.69	100	80.00
	D21	100	114.93	100	102.33
	A11	100	124.63	100	107.72
	T11	100	122.51	100	90.28
	R11	100	108.72	100	93.06
	V11	100	111.49	100	93.06
	B11	100	115.46	100	111.49
	L11	100	114.69	100	115.46
	Z11	100	112.93	100	114.69
	Q31	100	128.00	100	112.93
	U31	100	127.51	100	128.00
	G31	100	108.72	100	127.51
	X41	100	111.49	100	102.23
	Mean	100	117	100	105
	SD	9.45	6.95	10.23	8.72
Series 2	J21	100	122.69	100	105.67
	C21	100	115.46	100	98.36
	F21	100	114.69	100	93.00
	D21	100	112.93	100	102.33
	A11	100	128.00	100	104.06
	T11	100	127.51	100	102.28
	R11	100	108.72	100	93.06
	V11	100	111.49	100	93.06
	B11	100	127.46	100	102.33
	L11	100	112.69	100	127.72
	Z11	100	114.93	100	110.28
	Q31	100	124.63	100	103.06
	U31	100	122.51	100	105.08
	G31	100	108.72	100	111.49
	X41	100	122.45	100	115.46
	Mean	100	118	100	104
	SD	11.25	7.40	6.56	5.33

Appendix L

Data for COP Onset during step initiation

Series1	S_ ID	Visual pos	Sural pos	visual neg	sural neg
COP Onset	J21	230	149	207	187
	C21	250	156	255	167
	F21	195	157	193	149
	D21	244	148	297	150
	A11	193	174	220	169
	T11	189	144	195	156
	R11	295	146	279	137
	V11	238	135	228	138
	B11	205	164	255	127
	L11	244	144	193	141
	Z11	183	136	217	167
	Q31	182	135	220	139
	U31	290	156	195	150
	G31	257	157	279	169
	X41	228	148	229	143
	Mean	228	150	230.8	152.6
	SD	36.17	11.54	38.91	16.98
Series 2	J21	227	189	260	161
	C21	260	166	238	167
	F21	205	147	244	149
	D21	244	148	297	170
	A11	183	164	190	169
	T11	182	144	194	156
	R11	290	136	239	127
	V11	257	135	225	153
	B11	193	156	279	167
	L11	189	157	224	149
	Z11	295	148	255	150
	Q31	238	174	193	169
	U31	205	144	207	156
	G31	244	146	230	137
	X41	242	134	195	156
	Mean	230.3	152.5	231.3	155.7
	SD	38.8	18.28	34.6	14.2

Appendix M

Data for COP displacement

Series1	S_ ID	Visual pos	Sural pos	visual neg	sural neg
COP Displacement	J21	100	135.35	100	107.42
	C21	100	148.12	100	142.61
	F21	100	122.28	100	111.43
	D21	100	103.74	100	109.83
	A11	100	120.16	100	114.00
	T11	100	124.49	100	105.92
	R11	100	114.34	100	117.35
	V11	100	117.88	100	122.77
	B11	100	145.22	100	139.61
	L11	100	119.18	100	121.43
	Z11	100	105.66	100	125.83
	Q31	100	123.56	100	109.67
	U31	100	134.49	100	125.92
	G31	100	115.24	100	117.35
	X41	100	122.23	100	122.10
	Mean	100	123	100	120
	SD	13.55	13.45	12.34	11.91
Series 2	J21	100	123.34	100	106.22
	C21	100	144.22	100	140.51
	F21	100	119.18	100	112.73
	D21	100	106.66	100	109.83
	A11	100	116.46	100	104.00
	T11	100	134.49	100	125.92
	R11	100	115.24	100	129.35
	V11	100	117.88	100	132.79
	B11	100	148.12	100	109.83
	L11	100	122.28	100	124.00
	Z11	100	103.74	100	105.92
	Q31	100	120.16	100	119.35
	U31	100	124.49	100	122.74
	G31	100	114.34	100	142.61
	X41	100	117.88	100	129.67
	Mean	100	122	100	121
	SD	12.23	11.88	11.56	13.67

Appendix N

Data for Speed of COP Onset

Series1	S_ ID	Visual pos	Sural pos	visual neg	sural neg
Speed of COP onset	J21	125.23	135.67	135.11	158.71
	C21	111.23	134.11	128.08	158.78
	F21	123.78	145.89	134.76	138.92
	D21	138.93	150.78	151.13	172.1
	A11	123.09	156.56	122.12	166.49
	T11	135.81	158.9	131.65	150.89
	R11	155.16	170.11	151.05	146.44
	V11	138.78	144.19	131.34	158.94
	B11	138.76	151.9	136.01	145.23
	L11	123.62	145.23	127.65	150.34
	Z11	143.89	150.34	141.44	144.11
	Q31	125.34	134.11	123.67	161.78
	U31	150.32	161.78	141.23	156.78
	G31	138.45	156.78	113.48	134.11
	X41	128.22	145.23	145.02	145.89
	Mean	133	149	134	153
	SD	11.75	10.41	10.61	10.48
Series 2	J21	138.23	144.19	151.13	162.1
	C21	141.22	151.9	122.12	146.49
	F21	121.62	145.23	131.65	150.89
	D21	143.59	150.34	145.05	156.44
	A11	125.15	134.11	131.34	148.94
	T11	150.12	161.78	156.16	165.11
	R11	138.9	156.78	138.78	144.19
	V11	121.08	158.78	138.76	147.98
	B11	135.07	138.92	143.62	167.23
	L11	151.51	172.09	123.67	161.78
	Z11	122.91	165.49	141.23	156.78
	Q31	131.65	155.89	133.48	144.11
	U31	130.83	146.44	133.02	145.89
	G31	145.53	135.67	135.11	148.71
	X41	141.76	151.9	128.08	134.78
	Mean	136	151	137	152
	SD	10.10	10.88	9.53	9.14

Appendix O

Statistical Analysis for cutaneous reflex responses

Latency of a reflex response

Cue	Slope	Mean	Std Dev	ICC
Sural	Negative	76.20	3.61	0.79
Sural	Positive	75.67	5.56	0.86
Visual	Negative	74.33	2.66	0.70
Visual	Positive	80.13	4.93	0.61

Model:
Stimulus alone: p=0.2391
Slope alone: p=0.0715
Stimulus * slope: p=0.0811
Time (replicate): p=0.4496
Order: 0.3232
Comparisons of Interest:
Visual vs. Sural: p=0.2391
Visual vs. Sural, where slope=Positive: p=0.3821
Visual vs. Sural where slope=Negative: p=0.1926

Duration of the reflex response

Cue	Slope	Mean	Std Dev	ICC
Sural	Negative	31.20	3.93	0.78
Sural	Positive	30.73	5.31	0.73
Visual	Negative	28.20	4.16	0.71
Visual	Positive	31.73	5.24	0.60

Model:
Stimulus alone: p=0.1002
Slope alone: p=0.0786
Stimulus * slope: p=0.0963
Time (replicate): p=0.7707
Order: 0.3471
Comparisons of Interest:
Visual vs. Sural: p=0.1002
Visual vs. Sural, where slope=Positive: p=0.8242
Visual vs. Sural where slope=Negative: p=0.1167

Strength of a Reflex response

Cue	Slope	Mean	Std Dev	ICC
Sural	Negative	-34.60	2.90	0.73
Sural	Positive	73.07	3.22	0.83
Visual	Negative	43.27	2.69	0.66
Visual	Positive	53.80	3.12	0.69

Model:
Stimulus alone: $p<0.0001$
Slope alone: $p<0.0001$
Stimulus * slope: $p<0.0001$
Time (replicate): $p=0.2052$
Order: 0.9575
Comparisons of Interest:
Visual vs. Sural, where slope=Positive: $p = 0.0133$
Visual vs. Sural where slope=Negative: $p= 0.0067$
Positive vs. Negative where cue =Visual: $p = 0.0323$
Positive vs. Negative where cue = Sural: $p = 0.0105$

Net Reflex EMG Response

Cue	Slope	Mean	Std Dev	ICC
Sural	Negative	-18.32	2.63	0.84
Sural	Positive	54.35	2.37	0.76
Visual	Negative	24.72	2.73	0.59
Visual	Positive	35.01	3.13	0.58

Model:
Stimulus alone: $p<0.0001$
Slope alone: $p<0.0001$
Stimulus * slope: $p<0.0001$
Time (replicate): $p=0.3435$
Order: 0.5437
Comparisons of Interest:
Visual vs. Sural, where slope=Positive: $p<0.0001$
Visual vs. Sural where slope=Negative: $p<0.0001$

Standing vs. Step Initiation

Comparison between NRE for standing at 2RT and stepping for visual positive slope only

NRE	Mean	Std Dev	p-value comparing the two
Standing	-15.06	2.53	<0.0001
Step initiation (V+)	35.01	2.72	

Appendix P

Statistical Analysis for Kinetic, Kinematic and EMG data

Vertical Force Onset Time

Cue	Mean	Std Dev	ICC
Visual	245.83	39.29	0.56
Sural	169.35	19.89	0.61

Model:
Stimulus alone: p<0.0001
Time (replicate): p=0.9493
Order: 0.3681
Comparisons of Interest:
Visual vs. Sural: p= 0.0021

Vertical Force Amplitude

Cue	Mean	Std Dev	ICC
Visual	27.04	3.56	0.66
Sural	33.88	4.95	0.59

Model:
Stimulus alone: p<0.0001
Time (replicate): p=0.2944
Order: 0.5344
Comparisons of Interest:
Visual vs. Sural: p= 0.0073

Speed of Force Onset

Cue	Mean	Std Dev	ICC
Visual	125.73	12.15	0.61
Sural	142.61	17.02	0.63

Model:
Stimulus alone: p<0.0001
Time (replicate): p=0.5758
Order: 0.1471
Comparisons of Interest:
Visual vs. Sural: p= 0.0154

TA EMG onset time

Cue	Mean	Std Dev	ICC
Visual	223.1	30.63	0.71
Sural	147.62	16.96	0.61

Model:
Stimulus alone: p<0.0001
Time (replicate): p=0.9334
Order: 0.1550
Comparisons of Interest:
Visual vs. Sural: p = 0.0012

TA EMG Duration

Cue	Mean	Std Dev	ICC
Visual	452.58	29.91	0.59
Sural	402.88	34.32	0.63

Model:
Stimulus alone: p<0.0001
Time (replicate): p=0.6743
Order: 0.4283
Comparisons of Interest:
Visual vs. Sural: p = 0.0111

TA EMG Amplitude

Cue	Mean	Std Dev	ICC
Visual	100	9.37	0.58
Sural	111.25	7.1	0.60

Model:
Stimulus alone: p<0.0001
Time (replicate): p=0.8960
Order: 0.6696
Comparisons of Interest:
Visual vs. Sural: p= 0.0205

Posterior COP onset time

Cue	Mean	Std Dev	ICC
Visual	100	8.39	0.67
Sural	122.68	12.28	0.64

Model:
Stimulus alone: p<0.0001
Time (replicate): p=0.7552
Order: 0.6030
Comparisons of Interest:
Visual vs. Sural: p= 0.0054

Posterior COP displacement

Cue	Mean	Std Dev	ICC
Visual	100	8.39	0.61
Sural	122.68	12.28	0.62

Model:
Stimulus alone: p<0.0001
Time (replicate): p=0.6552
Order: 0.8931
Comparisons of Interest:
Visual vs. Sural: p= 0.0220

Speed of COP onset

Cue	Mean	Std Dev	ICC
Visual	135.00	10.49	0.69
Sural	151.25	10.22	0.71

Model:
Stimulus alone: p<0.0001
Time (replicate): p=0.9885
Order: 0.9528
Comparisons of Interest:
Visual vs. Sural: p = 0.0246

Appendix Q

CONSENT FORM

Effects of Non noxious Sural Nerve Stimulation on the modulation of reflex responses evoked in the human ipsilateral Tibialis Anterior (TA) muscle during non functional vs functional tasks.

You are invited to be in a research study concerned with how you take a step when prompted by different cues. You are selected as a possible participant because you responded to the announcement of the study. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

This study is being conducted by: Nupur Hajela, Graduate student, Program in Rehabilitation Sciences, Department of Physical Medicine and Rehabilitation at the University of Minnesota.

Background Information:

The purpose of this study is to examine how a sensory nerve that provides sensation to your foot influences motor nerves that control muscles that allow you to take a step. By activating the sensory nerve with an electrical stimulator, we can measure its effect by recording electrical signals from your leg muscles. We are interested in how these effects might differ from when you are sitting, when you are standing and when you are taking a step. In doing this experiment we will gain a better understanding of the role of these sensory nerves in activating the appropriate muscles needed to take a step.

Procedure:

If you agree to be in this study, we would ask you to do the following things.

1) Provide background information to the investigator about your age, height, weight and history of orthopedic or neurologic disorders that affect your ability to take a step.

2) Have bandage like electrodes placed on the skin overlying one muscle, a muscle on the right side of the shin bone.

3) Produce 3 maximum contractions of this muscle.

4) Allow us to stimulate a nerve that runs under your outside ankle.

5) Sit in a chair with your right leg attached and strapped to a wooden platform. You will be requested to first produce three voluntary contractions with your maximum effort.

You will then be asked to produce 1 minute contractions at 3 different levels of your maximum effort (15, 20 and 25% of maximum). During these contractions, you will receive electrical stimulation of a nerve that runs down the outside of your ankle. The electric stimulus should feel like a tingling sensation that radiates into your foot. The stimulus should not hurt and if it does we will stop testing immediately. Four different stimulus intensities will be used. You will therefore be required to produce a total of 12, 1 minute contractions.

In the second part of this experiment you will be asked to first stand for 1 minute on a wedge shaped wooden platform while the nerve at your ankle is stimulated at the four different intensities. Following this, you will stand with one foot (right) on a force platform with weight equally distributed. A light cue will signal you to get ready to take a step. This ready light cue will be followed by either a second light cue or stimulation of the nerve at your ankle, 1 to 2 seconds later. These second cues indicate that you are to take 3 steps as fast as possible. During the steps, you will again receive a stimulus to the nerve at your ankle. You will be required to take 120 steps and then given a 5 minute rest period. This procedure will then be repeated 3 more times.

6) All electrodes and stimulating electrodes will be removed at the end of the session. The testing does not involve any invasive procedures. The entire testing session will last approximately 3 hours.

Risks and Benefits of Being in the Study:

The study has some minimal risks: First, the nerve stimulation requires us to use an electrical device that delivers a pulse to the nerve. As with any electrical devices applied to the skin there is a remote possibility of an inadvertent electrical shock due to equipment malfunction. This risk is considered to be extremely remote in that safety mechanisms have been built in to the device to eliminate such a problem; second, the electric stimulator is capable of delivering very strong pulses of current. We will only use low intensities of stimulation that should feel like tingling sensation that radiates into

your foot. If the stimulus feels painful, you should inform us and the experiment would be stopped immediately.

The benefits to participate are: There are no benefits to you for participation in this study. There will be no reimbursement for participation in this study.

Research Related Injury:

In the event that this research activity results in an injury, treatment will be available, including first aid,emergency treatment and follow up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a research related injury let the study investigator know right away.

Confidentiality:

The records of this study will be kept private. In any sort of report we might publish, we will not include any information that will make it possible to identify a subject.

Voluntary Nature of the Study:

Your decision whether or not to participate will not affect your current or future relations with the University. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

Contacts and Questions:

The researcher conducting this study is Nupur Hajela. You may ask any questions you have now. If you have questions later, you may contact me at the Program in Physical Therapy, Box 388 MMC, The University of Minnesota, Minneapolis, MN 55455; Phone: 612-625-0522.

If you have any questions or concerns regarding the study and would like to talk to talk to someone other than the researcher(s), you are encouraged to contact the Research Subjects' Advocate Line, D528 Mayo, 420 Delaware St. Southeast, Minneapolis, Minnesota 55455; 612-625-1650.

You will be given a copy of this form to keep for your records.

Statement of Consent:

I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

Signature_____ Date_____

Signature of Investigator _____ Date _____

Appendix R

Exclusion Criteria Questionnaire

Name: _____

Please Mark yes/no for the specific questions or comment where needed.

1) Do you have diabetes?

Y / N_____

2) Have you ever had any spine surgery?

Y / N_____

3) Are you on any medication for orthopedic problem?

Y / N_____

4) Are you on any medication for neurologic problem?

Y / N_____

5) Do you currently have any spine related problem (e.g. back pain, herniated disc, disc prolapse)?

Y / N_____

6) Do you currently have any orthopedic/neurologic problem (e.g. sprained ankle, knee pain)

Y / N_____

7) Do you have any sight, hearing or sensory impairment?

Y / N_____

8) Do you have/ever had any nerve injury?

Y / N_____

9) Do you have/ever had any brain injury?

Y / N_____

Appendix S

Data Collection Sheet

Date: _____

Subject Name_____

Subject Code_____

Age _____

Height_____

Practice session: Y/ N_____

Sensory testing done: Y/N_____

<u>Step initiation</u>

Foot size drawn _____

Radiating Threshold (RT) _____milliamp

Body Weight (BW) _____

½ BW= _____

Positive slope (½ BW + 25 % *1/2 BW) = _____

Negative slope (½ BW - 25% * ½ BW) = _____

<u>Standing</u>

1.5 RT = _____

2.0 RT = _____

2.5 RT = _____

0.0 RT = _____

Appendix T

Survey Footedness Screen (Coren S, 1993)

Simply read each of the questions below. Decide which foot you use for each activity and then put a check mark next to the answer that describes you the best. If you are unsure of any answer, try to act out the action.

Name: _____

1. With which foot would you kick a ball to hit a target?
_____Left ____Right _____Either

2. If you wanted to pick up a pebble with your toes, which foot would you use?
_____Left _____Right _____Either

3. Which foot would you use to step on a bug?
_____Left _____Right _____Either

4. If you had to step up onto a chair, which foot would you place on the chair first?
_____Left _____Right _____Either

Sum = _____

Footedness = _____ Left _____ Right

Scoring Instructions:
For each 4-item subscale, compute (R-L), where R is the number of "right" responses and L is the number of "left" responses. For every "right" response they score +1, "left" response = - 1, for every "either" response they score 0. The score range from -4 to +4. Where +4 correspond to Right foot dominance and -4 corresponds to left foot dominance.