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Do humans drive spinal cord with limb velocity signal?

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Thesis submitted to the School of Medicine, Division of Exercise Physiology at West Virginia
University in partial fulfillment of the requirements for the degree of Master of Science in
Exercise Physiology

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2015

Keywords: locomotion, motor control, velocity, asymmetric locomotion, proprioception,
kinesthesia, control theory, control signal

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ABSTRACT

Do humans drive spinal cord with limb velocity signal?

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The ability to move in the environment is crucial to the survival of all animals. Neural pathways that control locomotion can be described as a hierarchy, with multiple levels of control, and those ultimately converge on spinal pattern generators. Neural pathways controlling locomotion are hierarchical, highly integrated, and well characterized anatomically, but functional explanations are lacking. Previous computational modeling of the CPG has proposed that the essential signal driving these spinal networks are expressed in the modality of desired velocity. To date, no published research has empirically tested velocity as being the control signal of locomotion. The purpose of this study was to evaluate human ability to discriminate inter-limb velocity on a split-belt treadmill. If the modality of locomotor control signal is indeed velocity then, according to the classical control theory, limb velocity should also be accurately sensed. We tested this hypothesis by probing human ability to detect minute changes in the velocity of each leg. Healthy volunteers with no previous history of neurological conditions or serious musculoskeletal damage to the lower extremities were recruited to walk on a split-belt treadmill with separately controlled belt speeds. Subjects were exposed to randomized asymmetric speeds of left and right legs for approximately 3 steps. A high-pitch cue instructed subjects to report the fastest leg. In addition, we tested velocity discrimination skills in two other conditions when subjects were either supported or loaded by 10% of their body weight. The perception threshold defined as the velocity detected with better than chance probability (above 50%) was $1.02 \pm 0.43\%$ m/s, with no significant differences between body weight conditions. Variance of step cycle was found to significantly impact probability detection at the differential speed of 0.01 m/s, which is equivalent to the 1% detection level. The accurate velocity discrimination ability supports the idea that the velocity signal is represented within the locomotor control pathways. We propose that errors in this velocity signal are ultimately used to tune heading direction. Solving for the signal controlling locomotion has positive clinical implications, as it could be used in therapies such as locomotor rehabilitation following neurological injury.

ABBREVIATIONS

CPG- Central Pattern Generator

CNS- Central Nervous System

CST- Corticospinal tract

DSCT- Dorsal Spinocerebellar tract

EEG- Electroencephalogram

EMG-Electromyography

JND- Just Noticeable Difference

MLR- Mesencephalic Locomotor Region

SCI- Spinal Cord Injury

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CHAPTER 1. INTRODUCTION

1.1. Introduction & Purpose

Vertebrates have the innate ability to precisely control locomotion to meet ever-changing demands of the environment. In general, control of locomotion is achieved with feed-forward and feedback signals converging on rhythmogenic spinal networks responsible for the regulation of timing and magnitude of muscle activity. These signals specifically alter flexor and extensor muscle activity to produce appropriate changes in phase modulation (i.e. swing and stance time). Alterations of phase modulation allow variables such as walking speed and heading of locomotion to be altered.

Both humans and animals are capable of adjusting locomotor properties with relative ease, but the execution of these adjustments has been difficult to characterize, though many attempts have been made in locomotor control research. Neural pathways controlling locomotion are hierarchical, highly integrated, and well characterized anatomically, but explanations of functional connections between pathways are lacking. Modeling of locomotor control provides researchers with a method to study and identify the signals driving this crucial behavior.

Computational models of locomotor pattern generation have been previously developed to assist in the interpretation of control dynamics (89, 101, 119). For example, a model has been recently used to demonstrate that the essential signal driving spinal networks is expressed in the modality of desired velocity (120). This result was found by using the outputs of locomotion, changes in swing and stance time, and inverse solving for the desired input. A strong positive correlation was found between the model inputs and desired velocity (Figure 1).

Figure 1. A. Schematic representation of Brown-based half-center model expressed with 4 leaky integrators. Excitatory connections are depicted with circles and inhibitory connections with lines. B. Empirical and simulated phase and cycle duration relationships during locomotion. C. Relationship between locomotor phases and CPG inputs follow a power function. D. External input (parameter u in A) and locomotor velocity are strongly correlated, which supports the idea that CPGs are driven by the desired velocity signal (120).

To our knowledge, no human research has been conducted exploring velocity as the control signal of locomotion. Therefore, the main purpose of this project was to test the general hypothesis that velocity is essential signal driving locomotion. We tested this hypothesis with the aims discussed below. Results of this study will provide insight into the functional pathways underlying the crucial task of locomotion. In addition, this project poses powerful clinical implication as a tool for locomotor rehabilitation following neurological injury. For example, assessing the strength of this signal post neurological injury could be a possible clinical evaluation tool.

1.2. Specific Aims

Specific Aims

Specific Aim 1: To determine the differential velocity detection threshold, above chance (50%), in normal healthy subjects.

Hypothesis 1: The velocity detection thresholds of humans, reported as a Weber's fraction, will be less than 5%.

Specific Aim 2: Alter proprioceptive input of the velocity signal by unloading and loading subjects and measure subsequent changes in velocity discrimination.

Hypothesis 2: Weber's fraction will increase with loading and decrease with unloading.

Specific Aim 3: To determine if variance of step cycle duration (and subsequently step velocities) produces changes in the success rate (i.e. Is this a Bayesian process?)

Hypothesis 3: Increased step cycle variance, which reflects uncertainty in the current velocity, will decrease the success rate.

1.3 Limitations

There are inherent limitations to all psychophysical studies. Two types of biases related to the psychophysical methodology are habituation and expectation. Habituation error results from the subject being accustomed to reporting that they detect the stimulus and therefore, report beyond the detection threshold. Expectation errors involve participants making anticipatory decisions about detecting the stimulus, or not. We protect against this limitation by using a method of constant stimuli. Trials and conditions were presented randomly, reducing the chance of habituation and anticipatory errors. Finally, due to the population recruited, results of this study can only be generalized to normal, healthy individuals.

1.4 Delimitations

The main goal of this study was to determine the velocity detection threshold of young healthy individuals. We recruited males and females from 18-35 years of age. Any participant that reported taking neurologically active drugs, any serious musculoskeletal injury to the lower extremity, or any neurological condition, was excluded, as these may affect their ability to perceive changes in speed. Cautions taken to prevent against psychophysical errors and limitations included, explaining the task to subjects thoroughly and giving a familiarization period for each altered body weight condition. Participants were asked to keep their eyes fixated on signs that will be placed at eye level, to ensure that they did not look down at the belts. Control trials, where both belts are moving at 1.0 m/s, were employed to protect against reporting bias. Because participants were forced to choose left or right, the correct response to these control trials should have been approximately 50%. Data from four subjects showed limb biases and they were excluded from further analysis.

CHAPTER 2. REVIEW OF LITERATURE

2.1 Reflex and Intrinsic Pathways.

Locomotion is a combination of movements, allowing for progression to different locations.

Animals move for various reasons, and this ability is crucial for survival, such as running from predators, finding a mate, or catching prey. Natural selection has equipped humans with a strong musculoskeletal system, providing the necessary framework for biped locomotion. As humans, we are able to move through the environment with little conscious effort. The central nervous system is capable of solving this complex and dynamic task, with apparent ease. How alterations in gait are accomplished remains a mystery to neuroscientists and biomechanists. Here, we have devised an experiment to unravel this unanswered question.

Metabolic Costs of Locomotion

Over-ground locomotion is, energetically, a demanding task requiring robust skeletal and muscular systems for support. Studies have proposed that many factors contribute to the control of locomotion, but most important is energetic cost (104), which influences the selection of desired speed of locomotion. With the overall goal of the CNS being minimization of energy use (1), simplistic mechanisms are used by the neuromuscular system to meet demands of this task. Preferred walking speed of humans has been measured to be approximately 1.4 m/s (13), and as we walk at faster speeds the overall energetic cost increases. Though we are capable of walking at speeds of 2.5 m/s, we typically only use a small range of speeds (84). Stability is an additional factor that influences speed selection. For example, when walking downhill, human subjects use energetically inefficient gait, which proposes that stability is favored over speed to minimize energetic cost (61). Older individuals

that are particularly concerned with stability, have higher metabolic cost associated with their locomotor patterns (118).

Dynamic Skeletal System

Though locomotion is a dynamic process, it can be partially described using a simple inverted pendulum model. In this model, balanced oscillation of kinetic and potential energy may produce stable locomotion (14, 15), without muscular contraction. This passive process is generally described as followed. During heel strike, the foot is interacting with the ground and some of the energy of the system is lost, but most is converted from kinetic to potential energy. This kinetic energy is regained when the COM falls during mid stance and the process is repeated when the other limb contacts the ground (14, 81). Though the inverted pendulum model is able to produce relatively stable gait, small perturbations or extrinsic factors in the environment can destabilize the passive process. Further, these simple mechanical models do not predict frequency adjustments during locomotion (8), or energy expenditure during transition (71). More robust models including passive dynamic properties and accounting for sensory feedback, metabolic demands, and anticipatory mechanisms, are needed to adequately describe control of locomotion (120).

Modulation and Controllability of Behavior

The modulation and controllability of gait relies on an animals' ability to adjust phases, velocity of progression, and heading; the latter can be accomplished by alteration of limb speeds. Electrical stimulation of an area between the mid and hindbrain was found to control locomotor speed in cats, such that when the strength of a single stimulation was increased, the cat transitioned from a slow walk to a gallop (110). This area, termed the mesencephalic

locomotor region (MLR), is found not only in cats, but also in many vertebrates. For example, in lampreys, stimulation of the MLR can induce locomotion that increases with stimulation strength (105) and asymmetric stimulation produces turning (113). In humans, when simply asked to think about locomotion, an increase of brain activity in this region is observed (65). It has been proposed that the MLR functions to filter influx of sensory information during locomotion (105) and activate networks in the spinal cord via monosynaptic connections with spinal neurons. These connections ultimately produce appropriate gait adjustments.

In both animals and humans, another determinant of the modulation of locomotion and walking speed is visual flow (19, 38). Specifically, studies in fruit flies show that flight speed is highly dependent upon retinal slip speed (38). Studies in cats have shown that when stepping over an obstacle, the activity of neurons in the brain and EMG activity in forelimb muscles are controlled by visual input (68). In humans, when the gain of the visual flow is altered, such as using virtual reality, subsequent changes in locomotor speed are observed (37). This suggests that visual information is coupled to the mechanical pathways controlling locomotion.

Stabilizing Roles of Muscles and Stretch Reflexes

Hill Type Muscle Model

Functionally, muscles are tunable springs, with intrinsic properties dependent upon the length and velocity of the muscle fibers. The Hill-type muscle model describes the muscle mechanical response using a contractile element with two spring elements (one in parallel and the other in series). In the model, the following equation describes the relationship between skeletal muscle contraction velocity (V) and force (F):

$$(V+b)(F+a)=b(F_0+a),$$

where, F_0 is the isometric maximum force generated by the muscle, a is coefficient of heat, and

$$b = a \cdot V_0 / F_0,$$

where, V_0 is maximum velocity at $F=0$ (57). The contractile component describes the active tension developed by cross bridging of two sarcomere proteins, actin and myosin. The parallel and series elastic components are described by the muscles' force-length curve, while the passive force is generated by the parallel components arising from the connective tissues. Muscle tendon and the inherent elasticity of muscle fibers represent the component in series, which provides energy storage (57). Overall, this model states that the amount of force produced by a muscle is based on two variables, the length of a muscle, and its contraction velocity.

The Force-Velocity and Force-Length Relationships

The force-length relationship can be described using a bell shape curve: if the length of a muscle is increased or decreased beyond its resting length, the ability of that muscle to produce force decreases (121). At resting length, the two proteins responsible for muscular contraction, actin and myosin, are in optimal interaction with each other. As a sarcomere shortens to contract the muscle, myosin binds actin and the myofilament band slide past each other, without changing length (sliding filament mechanism) (62). As the muscle shortening continues, force production decreases, because actin fibers overlap, and cross bridges are lost. Consequently, if the muscle is stretched beyond optimal length, the sarcomere lengthens. This pulls the actin band toward the end of the sarcomere, which this results disassociation of cross bridges, and this decreases force output (45).

Next, muscular force can also be described as a function of velocity and can be dependent on the load of the muscle (5). This relationship is also dependent on the total number of cross bridges, which require a finite time to attach. If we want to increase the velocity of a muscle contraction, force production is sacrificed because the cross bridges do not have time to adequately bind. Conversely, if we decrease the speed of contraction, force is able to increase because cross bridges have adequate time to attach and generate force. These muscle properties allow the muscle to function as tunable springs and dashpots, resisting stretch and stabilizing posture and locomotion.

Stretch Reflexes

The posture and balance of animals is controlled with short latency at the spinal level by stretch reflexes, which allow for smooth transition through locomotor phases. It has been estimated that between 20 and 60% of overall muscle activity during locomotion arises from stretch reflexes (93, 112). These reflexive pathways can be described as closed looped systems (see **General Control Theory Principles**). For example, during the yield phase of gait, muscles yield to body weight, absorbing the shock of the ground. Muscle spindles in the extensors are further activated by this stretching and this signal is propagated via Ia afferents to the spinal cord (60). This sensory signal activates an alpha motor neuron exiting the ventral horn of the spinal cord. Ankle extensors become further activated, which propels the foot through stance. Another example observed during locomotion is stretching of the hip flexor, which leads to reciprocal inhibition of extensors, producing the swing phase of locomotion. These transitions are highly dependent on sensory feedback mechanisms, as observed in the stretch reflex (94). Supra-spinal control centers are further able to influence this reflexive control by altering muscular

tone via gamma motor neurons. Ultimately, muscle spindles intrinsically stabilize this system via a negative feedback loop, allowing for inter-joint coordination during locomotion.

General Control Theory Principles

Control theory is a concept in engineering and can be used to explain the dynamic properties of physiological systems. Specifically, how feedback modifies their outputs, or behaviors. There are four main actions involved in a control mechanism: to measure, compare, compute, and correct for errors. They are composed of five different types of elements: a detector, transducer, transmitter, controller, and final control element (73). The detector, transducer, and transmitter are considered one unit responsible for the measuring property. The controller is responsible for comparing and computing the difference between the feedback signal and the desired signal and then, the final control element alters the output signal. In a closed-loop system, error feedback mechanisms adjust the control signal until the input matches the output of the system (73). Therefore, in order for a signal to be controlled, it has to be sensed accurately.

An example of a physiological control system is the stretch reflex, which plays a major part in controlling locomotion. These reflexes involve the incorporation of both positive and negative feedback loops (100) involving the muscle's length, velocity, and drive of the command signal. When central drive is low, stretch reflex is necessary, but as the central drive increases, the contribution of the stretch reflex decreases (100). Muscle spindles also provide feedback via Ia afferents to homonymous alpha motor neurons. Force development is established by the Golgi tendon organs in a positive feedback pathway (91). This functions to regulate motoneuron activity, according to the loading of the extensor muscle. In example, when muscle is

lengthened, force production increases, and this stimulates Golgi tendon organs, which activate pathways to return the muscle to resting length.

Central Pattern Generation

Numerous behaviors in animals involve repetitive actions, such as locomotion, chewing, and breathing. Control of locomotion can be described as a hierarchy, where descending pathways feed into central pattern generators distributed across lumbosacral spinal cord segments (22, 69, 70). These circuitries are intrinsically rhythmogenic, and following complete transection of the spinal cord (removal of all movement-related sensory information), can produce rhythmic alternating contractions. For this reason, Brown termed the spinal circuitry the intrinsic factor (12) and posited that two reciprocally activated inhibitory half centers (one per limb) controlled the timing of burst like activity of flexor and extensor motor neurons. To further explain the connections of this system, the flexor bursts are inhibitory to the extensor bursts on the ipsilateral side and vice versa, and in addition, the flexor burst is excitatory with the contralateral extensor. These alternating bursts of activity drive motor neurons of the flexor and extensor muscles and their connections allow for the simplification of locomotor control. While pattern generators allow for simplification of locomotor control in the absence of sensory feedback, and this drive is intrinsically rhythmogenic, it is largely dependent on sensory feedback and descending drive. These higher-level inputs allow for the fine-tuning of signals necessary for adaptation to environmental demands. In fact, these circuitries in a neurologically intact specimen are mostly dormant, waiting for activation from descending commands via descending neurons. Increasing the drive to the pattern generator produces increased activation of motor pools, which results in varying cycle durations (26).

There have been numerous studies providing evidence for CPGs in vertebrates, including humans (47). Basic evidence for CPG in humans is demonstrated in studies of infants. These studies show that if held over treadmill belts, infants are able to produce stepping movements. This provides evidence that the machinery needed to produce locomotion is present, but they cannot voluntarily step because the descending connections from the brainstem and motor cortex have not matured. Further evidence for central pattern generation in humans has been observed in studies of spinal cord injured patients. For these individuals, epidural stimulation has been shown to produce rhythmic EMG activity in the legs and trunk muscles (27, 83). Finally, bilateral and rhythmic oscillatory EMG activity is observed during facilitated stepping of SCI patients, which shows the importance of sensory input to pattern generators. (53). Overall, the spinal cord contains central pattern generators, which produce the basic rhythmogenic patterns needed for stepping. Descending pathways provide input, which alters the activity of these circuits to adjust phases to meet environmental demands. This organization allows for simplification of a dynamic task by reducing time delays using feedback loops housed in the spinal cord. Thus, this significantly reduces the complexity of control of locomotion between supra-spinal and mechanical systems of locomotion.

Input Signal to CPG

The anatomy of the central pattern generator has been highly characterized; however, functional and emergent properties resulting from these connections are difficult to study. Specifically, an unknown parameter of central pattern generation is the input signal driving CPGs to produce alterations in muscle activity and timing. Computational models have been developed to further study this missing information in locomotor control research. The main

model used in this study is based on Brown's intrinsic rhythmogenesis hypothesis (12). This model produces bilateral rhythm generated by 2 half-center oscillators expressed by the following differential equation,

$$d/dt(X) = X_0 + G_u * u + G_x^{UL} * x + G_x^{BL} * (1-x) | x > 0$$

,where the variables are: integrated inputs ($X_0 + G_u * u$), intrinsic leak ($G_x^{UL} * x$), and intrinsic interactions in the system ($G_x^{BL} * (1-x)$). The $[G_u]$ matrix consists of the gains of the input signals and $[G_x]$ is the strength of connections between elements of the half oscillator. These connections have internal states, $[x]$, which have a constant level of auto excitability $[x_0]$. The unilateral (UL) matrix can be represented by ($i * r_{leak}$) or the (identity matrix* the constant leak of the system). The bilateral (BL), represents the connections between the half centers. The integration of the equation above was performed using Runge–Kutta 4th order method (120).

In general, model changes states in response to signals from connection and intrinsic parameters $[G_u, G_x, X_0]$ and produces outputs [cycle time, flexor time, extensor time] based on these inputs. It can also be driven inversely, so that using power functions of phase modulation as input, produces desired parameters necessary to produce those outputs. By using regressions of phase modulations to drive the model inversely, a strong correlation ($r=.99$) relates the input signal to the CPG and desired velocity (120). This result indicates that velocity may be the main signal driving pattern generation at the level of the spinal cord. Additions modeling work done by Osaki, 2008 shows that velocity is key signal producing changes in phase modulation of locomotion(89). Uncovering the signals that drive pattern generation has key implications for neurological rehabilitation strategies, such as locomotor training. An

engineering approach can be used to further test that velocity is the signal driving pattern generation (See: **General Control Theory Principles**).

2.2 Descending Control of Locomotion

Locomotion is coordinated by functionally organized circuitry in the spinal cord and descending pathways (48, 49). While flexibly organized burst generators can produce the basic patterns needed for stepping, there are many regions of the brain feeding this circuitry. This descending drive is necessary to initiate and alter locomotion. By chemical and electrical stimulation, many regions have been identified in the initiation and modulation of locomotion (3, 85, 111). These regions include, the motor cortex, cerebellum, and brainstem.

Brainstem

The brainstem is involved in the control of many rhythmic processes, such as, heart rate, breathing, chewing, and locomotion. In addition, several brain stem regions play a role in control of locomotion, including the sub-thalamic motor region, pontine locomotor region, and MLR, as they can produce locomotor phases when stimulated. The connections and interactions between these brainstem regions in the context of locomotion are unknown. As discussed earlier, stimulation of the MLR in cats has been shown to initiate and alter gait speed of decerebrate cats while on a treadmill (111). In addition, stimulation produced proper inter-limb coordination. This locomotor region is located in the rostral pons, and therefore, does not directly project to the spinal circuitries that produce locomotion. Instead, the MLR transmits

information to the spinal locomotor system via descending spinal pathways. When these neurons are transected, stimulation of the MLR does not produce locomotion (87).

Motor Cortex

A region of the cerebral cortex, the motor cortex, functions to plan, control, and execute movements. It is composed of three areas, the primary motor cortex, premotor cortex, and supplementary motor area (SMA). Because locomotion does not necessarily require conscious attention, it would be expected to involve little cortical activity. Levels of cortical activity reach significant values when cats are presented with challenges during walking (i.e. stepping over obstacles) (3, 28, 29). Imaging studies show significant motor cortex activation in humans during real and fictive locomotion (39). Studies with trans-cranial magnetic stimulation (TMS) show the corticospinal tract (CST) is readily excited during the cycle of gait (96, 97, 108). During steady state treadmill walking, EEG and EMG activity from lower extremity muscles are coupled, indicating that the motor cortex and CST do play significant roles in the constant muscle activity of locomotion in human subjects (98). The motor cortex also processes information from the visual system, which provides crucial information to guide locomotion. The motor cortex and posterior parietal cortex play the main role in coordinating the visuo-motor transformation. If the motor cortex is lesioned, basic walking can be produced, but stepping over objects placed on a treadmill belt is severely impaired (79). Lastly, neurons in the motor cortex directly project onto the spinal cord and may directly influence the central pattern generators (92).

Cerebellum

The cerebellum is not involved in the initiation of movement; rather it functions to coordinate inputs to produce precise and accurate movements. It receives information about state of spinal networks via ascending pathways (92). Specifically, in cats, proprioceptors in the hind limbs strongly activate dorsal tract neurons, which feed information to the cerebellum about the position of the hind limb (95). The ventral neurons may provide the cerebellum with information about the state of the CPG via interneurons. These pathways allow the cerebellum to function as a controller, comparing actual movements of the limbs with the desired movements. Then, the cerebellum can compute the corrective signals to send to the brainstem, which alter locomotor output. The cerebellum and vestibular nuclei specifically interact together to allow for balance during walking (86). If the cerebellum is lesioned or damaged, serious locomotor complications are produced. This produces a condition known as ataxia. In this condition, joint range of motion, speed, and inter-limb coordination are affected, producing lifelong gait impairments (86).

The higher level organization of locomotor control in humans has been conserved through the transition from quadruped to biped locomotion (25). Case studies of patients with midbrain lesions support the fact that the MLR is involved in initiation of gait in humans (55). The motor cortex uses visual input to precisely alter stepping. The cerebellum fine-tunes locomotor pattern to ensure that the output of the system matches the input. The coordination and planning of movements guided by vision is housed in the posterior parietal cortex. Each of these brain structures feeds sensory information into the spinal pattern generator, allowing for adaptations in locomotion (16).

Psychometrics

A current challenge in locomotor research is how the brain recreates the external world through sensory stimulation in order to produce proper phase modulation. Psychometrics is a field of study addressing the measurement of mental processes. Tools in the field allow the relationship between the stimulus of a sensation and its perceived intensity to be studied and defined (42). Methodology in this field has been successful in determining the magnitude of a stimulus needed to produce responses in the visual, olfactory, gustatory, proprioceptive, and auditory systems (34, 41, 46, 64, 88). There are two main psychophysical quantifications of perception, the absolute and the difference thresholds. The absolute threshold can be described as the absolute minimum intensity that can be detected, where experiments include presenting differing stimuli to a participant and asking if they detect it or not (42). In addition, the difference, or just noticeable difference (JND) threshold, is the minimum intensity detected when compared against a constant stimulus. Given the inherent difficulty of reporting an absolute threshold, the difference threshold is mainly tested and reported in the literature (42). These experiments are conducted by presenting stimuli of differing magnitude against a constant stimuli, and asking the participants to report if there is a difference or not. An example of this would be asking a participant to compare two weighted objects, and asking which one is heavier (11). Following these tasks, proportion of correct responses (p-correct) is calculated for the different experimental intensities, and a linear relationship should exist between p-correct and stimulus intensity. The detection threshold reported is at the level where p-correct is 50 or 75% (35).

Ernst Weber was the first to quantify the relationship between the magnitude of a physical stimulus and its perceived intensity. Weber's law,

$$k = \Delta I / I,$$

states that the ratio between the JND threshold (ΔI) and the stimulus intensity (I) equals a constant (k) (35).

Weber's fraction values have been reported in a number of different physiological systems and provide insight regarding the relative sensitivities of these systems. The human eye, for example, can detect changes in light intensity as low as 1-3% (56), while cells in the ear are sensitive to tone differences ranging from 7-10% (80). The sensory capabilities of the proprioceptive system have shown that humans can discriminate 14% change in amplitude of mechanical vibration to the arm (20). When asked to compare the weight of objects, a change of 9-13% can be detected (66, 67). Studies show that when vibration is applied to a tendon, the perception of position and velocity of movement become impaired (106, 109). This effect is exacerbated when the tension of the muscle is increased, by applying a slight stretch (114). These findings imply that the spindles are the main source of kinesthetic information, which becomes important for perception of limb position and velocity. These proprioceptive detection thresholds are important in motor control research, because they allow us to sense body position, movement, force, and effort (103).

The execution of movements is a dynamic process involving integration of sensory systems (i.e. vision) and proprioceptive input (107). In order for the central nervous system to plan and execute successful movement, limb position and orientation must be known. Proprioception is an "inner sense" allowing the central nervous system to coordinate your limbs in time and space. Peripheral receptors provide sensory information, which is processed subconsciously via afferent pathways. The "outer sense" or awareness of the position of your limbs and body in

time and space refers to kinesthesia (103). It is processed consciously via the premotor cortex from sensory information of muscle spindles, and cutaneous receptors (9). These terms are often used interchangeably, but they encompass two different meanings. Generally, you are aware of kinesthetic changes and unaware of proprioceptive changes.

A challenge in motor control research is how to provide quantification of the sensory input producing changes in execution of movement. Descending drive from supra-spinal inputs constantly update the input to pattern generators, which produce necessary phases to meet environmental goals. The main structures involved are the brainstem, cerebellum and motor cortex. Online control of voluntary movements involves relaying these sensory signals to supra-spinal systems and the central nervous system uses kinesthetic information (current position and speed of limb) to execute motor commands (18). This kinesthetic information is used as online feedback to compare the intended movement to the actual movement and correct for error (i.e. does the output match the input?) (18). Though these neurophysiologic studies give us an understanding of the sensory systems that feed into locomotor pathways, there is a critical need to perform psychophysical tasks during locomotion. This would allow for quantification of sensory signals, using Weber's fraction, needed to produce responses during walking.

2.3 Neurological Injury and Locomotor Training

Spinal Cord Injury

Spinal cord injury (SCI) is a neurological condition resulting in serious locomotor complications; however, neurological rehabilitation strategies offer potential for patients to regain walking capacity. Any injury which disrupts the spinal cord's normal motor, sensory, or autonomic

function produces a SCI (25). This injury can disrupt descending commands from higher-level centers, as well as the circuitry of the spinal cord. It is estimated that there are 230,00 patients living with spinal cord injury (SCI) in the US, with 10,000 new cases occurring each year (CDC). These injuries mainly occur due to motor-vehicle accidents, sports injuries, falls, or violence (CDC). The American Spinal Injury Association uses a scale to diagnose the severity of a spinal cord injury, ranging from A (motor complete, sensory complete), B (motor complete, sensory incomplete), to C, D, and E (differing severities of motor incomplete, sensory incomplete). The impairments that arise primary and secondary to SCI are serious and debilitating. These impairments range from paralysis, loss of bowel and bladder function, severe rises in heart rate and blood pressure. This, in turn, puts SCI patients at higher risk for heart disease and stroke.

Locomotor Training

Several rehabilitation strategies may be used following neurological injury. Stem cells (74), neural stimulation (7, 51), exercise (31), acute intermittent hypoxia (4), and locomotor training (LT) are all neurological rehabilitation strategies, which aim to enhance neural plasticity (59). It has been demonstrated that LT produces greater enhancement of locomotor ability than other rehabilitation techniques (75, 82). It uses task specific paradigms to mimic the sensorimotor inputs associated with normal over ground locomotion (82). The capacity for improvement is dependent upon that initial severity of gait impairment. LT can be performed over ground or on a treadmill. Weight support can also be used during LT, specifically in patients with the greatest deficits (59). This strategy allows for higher treadmill speeds to be used, the patient to produce stepping, and reduces compensatory strategies (82).

Numerous animal experiments have been completed to test the functionality of locomotor training after spinal cord transection. When appropriate input is given to the CPG during step training, spinalized cats were able to stand and step (6). Rats were able to produce appropriate step phases after pharmacologic, electrical stimulation, and locomotor training (63). In humans, locomotor training has been reported to increase functional gait in SCI patients with motor incomplete injury (117). Recently, approaches have been designed to intervene and provide rehabilitation to patients with the most severe spinal cord injury, motor complete (52, 54). Using electrical stimulation, stand and step training, motor complete spinal cord injured patients were able to flex their lower extremity joint. Furthermore, motor complete and sensory complete patients were able to produce appropriate EMG activity activation of flexors and extensors during step training when instructed to think about walking (2). This shows that the lumbosacral spinal cord neurons are in tact and can process sensory information related locomotion (54). Locomotor training rehabilitation approaches could be further evolved if velocity is found to be a sensory input to the CPG in this proposed study.

Damage to the networks affecting central pattern generation can lead to movement disorders. The primary goal of patients following neurological injury is recovering of walking capacity (25). Uncovering the networks and functional connections of the CPG allow for facilitation of rehabilitation following neurological injury. A common principle for neurological rehabilitation is to take advantage of use dependent plasticity. However, more directed task specific training is needed to take advantage of the plasticity of the CNS (115). Discovering the signal driving central pattern generators use to alter muscle activity provides a rational target to facilitate locomotor training following neurological injury. In addition, many of the diagnostic techniques

to assess impairment following neurological injury lack the necessary testing to quantify the patient's ability to recover as well as their motor deficit (78, 90). The ability of a patient to sense inter-limb velocity could be a powerful clinical tool to reveal locomotor impairment, severity, and also track progress during rehabilitation strategies.

CHAPTER 3. STUDY DESIGN AND METHODS

In this study, the computational hypothesis that velocity is the signal controlling locomotion was tested in healthy individuals. To conduct this study, normal healthy individuals were recruited to perform a velocity discrimination task using a split-belt treadmill. During the walking task, the speed was perturbed during normal, unloaded, and loaded body weight conditions. Subject responses and ground reaction forces were collected and used for further analysis.

Subjects

Twenty nine normal, healthy, controls were recruited for this study (14F, 15M, $1.6 \pm 0.2\text{m}$, $71.9 \pm 12.0\text{ kg}$, 24.1 ± 2.8 years old), through flyers placed in the WVU Health Sciences Center. Participants interested were evaluated using a pre-screening interview (Appendix A) given either in person, or over the phone prior to the subject arriving for experimentation. Subjects were included if they were between the ages of 18-35, and excluded if they had any serious medical conditions (i.e. epilepsy, stroke), were taking any neurologically active drugs, had serious lower extremity impairments that effected their gait, any serious injury to the lower extremity, or were pregnant. If the subject met all criteria, an appointment was made for experimental testing at the in room 145 of the WVU Biomedical Research Center.

Informed Consent

Upon arrival to the lab, experimental procedure was explained to the subject and they were encouraged to ask questions about the task they were performing. Next, informed consent was obtained, with approval from the West Virginia University Institutional Review board (Appendix B).

Biomechanical Assessment

Subjects were instructed to remove their shoes and weighed using a standard medical scale.

Height and torso length were then measured using a tape measure. In addition, unilateral extremity lengths of the subject's dominant side were taken of the upper arm, lower arm, hand, upper leg, lower leg, and foot (Appendix C). To assess limb dominance, participants were asked which leg they would use to kick a ball.

Velocity Discrimination Task

Subjects were placed into a body weight support harness and asked to walk on a split-belt treadmill (Bertec, Columbus, OH) at 1.0m/s. The velocity discrimination task was performed by asking the subject to report difference in inter-limb velocities, based on 3s of locomotion (3 steps) per trial. One of the belt speeds remained 1.0 m/s and the other belt was altered to 1.0m/s $\pm$ 0.01, 0.02, 0.05, 0.1, or 0.2 m/s. This produced 11 total perturbations that were repeated

randomly 7 times for each leg, producing 154 total trials. In order to protect against subjects trying to use higher-level strategies (i.e. guessing) for this task, a built in sham trial, where both belts are moving at 1.0 m/s was used.

First, the subject was given a training period of approximately 2 minutes to acclimatize to the treadmill and to practice responding to the auditory cues described below. Following the

Figure 1: Pictorial representation of loaded body weight condition during the velocity discrimination task.

training period, a 5-minute rest was given. During the discrimination task, the start of each trial consisted of a low-pitch tone indicating that the belts were changing speeds. Two seconds later, a high pitch tone designated the response period was beginning, and the subject was instructed to verbally report which limb was moving faster (left or right). The answering period lasted 3 seconds and ended with a low pitch beep. This also denoted the start of the next trial and the belts changed speeds again. No feedback on performance was given to the participants and they were instructed to look directly forward to eliminate visual cues from the belts affecting their response. Participants were also asked to not hold onto the side rails of the treadmill during the discrimination task, as this could have altered their gait as well as weight condition. Subjects were randomly assigned to wear noise-cancelling headphones (Bose, Framingham, MA). This was to address the possibility that subjects used auditory cues resulting from the sound of the treadmill belts speeding up or slowing down.

Loading and Unloading

The velocity discrimination task was repeated under two other randomly ordered body weight conditions (unloaded and loaded) in addition to the normal weighted condition. This served to alter proprioception, and thus should subsequently alter velocity discrimination ability(23). Loading, or the weighted condition, was accomplished by placing weights equivalent to 10% of the subject's weight in a backpack placed on the subject's back and secured under the harness. In addition, the body weight support system (Pneumex, Sandpoint, ID) was used to unload, or un-weigh, the subject by 10% of their body weight. Subjects were re-weighed following the loading and unloading to ensure that the altered weight was achieved. Prior to performing the task under altered body weight, subjects were asked to walk for two minutes, which allowed

them to acclimatize to the condition. This also ensured that the subject was comfortable walking with the harness and backpack during the task. The experimenter visually inspected the subject's gait to ensure that the harness was not causing gait abnormalities. Participants were given a ten-minute washout period between conditions to allow for resetting of the load receptors.

Data Collection

Subject responses (left, right, or no response) were recorded for each trial during all conditions excluding the two-minute training session. No response trials were classified as any trial that the subject did not respond to, or if they responded outside of the answering period (i.e. between the high and low pitch beeps). All conditions were video recorded and responses were confirmed following the experiment. In addition, ground reaction forces (GRF), including three forces and three moments from each belt (500 Hz with a digital to analog card UE9-Pro, LabJack, Lakewood, CO) were recorded. Data were imported and processed offline with custom scripts in Matlab (MathWorks, Natick, MA).

Data & Statistical Analyses

Demographics of the population were calculated and these variables included average height, weight, age, and gender. One-way ANOVA was used with the independent variables of loading condition (BWL, BWS, and BWN), dependent variable of accuracy of detection, and factors of detection threshold. Significant results were further analyzed using Tukey's post-hoc analysis. Accuracy of detection or probability of success was calculated for all subjects using a ratio of total to correct responses for each experimental speed and condition. Alpha was set at 0.05.

Vertical ground reaction forces were low-pass filtered at 200 Hz using a 2nd order Butterworth filter (Figure 4). This filter was chosen based on visual analysis of GRF. Events were marked using a supervised automatic threshold method (119), so that the onsets and offsets of stance phase were detected. Cycle time was defined as the period of time between two onsets (green events). Each trial consisted of approximately five steps: the first step was excluded due to the belts changing speeds, and the last step was excluded because the participant had already made their decision, leaving the three middle steps analyzed. The mean cycle time variance of correct and incorrect trials was calculated and analyzed using bootstrap analysis (32).

CHAPTER 4. RESULTS

Experimental Velocity Detection Threshold

Specific Aim #1 was to determine the velocity detection threshold of human subjects above the level of chance (50%). Specific Aim #2 was to determine if alterations in proprioceptive input resulted in subsequent alterations in discrimination ability.

Figure 5 shows the experimental velocity detection thresholds using boxplot analysis by speed and condition. Normal, loaded, and supported conditions are depicted by black, red, and blue, respectively. The dashed line indicates the 50% level of detection. This was the level above chance for the task. Bars of the boxplots depict the maximum and minimum values. The boxes show the upper (25% of data greater than this value) and lower (25% data less than this value) quartiles. The line in the middle of each box shows the median, where 50% data is greater than this value, and outliers are indicated by plus signs. ANOVA demonstrates significant changes in success probability equal or above the speed of 0.02 m/s ($p < 0.05$). Tukey's post-hoc analysis shows that success probability increases significantly between the speeds of 0.02, 0.05, 0.1, and 0.2 m/s. Since the constant speed was 1.0 m/s, then the variation of 0.02 m/s represents a Weber's fraction of 2%. This indicates that humans were able to detect the experimental speed of 0.02 m/s above the level of chance.

Tuning Curves & Functional Velocity Detection Threshold

Figure 6 shows tuning curves generated by plotting the relationship of inter-limb velocity (VL-VR) against the probability of success for each speed. These were generated for each individual subject. Positive speed changes reflect right limb perturbations, while negative speed values indicate left limb perturbations. The dashed line is indicative of the 50% level of detection, or the level above chance. These curves were used to identify subjects using higher-level

strategies, such as guessing or limb bias, during the task. This was defined as the increase in detection above 50%, with the accompanied decrease below 50% in the other limb.

This allowed us to determine the analytical relationship between success probability and speed. Because this relationship is a logical function, the psychophysical tuning curves were further analyzed using Weibull analysis. This allowed for the detection level threshold to be calculated at the standard level of 50% correctness (v_{50}) (35). Following, the average JND thresholds were calculated by averaging the v_{50} for each subject. The JND threshold is defined as the speed where the subject was correct 50% of the time. ANOVA test showed no differences between detection ability and loading condition ($p=.73$). Figure 7 shows the functional fitting of success probability and speed difference for all subjects and all conditions. The t_{50} for all subjects and conditions, reported by Weber's fraction, is $1.02 \pm 0.43\%$. This threshold describes the functional differential threshold of velocity discrimination calculated by Weibull analysis. The threshold reported earlier (2%) is indicative of the experimental threshold.

To test if ground reaction forces were significantly altered, the averages of these forces were calculated across subjects and confidence intervals were calculated. Figure 8 depicts the average vertical ground reaction forces by condition with confidence intervals. Significant changes in ground reaction forces were observed between loading conditions, as the confidence intervals for each condition do not overlap. When confidence intervals do not overlap, we are at least 95% sure that there is a statistically significant difference between the two estimates.

Bayesian Processing

We wanted to further investigate the processing of this velocity signal. Specific Aim #3 was to examine if step variability influenced error rate in the performance of detection. It was hypothesized that this velocity signal was extracted at a high level and it was a bayesian process. Filtered vertical ground reaction forces were used for this analysis. We expected a negative correlation between the two variables, so that increased variance in step cycle would produce less probability of success in those trials. In order to test this, we examined the relationship between step cycle variance and detection ability using two-tailed bootstrap analysis across subjects. This test uses a method of resampling data with replacement. Figure 9 was generated by plotting the discrimination ability above chance as a function of variance by speed. This demonstrates the relationship between increased variance and decreased intralimb velocity detection ability. Significance of these plots is observed when the confidence intervals are to the left of 0, because we expected a negative relationship between our two variables. A statistically significant negative relationship between cycle variance and detection ability at the experimental speed of 0.01 was observed. A negative trend was observed for the speeds of 0.02, 0.05, and 0.10 m/s.

CHAPTER 5. DISCUSSION

Locomotion is a dynamic task that is crucial to the survival of all animals. The main purpose of this study was to test the hypothesis that velocity is the essential control signal, within the CNS networks, responsible for locomotion. We found that humans have a precise sensory representation of each limb velocity. This was tested with the velocity differentiation task in this study, which showed the lowest threshold values compared to other psychometric results.

In closed-loop systems, a control signal must be accurately sensed (73). This, in turn, indicates that the locomotor control system may be using a velocity signal to drive spinal neural networks.

Weber's Fraction

The Weber's fraction, found by functionally fitting the relationship between success probability and speed, shows that humans are able to detect a 1% change in differential limb velocities. This result indicates that when walking at 1.0 m/s, perturbations of 0.01 m/s can be accurately detected. This fraction is lower than ones reported in other proprioceptive psychometric tasks. For example the fraction reported for differential mass detection is approximately 10%. During this task, subjects were asked to hold two weights, compare them, and report the heavier object. This indicates that the individual can accurately discriminate 1.1 kg from 1 kg (11). For vibrotactile discrimination, the threshold reported is 14%. During this task, subjects were stimulated at different frequencies and were asked to report the higher stimulus(21). Our findings support the hypothesis that the locomotion control system uses velocity as the control

modality. This conclusion is based off classical control theory, which states that in a closed loop system, a control signal must be accurately sensed.

Alterations of Proprioceptive Drive

In order to test our secondary hypothesis, we manipulated proprioceptive signals via loading and unloading subjects by 10% body weight. Loading the subject should have increased the strength of the velocity signal, which should have resulted in the subject having a higher success rate for each speed. On the other hand, unloading the subject should have decreased strength of the velocity signal, which should have caused a subsequent decrease in their discrimination ability at each speed. However, no significant differences were observed between conditions. Surprisingly, we found no differences in detection ability. Afferent input from load receptors of the extensor muscles play a crucial role in the control of locomotion, as suggested from experiments completed in cats (17, 30, 94) and humans (24, 36). We hypothesized that this altered proprioceptive input produced alterations in the strength of the velocity signal, and this would result in subsequent changes in velocity detection. The afferent input that signals the position of the center of mass can be equated to the ground reaction forces that are observed during stance phase of the step cycle (108). During split-belt locomotion, these forces play a major role in adaptations (108). Dietz and colleagues studied these effects by loading and unloading subjects while belt speeds were different and when subjects were asked to match belt speeds (23). Results of the study show that loading and unloading subjects during a training period produced an improved ability to match belt speeds. They hypothesize that the altered weight conditions changed kinesthetic feedback with increased sensory acuity, allowing for better matching of speeds. In our experiment, we altered

bodyweight by 10% compared to the 30% alterations performed by Dietz (23). This could explain the differences in experimental findings.

The low threshold of velocity detection that is independent of loading suggests the differential velocity signal is expressed within high-level centers of the human CNS. One of the main sources of sensory information from proprioceptive input to high-level centers, such as the cerebellum, is the dorsal spinocerebellar tract (DSCT) (99). Recordings from DSCT neurons during single joint and whole-limb movements of cats indicated that the end-point of the limb (not individual joints) is encoded by circuitry and used to correct errors during movement (10). The DSCT neurons must compute endpoint position from sensory information. It has been found that these neurons encode limb axis position and velocity independently. Further, it has been hypothesized that the cerebellum extracts the velocity signal (9). Our study is consistent with these findings, as end point control creates velocity of the limb. This further points to a whole limb velocity control, consistent with limb end-point control.

In our study, the altered body weight condition did not affect detection ability. However, significant alterations in vertical ground reaction forces were observed. This result demonstrates that this low level proprioceptive signal is transformed at the spinal level. This high-level processing of this velocity signal lead us to our third specific aim; is this high-level velocity signal processed via a Bayesian mechanism?

Bayesian Processing

The last specific aim was to further examine higher level processing of this velocity signal. Bayesian theory has been previously used to model and characterize perception in numerous circumstances (77). These models have been successful in explaining the integration

of single (58) or multiple sensory modalities (33). In our study, we wanted to test if this velocity signal was a bayesian process by examining the relationship between step cycle variability and probability of correctness. We hypothesized that high cycle time variability would produce an ambiguous velocity signal, which would be reflected as the subject incorrectly reporting that trial. Results of bootstrap analysis show a significant negative correlation at the speed of 0.01 m/s, which is equivalent to our functional detection threshold of 1%. A negative trend was observed at the other experimental speeds. We hypothesize that at such a low speed difference, you are more reliant on the velocity command for adjustments during locomotion, and therefore, noise in the signal significantly affects detection ability. As the speed differences increase, other sensory cues are able to help with detection ability, so the variance in the velocity command does not affect success probability, significantly. Similar observations are made in spatial orientation studies. Two main sources of proprioceptive information arise from the visual and vestibular systems. Visual information is processed from optic flow, which is the pattern of motion observed by the retina, relative to the static environment (43). Visual motion signals are proportional to the velocity of optic flow pattern (50). Angular and linear head accelerations stimulate canal and otolith organs. When taken together, spatial orientation work done by MacNeilage found that visual cues are used to interpret “unsure” vestibular cues, such that the weight of signal was less when the sensory cue was less reliable (76).

Heading Direction

In order to successfully complete goal directed locomotor movements, we must be able to change direction, or heading. It is unknown how we monitor and adjust changes in

locomotor direction. For example, to avoid collision, it is necessary to instantaneously correct for errors, which would require heading to be updated rapidly (40) and precisely. A proposed mechanism behind heading strategy is that humans use optic flow to perceive and control locomotion (43, 44). The visuomotor processing of optic flow has been found to modulate velocity of locomotion in both humans and animals (19, 38, 102). Previous studies have demonstrated that humans are able to detect heading changes within 1-2 degree of visual angle (5, 116), which produces accurate, goal directed movements. Another mechanism hypothesized by Furlan involves generation of a signal of the direction and magnitude of heading changes. During locomotion at various speeds, this signal would provide simplification of calculations needed to navigate complex paths, and feedback would allow for corrective signals to avoid error (40).

Findings of our study propose that errors between intralimb velocity provide a feedback system which adjusts heading (Figure 10). When heading is changed, such as walking on a curved path, driving each limb speed separately allows for steering control. One leg moves faster than the other to produce an error in velocity between limbs. This is reflected in desired velocities produced by the execution system, which travels down to the control system, feeding into the spinal cord. Control feedback mechanisms stabilize this system (control of heading), by using error control of the desired velocity. We have experimentally tested the ability of humans to report this “heading error”, or error in limb velocities. We have shown that we do have access to these pathways, and because detection was so low, we may use these errors in velocity to tune heading direction. Future studies to tie velocity signals in the control of heading should include incorporating virtual reality and split-belt treadmill locomotion

Similar results have been observed in flies exposed to sine waves of varying spatiotemporal parameters (38). Fry demonstrated that flies used velocity to control their locomotion by altering their wing speed, such that control of their wing speed was highly dependent on the speed of retinal slip. The authors propose that the visual system extracts a velocity signal and this signal causes changes in wing speed (38).

Future Directives

The first specific aim of this study was to determine a differential velocity discrimination threshold above chance for normal, healthy individuals. We found that experimentally, humans could accurately detect changes in speed of 1-2%. The most similar study to our experimental protocol was done in older adults. Sixteen healthy elderly individuals were asked to walk on a split-belt treadmill during imposed (1.0m/s) and self-selected (average speed 1.25 m/s) walking speeds during ascending and descending conditions. The speeds were changed by 0.01 m/s every 5 seconds until the subject sensed asymmetry (ascending condition) or symmetry (descending condition). Speed thresholds for detection were 0.23 m/s and 0.19 m/s for the descending and ascending conditions, respectively. Stance time was found to be the gait parameter that most correlated with detection threshold (72). Together with our results this indicates that velocity detection could decrease with age. Our experimental protocol should be repeated in older individuals to examine how the quality of this signal changes as we age. In addition, the quality of this signal should be examined when locomotor pathways become diseased, damaged, or dysfunctional. These procedures should be repeated in stroke and spinal cord injured patients.

REFERENCES

1. Alexander RM. Models and the scaling of energy costs for locomotion. *J. Exp. Biol.* 2005;208(Pt 9):1645–52.
2. Angeli CA, Edgerton VR, Gerasimenko YP, Harkema SJ. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain* 2014;137(5):1394–409.
3. Armstrong D. The supraspinal control of mammalian locomotion. *J. Physiol.* 1988;405:1–37.
4. Baker-Herman TL, Fuller DD, Bavis RW, et al. BDNF is necessary and sufficient for spinal respiratory plasticity following intermittent hypoxia. *Nat. Neurosci.* 2004;7(1):48–55.
5. Banks MS, Ehrlich SM, Backus BT, Crowell JA. Estimating heading during real and simulated eye movements. *Vision Res.* 1996;36(3):431–43.
6. Barbeau H, Rossignol S. Recovery of locomotion after chronic spinalization in the adult cat. *Brain Res.* 1987;412(1):84–95.
7. Benazzouz A, Hallett M. Mechanism of action of deep brain stimulation. *Neurology* 2000;55(12 Suppl 6):S13–6.
8. Bertram JE, Ruina A. Multiple walking speed-frequency relations are predicted by constrained optimization. *J. Theor. Biol.* 2001;209(4):445–53.
9. Bosco G, Poppele RE. Proprioception from a spinocerebellar perspective. *Physiol. Rev.* 2001;81(2):539–68.
10. Bosco G, Poppele RE. Reference frames for spinal proprioception: kinematics based or kinetics based? *J. Neurophysiol.* 2000;83(5):2946–55.
11. Brodie EE, Ross HE. Sensorimotor mechanisms in weight discrimination. 1985;36(5):477–81.
12. Brown TG. The Intrinsic Factors in the Act of Progression in the Mammal. *Proc. R. Soc. B Biol. Sci.* 1911;84(572):308–19.
13. Browning RC, Baker EA, Herron JA, Kram R. Effects of obesity and sex on the energetic cost and preferred speed of walking. *J. Appl. Physiol.* 2006;100(2):390–8.

14. Cavagna GA, Heglund NC, Taylor CR. Mechanical work in terrestrial locomotion: two basic mechanisms for minimizing energy expenditure [Internet]. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* 1977;233:R243–61. Available from: <http://ajpregu.physiology.org/content/233/5/R243.abstract>
15. Cavagna GA, Thys H, Zamboni A. The sources of external work in level walking and running. *J. Physiol.* 1976;262(3):639–57.
16. Cheron G, Duvinage M, De Saedeleer C, et al. From spinal central pattern generators to cortical network: Integrated BCI for walking rehabilitation. *Neural Plast.* 2012;2012
17. Conway BA, Hultborn H, Kiehn O. Proprioceptive input resets central locomotor rhythm in the spinal cat. *Exp. Brain Res.* 1987;68(3):643–56.
18. Cordo PJ. Kinesthetic control of a multijoint movement sequence. *J. Neurophysiol.* 1990;63(1):161–72.
19. Davis WJ, Ayers JL. Locomotion: control by positive-feedback optokinetic responses. *Science* 1972;177(44):183–5.
20. Deco G, Scarano L, Soto-Faraco S. Weber's law in decision making: integrating behavioral data in humans with a neurophysiological model. [Internet]. *J. Neurosci.* 2007;27(42):11192–200. [cited 2014 Dec 15] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17942714>
21. Deco G, Scarano L, Soto-Faraco S. Weber's law in decision making: integrating behavioral data in humans with a neurophysiological model. *J. Neurosci.* 2007;27(42):11192–200.
22. Deliagina TG, Orlovsky GN, Pavlova GA. The capacity for generation of rhythmic oscillations is distributed in the lumbosacral spinal cord of the cat. *Exp. Brain Res.* 1983;53(1):81–90.
23. Dietz V, Duysens J. Significance of load receptor input during locomotion: A review. *Gait Posture* 2000;11(2):102–10.
24. Dietz V, Zijlstra W, Duysens J. Human neuronal interlimb coordination during split-belt locomotion. *Exp. Brain Res.* 1994;101(3):513–20.
25. Dietz V. Proprioception and locomotor disorders. *Nat. Rev. Neurosci.* 2002;3(10):781–90.
26. Dietz V. Spinal cord pattern generators for locomotion [Internet]. *Clin. Neurophysiol.* 2003;114(8):1379–89. [cited 2014 Oct 30] Available from: <http://linkinghub.elsevier.com/retrieve/pii/S1388245703001202>

27. Dimitrijevic MR, Gerasimenko Y, Pinter MM. Evidence for a spinal central pattern generator in humans. In: *Annals of the New York Academy of Sciences*. 1998 p. 360–76.
28. Drew T, Andujar JE, Lajoie K, Yakovenko S. Cortical mechanisms involved in visuomotor coordination during precision walking. *Brain Res. Rev.* 2008;57(1):199–211.
29. Drew T, Prentice S, Schepens B. Cortical and brainstem control of locomotion. [Internet]. *Prog. Brain Res.* 2004;143(03):251–61.[cited 2014 Dec 17] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14653170>
30. Duysens J, Pearson KG. Inhibition of flexor burst generation by loading ankle extensor muscles in walking cats. *Brain Res.* 1980;187(2):321–32.
31. Edgerton VR, Roy RR. Robotic training and spinal cord plasticity. *Brain Res. Bull.* 2009;78(1):4–12.
32. Efron B. Bootstrap Methods: Another Look at the Jackknife. *Ann. Stat.* 1979;7(1):1–26.
33. Ernst MO, Banks MS. Humans integrate visual and haptic information in a statistically optimal fashion. *Nature* 2002;415(6870):429–33.
34. Fechner G. *Elemente der Psychophysik*. 1860.572 Available from: <http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:No+Title#0>
<http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Elemente+der+Psychophysik#0>
35. Fechner, G. T . (1860). Elements of psychophysics.pdf[date unknown];
36. Finch L, Barbeau H, Arsenault B. Influence of body weight support on normal human gait: development of a gait retraining strategy. *Phys. Ther.* 1991;71(11):842–55; discussion 855–6.
37. Finley JM, Statton M a, Bastian AJ. A novel optic flow pattern speeds split-belt locomotor adaptation. [Internet]. *J. Neurophysiol.* 2014;111(5):969–76. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24335220>
38. Fry SN, Rohrseitz N, Straw AD, Dickinson MH. Visual control of flight speed in *Drosophila melanogaster*. *J. Exp. Biol.* 2009;212(Pt 8):1120–30.
39. Fukuyama H, Ouchi Y, Matsuzaki S, et al. Brain functional activity during gait in normal subjects: A SPECT study. *Neurosci. Lett.* 1997;228(3):183–6.
40. Furlan M, Wann JP, Smith AT. A Representation of Changing Heading Direction in Human Cortical Areas pVIP and CSv. [Internet]. *Cereb. Cortex* 2013;bht132 – . Available from: <http://cercor.oxfordjournals.org/content/early/2013/05/23/cercor.bht132.abstract>

41. Gaydos H. Sensitivity in the judgement of size by finger-span. *Am. J. Psychol.* 1958;71(3):557–62.
42. Gescheider G. *Psychophysics: The Fundamentals*. 3rd ed. Matwah: Lawrence Erlbaum Associates, Inc.; 2013.1-54
43. Gibson JJ. *The perception of the visual world*. 1950.19510701-19510701Available from: <http://bjp.rcpsych.org/cgi/doi/10.1192/bjp.98.413.717-a>
44. GIBSON JJ. Visually controlled locomotion and visual orientation in animals. *Br. J. Psychol.* 1958;49(3):182–94.
45. Gordon AM, Huxley AF, Julian FJ. The variation in isometric tension with sarcomere length in vertebrate muscle fibres. *J. Physiol.* 1966;184(1):170–92.
46. Gordon J, Abramov I, Chan H. Describing color appearance: hue and saturation scaling. *Percept. Psychophys.* 1994;56(1):27–41.
47. Grillner S, Wallén P, Saitoh K, Kozlov A, Robertson B. Neural bases of goal-directed locomotion in vertebrates-An overview. *Brain Res. Rev.* 2008;57(1):2–12.
48. Grillner S. Biological Pattern Generation: The Cellular and Computational Logic of Networks in Motion. *Neuron* 2006;52(5):751–66.
49. Grillner S. *Control of locomotion in bipeds, tetrapods, and fish*. V. Brooks. Baltimore: Waverly Press; 1981.1179-236
50. Gu Y, Watkins P V, Angelaki DE, DeAngelis GC. Visual and nonvisual contributions to three-dimensional heading selectivity in the medial superior temporal area. *J. Neurosci.* 2006;26(1):73–85.
51. Hallett M. Transcranial magnetic stimulation and the human brain. *Nature* 2000;406(6792):147–50.
52. Harkema S, Gerasimenko Y, Hodes J, et al. Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: A case study. *Lancet* 2011;377(9781):1938–47.
53. Harkema SJ, Hurley SL, Patel UK, Requejo PS, Dobkin BH, Edgerton VR. Human lumbosacral spinal cord interprets loading during stepping. *J. Neurophysiol.* 1997;77(2):797–811.
54. Harkema SJ. Plasticity of interneuronal networks of the functionally isolated human spinal cord. *Brain Res. Rev.* 2008;57(1):255–64.

55. Hathout GM, Bhidayasiri R. Midbrain ataxia: An introduction to the mesencephalic locomotor region and the pedunculopontine nucleus. *Am. J. Roentgenol.* 2005;184(3):953–6.
56. Hecht S. THE VISUAL DISCRIMINATION OF INTENSITY AND THE WEBER-FECHNER LAW. *J. Gen. Physiol.* 1924;7(2):235–67.
57. Hill A V. The Heat of Shortening and the Dynamic Constants of Muscle. *Proc. R. Soc. B Biol. Sci.* 1938;126(843):136–95.
58. Hillis JM, Watt SJ, Landy MS, Banks MS. Slant from texture and disparity cues: optimal cue combination. *J. Vis.* 2004;4(12):967–92.
59. Hubli M, Dietz V. The physiological basis of neurorehabilitation--locomotor training after spinal cord injury. [Internet]. *J. Neuroeng. Rehabil.* 2013;10:5. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3584845&tool=pmcentrez&rendertype=abstract>
60. Hulliger M, Dürmüller N, Prochazka A, Trend P. Flexible fusimotor control of muscle spindle feedback during a variety of natural movements. *Prog. Brain Res.* 1989;80:87–101; discussion 57–60.
61. Hunter LC, Hendrix EC, Dean JC. The cost of walking downhill: Is the preferred gait energetically optimal? *J. Biomech.* 2010;43(10):1910–5.
62. Huxley AF. Muscular contraction [Internet]. *J Physiol* 1974;243:1–43. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=4449057
63. Ichiyama RM, Courtine G, Gerasimenko YP, et al. Step training reinforces specific spinal locomotor circuitry in adult spinal rats. *J. Neurosci.* 2008;28(29):7370–5.
64. Indow T, Stevens SS. Scaling of saturation and hue [Internet]. *Percept. Psychophys.* 1966;1(4):253–71. Available from: <http://www.springerlink.com/index/10.3758/BF03207390>
65. Jahn K, Deutschländer A, Stephan T, et al. Supraspinal locomotor control in quadrupeds and humans. *Prog. Brain Res.* 2008;171:353–62.
66. Jones LA, Hunter IW. A perceptual analysis of viscosity. *Exp. Brain Res.* 1993;94(2):343–51.
67. Jones LA. Matching forces: Constant errors and differential thresholds. *Perception* 1989;18(5):681–7.

68. Kably B, Drew T. Corticoreticular pathways in the cat. I. Projection patterns and collaterization. *J. Neurophysiol.* 1998;80(1):389–405.
69. Kiehn O, Kjaerulff O. Distribution of central pattern generators for rhythmic motor outputs in the spinal cord of limbed vertebrates. In: *Annals of the New York Academy of Sciences*. 1998 p. 110–29.
70. Kremer E, Lev-Tov A. Localization of the spinal network associated with generation of hindlimb locomotion in the neonatal rat and organization of its transverse coupling system. *J. Neurophysiol.* 1997;77(3):1155–70.
71. Kuo AD, Donelan JM, Ruina A. Energetic consequences of walking like an inverted pendulum: step-to-step transitions. *Exerc. Sport Sci. Rev.* 2005;33(2):88–97.
72. Lauzière S, Miéville C, Duclos C, Aissaoui R, Nadeau S. Perception threshold of locomotor symmetry while walking on a split-belt treadmill in healthy elderly individuals. [Internet]. *Percept. Mot. Skills* 2014;118(2):475–90. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24897881>
73. Levine WS. *The Control Handbook*. 1996.1566 Available from: <http://www.amazon.fr/Control-Handbook-William-S-Levine/dp/0849385709>
74. Lu P, Woodruff G, Wang Y, et al. Long-Distance Axonal Growth from Human Induced Pluripotent Stem Cells after Spinal Cord Injury. *Neuron* 2014;
75. Macko RF, Ivey FM, Forrester LW, et al. Treadmill exercise rehabilitation improves ambulatory function and cardiovascular fitness in patients with chronic stroke: a randomized, controlled trial. *Stroke*. 2005;36(10):2206–11.
76. MacNeillage PR, Banks MS, Berger DR, Bühlhoff HH. A Bayesian model of the disambiguation of gravito-inertial force by visual cues. *Exp. Brain Res.* 2007;179(2):263–90.
77. MacNeillage PR, Ganesan N, Angelaki DE. Computational approaches to spatial orientation: from transfer functions to dynamic Bayesian inference. *J. Neurophysiol.* 2008;100(6):2981–96.
78. Mancini M, Horak FB. The relevance of clinical balance assessment tools to differentiate balance deficits. *Eur. J. Phys. Rehabil. Med.* 2010;46(2):239–48.
79. Marigold S., Drew T. Contribution of cells in the posterior parietal cortex to the planning of visually guided locomotion in the cat: effects of temporary visual interruption. *J. Neurophysiol.* 2011;105(5):2457–70.

80. McGill WJ, Goldberg JP. A study of the near-miss involving Weber's law and pure-tone intensity discrimination. *Percept. Psychophys.* 1968;4(2):105–9.
81. McMahon TA, Cheng GC. The mechanics of running: How does stiffness couple with speed? In: *Journal of Biomechanics*. 1990 p. 65–78.
82. Mehrholz J, Kugler J, Pohl M. Locomotor training for walking after spinal cord injury. *Cochrane Database Syst. Rev.* 2008;(2)
83. Minassian K, Jilge B, Rattay F, et al. Stepping-like movements in humans with complete spinal cord injury induced by epidural stimulation of the lumbar cord: electromyographic study of compound muscle action potentials. *Spinal cord Off. J. Int. Med. Soc. Paraplegia* 2004;42(7):401–16.
84. Minetti AE, Alexander RM. A theory of metabolic costs for bipedal gaits. *J. Theor. Biol.* 1997;186(4):467–76.
85. Mori, S, Matsuyama, K., Mori, F., and Nakajima K. *Supraspinal sites that induce locomotion in the vertebrate central nervous system*. Philidephia: 2001.25-39
86. Morton SM, Bastian AJ. Cerebellar control of balance and locomotion. *Neuroscientist* 2004;10(3):247–59.
87. Nagayama T, Hisada M. Opposing parallel connections through crayfish local nonspiking interneurons. *J. Comp. Neurol.* 1987;257(3):347–58.
88. Oberlin K. Variation in intensive sensitivity to lifted weights. *J. Exp. Psychol.* 1936;19(4):438–55.
89. Osaki Y, Kunin M, Cohen B, Raphan T. Relative contribution of walking velocity and stepping frequency to the neural control of locomotion. [Internet]. *Exp. brain Res.* 2008;185(1):121–35.[cited 2014 Dec 15] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17952421>
90. Pardasaney PK, Latham NK, Jette AM, et al. Sensitivity to Change and Responsiveness of Four Balance Measures for Community-Dwelling Older Adults. *Phys. Ther.* 2012;92(3):388–97.
91. Pearson KG, Collins DF. Reversal of the influence of group Ib afferents from plantaris on activity in medial gastrocnemius muscle during locomotor activity. *J. Neurophysiol.* 1993;70(3):1009–17.
92. Pearson KG, Gordon J. Spinal Reflexes [Internet]. *Princ. Neurosci.* 2000;713–36.Available from: [papers3://publication/uuid/5C2C23FB-0C8C-4D41-8685-4F912A1C508A](https://pubmed.ncbi.nlm.nih.gov/publication/5C2C23FB-0C8C-4D41-8685-4F912A1C508A)

93. Pearson KG, Misiaszek JE. Use-dependent gain change in the reflex contribution to extensor activity in walking cats. *Brain Res.* 2000;883(1):131–4.
94. Pearson KG. Common principles of motor control in vertebrates and invertebrates. *Annu. Rev. Neurosci.* 1993;16:265–97.
95. Perret C, Cabelguen JM. Main characteristics of the hindlimb locomotor cycle in the decorticate cat with special reference to bifunctional muscles. *Brain Res.* 1980;187(2):333–52.
96. Petersen N, Christensen LO, Nielsen J. The effect of transcranial magnetic stimulation on the soleus H reflex during human walking. *J. Physiol.* 1998;513 (Pt 2:599–610.
97. Petersen NT, Butler JE, Marchand-Pauvert V, et al. Suppression of EMG activity by transcranial magnetic stimulation in human subjects during walking. *J. Physiol.* 2001;537(Pt 2):651–6.
98. Petersen TH, Willerslev-Olsen M, Conway B a, Nielsen JB. The motor cortex drives the muscles during walking in human subjects. [Internet]. *J. Physiol.* 2012;590(Pt 10):2443–52. Available from:
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3424763&tool=pmcentrez&rendertype=abstract>
99. Poppele R, Bosco G. Sophisticated spinal contributions to motor control. *Trends Neurosci.* 2003;26(5):269–76.
100. Prochazka A, Gritsenko V, Yakovenko S, Control IS, Proske SGGU, Stuart DG. SENSORY CONTROL OF LOCOMOTION : REFLEXES VERSUS HIGHER-LEVEL CONTROL. 2002;
101. Prochazka A, Yakovenko S. The neuromechanical tuning hypothesis. [Internet]. *Prog. Brain Res.* 2007;165:255–65.[cited 2014 Dec 15] Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/17925251>
102. Prokop T, Berger W, Zijlstra W, Dietz V. Adaptational and learning processes during human split-belt locomotion: interaction between central mechanisms and afferent input. *Exp. Brain Res.* 1995;106(3):449–56.
103. Proske U, Gandevia SC. The Proprioceptive Senses: Their Roles in Signaling Body Shape, Body Position and Movement, and Muscle Force. *Physiol. Rev.* 2012;92(4):1651–97.
104. Ralston HJ. Energy-speed relation and optimal speed during level walking. *Int. Zeitschrift für Angew. Physiol. Einschl. Arbeitsphysiologie* 1958;17(4):277–83.

105. Le Ray D, Juvin L, Ryczko D, Dubuc R. *Supraspinal control of locomotion. The mesencephalic locomotor region*. 2011;51-70
106. Redon C, Hay L, Velay JL. Proprioceptive control of goal-directed movements in man, studied by means of vibratory muscle tendon stimulation. *J. Mot. Behav.* 1991;23(2):101–8.
107. Sainburg RL, Poizner H, Ghez C. *Loss of proprioception produces deficits in interjoint coordination*. 1993.
108. Schubert M, Curt A, Jensen L, Dietz V. Corticospinal input in human gait: Modulation of magnetically evoked motor responses. *Exp. Brain Res.* 1997;115(2):234–46.
109. Serrien DJ, Teasdale N, Bard C, Fleury M. Age-related differences in the integration of sensory information during the execution of a bimanual coordination task. *J. Mot. Behav.* 1996;28(4):337–47.
110. Shik M.L., Severin, F.V., & Orlovsky GN. Control of walking and running by means of electric stimulation of the mesencephalon. *Electroencephalogr. Clin. Neurophysiol.* 1969;26(5):549.
111. Shik ML, Orlovsky GN. Neurophysiology of locomotor automatism. *Physiol. Rev.* 1976;56(3):465–501.
112. Sinkjaer T, Andersen JB, Ladouceur M, Christensen LO, Nielsen JB. Major role for sensory feedback in soleus EMG activity in the stance phase of walking in man. *J. Physiol.* 2000;523 Pt 3:817–27.
113. Sirota MG, Di Prisco GV, Dubuc R. Stimulation of the mesencephalic locomotor region elicits controlled swimming in semi-intact lampreys. *Eur. J. Neurosci.* 2000;12(11):4081–92.
114. Sittig AC, Denier van der Gon JJ, Gielen CC. Separate control of arm position and velocity demonstrated by vibration of muscle tendon in man. *Exp. Brain Res.* 1985;60(3):445–53.
115. Ting LH, Van Antwerp KW, Scrivens JE, et al. Neuromechanical tuning of nonlinear postural control dynamics. *Chaos* 2009;19(2)
116. Warren WH, Hannon DJ. Direction of self-motion is perceived from optical flow. *Nature* 1988;336(6195):162–3.
117. Wernig A, Müller S. Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries. *Paraplegia* 1992;30(4):229–38.

118. Winter DA. Biomechanics and motor control of human Gait. In: *Biomechanics and motor control of human Gait: Normal, Elderly and Pathological*. 1991 p. 143.
119. Yakovenko S, McCrea D a, Stecina K, Prochazka a. Control of locomotor cycle durations. [Internet]. *J. Neurophysiol.* 2005;94(2):1057–65.[cited 2014 Dec 15] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15800075>
120. Yakovenko S. *Chapter 10--a hierarchical perspective on rhythm generation for locomotor control*. 1st ed. Elsevier BV.; 2011.151-66[cited 2014 Dec 15] Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21333808>
121. Zajac FE. Muscle and tendon: properties, models, scaling, and application to biomechanics and motor control. *Crit. Rev. Biomed. Eng.* 1989;17(4):359–411.

Figures

Figure 3. Study schematic and design. A descending velocity signal is relayed to CPGs at the spinal cord which produce phases appropriate for the desired speed. An ascending velocity signal is used to compare the actual to the desired speed. Appropriate adjustments are made so that the actual output matches the desired. This schematic is based off control theory. In order for velocity to be a control signal, it must be sensed accurately.

Figure 4. Ground reaction force analysis. Ground reaction forces were filtered at 200 Hz, using a low pass 2nd order Butterworth filter. ON and OFF events are depicted by green and red events, respectively and were marked using supervised automatic thresholding. To calculate cycle time, 2 corresponding green events were subtracted from one another.

Figure 5. Experimental velocity detection threshold. ANOVA of success probability for trials with alterations in proprioceptive drive with Tukey's post hoc test for significance. No significant differences were present between loading condition and detection ability. However, significant differences were present between the speeds of 0.02, 0.05, 0.10, and 0.20 m/s ($p < .05$). This indicates subjects were able to significantly detect changes in speed at the level of 0.02 m/s, or a Weber's fraction of 2%.

Figure 6. Functional velocity detection threshold calculations. Weber's fraction calculation by functionally fitting success probability with speed in each subject. The left panel shows the tuning curve for velocity detection, with left limb perturbations reflected by negative velocity changes and positive changes reflecting right limb perturbations. These differences in speed were plotted against success probability. The relationship between success probability and speed difference was functionally fit using Weibull analysis. This single subject was able to accurately detect 0.009 (0.9%), 0.006 (0.6%), and 0.007 (0.7%) for the normal, loaded, and unloaded conditions, respectively.

Figure 7. Group analysis of success probability between conditions (normal, loaded, and unloaded). Subjects were able to detect changes in velocity of 1% at the level of 50%. ANOVA test for significance indicates no differences between loading condition and detection ability.

Figure 8. Averages of vertical ground reaction forces display significant differences in loading between conditions. The intervals of each condition do not overlap, so there is 95% confidence that loading was significantly different.

Figure 9. Analysis of step cycle variability as a function of success by speed using bootstrap analysis. We expected there to be a negative relationship, indicated by the arrow. The variance of incorrect trails was subtracted from correct trials and a two-tailed t-test was done on the means at each speed. Significance is reached on this test if the confidence intervals are to the left of 0. Step cycle variance did significantly effect detection ability at the speed of 0.01 m/s (1%). A negative trend was observed for the other speeds of 0.02, 0.05, and 0.10 m/s. The mean observed at the speed of 0.10 m/s could be due to excessive gait variability present at that perturbation.

Figure 10. Heading direction hypothesis. High velocity discrimination ability may be associated with the control of heading during locomotion. When heading is changes, the system creates a desired velocity signal (v^*), which is sent to each limb, seperately. This causes one leg to move faster than the other, and this produces an error signal between the limbs. This velocity signal is further propogated to control centers, feeding into the spinal cord. Velocity control feedback mechanisms stabalize the control of heading by using error control of the desired velocity. In this experiement, we asked subjects to report the error in velocity between limbs (error in heading), and found they were able to detect it at the level of 1%. Errors in this velocity signal appear to drive changes necessary to adjust locomotor phases and tune heading direction.

Appendices

A: Screening Questionnaire

Yakovenko

IRB Protocol - Screening Questionnaire

Script for Conducting a Phone Interview

Screening the Potential Participants for Research on Mechanisms of Neural Control of the Musculoskeletal System in Humans

Hi my name is _____. Let me begin by telling you that I am an employee of WVU and a member of the Neural Engineering Laboratory. We are doing research that investigates how the central nervous system makes our body move.

I'd like to take a few minutes to explain our research study with the hope that you might consider participating. I want to be sure that you understand what I'm doing and what your participation would mean for you if you agree to participate.

The title of the study is Mechanisms of Neural Control of the Musculoskeletal System in Humans. We will ask you to participate in one of three experiments. We will ask you to either walk on the ground along predetermined paths, or to point to visual targets with your right arm. During these movements we will use either transcranial magnetic stimulation, electrical stimulation, or mechanical vibration to evoke responses in the muscles at different times during these tasks. Results of this study will help understand the mechanisms of movement control in humans. This insight will be valuable for developing rehabilitation treatments for neurological patients.

If you want to participate in this important study, I will ask you to sign a consent form when you arrive to the laboratory. To determine if you can participate in our study, may I ask you a few questions about your health?

1. Are you between the ages of 18 and 70?
2. Do you have any serious medical conditions, for example epilepsy, stroke, chronic pain, or other conditions that involve the nervous system or the muscles or bones?
3. Do you take any neurologically active drugs, for example prescription medication that affects mood, sleep, movements, or reduces pain?
4. Have you ever had injuries to your arms or legs?
5. Are you or do you think you might be pregnant?
6. Have you ever been diagnosed with epilepsy or do you have a family history of epilepsy or unexplained loss of consciousness?
7. Do you have tinnitus?
8. Do you have migraines?
9. Do you have metal or medical implants in the head or a pacemaker?
10. Are you taking any medication that prevent or may cause seizures?

1 of 3

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11. Are you recovering from alcohol or other drug use?

If you agree to participate in the study, we will ask you to come to our laboratory at WVU for one visit. Before the beginning of the experiment, we will ask you to read and sign a Consent Form. Would you like to see or read the consent form before your visit? Do you have any questions? When would you be available for the visit to our laboratory?

Appendix - List of Medications that May Cause Seizure

Relative Hazards

Mianserin (Bolvidon, Norval, Tolvon)
Fluoxetine (Prozac)
Fluvoxamine (Luvox)
Paroxetine (Aropax, Paxil)
Sertraline (Zoloft)
Citalopram (Celexa, Cipramil)
Reboxetine (Edronax, Vestra)
Venlafaxine (Effexor, Efexor)
Duloxetine (Cymbalta, Yentreve)
Bupropion (Aplenzin, Wellbutrin, Wellbutrin SR, Wellbutrin XL)
Mirtazapine (Remeron, Avanza, Zispin, Reflex)
Fluphenazine (Prolixin)
Pimozide (Orap)
Haloperidol (Haldol)
Olanzapine (Zyprexa, Zalasta, Zolafren, Olzapin, Oferta, Zypadhera or in combination with fluoxetine Symbyax)
Quetiapine (Seroquel)
Aripiprazole (Abilify, Abilify Discmelt)
Ziprasidone (Geodon)
Risperidone (Risperdal)
Chloroquine (Aralen)
Mefloquine (Lariam)
Imipenem (Primaxin)
penicillin
ampicillin (Omnipen, Polycillin, Principen)
cephalosporins (Cephalosporium)
metronidazole (Flagyl)
isoniazid (Laniazid, Nydrazid)
levofloxacin (Levaquin)
cyclosporine (USAN, BAN)
chlorambucil (Leukeran by GlaxoSmithKline)
vincristine (Oncovin)
methotrexate (Trexall, Rheumatrex)

cytosine arabinoside (Cytarabine)
BCNU (Carmustine)
Lithium (Eskalith CR, Eskalith, Lithobid)
Anticholinergics (ipratropium, Atrovent, ipratropium, albuterol, Combivent, DuoNeb)
Antihistamines (Allegra, AllegraD, Astelin, Clarinex, Claritin)
Sympathomimetics (ephedrine, pseudoephedrine, amphetamine, methamphetamine, methylphenidate (Ritalin), lisdexamfetamine (Vyvanse), cocaine (found in Erythroxylum coca, Coca), cathinone, cathine, benzylpiperazine (BZP), methylenedioxypyrovalerone (MDPV), 4-methylaminorex, pemoline (Cylert), phenmetrazine (Preludin), propylhexedrine (Benzedrex)

Strong Relative Hazards

Participants are considered a strong relative risk of seizures if they are going through withdrawal from one of the following drugs

alcohol
barbiturates (Examples include amobarbital, butalbital, cyclobarbitol, pentobarbital, allobarbitol, methylphenobarbital, phenobarbital, secobarbital, vinylbital)
benzodiazepines (Examples include Xanax, Valium, Klonopin, Ativan, Restoril, Halcion)
meprobamate (Equanil, Mepriam)
chloral hydrate (Somnote, Aquachloral Supprettes)

B: Consent Form

Human Research Protocol
More Than Minimal Risk Form
(With HIPAA)

Consent Form

Principal Investigator Yakovenko, Sergiy
Department MEDICINE – Exercise Physiology
Protocol Number 1309092298
Study Title Mechanisms of neural control of the musculoskeletal system.
Co-Investigator(s) Valeriya Gritsenko, Paola Pergami, Kyla Galbreath, Erienne Olesh
Sponsor (if any) WVU

Contact Persons

In the event you experience any side effects or injury related to this research, you should contact Dr. Yakovenko at (304) 293-7316 or Dr. Pergami at (304) 293-7331. (After hours contact Dr. Yakovenko at (304) 602-2026).

If you have any questions, concerns, or complaints about this research, you can contact Dr. Yakovenko at (304) 293-7316.

For information regarding your rights as a research subject contact the Office of Research Compliance at (304) 293-7073.

In addition if you would like to discuss problems, concerns, have suggestions related to research, or would like to offer input about the research, contact the Office of Research Integrity and Compliance at (304) 293-7073.

Introduction

You, _____, have been asked to participate in this research study, which has been explained to you by _____. This study is being conducted by Dr. Sergiy Yakovenko, PhD, Dr. Valeriya Gritsenko, PhD, and Dr. Paola Pergami, MD, PhD in the Department of Human Performance at West Virginia University with funding provided by WVU.

Purpose(s) of the Study

The purpose of this study is to learn more about how the brain and spinal cord are involved in the control of walking. To conduct this study, we will recruit healthy volunteers, who will be asked to either walk on the ground along a path, or to walk on a treadmill. During walking, we will use no stimulation, magnetic stimulation, electrical stimulation, or mechanical vibrations on the brain. This will cause responses in the muscles at different times during walking. We will record joint movements and muscle activity during these tasks using video and electrical recordings. Results of this study will help understand movement control in humans. This insight will be valuable for developing rehabilitation treatments for neurological patients. WVU expects to enroll approximately 100 subjects.

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Subject's
Initials _____
Date _____

Approved:2-Mar-2015Expires:1-Mar-2016Number:1309092298

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Description of Procedures

You will be assigned to one of the following six groups based on (1) whether or not you have any medical exclusions to stimulation; and, (2) the availability of laboratory personnel. If you have any medical exclusions to stimulation, you will be assigned to one of the following groups:

Group 1:

You will be asked to move on a treadmill with two different belts for several 15 min trials with resting time in between. You will be wearing a safety harness to prevent falls and help maintain your balance. While you are walking, we will record your muscle activity, ground reaction forces, and joint movements. To test your postural stability, you will be based to maintain standing posture when the support surface is moved front-to-back and/or side-to-side. We will record your reflexive responses to these movements. This task will take about one hour.

Group 2:

You will be asked to walk on a treadmill with two belts at different speeds. You will be wearing a harness to prevent falls and to help keep your balance. We will unload a part of your weight (5-15%) using the body weight support system in the unloaded 15 min trial. Also, we will load you with additional 5-15% of your weight in the loaded 15 min trial. We will record the ground reaction forces, video of movement, and muscle activity. You will be asked to tell us differences in speed between the belts on the treadmill.

Group 3:

You will be asked to walk on a treadmill while wearing a light-weight and elastic object attached to one leg. You will be asked to wear a harness to help you maintain your balance and prevent you from falling during locomotion. As you walk, you will avoid touching the obstacle. This way, we will modify the swing of one of your legs during the 15 min trial of walking at your preferred speed. We will ask you to walk another 15 min without the obstacle after each trial with the obstacle. We will record your forces, muscle electrical activity, and joint movements with video.

Group 4:

You will be asked to walk along a curved path while wearing a light-weight and elastic object attached to one leg. As you walk, you will avoid touching the obstacle. This way, we will modify the swing of one of your legs during 15 min trial of walking at your preferred speed. We will ask you to walk for another 15 min without the obstacle after each trial with the obstacle. We will record your forces, muscle electrical activity, and joint movements with video.

If you do not have any medical exclusions to stimulation, you will be assigned to one of the following two groups. If you are in Group 5 or 6, you will also be given the opportunity to take part in the activities described in Group 1:

Group 5:

We will briefly stimulate your brain using a magnet held above your head. This stimulation produces a very brief, clicking sound so you will be asked to wear earplugs during this procedure. Since we are studying the area of the brain responsible for walking movements, you may see and feel a muscle twitch during stimulation. The stimulation may also cause twitches in your face muscles. We will pair the TMS with a brief stimulation of a single peripheral nerve or mechanical vibration of a muscle. We will stimulate at different times in the movement. The investigator will

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Subject's

Initials _____
Date _____

Approved:2-Mar-2015Expires:1-Mar-2016Number:1309092298

demonstrate the effect of TMS on another investigator before you decide to begin participation in the study.

Group 6:

We will apply a low-level constant current to the scalp of your head during locomotion on the treadmill. The low-level of current produces no muscle twitches. It is equivalent to a regular constant level battery attached to your skin. The current will be applied for 15 min. We will also vibrate your leg muscles using physiological vibrators.

Prior to any experimentation, you will be asked to fill out a questionnaire to determine if you are able to participate in any of the groups. You will have the opportunity to see the questionnaire before signing this consent form.

Risks and Discomforts

Please be aware that this particular procedure might involve risks, which are currently unpredictable. TMS is a technique that has been used for about more than 20 years. When used briefly, such as in these experiments, and used at the recommended settings, TMS is not believed to have long-term effects or be dangerous. It cannot interfere with critical brain functions (like breathing) because the magnetic fields reach only the forebrain, which does not perform functions critical for life support.

Electrical stimulation of nerves and direct current stimulation of the brain are techniques that have been used for more than 50 years. When used briefly, such as in these experiments and used at the recommended settings, the stimulation is not believed to have long-term effects or be dangerous. Thousands of people have been studied using electrical stimulation of nerves and direct current stimulation of the brain without any reported side effects.

Subjects who may be potentially harmed by TMS or tDCS due to their medical or metal implants history of seizures or epilepsy or tinnitus or migraine or pregnancy or another other medical condition will be excluded from the study. This minimizes the risk of the experimental procedures aggravating preexisting medical conditions. These risks do not apply to people without preexisting medical conditions. TMS can cause a headache that may last for one or two hours after the experiment. If subjects develop a headache during the experimental session, the experiment will be stopped and he or she will be advised to contact his/her health provider. TMS produces a very brief clicking sound. When the TMS is set at a higher setting, the sound generated will be more intense, such as slamming a door. This could cause hearing damage if the necessary precautions are not taken. We will protect the ear by using earplugs throughout the experiment. There may be an allergic reaction to the substance used in the gel and adhesive tape of EMG electrodes. There is also the possibility of uncommon or previously unknown side effects to any of the procedures used in this study. If a subject feels uncomfortable, the experiment will stop immediately and he or she will be advised to contact his/her health provider. Subjects who may be potentially harmed by TMS or tDCS due to their medical or metal implants history of seizures or epilepsy or tinnitus or migraine or pregnancy or any other medical condition will be excluded from the study.

Thousands of people have been studied using TMS without any reported side effects except headache. Migraine headache can be triggered in people with a history of migraine headache. There have been no reports of single-pulse TMS producing seizures in normal subjects. However, there have been some reports of seizures following repetitive high frequency TMS in patients who had an existing seizure disorder or a brain injury from problems such as stroke, although a causal relationship was not established. Although repetitive TMS has been used to treat seizure disorders (refractory

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epilepsy), if you have a diagnosed seizure disorder you will not be allowed to participate. It should be noted too that there is no relationship between TMS and new onset of seizure disorder.

You understand that if you take any active drugs that act on the central nervous system (CNS active drugs) you would not be allowed to participate. Examples of such drugs are prescription medication that affects mood (medication to treat depression), sleep (medication to treat insomnia), movements (medication to treat Parkinson's disease), or pain (medication to treat chronic pain). For most CNS active drugs, there is no reported ill effect with using these drugs during our experiments, they will however, interfere with the data collected. You would not be allowed to participate if you have any clips or implants in your head because TMS or ES could make the metal in them move out of place causing injury. TMS and ES could also disturb the electrical function of a pacemaker causing it to malfunction. TMS produces a very brief clicking sound. When the TMS is set at a higher setting, the sound generated will be more intense such as slamming a door. This could cause hearing damage if the necessary precautions are not taken. The use of ear protection, such as ear plugs is required to prevent the risk of hearing impairment. The effect, if any, of using TMS on the developing baby is unknown. Participating in this study may involve risks to the unborn child, such as in the case of the unlikely event of a seizure may harm the developing baby. For this reason, females who are pregnant will not be allowed to participate in this study. If you are a female subject and may be pregnant you must notify the investigator immediately. There are no known risks or side effects from having electrodes attached to your skin, a measure commonly used in everyday medical practices. There may, however, be an allergic reaction to the substance used in the gel and adhesive tape from attaching these electrodes. There is also the possibility of uncommon or previously unknown side effects to any of the procedures used in this study. You understand that you may ask to stop at any time and withdraw from the study. If you feel uncomfortable, you will need to tell the investigator and withdraw from the study.

Alternatives

You do not have to participate in this study.

Benefits

There will be no direct benefit to the subject for participation in this research study. The knowledge gained from this study may eventually benefits others. The potential benefit to neurological patients in the future is the improved understanding of the motor control mechanisms that will lead to more effective rehabilitation.

Financial Considerations

There are no special fees for participating in this study.

You will be paid \$20 for a single visit, up to a total of \$20 if you are involved in a group without magnetic or electrical stimulation of the brain. If you participate in a study involving magnetic or electrical stimulation of the brain, you will be paid \$50, up to a total of \$50. If you withdraw before the end of the study, no additional payments will be made.

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Voluntary Compensation

If you are injured as a result of this research, treatment will be available. Responsibility for this treatment will be borne by: (1) the insurance company; OR (2) by you. In the event that you are physically injured as a result of participating in this research, care will be available. You will, however, be responsible for the charges for the care. There is no commitment to provide any compensation for research-related injury. You should realize, however, that you have not released this institution from liability for negligence. Please contact the investigator, Sergiy Yakovenko, PhD at 304-293-7316 if you are injured or for further information.

Confidentiality

Any information about you that is obtained as a result of your participation in this research will be kept as confidential as legally possible. Your research records and test results, just like hospital records, may be subpoenaed by court order or may be inspected by the study sponsor or federal regulatory authorities (including the FDA if applicable) without your additional consent.

In addition, there are certain instances where the researcher is legally required to give information to the appropriate authorities. These would include mandatory reporting of infectious diseases, mandatory reporting of information about behavior that is imminently dangerous to your child or to others, such as suicide, child abuse, etc.

Audiotapes or videotapes will be kept locked up and will be destroyed as soon as possible after the research is finished.

In any publications that result from this research, neither your name nor any information from which you might be identified will be published without your consent

Persons/Organizations Providing the Information

Participant

Persons/Organizations Receiving the Information

- The research site(s) carrying out this study. This includes UHA or UHA Affiliated, WVU, WVU Hospitals. It also includes each site's research staff and medical staff
- Laboratories and other people and groups that look into your health information as part of this study in agreement with the study protocol.
- The United State Department of Health and Human Services (which includes the National Institutes of Health (NIH), Food and Drug Administration (FDA)) and other groups that have the right to use the information as required by law.
- WVU and the people and companies that they use to oversee, manage, or conduct the research.
- The members and staff of any Institutional Review Board (IRB) that oversees this research study.
- West Virginia University Office of Research Compliance and Office of Sponsored Programs.

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The Following Information Will Be Used

Information provided by you and new information about you that is created or collected during the study such as medical history, laboratory results, and study forms.

The Information is Being Disclosed for the Following Reasons

- Review of your data for quality assurance purposes
- Publication of study results (without identifying you)
- Other research purposes such as reviewing the safety or effectiveness of the study drug and other products or therapies; conducting performance reviews of the study drug; evaluating other products or therapies for patients; developing a better understanding of disease; improving the design of future clinical trials.

You May Cancel this Authorization at Any Time by Writing to the Principal Investigator

Dr. Sergiy Yakovenko, Division of Exercise Physiology, WVU School of Medicine, PO Box 9227, Morgantown, WV 26506

If you cancel this authorization, any information that was collected already for this study cannot be withdrawn. Once information is disclosed, according to this authorization, the recipient may redisclose it and then the information may no longer be protected by federal regulations.

You have a right to see and make copies of your medical records. You will not be able to see or copy your records related to the study until the sponsor has completed all work related to the study. At that time you may ask to see the study doctor's files related to your participation in the study and have the study doctor correct any information about you that is wrong.

This authorization will expire at the end of the study unless you cancel it before that time (or has a specific expiration date).

Voluntary Participation

Participation in this study is voluntary. You are free to withdraw your consent to participate in this study at any time.

Refusal to participate or withdrawal will not affect [your class standing or grades, as appropriate] and will involve no penalty to you. Refusal to participate or withdrawal will not affect your future care, or your employee status at West Virginia University.

In the event new information becomes available that may affect your willingness to participate in this study, this information will be given to you so that you can make an informed decision about whether or not to continue your participation.

You have been given the opportunity to ask questions about the research, and you have received answers concerning areas you did not understand.

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Upon signing this form, you will receive a copy.

I willingly consent to participate in this research.

Signatures

Signature of Subject

Printed Name

Date

Time

The participant has had the opportunity to have questions addressed. The participant willingly agrees to be in the study.

Signature of Investigator or Co-Investigator

Printed Name

Date

Time

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C: Subject Information Form

Subject Information

Subject Name/ ID: VK _____

Date (YYYYMMDD): _____

New (Y/N): _____

DOB: _____

(If new continue to fill out portions 1-6, if returning skip to Data collection table)

- 1.) Height: _____
- 2.) Weight: _____
- 3.) 10% body weight: _____
- 4.) Weight + 10%: _____
- 5.) Weight - 10%: _____
- 6.) Upper Arm Length: _____
- 7.) Lower Arm Length: _____
- 8.) Hand Length: _____
- 9.) Torso Length: _____
- 10.) Upper Leg Length: _____
- 11.) Lower Leg Length: _____
- 12.) Foot Length: _____
- 13.) Dominant Hand (L/R): _____
- 14.) Dominant Foot (L/R): _____
- 15.) Walking Speed: _____