The Reflexive Control of Knee Stability During Movement

By

Muhammet Berkan Kocer

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Department of Physiology and Pathophysiology Rady Faculty

of Health Sciences University of Manitoba Winnipeg,

Manitoba, Canada

Abstract

Stimulation of the common peroneal nerve (CPN) excites quadriceps (Q) motoneurons, and it is called the CPQ reflex. It has been suggested that the CPQ reflex assists in ground reaction force (GRF) generation during walking when conditions require that, for example, at most commonly used walking speeds or on an incline. This reflex is evoked by neurons in a spinal pathway relaying sensory input from muscle afferents and descending locomotor commands. The CPQ reflex pathway is thought to coordinate sensory input with ongoing motor activity. The aim here was to evaluate the effects of the walking speed of the stimulated leg on the CPQ reflex. The hypothesis that increased speed on one side will reduce the CPQ was tested. Neurologically intact, generally healthy participants (n=12) in the 20-48 years old age range were evaluated under different treadmill walking conditions: both legs walking at the same speed (BLW) or legs walking with different speeds at a ratio 1 to 1.25 (R1.25), 1 to 1.5 (R1.5) and 1 to 2 (R2) so that the right (R) belt speed was increased, and the left belt was kept constant. EMG responses in lower leg muscles were compared in steps with and without stimulation of the CPN at an optimal window after the R heel strike. Our result showed that as speed increased on the R side, the size of the R CPQ reflex showed a tendency to decrease but no significant changes were found, likely due to our sample size (n=5). To understand the factors that may influence the CPQ reflex, the effect of walking speed under the stimulated side on ground reaction forces (GRFs), the stance and swing time and the left-right asymmetry were also examined. Increasing speed amplified the peaks of the anterior-posterior and vertical components of GRFs. We also found that R CPN stimulation altered the left-right asymmetry of the propulsive peak of the GRFs. The findings of this study are important for a better understanding of the CPQ reflex and for using CPN stimulation in clinical settings to improve knee stability during walking.

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List of Abbreviations

CPQ: Common peroneal nerve stimulation evoked excitation in Quadriceps

CPN: Common peroneal nerve

GRFs: Ground reaction forces

CPG: Central Pattern Generator

BLW: Both legs are walking at the same speed.

R1.25: Both legs are walking with different speeds at a ratio 1 to 1.25.

R1.5: Both legs are walking with different speeds at a ratio 1 to 1.25.

R2: Both legs are walking with different speeds at a ratio 1 to 2.

CNS: Central nervous system

Q: Quadriceps Femoris

CPN: Common peroneal nerve

TA: Tibialis anterior

VL: Vastus lateralis

SOL: Soleus

HAMS: Hamstrings

BF: Biceps Femoris

ER: Erector Spinae

RF: Rectus femoris

VL: Vastus lateralis

VM: Vastus medialis

VIM: Vastus intermedius

TMS: Transcranial magnetic stimulation

Ins: Interneurons

ML: Medial-lateral

AP: Anterior-posterior

SI: Rabinson index- Symmetry Index,

RI: Ratio index

Mmax: Maximal motor response

MT: Motor threshold

Chapter I: Introduction

Locomotion as an automatic motor function

The way people move is one thing that makes them different from other animals. Humans are the only animals that walk and move around on two legs and use their upper limbs in a skilled way (1). We do not know precisely how the brain controls movement. Still, finely controlled motor activity requires the central nervous system (CNS) and the peripheral sensory system. Most fine-motor actions, like brushing your teeth, holding a pencil/pen to write, and using a fork or spoon to feed yourself, are used at the cortical level. On the other hand, certain motor activities, mainly rhythmic movements like walking, swallowing, breathing are performed automatically. Studies on animals suggest that these rhythmic movements are caused by neuronal circuits in the brainstem or spinal cord (2). Even in the absence of supraspinal inputs, patients with spinal cord injury are able to generate step-like oscillating motor patterns in their lower limbs (3). These oscillatory patterns seem to be reflex responses; and sensory inputs are necessary to trigger them.

Reflexive connectivity of leg muscles

Heteronymous reflex pathways connect multiple muscles, and these pathways play a role in the modulation of activity between muscles acting at different joints. Therefore, heteronymous connections are thought to be important pathways for muscle coordination during multi-joint movements such as locomotion (4). One heteronymous reflex pathway consists of connections between the knee extensor quadriceps (Q) and the ankle flexor tibialis anterior muscle that is innervated by the common peroneal nerve (CPN) – hence often referred to as the CPQ reflex. This excitatory pathway may be involved in knee stabilization as the CPQ reflex increases EMG activity in Quadriceps followed by common peroneal nerve stimulation at the appropriate moment during walking and also during standing (5,6).

The common peroneal nerve is the smaller and terminal branch of the sciatic nerve, which is related to the posterior divisions of L4, 5, S1, and S2 spinal segments (and ventral roots). It runs along the upper lateral side of the popliteal fossa and beneath the biceps femoris until it reaches the posterior portion of the fibula's head. It passes forward around the neck of the fibula within the substance of fibularis (peroneus) longus, where it divides into the superficial and deep fibular (peroneal) nerves. At the neck of the fibulae, the nerve is situated closer to the surface (skin) and often this is where its non-invasive stimulation is applied. The common fibular (peroneal) nerve supplies the knee and superior tibiofibular joint with articular branches. The posterolateral side of the proximal two-thirds of the leg is supplied by the lateral cutaneous nerve of the calf (7).

The Tibialis Anterior (TA) muscle in humans originates along the upper two-thirds of the lateral (outside) surface of the tibia and inserts into the medial cuneiform and first metatarsal bones of the foot. It acts to dorsiflex and invert the foot. This muscle is mostly located near the shin bone and TA is the strongest dorsiflexor of the ankle and also helps to pronate the foot (8).

The Quadriceps femoris is the most voluminous muscle of the human body (9). The Quadriceps femoris is both a hip flexor and a knee extensor. It is divided into distinct portions, Rectus femoris or RF, Vastus lateralis or VL, Vastus Medialis or VM and Vastus intermedius or VIM. The RF is the muscle in the middle of the thigh that connects to the ilium. The other three are right next to the body of the femur. They cover the area between the trochanter and the condyles. The VL is the biggest part on the outside of the femur. The VM is the part on the inside, and the VIM is the part on the inside-front of the thigh (10). The specific excitatory reflex connectivity between the TA and the VL muscles has been established by recording the activity of VL following CP stimulation; and the amount of excitation is less understood in the RF, VM and VIM.

Characteristics of different afferents originating in muscle tissue

It is thought that different sensory fibers play role in evoking the CPQ reflex. These sensory fibers are Group 1a, Group2 in the muscle spindle, and Group 1b fibers originating from Golgi tendon organs (11,12,13). Muscle spindles are small, spindle-shaped sensory receptors found in skeletal muscle tissue. A muscle spindle is comprised of differentiated muscle fibers (intrafusal fibers). The ends of intrafusal fibers are contractile, whereas the central portion is noncontractile and innervated by gamma motor neurons, which are specialized neurons (14). Muscle spindles are sensitive to both phasic and tonic strain (the rate at which a muscle stretches). Stimulation of muscle spindles causes a contraction in the stretched muscle (myotatic reflex, or stretch reflex), while simultaneously inhibiting action potentials in antagonistic muscles.

There are three different kinds of muscle spindle fibers (Nuclear Chain fibers, Static Nuclear Bag fiber, and Dynamic Nuclear Bag fibers). Nuclear Chain fiber, the nuclei of these fibers are aligned in a single row (chain) at the center of the fiber, hence the name. They convey information regarding the muscle's static length. The “Static Nuclear Bag Fiber” name was derived from the fact that their nuclei are bundled in the center of the fiber. These fibers, like the nuclear chain fiber, transmit information regarding the static length of a muscle. Dynamic Nuclear Bag fibers are anatomically identical to static nuclear bag fibers, but they mainly transmit information regarding the rate of change (velocity) of muscle length. Muscle spindles typically include 1 dynamic nuclear bag fiber, 1 static nuclear bag fiber, and 5 nuclear chain fibers (15).

Since the muscle spindle is parallel to the extrafusal fibers, it stretches along the muscle. Two kinds of specialized sensory fibers convey muscle length and velocity to the central nervous system from the muscle spindle: Group Ia and Group II afferents. Group Ia afferents (also known as primary afferents) wrap around the central portion of all three classes of intrafusal fibers to form annulospiral endings. These fibers provide information about length and velocity. Group II afferents (also known as secondary afferents) innervate the endings of nuclear chain fibers and nuclear bag fibers. These fibers transmit only information about muscle length, as they do not innervate the dynamic nuclear bag fibers. When these fibers are activated, Group Ia afferent fires at very high rate to convey information about the velocity of the muscle length change. At the end of the stretch, its firing rate decreases, as the muscle is no longer changing length. Compare the response of the Group Ia afferent to the Group II afferent, the firing rate of group II afferents increases constantly as the muscle is stretched. Its firing rate is not dependent on the rate of change of the muscle, but rather on the muscle's immediate length. Another crucial structure for locomotion is the Golgi tendon organ. The organ is innervated by Group Ib fibers. When force is applied to a muscle, the Golgi tendon organ is stretched, which causes Group Ib fibers depolarisation, and the action potential (14).

Type1a, Type 1b, Type 2; they are all myelinated fibers, and their sizes range form large to medium (Type1a>Type1b>Type2). Type 1a is the largest one and has the highest number of node of Ranvier. The nodes of Ranvier are specialized regions in the axonal membrane that lack myelin insulation. The nodes contain significant concentrations of voltage-gated sodium ion channels, which increase membrane voltage during the formation of action potential (16). The node of Ranvier can be manipulated with stimulations. Since there are many nodes of Ranvier in large fibers, even a small current or manipulation can be enough to recruit the larger fibers. Therefore, Group1a fibers are the most excitable sensory fibers, then Group I and then group II because of the high amount nodes of Ranvier (17).

Early research (18,19) demonstrated that electrical stimulation of the CPN leads to an early inhibition followed by an excitatory response. They attributed the early inhibition to la afferents and the short latency excitation to Ib afferents based on the assumption that group la afferents are faster than Ib afferents.

The study by Brooke and Mcllroy (6) provided additional evidence that Ib afferents are the origin of this excitatory response in Quadriceps. They discovered that electrical stimulation of CPN before and after 20 minutes of vibration at 80 Hertz over the prétibial muscles did not diminish the reflex magnitude significantly. It has been demonstrated that prolonged vibration raises the electrical threshold of group la axons above that of Ib afferents (20). Consequently, Brooke concluded that group Ib afferents are most likely responsible for this excitatory response. In Pierrot-Deseilligny, and Simonetta-Moreau (13) reported that increasing the stimulation intensity at CPN will result in a second excitation with a longer latency. This second peak with a higher threshold has a 4-8 millisecond (ms) longer latency than the first peak. When they cooled the CPN, the second peak's latency increased more than the first peak. This showed that the second peak is evoked by lower velocity axons than group I. This second excitation was attributed to group II afferents. It has been proposed that this group II excitation is mainly stimulated by Group II afferents (21). These studies demonstrated these afferents (group la, Ib, and II) and descending pathways all connect to the same interneuron system. They concluded that the observed facilitative interactions between cortical and peripheral volleys are consistent with interactions in a population of lumbar excitatory pre motoneurons co-activated by group I and II afferents. These interactions between the corticospinal tract and group I and II afferents occurred via propriospinal interneurons.

Defining the propriospinal system

Propriospinal INs receive inputs from descending locomotor pathways and propagate motor commands rostrocaudally to locomotor circuits via short or long, ipsilateral, or commissural axons. Some propriospinal INs project axons that travel only a few segments (short propriospinal) while others project axons that travel many more segments, spanning far enough to connect cervical with lumbar segments (long propriospinal). Some short and long IN axons can remain on the same side of the body as their cell bodies, whereas others can travel to the opposite side (22).

Specifically, one known propriospinal pathway that controls knee stabilizations is the CPQ reflex pathway, and this reflex is one of the mechanisms involved in knee joint control during walking (23).

Assessment of human locomotion and gait mechanics

Human walking has been investigated years. Even before the invention of computers, early scientists such as Giovanni Borelli (1608-1679), Willhelm Weber (1804-1891), Eduard Weber (1871-1871), and Eadweard Muybridge (1856-1910) made significant contributions to the comprehension of walking (24). In the early 20th century, foundational papers authored by VerneT. Inman (1905-1980) led to the development of six hypotheses known as "determinants of gait" (25). Since the 1980s, gait analysis has greatly improved with the help of modern computers and advanced motion capture technology. Numerous renowned authors, including D.A. Winter, M.W. Whittle, C.L. Vaughan, S. Ounpuu, P. De Leva, and T.P. Andracchi, have contributed to a comprehensive understanding of the characteristics of walking.

Today, the majority of gait research concentrates on the study of walking as it deviates from the ideal condition of walking. Perturbations such as slopes (26,27), stairs (28,29), obstacles (30), slippery surfaces (31,32) limited sensory input (33) and locomotion of special populations (34,35,36) are of great interest within the gait analysis community. Most commonly analyzed biomechanics parameters are spatiotemporal gait parameters and Ground reaction forces.

Walking can be defined as ‘involving the use of the two legs, alternately, to provide both support and propulsion” (37). Formal walking is a series of repeated arm and leg movements that move the body forward while maintaining the stance stability. The gait cycle begins when the heel of the referenced extremity contacts the ground and ends when the heel of the same extremity contacts the ground again.

The gait cycle has been mainly divided into two phases: stance phase and swing phase. These phases can then be further subdivided and discussed in terms of the percentage of each within the gait cycle. The stance phase is the interval in which the foot of referenced lower extremity is in contact with the ground. It consists of 60 percent of the gait cycle. It can be subdivided into a double-support phase and single support phase. Double support phase refers to the two periods in a gait cycle in which body weight is transferred from one foot to the other and both right and left feet are in contact with the ground at the same time. First periods occur in beginning of the stance phase of referenced extremity and the other occurs in end of stance phase of the referenced extremity. At an average walking speed, it represents 20 percent of the entire gait cycle, but decreases with increased walking speed and ultimately disappears as one begins to run. At slower walking velocities the double-leg support times are greater. Single-leg stance comprises up to 80 percent of the normal gait cycle.

The swing phase is the interval in which the foot of referenced lower extremity is not in contact with the ground. It constitutes 40 percent of the gait cycle. Stance phase is subdivided into 5 phases: Initial contract, Loading response, Midstance, Terminal stance and Pre-swing. Swing phase is subdivided into 3 phases: Initial swing, Mid-swing and Terminal swing (Fig1).

Heel strike (Initial contact) occurs at the beginning of the stance phase when referenced heel contacts the ground.in this phase, most muscles work eccentrically. Hip extensors contract eccentrically to slow down and stabilize the limb for initial contact. Quadriceps contract concentrically initially for knee extension, then contract eccentrically to control the amount of knee flexion on contact. Tibialis anterior contracts eccentrically to prevent foot slap.

At the heel strike point, Hip is 30° flexion, knee angle changes 0^0-15^0 flexion, and the ankle angle changes 0°- 15° plantar flexion.

Loading response (foot flat) occurs after the initial contact until the opposite limb's bodyweight is transferred onto the supporting limb. Quadriceps initially contract eccentrically to stabilize knee and then contract concentrically to move knee towards extension. Tibialis anterior continues to contract eccentrically to control plantar flexion moment at the ankle.

Hip angle changes from 30° flexion to 5° flexion; Knee angle alters from 15° flexion to 5° flexion; Ankle angle changes from 15° plantar flexion to 10 dorsiflexion.

Midstance phase, it begins when the opposite limb leaves the ground, and the body is aligned directly over the stance leg. Hip extensors and quadriceps contract concentrically to advance body forward over the stance leg. Gluteus Medius contracts eccentrically throughout the stance to control pelvic alignment and stabilize the hip. Gastrocnemius and soleus contract eccentrically to control the advancement of the tibial over foot.

Hip angle changes from 5° flexion to 5° hyperextension; Knee angle alters from 5° flexion to neutral position; Ankle angle changes from 10° dorsal flexion to 15° dorsiflexion.

Terminal Stance phase, it begins when the supporting heel rises from the ground and continues until the opposite heel touches the ground. In this stage, Gastrocnemius, and soleus contract concentrically to plantarflex the ankle.

Hip angle changes from 10° hyperextension - 0° (neutral), knee angle alters from neutral (0) to 5 flexion. Ankle angle changes from 15° dorsal flexion to 20° dorsiflexion.

Pre-swing phase(toe-off), it is the second double-support phase. It begins when the opposite limb contacts the ground, and it finishes with an elevation of the reference limb. In this stage, Hip flexors contract to provide hip flexion, Ankle Plantar flexors continue to contract concentrically to push off the reference limb.

Hip angle changes from 0° neutral - 20° flexion, Knee angle alters from 5° flexion to 40^0 flexion: Ankle angle changes from 20° plantar flexion to 0° neutral position.

Initial swing, it is from the elevation of limb to the point of maximal knee flexion. In this stage, Hip flexors contract concentrically to advance the swinging leg. Knee flexors contract concentrically to flex the knee. Ankle dorsiflexors contract concentrically to maintain foot dorsiflexion.

Hip angle is 20°-30^0 flexion, Knee angle is 40^0-60^0 flexion; Ankle angle mainly maintain neutral position.

Mid-swing phase, it is from maximal knee flexion to the point where tibia is vertical. Knee extensors begin to contract concentrically to extend the knee. Ankle dorsiflexors continue to contract concentrically.

Hip is about 30° flexion, Knee is 60°- 30° flexion and Ankle is in neutral position.

Terminal swing, it is the phase from point where tibia is vertical to just prior to initial contact. Hamstring muscles contract eccentrically to decelerate forward motion of thigh.

Hip is about 30° flexion; Knee angle alters from 30° flexion to 0° (neutral) and Ankle is in the neutral position (38-43).

<u>Basic description of Ground Reaction Forces (GRFs)</u>

Typically, the GRF is represented by one or more discrete-time signals that measure the force exerted by the ground on the foot at various locations during the footstep (44). As a consequence of gravity, the body's weight exerts a vertical downward force on the ground. According to Newton's third law, a force of equal and opposite direction must operate upward on the foot from the ground. The term for this is ground reaction force (GRF). In static situations, the magnitude of GRFS is equal to the mass of the person multiplied by gravitational acceleration (F=m.g). In dynamic situations, however, such as locomotion, GRFs vary in a repetitive manner. When the line of GRF is located a distance from the center of rotation of a joint, an external movement is generated. The external moment increases proportionally to the perpendicular distance between the line of action of the GRF and the joint center. If the GRF is aligned near the center of the joint, the external moment is reduced. If the GRF passes through the center of the joint, there will be no external moment. The presence of an external moment causes motion at joint, that requires the generation of opposing internal muscle moment in order to generate equilibrium or to control the motion. In static situations, the internal and external moments are equal and opposite and thus in equilibrium. In dynamic situations, internal moment may slightly greater or less than external moment to control angular motion at joint (45).

During gait cycle, GRFs starts at the heel as initial contact, progresses forward through the foot, and end at the toes as the limb pushes off into swing. The magnitude and the line of GRFs vary through the gait cycle. (Figure2) shows the sagittal plane component of GRF is through one gait cycle which is called Pedotti diagram or butterfly diagram. In the sagittal plane, First GRFs have aligned posterior to ankle joint, anterior to knee and hip joint at the heel strike. At initial contact phase, GRFs lay down posterior ankle, knee and anterior to hip joint. Midstance to analogues to stance phase. In this phase, the ground reaction force and line of the gravity have coincidental action lines. Ground reaction forces move anterior the ankle and knee, posterior the hip joint. Following midstance, it continues to travel anterior ankle and knee, posterior the hip at heel off (terminal stance phase). at the toe off phase, it lays down anterior ankle joint, posterior to knee and hip joints (46). During walking, however GRF factors do not account for the weight and internal forces of specific joints because of distance from the point of contact.

Typically, GRF measurements are collected at regular intervals using either the floor sensor approach with force plates or, less frequently, a shoe-based Wearable sensor approach. Today, the majority of research focuses on GRF captured via force plate sensors, but there are projects, such as Plantiga Technologies Inc.'s (47) research, that examine the incorporation of GRF recognition into a shoe-based wearable sensor. The variety of technologies available for GRF capture results in a variety of data formats; the data available for study may include either an overall representation of total aggregate footstep force or be broken down into smaller subcomponents of force that better characterise the nuances of the step. The most typical representation of the GRF positions it in a three-dimensional Cartesian space with force components running along each axis. The Kristler force place coordinate system, depicted in Figure 3 is one of most common representation of GRF component decomposition. In this system, the GRF is represented by a three-component force vector, with each component reflecting a distinct aspect of the footstep that is either perpendicular or parallel to the ground. Anterior-posterior and medial-lateral components are parallel to the ground. Vertical component is horizontal the ground (48).

First component of GRFs is medial-lateral GRF (Figure 4). Medial-Lateral component of GRFs is generally very small and shows a lot of variabilities. Therefore, analysis of temporal and force variables in the mediolateral direction is used less frequently (49) due to their relatively high variability (50). This ground reaction force is mainly shaped ankle movements on the transverse plane (supination and pronation). At the beginning of the stance phase, supination movement occurs in the ankle, and that causes body weight distributed on the lateral side of the foot. That supination movement forms the lateral peak which is the first peak in medial-lateral component of ground reaction force. After the loading response stage, pronation movement occurs in the ankle, which causes the to shift more weight on the medial side of the foot. The pronation movement forms the medial peaks.

Second component of GRFs is anterior-posterior component which is shown as Fy (Figure 5). The anterior-posterior component is characterized by 2 peaks: Breaking peak and propulsive peak. The first peak (breaking peak) occurs in loading response phase. At this phase, the knee is flexed for shock absorption due to quadriceps eccentric contraction to prevent excessive loading on the reference extremity. In this phase, eccentric contraction of Quadricep femoris muscle is one of the main contributors of deceleration movement, which forms a breaking peak in the anterior-posterior component. The second peak (propulsive peak) occurs in terminal stance phase. At this phase, especially contractions of the gastrocnemius and soleus muscles create acceleration movement to push the body forward, which forges a propulsive peak.

Last component of Ground reaction forces is vertical component. It is shown as Fz (Figure 6). The vertical component is characterized by 2 peaks and 1 trough. When the force exceeds the body weight line, vertical acceleration occurs which creates upward force in response to loading in the loading response and terminal stance phases. Therefore 2 peaks are called loading response and terminal stance peak respectively. When the force is below the weight line, vertical acceleration creates downward force in response to loading in the midstance phase which forms midstance valley in the vertical component ground reaction force graph (50).

Quantification of gait asymmetry

Gait is characterized by a cyclical and laterally alternating progression from an unstable balance during the single-limb stance phase to a nearly stable balance during the dual-limb stance phase. Due to the need to coordinate the work of a large number of skeletal muscles and the large number of degrees of freedom in the locomotor system, each stride differs slightly from the other. A healthy person's gait is typically symmetrical with minor deviations: only subtle differences between the dominant and non-dominant limbs. Thus, asymmetry or lack of symmetry - appears to be a significant factor in distinguishing between normal and pathological gait (51). In spite of a no gold standard consensus regarding the presence or the degree of lower extremity asymmetry in the healthy populations (52), asymmetric gait is accepted as inefficient gait due to increased oxygen consumption and the energy cost of locomotion. Gait asymmetry can also lead to a reduction of bone mass density(osteoporosis) in the affected limb (53) and increased excessive loading on the contralateral limb which may cause osteoarthritis and musculoskeletal injury (54). For these reasons, it is important to examine whether asymmetry exists and its extent in various locomotion parameters.

Several kinematic and kinetic parameters, including walking speed, stride length, foot rotation angle, joint range of motion, duration of stance, swing phase of gait and GRFs are generally used to evaluate and monitor the motor locomotion (55-58). The most prevalent method for assessing a segment of the body movements relies on discrete indicators, involving equations to calculate and/or display the asymmetry of kinematic parameters. The most common equations for quantifying gait asymmetry are the symmetry index (Rabinson index) (SI), ratio index (RI), and Symmetry angle (59). In order to describe the split-belt walking I have used in my research; I have arbitrarily chosen the Rabinson index. Rabinson Index (symmetry index): Rabinson et al. developed an index to measure the symmetry of a ground reaction force in patients with chronic unilateral sacroiliac dyskinesia. The Rabinson index, also known as the symmetry index (SI) is calculated using the following formula: $\text{SI (Symmetry Index): SI} = \frac{|X_L - X_R|}{0.5 \cdot (X_L + X_R)}$

XL represents the kinematic parameters value of the left leg and XR represents kinematic parameters value of the right leg. If index value equals zero, it is considered a symmetrical gait, divergence from zero means asymmetry. The SI index became most commonly used and cited in publications.

This index was used to quantify spatial and temporal parameters, such as the duration of locomotion phases. Robinson et al., and many other researchers used the index for the analysis of ground reaction forces (64-68). In addition to GRF paraments, the Robinson index was also used to assess the asymmetry of gait (69,70).

<u>Gaps in knowledge, rationale and hypothesis tested.</u>

During walking, automatic motor coordination of different leg muscles relies on sensory afferent input. Reflex pathways between lower leg and thigh muscles are important for controlling muscle tension around the knee joint. One specific reflex, the CPQ reflex that is a an excitatory short-latency (spinal) pathway between the TA and the VL muscles has been hypothesized to be sensitive to GRFs and control knee stability by changing the excitatory feedback to VL based on the speed of walking or type of gait i.e., slow walking or running or the symmetry of the gait i.e., muscle activity on the left-right sides. The CPQ reflex has been examined in terms of it walking sensitivity to speed (71) and the CPQ reflex is larges at optimal speeds and decreased as when one's walking speed is lower or higher than the comfortable speed. The CPQ is also known to be modified, primarily reduced by input from the motor cortex (72) but it is unknown how the CPQ reflex is modulated by gait asymmetry. In order to examine if the CPQ reflex is modulated by gait asymmetry, a split-belt treadmill was used. This set-up allowed to ask people to walk in conditions when one leg was forced to walk at a higher speed than the other leg. The left-right speed difference was expected to change the gait asymmetry and allow the comparison of the CPQ reflex size across the different walking conditions.

Hypothesis 1: The excitation of VL after CPN stimulation i.e., the CPQ reflex is reduced when the walking speed is higher on the side where the reflex is evoked.

As the CPQ reflex is part of propriospinal reflex pathways that help with knee stabilization, it is plausible that other muscles are also reflexively affected by the CPN stimulation. As previous studies have only examined specific (tibialis anterior and gastrocnemii muscles) it is unknow if there is reflexive excitation or inhibition to other targets during walking. Therefore, we sought to characterize the effects of CPN stimulation in multiple trunk and leg muscles during different walking conditions. This was achieved by quantifying changes in ongoing EMG activity of ten different muscles.

Although, spilt-belt and unequal left-and right belt speeds are often used for studying walking in humans; there was no information available regarding the changes in GRFs and asymmetry when changing speed in one leg. Therefore, in this project, the changes in the GRFs and in other typical gait parameters also needed to be quantified. The quantification of these parameters addressed stance and swing duration, specific components of GRFs (F1 to F7) and left-right asymmetry (as defined by the Rabinson index).

In terms of the GRFs and CPQ relationship, GRF amplitudes are known to increase with walking speed which is also a factor for CPQ reflex amplitude. Amplitude of the CPQ reflex was largest when it was elicited at optimal walking speed. Therefore, it would be expected to observe the biggest CPQ reflex amplitude in optimal GRFs values.

Hypothesis 2: During split-belt walking, the GRFs and left-right asymmetry increase while stance duration decreases with increasing belt speed on the side where the belt speed is higher.

Chapter II: Methods

The experiments were performed on a total of 12 generally healthy volunteers. Recordings were made during overground standing and during treadmill locomotion on a split-belt instrumented device with force-plates (MOTEK-Hocoma/M-Gait).

<u>EMG and kinematic data</u>

Electromyographic (EMG) activity was recorded with bipolar surface electrodes (1mm x 10mm silver bars with 1 cm inter-electrode distance) placed over the muscle belly of Tibialis Anterior (TA), Soleus (Sol), Biceps Femoris (BF)-(HAMS), Vastus Lateralis (VL), Erector Spinae L4 (ES) muscles on both right and left sides (Figure 7) according to international standard recommendations (73). EMG activity was amplified (Bagnoli 16-EMG system, Delsys., USA, amplified x100-1000), and filtered (3-10000 Hz).

Reflective markers were placed on specific anatomical landmarks (Right 2nd meta tarsal(RMT2),Left 2nd meta tarsal(LMT2),Right 5th meta tarsal(RMT5),Left 5th meta tarsal(LMT5),Right lateral malleolus of the ankle(RLM),Left lateral malleolus of the ankle(LLM*),Right medial malleolus of the ankle(RMM),Left medial malleolus of the ankle(LMM),Right shank,lateral(RLSHA),Left shank,lateral(LLSHA),Right lateral epicondyle of the knee(RLEK),Right medial epicondyle of the knee(RMEK*),Left lateral epicondyle of the knee(LLEK),Left medial epicondyle of the knee(LMEK*),Right thigh,lateral(RLTHI),Left thigh,lateral(LLTHI),Right anterior superior iliac spine(RASIS),Left anterior superior iliac spine(LASIS),Right posterior superior iliac spine(RPSIS) and Left posterior superior iliac spine(LPSIS)). The vertical ground reaction forces from each belt were collected at 2000 Hz. All data was digitized (10 KHz, NI-DAQ board, USA/ Nexus/Vicon/Motek AD converter, NL) and stored (Neuro-Capture, SCRC, Winnipeg,Canada) on a personal computer for later off-line analysis. Kinematic data of gait patterns were obtained via 12-Vicon Vero cameras (Vicon Motion Systems, Los Angeles, USA,) digitized at 100 Hz, by Vicon/Motek AD converter, NL.

Electrical nerve stimulation

Rectangular electrical pulses (1-ms duration) were delivered to the common peroneal (CP) nerve through bipolar surface electrodes (1x5mm) close to the neck of the fibula. The electrodes were positioned to evoke a motor response first in TA, without activation of the peroneal muscle group at the motor threshold. The effect of the stimulation was also checked by tendon palpation in standing subjects and by asking if the sensation radiated down to the toes. Deep peroneal nerve stimulation produces more spinal excitation in VL motorneurones than the superficial peroneal nerve suggesting that the CPQ-reflex is mainly mediated by TA afferents (74). A constant current stimulator, DS7A (Digitimer Ltd, Welwyn Garden City, England) was used, and the intensity of the stimulation was adjusted to evoke an M-response in TA during standing overground, which was then kept constant throughout the treadmill walking. The intensity of the CP stimulation was expressed in relation to the MT (MT). As described previously (71) 2.5 X MT intensity was sufficient for the excitation of VL. During walking and running, stimulation was applied at every 3 or 4-step cycle.

Experimental design

During standing, a range of CP stimulation was applied to identify the threshold and the intensity required for evoked the maximal M-wave response (Mmax).

At the beginning of the experiment, participants walked on the treadmill for 5-10 min before recordings to accustom themselves to the treadmill walking, and to determine their comfortable speeds:0.8-1.4 ms $^{-1}$. At this speed, which was not their maximum speed, the patients felt secure, and they were able to walk for 2-3 min. Using the preferred walking speed of each participant ensured that optimal CPQ reflexes were evoked (23).

Participants were then asked to walk at the preferred speed and every 3-4 steps they were subjected to CP nerve stimulation in 4 different walking conditions. The 4 conditions were the followings: Both legs are walking at the same speed (BLW), Both legs are walking with different speeds at a ratios 1 to 1.25 (R1.25), 1 to 1.5 (R 1.5) and 1 to 2 (R2) so that left leg speed was constant and the right leg's speed was increased (Figure 8).

The optimal time of CPN stimulation to evoke a reflex was a delay between 0 and 70 ms after heel contact of the stimulated leg. In each individual, and this delay was kept constant in the subsequent gait conditions for the timing of the CP stimulation that was triggered by real-time feedback from the force plate data (Motek medical trigger box).

Data analysis

The Spike2 (CED Co, UK) software (version 10.11) was used for processing of the force and EMG recordings and the Visual 3D (C-Motion Inc; Rockville, Maryland) was used to reconstruct and analyze kinematic data. The EMG recordings were rectified and then averaged. Peri-stimulus averages of all non-stimulated steps and the stimulated steps (n=25) were used to measure EMG amplitude changes as the reflex size with reference to CP stimulation.

Characteristics of responses such as onset latency and duration of the CPQ reflex, and area (under the curve) were also quantified. CPQ reflex window was determined as 26 ms to 54 ms followed by CP stimulation (23) (Figure 9). In this experiment, the window calculation of CPQ was conducted from the visually detected first peak to 12ms later, followed by the first peak in CPQ reflex window, which was indicated in Marchand-Pauvert (23) research.

The effect of CP stimulation on the VL was expressed relative to the VL area value in non stimulation conditions. This normalization is typical when examining the effects of spinal reflexes, especially when comparisons between subjects are performed.

To evaluate changes in the effect of CPN stimulation in asymmetric walking conditions on Tibialis Anterior (TA), Soleus (Sol), Biceps Femoris (BF), Vastus Lateralis (VL), Erector Spinae (ES) muscles,200 ms window was detected after the stimulation. The effect of CPN stimulation in asymmetric conditions was expressed to stim VL EMG activity in BLW.

In this study, the vertical GRF time series plots were utilized to select valid steps. To determine and analyze kinematic variables, approximately 150 ±10 consecutive steps were used in each walking condition. GRFs of the right and left limbs in each condition were collected. Then they were filtered using a fourth-order low-pass zero lag Butterworth filter with a 20Hz cut off frequency. Impulses, peak force values and temporal parameters were analyzed. The through and peak values of medial-lateral, anterior-posterior, and vertical GRFs were assigned as F1, F2, F3, F4, F5, F6 and F7. The vertical GRF was used to characterize the gait event (initial contact and toe-off) by determining the threshold force value at 40N. Spatiotemporal gait parameters such as step swing time, stance time were directly measured using vertical GRFs. Asymmetry ratio of each direction of GRFs was analyzed by using SI index. In this index ($\mathrm{SI} = \frac{|X_{\mathrm{R}} - X_{\mathrm{L}}|}{0.5(X_{\mathrm{R}} + X_{\mathrm{L}})} \times 100,$), a higher value indicates a higher level of asymmetry. XR represents the value of the kinematic parameter in the right limb, XL represents the value of the kinematic parameter in the left limb. SI is measured in percentage units.

<u>Statistics</u>

The background and conditioned EMG were compared with paired t-tests in each subject and in each walking condition. One-way ANOVAs were used to test the influence of the speed. A Friedman test was run to determine whether there is a significant effect of CPN stimulation in different conditions.

To compare the EMG activity in different walking conditions, change in area under the curve for each muscle activity was calculated by subtracting the value obtained in steps with CPN stimulation from those obtained in control steps (no CPN stimulation) and expressing these differences as a percent of values in the steps without CPN stimulation (or % non-stim). A one-way repeated measures ANOVA was conducted to determine statistically significant differences. First normal distribution of the data was assessed by the Shapiro-Wilk's test ($p > .05$), then if outliers were detected than the Mauchly's test of sphericity was used to correct the one-way repeated measures ANOVA testing. When the data was normally distributed, pairwise comparisons with Bonferroni corrections were used for post-hoc comparisons.

To determine the effect of speed on GRFs, one-way ANOVA test was used, and Bonferroni test was utilized as post hoc comparison. In case gait parameters were not normally distributed, Friedman test was used to assess the effect of speed.

For asymmetry ratio, the Shapiro–Wilk test was used to confirm data normality. For each gait parameter that demonstrated a normal distribution, a two-way mixed analysis of variance (ANOVA) (speed and CPN stimulation) was performed, and a Bonferroni test was utilized as a posthoc comparison. Statistical significance was defined as $p < 0.05$ in all statistical tests used in this study (IBM SPSS Statistics Version 23, IBM, Armonk, NY, USA).

Chapter III: Results

<u>CPN stimulation induced biphasic facilitation in VL EMG activity during different walking conditions.</u>

During walking, the stimulation of the common peroneal nerve (CPN, at the intensity that was 2.5 times the motor threshold, 2.5xMT) near the time of heel strike evoked facilitation of the ongoing vastus lateralis (VL) EMG activity in 5/12 participants, as shown in Fig.10 A-D. This facilitation was expected to be present based on previous studies (71), and this is also called the CPQ reflex. Comparing the area of the rectified VL EMG in different walking conditions during the steps with and without CPN stimulation was used to quantify the CPQ reflex. The walking conditions tested included sustained split-belt walking when the left leg walked under a constant speed of 1 ms^{-1} without altering the belt speed on the left side, while the right leg walked at different speeds ranging from 1 to 2 ms^{-1}. The participants were allowed to get used to each condition before the CPN stimulation was initiated. The area of the CPQ reflex was measured based on identifying the onset and the duration of this reflex in each participant under each condition, as shown from a single subject in Fig. 10 A-D, by the dotted lines. The rectified averaged VL EMG during the control steps, i.e., those without CPN stimulation, are exemplified in Fig. 10 A-D as blue trace, and steps in which CPN stimulation was applied are shown by the red traces. The facilitation of the VL EMG in one participant, as shown in Fig. 10E, was 58% in BLW and 60% in R1.25, 37% in R.15, and 12% in R2 conditions. Thus, the CPQ reflex was seemingly becoming smaller as the walking speed of the stimulated leg increased in this participant and also similarly in all others, as shown in Fig.10F from grouped data (n=5). Reflex size decreased from 44 ±18.4% at BLW to 37±14. 93% at R12.5, 29.66±8.87% at R1.5, and 35.33±8.76% at R2 conditions; however, these changes were not significant (one-way repeated measures ANOVA).

<u>The effect of CPN stimulation on the EMG activity of muscles did not change among the different walking conditions.</u>

As illustrated in Fig11, the effects of CPN stimulation were also examined in 9 other muscles in addition to Vastus Lateralis (VL), including tibialis anterior (TA), soleus (SOL), hamstrings (HAMS), and erector spinae (ER) by quantifying rectified EMG area under the curve of each tested muscle similarly to as described for VL but the window of 200 ms duration from the CPN stimulation; the effects of CPN stimulation in the different walking conditions were compared. Some variations in EMG amplitude were evident in specific muscles; for example, R TA (Fig. 11A) and R SOL (Fig. 11C) increased several 100-fold in some participants; overall, there was no significant increase or decrease in EMGs resulting from CPN stimulation as detailed in Table 1 showing results of statistical tests, with respective p-values for each muscle.

<u>Anterior-posterior and vertical GRFs were significantly different during some of the split-belt conditions in the ipsilateral leg, under which the treadmill speed was altered.</u>

After establishing that CPN stimulation evoked reflexes in the ipsilateral VL muscle in all walking conditions; next we examined the differences between the selected conditions in terms of ground reaction forces. The classical peaks and key transition points of medial-lateral, anterior-posterior, and vertical ground reaction forces (GRFs) were compared during the different conditions. Changes in GRFs amplitude in BLW, R1.25, R1.5, and R2 conditions were evident to different extents, as illustrated in Figure 12 (A-J). The magnitude of the GRFs parameters generally increased as walking speeds increased on the ipsilateral (right) side.

Medial-lateral GRFs had a tendency to become larger in each condition with increasing speed on the right side (F1 was R1.125 (Mdn=12%); R1.5 (Mdn=7.5%); R2 (Mdn=16%) of F1 during BLW and F2 was R1.25 (0.1 ±7%), to R1.5 (3±10%), to R2 (5±15% of F2 during BLW). However, that increase was not significant for both F1 (Fig.12A) and F2 (Fig12B).

The F3 and F4 anterior-posterior components of GRFs significantly increased with speed (Fig.12C-D). The mean F3 force values were 21±2% in R12.5 39±4% in R1.5 and 76±10% in R2 condition (Fig. 12C). Pairwise comparisons revealed differences among other conditions, such as between R1.25 and R1.5; and between R1.25 and R2; and lastly between R 1.5 and R2 ($p<0.05$, see in Table 2). Thus, the breaking peak or F3 forces were significantly different from each other in all walking conditions.

There was a statically significant increase also in the F4 force value in each condition as speed increased (Fig.12D). The F4 increase was 19±1% in R12.5; 41±2% in R1.5; and 43±8% in the R2 condition ($p<0.05$). Significant differences were also revealed among other conditions, such as the difference between R1.25 and R1.5; and between R1.25 and R2 conditions, amounting to 22% and 23%, respectively (see p values in Table 2).

As the speed increased, there was a significant increase in the loading response peak or F5 (Fig.12E) and in the terminal stance peak or F6 (Fig. 12F). However, the midstance valley or F7 decreased with speed (Fig. 12G). Post hoc analysis revealed a statistically significant difference in F5 between BLW and R2 (Mdn=12%) between R1.25 (Mdn=0%) and R2 (see p values in Table 2). There was a statistically significant difference in F6 between BLW and R2 (Mdn=10%) and between R1.25 (Mdn=2%) and R2 (see p values in Table 2). Post hoc analysis revealed a statistically significant reduction in F7 from forces in BLW and in R2 (Mdn=-22%) and in R1.5

(Mdn=-13%) as well a difference between from R1.25 (Mdn=-5%) to R2 (see p values in Table 2).

<u>During split-belt walking, increased right belt speed altered stance and swing durations on both sides.</u>

As the right belt speed increased, the right-side stance duration and left-side stance and swing duration decreased. Stance duration on the right side (Fig. 13A) was longest during BLW (Mdn=0.78) and it was reduced during R1.5 (Mdn=0.67) and R2 (Mdn=0.61) conditions ($\chi^2(3) = 25.20$, $p < .001$). The stance duration during R1.25 was (Mdn=0.67). Swing duration on the right side (Fig. 13B) during BLW (Mdn=0.44) increased during the R2 condition (Mdn=0.47) R2 ($\chi2(3) = 10.30$, $p < 0.05$). Left side stance duration (Fig. 13C) was statistically different at the different walking conditions $\chi^2(3) = 24.30$, $p < 0.\ 01$.There was a statistically significant decrease in left side stance duration from BLW (Mdn=0.73) to R1.5 (Mdn=0.70); from BLW (Mdn=0.73) to R2 (Mdn=0.67); and from R1.25 (Mdn=0.71) to R2 (Mdn=0.67). Similarly, left side swing duration (Fig.13D) was statistically different at the different walking conditions ($\chi2(3) = 33.700$, $p < 0.01$) with values in BLW (Mdn=0.45) being the largest, which decreased during R1.5 (Mdn=0.41); and during R2 (Mdn=0.32); and also different between R1.25 (Mdn=0.41) and R2 conditions.

<u>Speed altered left-right asymmetry of anterior-posterior and vertical GRFs.</u>

Another way of evaluating changes in gait as a result of different walking speeds on one side, we examined gait symmetry in terms of left-right side comparisons of GRFs. Left-right asymmetry was calculated by using the so-called “symmetry index” (see Methods), with 0 % indicating full symmetry between the left and right sides while 100% referring to the least symmetry. The asymmetry increased with increasing right belt speed for anterior-posterior forces (F3, F4) and vertical forces (F5, F6 and F7). The left-right asymmetry showed high variability for the mediolateral components (F1, F2) without significant changes across conditions.

As shown in Fig.14A, there was no statistically significant two-way interaction between the effect of the CPN stimulation and the effect of increased right belt speed for F1 asymmetry (see table 3 for p and F values). There was no statistically significant difference in F1 asymmetry as a function of CPN stimulation. As shown in Fig.14B, there was no statistically significant two-way interaction between the effect of the stimulation and the effect of increased right belt speed on F2 asymmetry.

As shown in Fig.14C, there was no statistically significant two-way interaction between the effect of the stimulation and the effect of increased right belt speed for F3 asymmetry. There was no statistically significant difference in F3 asymmetry as a function of CPN. Increasing the right belt speeds evoked a statistically significant effect for F3 asymmetry with a significant increase from R1.5 (17.16 ± 3.04) to R2 (35.76 ± 6.16).

As shown in Fig.14D, there was a statistically significant two-way interaction between the effect of the stimulation and the effect of increased right belt speed on F4 asymmetry. Increasing the right belt speeds resulted in a statistically significant difference in F4 asymmetry between conditions. There was a significant increase of F4 from BLW ($7.53 \pm 1.56\%$) to R1.25 ($22.62 \pm 2.90\%$) ($p<0.05$); from BLW to R1.5 ($43.65 \pm 3.75\%$) ($p<0.05$); from BLW to R2 ($43.057 \pm 7.80\%$) ($p<0.05$); and from R1.25 to R1.5 ($p<0.05$).

As shown in Fig.14E, there was no statistically significant two-way interaction between the effect of stimulation and the effect of increased walking speed for F5 asymmetry. The main effect of stimulation showed that there was not a statistically significant difference in F5

Asymmetry between stim and non-stim conditions. However, the main effect of increased right belt speeds showed a statistically significant difference in F5 asymmetry between conditions. A significantly increased in the Asymmetry value of F5 was revealed from BLW (6.92±1.81%) to R12.5 (12.94± 2.81%) ($p<0.05$); and from BLW to R1.5 (14.58± 2.64%) ($p<0.05$).

As shown in Fig 14F, there was no statistically significant two-way interaction between the effect of stimulation and the effect of increased walking speed for F6 asymmetry. There was no statistically significant difference in F6 asymmetry as a function of CPN stimulation. Increasing the right belt speeds evoked a statistically significant effect for F6 asymmetry with a significant increase from BLW (3.35±0.84%) to R2 (13.05± 1.57%) ($p<0.05$); from R1.25 (3.38%) to R2 ($p<0.05$); and from R1.5 (4.66±0.71%) to R2 ($p<0.05$).

As shown in Fig 14G, there was no statistically significant two-way interaction between the effect of stimulation and the effect of increased walking speed for F7 asymmetry. There was no statistically significant difference in F6 asymmetry as a function of CPN stimulation. Increasing the right belt speeds evoked a statistically significant effect for F6 asymmetry with a significant increase from BLW (4.10 ± 0.69%) to R12.5 (6.42± 1.20%); from BLW to R1.5 (11.40±1.3%); from BLW to R2 (19.12± 2.16%); from R1.25 to R1.5; from R1.25 to R2; and from R1.5 to R2.

<u>CPN stimulation altered the left-right asymmetry of the propulsive peak(F4)</u>

As shown in Fig.14D, there was a statistically significant two-way interaction between the effect of the stimulation and the effect of increased right belt speed on F4 asymmetry CPN stimulation resulted in a statistically significant difference in F4 asymmetry between conditions. The mean Asymmetry value of F4 was statically different in the non-stim condition (43.65±3.75%) at the R1.5 compared to the stim condition (13 ±68). Also, changes in the median value of the symmetric index for each GRF in stimulation and non stimulation conditions were reported in table 4.

Chapter IV: Discussion

The main goal of this project was to evaluate how split-belt walking affects the CPQ reflex. We hypothesized that the size of the right CPQ reflex and stance duration decreases while GRFs and asymmetry increase as walking speed increases on one side. The results partly supported some of the hypothesized changes.

The CPQ reflex evoked on the right side showed no change with increased right belt speed. When the belt speeds were the same on each side, common peroneal stimulation of the right leg shortly after the right heel strike significantly increased the right VL EMG– as expected via the CPQ reflex pathway – in all 5 participants, which was also possible to evoke in each other condition when the belt speeds were different. The CPQ reflex was maximal during the condition when both legs were walking at the same speed (BLW), and the size of the reflex size showed a decreasing pattern with increased right belt speed; however, there was no significant change. Stimulation of the right CPN was expected to generate 2 peaks of excitation in right VL motor neurons through propriospinal interneurons. The first peak was attributed to group Ib fibers, and the second peak was associated with group II fibers of ankle dorsiflexor muscles (71,72,75). Previous studies examined these 2 peaks separately. However, in this study, the two peaks could not be differentiated in all conditions, and the total CPQ reflex response was evaluated in a single window with onsets (≈ 26ms) and offsets (≈54ms) consistent with a spinally mediated reflex pathway.

Background activity in VL and other factors contributing to changes in the CPQ reflex.

Marchand-Pauvert et al. reported that the size of the responses tended to vary with the background VL EMG activity level, and the CPQ reflex was observed to increase as background EMG increased (23). Increasing background EMG activity of VL and TA muscles has an effect on the size of the CPQ reflex as increased background EMG activity is known to increase reflex size via homonymous and heteronomous pathways (75,21). However, recent studies stated that background EMG is not always the main determinant of CPQ reflex size. Iglesias et al. (71) investigated whether the modulation of the CPQ reflex was related to the speed of walking. They reported that the CPQ reflex was absent at low (<2 km/h) and higher speeds (6km/h). The biggest CPQ reflex was observed at medium speed, which was 3 and 4 km/h. Therefore, even though the background EMG activity was smaller at medium (comfortable speeds) than at the highest walking speeds, the size of the CPQ reflex was not consistently increasing with speed. Another research that reported that there was no direct effect of the CPQ reflex was conducted by Achache et al. (72). Healthy participants were asked to walk at 1km/h and at their comfortable speed (ranging from 3-4km/h) speed and significant CPQ reflex was revealed at the 3-4km/h speed. In the present study, we found that the biggest CPQ reflex at the BLW walking conditions, the size of the CPQ reflex decreased with increased right belt speed. Although we did not quantify the background VL EMG activity increase on the right side with increasing belt speed, but assuming that right VL activity increased with speed, our result confirms the findings of Iglesias et al. and Achache et al. that CPQ reflex size is not necessarily defined by the background VL emg but other factors can also influence this reflex.

One factor that might affect the size of the CPQ reflex is the intensity of stimulation. Simonetta-Moreau et al. (76) showed that stimulus intensity of 1.5xMT could not facilitate group II afferents in CPN, and It was demonstrated that the threshold of group II afferents was approximately 2.1 times that of group I afferents. Marchand-Pauvert et al. (23) showed that stimulus intensities exceeding 2xMT at the caput fibulae elicit double excitatory responses in Q muscles. Therefore, in this experiment, 2-2.5xMT- the intensity of stimulation was used to elicit the CPQ reflex like in other experiments (71,72).

It is unlikely that cutaneous afferents could provide strong excitation to Q motoneurons to elicit the CPQ reflexes observed in the present experiments based on previously established facts. Stimulation of the caput fibula could activate cutaneous receptors beneath the electrodes, but Forge et al. (77) and Chaix et al. (12) reported that cutaneous stimulation alone was unable to evoke any response in Quadriceps.

Although the direct involvement of cutaneous afferents in the CPQ reflex is highly unlikely; however, stimulation of specific skin regions of the foot sole can produce excitatory effects on the transmission of certain spinal pathways to a given motoneuron pool (78,79). Therefore, afferents originating from the pressure-sensing receptors on the foot sole and toes during stance may have an excitatory effect on the transmission of the CPQ reflex. This was not investigated in this study, but future experiments could incorporate stimulation of the posterior tibial nerve in order to address this.

Another factor that may alter the CPQ reflex was changes in joint angles during walking. Prochazka et al. (80) and Watson et al. (81) reported that the excitatory pathway from the ankle dorsiflexors to Q arises mainly from some component of the somatosensory receptor array altered as a consequence of changes in the knee position and/or the hip position. Joint angles were not quantified here during the different walking conditions; however, this information could be extracted from the data we collected as kinematic marker positioning allowed to follow knee joint angles in all walking conditions for all participants. Changes in the length of the knee ligaments during locomotion were thought to influence the CPQ reflex. Stimulation of collateral ligaments of the knee joint in humans (82) and the knee joint capsule in cats (83) are shown to have an excitatory effect on the Q motoneurons. These receptors could have an excitatory effect on the reflex at the fully extended position of the knee when they are active, and an inhibitory effect on the CPQ reflex at the flexed position of the knee where the joint receptors are mainly silent. Therefore, the researchers concluded that it is unlikely that these receptors could have a major role in the formation of the CPQ reflex during walking (84). Iglesias et al. (71) reported that the largest variations in joint angle were observed at the highest speed (6 km/h), whereas the reflex size showed no further increase above speeds of around 4 km/h. The size of the CPQ reflex was smaller in asymmetric walking conditions than with both belts going at the same speed, which was expected to show more angle variations thus, increasing joint angle variations might affect the size CPQ reflex during split-belt walking. However, more research is needed to assess the effects of joint positions and muscle length on the CPQ reflex.

Central Process

It seems unlikely that peripheral changes alone are responsible for the increased CPQ-reflex activity at BLW, as reflex size changes did not parallel those in background EMG activity and joint angle variations (23). Another input that might modify the CPQ reflex is cortical input. It has been suggested that the interneurons mediating the CPQ reflex also relay the cortical commands to the motoneurons of the thigh muscles (21). Marchand Pauvert et al. (21) showed that when CPN stimulation was applied, that caused a sizeable facilitation of the Q EMG (i.e., 15% of maximal motor response, Mmax), additional cortical stimulation with transcranial magnetic stimulation of the VL motor cortical area doubled this response in Q (i.e., 30% of

Mmax). Achache et al. (72) showed that the second peak of the CPQ reflex, the group II component, can be enhanced during walking in post-stroke patients, and they explained this increase with impaired corticospinal control on interneurons. In other words, the lack of cortical input in stroke patients increased the response as normally cortical inhibition dominates.

In this experiment, CPQ reflex was elicited 5 participants out of 12. As reported in different studies, CPQ reflex is affected by different gait paraments such as speed, background EMG activity, peripheral inputs, joint angle variation and stimulation latency. Since the reflex is susceptible to different components, that makes the reflex difficult to elicit in some individuals . Iglesias et al (71) show that the CPQ reflex was elicited in 4 out of 19 participants at 3km/h which was reported as the optimal speed to elicit the CPQ reflex. In another research (72), CPQ reflex was observed in 4 out of 14 participants at 100ms stimulation latency.

Linking increased right belt speed to changes in some of the GRFs on the right side.

Increased speed mainly caused a trend for an increase in the amplitude of GRFs in all directions, with no significant changes in medial-lateral (ML) GRFs (F1 and F2). In the present experiment, as the walking speed increased on the right side, the AP peak of GRFs significantly increased. At higher walking speeds, the body generated more forward momentum to maintain the gait cycle, resulting in the greater force exerted in the anterior-posterior direction during the loading response phase (foot flat), where the breaking peak occurs, and the terminal stance phase, where the propulsive peak occurs (85,86). In addition, muscle activities could play a role in increased AP peak of ground reaction forces during walking (87,88). At the loading response phase (foot flat), Q initially contracts eccentrically, then it contracts concentrically to move the knee towards the extension. That creates deceleration and slows down the body’s forward motion. In contrast, at the terminal stance phase, gastrocnemii and soleus contract concentrically to generate forward propulsion. These muscles generate force to lift the heel and push the body forward. Also, the extensor and flexor muscles, including glutes maximus, rectus femoris, iliopsoas, and iliacus, can influence anterior-posterior GRFs by controlling the anterior-posterior movement of the pelvis (38,40,46). Increased EMG activity of these muscles with speed may be a factor for increased anterior-posterior GRFs.

In terms of the vertical component of GRFs, there was a significant increase in the loading response peak (F5) and terminal stance peak (F6). The increase in F5 and F6 might be explained by variations in the position of the center of mass (COM) as walking speed increases. During the stance phase, the center of mass (COM) moves higher and forward, requiring increased vertical GRFs to support the body's weight. (89,90,91,92). In addition, increased speed caused increased impact forces during the stance phase. These increased impact forces were related to the increased vertical peaks of ground reaction forces.

On the other hand, there was a significant decrease in the midstance valley with speed. It might also change in COM with speed. At the lower speed, the midstance valley dropped under the body weight line; however, at the higher speed, valley values were slightly higher than the body weight line (93). This could explain why the midstance valley value decreased with speed.

In the present research, the ML components of GRFs showed high variability with speed. Some studies have suggested that medio-lateral GRFs increased with walking (94-97). However, other studies have reported no significant changes in medio-lateral GRFs with walking speed (98,99). One study found that the ML-GRFs did not significantly change as walking speed increased, although there was a trend towards a slight increase (98) while the other study reported no significant differences in peak ML-GRFs across a range of walking speeds (99). Overall, the relationship between ML-GRFs and walking speed appears to be more complex than that of vertical and anterior-posterior of GRFs. This variability may be due to differences in study design, participant characteristics, and measurement methods.

In addition, an important point to emphasize is that these observations from previous studies I have cited stem from measurements on GRFs made during both legs walking at the same speed, or at the non-adopted portion of split-leg walking. No information about changes in GRFs has been reported to date, to our knowledge, from split-belt walking conditions when participants are asked to walk for several minutes in the split mode.

<u>Effect of split-belt speed on left-right GRF asymmetry and stance and swing durations.</u>

Right-left asymmetry of the vertical and anterior-posterior peaks of GRFs significantly increased with increasing right belt speed in the present experiment. Changes in stance and swing time might play a role in changes in the left-right asymmetry of GRFs. The vertical GRFs tend to be greater when the stance time is reduced, such as during running. This is due to the fact that the body must generate more force in less time to lift off the ground and move forward (100,101). In contrast, when the stance time is longer, such as during walking, the vertical GRFs tend to be lower. This is because the body has more time to gradually transfer weight from one foot to the other, reducing the impact of each step (102,103).

In terms of the Anterior-Posterior component of GRFs, as speed increases and stance time decreases, the force distribution in the anterior-posterior direction becomes more anterior because the body must generate more forward momentum to progress forward. (104,105). As a result, the increase in the propulsive peak with an increase in the breaking peak due to increased required stabilization contributes to an increase in the anterior-posterior component of GRFs.

In the present experiment, although both stance duration of the Right and Left sides decreased with increased Right belt, decreased stance duration was bigger on the right side with speed

(Figure 13). That might cause an increase in the right-left asymmetry of Vertical and Anterior-posterior GRFs.

Since walking conditions were performed consecutively by participants, kinetic adaption might have an effect on Right and Left Asymmetry. Mawase et al. (105) investigated kinetic adaption during locomotion on a split-belt treadmill by examining changes in GRFs. Participants were asked the walk at baseline condition (Left-Right same speed) and adaption (Right belt speed 1ms, Left belt speed 0.5 ms^{-1}). In the early stage of adaption, which is about the first 150 steps, the biggest Left- Right alteration was observed in the first 150 steps at the adaption period. After the early adaption period, Right-Left asymmetry decreased and gradually returned to the baseline condition. However, in our experiment, Since the Right side speed constantly increased, that might impair kinematic adaption. Therefore, as speed increased, increasing Right and Left asymmetry was observed.

In addition, Fatigue can also influence walking asymmetry. Radzak et al. (106) conducted an experiment on health participants to evaluate the asymmetry of kinetic and kinematic variables in both rested and fatigued state running. Participants ran on the treadmill until reaching volitional exhaustion. The research showed that internal knee rotation and knee stiffness become more asymmetrical with fatigue between limbs. Alteration in knee mechanics resulting from fatigue caused a significant increase in Left and right asymmetry. Another research which was examined the effect of Fatigue on Left-Right asymmetry was conducted by Wong et al. (107). They investigated the effect of long-distance walking on variability and inter-limb asymmetry of joint angular velocity. Active elderlies were instructed to walk on the treadmill for a total of 60 min. Gait analyses were conducted over-ground at the baseline (before the treadmill walk), after the first 30 min (30-min), and the second 30 min (60-min) of the walk. The study showed that the stance time of the dominant side was significantly reduced after both 30 and 60 min of walking with Fatigue (107). In our experiment, Fatigue was not measured. However, reduced right stance time with increased right belt speed, as Wong et al. showed, might be another factor that increased right-left asymmetry.

<u>Effect of CPN stimulation on GRFs left-right asymmetry.</u>

In this experiment, CPN stimulation did not change the left-right symmetry of GRFs significantly except the F4, the propulsive peak of the AP GRFs when the right leg was 1.5 times faster than the left leg (R1.5 condition). Although no studies have analyzed what happens to left-right symmetry in terms of GRFs after CPN stimulation, we expected the symmetry to be affected by the CPQ reflex when the walking speed was altered on one side.

The effect of CPN stimulation on GRFs has been worked on in a couple of experiments. Most research has mainly been focused on the effect of FES on GRFs (108,109,110). Kesar et al. (108) compared AP GRFs at walking with and without FES of tibialis anterior muscle conditions in patients with stroke. FES stimulation was applied to dorsiflexor muscles at the swing phase and to plantar flexor muscles at the terminal stance phase by using surface electrodes. They reported that FEST stimulation caused a significant increase in the peaks of AP GRFs. Berenpas et al. (111) used The ActiGait® system, which provides a 4-channel peroneal nerve stimulator. Those 4 electrodes embedded in the cuff stimulate different nerve muscles: Tibialis anterior, peroneus longus/brevis, and toe extensor muscles. AFO with FES increased 10% percent of AP-GRFs peak as compared to just the use of AFO during walking. That increase in GRFs was explained by changes in COM due to the alteration of ankle and knee position when FES was applied (113,114).

Increased plantar flexion foot drop because of atrophic dorsiflexor muscles at the beginning of the stance phase caused COM to shift more anterior in patients. That created an external momentum and caused knee hyperextension. During FES application, the foot was placed on the ground in a dorsiflexed position, with the center of pressure shifted back to the heel. As a result, GRF was directed posteriorly to the knee, allowing for correction of the knee hyperextension (113,114). That might be a reason for the increased breaking peak of the anterior-posterior component of GFRs with FES stimulation. In addition, increasing braking impulse in severe stroke patients has been linked to increased vastus lateral muscle force (114).

In terms of the effect of common peroneal stimulation on GRFs, a few research studies evaluated the effect of peroneal nerve stimulation on GRFs. Sheffler. et al. (110) applied peroneal nerve stimulation on patients with stroke for 12 weeks and evaluated the effect of peroneal stimulation on the anterior - posterior GRFs. There was no significant effect of peroneal stimulation on the peak of A-P GRFs.

Here, CPN stimulation significantly decreased the left-right asymmetry of the propulsive peak of the A-P GRFs at the R1.5 condition. That might be explained by reciprocal inhibition acting unilaterally on R SOL. Common peroneal stimulation might cause reciprocal inhibition in the Sol muscle (115). Decreased CPN facilitation on R SOL EMG activity may lead to decreased R GRFs values. This could be verified by examining the EMG activity of SOL. There was no difference between mean SOL EMG activity between CPN stimulation and non-stimulation steps (data not shown). In addition, decreased CPN facilitation on VL may relativity decrease knee extension, and that might also lead to a unilateral decreased propulsive peak of A-P GRFs. Commissural reflex actions might also underscore the left-right asymmetry observed after CPN stimulation. However, further research should be conducted to explain that result.

We did not separately compare the subgroups (CPQ obtained vs no CPQ obtained. As discussed in the CPQ reflex section, the presence or absence of CPQ reflex depends on several factors, therefore analysing reflex amplitude in these two subgroups would be warranted in future studies with larger sample size.

Limitations

The study included only healthy young adults, which may limit the applicability of the findings to other populations, such as older adults, children, or patients with neurological disorders. Extending the examination of the CPQ reflex in people with unilateral walking deficits and existing left-right asymmetry would be important in order to use the electrical stimulation of the CPN during rehabilitation and locomotor training in the clinics. Also, the study was conducted under controlled laboratory conditions, which may not fully reflect the variability and complexity of real-world situations.

This study only examined the effects of increased right belt speed on CPQ reflex and GRFs. Maybe slowing the speed would have been more effective in altering the GRFs and disclosing an even larger effect of the CPQ reflex. Multiple left-right gait coupling patterns, including slower as well as faster speeds of the stimulated leg, should be used in future studies.

The phrase "Type 1 statistical error" relates to a notion in statistics and hypothesis testing. This error occurs when a null hypothesis that is actually true is rejected. A Type 2 error is a statistical error that occurs in hypothesis testing. It is the error made when a null hypothesis that is actually false is not rejected. Insignificant results in the assessment of the CPQ reflex and EMG activities in different conditions could represent Type1 statistical error.

Chapter VI: Conclusion

This is the first study, to our knowledge, to examine how a spinal reflex is affected by split-belt walking in humans. The CPQ reflex was expected to be present at around the heel strike, and it was also evoked when the belt speed was different under the left and right legs. Although the right-side stance duration was significantly shorter in the conditions when the right belt was one and a half and two times as fast as the left belt (R1.5 and R2 on Fig. 13); the CPQ reflex in the right VL did not show a significant decrease with increasing right belt speed; there was only a trend for CPQ reflex reduction (Figure 10). In addition, this study has found that this reflex is powerful enough to change the asymmetry of the propulsive peak of the A-P GRFs (F4) when the right leg was walking one and half times faster than the left (R1.5). Moreover, the results provide a detailed description that increasing speed unilaterally alters the asymmetry of the vertical and anterior-posterior of GRFs significantly, as those increased with increasing right belt speed.

Tables

Muscle	BLW	R1.25	R1.5	R2	$\chi 2$	p
RTA(Mdn)	848	1116	1276	784	6.25	.10
RVL(Mdn)	15	19	13	15	1.43	.69
RSOL(mean)	334.422	228.286 ±	169 ±44.50	83.429 ±31.350	5.65	>0.05
RHAMS(Mdn)	29	19.5	14	9	1.54	.67
LVL(Mdn)	7	4	5	5	1.22	.74
LHAMS(Mdn)	7	3	2	3	1.44	.69
LTA(Mdn)	3	6	1	3	1.71	.63
LSOL(Mdn)	1	0	7	8	1.56	.90

Table 1. Summary of the changes in rectified EMG activity in a 200 ms window from CPN stimulation. Percent median changes in EMG amplitude in all tested muscles (listed in the first column) obtained in the different walking conditions: both treadmill with a walking speed of 1 ms $^{-1}$, BLW; right belt speed 1.25 ms $^{-1}$, R1.25; right belt 1.5 ms $^{-1}$, R1.5; right belt speed 2 ms $^{-1}$, R2). Changes in the EMG amplitude (measured as the area under the curve) were calculated by subtracting the value obtained in steps with SPN stimulation from those obtained in control steps (no CPN stimulation) and expressing these differences as a percent of values in the steps without CPN stimulation (% non-stim). Statistical significance between the results in the different conditions was made by using Friedman's tests with the chi-square and except for RSOL) and p-values reported in the last two columns, respectively. A one-way repeated measures ANOVA was conducted to determine whether there was a statistically significant difference in Right Sol EMG activity in stimulation condition (nonstim%) in the different walking conditions. There were no outliers in the data, as assessed by inspection of a boxplot. Stim Right SOL EMG activity (nonstim%) was normally distributed, as assessed by Shapiro-Wilk's test ($p > .05$).Mauchly's test of sphericity indicated that the assumption of sphericity had been violated, $\chi^2(5) = 16.47$, $p = 0.01$ .Epsilon (ε) was 0.64, as calculated according to Greenhouse & Geisser (1959), and was used to correct the one-way repeated measures ANOVA. Different walking conditions did not elicited statistically significant changes in stim R sol EMG stim(%nonstim), over different conditions(1.685, 10.112) = 5.65, $p < .005$

	P VALUE	R1.25 (MEAN OR MDN)	R1.5 (MEAN OR MDN)	R2(MEAN OR MDN)	BLW-R1.25,R1.5,R2(p-VALUE)	R1.25-R1.5(p value)	R1.25-R2(p-value)	R1.5-R2(p-value)
F1	P>0.05	12%	7.50%	16%	NS			
F2	P>0.05	0.182±7%	2.27±9%	4.9±14%	NS			
F3	P<0.05	20.63±2%	38.81±4%	75.81±10%	0.001(BLW-R1.25);0.001(BLW-R1.5).0.001 (BLW-R2)	0.01	0.001	0.001
F4	P<0.05	19.27±1%	41.27±2%	42.54±9%	0.001(BLW-R1.25);0.001(BLW-R1.5);0.01(BLW-R2)	0.001	NS	NS
F5	P<0.05	0%	2.5%	12%	0.04(BLW-R2)	NS	0.1	NS
F6	P<0.05	2%	2%	10%	0.001(BLW-R2)	NS	0.01	NS
F7	P<0.05	-5%	-13%	-22%	0.001(BLW-R2);0.001(BLW-R1.5)	NS	0.001	NS

Table 2. Summary of the changes in Right side GRFs with increased speed under Right side**.** Percent median/mean changes in Medio-Lateral(F1/F2), Anterior-Posterior(F3-F4), and Vertical Component of GRFs obtained in different walking conditions: both treadmill with a walking speed of 1 ms $^{-1}$, BLW; right belt speed 1.25 ms $^{-1}$, R1.25; right belt 1.5 ms $^{-1}$, R1.5; right belt speed 2 ms $^{-1}$, R2). Changes in the GRFs amplitude in R1.25, R1.5, and R2 conditions were calculated by subtracting the GRFs values obtained in BLW, and these differences were expressed as a percentage. Statistical significance between the results in different conditions was tested by the One-way ANOVA test and Friedman's test and reported with P values for each condition.

		BLW	R1.25	R1.5	R2	F	P	PairwiseF	Pairwisep
F1	Pairwise	35%	29%	48%	48%	0.54	p>0.05.	1 .65	p>0.05.
F2	Pairwise	27%	36%	44%	41%	2.12	p>0.05	0,88	p>0.05
F3	Pairwise	19%	14%	17%	3577%	6.05	p=0.04(R1.5-R2)	1 .90	p>0.05
F4	speed	7%	22%	43%	43%	11.10	p=0.001(BLW-R1.25) p=0.001(BLW-R1.5) p=0.01(BLW-R2) p=0.001(R1.25-R1.5)	22 .10	p=0.01
	Stim/non stim	Stim:6% NonStim:7%	Stim:24 NonStim:23%	Stim:13 NonStim:43%	Stim:43%nonstim:42%	4.99	p=.01 (Stim-Nonstim) in R1.5	22 .10	p=0.01
F5	Pairwise	7%	13%	14%	17%	0.95,	p=0.03(BLW-R1.25) p=0.1(BLW-R1.5)	0.95	p>0.05
F6	Pairwise	3%	3%	4%	13%	27.34	p=.0.001(BLW-R2) p=0.001(R1.25-R2) p=.001(R1.5-R2)	0.20	p>0.05
F7	Pairwise	4%	6%	11%	19%	30.60	p=0.03(BLW-R1.25);0.001(BLW-R1.5);0.001(BLW-R2);0.01(R1.25-R1.5);0.001(R1.25-R2);0.04(R1.5-R2)	3 .68	p>0.05

Table 3. Summary of changes Left-Right asymmetry of GRFs with increased right belt speed and CPN stimulation**.** Symmetry value value was demonstrated for Medio-Lateral (F1. F2), Anterior-Posterior(F3-F4), and Vertical Components (F5, F6 and F7) of GRFs. Statistical significance between the results in different conditions was tested by A two-way repeated measures ANOVA test.

	STIM				NONSTIM			
	BLW	R1.25	R1.5	R2	BLW	R1.25	R1.5	R2
F1	34%	32%	51%	61%	48%	31%	48%	56%
F2	33%	35%	42%	37%	19%	34%	46%	46%
F3	19%	14%	14%	37%	16%	14%	21%	34%
F4	6%	24%	14%	42%	7%	23%	44%	43%
F5	7%	12%	16%	17%	5%	12%	14%	17%
F6	2%	3%	4%	12%	4%	4%	5%	15%
F7	5%	8%	11%	19%	2%	5%	12%	19%

Table 4. Summary of the changes in GRFs with increased speed on the Right side and CPN stimulation. The median value of the Symmetric index is shown for each GRF.

Figures

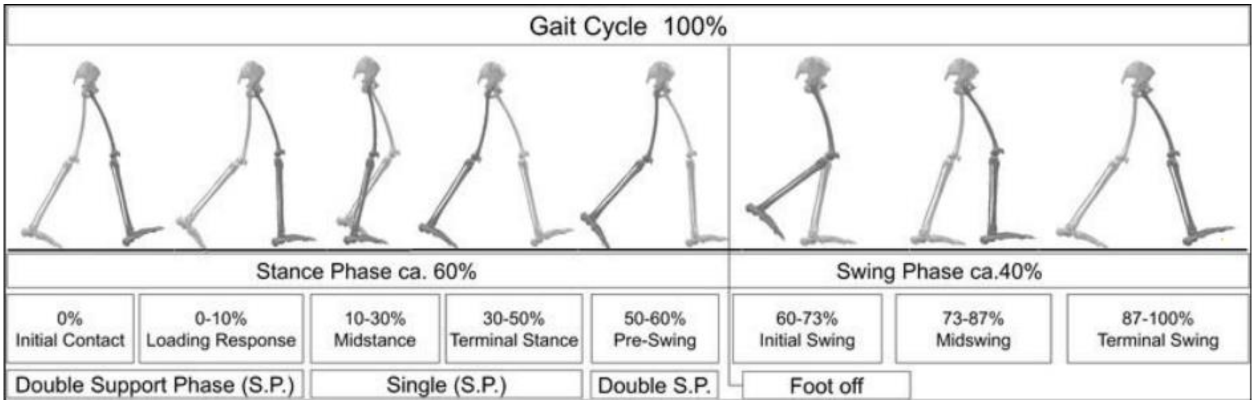

Gait Cycle 100%
Stance Phase ca. 60%
Swing Phase ca.40%
0%
Initial Contact
0-10%
Loading Response
10-30%
Midstance
30-50%
Terminal Stance
50-60%
Pre-Swing
60-73%
Initial Swing
73-87%
Midswing
87-100%
Terminal Swing
Double Support Phase (S.P.)
Single (S.P.)
Double S.P.
Foot off

Figure1: Gait Phases

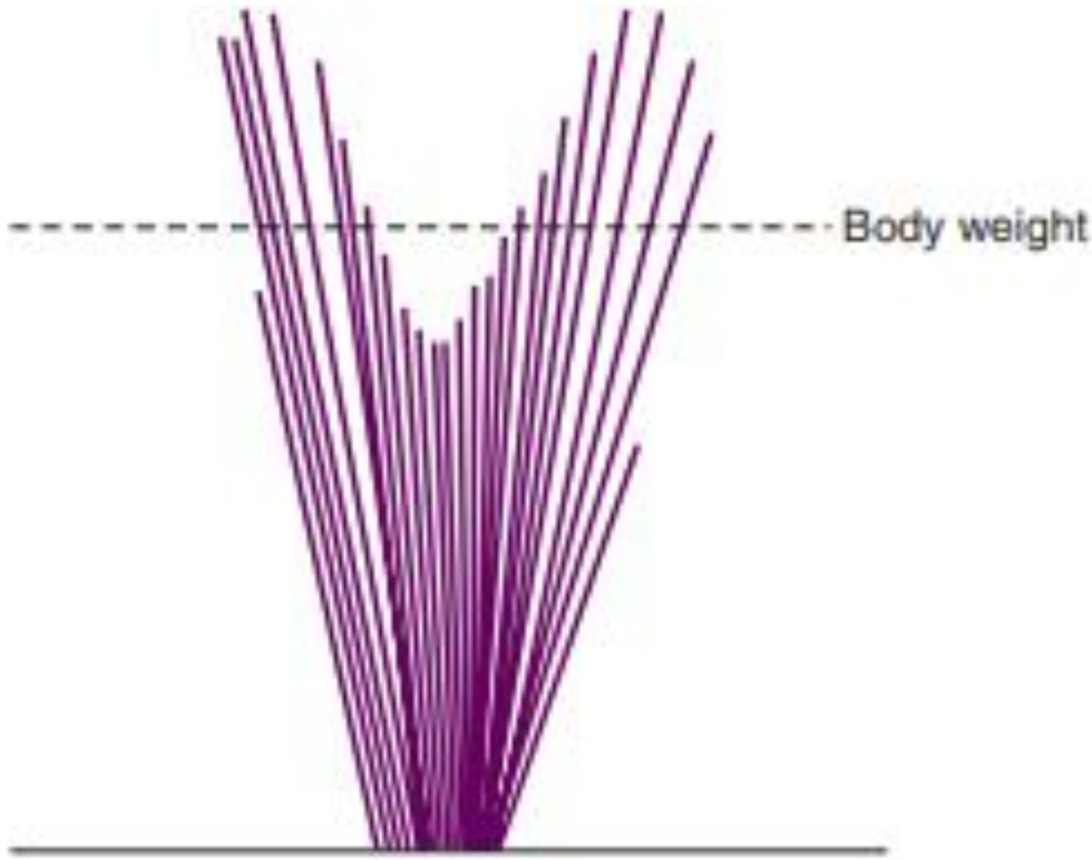

Body weight

Figure 2: During loading response/weight acceptance and terminal stance/push-off, the magnitude of ground reaction force exceeds body weight.

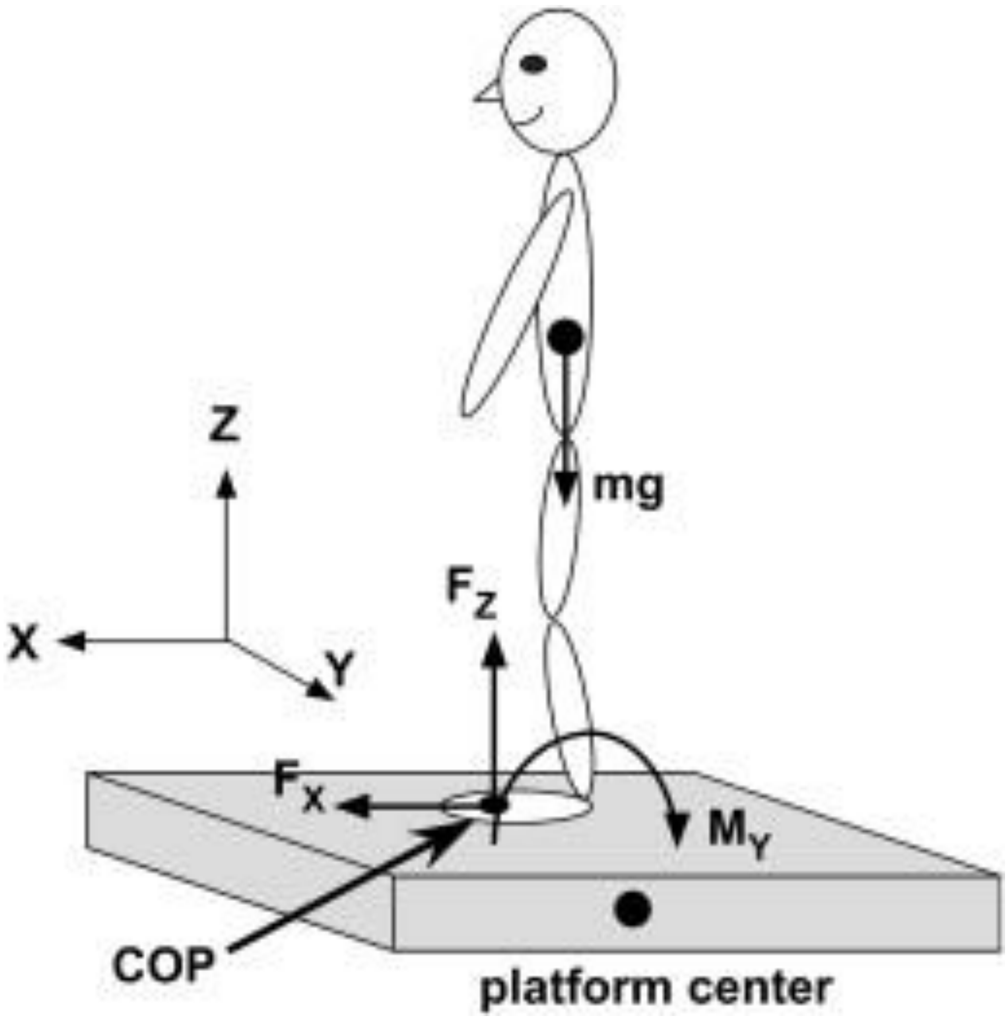

Z
mg
F_Z
X
Y
F_X
M_Y
COP
platform center

Figure 3. Kistler Force Plate Coordinate System. This figure represents the Kistler coordinate system, with the force labeled ‘F’ representing the stepping force vector. The force plate translates this into its vertical (Fz), anterior–posterior (Fy), and medial–lateral (Fx) components using four different sensors.

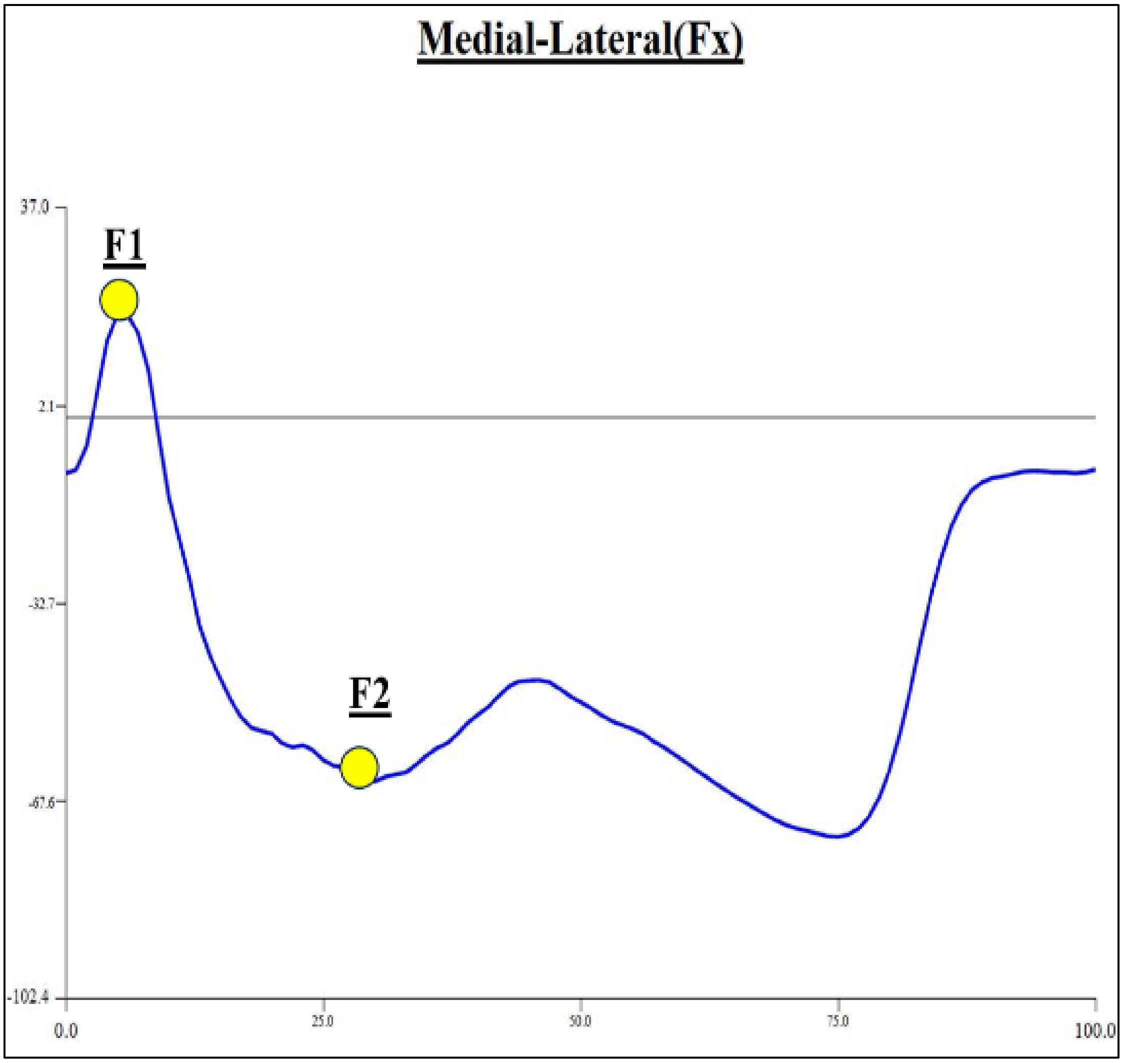

Medial-Lateral(Fx)
37.0
2.1
-32.7
-67.6
-102.4
F1
F2
0.0
25.0
50.0
75.0
100.0

Figure 4. Footstep GRF Medial–Lateral Force. This figure demonstrates the GRF medial–lateral force for a footstep.

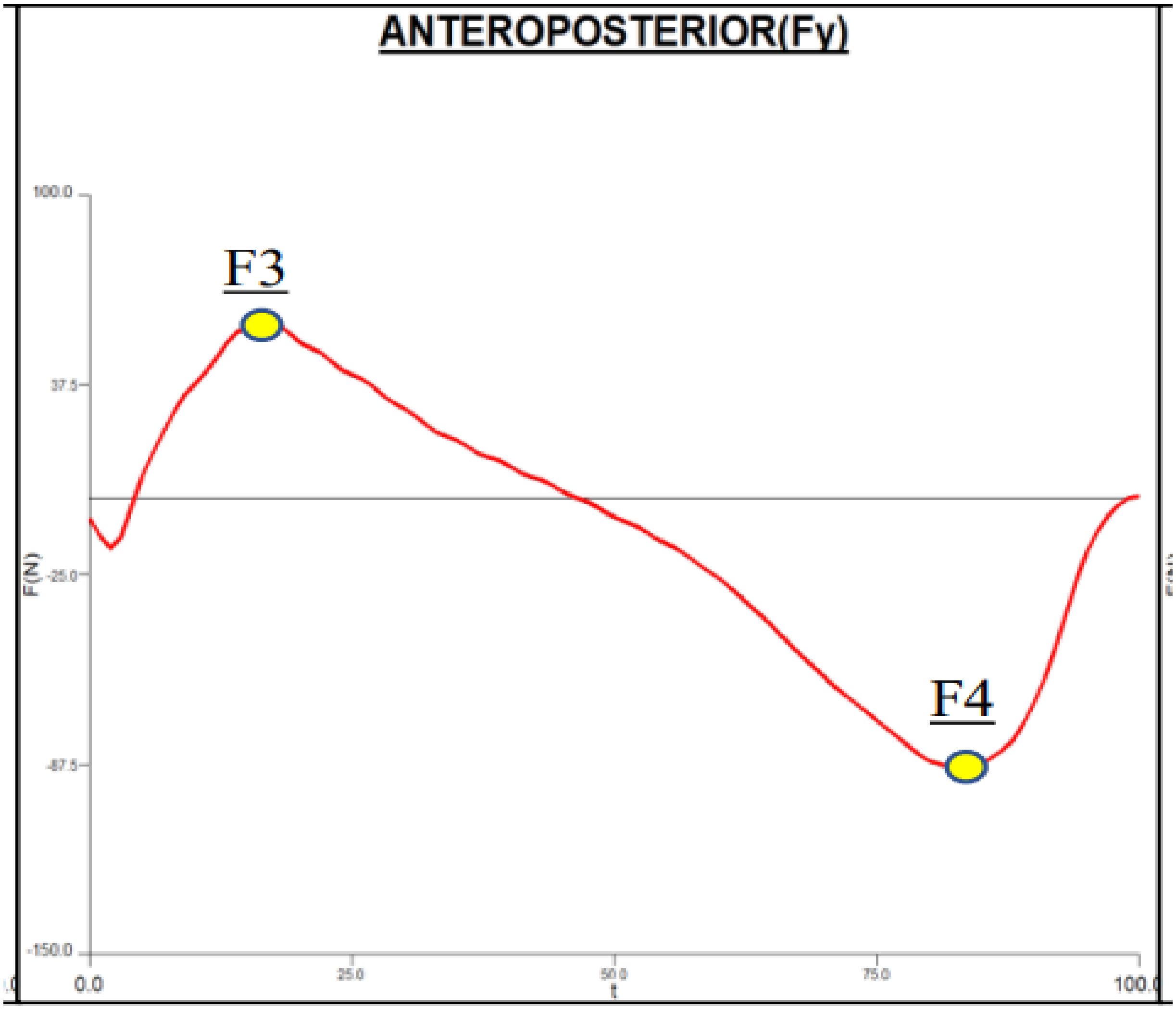

ANTEROPOSTERIOR(Fy)
100.0
37.5
-25.0
-87.5
-150.0
F(N)
F3
F4
0.0
25.0
50.0
75.0
100.0
t

Figure 5. Footstep GRF Posterior–Anterior Force. This figure demonstrates the GRF posterior–anterior force for a footstep.

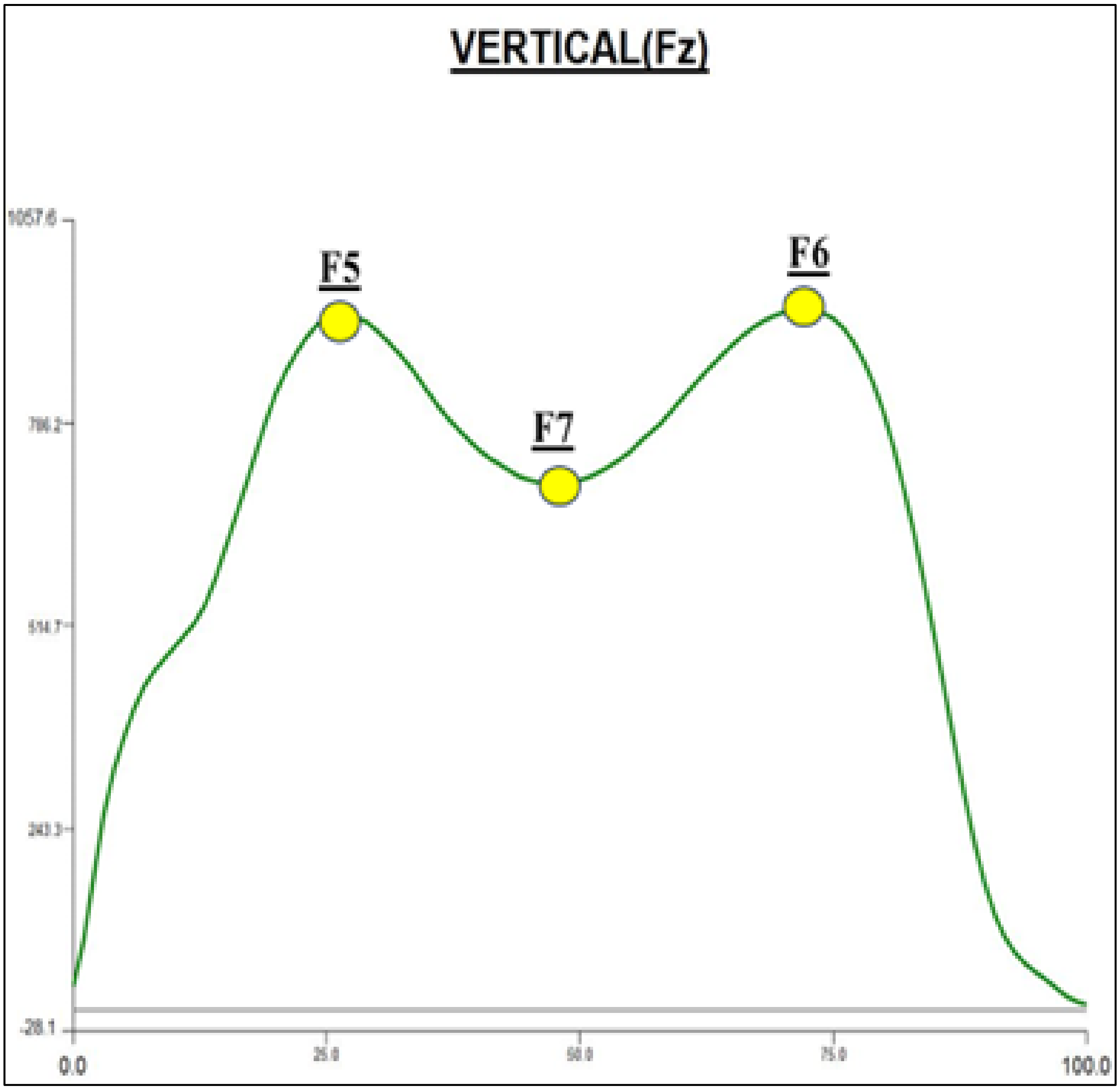
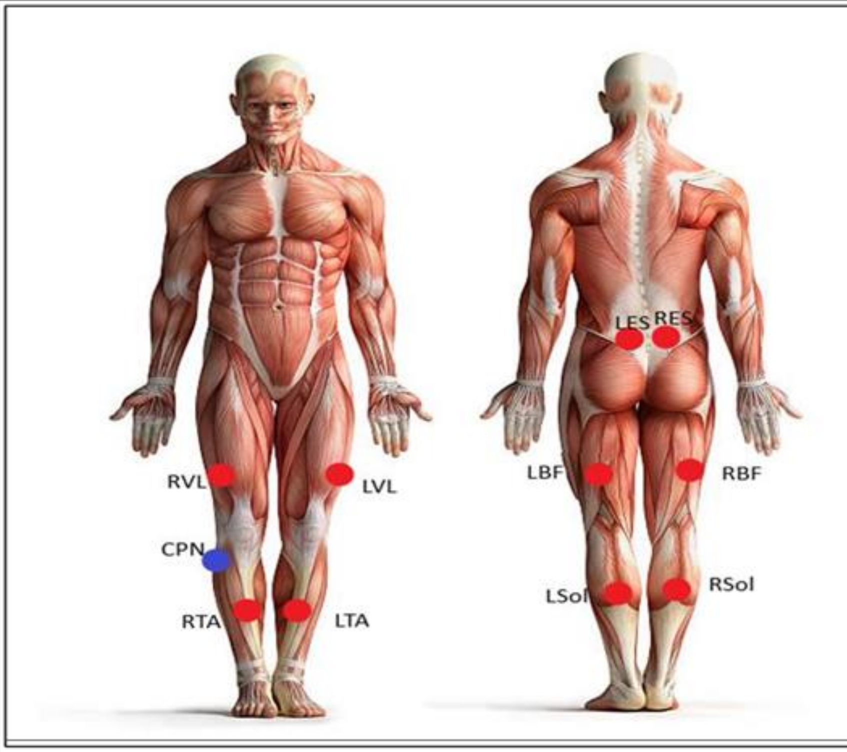

VERTICAL(Fz)
F5
F6
F7
1057.6
-28.1
0.0
25.0
50.0
75.0
100.0

Figure 6. Footstep GRF Vertical Force. This figure demonstrates the GRF vertical force for a footstep.



Surface EMG Recording

1)Right Tibialis Anterior(RTA)

2)Left Tibialis Anterior(LTA)

3)Right Soleus(RSOL)

4)Left Soleus(LSOL)

5)Right Vastus Lateralis(RVL)

6)Left Vastus Lateralis(LVL)

7)Right Biceps Femoris(RBF)

8)Left Biceps Femoris(LBF)

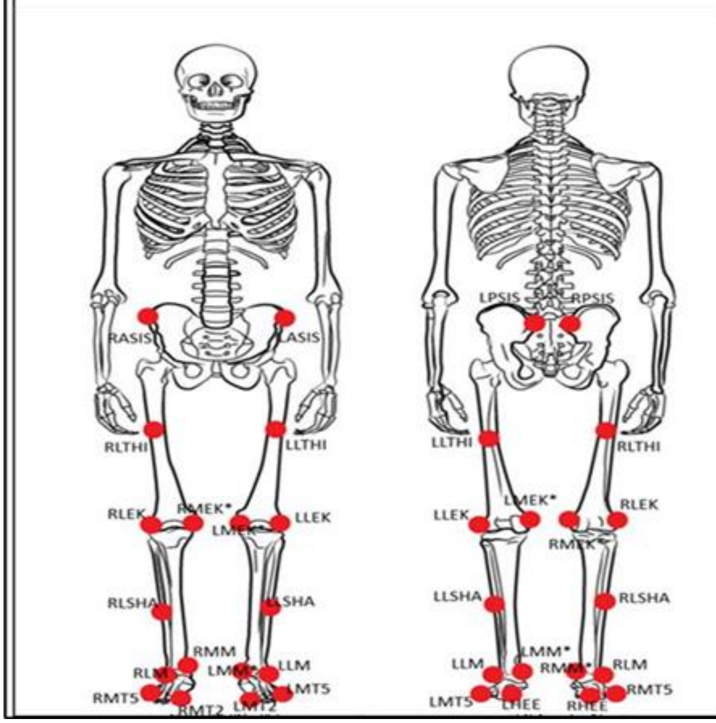
9)Left Erector Spinae(LES)

10)Right Erector Spinae(RES)

Stimulation

Common peroneal nerve(CPN)

Stimulation.



Markers Position

1)Right 2nd meta tarsal(RMT2)
2)Left 2nd meta tarsal(LMT2)
3)Right 5th meta tarsal(RMT5)
4)Left 5th meta tarsal(LMT5)
5)Right lateral malleolus of the ankle(RLM)
6)Left lateral malleolus of the ankle(LLM*)
7)Right medial malleolus of the ankle(RMM)
8)Left medial malleolus of the ankle(LMM)
9)Right shank,lateral(RLSHA)
10)Left shank,lateral(LLSHA)
11)Right lateral epicondyle of the knee(RLEK)
12)Right medial epicondyle of the knee(RMEK*)
13)Left lateral epicondyle of the knee(LLEK)
14)Left medial epicondyle of the knee(LMEK*)
15)Right thigh,lateral(RLTHI)
16)Left thigh,lateral(LLTHI)
17) Right anterior superior iliac spine(RASIS)
18)Left anterior superior iliac spine(LASIS)
19)Right posterior superior iliac spine(RPSIS)
20)Left posterior superior iliac spine(LPSIS)

Figure 7. Schematic illustration of the EMG electrodes, CPN stimulation, and markers set up**.** The surface EMG electrodes are placed on Tibialis Anterior(TA), Soleus(Sol), Biceps Femoris(BF), Vastus Lateralis (VL), Erector Spinae (ES) muscles on both right and left sides.Retroreflective markers are placed on specific anatomical landmarks: Right 2nd meta tarsal(RMT2),Left 2nd meta tarsal(LMT2),Right 5th meta tarsal(RMT5),Left 5th meta tarsal(LMT5),Right lateral malleolus of the ankle(RLM),Left lateral malleolus of the ankle(LLM*),Right medial malleolus of the ankle(RMM),Left medial malleolus of the ankle(LMM),Right shank,lateral(RLSHA),Left shank,lateral(LLSHA),Right lateral epicondyle of the knee(RLEK),Right medial epicondyle of the knee(RMEK*),Left lateral epicondyle of the knee(LLEK),Left medial epicondyle of the knee(LMEK*),Right thigh,lateral(RLTHI),Left thigh,lateral(LLTHI),Right anterior superior iliac spine(RASIS),Left anterior superior iliac spine(LASIS),Right posterior superior iliac spine(RPSIS) and Left posterior superior iliac spine(LPSIS).

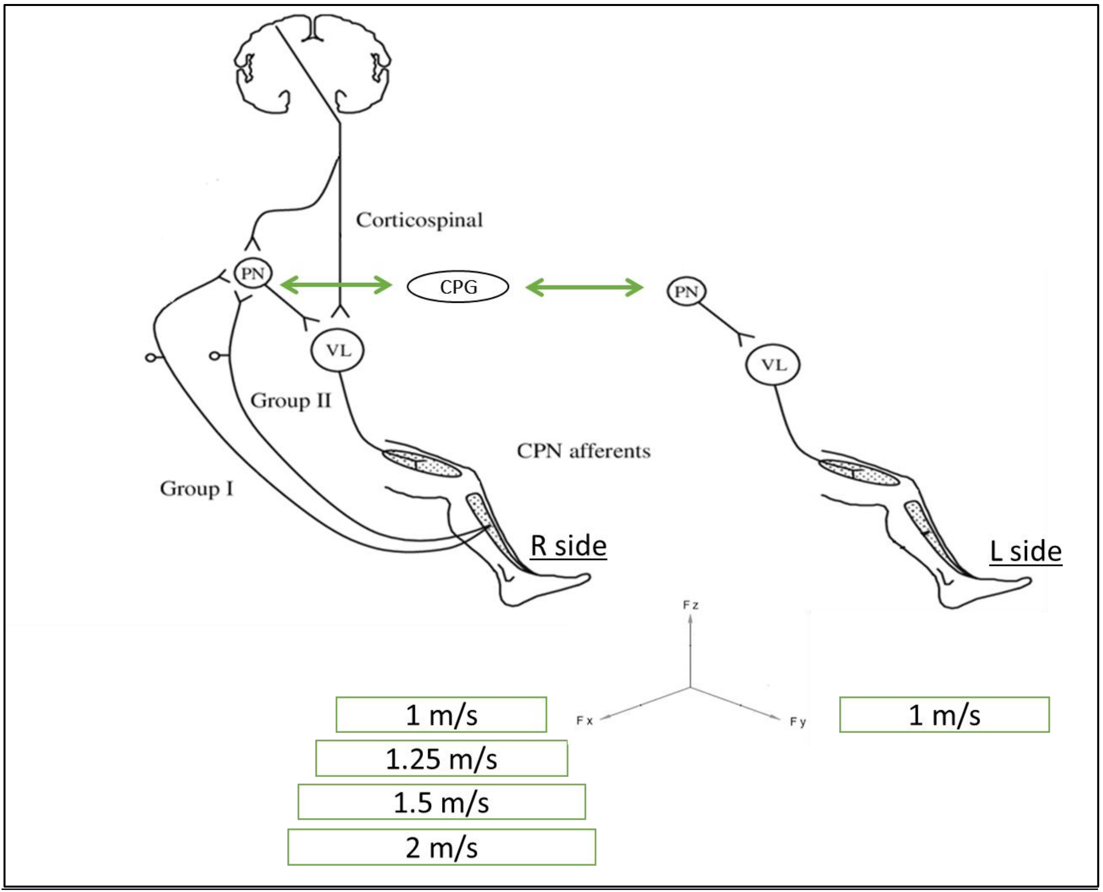
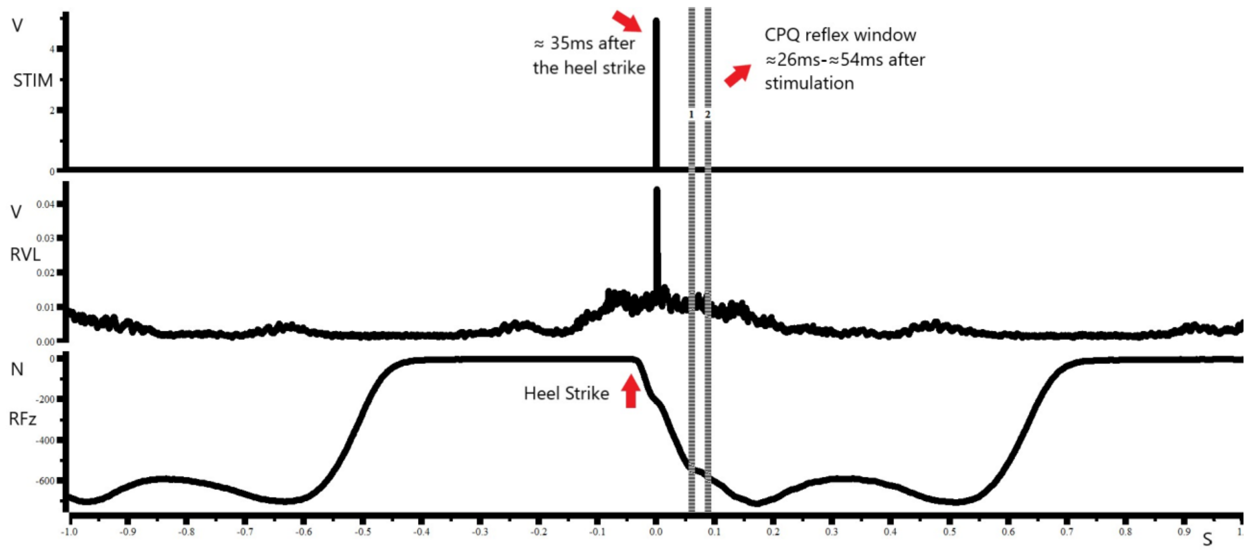

Corticospinal
PN
CPG
PN
VL
VL
Group II
CPN afferents
Group I
R side
L side
Fz
Fx
Fy
1 m/s
1.25 m/s
1.5 m/s
2 m/s
1 m/s

Figure 8. Illustration of CPQ reflex and changes right and left belt speeds in different walking conditions.



V
STIM
≈ 35ms after
the heel strike
CPQ reflex window
≈26ms-≈54ms after
stimulation
V
RVL
N
RFz
Heel Strike
S

Figure 9. Illustration of stimulation point, CPQ reflex window and right side Fz value (Force value goes downward) in one participant.Common peroneal nerve (CPN) stimulation (top trace) during both leg walking condition, 1 ms $^{-1}$ Rectified Right VL EMG (middle trace) and Right side force (Fz) (bottom trace).CPN stimulation was applied at 35 ms latency after the right heel strike.Analaysis of CPQ reflex was performed in the window which is indicated by the vertical lines (1:26ms-2:54ms after the CPN stimulus). This CPQ reflex window was adjusted for each participant based on the CPQ reflex amplitude.

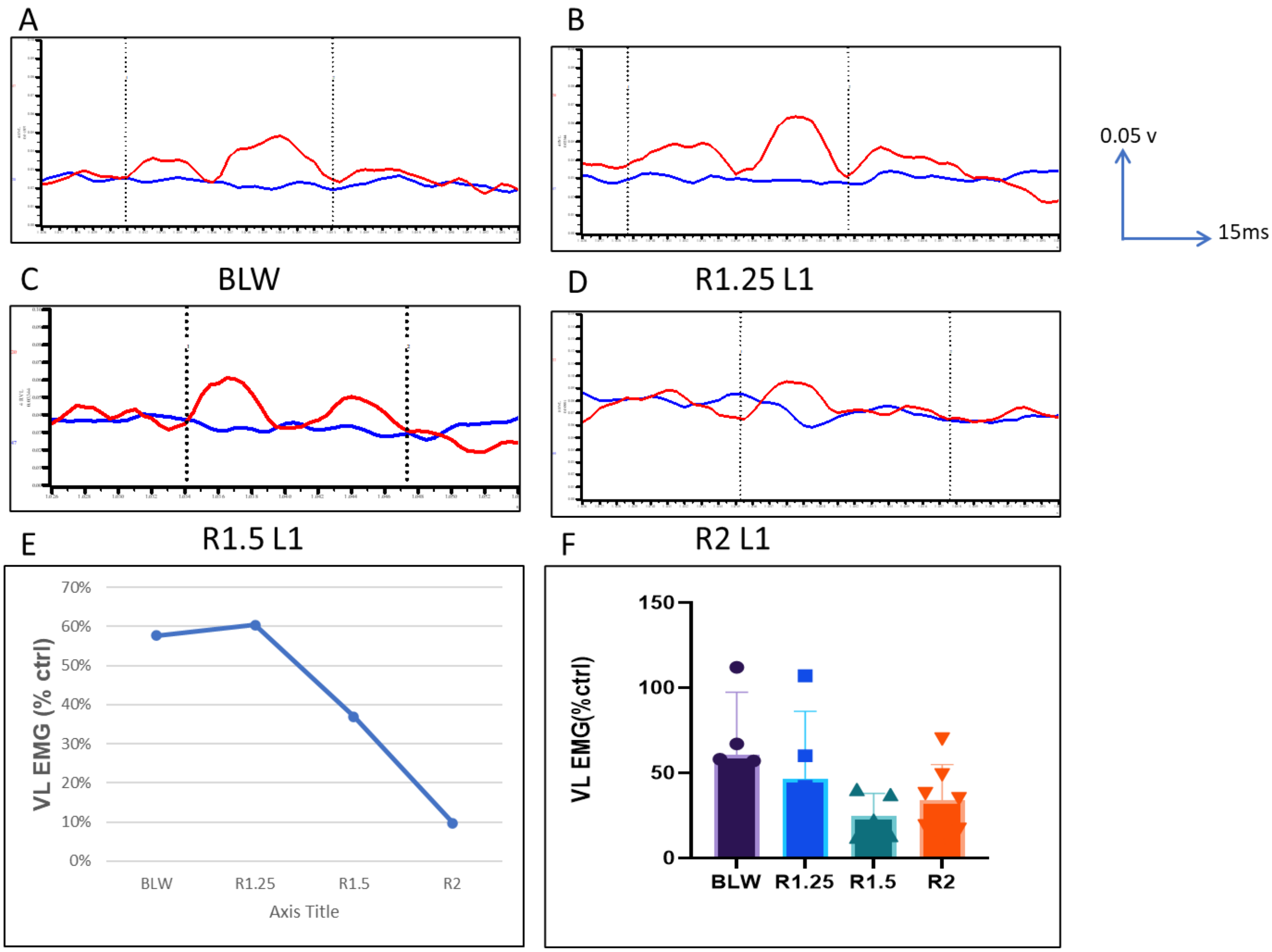
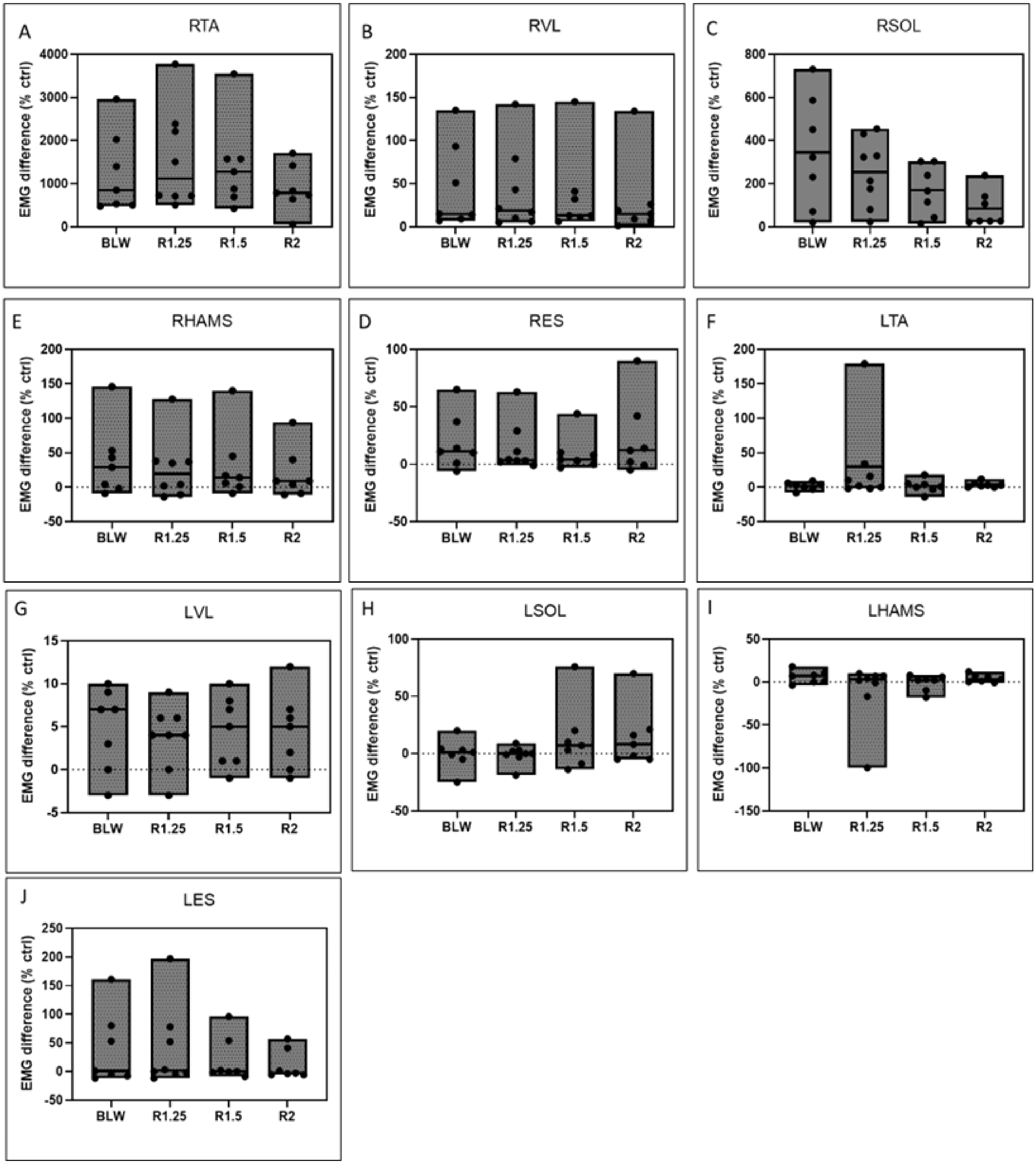

A
B
0.05 v
15ms
C
BLW
D
R1.25 L1
E
R1.5 L1
F
R2 L1
VL EMG (% ctrl)
70%
60%
50%
40%
30%
20%
10%
0%
BLW
R1.25
R1.5
R2
Axis Title
VL EMG(%ctrl)
150
100
50
0
BLW
R1.25
R1.5
R2

Figure 10. CPN-induced facilitation in Q EMG activity reduced during different walking conditions. A-D**.** Averaged rectified right (R) vastus lateralis (VL) EMG activity in a single subject walking in different conditions on a split-belt (with left leg speed always kept at 1 ms $^{-1}$). These conditions were both legs walking at the same speed, BLW (A); right leg walking at 1.25 ms $^{-1}$, R1.25 (B); right leg walking at 1.5 ms $^{-1}$, R1.5 (C); right leg walking at 2 ms $^{-1}$, R2 (D). The averages show steps without common peroneal nerve (CPN) stimulation (blue lines, NONSTIM, n=90-120 steps) and step in which CPN stimulation (red lines, STIM, n=25-35 steps). CPN stimulation was applied near the R heel strike, and the onset of the VL EMG facilitation (also known as the CPQ reflex) has been indicated by the dotted lines to the left, with the dotted lines to the right indicating the end of the VL facilitation (30-42 ms in BLW, 29-41 ms in R1.25; 34-46 ms in R1.5; 35-47 ms in R2 with respect to the stimulus onset). The dotted area indicates the period when the CPQ reflex excitability is enhanced during walking. E. The facilitation of the VL EMG during steps with CPN stimulation (i.e., the CPQ reflex size) is expressed as the percent of VL EMG activity during non-stimulated steps as a function of the walking conditions in a single subject (same as in A-D). Note the reduction in the CPQ reflex size during the different conditions. F. Averaged data (n=5 participants) showing the CPQ reflex size expressed as the percent of VL EMG activity during non-stimulated steps



A
RTA
B
RVL
C
RSOL
E
RHAMS
D
RES
F
LTA
G
LVL
H
LSOL
I
LHAMS
J
LES
EMG difference (% ctrl)
BLW
R1.25
R1.5
R2

Figure 11. Effects of CPN stimulation on different muscles in different walking conditions. Differences in the EMGs evoked by CPN stimulation during split-belt walking in the same walking conditions as described in Fig. 1, BLW, R1.25, R 1.5, and R2, including Tibialis Anterior (TA). Vastus Lateralis (VL), Soleus (SOL), Hamstrings (HAMS) Erector Spinae (ES) were recorded on the left (L) and the right (R) sides. Mean EMG area value during non-stimulated steps subtracted from mean EMG area during stimulated steps expressed as % of mean EMG area during non-stimulated steps. Each dot represents an individual participant (n=5), and the black lines inside the bar graphs indicate the median value (except for Fig C-black line represents the mean value of RSOL).

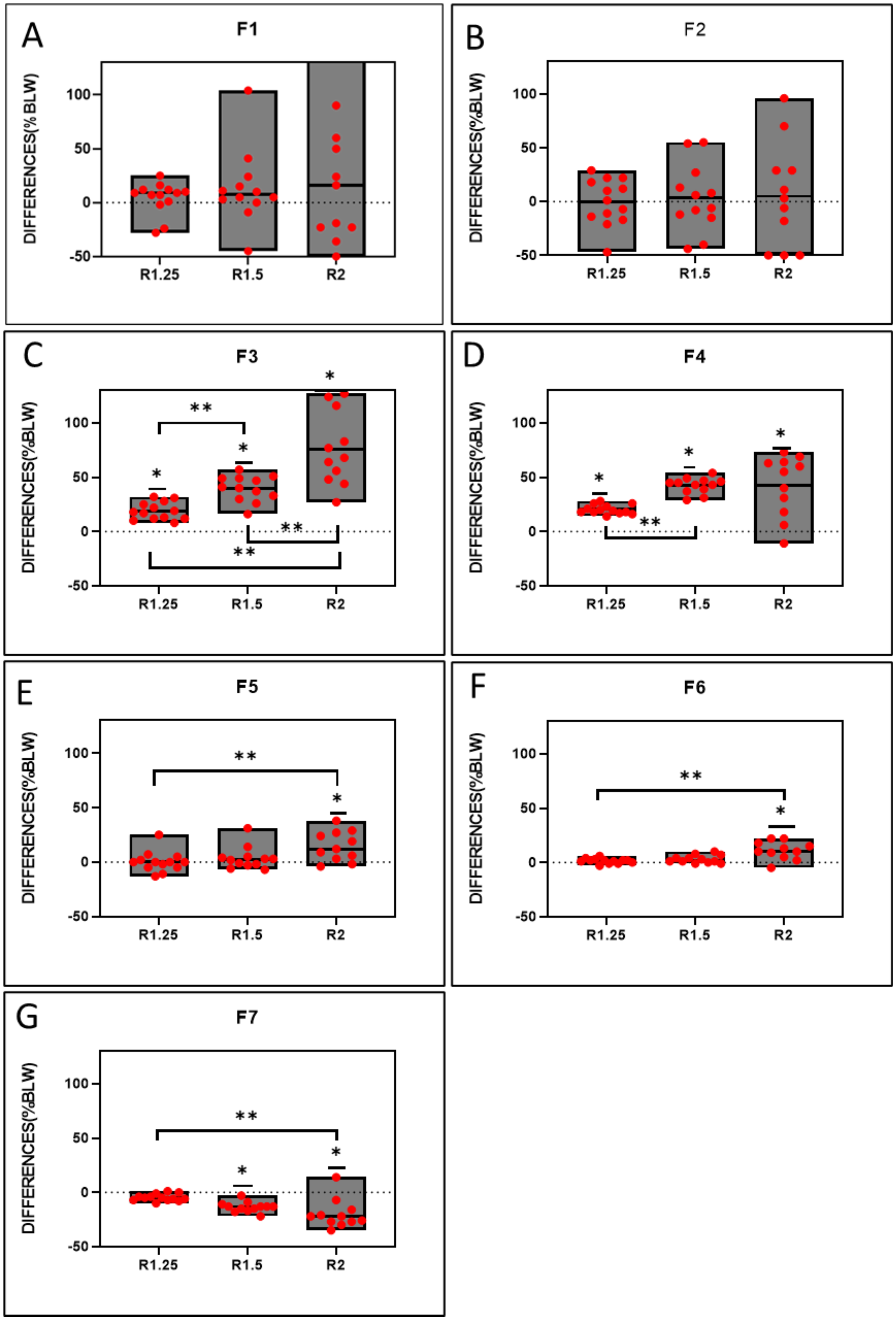
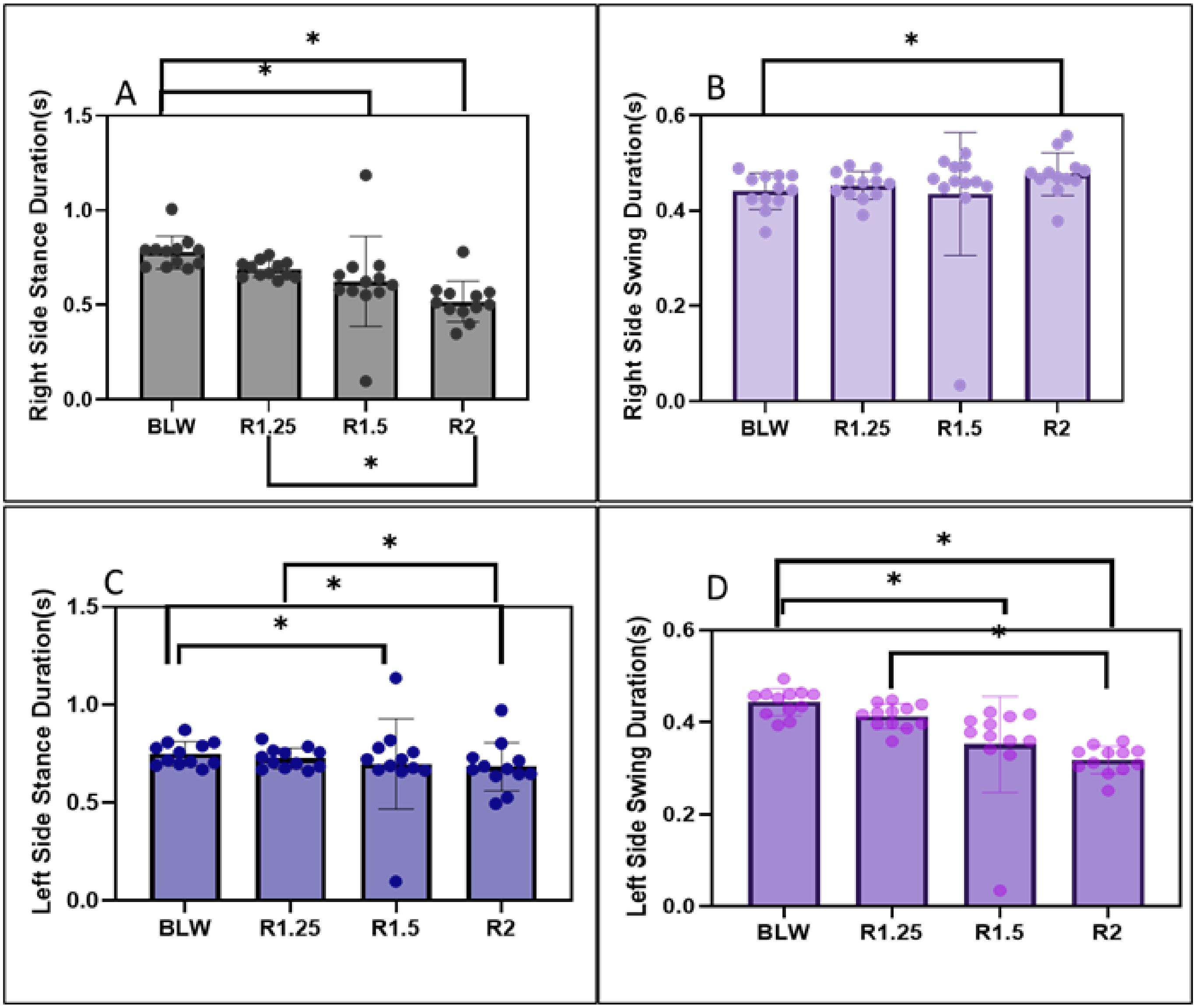

A
F1
B
F2
C
F3
D
F4
E
F5
F
F6
G
F7
DIFFERENCES(% BLW)
DIFFERENCES(%BLW)
100
50
0
-50
R1.25
R1.5
R2
*
**

Figure 12. Differences in ground reaction forces (GRFs) during split-belt walking. Right side ground reaction force values, medio-lateral F1 (A), F2 (B); anterior-posterior F3 (C), F4 (D) and vertical F5 (E), F6 (F) and F7 (G) obtained in different walking conditions (R1.25, R1.5, and R2) were subtracted from GRFs obtained in BLW condition (during the same session). The differences were normalized to the GRFs obtained during BLW and expressed as % BLW. Each red dot indicates the normalized changes in force values of individual subjects (n=12). Black lines indicate the median changes in forces (as % BLW) in A, E, F, and G, and it indicates the mean value in B, C, F, and E figures. Stars indicate significant differences, and single star (*) indicates the difference between the respective condition and BLW; double star (**) indicates differences between the conditions as shown by the black line in each panel. All values were measured in control steps, i.e. those with no CPN stimulation in all of the walking conditions:



A
Right Side Stance Duration(s)
0.0
0.5
1.0
1.5
BLW
R1.25
R1.5
R2
*
*
*
B
Right Side Swing Duration(s)
0.0
0.2
0.4
0.6
BLW
R1.25
R1.5
R2
*
C
Left Side Stance Duration(s)
0.0
0.5
1.0
1.5
BLW
R1.25
R1.5
R2
*
*
*
D
Left Side Swing Duration(s)
0.0
0.2
0.4
0.6
BLW
R1.25
R1.5
R2
*
*
*

Figure 13. Stance and swing duration on the left and right sides during the different walking conditions. Each red dot indicates the swing or stance duration of each subject(n=12). Black lines in each bar graph indicate the mean value SI index of forces. *: Significant difference among walking conditions.

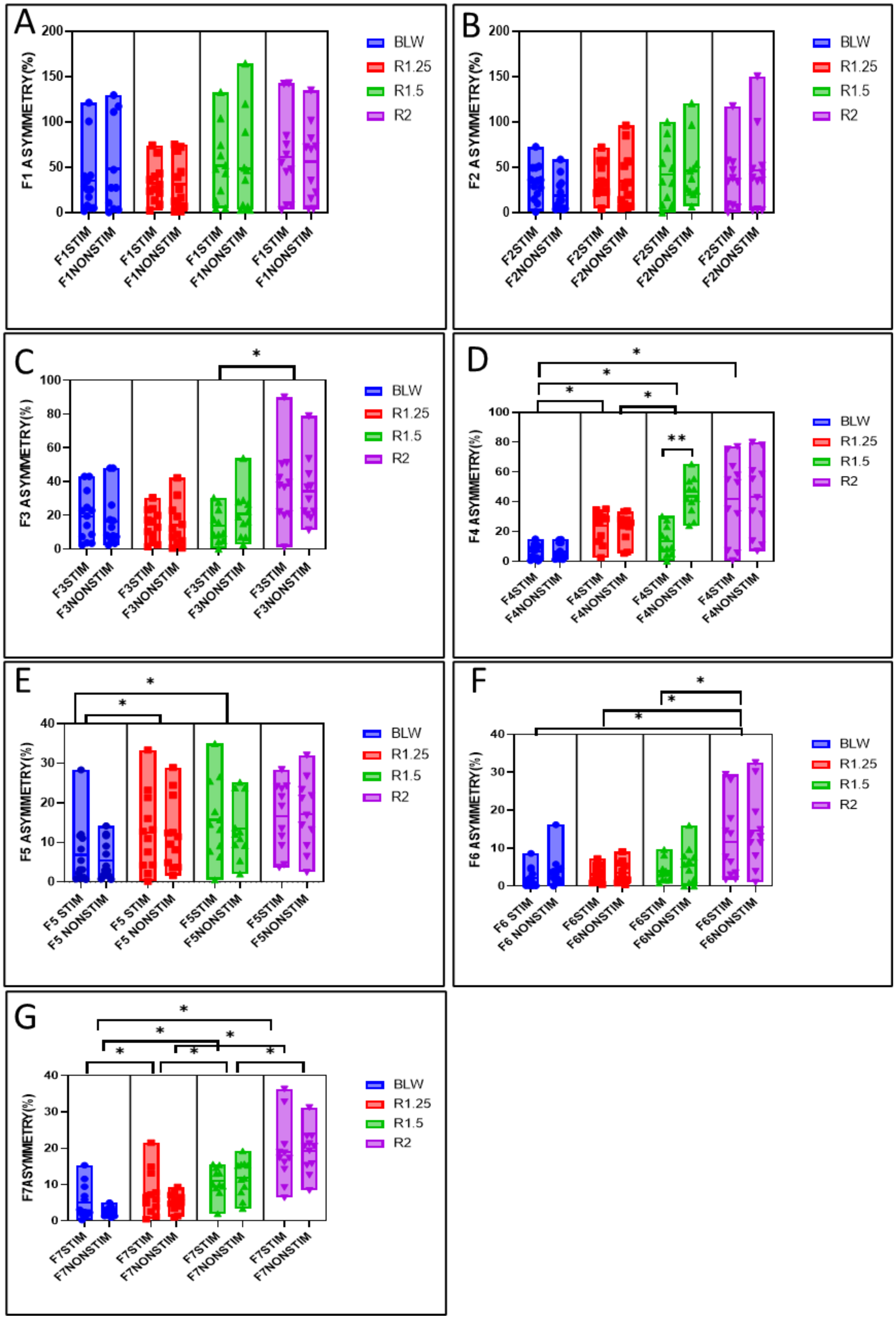

A
F1 ASYMMETRY(%)
F1STIM
F1NONSTIM
B
F2 ASYMMETRY(%)
F2STIM
F2NONSTIM
C
F3 ASYMMETRY(%)
F3STIM
F3NONSTIM
D
F4 ASYMMETRY(%)
F4STIM
F4NONSTIM
E
F5 ASYMMETRY(%)
F5 STIM
F5 NONSTIM
F5STIM
F5NONSTIM
F
F6 ASYMMETRY(%)
F6 STIM
F6 NONSTIM
F6STIM
F6NONSTIM
G
F7ASYMMETRY(%)
F7STIM
F7NONSTIM
BLW
R1.25
R1.5
R2

Figure 14. Effect of CPN stimulation and split-belt walking on the left/right asymmetry index calculated for all ground reaction forces**.** Changes in the Asymmetry value of GRFs showed in stimulation/non stimulation conditions at different walking conditions. Left/Right Asymmetry was calculated by using the Symmetry index Each dot indicates SI index value of each participant (n=12). Black lines in each bar graph indicate the mean value SI index of forces. *: Significant difference among walking conditions**: Significant difference in stim and non-stim condition.

Chapter VII: References

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