STEPPING FORWARD

Postural Control Mechanisms in Stance and Step Initiation

by

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A DISSERTATION

Presented to the Department of Physiology
and the Neuroscience Graduate Program
of the Oregon Health Sciences University
in partial fulfillment of
the requirements for the degree of

Doctor of Philosophy

June 8, 1995

APPROVED:

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(Professor in Charge of Dissertation)

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(Chairman of Graduate Council)

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Acknowledgements:

I would like to thank all of our subjects for their participation in these studies. Also acknowledged are Fay Horak, PhD, Francine Malouin, PhD, Jim Frank, PhD, Kim Burchiel, MD, John Nutt, MD and Jose Obeso, MD for their contributions to the discussion of the findings and suggestions for manuscript revisions. John Nutt, MD and Jose Obeso, MD also conducted the clinical evaluations of the subjects with Parkinson's disease. The data utilized in Chapter 5 of this thesis was collected by Fay Horak, PhD and Jim Frank, PhD. This work has been supported by a Doctoral Award from the Foundation for Physical Therapy awarded to Anne Burleigh, PT and Grant # AG-06457 from the National Institute on Aging awarded to Fay B. Horak, PhD, PT.

Personal Acknowledgements

I remember receiving the letter informing me that I had been accepted to the Department of Physiology and the Neuroscience Graduate Program at OHSU. Without any hesitation, I packed my belongings and drove down to Portland, Oregon. I didn't know anybody here, and I was, Oh... so naive. Reflecting back, the completion of this thesis has been one of the most difficult and yet significant achievements in my life. There are many people who deserve recognition, for they have certainly been appreciated. To the following people, as well as others not specifically mentioned, I offer my thanks.

Classmates - My first impression was that of my classmates. It was the course work which brought us together, and friendships which kept us going. My dear friend, Susie Ingram, certainly cannot go without the recognition of a true war hero.

Instructors - My appreciation in specific goes out to Bill Woodward, who soothed my frustrations and shared my laughter; Dick Brennan who let me write the answer on the wall with my finger, and having proved myself counted it as credit; and John Williams who taught me never to take life so seriously that I forgot to play.

Post-doc friends - Success stories and the people behind them are always good to remember. In particular, I thank Suzanne Giordano for the many conversations and long walks in Forest Park; Pierangelo Errico for the warm "family" dinners served at his home; and John Clements for his honest opposition to the establishment and his immeasurable help by providing Axograph.

My advisor - Fay Horak, was the first person to encourage my pursuit of a doctoral degree, and continued to encourage me through the entire completion. At times, I felt that we had a child/parent relationship with the many challenges of growth and maturity along the way. After having thought and rethought, written and rewritten, I feel proud to consider myself a budding colleague.

Technicians - Kim James, Catherine Schutz, Matthew Cohen, Jill Knop, and Harriet Barshofsky will be remembered fondly, because of their energy and their laughter. Also remembered, is Charley Russell, the general lab guru, who never gave me the answers, but always suggested where I may look to find them.

Rotating office mates - Charlotte Shupert was always there with her methodical answers to my frequent questions about writing styles, child-rearing, eastern philosophy and the latest on NPR. Christie Jones, Helga Hirschfeld (endearingly, Hurricane Helga), Frantisek Hlavacka, Jim Frank, and many others offered new ideas, and always kept the chairs warm.

Collaborators - In particular Jose Obeso, John Nutt and John Rothwell are recognized for the encouragement they provided to my Parkinson's research, and the opportunities they helped promote for my experiences in Europe.

Kids Can - The search for human contact, after too many hours at the computer, introduced me to a wonderful group of people. While talking with children about their rights to be safe, strong, and free I found myself growing stronger. In particular, I thank my friend Jan, who impressed me the first day we did a class together by taking off her shoes. Why sit down to a meaningful conversation wearing shoes that are restrictive and uncomfortable? During our many lunch-time walks, I experienced her integrity and honesty which I hope I can practice in my own life.

For the past two years, Ron Jacobs has encouraged and applauded my efforts. Together, we have made our home and our dreams for the future. In this short space, I cannot possibly say enough to express how truly fortunate I am to have his support.

Finally, the encouragement which has been with me through every challenge in my life comes from my family. My mother, who taught me to "bounce back up after every fall", has certainly been the most consistent and loving influence in my life. She raised a houseful of children who have all excelled in their own lives and supported each others efforts. If all of our teachers were so sincere, the paths we walk may have fewer obstacles.

Chapter 1.

Abstract

What are the postural control mechanisms necessary for bipedal stance and step initiation, and how does the nervous system integrate a motor command for voluntary movement with an involuntary response to a passive perturbation? These questions are addressed in this dissertation in order to increase our understanding of how the nervous system organizes postural control. To answer these questions human subjects were studied under conditions of maintained stance, and both perturbed and non-perturbed voluntary step initiation. Young and elderly subjects without neurological impairment, and subjects with Parkinson's disease were studied. The study of subjects with Parkinson's disease provided insight into the role of the basal ganglia dopaminergic system for postural control. During testing, all subjects stood on two adjacent plates of a hydraulically driven force platform. Surface electromyographic (EMG) recordings, ground reaction forces, and movement kinematics were recorded and quantified.

When a voluntary step is initiated in response to a surface perturbation, both the automatic postural responses to the perturbation and the anticipatory postural adjustments for the pre-planned step initiation are modified. Even prior to its execution, a descending central command specific to the intended movement interacts with the ascending peripheral information associated with an external perturbation. Several mechanisms by which the nervous system modulates these postural interactions are identified.

Furthermore, postural control for stance and step initiation is disrupted in subjects with Parkinson's disease. Excessive muscle tone in stance and deficits of force production during voluntary, self-generated movement contribute to the disruption of postural control. Adminstration of levodopa effectively reduces abnormal muscle tone during stance and increases force production during self-generated step initiation. In contrast, adminstration of levodopa appears to have no influence on force production when a step is initiated in response to an external stimulus.

In summary, these studies have increased our understanding of the basic postural control mechanisms employed by the nervous system. The results support the concept that the nervous system regulates postural control in an adaptive, task-specific manner. The peripherally-triggered automatic postural responses to perturbation are modified by central influences of task instruction and prediction of the perturbation. The pre-planned, centrally-initiated anticipatory postural adjustments associated with voluntary movement are modified by peripheral sensory information. The findings in subjects with Parkinson's disease suggest that the basal ganglia dopaminergic system contributes to the regulation of postural muscle tone in stance and to force production in self-generated but not externally-triggered step initiation.

Introduction

This dissertation originated from a basic therapeutic question which led to a series of experiments investigating postural control during stance and step initiation. The original question evolved from the treatment of patients, disabled by traumatic brain injuries, cerebral vascular accidents, and neurological diseases, who exhibited deficits in standing posture and an inability to initiate locomotion. In some patients, a small, passive forward displacement of the body promoted the initiation of locomotion. In others, however, this passive displacement was of no help in initiating the first step, since they responded with a postural response that restored their equilibrium. Since the first step for locomotion requires that the body center of mass be displaced forward and lateral from the initial position of equilibrium prior to heel-off, it seemed that the passive "push" could provide the postural adjustments necessary to step. Why then, was it helpful in only some patients? Was the nervous system required to integrate the passive displacement with a motor command for voluntary movement? Could the equilibrium response to the perturbation be inhibited so that the forward displacement of the body could promote forward step initiation rather than elicit a response to restore the original position of equilibrium? Together, these questions established the basis of this dissertation. What are the postural control mechanisms necessary for bipedal stance and movement, and how does the nervous system integrate a motor command for voluntary movement with an involuntary response to a passive displacement? To address these questions, postural conditions associated with stance and step initiation were studied in neurologically normal subjects and subjects with Parkinson's disease. The results of these studies have increased our understanding of normal nervous system function and have contributed to our understanding of how the basal ganglia are involved in the maintainance of postural control during stance and the regulation of force associated with the anticipatory postural adjustments for voluntary movement.

• Addressing the problem

While clinical observations may stimulate research questions, establishing a sound research protocol to address these questions poses a separate problem. Denny-Brown (1966) clearly stated the dilemma with his statement; "In the clinic, the intriguing problems in disturbed function are abundant but a multitude of uncontrolled variables make scientific analysis eternally frustrating". How then, can motor control be studied? Several animal models and neuro-physiological approaches have provided useful information about the organization of the nervous system, and the control of involuntary responses and voluntary movements. However, to investigate the postural control of bipedal stance and movement, experimental paradigms using human subjects are required.

In this dissertation, postural control for an involuntary response to an external perturbation and for voluntary step initiation were investigated. It is however, difficult to separate posture from movement since the nervous system has to maintain balance of the body center of mass during all motor activities performed in stance. Every movement, thus begins and ends with a postural adjustment. Sherrington believed that voluntary movement involved interaction between descending pathways and segmental reflex arcs (1906). Accordingly, there could be no strict dichotomy between reflex and voluntary muscle activation; rather, there must be convergence resulting in an interaction between reflexive and voluntary control. Such convergence cannot be investigated using reduced animal preparations. Therefore, natural movements are needed to understand reflexive and volitional interactions, and the experimental paradigms must be simplified to control for the multiple input and output variables.

To investigate the postural control mechanisms of stance and step initiation, human subjects were studied under conditions of maintained stance, and both perturbed and non-perturbed voluntary step initiation. Young and elderly subjects without neurological impairment, and subjects with Parkinson's disease were tested. The study of subjects with Parkinson's disease provided insight into the role of the basal ganglia dopaminergic system for postural control. During testing, all subjects stood on two adjacent plates of a hydraulically driven platform.

Surface electromyographic (EMG) recordings, ground reaction forces, and movement kinematics were recorded and quantified.

The interactions between the *automatic postural responses* to an external perturbation, and the *anticipatory postural adjustments* for step initiation were investigated by introducing a perturbation to the step initiation. In the perturbation paradigms used, a backward surface translation of the platform caused forward sway of the body. The automatic postural response elicited by the perturbation included involuntary activation of the ankle plantar-flexors in order to bring the body backward and restore stance equilibrium. In contrast, the anticipatory postural adjustments for voluntary step initiation included activation of the ankle dorsi-flexors and hip abductors, to promote the forward and lateral movement of the body for foot-off. Since the action of the automatic response opposed that of the anticipatory postural adjustments, a postural conflict was established, allowing for investigation of the postural interaction between the automatic and voluntary motor behaviors.

• Characteristics of an automatic postural response

An automatic postural response is an involuntary response (70-110 ms onset latency in adult human lower extremity) triggered by a perturbing stimulus, such as a surface translation. This involuntary postural response is considered to be synonymous with involuntary arm, hand, and leg muscle responses to perturbation. Different terminology used to define these responses in the arm and hand includes the following: the long-loop stretch reflex (Hammond 1956); the transcortical stretch reflex (Phillips 1969); the long-latency automatic responses (Marsden et al. 1973); the M2 response (Lee and Tatton 1975); and in the lower extremity, the functional stretch reflex (Nashner 1976). Throughout this dissertation, the term automatic postural response will be used in reference to the involuntary response elicited by an external perturbation of the body.

Although involuntary, an automatic postural response cannot be regarded as a simple stretch reflex, since the latency suggests a polysynaptic pathway. On the other hand, the

postural response cannot be regarded as purely voluntary, since onset latencies precede voluntary reaction time. In general, these responses to external displacement are considered to be centrally organized but triggered by peripheral sensory input.

Although the mechanisms mediating the automatic postural response are still unknown, the responses are probably triggered by sudden stretch of muscle spindles (Berger et al. 1984; Lundberg et al. 1987), and at high velocities of perturbation, may be either modulated or triggered by stimulation of the vestibular organs (Allum et al. 1993; Horak et al. 1990; Horak et al. 1994). In general, two relatively stereotyped responses have been categorized when subjects are perturbed by a surface translation and instructed to keep their feet in place (Horak and Nashner 1986; Horak et al. 1989). The first involves activation beginning at the ankle muscles and proceeding proximally. This results in a pendular-type sway as the body center of mass is returned to upright equilibrium. The second involves activation beginning with trunk and thigh muscles and proceeding distally. There is some evidence that this response may be in part triggered by stimulation of the vestibular organs resulting in rapid trunk flexion or extension to maintain equilibrium (Runge et al. 1994)

In the perturbation paradigms used in this dissertation, the velocities and amplitudes of translation were controlled to limit movement to pendular sway about the ankles when the subjects maintained their stance. Two possible mechanisms involved in triggering the responses include: 1) the stretch of multiple muscles activates central pathways which convey sensory information centrally to the cerebellum or sensorimotor cortex; 2) excitation of a poly-synaptic spinal pathway which triggers a pre-programmed sequence of muscle activation. Fast conduction of afferent proprioceptive information via the type II fibers (Lundberg et al. 1987) is a proposed mechanism involved in triggering the automatic postural response. Using the local somatosensory information, the appropriate postural response may be triggered, while specific sensory information is then used to tune the response to the stimulus parameters (Diener et al. 1988).

Several lines of evidence suggest a role for supraspinal input that both triggers and modifies the automatic postural response. This medium latency response is often absent in patients with spinal cord lesions (Dichgans and Diener 1987), and although some response is observed in chronic spinal cats, it is probably only related to passive muscle properties and segmental reflexes (Pratt et al. 1994). Furthermore, supra-spinal influence, i.e. central set, can modify the amplitude of the automatic response as demonstrated by the influence of prediction of perturbation velocity or amplitude (Diener et al. 1988; Horak et al. 1989) and instructional set (Hammond 1956; Evarts 1974; Crago et al. 1976).

In this dissertation, the organization of automatic postural responses was further investigated. Experiments were conducted to determine whether the automatic postural response to a backward surface translation could be inhibited when subjects were instructed to step forward in response to the perturbation rather than maintain stance.

• Characteristics of an anticipatory postural adjustment

Anticipatory postural adjustments promote the adjustment of body position in preparation for the voluntary movement of a limb (Belinkii et al. 1967). Onset latencies are generally longer than those of the automatic postural responses, with reaction times exceeding 160 ms in the distal leg muscles of humans. Babinski (1899), provided the first documentation of the critical requirement for involuntary postural adjustments coupled with primary voluntary movement. In his classical observation of disrupted postural control, a patient diagnosed as "asynergie cerbelleuse" fell backwards whenever he attempted to arch his back and look towards the ceiling. Babinski noted that the patient failed to make any compensatory adjustment at the ankles to counter-balance the voluntary trunk motion.

These involuntary postural adjustments in anticipation of voluntary movement, may serve either to stabilize the body against disturbances caused by voluntary movement, or to re-position the body to allow the limb movement. Similarly, the postural adjustments preceding

the lifting of an arm serve to prevent a disturbance of equilibrium as the limb segments move to a new position (Lee 1980; Cordo and Nashner 1982; Lee et al. 1987).

During step initiation, anticipatory postural adjustments are executed to move the body forward and over the stance limb in preparation for foot-off (Mann et al. 1979; Breniere et al. 1981; Nissan and Whittle 1990). These anticipatory postural adjustments are proposed to involve a centrally-mediated motor program that is relatively invariant (Crenna and Frigo 1991; Das and McCollum 1988; Nissan and Whittle 1990). In this dissertation, the organization of anticipatory postural adjustments for step initiation was further investigated. Experiments were conducted to determine whether the anticipatory postural adjustments are pre-planned and invariant or can be modified by changes in peripheral conditions when a step is initiated in response to a backward surface translation. In addition, the hypothesis that the basal ganglia are involved in the selection and organization of the anticipatory postural adjustments for voluntary movement was tested.

• Parkinson's disease: a model to investigate basal ganglia function

Parkinson's disease is a commonly accepted model for basal ganglia disease, although advanced pathology may include other brain regions. The disease was first described by Dr. James Parkinson in 1817, and is commonly characterized by three primary features: resting tremor, rigidity, and bradykinesia. The cause of Parkinson's disease is still not known, however, the disease process involves degeneration of the substantia nigra pars compacta of the basal ganglia. Since this cell region produces the neurotransmitter, dopamine, there is a consequent deficiency of dopamine transmission in the basal ganglia.

The basal ganglia are proposed to have a role in the selection of appropriate muscle activation patterns during the postural preparation for the initiation and execution of movement. Martin (1967) suggested that the deficits seen in parkinsonian movements are due to the absence of postural adjustments which must precede the execution of voluntary movements. EMG studies in parkinsonian patients have demonstrated that the anticipatory postural

adjustments preceding arm movements during standing are impaired (Traub et al. 1980; Rogers et al. 1987). Furthermore, the anticipatory postural adjustments preceding heel-off during voluntary self-initiated step are disrupted (Crenna et al. 1990). These findings suggest that these patients have an impairment of central programming of postural adjustments for voluntary movement and an inability to select the appropriate motor program.

The basic circuitry of the basal ganglia and their involvement in the Parkinson's disease suggest that both their cortical and brainstem projections influence motor behavior. The primary output of the basal ganglia exerts an inhibitory influence over both the ascending thalamo-cortical pathways, and the descending brainstem pathways (Albin et al. 1989; Mori 1989; Parent 1990; Hallett 1993). In Parkinson's disease, the inhibitory output is excessive, suggesting that the disturbances of movement result from an increased inhibition of the regions receiving the output projections from the basal ganglia (DeLong 1990). It is proposed that the basal ganglia projections to the supplementary motor area via the thalamus contribute to movement of the extremities, while pathways to the brainstem nuclei contribute to the setting of postural tone and regulate reflex interactions (Hallett 1993). The cortical supplementary motor area is innervated by the output of the basal ganglia via the thalamus (Alexander and Crutcher 1990; Parent 1990). Because the supplementary motor area is involved in the execution of self-generated movements (Roland et al. 1980; Eccles 1982; Brinkman 1984), disruption of these pathways may account for some of the disturbances of movement in Parkinson's disease. Bereitschaftspotentials (readiness potential preceding voluntary movement) are diminished in amplitude, particularly over the supplementary motor area, in Parkinson's subjects during voluntary finger extensions (Dick et al. 1989) as well as step initiation (Vidailhet et al. 1993). Disruption of the thalamic pathways is also attributed to tremor generation in Parkinson's disease, since thalamotomy and thalamic stimulation procedures alleviate tremor in the extremities (Benabid et al. 1987; Narabayshi 1989). Descending projections from the basal ganglia have been demonstrated to influence the setting of distal muscle tone and the initiation of locomotion in cats (Garcia-Rill 1986; Mori 1989). Although abnormal stance posture,

including flexion of the trunk, hips, knees and elbows, is characteristic of Parkinson's disease, the degree to which dopaminergic pathways modulate postural tone is uncertain. Furthermore, it is not clear, whether the flexed posture during stance represents a compensatory mechanism for reduced stability, or is a component of the primary motor problem.

The studies in this dissertation have addressed two aspects of postural control which may be regulated by the basal ganglia: postural tone during maintained stance, and the anticipatory postural adjustments during step initiation. To determine the influence of the dopamine deficiency on postural control, subjects with Parkinson's disease were tested both when their symptoms were diminished by the administration of levodopa (ON), and when symptoms were enhanced by withholding levodopa (OFF). In a single subject, with a surgically implanted thalamic stimulator, changes in tremor, balance and the postural adjustments for voluntary step initiation were investigated with and without the stimulation.

• Specific Aims

The aim of this research was to determine how the nervous system organizes postural control during bipedal stance and step initiation. To address this aim, two major questions were investigated: 1) how is postural control organized during perturbed voluntary step initiation; 2) what is the role of the basal ganglia dopaminergic system in the control of stance and voluntary step initiation? The following chapters have specifically addressed these questions.

Chapter 2. This study investigated the interaction between the automatic postural responses to perturbation and the anticipatory postural adjustments for step initiation. Young healthy subjects were studied to determine if the automatic postural response is suppressed when they are instructed to step in response to a perturbation rather than maintain stance; and to determine if the anticipatory postural adjustments for the pre-planned step are modified by the imposed perturbation.

Chapter 3. This study investigated how prediction of perturbation velocity and afferent sensory information influence the interaction between the automatic postural responses to

perturbation and the anticipatory postural adjustments for step initiation. Young healthy subjects were studied using a series of perturbation velocities in both predictable and unpredictable order and instructed to step rather than maintain stance in response to the perturbation.

Chapter 4. This study investigated the influence of the basal ganglia dopaminergic system for organization and execution of anticipatory postural adjustments for step initiation. Subjects with Parkinson's disease and age-matched controls were studied to quantify the postural adjustments during self-generated, externally-cued, and externally-perturbed step initiation. The subjects with Parkinson's disease were studied in both ON and OFF.

Chapter 5. This study investigated the influence of the basal ganglia dopaminergic system on the regulation of muscle tone during stance. Subjects with Parkinson's disease (ON and OFF) and age-matched controls were studied.

Chapter 6. This study investigated the influence of thalamic stimulation on the regulation of upper extremity tremor and lower extremity automatic postural responses to perturbation and anticipatory postural adjustments for step initiation. A single subject was studied.

• Research Tools

EMGs Electomyography is the study of muscle function using the electrical signal recorded from the muscle. The relationship between electricity and muscle activity was first demonstrated in 1786, by Galvani. He suspended the lumbar region of a frog from a zinc balcony by its sciatic nerve, then connected the nerve branches to a copper stick and observed contraction of the leg muscles. Later, Galvani further demonstrated that a muscle contraction could be evoked by placing a free nerve ending across the belly of the muscle (In: Basmajian and de Luca 1985). Thus, the initial basis of muscle electrophysiology was established. Application of electrical stimulation to investigate the systematic contractions and function of intact human skeletal muscles was common during the 19th century.

In 1849, Du Bois-Reymond detected electrical signals from human muscle during a voluntary contraction. He had devised a surface electrode made of wire attached to saline soaked blotting-paper. The introduction of metal surface electrodes by Piper in 1907 made recording of muscle activity more common, and accordingly, there was an increased need for interpretation of the signal. In 1922, Gasser and Erlanger employed a cathode ray oscilloscope to view the electrical signal from the muscles. Previously, galvanometers had been used with limited visualization of the signal. Development of methods to interpret the action potentials recorded on the cathode ray oscilloscope established Gasser and Erlanger as the winners of the Nobel Prize in 1944 (In: Basmajian and de Luca 1985). Over this century, the development of surface silver-silver chloride electrodes and computerized techniques for storing and analyzing EMG data has promoted research dedicated to the understanding of muscular function during human movement. Insight into the neural organization of movement can be deduced since muscle activity is the one of the final outputs of the nervous system.

EMG can indicate, not only the start and end of muscular activity, but also the relative amount of activity. However, when considering the relative amount, interpretations are limited to very controlled comparisons. Skin impedance, electrode placement, and muscle fiber condition all influence the magnitude of the recorded response. For these reasons, comparisons of EMG magnitudes cannot be directly made between different subjects or different placement sites. Magnitudes can be compared for a single subject and single placement site, otherwise, normalization techniques must be employed for comparisons. In order to quantify the EMG data for this dissertation, all raw EMG signals were filtered, full-wave rectified and integrated prior to analysis. A schematic representation of the signal processing is illustrated in Figure 1.1

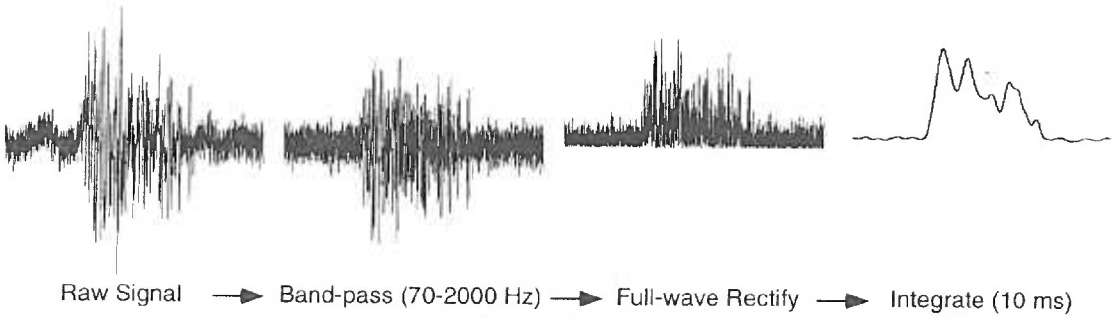

Figure 1.1. Example of EMG processing. The total amplification of the signal is 5000x. The raw signal is band-pass filtered with an envelope of 70-2000 Hz, then full-wave rectified, and low-pass filtered with a time constant of 10 ms.

FORCES In order to understand the control mechanisms used by the nervous system, it is necessary to consider the influences of both external and internal forces. Internal forces include those generated by the muscle activity and from friction in the muscles and joints during movement. External forces include those generated by any force acting on the body.

The first force platform, called a "dynometric table" was designed by Etienne-Jules Marey in approximately 1883. Marey based his design on the concept, that "...as action is equal to reaction, the ground is pushing back on our feet with a force which equals that tending to sustain our body...A recording dynamometer, located between the feet and the ground, can be used to measure this force instantaneously..." This first force plate, included sensors made of rubber tubing wound into a flattened spiral and glued between two pieces of rubber. Both vertical and anterior-posterior components of the ground reaction forces were recorded (Boissett, In: Biolocomotion, p 79-80).

In 1937, Kelso and Hellebrant introduced a balance platform to record the involuntary postural sway of humans during stance. (In: Oddsson, Hellerbrandt et al. 1938). Based on their recordings, they proposed that the change in weight distribution over time, now regarded as the center of foot pressure, directly corresponded to the change in the body center of mass. In the late 1950's, Thomas and Whitney further determined that "For dynamic reasons, the center of foot pressure must exaggerate the accompanying movements of the center of gravity

of the mass" (Thomas and Whitney, 1959). Thus, during bipedal stance, the body center of mass, must be maintained within the base of support defined by the foot center of pressure excursions. In contrast, during step initiation, postero-lateral displacement of the center of pressure results in the body center of mass being displaced forward and over the stance limb (Alble 1994; Breniere et al. 1987; Rogers 1993).

The experiments conducted for this dissertation utilized a hydraulically driven platform designed by Nashner in 1972, and a similar platform, further developed by Horak in 1992. For both platforms, the force-plate movements were generated by servo-mechanisms under the control of a DEC LSI 11/23 computer. Vertical and horizontal forces were measured with strain gauges mounted in the corners of each of the two plates. Quantification of the excursions of the center of foot pressure were calculated using the recorded forces. Figure 1.2 illustrates the path of the foot center of pressure commonly recorded in control subjects during stance and during step initiation. The total excursion can be separated into the anterior-posterior and lateral components for specific analysis.

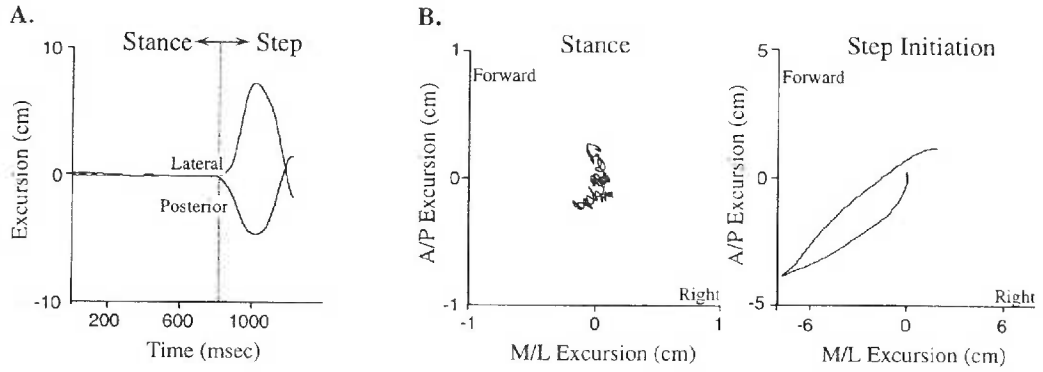

Figure 1.2. A) Example of Posterior and Lateral excursions of the center of pressure (COP) demonstrating the transition from quiet stance to step initiation. B) Anterio-posterior (A/P) versus medio-lateral (M/L) plots of the center of pressure during quiet stance and during step. During step initiation, the COP moves backward and toward the left (initial swing) limb. Data is plotted until the time of heel-off. Note differences in axis scale.

KINEMATICS Just over a century ago, the first multi-frame photos of walking and running were used to analyze human movement. Eadward Muybridge (1830-1904) and Etienne-Jules Marey (1830-1904) are recognized as the founders of scientific cinematography. Muybridge, a photographer, used a series of cameras with shutter speeds set so that they opened sequentially

to capture phases of locomotion in both humans and horses. He then designed the original "zoopraxiescope" to project the series of photos as a movement sequence. Marey, a French scientist, designed the photographic gun in 1882, which allowed 12 images per second to be shot by using a rotating plate. Later, serial images of a man walking were recorded by Marey using his "chronophotograph". The subject wore a black suit with white stripes with brighter points to indicate the position of the joints on one arm and one leg. (Tosi, In: Biolocomotion: A century of research using moving pictures 1992).

The image obtained from Marey's chronophotograph is remarkably similar to the stick-images obtained from modern high-speed kinematic systems. Today, reflective markers or infra-red light emitting diodes (IREDS) are placed over specific joints and land-marks on a subject, and their position is recorded using high-speed cameras. The automation of tracking and analyzing data points allows common use of kinematics for the analysis of human movement. An example stick-figure is shown in Figure 1.3, demonstrating the position and relationship of IREDS used during the experiments conducted in this dissertation. Length measurements of each individual subject's hand, forearm, upper arm, trunk, leg and foot, as well as ankle height, were used to determine the center of mass (COM)

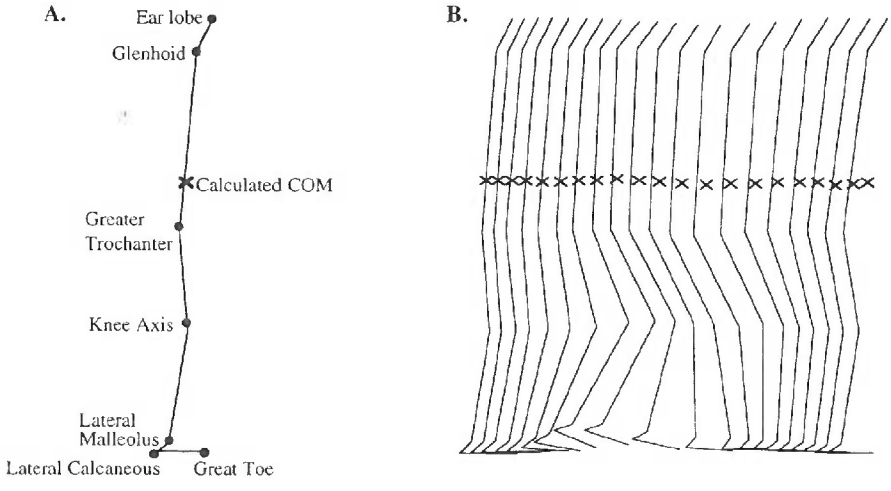

Figure 1.3. A) Example of image collected during quiet stance, representing the position of the 8 IREDS and calculated center of mass (COM). B) Time series of the kinematic image during step initiation.

of each segment based on a fractional mass table specific to males and females (Diffrient et al. 1974). The fractional mass of each segment relative to the total body mass and the IRED coordinates were then used to calculate the body COM in the sagittal plane according to the following formula.

$$X_{COM} = X_{foot}m_{foot} + X_{shank}m_{shank} + X_{thigh}m_{thigh} + X_{trunk}m_{trunk+arms} + X_{head}m_{head+neck}$$

X = sagittal plane coordinates
m = fractional mass of each segment relative to total body mass

The primary analysis presented in the following chapters concerns the displacement and velocity of this calculated body center of mass.

Chapter 2.

Based on *J. Neurophysiol.* 72(2): 2892-2902, 1994

Modification of Postural Responses and Step Initiation: Evidence for Goal-directed Postural Interactions

A. Burleigh, F. Horak and F. Malouin

SUMMARY AND CONCLUSIONS

1. In this study, the interaction between anticipatory postural adjustments for step initiation and automatic postural responses to an external perturbation were investigated by having subjects initiate a voluntary forward step while perturbed by a backward surface translation which caused forward sway of the body. The postural adjustments for step initiation act to move the body center of mass (COM) forward, while the automatic postural responses act to move the COM backward to restore stance equilibrium. Because the postural behaviors are in opposition, we asked whether a temporal hierarchy exists in which automatic postural responses are executed to restore equilibrium and followed by stereotypic postural adjustments for step initiation, or whether the interaction between these two postural behaviors is more dynamic.

2. Lower extremity EMGs, ground reaction forces, and kinematics were recorded from ten subjects during the following three conditions: 1) To quantify the anticipatory postural adjustments for step initiation, subjects stepped forward as soon as they felt a proprioceptive cue; 2) To quantify the automatic postural responses to perturbation, subjects maintained stance equilibrium in response to a backward surface translation under both feet; 3) To quantify the interaction between the postural adjustments for the voluntary step and the automatic responses to the perturbation, subjects were exposed to a backward surface translation and instructed to step forward as soon as they felt the platform begin to move.

3. The anticipatory adjustments for step initiation included tibialis activation [stance limb = 163 ± 28 ms (mean ± SD); swing limb = 173 ± 33 ms] and soleus inhibition resulting in center of foot pressure (COP) moving backward and lateral toward the swing limb to propel the COM forward over the stance limb. Subsequently, activation of the swing limb gastrocnemius resulted in heel-off. In contrast, the automatic postural adjustments for maintenance of stance equilibrium during a backward surface translation included activation of soleus and gastrocnemius (104 ± 23 ms and 115 ± 14 ms respectively) resulting in a symmetrical forward displacement of the COP that moved the COM back to its original position with respect to the feet.

4. When a forward step was initiated in response to the translation, the automatic postural responses were reduced in amplitude bilaterally in soleus and in the stance limb gastrocnemius. When present, the postural response occurred at the same latency when the goal was to initiate a step as when the goal was to maintain standing. The amplitude of the swing limb gastrocnemius was less affected, suggesting that reduction of the postural response was specific to the role of the limbs in the impending step.

5. Even though the onset of tibialis for step initiation was unchanged when a step was initiated in response to the translation rather than in response to a proprioceptive cue, the duration of the postural adjustments for step initiation were shortened and the muscle activation patterns were modified with respect to the passive forward displacement of the body COM. In contrast to the fixed onset of the tibialis, the lateral excursion of the COP began earlier when the step was initiated in response to the translation (150 ± 27 ms) rather than the proprioceptive cue (204 ± 40 ms), suggesting that a more rapid unweighting of the swing limb was required in the perturbed condition since the COM was displaced further forward and faster in the perturbed condition.

6. These results demonstrate that both the automatic postural responses to platform translation and the postural adjustments for step initiation were modified, both by changes in body position and by changes in the intended movement goal. This suggests that the descending central motor program for step initiation and the ascending information associated with the platform translation interacted even though the voluntary reaction time for step initiation was considerably longer than the onset latency of the automatic postural response. These results are not consistent with a temporal hierarchy for postural organization. Rather, there is a dynamic interaction between the automatic postural responses to an external perturbation and anticipatory postural adjustments for goal directed movements.

INTRODUCTION

Recurring concepts in motor control physiology are that the goal of a movement determines its motor planning and performance, and that the central nervous system (CNS) must continually compare the actual state of the body to the desired state of the body to coordinate movement. Two main types of postural control with respect to different goals have been identified (Massion 1992). One type of control functions to maintain quasi-static equilibrium with respect to a reference value against an internal or external perturbation. A second type of control maintains dynamic equilibrium during the displacement of segments of the body or the

whole body along a specified trajectory towards a goal. An internal representation of the body position and dynamics may be required for selection of postural adjustments necessary for efficient and effective movement (Belinki et al 1967; Gurfinkel and Levik 1978; Lestienne and Gurfinkel 1988).

Organization of the internal representation of body position and dynamics may be distributed at several levels of the CNS. Lower levels may be involved in organizing automatic postural responses to perturbations. Higher levels of organization may be involved in establishing anticipatory postural adjustments for voluntary movement. The relationship between automatic postural responses and anticipatory postural adjustments, when their goals conflict, is not clear. How does the nervous system organize a response when the body is externally perturbed forward and the goal is not a return to equilibrium, but rather to initiate a voluntary forward step?

In this experiment, standing subjects were exposed to backward translations of the platform under both feet and instructed to take a forward step as soon as the platform began to move. The backward translation caused forward sway of the body. When the goal was to maintain upright standing equilibrium, a rather stereotyped automatic postural response was expected to return the body to equilibrium (Horak and Nashner 1986; Horak et al. 1989). However, when the goal was to take a step forward and not restore standing equilibrium, the automatic postural response may no longer be appropriate. If the automatic response took precedence and was not modified, the postural adjustments for the step could either be delayed until the equilibrium response was completed, or there could be a temporal addition of the equilibrium and step related postural responses. However, for the most efficient execution of the step, the automatic response should be suppressed and the postural adjustments anticipatory to the step should be modified since the COM has been passively perturbed forward.

Automatic postural responses to perturbations

Automatic postural responses to external displacements are proposed to be centrally programmed (Chan et al. 1979), and triggered by peripheral input. The classical study by Hammond, was the first to demonstrate that components of automatic postural responses may be modified by prior instruction (Hammond 1956). Biceps responses elicited by an arm perturbation could be reduced or amplified by instruction to the subject to either resist or not resist, suggesting that the automatic response could be modified by cortical activity related to the intended task. In postural studies with standing humans, an automatic response is elicited to hold the body COM over the base of support (Gollhofer et al. 1989). Awareness or expectation of an impending perturbation does not affect the initial EMG onset latencies, or the relative pattern of muscle activation (Diener et al. 1991; Horak et al. 1989). However, expectation of a perturbation amplitude, based on prior experience, does affect the initial torque generated by muscle activation since the magnitude of the initial response to perturbation may be appropriately scaled up or down (Horak et al. 1989).

When Cordo and Nashner attempted to alter an automatic postural response for standing equilibrium by having the subject voluntarily sway in the same direction as sway induced by a surface perturbation, they found that the voluntary movement could be initiated only after the automatic response was completed (Nashner and Cordo 1981). They proposed a hierarchical relationship in which the execution of reaction-time voluntary movements are delayed until after unmodified postural responses restabilize stance. The voluntary muscle activations only occasionally preceded the automatic postural response if the cue for voluntary movement preceded the destabilizing perturbation by at least 50 ms.

Anticipatory postural adjustments for the initiation of locomotion

The coordination of postural adjustments preceding locomotion, which promote the transition from quiet stance to the cyclic movement of walking, also involve a centrally mediated motor program (Crenna and Frigo 1991; Das and McCollum 1988; Forssberg 1985). The muscle activation and mechanical forces associated with gait initiation include bilateral

activation of the tibialis anterior and inhibition of the soleus resulting in backward displacement of the center of foot pressure (COP) (Crenna and Frigo 1991; Breniere et al. 1981,1986,1987,1991; Herman et al. 1975; Mann et al. 1979; Nissan and Whittle 1990). In addition to the initial backwards displacement, the COP is also displaced towards the initial swing limb, then to the stance limb during the swing phase. The muscle activation for the lateral shift has not been characterized, but is proposed to be related to more proximal hip musculature (Winter et al. 1993). The asymmetrical displacement of the COP is important in the initiation of locomotion, since it probably generates the propulsive force to move the body COM forward and over the stance limb and align the body so that a gastrocnemius burst is effective for heel-off. The amplitude of the initial tibialis anterior activation is generally reduced when subjects initiate a step from a voluntary forward lean position, and has also been correlated with the velocity of the body upon completion of the initial step (Crenna and Frigo 1991), These results suggest that tibialis activation has a role in establishing the forward position and velocity of the body COM. Biomechanical studies have demonstrated that the steady-state velocity of locomotion is reached within the first step and the time necessary to reach steady state is invariant (Breniere and Do 1986,1991; Nissan and Whittle 1990), suggesting that the motor program for step initiation is invariant. However, these studies have only investigated the initiation of gait from quiet stance, and have not addressed how the behavior may change when the step is paired with a perturbation.

Postural control must include comparison of an internal representation of the body in space with the desired movement so that discongruencies between actual and expected conditions are used to modify the ongoing response (Gurfinkel and Levik 1978; Lestienne and Gurfinkel 1988). For example, if the goal is to initiate locomotion in response to a surface translation in which forward sway of the body has been induced, would the postural adjustments associated with the step initiation be the same as if the body had been at upright equilibrium?

In this experiment, the interaction between the automatic postural responses to maintain standing after a perturbation, and the anticipatory postural adjustments for the initiation of

voluntary step were explored. The automatic postural response to sway induced by a platform translation was modified when subjects were instructed to take a forward step rather than maintain standing; and the postural adjustments for the initiation of the step were modified with reference to the passive change in position of body center of mass.

METHODS

Informed consent was received from 10 normal, healthy subjects between the ages of 21 and 32 years (26.5 $\pm$ 3.2 yrs). Subjects stood on a platform with two plates that moved under the control of a hydraulic servomotor. Subjects were tested under 3 different conditions with ten trials in each condition. All subjects were tested in the following order:

Condition 1. Step-to-cue

The plate of the initial swing limb moved vertically downward approximately 0.1 cm at 10 cm/s, producing a reliable somatosensory cue, but did not elicit any automatic EMG response. Subjects were instructed to take a forward step with the left foot *as soon as* they felt the plate begin to move, and continue the step through with the right foot.

Condition 2. Sway-to-translation

Both plates were translated horizontally 8 cm at 20 cm/s in the backward direction. Subjects were instructed to simply maintain standing equilibrium.

Condition 3. Step-to-translation

Both plates were translated horizontally 8 cm at 20 cm/s in the backward direction. Subjects were instructed to take a forward step with the left foot "*as soon as* they felt the plates begin to move", and continue the step through with the right foot. Based upon voluntary step initiation data from 4 preliminary subjects, this translation was determined to cause forward body sway with the average displacement and velocity of the COM progression approximately equal to that at the time of foot-off during a voluntary forward step.

Figure 2.1 demonstrates the complexity of the Step-to-translation condition since the goals of the automatic response and the step initiation are in opposition. The backward platform translation resulted in disequilibrium by causing a forward motion of the body COM with respect to the base of support. An automatic postural response acts to move the COM backwards over the feet to restore stance equilibrium, while the postural adjustments for step initiation act to move the COM forward and then move the foot under the falling COM by taking a step.

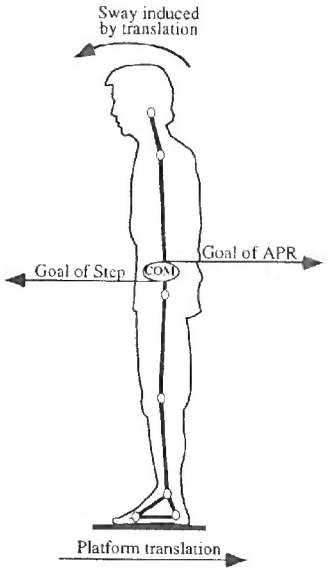

Figure 2.1. Cartoon representation of Condition 3, Step-to-translation. A backward surface translation of 8 cm at 20 cm/s results in passive forward sway of the body. The goal of an automatic postural response is to bring the body center of mass (COM) backward and restore stance equilibrium. The goal of the postural adjustments for the step is to move the COM forward to initiate a step.

For all conditions, the subjects stood with one foot in the center of each plate and with weight equally distributed between both feet. To ensure that the weight distribution and the initial stance position was the same across all trials, tracings of the feet during quiet stance were made and the distribution of weight bearing between the right and left limbs was recorded and viewed on-line. Forces were measured with strain gauges mounted in the force plates, sampled at 500 Hz, and stored for later analysis. The COP was calculated using the forces recorded by the strain gauges in each plate. A pressure sensitive resistor, taped to the platform under the heel of the initial swing limb was used to determine the precise time of heel-off

during the initiation of step. Foot-off was determined as the precise moment there were no vertical forces exerted through the initial swing limb plate.

Bilateral EMG activity of the tibialis anterior, soleus, and medial gastrocnemius was recorded using 2.0 cm surface electrodes. The raw EMG signals were pre-amplified x100 and band-pass filtered (70-2000 Hz). They were then rectified and low pass filtered with a time constant of 10 ms, amplified again then sampled at 500 Hz, and stored for off-line analysis. Although no attempt was made to calibrate EMGs on an absolute scale, amplifier gains were set throughout each experimental session.

Kinematic data was collected using Northern Digital's Watsmart motion analysis system. The system consists of two optoelectric cameras that detected the position of infrared light emitting markers (IREDs) attached to the platform, and the subject on the side of the initial swing limb at the fifth metatarsal head, heel, lateral malleolus, knee, greater trochanter, shoulder and ear. During each trial, two-dimensional spatial positions of the IREDs were sampled by each camera at 100 Hz. Data was stored for calculation of body COM and later analysis of the segment positions and progression of the body COM.

Data Analysis

EMGs To quantify the magnitude of muscle activations, the integrated area under the rectified EMG curve (IEMG) was calculated over 50 ms windows of the burst in each trial. A burst was defined as EMG activity greater than 2 S.D. above the mean baseline activity and lasting more than 25 ms. To eliminate the influence of background activity, the mean amplitude for 100 ms of baseline EMG activity before the perturbation onset was subtracted from the burst integral. When no burst was apparent in an individual trial, the average time of onset for the condition was used to calculate the burst integral. Quantification of the automatic postural adjustments included comparison of onset latencies and burst integrals for the gastrocnemius and soleus during the Sway-to-translation and Step-to-translation conditions. In order to compare across subjects, the magnitude of the individual muscle IEMG was normalized by dividing the 50 ms blocks of data for each trial in Sway-to-translation and Step-to-translation

by the mean IEMG of the same block of time averaged across the ten trials of the Sway-to-translation. The normalized data was then averaged across the first three trials and last three trials of each condition in order to determine the effects of instruction and the effects of practice on the modification of the automatic postural response. The percent difference of IEMG between the sway and step conditions was also compared between subjects and averaged for the group. Quantification of the anticipatory postural adjustments for step initiation included comparison of reaction time for the onset of the initial swing limb tibialis contraction, onset of the gastrocnemius burst for push-off, and the integrated areas of the bursts in the Step-to-cue and Step-to-translation conditions. The last five trials in each condition were compared to determine if the anticipatory postural adjustments were modified by the perturbation.

FORCES The initial change in the lateral COP was used to indicate the onset of the postural adjustments for step. The total duration of the postural adjustments for step initiation was defined as the time from the platform cue or translation onset to the time of foot off. This total duration was then further subdivided into three phases: 1) reaction time phase (platform cue to first change in lateral COP); 2) anticipation phase (first change in lateral COP to heel-off); and 3) execution phase (heel-off to foot-off). We chose not to use Breniere and colleagues (Breniere, et al. 1987) definition of the execution phase as heel-off to maximum velocity of the COM since we were interested in the anticipatory postural adjustments prior to actual movement of the limbs.

KINEMATICS The movement of the platform marker was subtracted from each joint marker in order to calculate COM trajectory with reference to the surface. The estimated COM was calculated using a three-dimensional model (Koozekanani et al. 1983). Since the A/P progression of the body COM was symmetrical until the time of foot-off, the forward displacement of the COM at the time of heel-off and foot-off could be determined. Data was normalized across subjects by dividing the COM displacement in centimeters by the length of the foot and multiplying by 100 to get displacement as a percentage of foot length. The

velocity of the COM at the time of heel-off and foot-off was calculated based upon differentiation of the displacement data.

STATISTICAL ANALYSIS To determine if the change in goal made a significant difference on the automatic postural response, a Student's t-test compared the normalized IEMG from the last three trials of Sway-to-translation versus Step-to-translation for each subject. A two-way MANOVA tested the effects of practice between conditions and the difference between the intended stance and swing limbs. In the Step-to-cue and Step-to-translation conditions, statistical difference between the displacement of the COM and the velocity of COM at foot off was verified using a paired t-test. The IEMG from the Step-to-cue and Step-to-translation conditions were compared using a paired t-test to determine if activation patterns for step initiation were changed as a result of the different tasks. Statistical significance was determined as at least $p \leq 0.05$ level for all analysis. When multiple comparisons were run between the same groups, a Bonferonni correction was used to verify statistical significance.

RESULTS

Characteristics of anticipatory postural adjustments for the initiation of step (Step-to-cue)

The reaction time for stereotypic activation of tibialis was 163 ± 28 ms for the stance limb and 173 ± 33 ms for the swing limb, when subjects were instructed to take a forward step with the left foot *as soon as* they perceived the small vertical platform cue. In the initial swing limb, a gastrocnemius burst at 417 ± 80 ms preceded heel-off by 143 ± 12 ms. Backward excursion of the COP was generally symmetrical for the initial stance and swing limbs, promoting a forward propulsion of the COM. Lateral excursion of the COP initially towards the swing limb presumably resulted in propulsion of the COM towards the stance limb. At the time of heel off, the stance limb maintained a posterior COP while the swing limb COP moved forward with the roll-off phase. Figure 2.2A illustrates the EMG activation and the lateral and anterior-posterior COP for the initial swing limb (left limb) with relationship to the forward displacement of the body COM.

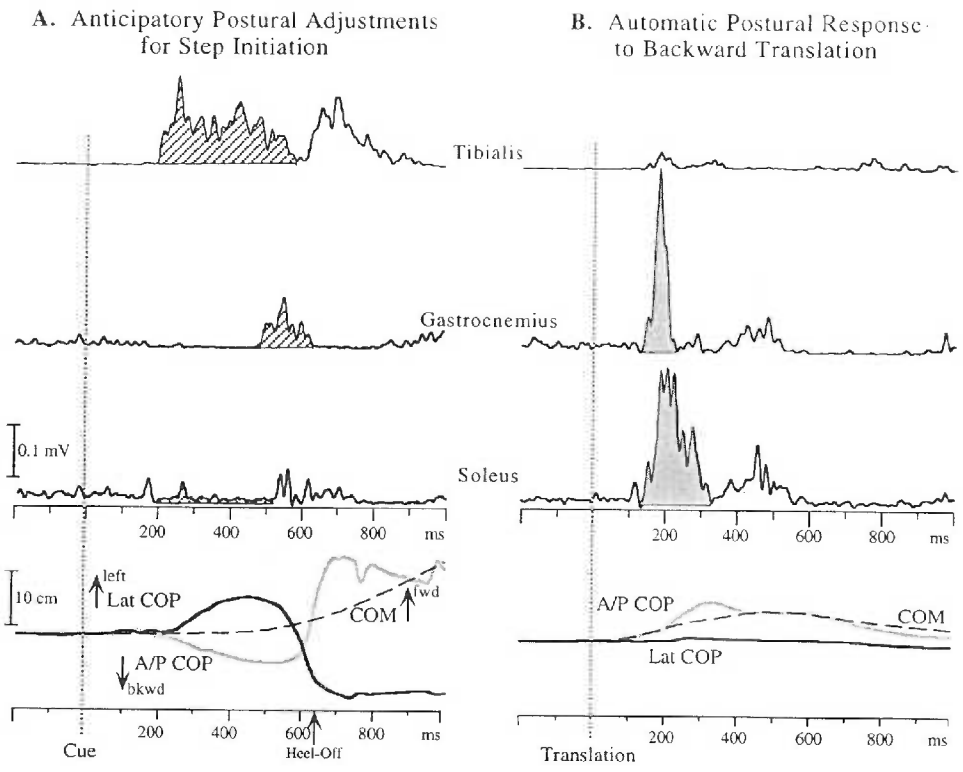

Figure 2.2. Average EMG activity and resulting COM/COP relationships for subject SD showing postural adjustments associated with Step-to-cue (A) and automatic postural responses for Sway-to-translation (B). Traces are from the left limb (intended swing limb). Shaded areas of the EMGs represent postural components of the muscle activations. In (A) an upward displacement of the lateral COP (solid line) indicates excursion of the COP towards the left, while a downward displacement indicates excursion to the right (stance limb). There is no change in the lateral COP in the Sway (B) condition. In (A) a downward displacement of the A/P COP (shaded line) indicates backward excursion of the COP related to tibialis, and the upward displacement indicates a forward excursion related to gastrocnemius during push-off. In (B) the forward excursion of the COP is initially passive and then enhanced by the gastrocnemius and soleus automatic response to restore equilibrium. The COM (dashed line) is passively displaced forwards and continues forward with the Step (A), but returns to equilibrium in the Sway (B) condition.

Characteristics of automatic postural responses to backward platform translation (Sway-to-translation)

When subjects were perturbed by a backward platform translation (8 cm at 20 cm/s) and instructed to remain standing, there was a stereotypic activation of bilateral soleus and gastrocnemius. The onset latency of the bilateral gastrocnemius was 114 ± 16 ms and 119 ±

14 ms, and of the bilateral soleus 104 ± 24 ms and 104 ± 22 ms. Unlike step initiation, the forward displacement of the body COM was counteracted by a forward excursion of the foot COP resulting from activation of the ankle extensor muscles. There was no apparent lateral shift of the COP for any of the subjects. Figure 2.2B illustrates the muscle activation patterns for the left limb and the corresponding changes in the COP and COM relationship for the automatic response to perturbation.

Modification of the automatic postural response by the initiation of step (Step-to-translation)

Since the automatic response of gastrocnemius and soleus to backward translation occurred at least 50 ms before the onset of tibialis for step initiation, the automatic postural response could have preceded the tibialis activation for step initiated in response to the backward platform translation. Figure 2.3 shows that the automatic gastrocnemius and soleus response was reduced or eliminated even prior to the onset of the tibialis related to step initiation in the perturbed condition. In the subject shown, the stance limb gastrocnemius and soleus were significantly reduced, as was the swing limb soleus but not gastrocnemius.

The modification of the automatic postural response was more apparent in the initial stance limb across all subjects. In the swing limb, there was a more significant reduction of the soleus than the gastrocnemius. The first 50 ms of the automatic response preceded the onset of the tibialis for step initiation, while the next 50 ms of the response coincided with activation of the tibialis.

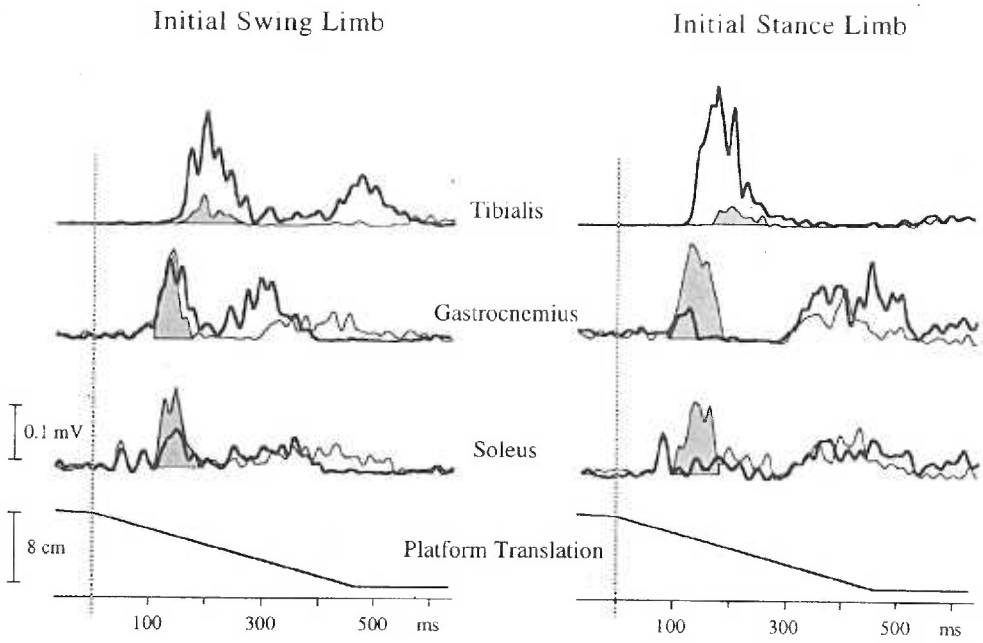

Figure 2.3. Overlapping EMG activity of the average of the last three trials of Sway-to-translation (automatic postural response shaded), and the Step-to-translation (overlapping bold line) for subject SC. Reduction of the automatic postural response during Step is clearly demonstrated for the initial stance limb gastrocnemius and soleus, and to a lesser degree the soleus of the initial swing limb. The gastrocnemius of the swing limb does not exhibit a reduced amplitude of the initial 50 ms of the response during Step-to-translation in this subject, but across the mean of all subjects there is a significant ($p \leq 0.05$) reduction in the first 50 ms.

In the initial stance limb there was a significant reduction ($p \leq 0.001$) of both the gastrocnemius and soleus IEMG in the first 50 ms, across all subjects (Figure 2.4) when comparing the IEMGs of the well practiced trials (last three Sway-to-translation vs. Step-to-translation). During the next 50 ms, reduction of the stance limb EMG response remained significant (gastrocnemius $p \leq 0.01$; soleus $p \leq 0.05$). Two of the ten subjects had greater than an average of 90% reduction of the stance limb gastrocnemius IEMG when the goal was to step, and four subjects had greater than an average of 90% reduction in stance limb soleus.

In contrast to the stance limb, modification of the automatic postural response in the initial swing limb differed between the gastrocnemius and soleus. In the first 50 ms of the response, both the gastrocnemius and soleus IEMG were significantly reduced (gastrocnemius $p \leq 0.05$;

soleus $p \leq 0.001$), but during the next 50 ms only the soleus activity remained reduced ($p \leq 0.05$). The IEMG over the 50-100 ms block of gastrocnemius showed no reduction and even increased in three of the ten subjects. This lack of suppression of the swing limb gastrocnemius during the step-to-translation may have been related to descending drive increasing excitability of the gastrocnemius for heel-off in the step initiation.

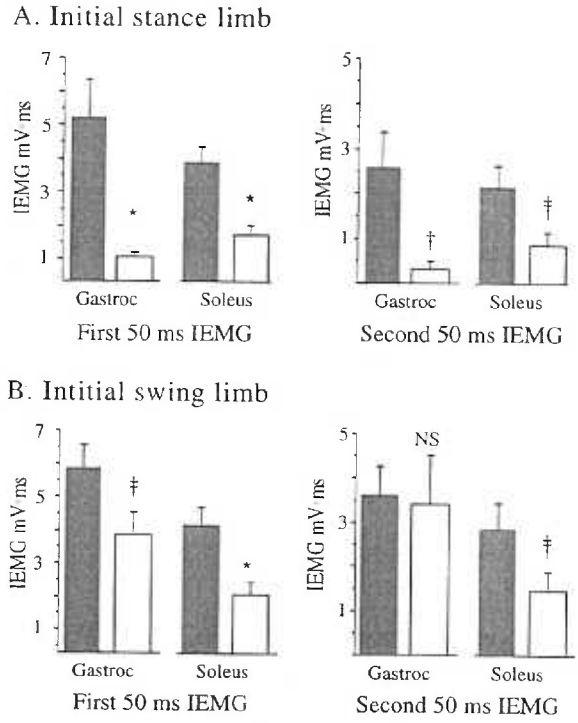

Figure 2.4. Mean and standard error of the integrated EMG (IEMG) from the last three trials of Sway-to translation (shaded bars) and Step-to-translation (open bars) for ten subjects. Panel (A) shows the difference in integrated EMG for the initial stance limb gastrocnemius (gastroc) and soleus over the initial and subsequent 50 ms of the response. Panel (B) shows the difference in integrated EMG for initial swing limb gastroc and soleus. There is significant reduction of the stance limb gastroc and soleus in the Step-to-translation condition, and of the swing limb soleus and the first 50 ms of the swing limb gastroc. Statistical significance was determined from a paired t-test of normalized IEMG data (*$p \leq 0.001$; † $p \leq 0.01$; ‡ $p \leq 0.05$)

There was a learning trend across trials with a greater percent reduction of the swing limb gastrocnemius and soleus, and the stance limb gastrocnemius during the first 50 ms of the response in later trials versus early trials of Step-to-translation. The overall percent reduction of gastrocnemius and soleus for the Step-to-translation condition compared to the Sway-to-translation is shown in Table 2.1. To determine if the gastrocnemius and soleus response was

reduced simply by habituation to repeated trials, since the Step condition always followed the Sway condition, normalized IEMGs were also compared for the first three and last three trials of the Sway-to-translation condition. There was no significant difference ($p \geq 0.05$) between the early and late trials of the Sway conditions suggesting that the reduction of the automatic postural response was due to the instruction to step and not simply to habituation.

TABLE 1. *Percent reduction in the automatic response of gastrocnemius and soleus IEMG during Step-to -Translation. Comparison between the early and late trials to assess a learning effect.*

	% Reduction IEMG 0-50 ms			% Reduction IEMG 51-100 ms		
	trials 1-3	trials 7-10	p-value	trials 1-3	trials 7-10	p-value
Swing Limb						
Soleus	27.8 ± 2.5	53.0 ± 3.0	.002	32.8 ± 4.6	42.5 ± 5.0	NS
Gastroc	(14.0 ± 5.8)	31.0 ± 4.5	.02	69.7 ± 16.9	4.2 ± 7.2	.05
Stance Limb						
Soleus	56.6 ± 2.2	64.7 ± 2.2	NS	39.9 ± 7.2	46.3 ± 8.2	NS
Gastroc	54.4 ± 1.8	80.1 ± 1.8	.01	56.8 ± 6.8	71.2 ± 4.6	.05

Values are mean ± SE. Parenthetical information represents a percent increase in gastrocnemius activity. *P* values represent the significant difference between early and late trials using a Student's *t*-test. Comparisons are between early and late trials to assess the learning effect. IEMG = rectified, integrated electromyography.

Effects of translation on the anticipatory postural adjustments for voluntary step initiation (Step-to-translation)

The duration of the postural adjustments for step was not strictly invariant. Figure 2.5 illustrates how stepping in response to the translation modified the swing limb EMG, and displacements of the COM and COP. Even though the translation was of greater amplitude than the vertical cue, the postural adjustments for the step were initiated in all subjects before the plate had translated more than 2-3 cm. Onset of the swing limb tibialis was not different between the Step-to-cue (173 ± 33 ms) and the Step-to-translation (170 ± 24 ms) conditions. However, when the onset of the postural adjustments was determined from the calculated lateral COP, the step was initiated much sooner in the Step-to-translation (150 ± 27 ms) than in the Step-to-cue condition (204 ± 40 ms; $p \leq 0.001$). In fact, the initial active response to

backward translation was the lateral change COP, rather than a forward change in COP being generated in direct opposition to the perturbation. The total duration of the initiation phase (onset of platform to foot-off) was also significantly decreased from Step-to-cue (674 ± 70 ms) to Step-to-translation (516 ± 51; $p \leq 0.001$). Of this shortened duration, only 72.6 ± 4.7 % of the time was spent in the anticipation phase (first change in lateral COP to heel-off) in the Step-to-translation condition, compared to 82.0 ± 5.4 % in the Step-to-cue condition.

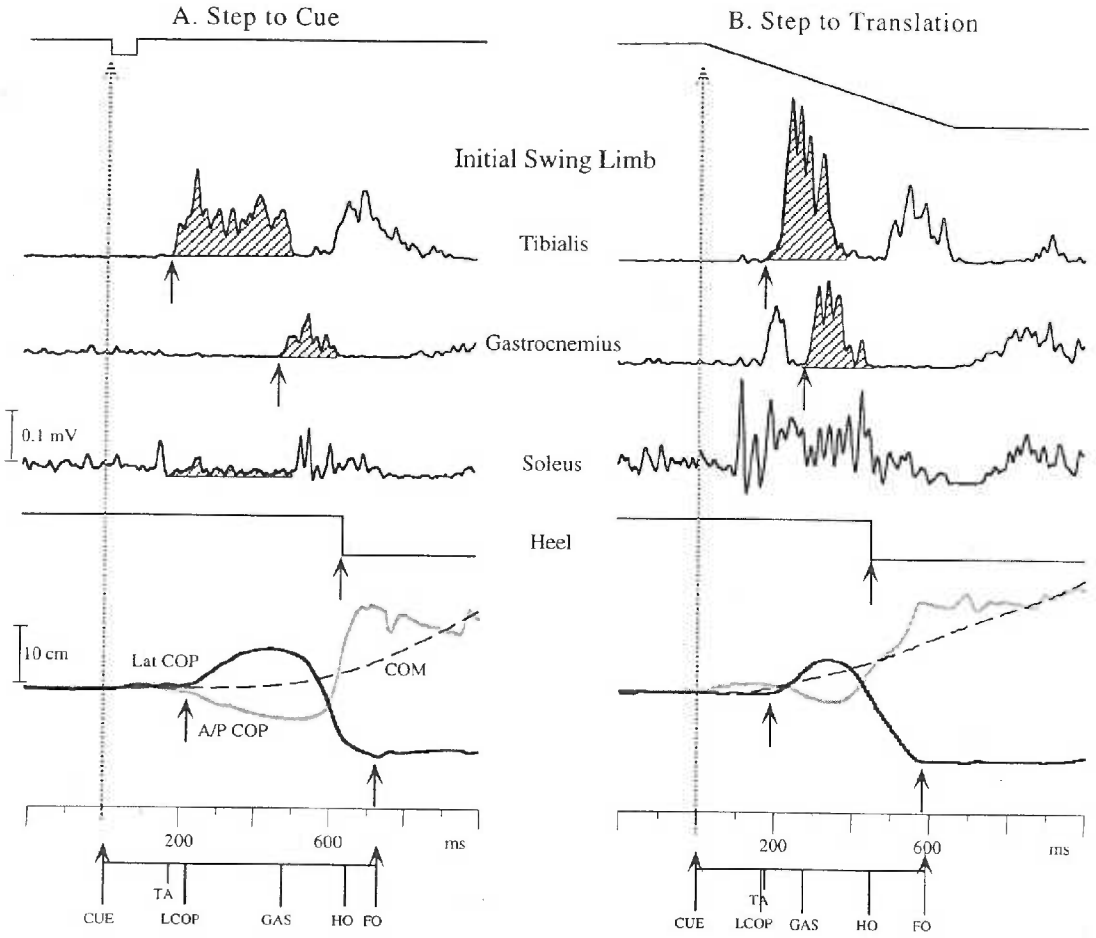

Figure 2.5. Average traces for initial swing limb in subject SD for (A) Step-to-cue, and (B) Step-to-translation. Figure demonstrates differences in total duration of the step initiation and related onset latencies. Shaded areas correspond to postural components of muscle activation. In (A) and (B) an upward displacement of the lateral COP (solid line) indicates excursion of the COP towards the left (swing limb), while a downward displacement indicates excursion to the right (stance limb). In (A) and (B) a downward displacement of the A/P COP (shaded line) indicates backward excursion of the COP related to tibialis. Note that in (B) there is an initial forward displacement of the A/P COP related to the perturbation, which is then reversed with the initiation of the step. The COM (dashed line) is displaced forward in both conditions, but the displacement is greater in the Step-to-translation and the steeper slope is representative of a faster velocity of displacement. TA = tibialis, LCOP = lateral COP, GAS = gastrocnemius, HO = heel-off, FO = foot-off.

Change in muscle activation patterns during perturbed step

Performance of step initiation during the translation did not result from temporal addition of an unmodified automatic postural response followed by fixed anticipatory adjustments for the voluntary step. Figure 2.6 compares averaged EMGs of the last three trials for one subject from the actual Step-to-translation data, and the computer addition of EMG from Sway-to-translation and Step-to-cue responses. Several differences in the muscle activation patterns are seen in this representative figure of the swing limb activity. First, the initial tibialis burst in the actual Step-to-translation was shorter in duration and had a greater initial amplitude and area. Second, the second gastrocnemius burst, related to heel-off, was of much greater amplitude and had an earlier onset. Finally, the automatic soleus response was clearly reduced in the actual data compared to the computer addition data.

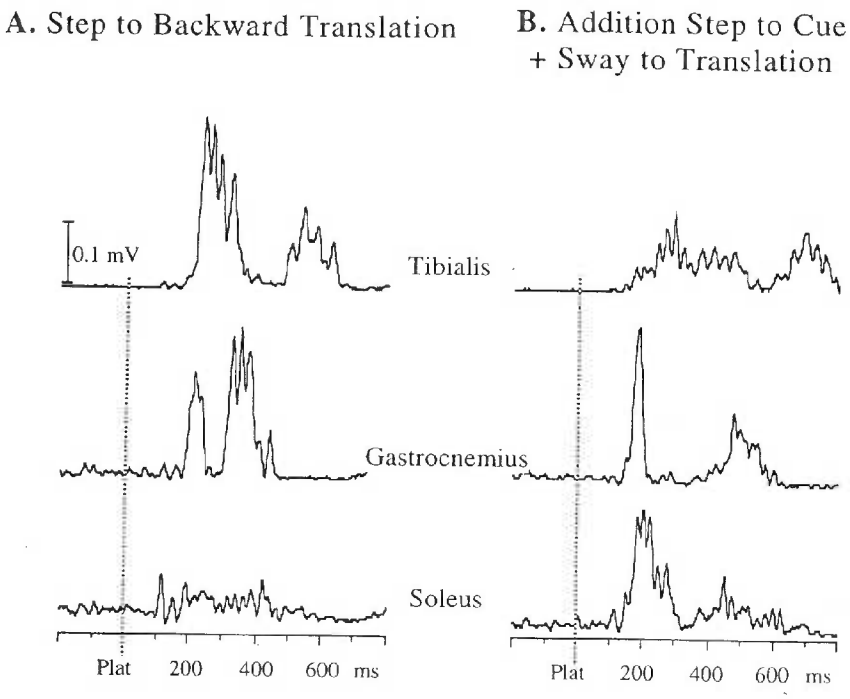

Figure 2.6. Comparison of (A) actual averaged data for initial swing limb in a single subject for the Step-to-translation condition, and (B) computer addition of swing limb EMGs for the Step-to-cue and Sway-to-translation conditions. Figure clearly represents that in the Step-to-translation condition, there is not a simple addition of an automatic postural response followed by the postural adjustments for the step.

Across all subjects, the initial tibialis burst of both limbs had a significantly shorter duration ($p \leq 0.0001$) in the Step-to-translation Conditions (swing = 217 ± 93 ms, stance = 256 ± 157 ms) than in the Step-to-cue condition (swing = 353 ± 149 ms, stance = 425 ± 201 ms). Although the total duration of the tibialis burst was reduced, the integrated area of the first 100 ms of the burst was significantly greater ($p \leq 0.0005$) in the Step-to-translation (swing 17.8 ± 11.4 mV•ms, stance 19.4 ± 13.7 mV•ms) compared to the Step-to-cue condition (swing 11.4 ± 6.9 mV•ms, stance 10.9 ± 5.6 mV•ms). This enhanced tibialis activation may have resulted in the increased displacement and velocity of the COM during the perturbed step initiation. The duration of the gastrocnemius response for push-off was not significantly different in the two conditions (Step-to-cue = 149 ± 50 ms, Step-to-translation = 141 ± 49 ms). However, the integrated area of the first 100 ms was significantly increased ($p \leq 0.0001$) in the Step-to-translation (16.5 ± 10.4 mV•ms) compared to the Step-to-cue (9.4 ± 6.7 mV•ms). Furthermore, the initial onset of the gastrocnemius burst for push-off occurred earlier in the perturbed condition (Step-to-translation = 272 ± 43 ms, Step-to-cue = 417 ± 80 ms; $p \leq 0.0001$).

Progression of the body COM during step initiation

In the Step-to-translation condition, step initiation was imposed upon an already forward moving body COM, which had not been entirely slowed since the automatic postural response was reduced. At the time of heel-off and foot-off, the forward displacement of the calculated COM was much greater in the perturbed condition, suggesting that the initiation phase had to be shortened to prevent a fall. During Step-to-cue, the average displacement of the normalized COM at heel-off was 12% of the foot length and at foot-off was at 23% of foot length. Both measurements were significantly different ($p \leq 0.0001$) from the Step-to-translation condition in which the COM at heel-off was forward 31% of foot-length while at foot-off the COM was forward by 51% (range 11.0 - 15.5 cm). Thus, in the perturbed step, the COM was

approaching the limits of foot stability and this may have forced a more rapid execution of the anticipatory postural adjustments for the step.

Not only was the body COM further forward at the time of heel-off and foot-off in the Step-to-translation condition, but its velocity was also significantly greater ($p \leq 0.0001$). During Step-to-cue, the average velocity of the forward moving COM was 18.0 ± 4.5 cm/s at heel-off compared to 31.4 ± 3.4 cm/s during Step-to-translation. Since the platform translation alone could only move the COM forward at 20 cm/s, the additional velocity must have been generated by the anticipatory postural adjustments for the step initiation. It is noteworthy that by the time of heel-off in the Step-to-cue condition, the velocity of the body COM had greatly increased (18.0 ± 4.5 cm/s at heel-off versus 28.4 ± 5.9 cm/s at foot-off) but in the perturbed condition, the velocity was not greatly different between heel-off (31.4 ± 3.4 cm/s) and foot-off (35.2 ± 6.8 cm/s). When the COM was displaced forward near the limits of the base of support, the gastrocnemius contraction for heel-off may have resulted in slowing the progression of the whole body, and promoting completion of the step by increasing the foot velocity at heel-off. The velocity of heel-off, determined from the heel IRED, was significantly greater ($p \leq 0.0001$) in the Step-to-translation (19.3 ± 2.34 cm/s) compared to the Step-to-cue condition (15.4 ± 2.2 cm/s), suggesting that the forward position of the body required the more rapid heel-off.

DISCUSSION

Evidence for goal directed postural interactions has been presented. The externally-triggered automatic postural responses were modified by a change in central command to step rather than maintain standing, and the centrally initiated postural adjustments for step initiation were modified by an externally imposed change in body position. The automatic postural responses of the stretched gastrocnemius and soleus were reduced to allow the COM to progress forward. The duration and activation amplitude of the postural adjustments for the step were modified to promote a more rapid execution of the step and accommodate the passively imposed change in COM position and velocity.

MODIFICATION OF THE AUTOMATIC POSTURAL RESPONSE

Previous research has suggested that when reaction time voluntary movements are triggered by a perturbation causing postural instability, their execution is delayed until after the automatic postural response (Nashner and Cordo 1981). In contrast, in the data we have presented some subjects had complete absence of an automatic response in the gastrocnemius and soleus of the initial stance limb when the goal was to continue moving the COM forward with a step. When the automatic response was present, it was of normal latency and did precede the onset of the tibialis for voluntary step initiation, but it was significantly reduced in amplitude. Asymmetries between the stance and swing limb suggested that the reduction of the automatic postural response was not generalized, but was specific to the task. The automatic response was modified by a centrally-initiated postural program, and there was not simply temporal summation or delay between postural components. Our results may differ from previous findings of Nashner and Cordo (1981) because of different biomechanical requirements of the tasks. In their paradigm, postural equilibrium was a prerequisite to the performance of the voluntary sway movement. Subjects needed to stabilize the COM well within the foot base of support before they could voluntarily sway forward. In contrast, in our study, brief disequilibrium with movement of the COM out of the base of support was required for the forward step.

Asymmetry in modification of the automatic postural response

The asymmetry of the modification of the automatic response supports the idea that the centrally-initiated program for a forward step may have resulted in alteration of neuronal excitability prior to the actual perturbation, in a task specific manner. The reduction of the automatic postural response, by the intent to step, was not a global effect in the muscles recorded. There was marked asymmetry in the gastrocnemius which was more reduced in the stance than swing limb, while the soleus response was reduced bilaterally. These findings correspond to the fact that the initiation of step from quiet stance requires bilateral inhibition of the tonically active soleus for forward movement of the COM, and asymmetrical activation of

the swing limb gastrocnemius for the propulsion during heel-off. The presence of the automatic response in the swing limb medial gastrocnemius may have also contributed to the early generation of a lateral change in the COP during the perturbed step (Mouchnino et al. 1992).

Role of prior experience and prior instruction

In this experiment, modification of the automatic response in the gastrocnemius and soleus may have been dependent upon whether the subcortical structures were set prior to the actual perturbation, to the goal of "Sway" or "Step" (Evarts and Tanji 1974; Hammond 1956; Horak et al. 1989). When the goal was to step, the reduction of the automatic response and the early generation of a lateral COP resulted in a significant change in behavior to the perturbation. Instead of forces being generated in direct opposition to the perturbation, the initial response to the backward translation was generation of lateral forces. Experience with the perturbation may also have been configured into the internal representation of body position in space (Gurfinkel et al. 1988) with the velocity and degree of passive forward sway anticipated in advance of the actual cue to step. By using a fixed order of testing we have demonstrated that together, instructional set and prior experience can alter both automatic and anticipatory postural behavior. Future experiments will determine whether instruction or experience has a more critical role in this modification of postural responses. To assess the effects of prior instruction for the goal, random and fixed commands to Sway or Step in response to a backward platform translation will be compared. To assess the effect of experience versus on-line velocity dependence on modification of both the automatic response and the anticipatory adjustments, random and fixed presentation of platform velocities will be compared.

MODIFICATION OF POSTURAL ADJUSTMENTS FOR STEP INITIATION

Activation of the tibialis prior to a step is critical for aligning the COM forward (Breniere et al. 1987; Crenna and Frigo 1991), such that gastrocnemius activation will result in heel-off for swing and forward propulsion of the body (Winter et al. 1990), rather than a return of the body to the initial stance position. Voluntarily assuming a forward lean before initiating locomotion has been shown to progressively reduce the amplitude of the swing limb tibialis since the forward position of the body has already been achieved (Crenna and Frigo 1991). In our results, the amplitude of the tibialis was actually larger and the onset of the tibialis was present at the same latency during the Step-to-translation as it had been during the Step-to-cue condition, despite the fact that the body had already been passively displaced forward by the platform translation. Because the anticipatory postural adjustments for step initiation are considered part of the central movement program (Crenna and Frigo 1991; Das and McCollum 1988; Forssberg 1985), the initial activation of tibialis may require minimum programming time and descending drive from cortex (Eccles 1982). Our data suggests that the initial onset of the tibialis was related to the motor program for step initiation being executed when the body was in its initial upright position.

In contrast to the fixed onset, changes in the tibialis amplitude and duration, and the subsequent modification of the gastrocnemius activity were affected by the peripheral sensory information signaling passive changes in the body position. Phasic modulation of both anticipatory and reactive postural responses during locomotion suggests that the position and velocity of the body segments must be continuously encoded to ensure smooth performance of a movement task (Hirschfeld and Forssberg 1991; Nashner and Forssberg 1986). In our study, the enhanced amplitude of the tibialis burst is consistent with the faster forward velocity of the COM in the perturbed step. The overall shortened duration of the tibialis burst is also consistent with the shortened duration of the entire step initiation with respect to the greater displacement and velocity of the COM in Step-to-translation. The tibialis burst amplitude may

have also been enhanced since the tibialis activation was in opposition to the automatic gastrocnemius and soleus responses to the translation which were not entirely suppressed.

Although the tibialis burst amplitude was enhanced in the Step-to-translation, this was not directly reflected by an increase in the backward COP. The A/P COP reflects both the dynamic forces produced by tibialis activation for the step initiation and the forces produced by any preserved gastrocnemius or soleus response to the perturbation. In addition, the passive forces resulting from the forward displacement of the COM also influence the COP. Thus, the A/P COP does not reflect only the propulsive forces developed by the tibialis during the perturbed step initiation. The fact that the A/P COP was not symmetrical between the swing and stance limbs corresponds to the asymmetry in suppression of the automatic gastrocnemius response.

The lateral change in the COP occurred earlier in the perturbed step condition, and was executed more rapidly than in the static condition. We suggest that because of the passive forward movement of the body, the rapid production of lateral COP was critical to propel the forward moving body COM over the stance limb for execution of the step (Mouchnino et al. 1992).

Dynamic modulation of the central program during the perturbed step was also clear in the large gastrocnemius burst for heel-off. When the COM was displaced forward near the limits of the base of support, in the Step-to-translation condition, the large gastrocnemius contraction for heel-off produced both a knee flexion moment and ankle plantar flexion moment. The reaction force produced was directed in front of the body COM. Because of the knee flexion moment acting on the upper leg, the forward angular velocity of the body segment was reduced (Jacobs and Ingen Schenau 1992, Jacobs et al. 1993). At the same time, because of the plantar flexion moment, the movement velocity of the ankle was increased and the heel-off hastened (Jacobs and Ingen Schenau 1992, Jacobs et al. 1993). Together, the effects of the enhanced gastrocnemius burst acted to prevent a fall by slowing the progression of the body, and promoted completion of the step by increasing the foot velocity at heel-off.

It is clear that the passive perturbation affected the step velocity and the duration of the gait initiation period. Whether the changes were based upon on-line reference to the changing body position or prior updating of the internal reference with respect to the earlier sway conditions is not entirely clear. Previous studies which found an invariance in the gait initiation (Breniere and Do 1986) were from steady state, thus updating of the motor program with respect to passive changes in body position and an internal representation of body in space may not have been as critical.

Overall, our results suggest that even prior to its execution, the descending central command to step must interact with the ascending peripheral information associated with the platform perturbation. Neither the automatic postural responses nor the gait initiation process were strictly invariant and fixed to a temporal hierarchy. The modifications of postural control may have been dependent upon the convergence of sensory inputs and descending drive to locomotor and postural circuits.

Acknowledgements

We gratefully acknowledge Dr. Jane Macpherson for time and consideration in reviewing the data, Dr. Ron Jacobs and Dr. John Clements for assistance in programming, and Matthew Cohen for technical assistance in preparing the figures. This work was supported by a doctoral research award from the Foundation for Physical Therapy, and Grant AG-06457 from the National Institute on Aging.

Chapter 3.

Based on *J. Neurophysiol.* (submitted): 1995

Influence of Predicted and Actual Perturbation Velocity on the Postural Organization of Perturbed Step Initiation

A. Burleigh and F. Horak

SUMMARY AND CONCLUSIONS

1. This study addresses how the CNS may use prediction of perturbation velocity and actual perturbation velocity information to modify both the automatic responses to perturbation and the anticipatory postural adjustments for a pre-planned voluntary step. Our previous study showed that when subjects were perturbed by a backward surface translation and instructed to step rather than maintain stance, two distinct postural modifications occurred during perturbed step initiation: 1) the automatic postural response to the surface perturbation was reduced in magnitude; 2) the anticipatory postural adjustments promoting foot-off were shortened in duration.

2. Eleven human subjects were instructed in advance to either maintain stance, or step forward in response to a backward surface translation. Four different velocities of translation were used to perturb equilibrium. To assess the influence of prediction versus actual velocity information, the surface translations were presented in both a blocked order of increasing perturbation velocity (predictable) and a random order (unpredictable). Lower extremity electromyographs (EMGs), ground reaction forces and movement kinematics were quantified.

3. The influence of task instruction and prediction of the perturbation velocity, for reduction of the automatic response magnitude, was determined by comparing trials in which subjects maintained stance and those in which they voluntarily stepped forward when perturbed by translations of both predictable and unpredictable velocities. The influence of predicted or actual velocity information, for reduction of the anticipatory postural adjustment duration, was determined by comparing trials in which subjects stepped in response to predictable versus unpredictable perturbation velocities.

4. Prediction of perturbation velocity was required for significant reduction of the early automatic postural response when subjects stepped in response to the perturbation. When compared to the stance condition, the magnitude of the automatic response in bilateral soleus and the left limb gastrocnemius (initial stance limb) was significantly reduced only when the perturbation velocities were presented in a blocked order. The magnitude of the automatic

response was not reduced in the gastrocnemius of right limb, which was always the initial swing limb and recruited for heel-off in the step conditions. The asymmetrical reduction of the gastrocnemius suggests that modification of the response was specific to the instruction, rather than a general decrease in the extensor muscle excitability.

5. The reduction of the early automatic postural response magnitude involved a change in the *bias* of the response. Despite the reduced magnitude during the predictable velocity step conditions, the slope (i.e. gain) of the response with increasing velocities was not different from that of the stance condition. Thus, the excitability of the automatic response was reduced by a relatively constant amount for each velocity when the perturbation velocity was predictable.

6. In contrast to the importance of velocity prediction for modification of the automatic postural response, actual velocity information influenced the anticipatory postural adjustments for perturbed step initiation. Regardless of whether the perturbation velocities were presented in a blocked or random order, the postural adjustments were rapidly initiated and the duration of the postural adjustments for step initiation was shortened as the velocity of perturbation increased.

7. We conclude that the CNS uses *prediction of perturbation velocity*, to modify the excitability of the early automatic postural response when the postural goal changes. In contrast, *actual afferent velocity information* can be used to modify the duration of the anticipatory postural adjustments during perturbed voluntary movement. Thus, the CNS utilizes feed-forward, predictive processes to modify peripherally-triggered reflexive responses, and utilizes immediate afferent information to modify the postural adjustments preceding centrally-initiated voluntary movement.

INTRODUCTION

The postural control system is critically involved in both responding to external perturbations and preparing for the execution of voluntary movements. When the body undergoes an external perturbation, an *automatic postural response* restores equilibrium. These automatic postural responses to perturbation are peripherally-triggered by sensory information related to the perturbation. In contrast, during the execution of a voluntary movement, *anticipatory postural adjustments* promote movement of the body to a new position. These anticipatory postural adjustments associated with voluntary movement are considered to be pre-programmed and centrally-initiated by the intention to move. Our previous study

(Burleigh et al. 1994) showed that both the automatic response to perturbation and the anticipatory postural adjustments for a pre-planned movement can be modified by task constraints. When subjects voluntarily stepped in response to a backward translation of the support surface, which is defined as perturbed step initiation, two distinct modifications occurred: 1) the automatic postural response to the perturbation was reduced in magnitude; 2) the anticipatory postural adjustments for the step were shortened in duration. However, in this previous experiment, only one translation velocity was imposed over repeated trials; thus, the cause of the modifications was unclear. It is possible that the instruction to step by itself resulted in these modifications. However, it is also possible that the nervous system used either prior experience of the perturbation velocity, and/or afferent sensory information about perturbation velocity to modify the two postural behaviors.

It is known from previous work that instruction for voluntary movement is associated with cortical and cerebellar activity that can modify non-volitional, automatic responses to external perturbations (Evarts 1973; Evarts and Tanji 1974; Crago et al. 1976; Marsden et al. 1978; Strick 1983). Medium latency, automatic responses in the arm are modified in magnitude when subjects are instructed to voluntarily resist or assist an external perturbation of arm position (Hammond 1956; Evarts and Tanji 1974; Crago et al. 1976). Consistent with these findings is the reduction of medium latency, automatic postural responses in stance when subjects are instructed to step in response to a surface perturbation (McIlroy and Maki 1993a; Burleigh et al. 1994). However, all of these studies showing modification of the automatic response have involved a predictable perturbation paradigm. Prediction of the perturbation *amplitude* has been previously shown to influence the magnitude of automatic postural responses (Horak et al. 1989). These findings suggest the possibility that prediction of perturbation velocity may also influence response magnitudes. Thus, during perturbed step initiation (Burleigh 1994), it is unclear how much the reduction of the response was due to the task instruction, and how much was due to prediction of the perturbation.

In contrast to what is known about the modification of automatic postural responses, relatively less is known about modification of anticipatory postural adjustments for step initiation. It is generally accepted that step initiation involves a centrally-mediated motor program which is relatively invariant (Breniere and Do 1986; Crenna and Frigo 1991; Das and McCollum 1988; Forssberg 1985). However, our previous study showed that the postural adjustment phase can be reduced in duration when subjects step in response to a backward translation of the support surface. This reduction of duration may be necessary because the translation results in a forward displacement of the body requiring a faster initiation of step. It is unclear whether the nervous system used afferent sensory information from the perturbation itself, or prediction of the perturbation velocity based on prior experience to decrease the duration of the postural adjustments.

This current study was based on the hypothesis that the postural modifications during perturbed step initiation were not due solely to the change of instruction, but were dependent upon prediction of the perturbation velocity and actual velocity information. Accordingly, the specific purpose of the present study was twofold: 1) to determine if prediction of perturbation velocity was required for reduction of the magnitude of the automatic postural response during perturbed step initiation; 2) to determine if prediction of perturbation velocity or afferent velocity information was used for reduction of the duration of the anticipatory postural adjustments during perturbed step initiation.

This study shows that prediction, based on prior experience, is required for the modification of an automatic postural response to perturbation. Furthermore, this study shows that afferent information is used to modulate the anticipatory postural adjustments associated with voluntary movement. The postural components of the voluntary movement are not fixed, but can be updated depending on the environmental context in which the movement occurs.

METHODS

Informed consent was received from 11 normal, healthy subjects (24.5 ± 2.8 years). Throughout testing, subjects stood on a platform with two force plates that moved under the control of a hydraulic servo motor. One foot was centered in each of the two force plates, with weight equally distributed between both feet. The data collection and processing have been previously described in detail (Burleigh et al. 1994). In brief, bilateral EMG activity of the tibialis anterior, soleus and medial gastrocnemius was recorded using surface electrodes. Vertical forces were measured in each of the two force plates. The center of foot pressure (COP) for the whole body was calculated using the recorded forces. The body center of mass (COM) displacement and velocity was calculated from the kinematic data collected with Northern Digital's Watsmart motion analysis system.

Protocol

All subjects were tested under the following conditions:

Condition A. Stance

Subjects were instructed to maintain stance with feet in place during a backward surface translation. The translations were 12 cm in amplitude with velocities of 10, 15, 20, and 25 cm/s presented in blocks of five trials at each velocity, in order of increasing velocity.

Condition B. Step - blocked velocity (Predictable)

Subjects were instructed to step forward *as soon as* they felt a 4 ms current pulse to the earlobe. This cue was either directly paired with the onset of a backward surface translation (perturbed step) or presented alone (non-perturbed step). The translations were 12 cm in amplitude and the velocity was 10, 15, 20, or 25 cm/s. The cue alone and the cue paired with each perturbation velocity were presented in blocks of five trials at each velocity, in order of increasing velocity (predictable). For all trials, subjects initially stepped with the right limb and followed through with the left.

Condition C. Step - random velocity (Unpredictable)

This instruction was the same as in condition B. However, in this condition, five trials of the cue alone and the cue paired with each perturbation velocity were presented in a random order (unpredictable).

Data Analysis

EMGs The first purpose of this study was to determine whether prediction of perturbation velocity was required for reduction of the magnitude of the automatic postural response during perturbed step initiation. To address this question, EMG magnitudes for the automatic response for the maintained stance trials were compared to the perturbed step initiation trials when the perturbation velocity was both predictable and unpredictable.

Based on previous studies, muscle activations were divided into a component related to the automatic postural response and a component related to the postural adjustments for step initiation. The component of the EMG related to the automatic postural response was defined as a burst of gastrocnemius and soleus activation which occurred 90-120 ms after the onset of surface translation (Horak and Nashner 1986). The component of the EMG related to postural adjustments for step initiation was defined as the activation of the tibialis at onset latencies greater than 120 ms. The tibialis has been previously characterized in the postural adjustments associated with gait initiation (Herman et al. 1975; Mann et al. 1979). Later activation of the right gastrocnemius (greater than 180 ms) was attributed to heel-off for step initiation.

For all muscles, a burst onset was defined by EMG activity 2 S.D. above the mean baseline activity and lasting more than 25 ms. The magnitude of the automatic postural response was quantified by the integral under the rectified EMG curve (IEMG) for the gastrocnemius and soleus. Two periods were quantified: an early period (onset to 50 ms) and a late period (50 to 100 ms). To eliminate the influence of background activity, the mean amplitude for 100 ms of baseline EMG activity before the onset was subtracted from the burst integral. When no burst

related to the automatic response was apparent in an individual trial, the average time of onset for all trials in the same condition was used to calculate the integral.

FORCES The second purpose of this study was to determine if prediction of perturbation velocity or afferent velocity information was used for reduction of the duration of the anticipatory postural adjustments during perturbed step initiation. To address this question, the onset and duration of the postural adjustments were compared between the step trials, when the perturbation velocity was both predictable and unpredictable.

During step initiation, the COP moves backward and lateral toward the swing limb. The onset of change in the lateral COP was used to indicate the onset of the postural adjustments for step. The duration of the postural adjustments initiation was defined from the onset of change in the lateral COP to heel-off. The precise time of heel-off was indicated by a pressure sensitive resistor taped under the heel of the initial swing limb. Two components of the anticipatory postural adjustments were analyzed: 1) reaction time phase (onset latency from cue to first change in lateral COP); 2) anticipation phase (duration from first change in lateral COP to heel-off).

KINEMATICS To determine whether afferent information about perturbation velocity could be derived from the body movement, the displacement and velocity of the calculated COM were quantified at the time of heel-off for both perturbed and non-perturbed step. Until heel-off, the anterior progression of the body is essentially symmetrical. During the perturbed step trials, the forward COM displacement was referenced to the moving platform surface and expressed as a percentage of foot length. The velocity of the COM at the time of heel-off was calculated by differentiating the COM displacement data. To determine whether the duration of the anticipation phase of the postural adjustments influenced step length, displacement of the swing foot was determined from the trajectory of a heel-diode.

RESULTS

I. Influence of prediction on automatic postural responses

During perturbed step initiation, reduction of the earliest period of the automatic response (onset-50 ms integral), which preceded the onset of step-related EMG, was dependent on prediction of perturbation velocity. In contrast, reduction of the later period of the response (50-100 ms integral), which overlapped with onset of step-related muscles, was not dependent on prediction of perturbation velocity. The data also show that for both the early and late periods of the response, despite the reduced magnitude, the response still increased with increasing velocities

Reduction of early automatic postural response: Dependent on prediction

To determine if prediction of perturbation velocity influenced the automatic response magnitude during perturbed step, the response magnitudes for the maintained stance trials were compared to the perturbed step trials when the perturbation velocity was both predictable and unpredictable. Figure 3.1 shows the left gastrocnemius IEMG for the three experimental conditions. The instruction to step was not solely responsible for the reduction of the response magnitude. A predictable (blocked) perturbation velocity was required for significant reduction of the IEMG magnitude for the step condition compared to the stance condition.

A two-way ANOVA with condition and velocity as repeated variables demonstrated that during the initial 50 ms of the response, the IEMG were significantly different across conditions for the left gastrocnemius ($F = 16.8$, $p \leq 0.001$) and bilateral soleus (left: $F = 7.7$, $p \leq 0.005$; right: $F = 5.76$, $p \leq 0.001$). Post-hoc analysis (Newman-Keuls) revealed that the difference among stance and step conditions was significant only when step was initiated in response to predictable (blocked) perturbation velocity (Table 3.1).

The reduction of this early component of the automatic response was not due to a delay of the response or collision with step-related muscle activation. The latency of the automatic response clearly preceded the onset of EMG associated with voluntary step initiation. The onset (mean $\pm$ S.D.) of the automatic response with respect to the onset of the platform

perturbation during the step conditions was 105 (± 7) ms for the right gastrocnemius, 108 (± 7) ms for the left gastrocnemius, 106 (± 11) ms for the right soleus, and 105 (± 8) ms for the left soleus. In contrast, the onset of the step-related tibialis was 177 (± 5) ms for the right and 178 (± 6) ms for the left limb. Because there was no significant difference in onset latency for any velocity, these values are the mean onsets of the four velocities for the predictable (blocked) velocity conditions.

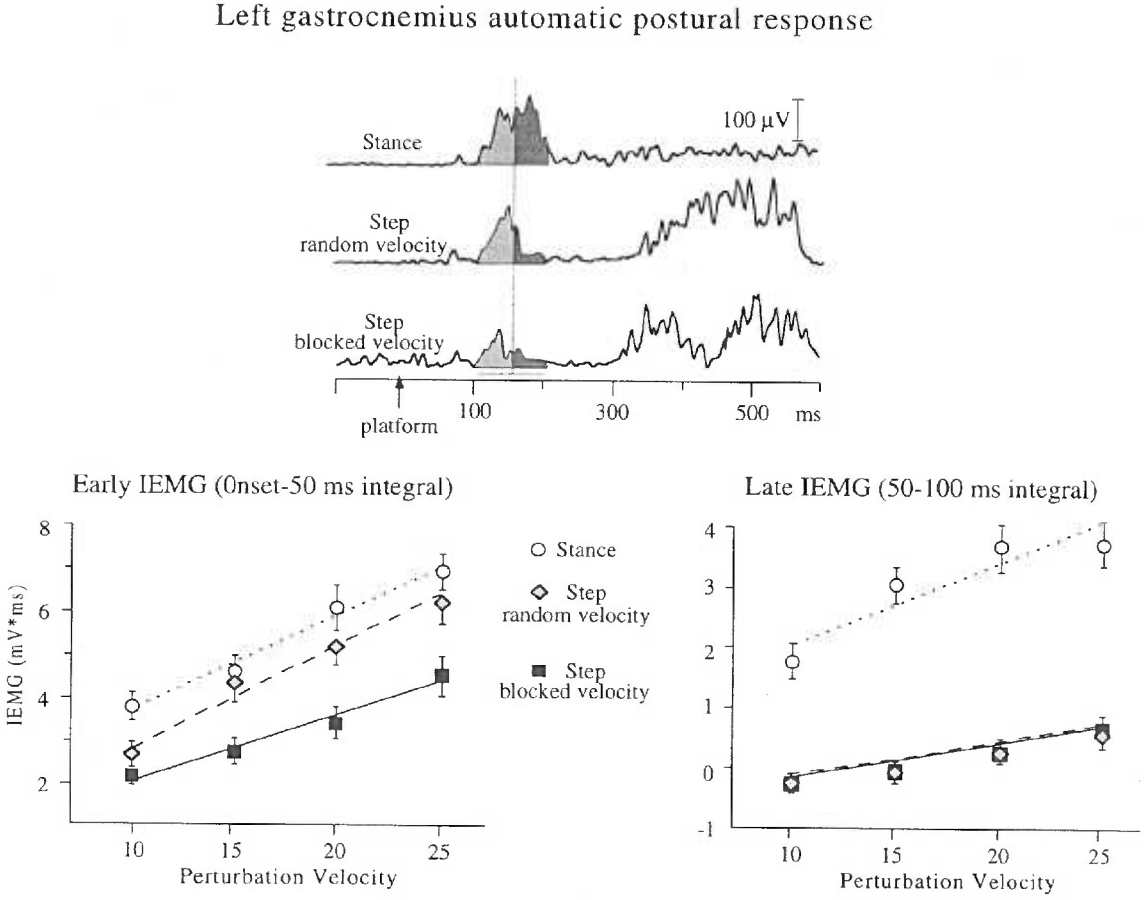

Figure 3.1. Upper panel shows the average left gastrocnemius EMG activity from five trials of 20 cm/s perturbations, each condition, for a single subject. Data is plotted versus time with respect to the platform onset. Light shading indicates early period (onset to 50 ms integral) of the automatic response, and dark shading indicates the late period (50-100 ms integral) of the automatic response. Lower panel shows integrated EMG (IEMG) for the early period and late period of the automatic response for each condition. Compared to the stance condition, the early period of the gastrocnemius was reduced only when step was initiated in response to predictable velocities of perturbation (blocked velocity). In contrast, when compared to the stance condition, the late period of the gastrocnemius was reduced when step was initiated in response to both predictable (blocked velocity) and unpredictable (random velocity) perturbation velocities.

TABLE 3.1. *Reduction of IEMG for the early automatic postural response: Step conditions versus Stance*

	Left Limb (stance)				Right Limb (swing)			
	Gastrocnemius		Soleus		Gastrocnemius		Soleus	
Velocities	Blocked	Random	Blocked	Random	Blocked	Random	Blocked	Random
10 cm/s	≤ 0.05	≤ 0.05	ns	ns	ns	ns	ns	ns
15 cm/s	≤ 0.005	ns	≤ 0.005	ns	ns	inc	≤ 0.01	ns
20 cm/s	≤ 0.0001	ns	≤ 0.001	ns	ns	ns	≤ 0.005	ns
25 cm/s	≤ 0.001	ns	≤ 0.0001	≤ 0.01	ns	inc	≤ 0.01	ns

Newman-Keuls post-hoc analysis; Blocked = step, predictable velocity condition; Random = step, unpredictable velocity condition; inc = increase in the IEMG.

Reduction of late automatic postural response: Independent of prediction

In contrast to the early period of the automatic response, prediction of perturbation velocity was not required for significant reduction of the next 50 ms integral of the automatic response during the perturbed step conditions (see Figure 3.1). During this late period, the IEMG were again significantly different across conditions for the left gastrocnemius ($F = 31.4$, $p \leq 0.001$). However, in contrast to the initial 50 ms of the response, the response was decreased for the step condition regardless of whether the perturbation velocity was predictable or unpredictable (Figure 3.1). Significant suppression ($p \leq 0.001$) of the response in the stance limb gastrocnemius (left) was demonstrated regardless of whether the perturbation velocity predictable (blocked) or unpredictable (random). It is possible that diminished response magnitude resulted from the activation of the step-related muscles, since there was an overlap of the late period of the automatic response in gastrocnemius and the onset of the step-related tibialis. The late period of the response in the soleus was not compared since the IEMG was generally very small, even in the control condition when stance was maintained in response to the perturbation.

Reduction of automatic postural response involves a central bias

Modification of the automatic response involved a reduction of magnitude without altering the ability to scale the response to increasing velocity. Figure 3.1 shows the early and late IEMG plotted as a function of platform velocity for all three conditions. The slopes of the regressions (i.e. gain) were not significantly different across conditions, but the intercepts were different between the stance and step conditions. The lower intercepts, without a change of slope, indicate similar reduction of magnitude at all velocities. During the early period of the automatic response, the intercept for the perturbed step condition was significantly lower only when the step was initiated in response to a predictable (blocked) perturbation velocity (Student's t-test: swing gastrocnemius, $p \leq 0.01$; swing soleus, $p \leq 0.01$; and stance soleus, $p \leq 0.02$). In contrast, the intercepts of the late period were significantly different between the stance (2.09 ± 1.4 mV•ms) and step conditions when the perturbation was both predictable (blocked velocity = $-0.13 \pm .48$ mV•ms, $p \leq 0.001$) and unpredictable (random velocity = $-0.11 \pm .55$ mV•ms, $p \leq 0.001$).

Asymmetry of the automatic postural response is specific to instruction

Reduction of the automatic response during perturbed step initiation did not involve a general decrease in the extensor muscle excitability, since there were differences between the swing (right) and stance (left) limbs. Despite reduction of the stance limb gastrocnemius and bilateral soleus, the magnitude of the swing limb gastrocnemius response was not reduced during step initiation (Table 3.1 and Figure 3.2). The asymmetry between the right and left gastrocnemius suggests that the reduction was specific to the instruction to step, since the pre-planned step included activation of the right gastrocnemius for initial heel-off. As the velocity of perturbation increased, the late period of the right gastrocnemius IEMG actually increased during the step conditions, and the slope of the response became significantly steeper ($p \leq 0.01$) than for the stance condition (Figure 3.2).

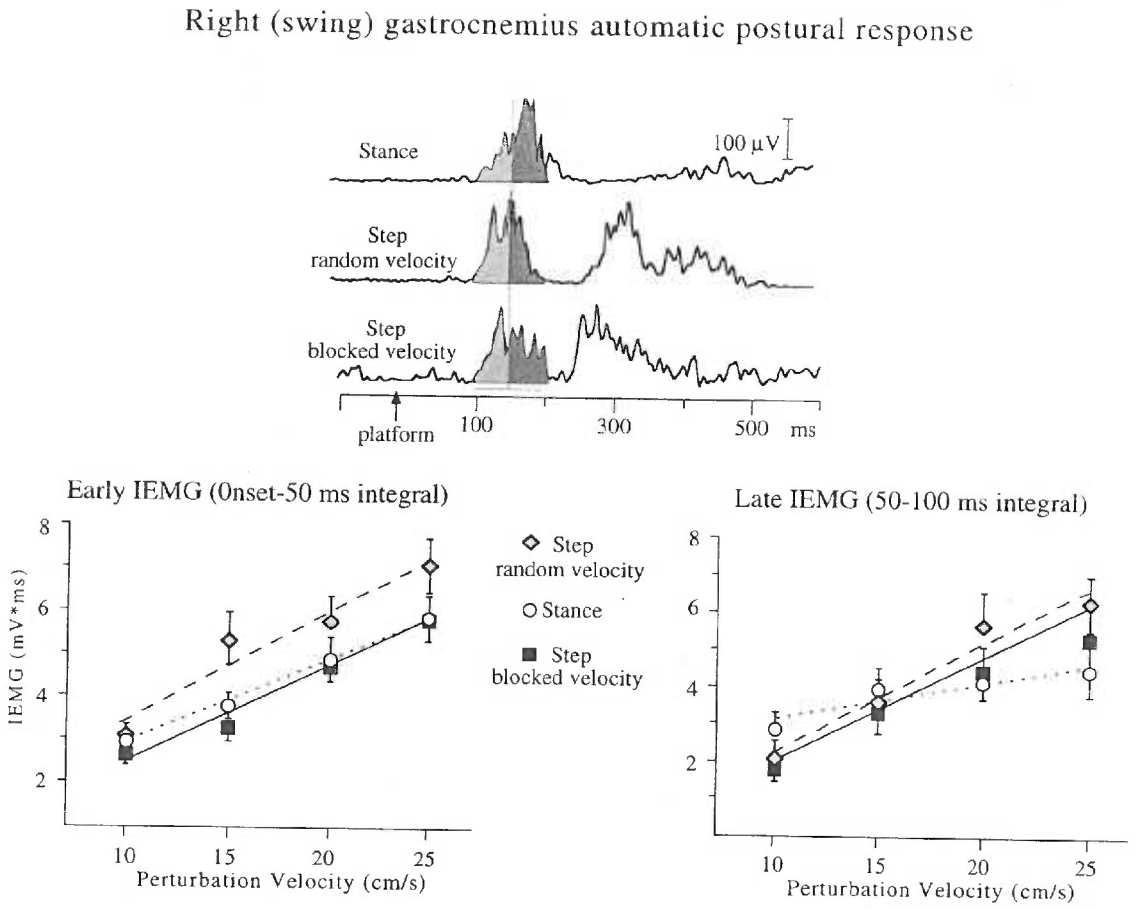

Figure 3.2. Upper panel shows the average right gastrocnemius EMG activity from five trials of 20 cm/s perturbations, each condition, for a single subject. Data is plotted versus time with respect to the platform onset. Light shading indicates early period (onset to 50 ms integral) of the automatic response, and dark shading indicates the late period (50-100 ms integral) of the automatic response. Lower panel shows integrated EMG (IEMG) for the early period and late period of the automatic response for each condition. Compared to the stance condition, neither the early period or late period of the gastrocnemius is reduced when step was initiated in response to either predictable (blocked velocity) and unpredictable (random velocity) perturbation velocities. This demonstrates an asymmetry between the left (Figure 3.1) and right gastrocnemius when step was initiated in response to the perturbation. The right limb was always the initial swing limb for step trials.

II. Influence of actual perturbation velocity on the postural adjustments for step initiation

The onset latency for step initiation was earlier for the perturbed step compared to the non-perturbed step conditions, but this latency was not influenced by either prediction of velocity or actual perturbation velocity. In contrast, the duration of the anticipation phase of the postural adjustments was influenced by perturbation velocity, regardless of whether the perturbation velocity was predictable or unpredictable.

Onset of postural adjustments for step initiation: Independent of perturbation velocity

The reaction time phase for step initiation was significantly shorter for the trials in which subjects stepped in response to the perturbation compared to those in which they stepped in response to the somatosensory cue alone. Figure 3.3 shows that when the cue was presented alone onsets were on the average 57 ms (blocked) and 73 ms (random) longer than when the cue was paired with the perturbation.

It is generally accepted that reaction time to a random, non-predictable cue is longer than for a predictable cue (Hick, 1952). This was true for the non-perturbed step, in which onset latency to the initial change in lateral COP was longer when the cue alone was presented at random rather than in a blocked order ($p \leq 0.0001$) (Figure 3.3). In contrast during perturbed step initiation, there was no difference in onset of the lateral change in COP, regardless of whether the perturbation velocity was predictable or unpredictable. The early onset of a change in the lateral COP during perturbed step was independent of velocity prediction. A two way

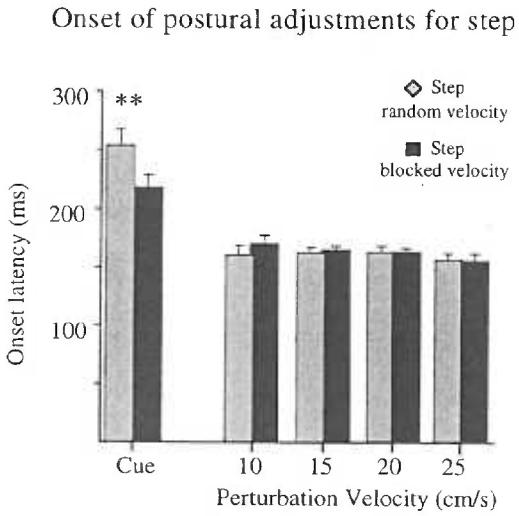

Figure 3.3. The mean onset latencies of the postural adjustments for step initiation during the step-to-cue and the perturbed step conditions are shown, demonstrating the early and consistent onsets during perturbed step initiation. Onset was determined from the initial change in the lateral center of pressure. When the cue alone (Cue) was presented in a predictable order (blocked), the onset was significantly earlier than when presented in an unpredictable order (random). When the cue was paired with the onset of perturbation, the onset latency was consistent and rapid, with no influence of whether the perturbation velocity was predictable (blocked velocity = dark-fill bars) or unpredictable (random velocity = light-fill bars). Each value represents the mean and standard error for eleven subjects, average of five trials at each velocity for each condition. (** indicates a significant difference ($p \leq 0.0001$) between blocked and random velocity conditions.

ANOVA with condition and velocity as repeated variables demonstrated no effect of condition ($F = 0.016$, $p = 0.899$). This consistent and early onset of step initiation in response to the perturbation, regardless of predictability, suggests that the platform onset acted as a strong peripheral trigger providing an external "go", with no requirement for anticipation of the stimulus velocity.

Duration of anticipatory postural adjustments for step: Dependent on perturbation velocity

The duration of the anticipation phase (initial change in COP to the time of heel-off) of the postural adjustments for step initiation decreased as the velocity of perturbation increased. A two-way ANOVA demonstrated that the reduced duration was independent of velocity prediction since there was no significant effect of condition for the duration of the anticipation phase ($F = 0.249$, $p = .63$). Figure 3.4A shows the duration of the anticipation phase of the postural adjustments plotted versus perturbation velocity for both the predictable and unpredictable velocity step conditions. Post-hoc analysis (Newman-Keuls) revealed that each of the perturbation velocities resulted in a shortened duration when compared to the non-perturbed step conditions ($p \leq 0.0001$). As the velocity of perturbation increased, there was a significant difference ($p \leq 0.0001$) between the duration of the anticipation phase at 10 cm/s compared to 25 cm/s. Regression of the duration over the different velocities demonstrated a negative slope with increasing velocities which was significantly different from zero ($p \leq 0.001$) for both the predictable (blocked) and unpredictable (random) velocities. Even when the non-perturbed step conditions were excluded, there was still a significant negative slope (blocked velocity, $p = 0.001$; random velocity, $p = 0.003$) as the duration shortened from the 10 cm/s to the 25 cm/s condition. The duration of the anticipation phase did not influence the step length, since there was no difference in step length regardless of whether step initiation was perturbed or non-perturbed (not shown). Nor was there any difference in step length when different velocities of perturbation were imposed. The mean ($\pm$ S.D.) step length across all velocities in both blocked and random velocity conditions was 39.8 ± 3.3 cm.

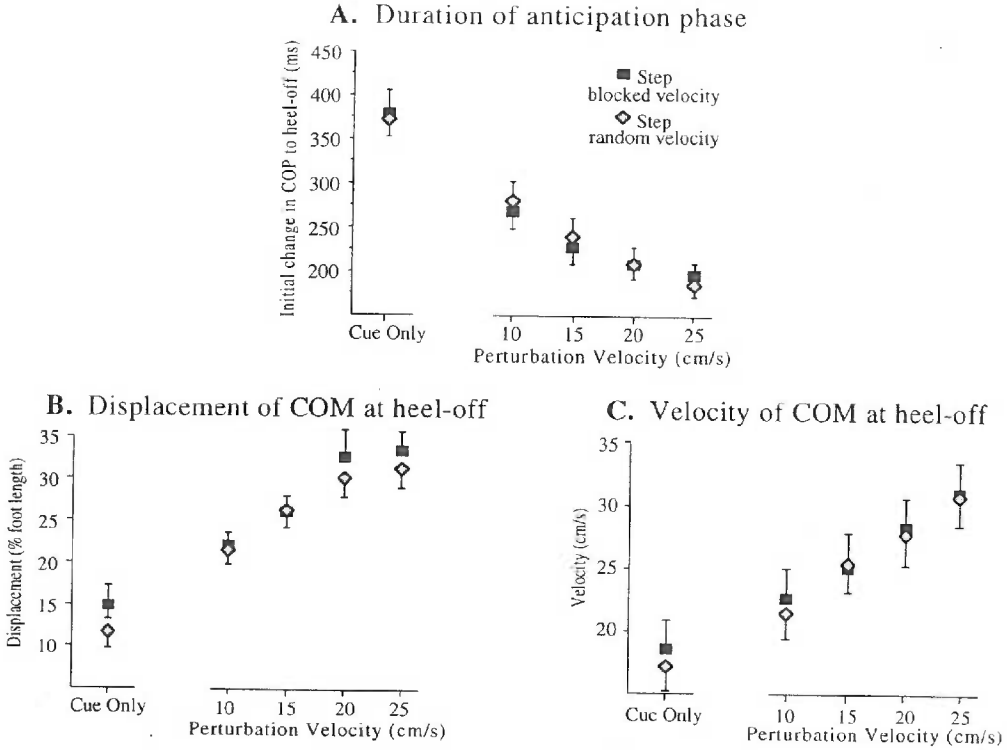

Figure 3.4. The influence of afferent velocity information is shown. A) The duration of the anticipation phase of the postural adjustments, B) the displacement of the body center of mass (COM) and C) the velocity of the COM at heel-off are plotted against perturbation velocity. There are no differences between the predictable (random velocity = light-fill diamond) and unpredictable (blocked velocity = dark-fill diamond) conditions demonstrating that there is no influence of velocity prediction. Each value represents the mean and standard error for eleven subjects, five trials at each velocity for each condition.

Although velocity information influenced the duration of the anticipation phase of the postural adjustments, it does not appear that a strict body position or velocity was used to trigger heel-off for step initiation. The step was not initiated at a constant COM displacement or velocity, regardless of whether the perturbation was predictable or unpredictable. As the perturbation velocity increased, the forward displacement of the COM at the time of heel-off also increased (Figure 3.4B). The velocity of the body COM at the time of heel-off also increased as the perturbation velocity increased (Figure 3.4C). The slope was positive and significantly different from zero for both COM displacement and COM velocity versus perturbation velocity ($p \leq 0.0001$; $r^2 = 0.56$ blocked, 0.58 random for displacement; $r^2 = 0.37$ blocked, 0.42 random for velocity). Despite the forward movement of the body during

perturbation, even at the highest velocity of 25 cm/s the step was not considered an automatic compensatory response, since all subjects were able to maintain standing with feet in place when instructed to do so.

DISCUSSION

The findings presented in this study demonstrate that central mechanisms involving prediction of perturbation velocity, as well as the task instruction, influenced the magnitude of the automatic postural response to the perturbation. In addition, the findings demonstrate that the organization of the anticipatory postural adjustments for step was not entirely pre-planned. Rather, the onset and duration of the postural adjustments for the step initiated in response to perturbation were dependent on peripheral sensory information from the surface perturbation. The onset of the postural adjustments was rapidly triggered by fast afferent information related to the onset of the perturbation, independent of the perturbation velocity. The duration of the postural adjustments was influenced by afferent sensory information related to the velocity of the perturbation.

Central influences on automatic postural responses

Long loop, medium latency stretch reflexes in the limbs can be modified by prior instruction (Hammond 1956; Gottlieb and Agarwal 1980). In addition, medium latency responses to arm perturbations are gated and modulated by learning and instructional set, when a voluntary movement opposes the automatic response (Evarts and Tanji 1974). Our findings are consistent with an instruction-specific modulation of the medium latency, automatic postural responses to perturbation. However, our findings further demonstrate that the magnitude of the earliest response magnitude is more strongly influenced by the predictability of the perturbation, than by the task instruction.

In our study, when the perturbation velocity was predictable and subjects voluntarily stepped in response to the perturbation, the automatic postural response which opposed the voluntary movement was reduced in magnitude. Reduction of the postural response magnitude

did not alter the gain, or slope of the response, with increasing velocities, suggesting a bias effect by which prediction resulted in a fixed amount of reduction at all velocities. A similar bias effect on the velocity scaling of postural responses is seen when a large or small amplitude of perturbation is predicted based on prior experience (Horak et al. 1989; Horak and Diener 1994). This effect has been attributed to changes in the "sensorimotor set" (Prochazka 1989; Horak and Diener 1994).

In addition to the important role of prediction, the instruction to step also contributed to the task-specific modification of the automatic postural response to perturbation. This task specificity was apparent in the asymmetrical reduction of the stance and swing limb gastrocnemius response. In voluntary reaction time tasks, 60-80 ms prior to the appearance of voluntary muscle activity, mono-synaptic reflexes in the agonist muscles are facilitated while those in the antagonists are depressed (Michie et al. 1975, 1976). In our study, the automatic response in stance limb gastrocnemius and bilateral soleus was antagonistic to the postural adjustments for step, since their activation would prevent the forward progression of the body. In contrast, activation of the swing limb gastrocnemius is required during step initiation to promote heel-off. Accordingly, if neural structures were preset to the task of stepping, the stance limb gastrocnemius and bilateral soleus would be depressed and the tibialis and swing limb gastrocnemius would be facilitated. Thus, the task-specific reduction of the early phase (onset - 50 ms integral) of the response preceded onset of the step-related tibialis by approximately 70 ms and corresponded to the reflex depression noted in the work of Michie et al. (1975).

The instruction to "step as soon as" the stimulus was perceived also resulted in a direct interaction between the automatic response to perturbation and the initiation of the voluntary movement. We did not observe a fixed temporal sequence in which the postural adjustments for step followed the automatic response (see Nashner and Cordo 1981). Rather, there was a "collision" between the two postural behaviors. The later period (50-100 ms integral) of the automatic response may have been canceled by the simultaneous activation of antagonist motor

neurons for the postural adjustments related to step initiation. Thus, the suppression of the later period of the response was the same regardless of the predictability of the stimulus.

Results from this study demonstrate set-dependent, feed-forward modulation of postural responses to external perturbations. The same sensory information elicited different responses dependent on prediction of the perturbation velocity and the intended response. Although specific reference to the neural systems involved in the modification of the automatic postural response cannot be made based on the findings of this study, it is intriguing to consider a role for central structures. Hore and Villis (1984) have demonstrated that the cerebellum contributes to modulation of medium latency response magnitudes based on prediction of stimulus characteristics. Accordingly, the cerebellum may be involved in pre-setting of muscle excitability prior to onset of the perturbation. Such a role for the cerebellum is supported by the findings that patients with anterior cerebellar lesions show increased bias of an automatic response to perturbation and an absence of predictive scaling to anticipated perturbation amplitudes (Horak and Diener 1994). In addition, voluntary movement preparation clearly alters the response of cerebellar neurons (dentate) to sensory input (Strick 1983). If cerebellar neurons were pre-set in preparation for the intended step initiation, their response to incoming sensory information may have been changed. Task-specific descending impulses resulting from activation of motor cortex may also serve as a basis for presetting of sub-cortical or spinal reflexes (Evarts and Tanji 1974). The role of the motor cortex for pre-setting of the response magnitude is further suggested by the findings that motor cortex activity changes when passive limb displacements are predictable (Lamour et al. 1980).

Peripheral influences on anticipatory postural adjustments

Anticipatory postural adjustments associated with voluntary movement are generally considered to be centrally-programmed and initiation does not require a peripheral trigger. However, our findings suggest that the postural adjustments for the pre-planned step can be triggered by peripheral sensory input, when subjects are instructed to voluntarily step in

response to a surface perturbation. Furthermore, although the step was pre-planned, the anticipatory postural adjustments were modified with respect to changing sensory information.

The consistent and early onset of the postural adjustments when the step was initiated in response to the perturbation suggests a mode of control which is intermediate to purely reflexive and purely voluntary control. Onset latencies were too long to be considered purely reflexive. However, two findings demonstrate that the postural adjustments for perturbed step initiation were not entirely under voluntary control. First, the onset latency was always shorter and less variable in the perturbed compared to non-perturbed step conditions. Second, there was no difference between onset latencies for predictable and unpredictable perturbation velocities. This rapid, pre-planned response to a sensory stimulus may be comparable to the performance of a well trained skill, in which the response to a stimulus is not purely reflexive, but is specific to the movement plan and rapidly executed to assure smooth performance of the task.

The rapid onset of the postural adjustments when the step was initiated in response to the perturbation may be mediated by several different mechanisms. First, the asymmetrical suppression of the automatic response may have resulted in the early contribution of the swing limb gastrocnemius to the lateral change in the center of pressure. It has been previously shown that when skilled dancers rapidly execute a foot-lift, activation of the medial gastrocnemius of the moving leg precedes the onset of the lateral center of pressure change (Mouchnino et al. 1992). If the preservation of the swing limb automatic gastrocnemius response to perturbation contributed to the postural adjustments for step initiation, it suggests that movement plan utilized the asymmetry of the automatic response to promote the rapid execution of the voluntary movement.

A second explanation for the rapid onset of the postural adjustments during perturbed step initiation is that the reaction time for step was dependent on the intensity and modality of the stimulus (Keele 1973). The platform perturbation was larger in magnitude and may have involved a faster sensory modality than the cutaneous pulse to the earlobe. The final

explanation is not dependent on the sensory modality, but rather on the central intention of the subject. If the subject planned to step faster in response to the perturbation, then the faster reaction time in the perturbed step conditions may have been related to the faster velocity of movement (Temprado et al. 1994). However, this mechanism is unlikely since there was no effect of velocity prediction, suggesting that the subjects did not plan to step faster in response to the perturbation. Rather, the passive forward velocity of the body center of mass induced by the perturbation was added to a constant active forward velocity generated by the individual.

In addition to being triggered by sensory input, the temporal organization of the postural adjustments for the pre-planned step initiation was directly modified by sensory information. This modification of the anticipatory postural adjustments is contrary to the concept of fixed motor programs that are structured before a movement sequence begins and executed with no influence of peripheral feed-back. When a pre-planned step was initiated in response to the perturbation, the duration of the anticipation phase progressively decreased as the perturbation velocity increased. The decreased duration of the anticipation phase with increased velocity is opposite to the findings reported by Breniere and colleagues (Breniere et al. 1987). They demonstrated that when subjects pre-planned the execution of a fast versus slow step, the duration of the anticipation phase was longer for the fast step compared to the slow step. This increased duration for the fast step was considered necessary in order to allow time to generate greater force to move the body faster. In our study, subjects did not pre-plan to step faster, rather they were "passively pushed" faster. Because the body was perturbed forward at a relatively high velocity, increased force was not required to move the body faster. On the contrary, because the duration of the anticipation phase did not influence the step length, the shortened duration of the postural adjustments may have resulted from an external requirement for rapid foot-off to prevent a loss of balance. It is possible that at even higher velocities, the anticipatory postural adjustments might be eliminated, resulting in an automatic, compensatory step which serves only to restore balance (McIlroy and Maki 1993b; McIlroy et al. 1994).

Although it has been previously demonstrated that afferent information is essential for modulation of on-going locomotion (Duysens and Pearson 1976; Grillner 1979), our findings demonstrate that afferent information also influences the earliest postural components during the initiation of locomotion. Even prior to establishing the reciprocal pattern of locomotion, sensory information is used to adjust the motor output to the external requirements. Certainly, further research is needed to determine the specific mechanism by which the nervous system uses on-line afferent information to modify the organization of the anticipatory postural adjustments associated with the execution of a pre-planned movement.

Concluding remarks

This study has investigated the mechanisms involved in the organization of postural control when a pre-planned voluntary movement is initiated in response to an external perturbation. It is concluded that the CNS utilizes feed-forward, predictive processes to modify peripherally-triggered reflexive responses, and utilizes immediate afferent information to modify the postural adjustments associated with a pre-planned voluntary movement. The rapid postural adaptation for execution of the voluntary movement, with respect to changes in the external conditions of the body, supports a role for multiple distributed and interactive systems for postural control.

Acknowledgements

We gratefully acknowledge Dr. Ron Jacobs, and Dr. Charlotte Shupert for their time in reviewing this manuscript. This work was supported by a doctoral research award from the Foundation for Physical Therapy, and Grant AG-06457 from the National Institute on Aging.

Chapter 4.

Based on *Brain* (submitted): 1995

Step Initiation in Parkinson's Disease: Influence of Levodopa and External Sensory Triggers

A. Burleigh, F. Horak, J. Nutt and J. Obeso

ABSTRACT

The process of gait initiation requires coordination of anticipatory postural adjustments to move the body mass forward and over the stance limb in preparation for the initial step. The purpose of this study was to identify deficits in the anticipatory postural adjustments which may contribute to the gait initiation problems characteristic of Parkinson's disease (PD), and to determine if these deficits could be improved either by administration of levodopa or by the presentation of external stimuli. Ground reaction forces and body kinematics were recorded and quantified for both self-generated and externally-triggered step initiation. To determine the effects of levodopa, PD subjects were tested both OFF and ON. To determine the effects of external stimuli two types of stimuli were tested: 1) a cutaneous cue, 2) a backward surface translation paired with a cutaneous cue. The surface translation was chosen to promote step initiation by promoting forward displacement of the body.

We have shown that dopamine deficiency in PD subjects when OFF is associated with decreased force production, decreased velocity of movement, and delayed execution of the anticipatory postural adjustments for self-generated step. These impairments were significantly improved when the PD subjects were ON. When a cutaneous cue was introduced as a go signal, all subjects demonstrated an increase in force and velocity of movement, with no differences between PD and control subjects. When the cue was combined with the postural perturbation, all subjects responded to the combined stimuli by rapidly initiating the postural adjustments for step. However, unlike the controls, the PD subjects both ON and OFF failed to increase force to more rapidly execute foot-off when perturbed. Thus, both dopaminergic replacement therapy and the presentation of an external stimulus improve force production for the anticipatory postural adjustments associated with step initiation. However, the inability to increase force to compensate for the forward sway induced by an external peturbation is not influenced by the administration of levodopa.

INTRODUCTION

Difficulties with gait initiation are characteristic of Parkinson's disease (PD). When attempting to voluntarily initiate the first step to begin walking patients often exhibit start hesitation and freezing. The foot appears to be "stuck" to the floor. When they do begin walking, the movements are slow and the steps are small. Clinical observations suggest that these abnormalities of gait initiation can be responsive to levodopa replacement, although start hesitation can also be a potential side effect of long-term levodopa therapy (Ambani and VanWoert 1973). Gait initiation in PD patients is also commonly sensitive to external stimuli. An auditory stimulus, such as counting out loud, or a visual stimulus, such as lines on the floor, often assists the patient with gait initiation.

The process of gait initiation requires coordination of anticipatory postural adjustments to move the body mass forward and over the stance limb in preparation for single-limb support during the first step. These postural adjustments involve the production of both vertical and horizontal forces to move the foot center of pressure (COP) backward and toward the swing limb (Mann et al. 1979; Breniere et al. 1981, 1987; Nissan and Whittle 1990; Breniere and Do 1991; Crenna and Frigo 1991). As a result, the body center of mass (COM) moves forward and lateral over the stance limb in preparation for foot-off. Abnormalities of gait initiation have been previously identified in PD. The transfer of the body mass laterally over the stance limb is impaired (Ingvarsson et al. 1986); propulsive forces are decreased, and the anticipatory postural adjustments are prolonged (Crenna et al. 1990). It is not known how administration of levodopa in PD influences these anticipatory postural adjustments associated with gait initiation. Nor is it known how an external stimuli contributes to the clinically apparent improvement in gait initiation in PD.

The purpose of this study was to identify deficits in the anticipatory postural adjustments that contribute to the abnormal gait initiation in PD subjects with prominent freezing, and to determine if these deficits could be improved either by administration of levodopa or by the presentation of external stimuli. To determine how dopamine deficiency influences gait

initiation, PD subjects were tested both OFF (i.e. usual dosage of levodopa withheld so that parkinsonian features and gait difficulties were prominent) and ON (i.e. usual dosage of levodopa administered so that parkinsonian features and gait difficulties were diminished). To determine the effects of external stimuli two types of stimuli were tested. The first was a current pulse delivered to the either the hand or the earlobe, producing a cutaneous cue. The second form of stimuli was a small backward surface translation paired with the same cutaneous cue. We have previously shown that anticipatory postural adjustments are more rapid and forceful when healthy young subjects initiate step in response to a backward surface translation (Burleigh et al. 1994; Burleigh and Horak 1995). Because the backward surface translation causes forward displacement of the body which promotes rapid step initiation, we predicted that the translation would further promote gait initiation in the subjects with PD.

METHODS

The experimental protocol in accordance with the 1964 Helsinki Declaration was approved by the Internal Review Boards of Legacy Good Samaritan Hospital and Medical Center, and of the Oregon Health Sciences University. Six subjects (age 66.7 ± 6.2 yrs; height 173.8 ± 7.4 cm) with idiopathic Parkinson's disease (Hoehn and Yahr stages III to IV when OFF) and six neurologically normal age- and height-matched controls (age 66.3 ± 6.4 yrs; height 179.8 ± 8.7 cm) participated after having given informed consent. The duration of disease from the time of diagnosis ranged from 8 to 34 years. All PD subjects could stand and walk independently when ON, but exhibited prominent gait initiation problems (freezing, start hesitation) when OFF. Three PD subjects reported to the laboratory in the morning, having withheld levodopa/carbidopa (Sinemet) overnight, and were initially tested when OFF. They then took their normal dose of medication and were retested approximately one hour later when ON. The other three PD subjects reported to the laboratory for the initial testing ON, and then approximately three to four hours later were retested when OFF. All subjects stood on a

platform with two force plates that could be translated under the control of a hydraulic servo motor. The test conditions were as follows:

CONDITION 1: Self-generated-step Subjects were instructed to take a forward step with the left foot and follow through with the right. They were to self-initiate and execute the step anytime following notification that the recording device was ready.

CONDITION 2: Step-to-cue Subjects were instructed to take a forward step with the left foot *as soon as* they perceived a brief, 4 ms current pulse delivered to either the hand or the earlobe, and to continue the step through with the right foot. Subjects had no advance notice prior to onset of the cutaneous cue. No differences in latency of response were noted between the two subjects who had the cue to the hand and the other subjects who had the cue to the earlobe; thus data was pooled for analysis.

CONDITION 3: Step-to-perturbation Subjects were instructed to take a forward step with the left foot *as soon as* they perceived the cutaneous cue, and continue the step through with the right foot. In this condition, the onset of the cutaneous cue was directly paired with the onset of a backward surface translation. Subjects had no advance notice prior to onset of the cue. Both plates were translated horizontally 3.6 cm at 5 cm/sec in the backward direction, resulting in forward body sway. This relatively small amplitude, low velocity translation was chosen to cause a small forward sway that might promote step initiation in the PD subjects. The translation did not cause a loss of balance or force a compensatory step. Subjects stepped from the moving surface to a fixed surface. All subjects were familiarized with the perturbation by having five trials of the surface translation during which they remained standing on the platform.

For all conditions, subjects stood comfortably with arms folded across the waist, with one foot in the center of each plate and with weight equally distributed between both feet. To ensure that weight distribution and the initial stance position was the same across all trials, the distribution of weight bearing between right and left limbs was viewed on-line. For each trial, subjects stood in tracings of their feet made on the platform during quiet stance.

Forces were measured with 4 strain gauges mounted in the corners of each force plate, sampled at 500 Hz and stored for later analysis. The relative position of the COP between the two feet, in the medio-lateral and anterio-posterior planes was calculated using the forces recorded in both plates. The magnitude and direction of the COP vector was calculated from the forces in the two plates using the peak change in the lateral and posterior components of the COP prior to heel-off. Two components of the ground reaction forces of the initial swing limb were analyzed: the initial increase in the vertical force (F_Z), and the horizontal (anterior/posterior) force (F_X). Both contribute to the COP excursion lateral toward the swing limb and backward prior to heel-off. Together, these ground reaction forces have the effect of propelling the body COM lateral over the stance limb and forward. In order to compare forces between subjects, F_Z and F_X were normalized as percent of body weight. A pressure sensitive resistor, taped to the platform under the heel of the initial swing limb, was used to determine the precise time of heel-off during step initiation. Foot-off was determined as the precise moment there were no vertical forces exerted through the initial swing limb plate. Three phases of the anticipatory postural adjustments for step initiation were studied: 1) reaction time phase (cue to initial increase of swing limb F_Z); 2) anticipation phase (initial increase of swing limb F_Z to heel-off); 3) push-off phase (heel-off to foot-off of the initial swing limb).

Body kinematics were collected using Northern Digital's Watsmart motion analysis system. Two optoelectric cameras detected the position of infrared light emitting markers (IREDs) attached to the platform, and the subjects on the side of the initial swing limb at the fifth metatarsal head, heel, lateral malleolus, knee, greater trochanter, shoulder and ear. During each trial, two dimensional spatial positions for the IREDs were sampled at 100 Hz. The forward displacement and velocity of the body COM was calculated using the IRED coordinates. Step length was determined from the displacement of the heel IRED.

Planned-comparisons were conducted between control and PD subjects using unpaired t-tests and between PD subjects ON and OFF using paired t-tests. The Bonferoni correction for multiple t-tests required an adjusted level of $p \leq 0.025$ for statistical significance. Planned

comparisons were also made between the step-to-cue and step-to-translation conditions within each group using paired t-tests.

RESULTS

General Observations

All PD subjects tested exhibited difficulty walking when OFF and exhibited episodes of freezing when walking into the laboratory. However, when required to execute a single step from the platform, the PD subjects were consistently able to step. Only two of the PD subjects were unable to self-generate the step during two trials each when OFF. In these trials, no clear initiation phase could be discerned from the COP trajectory or from the ground reaction forces.

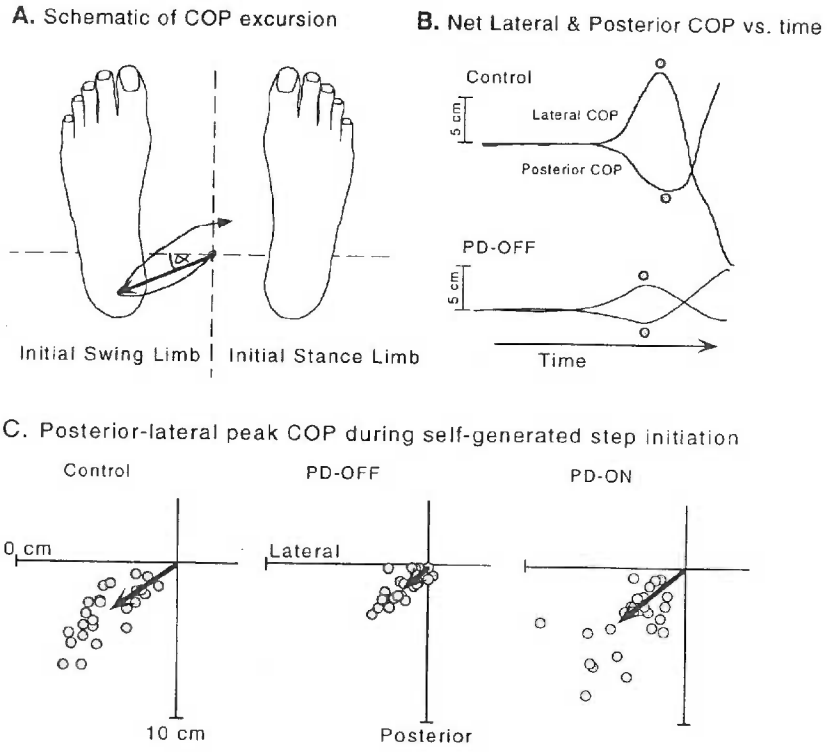

Figure 4.1. Group data of center of foot pressure (COP) during self-generated step is shown, demonstrating that in general the PD subjects exhibit the appropriate direction of posterior-lateral COP excursion, but the magnitude of the excursion is reduced when the subjects are OFF. A) Schematic demonstrates that the net COP initially moves backward and lateral towards the swing limb. B) The posterior and lateral components of the COP are plotted independently versus time, allowing for the peak posterior and peak lateral excursion to be quantified. C) Using the data determined from peak posterior and peak lateral excursions, the magnitude and direction of the combined vector is plotted. Four trials for each subjects are represented.

During successful step initiation, all subjects exhibited an appropriate posterio-lateral COP trajectory for the anticipatory postural adjustment phase in all three test-conditions. In order to propel the body COM forward and over the initial stance limb, the COP moved backward and toward the swing limb (Figure 4.1). During self-generated step, the PD subjects OFF exhibited a reduced magnitude of the vector and more variability in the initial direction of the COP excursion when compared to the same subjects ON and to the controls.

Self-generated step initiation

Several aspects of the anticipatory postural adjustments preceding the first step were abnormal in the PD subjects OFF when compared to the control subjects. In contrast, the controls and the PD subjects ON did not differ for any of the variables measured, suggesting that administration of levodopa improved motor performance for gait initiation. Figure 4.2 shows the slow and diminished vertical force production in a PD subject OFF compared to ON

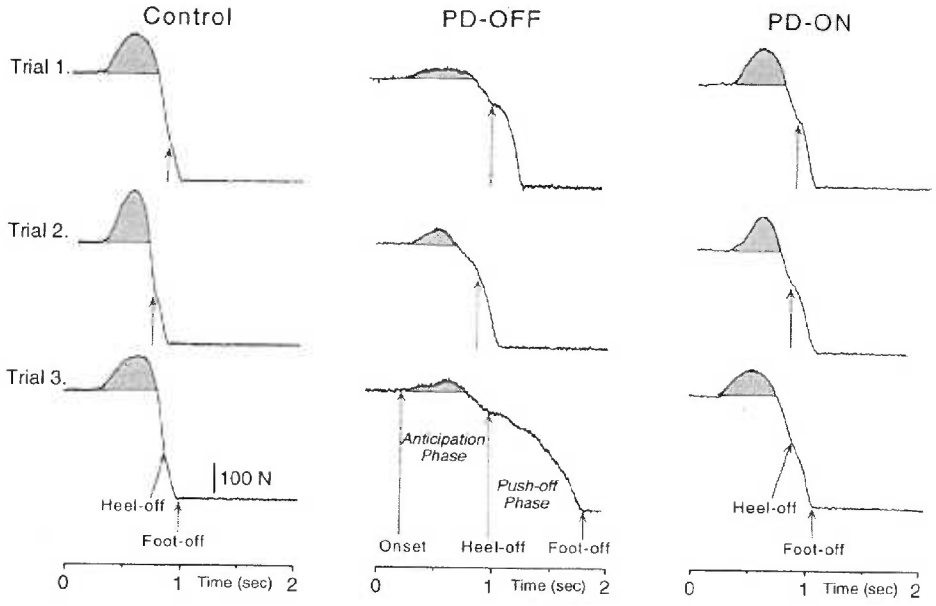

Figure 4.2. Examples of the swing limb vertical forces (Fz) for a representative PD subject OFF and ON and a height- and weight-matched control subject during three trials of self-generated step. When OFF, the PD subject fails to generate the same degree of force compared to ON or compared to the control subject. Furthermore, the PD subject OFF demonstrates a high degree of variability in the duration of the anticipation and push-off phases. In upper panels, arrows indicate the time of heel-off.

and to a control subject. Corresponding to the diminished generation of force in the PD subject OFF, both the anticipation phase and push-off phase of the anticipatory postural adjustments were prolonged.

These deficiencies in the anticipatory postural adjustments were characteristic of the entire PD subject group when OFF (Figure 4.3A). The peak increase in the swing limb F_Z was significantly diminished ($p \leq 0.0005$) in the PD subjects OFF compared to the controls. The forward velocity of the COM at heel-off was also significantly reduced ($p = 0.011$) in the PD subjects OFF compared to the controls (Figure 4.3B). The decreased velocity for the PD subjects OFF was not related to a smaller forward displacement of the COM, since the forward displacement of the COM at heel-off was not significantly different between groups (control = 2.6 + 0.2 cm; OFF = 2.2 + 0.2 cm). In addition, the duration of the anticipation phase of

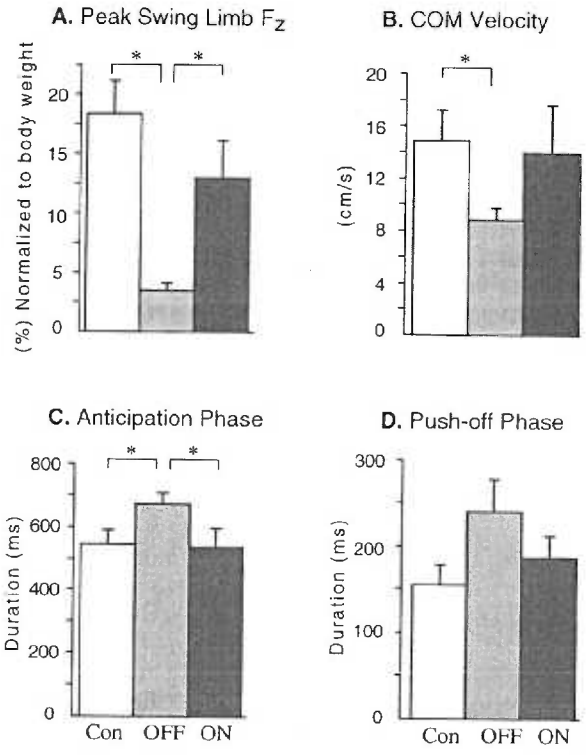

Figure 4.3. Means and standard errors of group data for self-generated step are shown. The PD subjects OFF (light shaded bars) exhibit A) decreased swing limb vertical forces (Fz), B) decreased velocity of the COM at heel-off, C) prolonged duration of the anticipation phase, and D) prolonged duration of the push-off phase when compared to the same subjects ON (dark shaded bars) and to the controls (open bars). (* indicates $p \leq 0.01$)

postural adjustments (initial increase in the swing limb F_Z to the time of heel-off) was prolonged for the PD subjects OFF compared the controls, ($p = 0.025$) (Figure 4.3C).

Administration of levodopa improved motor performance in the PD subjects. There were no differences between the PD subjects ON and the controls, but there were significant differences between the PD subjects ON and OFF. The peak increase in the swing limb F_Z was significantly diminished in the PD subjects OFF compared to ON ($p = 0.006$; Figure 4.3A). In the PD subjects OFF, the peak increase of the swing limb F_X was also diminished (not shown). Four PD subjects showed an increase in F_X when ON compared to OFF, however due to variability the increase was not significant for the group. The duration of the anticipation phase of postural adjustments (Figure 4.3C) was significantly prolonged for the PD subjects OFF compared to ON ($p = 0.0046$). Likewise, the duration of the push-off phase (heel-off to foot-off) was also prolonged in the PD subjects OFF compared to ON ($p = 0.03$; (Figure 4.3D).

Characteristics of externally-triggered step initiation

STEP-TO-CUE: The presentation of the cutaneous cue improved the motor performance for gait initiation in the PD subjects OFF, similar to the effect of levodopa administration. When step was initiated in response to the cue, the force production was similar between PD subjects both OFF and ON and the controls, and administration of levodopa did not further influence the motor performance.

Figure 4.4 illustrates that the PD subject OFF increased the swing limb vertical forces during the step-to-cue compared to the self-generated step condition. In contrast, the control subject showed minimal differences between the two conditions. With presentation of the external cue, the magnitude of vertical force (F_Z) production and the duration of both the anticipation and push-off phases were similar for the PD subject OFF and the control (Figure 4.4).

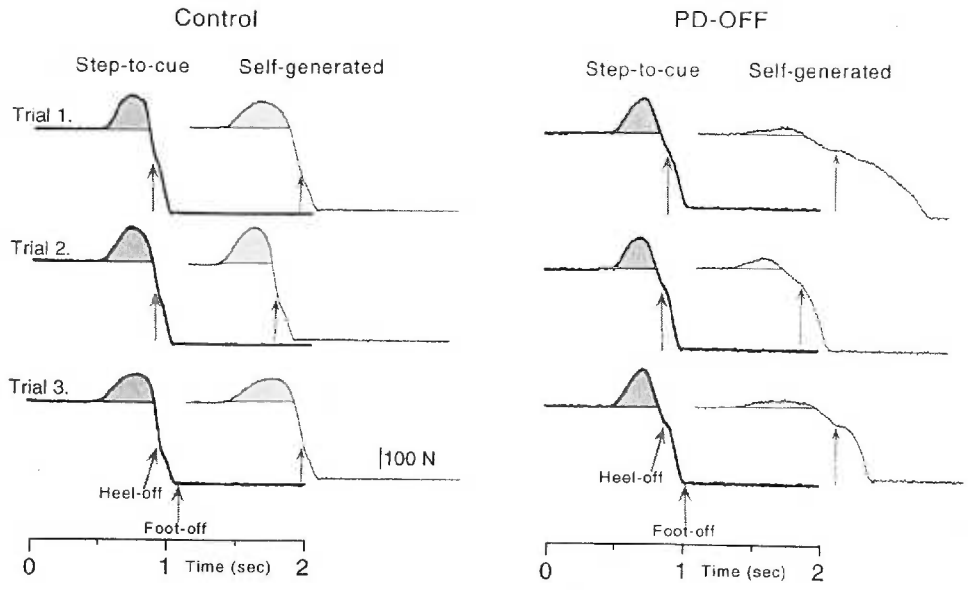

Figure 4.4. Examples of the swing limb vertical force (Fz) for a PD subject OFF and a height-and weight-matched control subject during three trials of externally triggered, step-to-cue (bold lines) contrasted to three trials for the same subjects during the self-generated step (light lines). In the step-to-cue condition, the PD subject generates approximately the same degree of force as compared to the control. Furthermore, the PD subject demonstrates minimal variability in the duration of the anticipation (onset to heel-off) and push-off (heel-off to foot-off) phases of step initiation. In the upper panels, the arrows indicate the time of heel-off.

Figure 4.5 shows that F_Z and the velocity of the COM were increased, while the duration of the postural adjustments were decreased for the step-to-cue condition compared to the self-generated-step condition. These changes were especially clear for the PD subjects OFF. In contrast to the differences noted for the self-generated step initiation, the performance of the PD subjects OFF was no longer different from either the controls or the same subjects ON when step was initiated in response to the external cue.

STEP-TO-PERTURBATION: When the onset of a backward surface translation was directly paired with the cutaneous cue, the combined external stimuli promoted rapid onset of the postural adjustments for step initiation. Although the control subjects responded to the perturbation with increased force compared to the step-to-cue condition, the PD subjects did not produce a similar increase in force. Administration of levodopa did not influence the motor

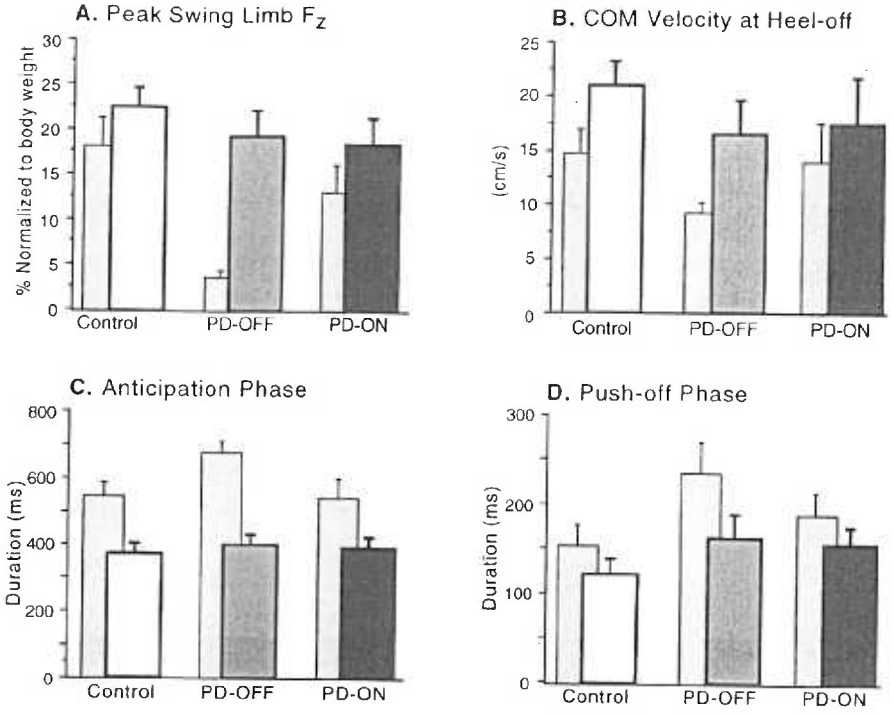

Figure 4.5. The means and standard errors of group data for the externally triggered step-to-cue condition are shown contrasted to the self-generated step (lightly-shaded background bars). data as shown in Figure 4.3. During step-to-cue Controls (open bars); PD subjects OFF (light shaded bars) and ON (dark shaded bars). There are no significant differences between groups for A) the swing limb vertical forces (Fz); B) the velocity of COM at heel-off; C) the duration of the anticipation phase; and D) push-off phase of step initiation.

performance since there were no differences between the PD subjects ON or OFF for any variable measured.

All subjects had significantly shorter reaction times ($p \leq 0.01$) for the initial increase in F_z in the step-to-perturbation condition compared to the step-to-cue condition (Figure 4.6A). There were no differences among groups for reaction time in either the step-to-cue (control = 260 ± 25 ms; OFF = 287 ± 54; ON = 268 ± 67) or step-to-perturbation conditions (control = 189 ± 20 ms; OFF = 208 ± 49; ON = 195 ± 18). The duration of the anticipation phase (onset to heel-off) was also shortened for all subjects in the step-to-perturbation com-pared to step-to-cue condition (Figure 4.6B). In contrast to the shortened anticipation phase, the push-off phase was prolonged for the PD subjects OFF ($p = 0.0027$) and ON ($p = 0.025$) compared to the controls when step was initiated in response to the perturbation (Figure 4.6C).

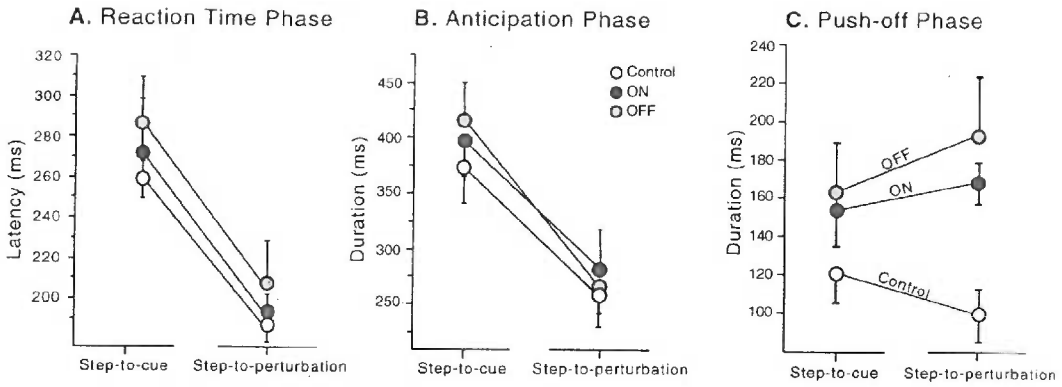

Figure 4.6. The means and standard errors of group data are shown, demonstrating the A) shortened reaction time phase and B) shortened anticipation phase of the postural adjustments for all subjects in the step-to-perturbation compared to the step-to-cue condition. In contrast to the shortened anticipation phase, in C) the PD subject show an increased duration of the push-off phase during the step-to-perturbation, resulting in significant differences from the control.

Visual observation of the PD subjects demonstrated that although they quickly initiated heel-off in response to the perturbation, the foot appeared to be "stuck" in hesitation before the toe was lifted from the platform.

Control subjects increased the magnitude of ground reaction forces during the anticipation phase and were therefore able to rapidly execute foot-off when the perturbation imposed a passive forward sway of the body. In contrast, the PD subjects failed to significantly increase the magnitude of the vertical and horizontal swing limb forces to rapidly execute foot-off when perturbed. Figure 4.7 shows the differences between the control and PD subjects in the step-to-perturbation condition, in contrast to the step-to-cue condition in which there were no significant differences between groups. When step was initiated in response to the perturbation, the peak Fz and Fx was increased in the control subjects ($p \leq 0.03$) but remained unchanged in the PD subjects when compared to the step-to-cue condition. Accordingly, the peak swing limb F_Z was significantly less in the PD subjects OFF ($p = 0.0026$) and ON ($p = 0.025$) compared to the controls in the step-to-perturbation condition (Figure 4.7A). The peak swing limb F_X also tended to be less in the PD subjects compared to the controls, however the difference was not significant (Figure 4.7B).

Corresponding to the force production during the perturbed step initiation the velocity of the COM at heel-off was increased in the control subjects ($p \leq 0.02$), but not in the PD subjects. The COM velocity was significantly less in the PD subjects both OFF ($p = 0.0028$) and ON ($p = 0.017$) compared to the controls for the step-to-perturbation condition (Figure 4.7C). Likewise, when step was initiated in response to the perturbation, the control subjects increased their step length whereas the PD subjects did not (Figure 4.7D). Only the control group showed a significant difference between conditions ($p = 0.016$) when step length was normalized to the step-to-cue condition.

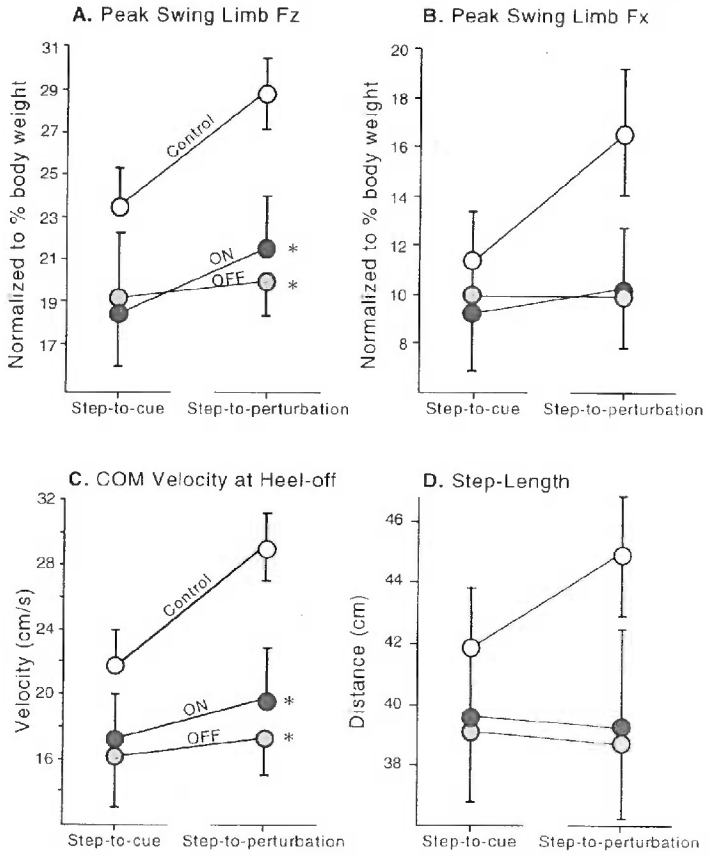

Figure 4.7. The means and standard errors of group data for step-to-cue versus step-to-pertubation conditions are shown. In contrast to the control subjects, the PD subjects fail to increase A) vertical force (F_Z), B) horizontal force (F_X), C) velocity of COM at heel-off, and D) step length during the step-to-perturbation condition.

DISCUSSION

We have shown that dopamine deficiency in subjects with Parkinson's disease (PD), is associated with decreased force production and delayed execution of the anticipatory postural adjustments for self-generated step. These impairments were most pronounced when the PD subjects were OFF and improved with the administration of levodopa, suggesting that they are, in part, related to dopamine deficiency. When an external cutaneous cue was introduced as a go signal, control subjects as well as PD subjects ON and OFF demonstrated an increase in force and velocity of movement. When the cue was combined with a perturbation that caused forward sway of the body, all subjects responded to the combined stimuli with a shortened reaction time for initiation of the postural adjustments for step, and shortened duration of the anticipation phase of the postural adjustments. However, unlike the controls, the PD subjects failed to increase force to more rapidly execute foot-off when perturbed. Administration of levodopa did not improve force production during perturbed step initiation.

Influence of levodopa administration for self-generated step initiation

Our results show that subjects with Parkinson's disease can execute a motor command for self-generated gait initiation, but the execution is impaired due to deficient force production. These findings are similar to those previously reported (Ingvarsson et al. 1986; Crenna et al. 1990), but in addition we show that these impairments are improved with the administration of levodopa. Ineffective force production results in a slower displacement of the body COM. If stable alignment of the body COM over the stance limb is not achieved, then unloading of the swing limb may be delayed (Rogers and Pai 1993; Elble et al. 1994; Burleigh and Horak 1995). Our current findings demonstrate that unloading of the swing limb is delayed in the PD subjects OFF. This delayed unloading is probably related to decreased propulsive forces and an inability to align the body COM over the stance limb during the postural adjustment phase of self-generated step initiation. The increased postural tone and flexed stance common to the PD subjects, could contribute to the deficits of force production. However, this cannot be the

primary explanation since performance is markedly improved with the external-stimulus, despite the persistence of a flexed posture.

Many studies suggest that one essential component of bradykinesia exhibited by PD subjects during voluntary arm movements is an inability to effectively generate muscle activity (Hallett and Khoshbin 1980; Berardelli et al. 1986; Marsden 1989; Godaux et al. 1992). These findings for arm movement are consistent with the diminished force production for the anticipatory postural adjustments associated with voluntary step initiation. Administration of levodopa is associated with increased velocity of upper extremity movement (Berardelli et al. 1986; Weinrich et al. 1988; Johnson et al. 1995). Similarly, we show that velocity of body movement during self-generated step initiation is improved with the administration of levodopa. In contrast to increased movement velocity of the extremities, it has been suggested that a decline of axial movement velocity following levodopa administration may actually impair gait in persons with advanced PD (Weinrich et al. 1988). However, our study shows that step initiation is actually improved by the administration of levodopa.

The deficient force production during self-generated step initiation in the PD subjects OFF does not explain the phenomenon of "freezing". Although our subjects with PD were selected because of problems with freezing when attempting locomotion, in our paradigm, freezing was seldom observed. In the two subjects who were unable to initiate step during a few trials, there was no organized pattern of anticipatory postural adjustments. Thus, freezing is not related to weak, ineffective postural adjustments (Winter 1995), rather it appears that no clear motor pattern for step initiation is evoked at all.

Influence of an external sensory trigger for step initiation

Similar to the improvements seen with the adminstration of levodopa for self-generated step initiation, presentation of an external cue also resulted in increased force production and movement velocity. When a cutaneous cue was used to trigger step initiation, the forces associated with the anticipatory postural adjustments were no longer different between the PD and control subjects. Consistent with the effective production of force, the timing of the

postural adjustment phases and the forward velocity of the body COM were similar between the PD and control subjects. Administration of levodopa had no further effect on the motor performance, which is not surprising since the PD subjects had essentially normal performance in this externally-triggered behavior.

Several possible mechanisms may explain the improved performance during the externally-triggered behavior. The subject's attention level may have been heightened in anticipation of the stimulus, resulting in a more rapid and forceful movement. Alternatively, the external cue may have substituted for a dopaminergic influence on the facilitation of the centrally-initiated voluntary movement (Marsden and Obeso 1994). The most attractive explanation is the hypothesis that different neural mechanisms mediate self-generated (internally-triggered) and reaction-time (externally-triggered) movements (Passingham 1987; Kurata and Wise 1988; Papa et al. 1991; Horak and Frank 1995). Electrophysiological correlates suggest that the supplementary motor area (SMA) is involved in the initiation of self-generated movements whereas other cortical regions, including the premotor cortex, are involved in the generation of movement in response to a visual (Passingham 1987; Kurata and Wise 1988; Glickstein and Stein 1991) or auditory stimulus (Deiber et al. 1991). Deficiencies of self-generated movement in PD support this hypothesis since one major output of the basal ganglia is to the SMA (Parent 1990). In addition to the previously described effect of visual and auditory stimuli on motor performance, our findings show that a somatosensory stimulus can provide an external-trigger, demonstrating that the phenomenon is not specific to the visual and auditory pathways.

Our findings indicate that the motor control mechanisms for step initiation are intact in PD, and that normal anticipatory postural adjustments can be elicited using an external sensory trigger. These findings are similar to the improvement of gait hypokinesias with the presentation of visual cues (Morris et al. 1994). When subjects are provided with external (visual) cues, both the temporal and spatial parameters during walking improved to near normal values. Similar mechanisms may contribute to the problems underlying both the initiation and continuation of gait in PD.

Failure to increase force production with change in external conditions

When a platform perturbation was paired with the cutaneous cue, reaction times were faster for all subjects, suggesting that combined cutaneous and fast proprioceptive stimuli can enhance reaction times for step initiation. In addition, the forward sway induced by the perturbation promoted a more rapid execution of heel-off. However, unlike the control subjects, the perturbation did not further enhance step initiation in the PD subjects by promoting increased force production for rapid foot-off.

It is not clear why the PD subjects fail to increase force, velocity of movement, and step length during perturbed step initiation. It is possible that their maximal force production had already been achieved. It is also possible that the external trigger serves only to initiate a motor command, and a separate mechanism is involved if the requirements for force production change after the command is initiated. Administration of levodopa has no influence on automatic, externally-triggered postural responses (Traub et al. 1980; Horak et al. 1992), nor on perturbed step-initiation, suggesting that non-dopaminergic mechanisms are involved in the modification of postural behaviors triggered by an external stimulus.

Although Parkinson's disease provides a model to study disruption of the basal ganglia dopaminergic system, the disease process involves multiple other systems which may also contribute to motor problems (Greenfield and Ragsdale 1953; Hornykiewicz and Kish 1986; Carlsson and Carlsson 1990). With progression of the disease, the emerging symptoms are often less responsive to levodopa therapy, suggesting that increased disability results from disruption of non-dopaminergic systems (Bonnet et al. 1987). The responsiveness to levodopa also appears to depend on the extent to which voluntary effort is involved (Knuttson and Martensson 1971), suggesting a mechanism by which the administration of levodopa has a more prominent effect on the cortical (i.e. self-generated) control of movement, and less effect on movements associated with automatic or externally-triggered responses.

In conclusion, both dopaminergic replacement therapy and the presentation of an external stimulus improve force production for the anticipatory postural adjustments associated with step initiation in subjects with Parkinson's disease. The findings suggest that force production during the postural adjustment phase of self-generated, but not externally-triggered, step initiation is influenced by dopaminergic pathways.

Acknowledgements:

The authors extend our thanks to the subjects who so willingly participated in this study and to Dr. Ron Jacobs who contributed to the discussion of the findings and stimulated new approaches to the data analysis. This research was supported by a grant from the Foundation for Physical Therapy awarded to Anne Burleigh, and a grant from the National Institute on Aging (AGO-6457) awarded to Fay Horak.

Chapter 5.

Based on *Can. J. Neurol. Sci.* (in press): 1995

Levodopa Reduces Muscle Tone and Lower Extremity Tremor in Parkinson's Disease

A. Burleigh, F. Horak, J. Nutt and J. Frank

ABSTRACT

Objective: We have quantified the effects of levodopa treatment in subjects with Parkinson's disease during maintained stance. Methods: Electromyographic muscle activity during quiet stance was assessed in subjects with Parkinson's disease, who exhibited a fluctuating response to levodopa, and in age-matched control subjects. Stance stability was also assessed from mean displacement and velocity of the center of pressure excursions during stance. Results: Lower extremity and trunk muscles showed high amplitude activity in all Parkinson's subjects when OFF, and a 4-5 Hz tremor in three of these subjects. When ON, the amplitude of muscle activity was reduced in the distal muscles more than the proximal, while tremor was suppressed in all muscles. Corresponding to the excessive muscle activity, the Parkinson's subjects had increased velocity and variability of velocity in the anterior-posterior center of foot pressure excursions, but the mean displacement of the center of pressure excursion was not different from the controls. The velocity of center of pressure excursions in the Parkinson's subjects ON, approached those of the control subjects suggesting that the excessive distal muscle amplitude and tremor contributed to the high velocity of the center of pressure. Conclusions: These findings suggest that dopaminergic systems are involved in the regulation of muscle tone during stance. Depletion of dopaminergic transmission results in increased muscle tone and tremor in the lower extremities which may contribute to changes in posture and stability.

INTRODUCTION

Parkinson's disease (PD) is characterized clinically by resting tremor, muscle rigidity, bradykinesia and disturbed postural responses (Marsden 1985). These motor disturbances are related to loss of dopamine in the nigrostriatal system. Treatment with the dopamine precursor, levodopa (L-dopa) typically improves the motor performance of persons with PD. Although

there is evidence that L-dopa is more effective in treating limb dysfunction than axial symptoms (Weinrich et al. 1988; Klawans 1986), quantification of the effects of L-dopa on muscle activity and stability during stance is lacking. We have quantified the effects of L-dopa treatment on the baseline muscle activity and tremor in lower extremity and trunk muscles, and on stance stability as assessed from mean displacement and velocity of the center of pressure excursions during stance.

METHODS

Eleven subjects (6 male, 5 female; age 61.6 y ± 4.5) with idiopathic Parkinson's disease (Hoehn and Yahr stages III to IV when OFF) and eleven neurologically normal, age-matched controls participated in the study. The mean duration of disease in the subjects with Parkinson's disease was 13 years, ranging from 6 to 35 years. Three PD subjects had clinically apparent tremor in both hands. Subjects with PD reported to the laboratory in the morning, having withheld their morning L-dopa/carbidopa (Sinemet®), and were initially tested when OFF (i.e., off medication and parkinsonian features prominent). Subjects then took their normal L-dopa dose and were re-tested approximately one hour later when ON (i.e., on medication and parkinsonian features diminished). During the testing sessions, subjects stood on a dual-plate platform, with one foot centered on each plate, arms folded in front of the body and gaze directed forward to the laboratory wall. Subjects had come to the laboratory to participate in another experiment, thus the data being presented in this paper results from single trials recorded for three seconds as a baseline measure of independent stance. All subjects were able to stand independently for longer than the reported three second interval. Two subjects with PD later returned for repeat testing, to verify the repeatability of the results.

Surface electrodes were used to record electromyographic activity (EMGs) unilaterally from the tibialis anterior, medial gastrocnemius, rectus femoris, biceps femoris, and paraspinals. Skin impedance was less than 15 KOhms for all subjects, with electrodes kept in place throughout the entire period of testing. The EMGs were amplified, band-pass filtered (70-

2000 Hz), full-wave rectified and low-pass filtered using a 5 ms time constant. The mean amplitude and standard deviation of muscle activity during quiet stance over the full 3 second period was quantified using a Macintosh program (Axograph) for wave analysis. The mean amplitude and standard deviation of one second intervals over the full period was also quantified to verify that the mean EMG level was stable over the 3 seconds. Fourier analysis of the individual muscle EMGs over the three seconds was used to determine the presence and frequency of tremor.

Surface forces were recorded using strain gauges mounted in the platform, and the anterior-posterior displacement of the center of foot pressure (COP) was calculated for the full 3 second period. The velocity of COP was calculated as the first derivative of the filtered COP displacement data. The mean anterior and mean posterior excursion of the COP and the pathlength over time were quantified to determine if the amount of sway was greater in the PD subjects compared to the controls. Both anterior and posterior excursions were expressed as positive change with respect to foot center. This allowed the mean amplitude of excursion about baseline to be quantified. The COP velocity data was rectified and the mean and standard deviation of the velocity were quantified. Velocity was therefore expressed as a positive value of mean rate of change of the COP with respect to the foot center. Increases in the velocity parameters correspond to decreases in stance stability (Riley et al. 1995). Information from the excursion and velocity of excursion of the COP thus provided a measure of stability (Hlavacka and Saling 1986; Riley et al. 1995) that could be directly compared across Parkinson's and control subjects. A Fourier analysis of the COP displacement data was used to determine if tremor was solely responsible for differences in the velocity parameters between the PD and control subjects.

A paired Student's t-test was used to compare mean EMG amplitude between PD subjects OFF and ON. Paired t-tests were also used to compare mean amplitude of excursion, mean velocity, and mean pathlength of COP between PD subjects OFF and ON. An unpaired t-test was used to compare mean amplitude of excursion, mean velocity, and mean pathlength of

COP between PD subjects and control subjects. A p-value of less than 0.05 was accepted for statistical significance. A coefficient of variation for the COP velocity was calculated for each subject group to control for differences as the mean velocity increased.

RESULTS

When OFF, the EMG activity of the PD subjects was excessive in all muscles recorded during quiet stance. High phasic activity and spiking of the EMG activity was a common feature in all PD subjects, but was not seen in control subjects, as illustrated by the representative PD and control subjects in Figure 5.1. A Fourier transform revealed multiple frequency components in EMGs of three PD subjects (Figure 5.1B).

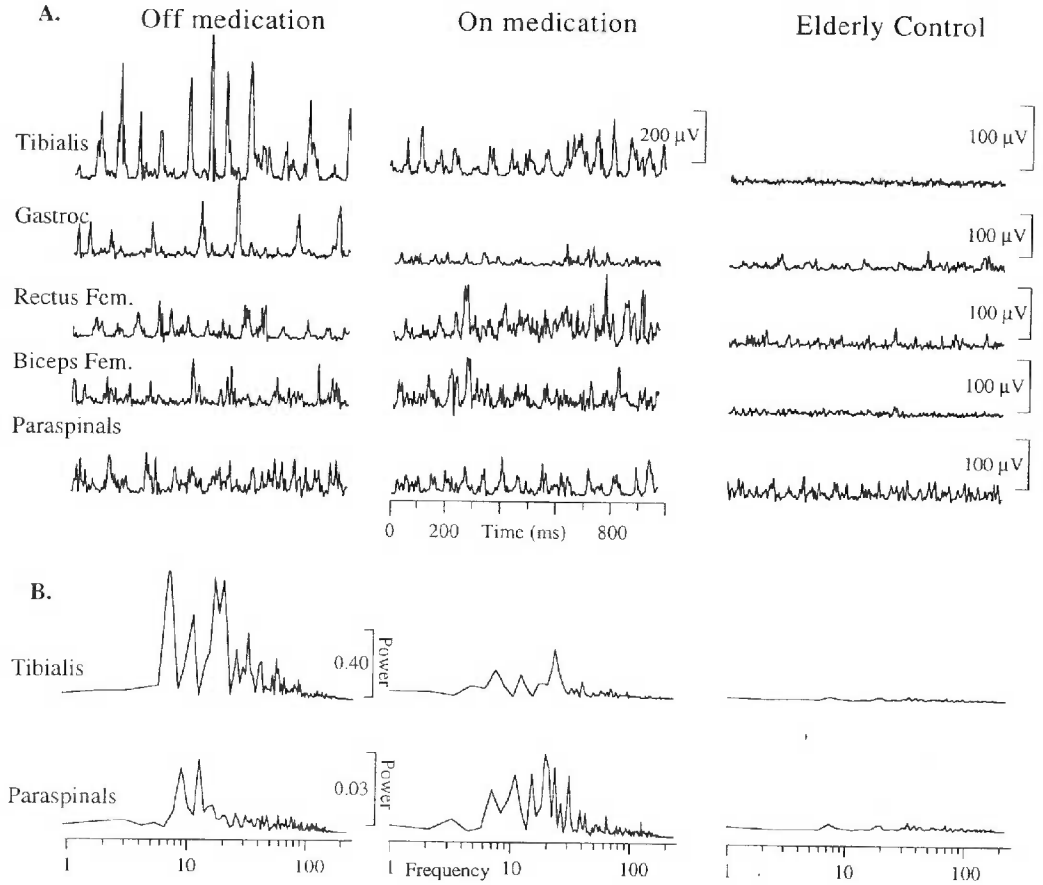

Figure 5.1. (A) EMG activity recorded from a Parkinson's subject off and on L-dopa medication and an elderly control subject during quiet stance. The PD subject exhibits high tonic activity in all muscles. Only the tibialis and gastrocnemius activity is clearly reduced with L-dopa medication. The 200 μV calibration applies to the tibialis EMG for the PD subject; all other calibration bars apply to the PD and control subject EMGs. (B) Corresponding Fourier analysis of the tibialis and paraspinal EMGs demonstrating multiple high-frequency components in the PD subject, that are not affected by L-dopa.

Administration of L-dopa resulted in significant reduction of excess amplitude in the distal lower extremity muscles but not the proximal lower extremity muscles or paraspinals. L-dopa did not significantly change the frequency components of the EMG. When ON, the mean amplitude of the tibialis and gastrocnemius was significantly reduced ($p \leq 0.01$) in the PD subjects with the administration of L-dopa (Figure 5.2), however, the spike-like firing pattern persisted. There was no significant reduction in the mean amplitude of the more proximal rectus femoris, biceps femoris, or paraspinal muscles, but there was a trend for EMG amplitude in these muscles to decrease after the administration of L-dopa (Figure 5.1 and Figure 5.2).

The mean percent reduction in EMG activity was $46.3 \pm 16.25\%$ for tibialis ($p \leq 0.01$), and $30.3 \pm 16.25\%$ for gastrocnemius ($p \leq 0.01$), but only $1.42 \pm 4.2\%$ for the rectus femoris (ns), $25.27 \pm 17.54\%$ for biceps femoris (ns), and $12.92 \pm 4.87\%$ for paraspinals (ns). There was no correlation between disease severity or duration and the percent reduction in the EMG amplitudes quantified in the PD subjects when ON. Although a direct comparison of EMG amplitudes between control and PD subjects is not possible, the mean amplitude of EMGs for the group of PD subjects OFF far exceeded EMG amplitudes recorded in control subjects with

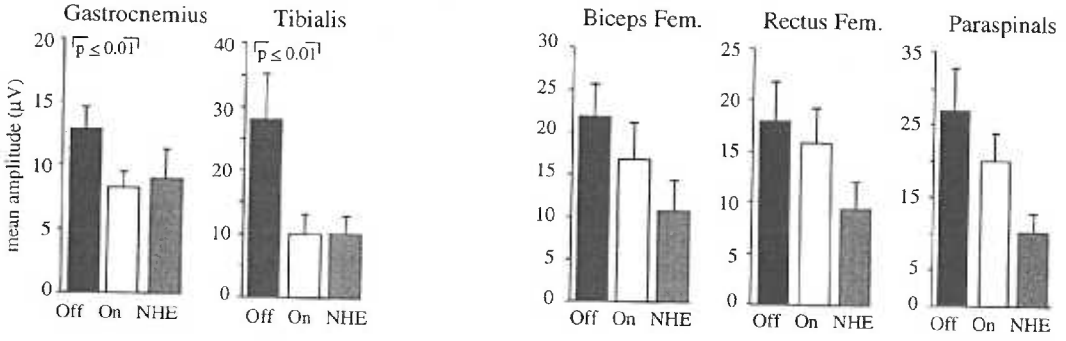

Figure 5.2. Mean amplitude and standard error of EMG activity recorded in eleven Parkinson's subjects off L-dopa medication (OFF = black bar) and on medication (ON = clear bar), and Normal Healthy Elderly controls (NHE = gray bar). When ON, a significant reduction ($p \leq 0.01$) of tibialis and gastrocnemius activity in the PD subjects was verified with a Student's t-test and EMG amplitudes approached those measured in NHE. L-dopa did not significantly reduce proximal muscle tone in PD subjects. No statistical comparison can be made between EMG amplitudes of PD subjects and the control subjects, however, the mean values demonstrate that tonic activity is consistently higher in the PD subjects OFF and approaches control values when ON.

similar electrode placement and impedance (Figure 5.2). Also, the phasic, spike-like firing pattern was unique to the PD subjects since it was never observed in the control subjects. Administration of L-dopa reduced mean EMG in the PD subjects ON, with levels approaching those measured in control subjects. The effect was reproducible as indicated by a similar reduction of distal muscle activity seen in the two PD subjects who returned to the laboratory for repeat testing. Furthermore, analysis of one second intervals in all subjects confirmed that the muscle activity remained stable over the full three seconds since there was no difference between the values obtained for the one second intervals and the full three second period.

In addition to high amplitude activity, three PD subjects also exhibited a distinct 4-5 Hz tremor in the lower extremity muscles and paraspinals when OFF. Although not apparent on clinical examination, the tremor was in all muscles recorded in two subjects, while in the third, tremor was recorded only from the tibialis and rectus femoris. Administration of L-dopa suppressed the tremor activity in all lower extremity muscles and the paraspinals, but reduced the mean amplitude of tonic EMG activity only in the tibialis and gastrocnemius (Figure 5.3)

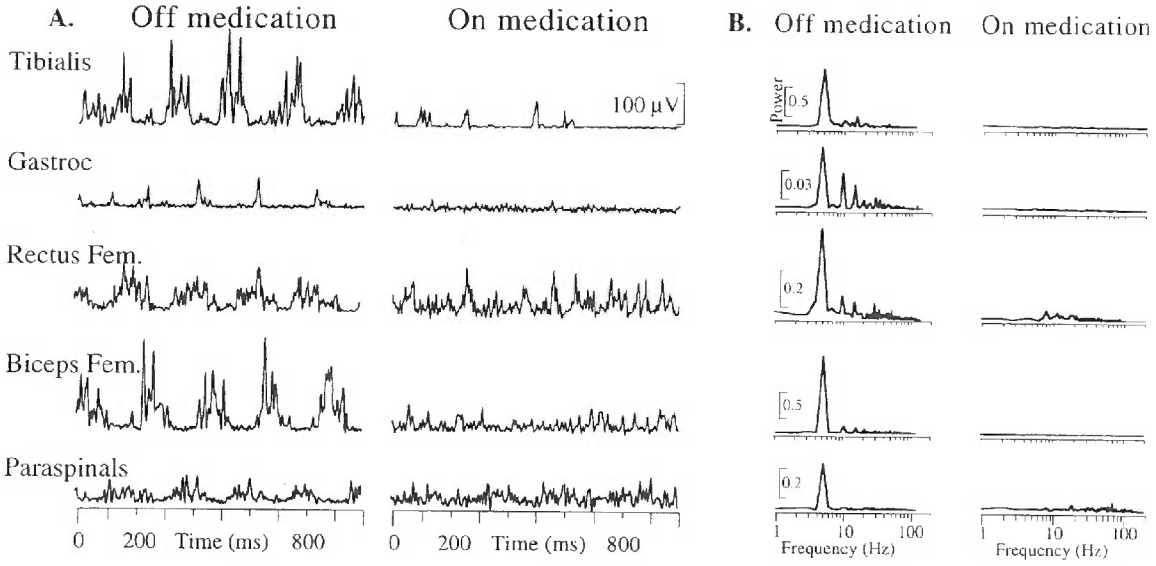

Figure 5.3. (A) EMG activity recorded from a Parkinson's subject off and on L-dopa medication during quiet stance; (B) corresponding Fourier analysis of the EMG. A 4-5 Hz tremor is present in all muscles when OFF, but suppressed when ON. The 100 µV calibration bar applies to all muscles.

Analysis of the COP suggested that the high amplitude and phasic muscle activity in the PD subjects contributed to a faster and less predictable excursion of the body during stance. The mean amplitude of the COP in the PD subjects was not significantly different from controls (Figure 5.4A) thus, the PD subjects did not exhibit a larger amplitude sway than the controls during stance. However, both the mean velocity of the COP excursion (figure 5.4B) and the standard deviation of the velocity were significantly greater in the PD subjects OFF compared to controls ($p \leq 0.02$) and the PD subjects ON compared to controls ($p \leq 0.05$; Table 5.1).

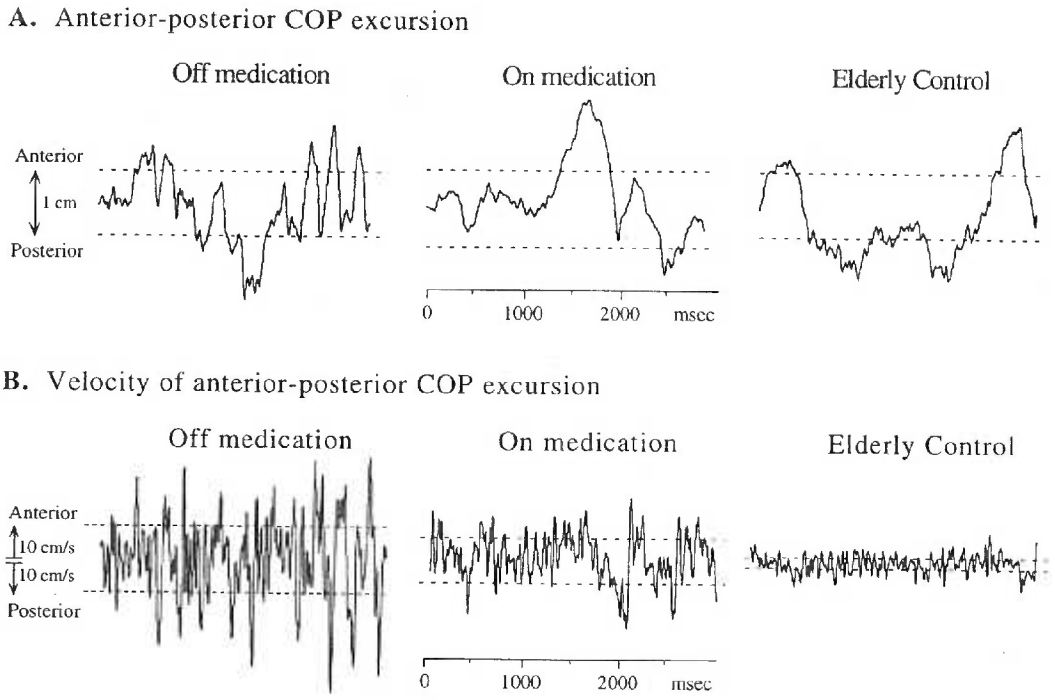

Figure 5.4. (A) Anterior-posterior COP recorded from a Parkinson's subject off and on L-dopa medication and an elderly control subject during quiet stance. The dashed lines indicate the mean amplitude of excursion from anterior to posterior which is not significantly different between the PD and control subjects. (B) Corresponding velocity of the COP. The dashed lines indicate the mean velocity of the anterior excursion and the posterior excursion which is significantly greater in the PD subjects compared to the control.

When OFF, the velocity measures of the PD subjects were almost 10 times greater than controls, even though the amplitude of the COP excursion was not significantly different. Corresponding to the higher velocity without increases in the amplitude of COP excursion, the mean pathlength was significantly greater in the PD subjects OFF compared to controls ($p \leq 0.02$) and the PD subjects ON compared to controls ($p \leq 0.05$; Table 5.1).

Table 5.1. Center of Pressure Measures and Significance

Group	Amplitude (cm)	S.D. of Amp.	Velocity (cm/s)	Pathlength (cm)
OFF	1.12 (1.22)	0.68 (0.75)	9.65 (10.84)	31.11 (34.46)
ON	1.26 (1.14)	0.76 (0.77)	6.56 (9.61)	16.89 (19.34)
NHE	0.93 (1.88)	0.26 (0.23)	1.08 (0.61)	2.98 (1.90)
Off vs. On	ns	ns	ns	ns
Off vs. NHE	ns	ns	$p < 0.02$	$p < 0.02$
On vs. NHE	ns	ns	$p < 0.05$	$p < 0.05$

NHE=elderly controls, OFF=Parkinson's subjects off L-dopa medication, ON=Parkinson's subjects on L-dopa medication. Values express as group mean and (standard deviation).

To verify that the significant differences in the standard deviation of velocity were not due only to increases in the mean, a coefficient of variation was calculated, with differences still existing between the PD subjects and controls (percent variability with respect to mean; control = 60%, off = 119%, on = 101%). When ON, all PD subjects showed a reduction in the velocity of the COP excursion, and the group mean approached that of the controls. Five PD subjects, when ON, had velocity measures within the normal control range.

DISCUSSION

Two distinct observations have been presented with respect to the effects of oral L-dopa on postural mechanisms in Parkinson's disease. First, PD subjects exhibit excessively high amplitude, phasic activity in lower extremity and trunk muscles which is significantly reduced in the distal but not proximal lower extremity and trunk muscles by administration of L-dopa. Second, the 4-5 Hz tremor in lower extremity and trunk muscles during stance was abolished by L-dopa, while 8-20 Hz components of phasic activity were unaffected by L-dopa. These observations suggest that dopaminergic systems, in part, regulate motor neuron activity for muscle tone during stance (Horak and Frank 1995). The increased muscle activity corresponds to an increased variability in the velocity of the anterior-posterior COP excursion for all PD subjects. Although the PD subjects do not exhibit a larger excursion of the COP during stance, the velocity is faster and less predictable. These findings are consistent with the notion that a

stiff system oscillates faster about a point of equilibrium. The increased variability in the velocity measures may represent a disruption in a constant control signal for maintenance of stance stability. Whether the baseline activity of the muscles contributes to the instability or is a result of instability is uncertain, but the abnormal spike-like EMG and tremor activity in the PD subjects suggests that the muscle activation contributes to the instability. The flexed-posture common in PD, may contribute to the excess muscle activity, however, when normal subjects stand in a similar flexed-posture, excessive muscle activity is not observed.

The output projections of the basal ganglia are somatotopically organized primarily from the internal globus pallidus and substantia nigra pars reticulata to the thalamus and the pedunculopontine tegmental region of the brainstem (Hallett 1993). We propose that there may exist descending brainstem projections involved in the regulation of postural muscle tone; while thalamocortical-spinal projections with a dopaminergic dependence may be involved in regulation of distal muscle tone and the 4-5 Hz tremor generation.

Support for the role of a dopaminergic influence on distal limb muscle tone comes from both animal and human studies. Increases in distal muscle tone following disruption of the dopaminergic system of the BG have been previously quantified in animal models of PD including the MPTP treated primates (Klockgether et al. 1991) and monoamine depleted (Klockgether et al. 1991) or 6-hydroxydopamine (6-OHDA) lesioned rats (Double and Crocker 1993). EMG activity of the gastrocnemius and tibialis is increased when dopaminergic transmission is reduced (Double and Crocker 1993). Although these animal studies have not quantified changes in proximal muscles, they do suggest that the dopaminergic system of the BG plays a critical role in the regulation of muscle tone. Administration of L-dopa in PD patients has been demonstrated to increase distal arm movement velocity more than axial movement velocity (Weinrich et al. 1988), further suggesting a stronger dopaminergic influence on the more distal muscles.

In the cat, the BG and the tegmental regions of brainstem have been demonstrated to be critical in the setting of hind limb postural tone for standing prior to locomotion (Garcia-Rill

1986; Mori 1989). These studies suggest that BG projections to brainstem pathways may contribute to regulation of stance and locomotion, however no specific involvement of the dopaminergic system has been quantified.

Because thalamic stimulation can be effective in reducing both arm and postural muscle tremor in PD patients (Burleigh et al. 1993), the thalamocortical and corticospinal pathways may be involved in the pathophysiology of the 4-5 Hz tremor during standing. Lower extremity tremor of 4-5 Hz during standing has been previously reported in early PD, but considered a variant of orthostatic tremor appearing as an initial symptom of PD (Kim and Lee 1993). The clinical features of orthostatic tremor, however include a 10-16 Hz tremor in the leg muscles during standing that disappears with walking or sitting (Thompson et al. 1986). The 4-5 Hz tremor in postural muscles reported in this study as well as previously reported from our laboratory (Burleigh et al. 1993) indicates that lower extremity tremor may be a more common characteristic of PD than previously recognized. Interestingly, this tremor activity persisted during postural adjustments to surface displacements and during a voluntary rise to toes task (Horak and Frank 1995).

In contrast to the 4-5 Hz tremor, the higher frequency components of EMG activity seen in three different PD subjects in this study are not affected by L-dopa administration. The general spike-like behavior of the EMG in the PD subjects may be reflective of basal ganglia influence on spinal circuitry, including decreased sensitivity of polysynaptic reflex pathways and increased recurrent and reciprocal inhibition (Obeso et al. 1985; Lelli et al. 1991). Further experimentation is necessary to differentiate the mechanisms involved in the abnormal regulation of muscle tone.

In conclusion, our findings offer some quantification for the observation of increased postural muscle tone and lower extremity tremor in Parkinson's disease, which is partially reduced by L-dopa. Quantification of the velocity parameters of the COP provides a tool to discriminate postural stability which may be related to high amplitude, phasic muscle activity during stance.

Note added to dissertation: A calibration error was made in the power spectra of Figure 5.1 when the original figures were submitted for publication. The power spectra reported in this dissertation have been corrected, thus are different than those reported in the published manuscript. The significance of all findings and conclusions remains unchanged.

Chapter 6.

Based on *Mov. Disord.* 8(4): 519-524, 1993

Effects of Thalamic Stimulation on Tremor, Balance, and Step Initiation: A Single Subject Study

A. Burleigh, F. Horak, K. Burchiel and J. Nutt

ABSTRACT

This study was conducted to evaluate the clinically apparent balance improvements in a patient with Parkinson's disease who had stimulating electrodes surgically implanted to the VIM nucleus of the right thalamus for control of left upper extremity tremor. Experiments were conducted to determine if balance improved simply because the large amplitude upper extremity tremor was reduced, or if the neural control of balance improved. Using EMGs and forceplate recordings, we quantified the effects of the thalamic stimulation on the contralateral upper extremity tremor, and on the lower extremity postural muscle activations for quiet stance, step initiation and equilibrium responses to surface displacements. The results demonstrated that besides reducing the amplitude and destabilizing effects of the upper extremity tremor, the thalamic stimulation was also effective in reducing tremor activity of the trunk and contralateral lower extremity muscles. In addition, the contralateral lower extremity muscle activation patterns, strengths, and durations for the balance tasks were enhanced during stimulation. These results suggest that thalamic stimulation improved this patient's balance by reducing tremor in the contralateral extremities, and by increasing burst duration and magnitude of the tibialis anterior which functions as the postural prime mover for the step initiation and balance tasks.

INTRODUCTION

Upper extremity tremor is a common symptom of Parkinson's disease. Although dopamine-replacement therapy often proves effective in reducing tremor, not all parkinsonian patients are responsive to L-dopa. Surgical intervention for the treatment of tremor includes thalamotomy, and more recently, implantation of high frequency electrical stimulating electrodes into the Ventralis Intermedialis (VIM) nucleus of the thalamus (Narabayashi 1989;

Benabid et al. 1991). Combined thalamotomy and stimulation procedures have been reported as a surgical approach for bilateral tremors associated with Parkinson's disease (Benabid et al. 1987). Although these procedures suppress the upper extremity tremor, no quantitative studies have been conducted to assess the effects of thalamic electrical stimulation on postural control and movement. We have studied a single patient to determine if the high frequency electrical stimulation of the right VIM nucleus of the thalamus affected only the left upper extremity tremor, or also improved muscle activation patterns for balance during quiet stance, voluntary step initiation, and automatic equilibrium responses to surface displacements.

MATERIALS AND METHODS

CASE HISTORY The patient was a 59 year old right handed male diagnosed with Parkinson's disease in 1986. He developed bilateral large amplitude upper extremity tremor which was non-responsive to any pharmacological intervention. The tremor was present at both rest and during movement, leaving the upper extremities essentially non-functional. In April 1990, a left thalamotomy was performed producing transient improvement in the right upper extremity. A repeat left thalamotomy in October 1990 permanently alleviated the right sided upper extremity tremor. A bilateral thalamotomy was contraindicated since the patient developed mild dysarthria. Surgical implantation of a contact platinum deep brain electrode (DBS®, Medtronic) into the VIM nucleus of the right thalamus, and installation of an internal programmable impulse generator (Itrel II ®, Medtronic) was performed in December 1991 to control the large amplitude tremor of the left upper extremity. Prior to stimulator implantation, the patient also presented with parkinsonian features of slightly flexed posture, poor axial mobility, impaired postural and balance reactions, and decreased stride length. Post-operatively, when the stimulation was ON, the patient demonstrated immediate reduction of upper extremity tremor, and clinically apparent balance improvements. In March 1992, the following experiments were conducted. At this time, the thalamic stimulation parameters were continuous, 11 volt, 120

msec, square waves at 160 Hz. The patient generally left the stimulator ON continuously through the day and night.

TESTING CONDITIONS The effects of stimulation were determined for three balance tasks: 1) Quiet stance; 2) Voluntary step initiation with the right foot in response to a proprioceptive cue; 3) Equilibrium response to forward translation of the platform causing backward sway of the body. Forward step with the right foot was studied in order to assess the postural muscle activation of the left lower extremity prior to the step. Each test condition was performed with the stimulation ON for five trials, and OFF for five trials, with the order of ON and OFF blocks varied among tasks. The patient stood with one foot on each plate of a hydraulically driven force platform. Tracings of the initial foot positions ensured that placement was the same over repeated trials, and on-line viewing of right and left weight distribution was used to ensure equal weight bearing at the start of each trial. The proprioceptive cue for voluntary step initiation was a slight pulse of the platform at a velocity of 10 cm/sec and amplitude of 0.1 cm. On some trials, the patient was asked not to step in response to the cue to verify that the cue did not trigger an automatic equilibrium response. The forward surface translation to elicit an equilibrium response to backward sway was presented at a velocity of 15 cm/sec and an amplitude of 8.5 cm.

DATA COLLECTION Surface EMGs were recorded bilaterally from the tibialis anterior, gastrocnemius, soleus, and quadriceps; and from the the left hamstrings, paraspinals, abdominals, and wrist extensors and flexors. Center of pressure calculations used data obtained from vertical force transducers located in each platform. The EMGs were collected at 500 samples/sec over a 3 second trial, amplified, band-pass filtered (70-2000 Hz), full-wave rectified, and low pass filtered on-line prior to analysis. Data analysis was performed using both PDP 11/73 software and a MacIntosh program for wave analysis.

Fourier analysis of the individual muscle EMG's was performed to determine the tremor frequency. Because the tibialis anterior is the postural prime mover for both step initiation and

the equilibrium response to backward sway, this muscle's activation onset times, EMG magnitudes, and bursts durations were determined .

RESULTS

Tremor during quiet stance

When the stimulation was OFF, Fourier analysis revealed a 4.5 Hz tremor in the left wrist muscles (Figure 6.1A) With stimulation, the left upper extremity tremor was immediately diminished in amplitude, yet the underlying frequency persisted during some of the conditions. Even with the stimulation ON, a small amplitude tremor was apparent when the subject was standing. However when sitting with hands at rest, the tremor was effectively dampened by the stimulation (Figure 6.1B). The muscle activation patterns clearly demonstrate alternating activation in agonists and antagonists, which is a common feature in parkinsonian tremor.

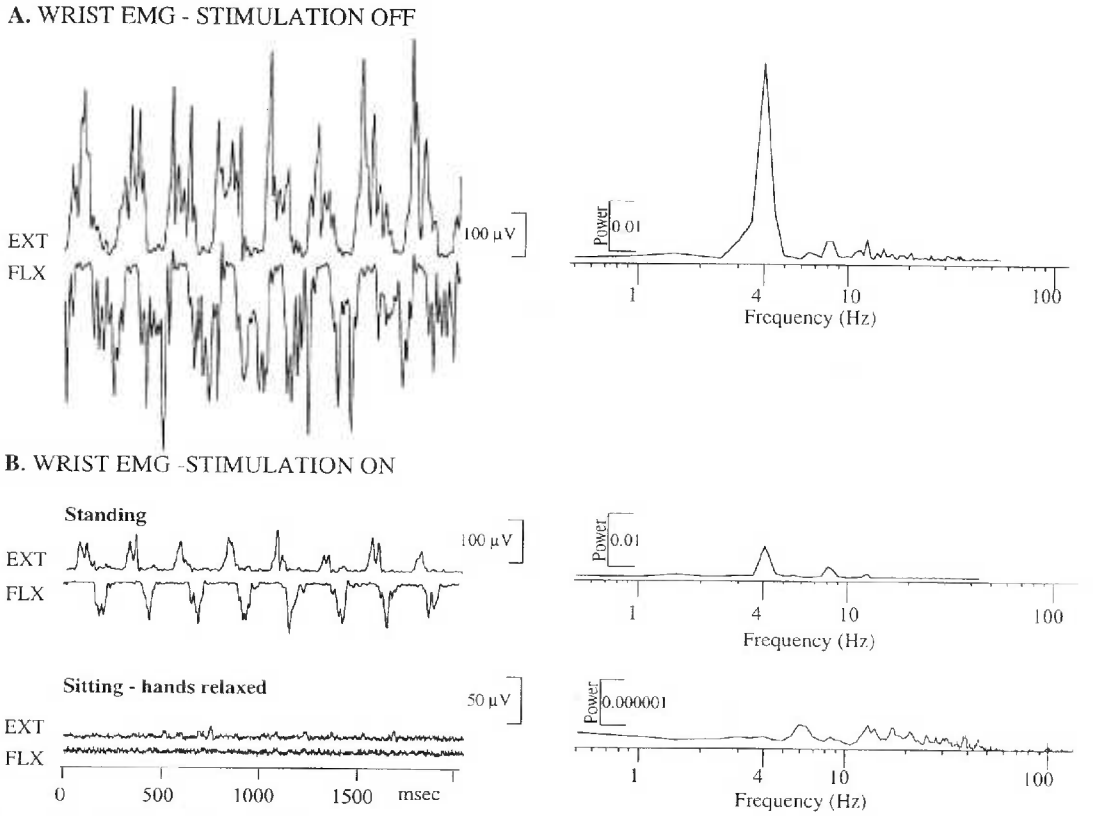

Figure 6.1. EMG activity of left wrist extensors (EXT) and flexors (FLX) is shown with the associated Fourier analysis. A) Large amplitude tremor is seen during quiet stance when thalamic stimulation is OFF, B) Reduced amplitude tremor is seen with stimulation ON - patient standing; there is an absence of tremor with stimulation ON and the patient sitting with hands relaxed.

A 4.0 Hz tremor was present in the contralateral tibialis anterior, gastrocnemius (not shown) and soleus, and in the paraspinals; and a 4.5 Hz tremor was present in the quadriceps (Figure 6.2A). The tremor in the lower extremity was characterized as alternating activation between agonists and antagonists for the tibialis anterior and gastrocnemius/soleus. Although there was high tonic activity of the left hamstrings, no distinct tremor activity was revealed as having a peak power > 0.001 by Fourier analysis. No tremor was evident in the abdominals, and no tremor was evident in the right lower extremities (not shown). When the stimulation was ON, the tremor was immediately abolished in the left lower extremity and paraspinals, and the overall tonic activity of all muscles was reduced (Figure 6.2B).

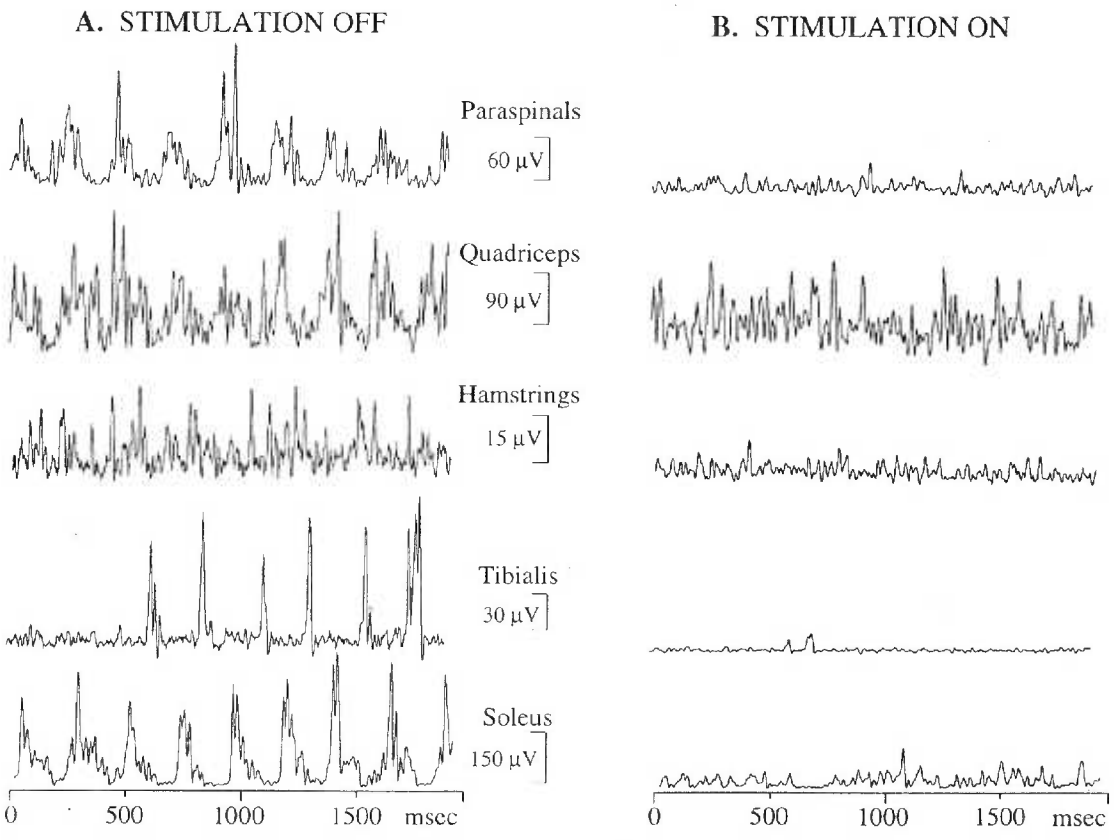

Figure 6.2. EMG activity during quiet stance is shown. A) There is tremor in the left paraspinals, quadriceps, tibialis anterior and soleus, and high tonic activity in all muscles when thalamic stimulation is OFF, B) There is an absence of tremor and an overall reduced level of tonic activity when stimulation is ON.

The tremor of the lower extremity and trunk muscles resulted in approximately 2 cm peak-to-peak oscillations of the foot center of pressure (COP) when the stimulation was OFF (Figure 6.3A). During quiet stance with the stimulation OFF, the average left COP position was approximately 7 cm in front of the center of the ankle axis. A large left-right asymmetry was apparent with the average right COP positioned approximately 1/2 cm behind the center of the ankle axis. There was no COP asymmetry when the stimulation was ON. The left and right average COP positions were both maintained approximately 3 cm in front of the ankle axis, as would be expected during normal quiet stance (Winter 1990) (Figure 6.3A).

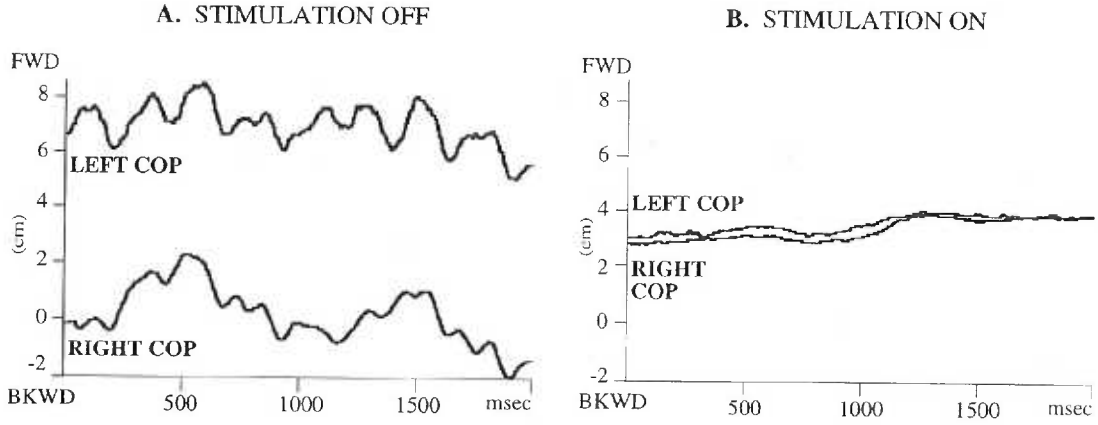

Figure 6.3. Center of Pressure (COP) position for each foot during quiet stance is shown. A) Tremor is evident in left COP which is 6-8 cm forward of the ankle axis, and right COP which is ± 2 cm from the ankle axis when the stimulation is OFF, B) A symmetrical relationship between left and right body is seen with COP approximately 3 cm forward of the ankle axis when stimulation is ON.

Step initiation

Lower extremity muscle activation for step initiation changed from tonic, short duration spikes when the stimulation was OFF to synchronous, phasic bursts of increased duration when the stimulation was ON (Figure 6.4). The patient demonstrated normal activation of the tibialis anterior and corresponding suppression of the soleus for step initiation when the stimulation was ON. The duration and magnitude of the tibialis anterior activation associated with step initiation was increased when the stimulation was ON (Table 6.1). Reaction time increased during stimulation, but was less than a 2 standard deviation change.

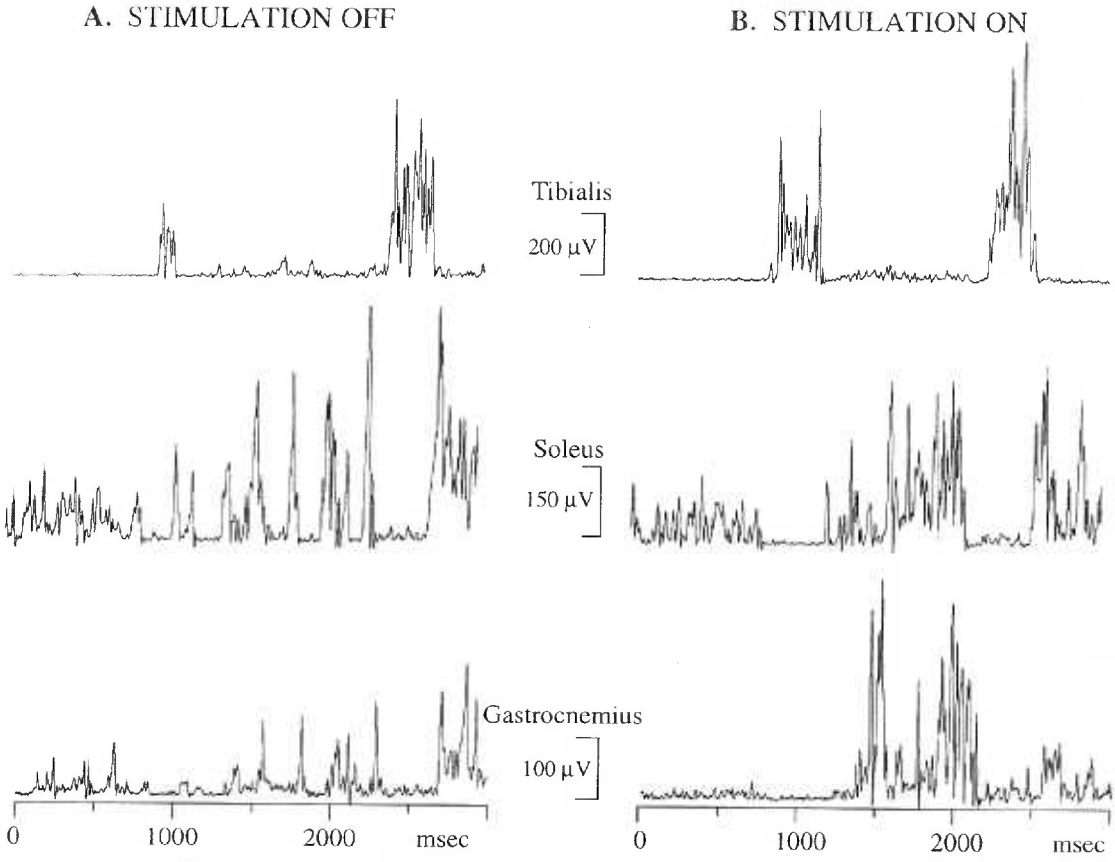

Figure 6.4. EMG activity during the initiation of a forward step is shown. A) There is a reduced initial tibialis anterior burst associated with soleus and gastrocnemius tremor activity when the stimulation is OFF, B) Increased initial tibialis, soleus and gastrocnemius burst amplitude and duration, and absence of soleus or gastrocnemius tremor activity are seen when the stimulation is ON.

Equilibrium response

Lower extremity muscle activation for an equilibrium response to backward sway changed from tonic short duration spikes when the stimulation was OFF to synchronous phasic bursts of increased duration when the stimulation was ON (Figure 6.5). When the stimulation was ON, the patient demonstrated bilateral activation of the tibialis anterior in response to backward sway of the body induced by the forward translation of the platform. The duration and magnitude of the left tibialis anterior activation in response to a forward platform translation was increased when the stimulation was ON (Table 6.1). Although the tibialis onset was delayed compared to normal (91 ± 13 msec) (Horak and Nashner 1986) it only increased by 2 standard deviations during stimulation.

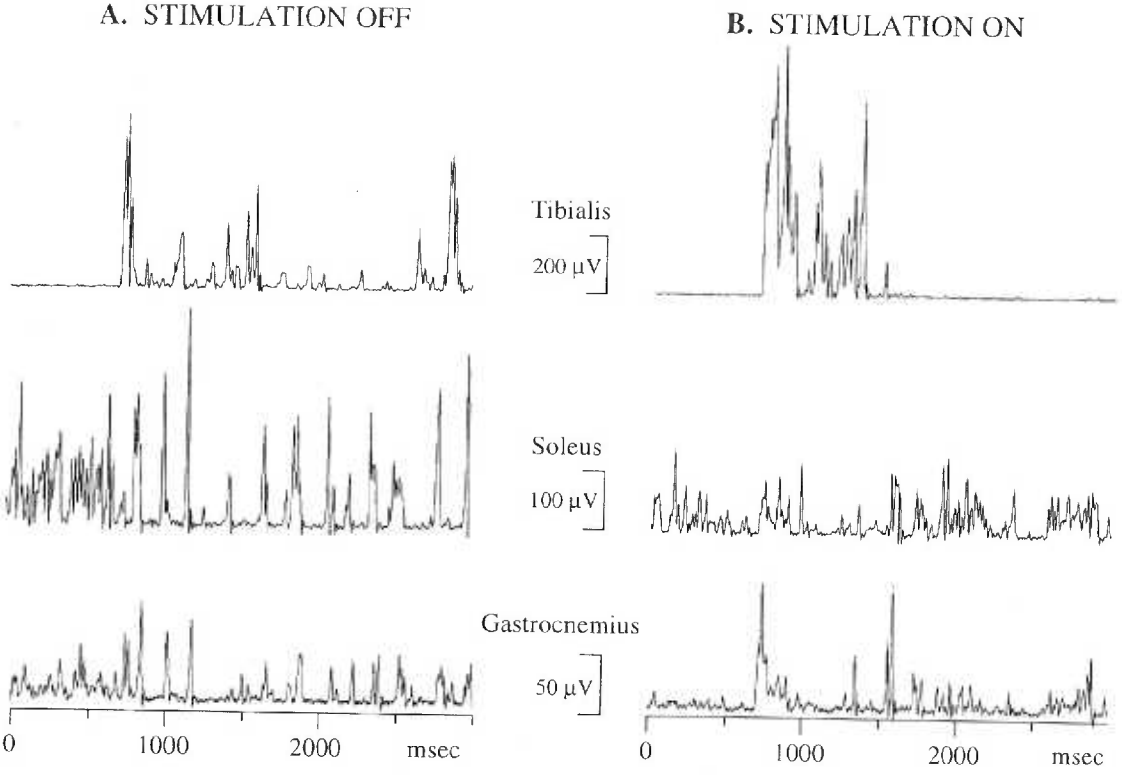

Figure 6.5. EMG activity during the automatic equilibrium response to backward sway is shown. A) There is a reduced initial tibialis anterior burst associated with soleus and gastrocnemius tremor activity when the stimulation is OFF, B) Increased initial tibialis anterior burst amplitude and duration, and absence of soleus or gastrocnemius tremor activity are seen when the stimulation is ON.

TABLE 6.1. *Left tibialis initial EMG*

Condition	Onset (ms)	Duration (ms)	Magnitude (mV • ms)
Step Initiation			
Off	326 ± 55	110 ± 41	12.7 ± 8.9
On	396 ± 71	309 ± 86	20.9 ± 11.7
Equilibrium response			
Off	173 ± 11	104 ± 27	19.6 ± 6.0
On	194 ± 9	237 ± 43	42.9 ± 17.6

Table 6.1. Left tibialis anterior onset latencies, burst durations and integrated EMG areas for the initiation of forward step, and for the automatic equilibrium response to backward sway with stimulation ON and OFF. Values are given as mean and standard deviation (s.d.) for five sequential trials. Onset times were determined as the initial burst onset minus 500 msec baseline.

Clinically apparent improvement in balance

Based upon clinical evaluation using a modified version of the Unified Parkinson's Disease Rating Scale (Fahn et al. 1987), when the stimulation was ON, the patient exhibited mild improvements in trunk mobility, voluntary ankle sway, retropulsion/propulsion response to a gentle push, initiation of walking, turning strategies and frequency of fall. The patient scored as moderately affected in each category when the stimulation was OFF, and slightly affected in each category when the stimulation was ON. Improvements in ambulation and the retropulsion response are demonstrated in the videotape that accompanies the published manuscript.

DISCUSSION

This study demonstrates that for this patient, the right thalamic electrical stimulation was effective in reducing the tremor activity not only of the left upper extremity, but also of the left lower extremity and trunk muscles. Electrical stimulation also proved effective in improving the patient's voluntary step initiation and postural equilibrium responses. It is proposed that the mechanism of action of the thalamic electrical stimulation involves dampening of output cells in the VIM thalamus which receive an oscillatory drive from the tremor cells. The motor improvement in step initiation and postural equilibrium results from more normal muscle activation patterns and burst durations, and improved stance stability due to effective suppression of the lower extremity tremor by the electrical stimulation.

The presence of cells firing at the same frequency as the tremor has been confirmed in the ventral nuclear group of the thalamus, as well as in the pallidum, putamen, caudate, and motor cortex using microelectrode recording techniques (Ohye 1982). Several researchers have proposed that the parkinsonian tremor may be due to excessive drive of the ventral thalamus tremor cells to the motor cortex (Ohye and Albe-Fessard 1978; Lamarre and Joffroy 1979). Lenz et al. (1988) have demonstrated that the activity of a specific population of thalamic tremor cells is directly correlated with upper extremity EMG's in patients having parkinsonian tremors which were non-responsive to dopamine therapy. Tremor activity in the 3-6 Hz range

was recorded from thalamic cells in the VIM during thalamotomy procedures for patients with Parkinson's disease. Thus, parkinsonian tremor may involve oscillatory, phasic firing of thalamocortical cells which may be released due to excess inhibition of other target cells in the thalamus receiving projections from the globus pallidus. Because the amplitude of the left wrist tremor was reduced, but the frequency remained unchanged, it is probable that the entire thalamocortical pathway was not disrupted, but rather the number of inputs driving the tremor was reduced. This would suggest that the stimulation is not switching off the tremor generating mechanism, but is, instead, inhibiting some of the relay cells of the thalamus which are oscillating. This may be due, in part, to the stimulation frequency of 160 Hz being used since 200 Hz has been suggested for optimal suppression of tremor (Benabid et al. 1991).

The ventral lateral tier of the thalamus is somatotopically organized with a large region associated with the hand and upper extremity, and an adjacent region associated with the lower leg (Lenz et al. 1990). In this single patient studied, electrical stimulation of the VIM nucleus effectively suppressed the tremor in all muscles exhibiting the tremor, and decreased the overall tonic activity of all muscles recorded. Thus, the high intensity stimulus probably spread to affect both the wrist and lower extremity related cells.

The patient's ability to maintain his COP well within his base of foot support was improved by the thalamic stimulation. It is proposed that the asymmetrical COP position, when the stimulation was OFF, was due to excessive gastrocnemius and soleus muscle activity resulting in tonic plantarflexion in the left lower extremity and a compensatory dorsiflexion in the right lower extremity. The anterior-posterior COP oscillations also contributed to instability. When the stimulation was ON, the mean left and right COP positions were matched and maintained well within the normal position for the base of foot support, allowing a greater degree of stability in stance.

The patient's voluntary step initiation and postural equilibrium responses were improved by the stimulation. It is proposed that reduction of the thalamocortical tremor activity was effective in allowing more normal muscle activation patterns to be utilized. The initiation of a

step involves activation of the tibialis anterior and inhibition of the soleus to allow the center of mass to progress forward beyond the COP (Herman et al. 1975; Breniere et al. 1991). When tibialis anterior activation of the stance limb is reduced, a shortened step has been predicted and excessive hip flexion is utilized by the swing limb (Breniere et al. 1991). The data clearly demonstrates that when the thalamic stimulation was OFF, the left tibialis anterior muscle activation was reduced and the soleus demonstrated asynchronous burst activity. When the stimulation was ON, there was a clear distinction of initial tibialis activation and soleus suppression.

The equilibrium response to backward sway of the body requires phasic activation of the tibialis anterior to generate a dorsiflexion force to return to equilibrium (Horak and Nashner 1986). Previous studies with parkinsonian patients have indicated that the initial activation of the tibialis anterior in response to a peripherally triggered stimulus has a normal response time and initial rate of rise; however there is inhibition of the contraction after approximately 75-100 msec resulting in reduced force generation (Nutt et al. 1992; Horak et al. 1992). In this single subject study, the left tibialis anterior muscle activation was reduced and the gastrocnemius and soleus demonstrated asynchronous burst activity when the stimulation was OFF. However, when the stimulation was ON, there was an increased tibialis burst duration and magnitude and reduced antagonist activity of the gastrocnemius and soleus; thus allowing a more effective equilibrium response even though the response time was delayed.

It is concluded that the thalamic stimulation for upper extremity tremor had positive effects on this patient's step initiation and balance. The improvements may be due, in part, to reduction of the destabilizing upper extremity tremor. However, a more significant improvement may be due to the reduction of excessive tonic activity and tremor in trunk and lower extremity muscles, and more synchronized EMG bursts for effective postural control.

Generally, thalamic stimulation is thought to be a functional thalamotomy (Benabid et al. 1991) and the same pattern of improvements as with the thalamotomy would be expected. Classical teaching suggests that unilateral thalamotomy improves tremor and rigidity, but is

contraindicated when the patient has significant bradykinesia. Occasionally, dysequilibrium is an adverse effect of the thalamotomy procedure (Benabid et al. 1991). The patient we studied had both a left thalamotomy and a right thalamic stimulator. By classical teaching, this would suggest that bilateral disruption of the thalamus may worsen balance. However, the results of this study demonstrate that balance was improved in this patient. Perhaps, the electrical stimulation is effective in reducing the activity of the tremor generating cells, but does not disrupt the thalamic relay circuitry in the same manner as does a thalamotomy.

This single case we have presented suggests that in some cases of Parkinson's disease, thalamic stimulation is effective in reducing tremor and improving muscle activation patterns for some aspects of balance control.

Note added to dissertation: A calibration error was made when the original figures were submitted for publication. The correct calibration involves multiplying all reported milliVolt values by (20). This multiplication results in the correct values expressed as microVolts. The values reported in this dissertation have been corrected, thus are different than those reported in the published manuscript. The significance of all findings and conclusions remain unchanged. The video tape segments which accompany the published manuscript are not available as part of this dissertation.

Chapter 7.

Conclusions

The series of studies in this dissertation have investigated the neural mechanisms for postural control. The findings demonstrate that there is a dynamic interaction between the automatic postural responses to perturbation and the anticipatory postural adjustments for goal-directed voluntary movement. Furthermore, studies involving subjects with Parkinson's disease suggest that the basal ganglia dopaminergic system contributes to the regulation of postural tone in stance, and the regulation of force during the execution of anticipatory postural adjustments associated with voluntary movement. This chapter will address the mechanisms mediating postural interactions during perturbed step initiation and the contributions of the basal ganglia to the neural organization of postural control.

• Postural interactions: Control of perturbed step initiation

During stance, backward translation of the support surface causes forward sway of the body. When subjects maintained stance during the perturbation, an involuntary automatic postural response was elicited in the leg extensor muscles to restore stance equilibrium. However, when subjects were perturbed by a backward surface translation and instructed to step rather than maintain stance, two distinct postural modifications occurred: 1) the automatic postural response to the surface perturbation was significantly reduced in magnitude; 2) the anticipatory postural adjustments promoting foot-off were significantly shortened in duration. These findings suggest that even prior to its execution, a descending central command for voluntary movement interacts with the ascending peripheral information associated with an external perturbation. Several mechanisms by which the nervous system modulates these postural interactions have been identified.

• *Task instruction contributes to the organization of the automatic postural response elicited by a perturbation of the support surface (Chapter 2 and Chapter 3).*

When a voluntary step was initiated in response to a surface perturbation, the reduction of the automatic postural response was asymmetrical between the stance and swing limbs, demonstrating that modification of the involuntary, automatic response was specific to the planned response. These findings suggest that, prior to the onset of a perturbation, the nervous system pre-sets the excitability of the muscles relative to the specific movement instruction.

• *Prediction of the perturbation velocity, based on prior experience, is required for maximal inhibition of the automatic postural response when a voluntary movement is made in opposition to the automatic response (Chapter 2 and Chapter 3).*

When a voluntary step was initiated in response to a surface perturbation, inhibition of the automatic postural response occurred only when the perturbation velocity was predictable. These findings demonstrate that combined with task instruction, feed-forward control based on prediction of the imposed perturbation biased the response in favor of the voluntary movement.

• *Changes in peripheral sensory information contribute to the modification of anticipatory postural adjustments associated with a pre-planned voluntary movement (Chapter 2 and Chapter 3).*

When a voluntary step was initiated in response to a surface perturbation, the duration of the anticipatory postural adjustments was shortened with respect to the perturbation velocity, regardless of whether the velocity was predictable or unpredictable. These findings demonstrate that the temporal aspects of the postural adjustment phase were not entirely pre-determined, but were specified by feedback from the periphery. Even before steady state locomotion had been achieved, integration of the movement plan and peripheral afferent information generated a response that was appropriate to the external conditions in which the body was moving.

• Parkinson's disease: Insight into basal ganglia function

Persons with Parkinson's disease commonly exhibit postural instability and an inability to self-initiate locomotion. Generally, the postural adjustments for step initiation, involve silencing of the muscles which are active during stance, and generation of ground reaction forces to move the body forward and over the stance limb. Utilizing Parkinson's disease as a model for basal ganglia disease, the following findings suggest that the basal ganglia dopaminergic system contributes to force production in self-generated but not externally-triggered step initiation, and contributes to the regulation of postural muscle tone in stance.

• *Force production during the anticipatory postural adjustment phase of voluntary, self-generated movement is impaired in Parkinson's disease, and influenced by dopaminergic mechanisms (Chapter 4).*

Subjects with Parkinson's disease exhibited an inability to produce force during the anticipatory postural adjustment phase of self-generated step initiation. This force impairment was more pronounced when subjects were OFF, and improved when ON. These findings suggest that force production during voluntary movements is in part regulated by the basal ganglia dopaminergic system. The bradykinesia and akinesia prominent in subjects with Parkinson's disease may be related, not to an inability to initiate and execute a motor command, but rather to an inability to effectively modulate the amount of force required for completion of the task.

• *Force production is improved in Parkinson's disease when the movement is initiated in response to an external stimulus (Chapter 4).*

Subjects with Parkinson's disease exhibited improved force production during the anticipatory postural adjustment phase of step initiation when the step was initiated in response to a cutaneous "go" stimulus. Administration of levodopa did not further influence the motor performance, since subjects with Parkinson's disease both ON and OFF produced a level of force comparable to the control subjects.

• *Modification of force during the anticipatory postural adjustments for perturbed, voluntary movement is impaired in Parkinson's disease, but the impairment is not strictly related to dopaminergic mechanisms (Chapter 4).*

Subjects with Parkinson's disease exhibited a rapid onset and shortened duration of the anticipatory postural adjustments preceding heel-off for step initiation when the step was initiated in response to an external surface perturbation. However, despite the temporal modification there was not an associated increase force generated to promote rapid foot-off. This failure to increase force in the externally-triggered movement was not influenced by administration of levodopa. These findings suggest that the postural instability and gait deficits prominent in subjects with Parkinson's disease result in part from non-dopaminergic mechanisms that alter the ability of the nervous system to use peripheral sensory information to modulate the force requirements for postural adjustments associated with voluntary movement.

• *Abnormal increases in lower extremity muscle tone and tremor contribute to stance instability in Parkinson's disease, and are influenced by dopaminergic mechanisms (Chapter 5).*

Activation of leg and trunk muscles contribute to the postural tone necessary to maintain bipedal stance. Subjects with Parkinson's disease exhibited abnormally high amplitude muscle activity and a 4 Hz tremor in the lower extremities. The abnormal muscle activity appeared to be regulated by dopaminergic systems, since it was more pronounced when subjects with Parkinson's disease were OFF. These findings suggest that dopaminergic systems are involved in the regulation of muscle tone during stance and the depletion of dopaminergic transmission contributes to the postural instability prominent in subjects with Parkinson's disease.

• *Implantation of thalamic stimulating electrodes can effectively reduce upper extremity tremor as well as improve the activation pattern of lower extremity muscles required for postural control of stance and step initiation (Chapter 6).*

In a single subject, with atypical Parkinson's disease, thalamic stimulation for treatment of upper extremity tremor resulted in improved balance and postural control. The improvements were associated with reduction of lower extremity tremor and enhancement of muscle burst amplitude and duration during both involuntary responses to perturbation and voluntary step initiation. These findings suggest that thalamic pathways contribute to the regulation of muscle activation patterns for both voluntary and involuntary in some cases of Parkinson's disease, thalamic projections associated with tremor generation also influence the activation magnitude of muscles associated with both involuntary and voluntary movement.

• Future directions

This dissertation originated from a basic therapeutic question which led to a series of experiments investigating postural control during stance and step initiation. The original question evolved from the treatment of neurologically disabled patients, who exhibited deficits in standing posture and an inability to initiate locomotion. In some patients, a small, passive forward displacement of the body promoted the initiation of locomotion. In others however, this passive displacement was of no help in initiating the first step, since patients responded with a postural response that restored their equilibrium. Why was the passive "push" helpful in only some patients?

The findings presented demonstrate that in subjects without neurological impairment the nervous system does integrate the passive displacement with a motor command for voluntary movement. The findings support the concept that the nervous system regulates postural control in an adaptive, task-specific manner. What then goes wrong in the patients who cannot integrate the automatic responses to the passive displacement with a voluntary command to initiate step? In subjects with Parkinson's disease, the temporal components of the postural

adjustments for step initiation are appropriately modified when step is initiated in response to a perturbation. However, the force components are not appropriately modified. The specific mechanisms involved in force production during externally-triggered movements remain unclear. Other specific lesions in the nervous system may result in an inability to use central mechanisms for feed-forward postural control or peripheral mechanisms for feed-back control. The cerebellum contributes to modulation of involuntary response magnitudes based on prediction of stimulus characteristics (Hore and Villis 1984). Accordingly, cerebellar disorders may result in an inability to suppress the involuntary automatic postural responses when a voluntary step is initiated in response to perturbation. Information from cutaneous afferents contributes to the modulation of on-going locomotion (Duysens and Pearson 1976). Accordingly, destruction of peripheral sensory nerves may result in an inability to modify the temporal and force components of the anticipatory postural adjustments when step is initiated in response to a perturbation.

Information gained from this dissertation supports the necessity of a systems approach for the rehabilitation of balance and postural control problems in stance. The systems approach is based on the concept that movement emerges from an interaction between the individual, the task, and the environment in which the movement occurs. Movement is not simply the result of pre-determined motor programs or stereotyped reflexes. Rather, movement results from a dynamic interaction between the individuals perception, the cognitive plan, the sensory information available, and the actions of the motor system.

Utilizing current information regarding the mechanisms employed by the nervous system, gait and balance disorders can be more objectively and effectively evaluated. New clinical tests can potentially be developed and used to determine the cause and severity of motor abnormalities. For example, assessment of postural control under different task-requirements and environmental conditions will help identify whether movement deficits result from disruption of either peripheral or central systems, or from a disruption of sensori-motor

integration. Thorough assessment will then allow for selection of the most appropriate treatment approach and prediction of a functional outcome.

New strategies for the treatment of Parkinson's disease should be developed to expand on the commonly characterized features of resting tremor, rigidity, and bradykinesia. Although these are the apparent symptoms, they do not clarify the mechanisms underlying the motor disabilities. Therapeutic approaches which promote increased force, attention to external cues, and education of ON - OFF motor fluctuations should be further developed.

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