CONTRIBUTIONS OF THE CEREBRAL CORTEX AND BASAL GANGLIA TO HUMAN ANTICIPATORY POSTURAL CONTROL IN HEALTHY AND PARKINSON'S DISEASE SUBJECTS

By

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ABSTRACT

Constraints on human postural equilibrium vary continually with changes to an individual's environment and sensory-motor state. Consequently, human dynamics require the continual maintenance of posture. Purely reactive postural adjustments, however, would not allow for efficient motion because a person would have to repeatedly interrupt an intended movement in order to correct posture and maintain balance. Instead, the human nervous system utilizes *anticipatory* postural control to prepare the body's posture for expected disturbances of equilibrium elicited by either voluntary movement or externally induced postural perturbations.

The neural substrates underlying anticipatory postural control before voluntary and externally induced postural perturbations remain unclear. Thus, under the hypothesis that the cerebral cortex and basal ganglia contribute to anticipatory postural control prior to both voluntary and externally induced postural perturbations, the purposes of this dissertation are to (1) identify the specific contributions of the basal ganglia and cerebral cortex to the anticipatory postural adjustments (APAs) and foot-swing of voluntary step initiation, (2) to understand the environmental contexts in which the human nervous system can take advantage of anticipatory control when responding to external postural perturbations, and (3) to elucidate how the cerebral cortex and basal ganglia contribute to anticipatory postural control before an external postural perturbation. We examined subjects with Parkinson's disease (PD) to assess how dysfunction of basal ganglia circuitry affects postural equilibrium.

Using repetitive transcranial magnetic stimulation, we disrupted function of the pre-supplementary motor area (pre-SMA), dorso-lateral premotor cortex (dPMC), or

primary motor cortex (M1) to determine each region's contributions to initiating a voluntary step. The results suggest that the pre-SMA regulates the timing of both the APA and foot-swing of a step, followed by segregated control of foot-swing by the dPMC and of APA amplitude by the M1. In addition, the results suggest that PD subjects exhibit impaired APA timing due dysfunction of the pre-SMA, whereas they exhibit diminished APA amplitude and foot-swing velocity due to dysfunction of the basal ganglia, without involving dysfunction of the pre-SMA, dPMC, or M1.

We found that, in anticipation of a postural perturbation, activity of the cerebral cortex correlates with a healthy subject's ability to optimize stability during the postural response when provided with prior warning of a perturbation. We also found that healthy subjects utilize anticipatory postural control, via pre-selection of a response strategy, even when responding to external postural perturbations with unpredictable characteristics. For subjects with PD, however, the ability to execute a context-specific, pre-selected response strategy becomes impaired so that PD subjects become dependent on selecting a postural response after perturbation onset. Despite being less proficient at modifying their postural responses based on initial context, we also found that PD subjects can use pre-existing visual targets to modify postural responses to external perturbations.

Therefore, our studies suggest that the neural control of postural equilibrium requires a dynamic exchange between cortical and sub-cortical motor centers. The cerebral cortex primes postural synergies within sub-cortical centers according to anticipated disturbances of postural equilibrium, thereby facilitating efficient, context-appropriate movement, with minimal neural processing during movement.

CHAPTER 1: Introduction

Motivation for Studies on Balance Control

Posture is defined as the orientation of body segments, and balance (also called postural stability or postural equilibrium) is defined as the dynamics of body posture to prevent falling (Winter 1995). Balance often becomes impaired with age, neurological disorders, sensory loss, and musculo-skeletal injury, leading to increased risks for falls and for the injuries and death that result from falls (Myers et al. 1996). Postural instability also leads to a decreased quality of life and is often associated with diminished physical activity and reduced socialization (Howland et al. 1998). Thus, postural instability represents a significant health care concern for society, leading to annual economic costs estimated to be in the billions of dollars in the United States (Englander et al. 1996). Impaired balance often manifests during voluntary step initiation (Brunt et al. 2005; Henricksson and Hirschfeld 2005) or as an inability to respond appropriately when balance is perturbed (Horak et al. 1989). Therefore, we require research on postural stability during these behaviors to identify how the human central nervous system controls balance. With a more clear understanding of the neural systems underlying postural control, we can more adequately direct behavioral, pharmacological, and surgical therapies aimed to improve postural instability.

Basic Concepts of Balance Control

Balance impairment pervasively affects mobility and functional independence because the maintenance of balance underlies every movement. To keep balance, mechanical principles require an individual to maintain the gravitational projection of the body's center of mass (CoM; the average position of mass for all of the body's segments)

within the base of support (BoS; the area outlined by the body's segments that are in contact with the support surface). Because upright human posture is mechanically unstable, controlling the CoM requires active correction by the neuromuscular system. These active corrections are often quantified by the body's center of pressure (CoP), defined as the sum position of all forces exerted on the support surface by the body. The CoP, therefore, is often thought of as a global control variable for displacing the CoM (Winter 1995). Active balance control is required in tasks as simple as quiet stance, as well as during voluntary stepping and when responding to an external perturbation of balance (such as when slipping, tripping, or being pushed). Given these principles of balance control, when standing on two feet without additional support, individuals must continually exert small corrective displacements of the CoP in order to keep the gravitational projection of the CoM within the area circumscribed around both feet. If balance becomes perturbed while standing, the neuromuscular system must exert larger counter-active forces against the support surface in order to shift the CoP beyond the displacement of the CoM and prevent the CoM from falling outside the BoS. During stepping, however, individuals require a more complicated interaction between the CoM and the BoS, because stepping requires a change in the BoS. Before lifting a foot for a step, the CoM is first thrust forward and toward the stance limb by an opposing displacement of the CoP (that is, backward and toward the swing limb) to facilitate propulsion and stability. Then, to enable forward locomotion, the CoM becomes displaced beyond the BoS (in a sort of self-induced fall) when the stepping foot leaves the ground. Finally, at the end of a step, the CoM is then re-acquired within the BoS as the stepping foot moves ahead of the CoM and returns to the ground (Winter 1995).

Balance control during stance and stepping becomes increasingly complicated because the human body is multi-segmental, interactive with its environment, and mobile through multiple degrees of freedom. Therefore, maintaining balance requires a complex integration of multiple sensory inputs and motor output centers in order to produce synergistic postural transitions that are appropriate to an individual's initial postural orientation, surrounding environment, and movement goals (Horak and Macpherson 1996).

In order to generate such context-dependent postural transitions, the central nervous system must first establish the body's current status relative to its environment. To accomplish this kinesthetic awareness, the nervous system primarily integrates (1) somatosensory input from cutaneous, muscle, and joint receptors, (2) visual input, and (3) vestibular input (Nashner 1982). Based on experiments testing perceptual and postural orientation in lesioned human subjects, the neural control of multi-sensory integration likely includes activation of the insula (Brandt et al. 1994, Karnath et al. 2005a, 2006), thalamus (Karnath et al. 2005b), and neo-cortex (Barra et al. 2006; Johannsen et al. 2006), and studies on balance control also report that subjects with lesions to these thalamo-cortical sites exhibit postural instability and abnormal sensory-motor coordination (Geurts et al. 2005; Barra et al. 2006).

Once establishing kinesthetic awareness, the stage is set for generating context specific postural transitions, and these transitions can be made in anticipation of a voluntary movement (Babinski 1899) or to prime specific responses to externally induced disturbances of balance (Prochazka 1989; Horak 1996). *With a focus on the contributions of the cerebral cortex and basal ganglia, the purpose of this dissertation is to understand*

how the human central nervous system (1) generates postural adjustments in anticipation of a self-initiated voluntary step, and (2) modifies postural responses to external perturbations of balance.

Anticipatory Postural Control During Voluntary Step Initiation

When moving voluntarily, the displacement of body segments generates both internal and external forces that disrupt postural equilibrium: gravity, interactions between the body and the environment (such as with the supporting surface), joint torques, and motion-dependent torques generated across linked body segments all disrupt balance during movement (Zernicke and Smith, 1996). In order to attain our movement goals safely and efficiently, the nervous system must counter-act these forces (Massion 1992). Many studies have demonstrated that, prior to a balance disturbance associated with a voluntary movement, the postural musculature necessary for maintaining equilibrium becomes selectively activated or deactivated before the prime movement in order to predictively counter-act the disturbance caused by the prime movement (the anticipatory postural adjustment, reviewed by Massion 1992). Commonly studied examples of prime movements and their anticipatory postural adjustments (APAs) include (1) a voluntary arm raise when standing (preceded by activation and deactivation of femoral and trunk muscles to maintain upright stance), (2) voluntary unloading of a weight from one arm by the other arm (preceded by deactivation of arm flexors to maintain a constant arm position), or (3) voluntary step initiation (preceded by a shift of the CoM toward the initial stance limb in order to counteract the destabilization caused by switching to a single-limb BoS). Research has shown that the characteristics of an APA are specifically suited for stabilizing the movement it precedes and are modified according to changes in

the anticipated destabilization caused by that movement (Cordo and Nashner 1982; Clement et al. 1984; Toussaint et al. 1998; van der Fits et al. 1998; Vernazza-Martin et al. 1999; Bouisset et al. 2000).

The neurophysiology underlying the coordinated generation of the APA and prime movement still remains in question, although research increasingly supports the hypothesis that separate, inter-connected neural circuits regulate the two phases of movement (Brown and Frank 1987; Nardone and Schieppati 1988; Viallet et al. 1992; Benvenuti et al. 1997; de Wolf et al. 1998; Schepens and Drew 2003). Research also suggests that the cerebral cortex and basal ganglia play vital roles in regulating the APA. Lesions of the motor and supplementary motor cortex disrupt the production of APAs prior to voluntary movements in both animals (Massion 1979) and humans (Gurfinkel and Elner 1988; Viallet et al. 1992). In addition, physiological evidence in healthy subjects suggests that a separate pre-movement cortical potential exists for planning or executing the APA, and the location of this potential is consistent with activation of the rostral (pre-) supplementary motor area and/or the caudal supplementary motor area (Saitou et al. 1996).

The basal ganglia are thought to contribute to regulating the APA because patients with Parkinson's disease (PD, a disease characterized by degeneration and dysfunction of the basal ganglia: Bernheimer et al. 1973; Damier et al. 1999), exhibit abnormally timed APAs with diminished amplitude (Martin 1967; Bazalgette et al. 1987; Viallet et al. 1987; Crenna et al. 1990; Lee et al. 1995; Gantchev et al. 1996; Burleigh-Jacobs et al. 1997; Frank et al. 2000; Rocchi et al. 2006). In addition, human intra-cranial recordings of the basal ganglia demonstrate pre-movement and movement-associated neural

potentials similar to those generated at the supplementary motor area (Rektor et al. 2001), suggesting a shared role for the basal ganglia and cerebral cortex in movement planning and execution.

Although studies examining subjects with PD or with cortical lesions have established that the cerebral cortex and basal ganglia contribute to the APA, they do not provide the resolution necessary to determine the specific contributions of the basal ganglia, motor cortex, supplementary motor cortex, and premotor cortex to coordinating the APA with the prime movement. In addition, these lesion studies only employed upper limb tasks that explicitly separate the body segments that execute the prime movement from those that execute the APA (Gurfinkel and Elner 1988; Viallet et al. 1992). Thus, it remains unclear whether the two phases of movement are regulated by a single neural circuit or by segregated neural circuits when, for step initiation, the APA and prime movement are both executed by the same limb. Further, although studies have established that PD subjects exhibit abnormal APAs, decreased step velocity, and shorter step length during step initiation (Martin 1967; Bazalgette et al. 1987; Viallet et al. 1987; Crenna et al. 1990; Lee et al. 1995; Gantchev et al. 1996; Burleigh-Jacobs et al. 1997; Frank et al. 2000; Rocchi et al. 2006), the neural substrates underlying these impairments also remain unclear.

The functional roles of different neural loci in studies utilizing subjects with chronic neural lesions remain unclear because (1) the spatial extent of the lesions are not homogenous or isolated to a specific functional region (for example, see Viallet et al. 1992), and (2) these lesions often lead to adaptive plasticity within the remaining intact nervous system (Ward 2005). Repetitive transcranial magnetic stimulation (rTMS)

provides a unique alternative for analyzing the functions of the cerebral cortex because the technique non-invasively induces a temporary dysfunction of relatively localized regions of cortex (often called a "virtual lesion", Walsh and Rushworth 1999), and multiple virtual lesions can be induced within the same subject (over separate experimental sessions) in order to assess the relative contributions of multiple neural loci to a motor behavior. To briefly explain rTMS, an electrical coil is placed tangential to an individual's scalp (over the cortex of interest), and a changing electrical current is passed through the coil to induce a magnetic field that passes into the brain tissue. This magnetic field then reciprocally induces a changing electrical current in the brain tissue, and this current induces stimulation of neurons (Ruohonen and Ilmoniemi 2002). Because the magnetic field decays exponentially with distance from the coil, the induced electrical current remains isolated to the cerebral cortex.

Stimulating repetitively allows for changes in cortical excitability that outlast the stimulation, and the frequency of stimulation determines whether cortical excitability becomes enhanced or inhibited: 1-Hz stimulations generally decrease excitability, whereas stimulations at or above 5 Hz increase excitability (Siebner and Rothwell 2003). The mechanism of inhibition induced by low-frequency (1-Hz) rTMS remains unclear, because many studies investigating these mechanisms have produced differing results (Fitzgerald et al. 2006). One possible mechanism, though, is that the inhibition represents decreased excitability of excitatory inter-neurons within the cerebral cortex due to stimulating low-threshold, pre-synaptic inhibitory inter-neurons (Romero et al. 2002). Thus, using 1-Hz rTMS to stimulate different loci of frontal motor-related cortex, we can

induce a reversible virtual lesion of each region in order to assess their relative contributions to the APA and foot-swing of a voluntary step.

Therefore, in CHAPTER 2 of this dissertation, the voluntary steps of PD subjects and healthy control subjects were tested, before and after selectively inhibiting the pre-supplementary motor area, dorso-lateral premotor cortex, and primary motor cortex with 1-Hz rTMS in order to (1) more accurately characterize the relative contributions of the basal ganglia and frontal motor-related cortices to the coordination of a voluntary step's APA and foot-swing, and (2) clarify the neural substrates that underlie impaired step initiation in PD patients.

Anticipatory Postural Control Prior to Externally Perturbed Balance

In addition to regulating voluntary disturbances of balance, an individual may also be required to respond to an externally induced loss of balance (also called an external postural perturbation). Examples of external postural perturbations include hitting and reactively avoiding obstacles, slipping while on wet, icy or compliant surfaces, or being pushed or pulled by an opponent during sport. In the laboratory, a subject's balance is often perturbed by translating or rotating a movable platform under the subject's feet (Nashner 1977; Allum 1983; Dietz et al. 1984; Horak and Nashner 1986; Woollacott et al. 1988; Nardone et al. 1990; Ackermann et al. 1991; Maki and Whitelaw 1993). These surface displacements provide a model of perturbed balance by inducing a disturbance of the CoM relative to the BoS, and because of their reproducibility, these laboratory perturbations facilitate comparisons between experimental conditions and subject groups.

To quickly characterize the postural responses that are associated with these laboratory perturbations, when the support surface is moved under a standing subject's

feet, muscles along the lower limbs and trunk activate to generate forces on the ground that counteract the forces imposed by the postural perturbation. For example, translating the floor backward induces a forward fall, and a subject responds by combining hip flexion with ankle plantarflexion in order to generate sheer and torque forces on the ground that return the body to an upright and stable position (Horak and Nashner 1986). These feet-in-place responses may also be accompanied by subsequent change-in-support responses, which include arm reaching or stepping (Maki and McIlroy 2005). The change-in-support responses extend the BoS beyond the fall of the body in order to re-acquire equilibrium.

The Contributions of the Cerebral Cortex to Anticipatory Control of Postural Responses

Historically, the neural control of postural equilibrium was thought to arise from brainstem and spinal circuits (Sherrington 1910, Magnus 1926), with little consideration for the role of the basal ganglia or cerebral cortex. The cortex and basal ganglia were not considered essential for the control of posture because animals with transections at the midbrain (thus eliminating input from the cerebral cortex and basal ganglia to lower neural centers) retain many "reflexes" that correct and maintain stance posture (Sherrington 1910, Magnus 1926); a point of view that was embodied by Magnus (1926) when he wrote, "the whole righting apparatus...is arranged sub-cortically in the brainstem, and in this way made independent of direct voluntary influences". In addition to these early reports, the idea that postural responses were regulated sub-cortically persisted with time, partly because postural responses are initiated more quickly and with less variability than cued, voluntary movements (Diener et al. 1984), suggesting further

that postural equilibrium arises from neural circuits that are separate from and subordinate to the neural circuits that underlie voluntary movements.

Although responses to postural perturbations occur more quickly than cued voluntary movements, the onset of postural responses occurs at longer latencies than those of spinal reflexes elicited by electrical stimulation (Chan et al. 1979), suggesting that postural responses exhibit greater potential for modification by neural centers located more rostral along the neural axis. Indeed, animals with cortical lesions that spare the brainstem exhibit abnormal postural responses to external perturbations (Rademaker 1931; Bard 1933; Brooks 1933; Magoun and Ranson 1938), thereby supporting the notion that postural equilibrium is influenced by the cerebral cortex. In addition, behavioral evidence implicates the cerebral cortex as contributing to postural responses because they are modified by complex cognitive-motor processes thought to be mediated by the cerebral cortex, including: ***(1)*** changes in cognitive load and attention when performing concurrent tasks (Brown et al. 1999; McIlroy et al. 1999; Maki et al. 2001; Brauer et al. 2002; Norrie et al. 2002; Quant et al. 2004; Zettel et al. 2005), ***(2)*** changes in a subject's intentions to respond with a specific strategy (McIlroy and Maki 1993a,b; Burleigh et al. 1994; Burleigh and Horak 1996; Buchanan and Horak 2003), and ***(3)*** learning and modification of postural responses with prior experience or with changes in initial conditions (Quintern et al. 1985; Horak and Nashner 1986; Diener et al. 1988; Horak et al. 1989; Ackermann et al. 1991; Maki and Whitelaw 1993, McIlroy and Maki 1993a,b; Chong et al. 1999; Henry et al. 2001; Zettel et al. 2002a,b; Tjernstrom et al. 2002). Thus, contrary to Magnus (1924), the righting apparatus is not independent of voluntary influence.

Changes in postural responses with alterations in cognitive state, initial sensory-motor conditions, or with prior warning of a perturbation all represent adjustments in "central set", defined as a modified neuro-motor state due to changes in initial contexts (Prochazka 1989). Although modified postural responses with changes in central set suggest the involvement of the cerebral cortex in anticipation of a perturbation, activity of the cerebral cortex preceding a perturbation has never been shown to relate to set-mediated changes in postural responses. Therefore, to detect this cerebral correlate for central set, in CHAPTER 3 of this dissertation, electroencephalographic readiness potentials were recorded, for the first time, prior to external postural perturbations. To determine whether readiness potentials (representing cortical activity related to movement planning and anticipation; van Boxtel and Brunia 1994) serve as a cerebral correlate for response modifications mediated by changes in central set, healthy subjects responded to postural perturbations, with and without a warning cue, and we correlated cue-related modulations of their readiness potentials with cue-related modifications in their postural responses.

The Contributions of the Basal Ganglia to Anticipatory Control of Postural Responses

The basal ganglia are also thought to contribute to postural responses because subjects with PD (a disease associated with basal ganglia pathology) exhibit impaired postural responses. Specifically, when responding to external postural perturbations, PD subjects exhibit co-contractions of antagonistic muscles and stiffened joint displacements that render them less stable, rather than exhibiting coordinated muscle activity that generates counter-active forces sufficient for balance recovery (Carpenter et al. 2004a; Jacobs et al. 2005a). Compared to healthy control subjects, PD subjects also fail to adapt

their postural responses when (1) intending to respond with different strategies, (2) transitioning from perturbations that induce a forward fall to perturbations that induce a backward fall, and (3) modifying initial stance configuration (Horak et al. 1992; Beckley et al. 1993; Bloem et al. 1995; Chong et al. 2000; Horak et al. 2005). Therefore, the basal ganglia seem to play an essential role in producing context-specific responses to postural perturbations.

Although studies have shown changes in postural responses with changes in central set, it remains unclear whether this type of anticipatory response modification can occur when responding to perturbations that are unpredictable in timing, amplitude, and direction. Because perturbations experienced outside the laboratory can be (at least to some extent) unpredictable, it is essential to understand human response strategies employed during an unpredictable loss of balance in order to clarify whether changes in central set – and the neural centers involved in set-mediated response modifications – influence postural responses in unpredictable situations.

Therefore, in CHAPTER 4 of this dissertation, healthy subjects were tested when responding to perturbations with unpredictable characteristics, without the ability to pre-select a response strategy, in order to determine how online response selection affects postural stability in response to external postural perturbations. To force subjects to select their response during a perturbation, the subjects were asked to respond according to the presentation of one of two possible visual cues that, at the onset of perturbation, instructed one of two potential strategies. Based on the findings of this study, CHAPTER 4 also includes an APPNEDIX that presents results from a previous experiment, demonstrating that PD subjects exhibit response characteristics similar to the responses of

healthy subjects when healthy subjects are unable to pre-select their response strategy. Together, then, the two experiments suggest that the basal ganglia contribute to the pre-selection of postural responses based on central set, and that pre-selection can occur when responding to unpredictable perturbation characteristics.

Although PD subjects exhibit difficulty generating context-specific postural responses with changes in central set (Horak et al. 1992; Beckley et al. 1993; Bloem et al. 1995; Chong et al. 2000; Horak et al. 2005), studies during voluntary stepping suggest that, with explicit sensory cues, PD subjects can improve step amplitude (Martin, 1967; Bagley et al. 1991; Burleigh-Jacobs et al. 1997; Suteerawattananon et al. 2004; Morris et al. 2005). Thus, compared to changes in central set through modified stance configuration or internally-induced changes in intention, the use of pre-existing or expected sensory cues seems to represent a unique case in which PD subjects can use modified central set to change their movement patterns. This sensory-cued improvement in motor control is thought to be possible because external cues elicit activation of the dorso-lateral premotor cortex (and its associated circuitry, including parietal cortex and cerebellum) to compensate for dysfunction of circuits that include the supplementary motor area and basal ganglia, which are thought to underlie the hypometria and bradykinesia exhibited by PD subjects (Hanakawa et al. 1999a; Cunnington et al. 2001). It is not clear, however, if this "kinesie paradoxale" (paradoxical movement, Souques 1921) is unique to voluntary movement, or if PD subjects can also utilize this cue-dependent change in central set to improve their postural responses to external perturbations of balance.

Therefore, CHAPTER 5 reports on the compensatory stepping (change-in-support) responses of PD subjects to postural perturbations, when the subjects responded

with and without a visual target that instructed step placement, in order to determine whether PD subjects can use visual targets to modify their compensatory steps, as they can for voluntary steps.

Together, CHAPTERS 2-5 help specify the contributions of the cerebral cortex and basal ganglia to anticipatory postural control during both voluntary and externally triggered postural perturbations. Based on the data from these studies, in the Summary and Conclusions of CHAPTER 6, I will present neural models for the control of voluntary step initiation and for the control of externally triggered postural responses, with insights into the neuropathology responsible for some of the postural impairments exhibited by PD subjects.

CHAPTER 2

Disruption of the Cerebral Cortex Modifies Anticipatory Postural Control During Human Voluntary Step Initiation

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ABSTRACT

The pre-supplementary motor area (pre-SMA), dorso-lateral premotor cortex (dPMC), and primary motor cortex (M1) are thought to contribute to step initiation, but their precise contributions to generating the postural phase and swing phase of a step are unclear. In addition, subjects with Parkinson's disease (PD) exhibit impaired step initiation, but the neural substrates underlying their impairments are also unclear. To clarify how the pre-SMA, dPMC, and M1 contribute to step initiation and to determine whether abnormal function of these areas contributes to impaired step initiation in PD subjects, we tested 8 PD subjects and 8 healthy control subjects performing self-initiated voluntary steps, before and after inhibiting the pre-SMA, dPMC, and M1 (in separate sessions) with 1-Hz, sub-threshold repetitive transcranial magnetic stimulation. The results showed decreases in the duration of the anticipatory postural adjustment (the APA, a stabilizing weight shift toward the stance limb before foot-lift) and in the duration of the step's swing phase for one trial after pre-SMA stimulation. Stimulating the dPMC also shortened swing-phase durations, whereas stimulating M1 decreased APA amplitudes. The severity of the PD subjects' symptoms correlated with the extent to which pre-SMA stimulation affected APA durations. The results suggest that the pre-SMA coordinates the timing of both the postural phase and swing phase of a voluntary step, the dPMC contributes to the timing of the swing phase, and the M1 contributes to the amplitude of the postural phase. The results support the hypothesis that PD subjects exhibit impaired APAs, in part, due to a progressive dysfunction of the pre-SMA.

INTRODUCTION

Patients with Parkinson's disease (PD) are at an increased risk for falls, and they fall most during dynamic transitions in their postural orientation (Bloem et al. 2001). Step initiation represents such a transition, and PD subjects exhibit impaired step initiation during both the postural phase and swing phase of a step taken from quiet stance (Crenna et al. 1990; Gantchev et al. 1996; Burleigh-Jacobs et al. 1997; Rocchi et al. 2006). Specifically, compared to healthy control subjects, PD subjects exhibit diminished, prolonged, and more variable anticipatory postural adjustments (APAs; increased pressure under the swing limb to displace and stabilize the center of mass over the stance limb in preparation for a step). In addition, during the swing phase of a step, PD subjects exhibit slowed step velocity and shortened step length. The neural substrates underlying these impairments, however, are not clear and need to be better understood in order to identify behavioral, pharmacological, and surgical therapies aimed to improve impaired step initiation in PD subjects.

Relatively little is understood about how parkinsonian neuropathology contributes to step initiation, in part, because little detail is available regarding the neural control of step initiation in healthy subjects, particularly at the level of the cerebral cortex. The pre-supplementary motor area (pre-SMA), SMA proper, dorso-lateral premotor cortex (dPMC), and primary motor cortex (M1) have all been identified as contributing to gait and to step initiation using single-photon or positron emission tomography (Hanakawa et al. 1999a,b; Malouin et al. 2003). Although these imaging studies identify cortical involvement in gait and in step initiation, they could not detail the relative contributions of these cortical regions to the timing and amplitude of the postural phase and swing

phase of step initiation. Lesion studies in both animals (Massion 1979) and humans (Gurfinkel and Elner 1988; Viallet et al. 1992) have shown that loss of the pre-SMA, SMA proper, and M1 leads to diminished APA amplitudes in preparation for limb movements, but these studies were not specific to step initiation and are subject to long-term compensatory changes subsequent to a neural lesion (Ward 2005). Therefore, we tested 8 PD subjects and 8 healthy control subjects during voluntary step initiation, before and after selectively inhibiting the pre-SMA, dPMC, and M1 with sub-threshold, 1-Hz repetitive transcranial magnetic stimulation (rTMS) in order to determine (1) the relative contributions of these regions to the generation of the postural and swing phases of step initiation, and (2) the neural substrates underlying impaired step initiation in PD subjects.

Consistent with lesion studies (Gurfinkel and Elner 1988; Viallet et al. 1992), we hypothesized that the pre-SMA and M1 would contribute to generating the APA, and we predicted that subjects would alter their APA amplitude and duration after rTMS to these regions. We further predicted that pre-SMA stimulation would also alter swing duration, because the pre-SMA has been implicated in coordinating the timing of complex motor sequences (Boecker et al. 1998; Kennerley et al. 2004) and would therefore act as a global coordinator for sequencing both the postural phase and swing phase of a step. We also hypothesized that the dPMC would contribute to generating the swing phase of a step because this region is activated during continuous gait, particularly when adapting the swing phase (Hanakawa et al. 1999a,b).

In addition, we hypothesized that PD subjects exhibit impaired gait initiation due to dysfunction of the pre-SMA because PD subjects exhibit (1) selective degeneration of cortico-cortical pyramidal neurons in the pre-SMA (MacDonald and Halliday 2002), (2)

abnormal pre-SMA function during sequential movements (Eckert et al. 2006), and (3) diminished pre-movement electroencephalographic potentials during step initiation (Vidailhet et al. 1993), which are thought to contribute to the generation of APAs (Saitou et al. 1996). We, therefore, predicted that APA durations and amplitudes would be altered by pre-SMA stimulation in PD subjects, and that the extent of these stimulation-induced changes would relate to the severity of their motor symptoms, because increasing motor impairment would associate with escalating pre-SMA dysfunction, which would increase a PD subject's susceptibility to rTMS. Further, we hypothesized that PD subjects compensate for pre-SMA dysfunction (and their resulting APA impairments) with activation of the dPMC (Hanakawa et al. 1999a; Cunnington et al. 2001). If activity of the dPMC substitutes for the dysfunction of the pre-SMA, then we predicted that rTMS over the dPMC would affect the production of APAs in severe PD subjects, but not in control subjects. Alternatively, as their disease severity progresses, PD subjects may become increasingly dependent on the dPMC for generating the swing phase of a step in order to compensate the swing phase for impaired postural control. In this case, we predicted that the severity of the PD subjects' motor symptoms would relate to the extent that rTMS over the dPMC affects foot-swing.

METHODS

Subjects

Eight patients with idiopathic PD (Hughes et al. 1992) and 8 healthy control subjects participated. Each group consisted of 7 males and 1 female. Subjects were chosen to ensure similar characteristics. Consequently, no significant differences were evident between the PD and control groups, respectively, in mean (± sd) age (62 ± 11

versus 64 ± 10 yr), height (176 ± 6 versus 174 ± 11 cm), and weight (74 ± 10 versus 81 ± 9 kg) [$T = 0.34\text{-}1.58$; $P = 0.14\text{-}0.74$].

All PD subjects were tested at least 12 hours after their last dose while in the practical "off" medication state. Subjects with other neurological, muscular, or psychiatric disorders (e.g., diabetes, peripheral neuropathies, uncorrected visual problems, hearing problems, joint pain, arthritis, fracture, stroke, seizure, migraine, or frequent severe headaches) were excluded. Subjects with surgical implants and PD patients with significant postural tremor, dysmetria, or dementia were also excluded. Prior to each experiment, a neurologist trained in movement disorders evaluated the severity of the PD subjects' motor symptoms using the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn & Yahr scale (Hoehn and Yahr 1967; Fahn and Elton 1987). Total scores ranged from 9-28 on the motor exam of the UPDRS and from 2-3 on the Hoehn & Yahr scale. Based on these evaluations, all PD subjects exhibited mild to moderate PD with limb rigidity, impaired gait, and bradykinesia.

All subjects gave written informed consent to participate in the protocol, consistent with the Helsinki agreement. The Institutional Review Board of Oregon Health & Science University approved the protocol.

Stepping Protocol

The task was for the subjects to stand on a platform with each foot on a force plate and then to take self-initiated, forward voluntary steps with their eyes closed. The subjects were asked to step without cues and with their eyes closed because previous studies have demonstrated that PD subjects increase APA amplitude, step length, and step velocity toward healthy values when provided with auditory, visual, or somatosensory

cues (Burleigh-Jacobs et al. 1997; Lewis et al. 2000; Morris et al. 1996, 2005; Suteerawattananon et al. 2004). In addition, when comparing neural activation during cued and self-initiated movements, cued movements preferentially activate the dPMC in PD subjects (Hanakawa et al. 1999a; Cunnington et al. 2001). Thus, in order to assess the neural circuitry responsible for healthy self-initiated stepping and to identify the neural substrates underlying impaired self-initiated stepping in PD subjects, the subjects performed the steps with their eyes closed and without sensory cues.

The subjects stood in a stance width that equaled 11 % of their body height as measured from the center of one heel to the center of the other. The perimeters of the subjects' feet were marked with tape to ensure that stance width remained consistent throughout the experiment. We monitored the force distribution of the 2 force plates under the subjects' feet by an oscilloscope to ensure that the subjects stood with an equal amount of weight under each foot. To prevent the subjects from falling to the ground, they were harnessed to a ceiling-mounted track that did not provide any support during the task unless they began to fall. The subjects also held a small, lightweight wooden dowel (2 cm in diameter, 66 cm long, and 113 g in weight) behind their back with both hands to prevent their arms from occluding reflective markers that were placed on their joints for analyzing the displacements of their body segments.

The subjects were instructed to stand upright, with their feet within the perimeters of the tape placed on the platform, and to distribute their weight evenly under each foot. The subjects were then instructed to close their eyes and, after a self-selected amount of time, to step forward with a pre-determined stepping foot, followed by a matching step with the initial stance limb to bring their feet back to parallel. Recording began for each

trial when the subjects were instructed to close their eyes. The PD subjects stepped with the leg most affected by the disease, as determined from the UPDRS motor exam, and the control subjects stepped with the same leg as their demographically matched PD subject. Each subject performed 9 steps before rTMS and 9 steps after rTMS. The subjects performed 3 sessions, one each for rTMS over the pre-SMA, dPMC, and M1. The order of the sessions was counter-balanced across subjects. The sessions were separated by at least 7 days, and the PD subjects always performed the experiment during morning hours. In addition to performing voluntary steps with their eyes closed, in an attempt to determine the effects of rTMS on other stance and stepping behaviors, the subjects also performed visually cued voluntary steps with their eyes open, forced steps in response to backward translations of the platform under their feet, and quiet stance trials with their eyes closed. The tasks were ordered such that the subjects first performed 3 trials of self-initiated steps, followed by 3 cued steps, 3 forced steps, and then one 30-second trial of quiet stance. This sequence was then repeated twice more to achieve a total of 9 self-initiated steps, 9 cued steps, 9 forced steps, and 3 trials of quiet stance. The first 3 self-initiated steps were, therefore, always ordered before the other tasks and, because the significant effects of rTMS were only evident for one trial after stimulation, the analyses for this study pertain only to the self-initiated steps with eyes closed.

rTMS Protocol

After completing the stepping protocol, the subjects sat upright in an adjustable dental chair mounted on locking wheels in order for us to prepare them for rTMS. For each subject, we first established the position of the skull's vertex according to the 10/20 international system of electrode placement (Jasper 1958). With a wax pencil, we then

created a 1-cm grid of lines on the subjects' scalp, with the lines drawn parallel and perpendicular to a mid-sagittal line drawn through the nasion, vertex, and inion. We located the optimal positions to stimulate the tibialis anterior (TA, a distal leg muscle) and the first dorsal interosseous (FDI, a hand muscle) ipsilateral to each subject's chosen stepping limb using single-pulse stimulations from a Magstim rapid rate device with a 70-mm, figure-eight, cooled-coil system (Magstim Company Ltd, Whitland, Dyfed, UK). We recorded muscle activity using pre-amplified differential electromyography from silver, silver-chloride electrodes placed over the muscles on the skin's surface. To find the optimal position (or hotspot) for stimulating the FDI, we began with the stimulator at 65 % of its maximal output and with the coil positioned 4 cm anterior and 4 cm lateral from the vertex, contralateral to the FDI muscle being stimulated. We oriented the coil so that its handle pointed approximately 45 degrees postero-lateral from the mid-sagittal line (Werhahn et al. 1994). We then applied stimulations at 1-cm increments, progressing to 0.5-cm increments, to find the scalp location at which we could elicit motor evoked potentials (MEPs) of maximal amplitude and shortest latency from the FDI muscle. If necessary, to prevent saturating FDI activity or to prevent a complete loss of FDI stimulation, the intensity of the stimulus was adjusted from the 65% output to elicit graded levels of FDI activation over several locations.

To find the TA muscle's hotspot, we began with the stimulator at 80 % of its maximal output and with the coil positioned at the vertex. We oriented the coil so that its handle pointed approximately perpendicular to the mid-sagittal line, ipsilateral to the TA muscle (Priori et al. 1993; Terao et al. 1994). We then applied stimulations at 1-cm increments, progressing to 0.5-cm increments, to find the scalp location at which we

could elicit MEPs of maximal amplitude and shortest latency from the TA muscle. If we could not activate the TA muscle at rest, we asked the subjects to dorsiflex the ankle in order to stimulate the muscle during contraction. If necessary, to prevent saturating TA activity or to prevent a complete loss of stimulation, the intensity of the stimulus was adjusted from the 80% output to elicit graded levels of TA activation over several locations.

After locating the stimulation hotspots for the TA and FDI muscles, we determined the threshold for stimulating the FDI muscle at rest. The rest motor threshold was defined to be the stimulation intensity that elicited MEPs of at least 50 μV in five out of ten consecutive trials of single-pulse stimulations (Rossini et al. 1994). This threshold was then used to determine the stimulation intensity that each subject would receive during rTMS. Although the subjects performed a stepping task, we chose to base our rTMS intensities on the FDI muscle because, in our experience, the FDI requires lower stimulation intensity than the TA to evoke muscle activation, and the FDI elicits more stable thresholds than the TA muscle when assessed on separate days. Therefore, using the FDI muscle's threshold, we could produce more consistent stimulation intensities across the experimental sessions (which were separated by several days) and employ lower stimulation intensities that are less likely to induce adverse effects.

After determining the subjects' rest motor threshold, we prepared the subjects for rTMS by reclining them in the adjustable chair and then fitting an elastic band around their head until the subjects felt comfortable while maintaining their head in a stable position (Fig. 1A). For each subject, the intensity of stimulation during rTMS was set to 80% of the FDI's rest motor threshold recorded during that day's session. Repetitive

TMS was delivered at 1 Hz for 30 minutes (1800 pulses) through the same stimulator and coil as when locating hotspots and determining motor thresholds. Sub-threshold, 1-Hz stimulations were chosen to maximize the safety of our protocol (Wassermann 1998), and because these stimulation parameters are thought to inhibit the region of cortex located just below the coil's center (Touge et al. 2001). In addition, sub-threshold, low frequency rTMS, compared to supra-threshold rTMS, may decrease spread of excitation to adjacent regions (Lang et al. 2006), thereby helping to ensure a more isolated stimulation to the regions of interest. Every 2.5 to 5 minutes during rTMS, we monitored the subjects to ensure they remained awake and that their head's position hadn't shifted.

When stimulating the pre-SMA, the coil was positioned 5 cm anterior from the TA muscle's hotspot along the mid-sagittal line. These coordinates are consistent with studies using image-guided TMS or functional imaging to localize the pre-SMA (Rushworth et al. 2002; Mayka et al. 2006). The coil was oriented with its handle pointing posterior along the mid-sagittal line (Cunnington et al. 1996; Obhi et al. 2002; Verwey et al. 2002). We chose the pre-SMA as a target site, rather than the SMA proper, because (1) the pre-SMA is located farther from the dPMC and M1, which helps ensure that the stimulation did not spread to the other regions of interest, and (2) in PD subjects, the pre-SMA exhibits anatomical degeneration of cortico-cortical pyramidal neurons, even with mild to moderate disease severity (MacDonald and Halliday 2002).

When stimulating the dPMC, the coil was positioned 2.5 cm anterior from the FDI muscle's hotspot, with the handle oriented approximately 45 degrees postero-lateral from the mid-sagittal line (Gerschlager et al. 2001; Chen et al. 2003). When stimulating the M1, the coil was positioned at the TA muscle's hotspot, with the handle perpendicular

to the mid-sagittal line and ipsilateral to the subjects' chosen stepping limb (Priori et al. 1993; Terao et al. 1994). For all sessions, the coil was held in place during rTMS by an adjustable clamp.

To confirm that our measured scalp locations placed the coil over the intended cortical regions, we obtained an anatomical magnetic resonance image (MRI) of one subject's brain for use with image-guided TMS. The structural MRI was acquired with a 1.5 tesla magnet using multi-echo, multi-planar acquisition. Images were obtained in the coronal plane at 4-mm thickness. For image-guided TMS, the subject's anatomical MRI was stereotactically co-registered with the subject's head using a Polaris infrared tracking system (Northern Digital, Waterloo, Canada) interfaced with Brainsight software (Rogue Research, Montreal, Canada). The position of the TMS coil was then monitored with respect to the subject's brain, and we acquired digital images of the coil's locations when it was centered over the hotspots and rTMS locations outlined in the methods above.

During the experimental sessions, when the 30 minutes of rTMS was complete, a trial was recorded on the computer to provide a timestamp of rTMS completion (1-minute resolution). We then electronically adjusted the chair to bring the subjects to an upright position. While the subjects remained in the chair, we moved them to the force platform in order to minimize how much the subjects actively moved before resuming the stepping protocol, because voluntary contraction can normalize cortical excitability after rTMS conditioning (Touge et al. 2001). After preparing the subjects on the force platform, they repeated the stepping protocol outlined above.

Data Collection and Analyses

Center of Pressure.

To capture the subjects' APAs, we recorded the lateral displacements of their center of pressure (CoP) from two force plates, one under each of the subjects' feet. Each force plate was equipped with 4 vertical and 2 horizontal strain gauge transducers. Force signals were amplified and sampled at 480 Hz. Total-body lateral CoP was calculated from the difference in loading of the right and left force plates as previously reported by Henry et al. (1998). Lateral CoP displacements were calculated after subtracting an initial CoP position, which was defined as the average CoP position over the first 500 ms of recording.

APAs were defined from the lateral CoP displacements that occurred from the moment that the platform began moving to the moment when the big toe of the stepping foot came off the force plate. The onset of an APA was defined manually with an interactive plotting function programmed in Matlab software (Mathworks, Inc., Natick, MA, USA). Using this plotting function, we identified the moment when the CoP began to displace toward the swing limb prior to foot-lift. When identifying APA onsets, the CoP plots were unlabeled and randomly ordered to prevent biased identifications. The duration of an APA was calculated as the time when the lateral CoP displacement came back to its initial position just prior to when a subject lifted a foot off the force plate, minus the time when the APA began. Peak APA amplitudes were defined as the maximum lateral displacement of the CoP toward the swing limb just prior to foot-lift.

Kinematics

To capture the characteristics of a step's swing phase, a reflective marker was placed on the tip of the subjects' first toe. Although not analyzed in this report, reflective markers were also placed at the subjects' ankles, knees, hips, shoulders, elbows, and

wrists, as well as on the head and on the platform. A high-resolution Motion Analysis System (Motion Analysis Corp., Santa Rosa, CA, USA), with 8 video cameras sampling at 60 Hz, provided 3-dimensional spatial coordinate information about the displacement of the subjects' body segments.

Using the marker placed on the stepping foot's toe, we quantified the length of the subjects' steps, the duration of a step's swing phase, and the peak velocity of the foot's forward swing. The duration of a step's swing phase was defined between the time when the toe left the ground (at the beginning of the step) and the time when it subsequently reached the ground (at the end of the step). These step times were defined manually using the interactive plotting function programmed in Matlab software. We identified the beginning of a step's swing phase as the moment when the toe marker began its vertical displacement, and we identified the end of the swing phase as the moment when the toe marker crossed back under its initial position (defined as the marker's average position during the first 500 ms of recording). When identifying step times, the marker displacement plots were unlabeled and randomly ordered to prevent biased identifications. Step length was defined as the anterior-posterior displacement of the toe marker during a step's swing phase. The peak velocity of a subject's step was determined from the derivative of the toe marker's anterior-posterior displacement during the swing phase of the step.

Statistical Analyses

We calculated each subject's average APA duration, peak APA amplitude, swing-phase duration, peak foot-swing velocity, and step length prior to rTMS. To determine whether these measures were different between the PD subjects and control subjects, and

whether each measure was stable across experimental sessions before stimulation, two-factor mixed-model ANOVAs tested for differences in each measure across groups (PD versus control) and experimental sessions (for rTMS over the pre-SMA, dPMC, and M1).

Graphical analysis of the results determined that the effects of rTMS on voluntary step initiation lasted for only one trial after stimulation. Consequently, our analyses tested for differences between a measure's mean value before stimulation and the value from the first trial after stimulation. To test for stimulation effects between the PD subjects and control subjects, for each site of stimulation, we performed a two-factor mixed-model ANOVA testing for differences in the dependent measures across groups (PD versus control) and due to stimulation (before versus after). Rather than evaluating stimulation effects with a 10- or 18-level factor that compares each individual trial with all other individual trials, we compared the mean value before rTMS with the value of the first trial after rTMS because this 2-level factor improved our statistical power given our small subject sample. The subject sample was small because our exclusion criteria did not allow testing any subject with atypical parkinsonism, surgical implants, or any impairment (other than PD) that might confound balance or the safe use of rTMS. Therefore, in order to provide a fair statistical evaluation, using the mixed-model ANOVA composed of 2-level factors for group and trial, we also compared a measure's value from each trial before stimulation with that measure's mean value before stimulation in order to ensure inter-trial variability exhibited random fluctuation and that significant differences were isolated to after rTMS. We applied a Greenhouse-Geisser epsilon correction to all ANOVA statistics, which adjusts the degrees of freedom applied to the F statistic according to the level at which the data did not meet the assumption of

sphericity (Greenhouse and Geisser 1959). All reported F statistics represent corrected values, and significance was defined as a corrected *P*-value of less than or equal to 0.05.

When rTMS over a single site was found to affect multiple measures, we used Pearson correlation coefficients to determine whether the effects were related. A lack of correlation among how two measures are affected by rTMS to the same site suggests a neural representation of the two measures as two separate motor functions coordinated in parallel, whereas correlated effects of rTMS may signify either (1) a neural representation of the two behaviors as one motor program, or (2) that a change in one behavior consequently alters another. Pearson coefficients were also analyzed to determine whether the effects of rTMS on the stepping behavior of PD subjects correlate with the clinical severity of the subjects' lower-body motor symptoms. The clinical severity of a PD subject's lower-body motor symptoms was defined as the sum of the UPDRS items of leg tremor, leg rigidity, leg agility, arise from chair, posture, postural stability, gait, and body bradykinesia (Jacobs and Horak 2006).

RESULTS

Locations and Intensities of Stimulations

The session of image-guided TMS confirmed that our measures located the FDI and TA muscles' hotspots over the M1 of the pre-central gyrus, and that the locations for rTMS over the pre-SMA and dPMC were consistent with previous reports localizing these regions (Fig. 1B; Gerschlager et al. 2001; Rushworth et al. 2002). Relative to the vertex of each subject's skull, the anterior and lateral positions of the FDI and TA muscles' hotspots were not significantly different between the PD subjects and control

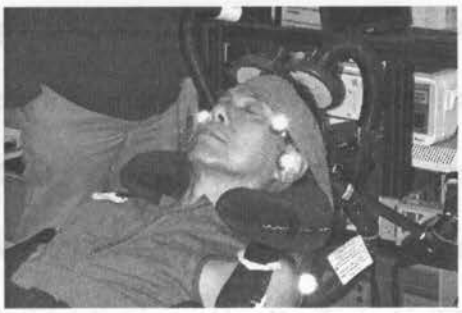
subjects, although the hotspot of the PD subjects' FDI muscle did trend toward a more anterior location [main effect of group: $F = 0.09\text{-}4.03$, $P = 0.066\text{-}0.77$] (Fig. 1C).

Rest motor thresholds were significantly lower in the PD subjects compared to the control subjects [main effect of group: $F = 9.53$, $P = 0.009$] (Fig. 1D). Rest motor thresholds were also unintentionally lower during sessions for rTMS over the M1 compared to the sessions for rTMS over the pre-SMA or dPMC [main effect of session: $F = 4.52$, $P = 0.02$], and this difference was largely isolated to the control subjects [interaction effect of group and session: $F = 3.39$, $P = 0.051$] (Fig. 1D).

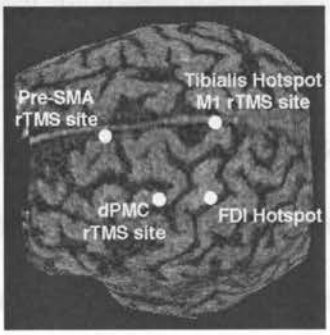
Based on timestamps associated with the electronic files for each trial, the first stepping trial was initiated from 0.57 to 1.25 minutes after rTMS for the control subjects, and from 1.13 to 1.43 minutes for the PD subjects. These first-trial onset latencies were not significantly different between experimental sessions [main effect of session: $F = 0.70$, $P = 0.49$] or between groups [main effect of group: $F = 3.64$, $P = 0.08$], although there was a trend for the PD subjects to begin at a later latency than the control subjects. The sessions' average latencies to begin the second trial after rTMS ranged from 1.00 to 1.63 minutes for the control subjects, and from 1.13 to 1.75 minutes for the PD subjects [main effect of group: $F = 1.51$, $P = 0.24$]. Thus, the first two trials began, on average, within 2 minutes after completing rTMS.

Stimulation characteristics

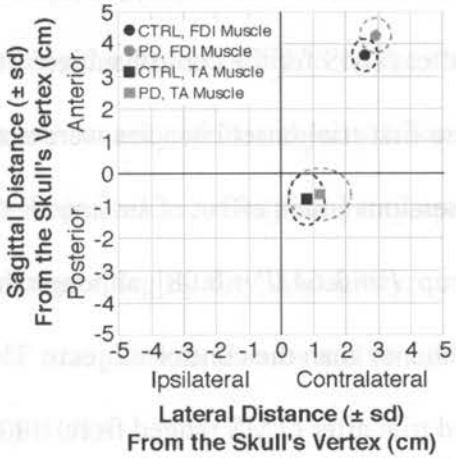
A. An Individual Subject Receiving rTMS



B. Cortical Locations of an Individual's Stimulations and Hotspots



C. Mean Positions of Stimulation Hotspots For the FDI and TA Muscles



D. Mean Thresholds for Stimulating the FDI Muscle at Rest

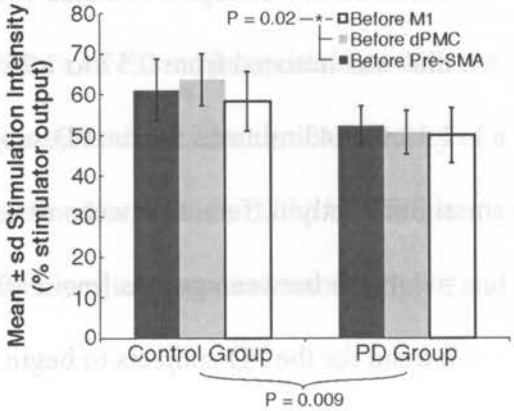


Fig. 1. Stimulation characteristics (A) A subject receiving rTMS over the pre-SMA. The subject sat reclined in an adjustable dental chair with a memory foam pillow supporting his head and neck. An elastic band was also wrapped around the forehead to prevent excessive movement. The air-cooled coil of the Magstim rapid device was held in place by an adjustable clamp. **(B)** Image-guided TMS, demonstrating the cortical locations of stimulation. The TA and FDI muscles' hotspots were located over the pre-central gyrus presumed to represent the primary motor cortex. The locations for the dPMC and the pre-SMA are also consistent with previous reports locating these regions (Gerschlager et al. 2001; Rushworth et al. 2002). **(C)** The average (sd) hotspot locations for the PD subjects (gray symbols and dashed lines) and the control subjects (black symbols and dashed lines), relative to the vertex of the skull. The squares represent the hotspots for stimulating the TA muscle, and circles represent those for stimulating the FDI muscle. **(D)** The average (sd) rest motor thresholds of the FDI muscle during the sessions for rTMS over the pre-SMA (dark gray bars), dPMC (light gray bars), and M1 (white bars). Repetitive TMS was applied at 80 % of each subject's rest motor threshold for that day's session. The p-value below the chart represents the main effect of group differences, and the p-value next to the inset legend represents the main effect of session differences, with the asterisk next to the session that was significantly different from the other sessions.

APA and Step Characteristics Before Stimulation

Compared to the control subjects, the PD subjects exhibited slow (bradykinetic) steps with impaired APA control. Specifically, during the postural phase of a step, although APA durations were, on average, similar among PD subjects and control subjects [main effect of group: $F = 1.49$, $P = 0.24$], APA durations were more variable for the PD subjects [main effect of group: $F = 4.77$, $P = 0.048$] (Fig. 2A and B). The PD subjects also exhibited smaller peak APA amplitudes than the control subjects [main effect of group: $F = 12.8$, $P = 0.003$] (Fig. 2C). In addition, during the swing phase of a step, the PD subjects exhibited slower peak foot-swing velocities than the control subjects [main effect of group: $F = 5.27$, $P = 0.039$] (Fig. 2D). Swing-phase durations and step lengths, however, were similar among the PD subjects and control subjects [main effects of group: $F = 0.71$-1.56, $P = 0.23$-0.42] (Fig. 2E and F). It seemed counter-intuitive, however, for the PD subjects to have similar average step lengths as the control subjects, when the PD subjects also exhibited similar swing durations but slower swing velocities. Therefore, for the PD subjects, we correlated the grand mean of these measures from all 3 sessions in order to determine whether one behavioral measure compensated for another. The results demonstrated that the PD subjects with the shortest swing durations exhibited the fastest swing velocities, and the PD subjects with the longest swing durations exhibited the slowest swing velocities [Pearson $r^2 = 0.54$, $P = 0.04$].

Each measure was stable across the experimental sessions: no significant differences were evident between the experimental sessions for APA duration, peak APA amplitude, peak foot-swing velocity, swing-phase duration, and step length [main effects of session: $F = 0.34$-2.95, $P = 0.70$-0.095] (Fig. 2).

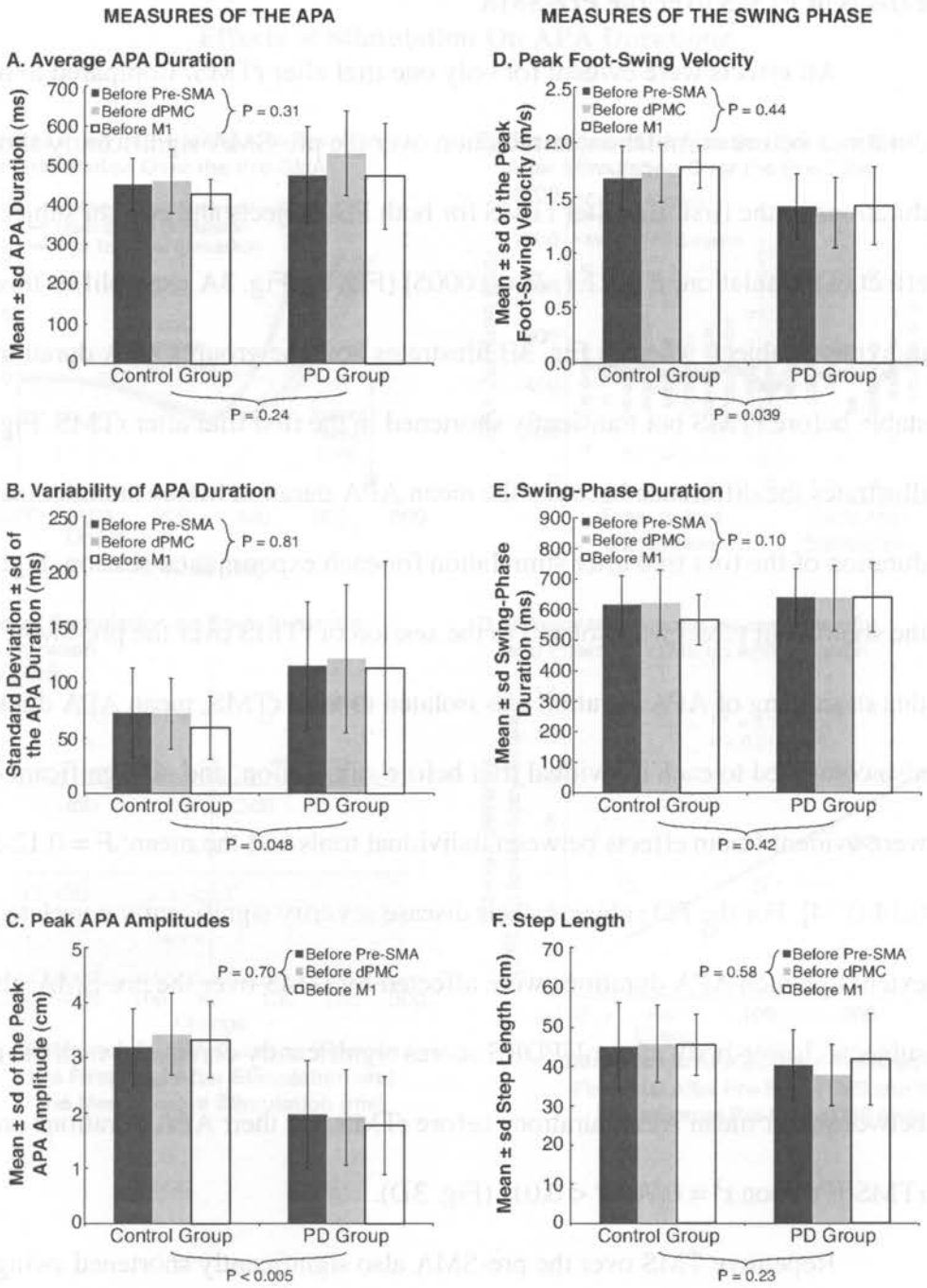


Fig. 2. Characteristics of the steps' postural phase and swing phase prior to stimulation. The charts illustrate each group's average (sd) **(A)** APA duration, **(B)** inter-trial variability of APA duration, **(C)** peak APA amplitude, **(D)** peak foot-swing velocity, **(E)** swing-phase duration, and **(F)** step length prior to rTMS during the pre-SMA (dark gray bars), dPMC (light gray bars), and M1 (white bars) sessions. P-values below the charts represent main effects for group differences, those next to the inset legends represent main effects for session differences.

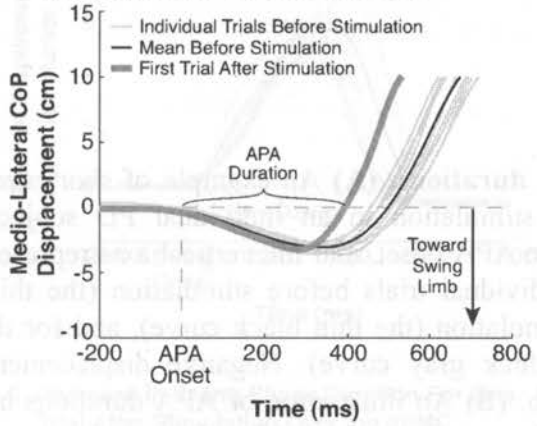
Effects of rTMS over the Pre-SMA

All effects were evident for only one trial after rTMS. Compared to mean APA durations before stimulation, stimulation over the pre-SMA significantly shortened APA durations in the first trial after rTMS for both PD subjects and control subjects [main effect of stimulation: $F = 21.1$, $P < 0.0005$] (Fig. 3). Fig. 3A exemplifies this effect for an individual subject, whereas Fig. 3B illustrates how the group's APA durations were stable before rTMS but transiently shortened in the first trial after rTMS. Fig. 3C illustrates the difference between the mean APA duration before stimulation and the APA duration of the first trial after stimulation for each experimental session, highlighting that the significant effect was isolated to the session of rTMS over the pre-SMA. To ensure this shortening of APA duration was isolated to after rTMS, mean APA durations were also compared to each individual trial before stimulation, and no significant differences were evident [main effects between individual trials and the mean: F = 0.12-2.48, P = 0.14-0.74]. For the PD subjects, their disease severity significantly correlated with the extent to which APA durations were affected by rTMS over the pre-SMA: the PD subjects' lower-body motor UPDRS scores significantly correlated with the difference between their mean APA durations before rTMS and their APA durations one trial after rTMS [Pearson $r^2 = 0.70$, $P < 0.01$] (Fig. 3D).

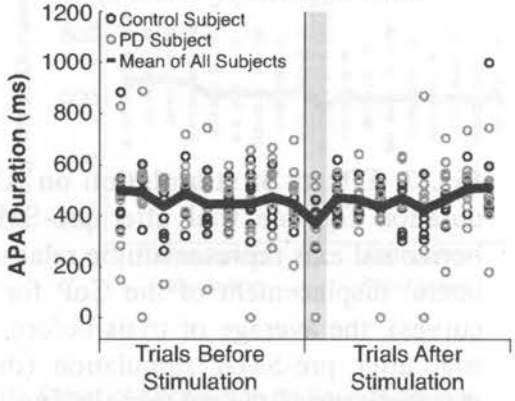
Repetitive TMS over the pre-SMA also significantly shortened swing-phase durations in both PD subjects and control subjects [main effect of stimulation: F = 9.48, P = 0.008] (Fig. 4A, B, D). Fig. 4A exemplifies this effect for an individual subject. Fig. 4B illustrates how the groups' swing durations transiently shortened for the first trial after rTMS. In the fifth trial performed before stimulation, however, the subjects' swing

Effects of Stimulation On APA Durations

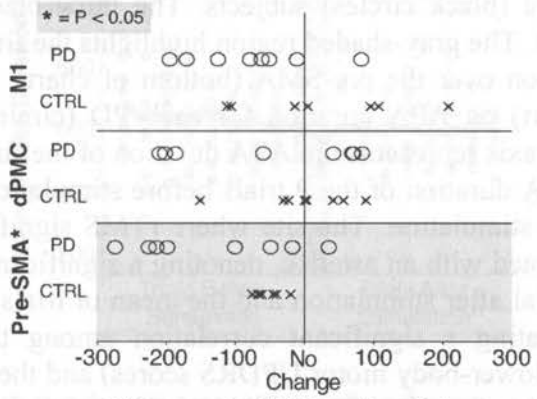
A. Decrease in an Individual's APA Duration After Stimulation Over the Pre-SMA



B. Decrease in APA Duration For One Trial After Stimulation Over the Pre-SMA



C. Effect of Stimulation on Each Subject's APA Duration



D. Relationship Among Disease Severity and Effects of rTMS on APA Duration

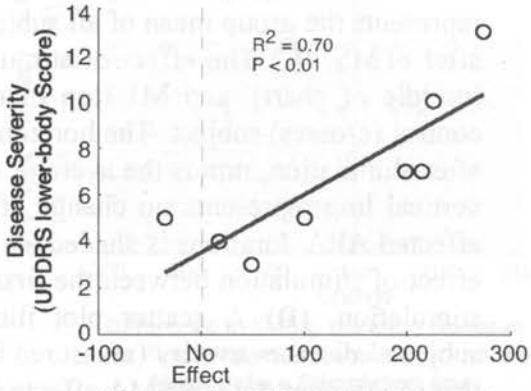
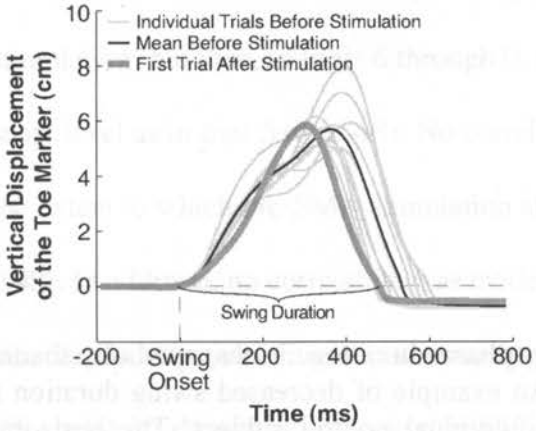


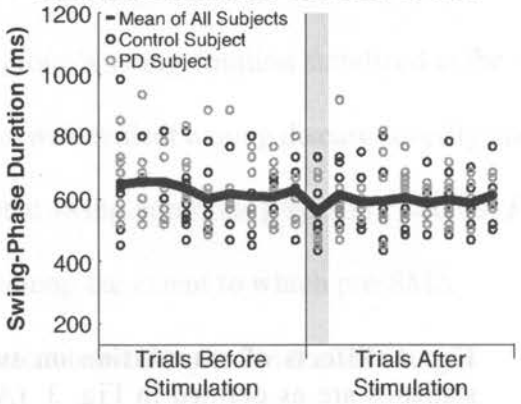
Fig. 3. Effects of stimulation on APA durations. **(A)** An example of shortened APA duration for one trial after pre-SMA stimulation in an individual PD subject. The horizontal axis represents time relative to APA onset, and the vertical axis represents the lateral displacement of the CoP for individual trials before stimulation (the thin gray curves), the average of trials before stimulation (the thin black curve), and for the first trial after pre-SMA stimulation (the thick gray curve). Negative displacements are directed toward the subject's swing limb. **(B)** An illustration of APA durations by trial, for each subject and as a group mean, demonstrating how APA durations decreased for only one trial after pre-SMA stimulation. The circles represent the APA duration of individual PD (gray circles) and control (black circles) subjects. The thick black line represents the group mean of all subjects. The gray-shaded region highlights the first trial after rTMS. **(C)** The effect of stimulation over the pre-SMA (bottom of chart), dPMC (middle of chart), and M1 (top of chart) on APA duration for each PD (circles) and control (crosses) subject. The horizontal axis represents the APA duration of the first trial after stimulation, minus the average APA duration of the 9 trials before stimulation. The vertical line represents no change after stimulation. The site where rTMS significantly affected APA durations is shaded and noted with an asterisk, denoting a significant main effect of stimulation between the first trial after stimulation and the mean of trials before stimulation. **(D)** A scatter plot illustrating a significant correlation among the PD subjects' disease severity (measured by lower-body motor UPDRS scores) and the extent that rTMS over the pre-SMA affected APA durations. The circles represent the values for individual PD subjects. The horizontal axis has been changed so that positive values represent a decrease in APA duration following rTMS in order to illustrate a positive correlation among disease severity and the effect of rTMS on APA duration.

Effect of Stimulation on Swing-Phase Duration

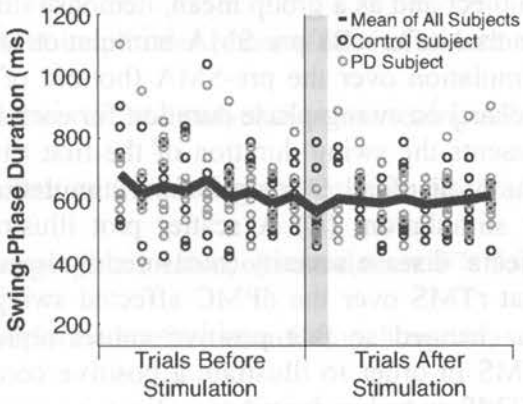
A. Decrease in an Individual's Swing-Phase Duration After Stimulation Over the Pre-SMA



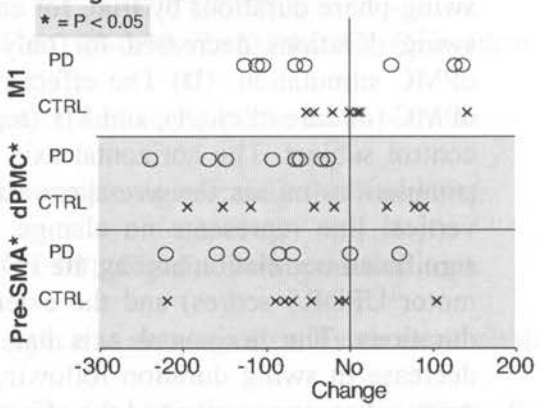
B. Decrease in Swing-Phase Duration For One Trial After Stimulation Over the Pre-SMA



C. Decrease in Swing-Phase Duration For One Trial After Stimulation Over the dPMC

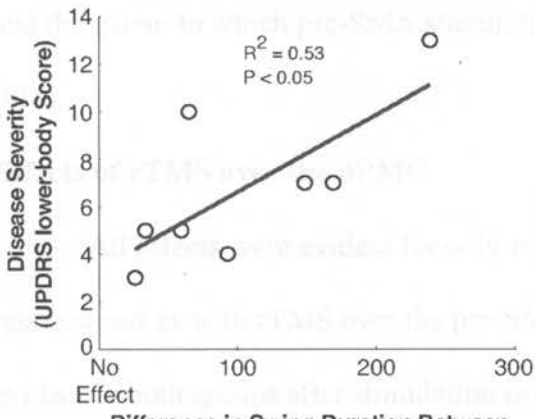


D. Effect of Stimulation on Each Subject's Swing-Phase Duration



Difference in Swing Duration Between the First Trial After Stimulation and the Mean Before Stimulation (ms)

E. Relationship Among Disease Severity and the Effects of dPMC rTMS on Swing Duration



Difference in Swing Duration Between the First Trial After dPMC rTMS and the Mean Before rTMS (ms)

Fig. 4. Effects of stimulation on swing-phase duration. Lines, symbols, shading, and statistics are as defined in Fig. 3. **(A)** An example of decreased swing duration for one trial after pre-SMA stimulation in an individual control subject. The horizontal axis represents time relative to swing onset, and the vertical axis represents the vertical displacement of the marker placed on the subject's first toe. **(B and C)** Illustrations of swing-phase durations by trial, for each subject and as a group mean, demonstrating how swing durations decreased for only one trial after **(B)** pre-SMA stimulation and **(C)** dPMC stimulation. **(D)** The effect of stimulation over the pre-SMA (bottom of chart), dPMC (middle of chart), and M1 (top of chart) on swing-phase duration for each PD and control subject. The horizontal axis represents the swing duration of the first trial after stimulation, minus the average swing duration of all 9 trials before stimulation. The vertical line represents no change after stimulation. **(E)** A scatter plot illustrating a significant correlation among the PD subjects' disease severity (measured by lower-body motor UPDRS scores) and the extent that rTMS over the dPMC affected swing-phase durations. The horizontal axis has been changed so that positive values represent a decrease in swing duration following rTMS in order to illustrate a positive correlation among disease severity and the effect of rTMS on swing duration.

durations decreased slightly, although significantly [main effect of trial from the mean: $F = 5.96$, $P = 0.03$], from the average swing duration of all the trials performed before stimulation, but then, in trials 6 through 9, the group's swing duration stabilized at the same level as in trial 5 (Fig. 4B). No correlation was evident among disease severity and the extent to which pre-SMA stimulation affected swing durations [Pearson $r^2 = 0.09$; $P = 0.48$]. In addition, no correlation was evident among the extent to which pre-SMA stimulation affected swing durations and the extent to which pre-SMA stimulation affected APA durations [Pearson $r^2 = 0.12$; $P = 0.40$].

Pre-SMA stimulation did not significantly affect foot-swing velocity, or peak APA amplitudes [main effects of stimulation: $F = 0.03$-0.12, $P = 0.74$-0.87]. Coincident with pre-SMA stimulation shortening APA duration and swing-phase duration, without affecting foot-swing velocity, pre-SMA stimulation also significantly shortened step length [main effect of stimulation: $F = 9.95$, $P < 0.01$] (Fig. 5). During the first trial performed before stimulation, however, step length was also significantly shorter than the average step length before stimulation [main effect of trial from the mean: $F = 20.40$, $P = 0.0005$] (Fig. 5B). For the PD subjects, no correlation was evident among disease severity and the extent to which pre-SMA stimulation affected step length [Pearson $r^2 = 0.30$; $P = 0.16$].

Effects of rTMS over the dPMC

All effects were evident for only one trial after rTMS. Although the effect was less obvious as with rTMS over the pre-SMA, shortened swing-phase durations were also evident in both groups after stimulation over the dPMC [main effect of stimulation: $F = 9.12$, $P = 0.01$] (Fig. 4C and D). During the sixth and eighth trial performed before

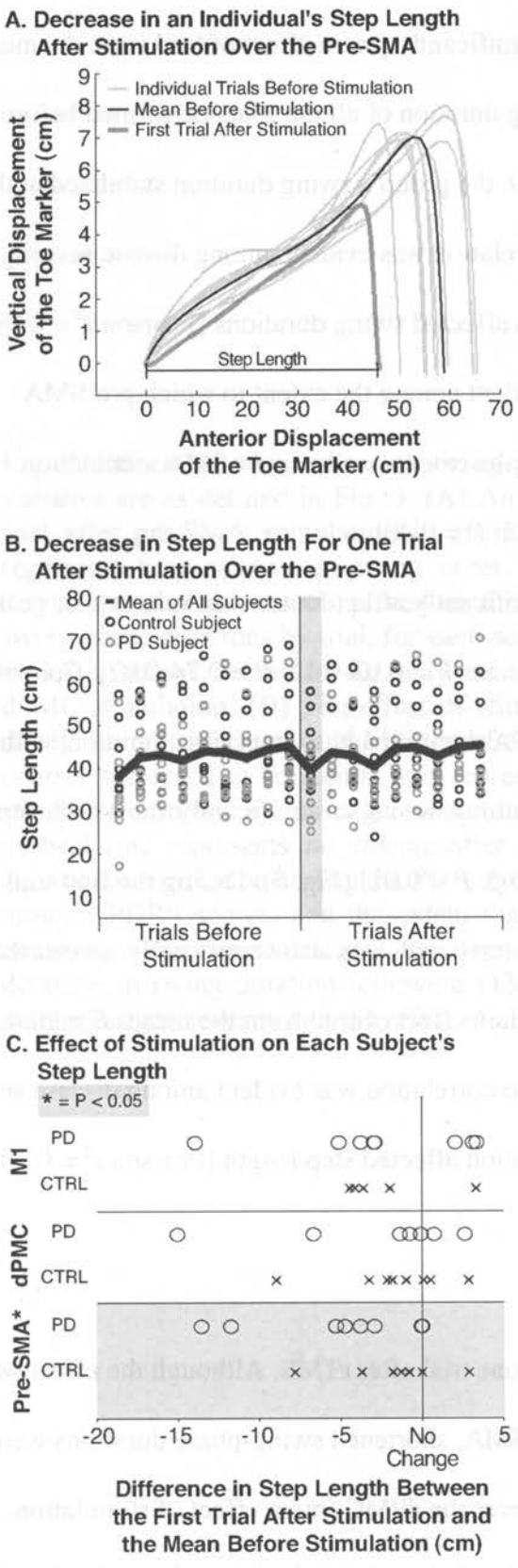


Fig. 5. Effects of stimulation on step length. Lines, symbols, shading, and statistics are as defined in Fig. 3. **(A)** An example of decreased step length for one trial after pre-SMA stimulation in an individual control subject. The horizontal axis represents the forward displacement of the marker placed on the subject's first toe; the vertical axis, the toe marker's vertical displacement. **(B)** An illustration of step length by trial, for each subject and as a group mean, demonstrating how step length decreased for one trial after pre-SMA stimulation. **(C)** The effect of stimulation over the pre-SMA (bottom of chart), dPMC (middle of chart), and M1 (top of chart) on step length for each PD and control subject. The horizontal axis represents the step length of the first trial after stimulation, minus the average step length of all 9 trials before stimulation. The vertical line represents no change after stimulation.

stimulation, however, the subjects' swing durations decreased significantly from the average swing duration [main effects of trials from the mean: F = 6.41-7.11, P = 0.018-0.024] (Fig. 4C). For the PD subjects, the extent to which rTMS over the dPMC affected swing durations significantly correlated with their disease severity: the difference in the PD subjects' mean swing duration before rTMS and their swing duration one trial after rTMS significantly correlated with their lower-body motor UPDRS scores [Pearson r^2 = 0.53, P = 0.041] (Fig. 4E). APA duration, peak APA amplitude, step length, and peak foot-swing velocity were unaffected by dPMC stimulation [main effects of stimulation: F = 0.07-2.49; P = 0.14-0.79].

Effects of rTMS over the M1

Although the effect was less robust than those reported above, stimulation over the M1 significantly decreased APA amplitudes in PD subjects and control subjects [main effect of stimulation: F = 5.15, P = 0.04]. APA amplitudes during the first trial performed before stimulation, however, were also significantly smaller than the average of the peak APA amplitudes before stimulation [main effect of trial from the mean: F = 7.44, P = 0.02]. For the PD subjects, no correlation was evident among disease severity and the extent to which M1 stimulation affected APA amplitudes [Pearson r^2 = 0.02; P = 0.71]. Although the data in Fig. 3C seem to suggest that M1 stimulation affected APA durations for the PD subjects, but not for the control subjects, the group-by-stimulation interaction did not reach the pre-set alpha level [interaction effect between stimulation and group: F = 3.69, P = 0.077]. APA duration, swing-phase duration, step length, and foot-swing velocity were all unaffected by M1 stimulation [main effects of stimulation: F = 0.002-2.74, P = 0.12-0.96].

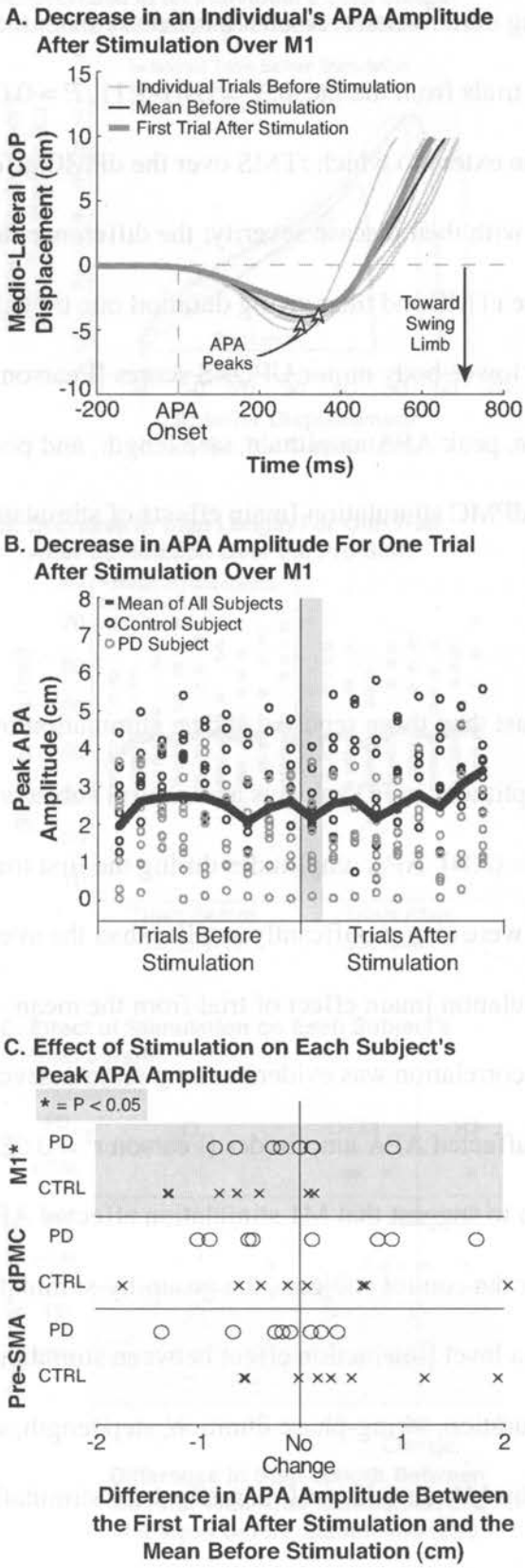


Fig. 6. Effects of stimulation on APA amplitude. Lines, symbols, shading, and statistics are as defined in Fig. 3. **(A)** An example of decreased APA amplitude for one trial after M1 stimulation in an individual control subject. The horizontal axis represents time relative to APA onset, and the vertical axis represents the lateral displacement of the CoP. **(B)** An illustration of APA amplitude by trial, for each subject and as a group mean, demonstrating how APA amplitude decreased for one trial after M1 stimulation. **(C)** The effect of stimulation over the pre-SMA (bottom of chart), dPMC (middle of chart), and M1 (top of chart) on APA amplitude for each PD and control subject. The horizontal axis represents the APA amplitude of the first trial after stimulation, minus the average APA amplitude of all 9 trials before stimulation. The vertical line represents no change after stimulation.

DISCUSSION

The results support (1) parallel, segregated neural control for regulating the APA and swing phase of a step, and (2) that PD subjects exhibit impaired step initiation, in part, due to progressive dysfunction of the pre-SMA. Specifically, rTMS over the pre-SMA shortened step durations for both the postural phase and the swing phase of a step, whereas rTMS over the dPMC selectively shortened swing-phase durations, and rTMS over the M1 selectively decreased APA amplitudes. The decreases in APA and swing-phase durations due to pre-SMA stimulation were not correlated. Therefore, these results suggest that the pre-SMA acts as a global coordinator, organizing both step phases as a sequence of separate motor programs. Then, the swing phase of the step becomes preferentially determined by the function of the dPMC, and the postural phase becomes preferentially determined by the function of the M1 (although the SMA proper may also contribute to generating the APA: Gurfinkel and Elner 1988; Massion 1992; Viallet et al. 1992). However, foot-swing velocity was not affected by rTMS to any site, suggesting that neither of the cortical motor centers tested in this study determine foot-swing velocity. Instead, the results suggest that basal ganglia dysfunction contributes to regulating foot-swing velocity (without involving the pre-SMA, dPMC, or M1) because PD subjects exhibited decreased foot-swing velocity compared to control subjects.

Previous research comparing the neural control of the APA with that of the subsequent prime movement has suggested that separate neural circuits control each phase of movement in parallel (Brown and Frank 1987; Nardone and Schieppati 1988; Viallet et al. 1992; Benvenuti et al. 1997; de Wolf et al. 1998; Schepens and Drew 2003), with convergence at a sub-cortical level (Viallet et al. 1992; Schepens and Drew 2004).

Specifically, Massion (1992) developed a neural model in which a circuit including the SMA, basal ganglia, and M1 regulate the APA, and that these regions send descending signals to a sub-cortical structure to be coordinated with the descending signal for the prime movement (regulated by M1). Schepens and Drew (2004) subsequently elaborated this model, describing an unknown cortical center for the global planning of both the APA and the prime movement, followed by separated descending signals for each phase, which then converge sub-cortically at the ponto-medullary reticular formation. Our current study supports these models, but further elaborates the pre-SMA as the global coordinator of both movement phases (that is, the APA and the prime movement), the dPMC as a regulator of the prime movement (in this study, the swing phase of step initiation), and the M1 as a contributor to regulating APA amplitudes. Although untested by this study, the SMA proper likely also participates in regulating APA amplitude (Gurfinkel and Elner 1988; Massion 1992; Viallet et al. 1992).

The inclusion of the basal ganglia in Massion's (1992) model was largely based on observations that PD subjects exhibit impaired APAs (Martin 1967; Bazalgette et al. 1987; Viallet et al. 1987; Crenna et al. 1990; Lee et al. 1995; Gantchev et al. 1996; Burleigh-Jacobs et al. 1997; Frank et al. 2000; Rocchi et al. 2006). Our study demonstrated that the extent to which pre-SMA stimulation affected APA durations depended on the clinical severity of the PD subjects' lower-body motor symptoms. The results also showed that (1) the M1 contributes to the regulation of APA amplitudes and (2) PD subjects exhibit diminished APA amplitudes, but (3) M1 stimulation does not affect APA amplitudes more in PD subjects than in control subjects. Therefore, although the M1 may contribute to regulating APA amplitude, the diminished APA amplitudes of

PD subjects are not likely a result of M1 dysfunction (although a floor effect may have contributed to this result, because PD subjects initially exhibited reduced APA amplitudes). Taken together, these results suggest that PD subjects exhibit abnormal APA *durations* due to a progressive dysfunction of the pre-SMA, and they exhibit diminished APA *amplitudes* due to abnormal modulation by the basal ganglia and, perhaps, the SMA proper (Massion 1992).

The clinical severity of the PD subjects' lower-body motor symptoms also correlated with the extent to which dPMC stimulation affected the duration of the swing phase, whereas dPMC stimulation did not selectively alter the APAs of the PD subjects. These results suggest that PD subjects utilize the dPMC to lengthen swing-phase duration as compensation for decreased foot-swing velocities in an attempt to maintain a larger step length: (1) PD subjects with the shortest swing-phase durations exhibited the fastest swing velocities, and PD subjects with the longest swing-phase durations exhibited the slowest swing velocities, and (2) step length was not significantly different between PD subjects and control subjects. Had the PD subjects' APAs been altered by dPMC stimulation, the result would have supported the hypothesis that the dPMC anatomically compensates for the dysfunction of the SMA by maintaining functions normally relegated to the SMA (Cunnington et al. 2001). Although this result was not statistically evident, the two most severe PD subjects did exhibit shortened APA durations following dPMC stimulation (for control subjects, a result found to occur after pre-SMA stimulation). Our protocol may not have elicited a more robust compensation by the dPMC for regulating the PD subjects' APAs because we ordered the self-initiated steps before the cued steps, and explicit sensory cues may be required to improve APAs (Burleigh-Jacobs et al. 1997)

as well as to elicit compensatory activity of the dPMC for functions not normally controlled by the dPMC (Hanakawa et al. 1999a; Cunnington et al. 2001). Our study does support the hypothesis that PD subjects become increasingly dependent on the activity of dPMC to alter swing-phase durations as compensation for their motor impairments, however, because the clinical severity of the PD subjects' lower-body motor symptoms correlated with the effect of dPMC stimulation on their swing-phase durations.

Methodological Considerations

As noted in our methods, our original intent was to study the effects of rTMS on many step behaviors, but significant effects lasted for only one trial after stimulation, thereby prohibiting any analysis beyond our self-initiated stepping task. We initially expected effects to last for about 15 minutes following stimulation because previous reports have demonstrated lasting effects on both cortical excitability and stretch reflexes for approximately 50%-100% of the stimulation time (Tsuji and Rothwell 2002; Chen et al. 1997). These protocols, however, did not require their subjects to perform large voluntary motor tasks following rTMS, as we did with our voluntary stepping task, and it has been reported that voluntary muscle activation can normalize rTMS-induced changes in cortical excitability (Touge et al. 2001). Thus, in our study, any rTMS-induced changes in the subjects' neuro-motor state may have been normalized after the first trial. The neurophysiologic basis for normalizing cortical excitability with voluntary motor activity has yet to be tested, but we speculate that our subjects may have been able to recalibrate their stepping behavior due to feedback processing during the first trial after stimulation. That is, the central nervous system, perhaps through cerebellar circuits, may have computed a comparison between expected and actual behavior performed during the

first trial after stimulation, and then recalibrated the neural circuitry in order reestablish the expected stepping behavior in subsequent trials (Diedrichsen et al. 2005). Longer lasting effects may have been achieved had the subjects received multiple sessions of high-frequency rTMS to the same site (Khedr et al. 2006).

The behavioral effects of rTMS to a specific region of the cerebral cortex may not represent a direct effect of that cortical region on the behavior. Studies have demonstrated that sub-threshold, 1-Hz rTMS over one site can elicit changes in the activity and excitability of other neural sites, presumably through communicating fibers (Gerschlager et al. 2001; Speer et al. 2003; Bestmann et al. 2005). Thus, in this study, any changes in step initiation after rTMS may represent an indirect influence of the stimulated site on other neural centers involved in regulating step initiation.

Consistent with previous reports (Tremblay and Tremblay 2002; Lou et al. 2003), the motor thresholds for stimulating the FDI muscle were lower for the PD subjects than for the control subjects. Consequently, rTMS intensities were lower for the PD subjects, and stimulating the groups with different absolute intensities may have diminished the effect of rTMS on the PD subjects. The intensities, however, were normalized to the cortico-spinal excitability of each subject, and our results never showed any group-by-stimulation interactions characterized by an effect of rTMS in the control group with no effect in the PD group.

Stimulation intensities were also lower when stimulating the M1 than when stimulating the dPMC or pre-SMA. Thus, it is likely that M1 stimulation was less effective than when stimulating the dPMC or pre-SMA because (1) the leg motor region is located deep within the longitudinal fissure, (2) stimulation intensities were based on

the more conservative motor thresholds of the FDI muscle, instead of the TA muscle, and (3) stimulation intensity was inadvertently lower when stimulating the M1. Therefore, null effects at the M1 may represent ineffective stimulation, rather than a lack of contribution to initiating a step. Nevertheless, the session of M1 stimulation did serve as a control to demonstrate that the significant effects evident after stimulation to the pre-SMA or dPMC were, in fact, specific to the stimulation of those regions.

Because the effects of rTMS lasted for only one trial after stimulation, we chose to compare a measure's value from the first trial performed after rTMS with the mean value of the 9 trials performed before rTMS. Despite considerable inter-subject variability, the systematic consistency with which rTMS altered stepping behavior across subjects revealed net group effects that could not be explained by chance.

Some significant effects, however, were also evident when comparing mean values of the dependent measures with values from individual trials performed before stimulation, violating the assumption that inter-trial differences exhibit random variability. Specifically, APA amplitudes from the first of the 9 trials performed before M1 stimulation were significantly smaller than the mean APA amplitudes of all 9 trials performed before stimulation. Thus, rather than an effect of stimulation, decreased APA amplitudes after M1 stimulation could represent an effect of trial order due to taking a step for the first time. An order effect is not likely, however, because such an effect should have been common to every experimental session, but decreased APA amplitudes were only evident in the sessions that included M1 stimulation. Therefore, we still attribute the decrease in APA amplitude after M1 stimulation as a true effect of stimulation.

Similarly, step lengths from the first of the 9 trials performed before pre-SMA stimulation were also significantly smaller than the mean step lengths of all 9 trials performed before stimulation. Thus, decreased step lengths after pre-SMA stimulation may also represent an order effect due to taking a step for the first time. The effect, however, was isolated to the sessions in which we stimulated the pre-SMA and, therefore, an order effect does not likely contribute to the decreased step lengths observed after pre-SMA stimulation. Instead, we attribute shortened step lengths after pre-SMA stimulation as representing a consequence of the stimulation decreasing the durations of both step phases, without altering foot-swing velocities (that is, decreased movement time with unchanged velocity would lead to smaller displacements).

During the sessions for rTMS over both the pre-SMA and dPMC, swing-phase durations of some individual trials performed before stimulation were significantly different from the mean swing-phase durations of all 9 trials performed before stimulation. We still attribute the decrease in swing durations after pre-SMA stimulation as a true effect of stimulation because graphical analysis (Fig. 4B) shows a clear, transient decrease in swing-phase duration during the first trial after rTMS compared to the swing-phase durations exhibited during the surrounding trials, whereas the decrease evident in the fifth trial before stimulation seemed to reflect a coincidental shift in swing-phase duration that was subsequently maintained in the last 4 trials before stimulation. For the dPMC session, we also attribute the decrease in swing durations after rTMS as a true effect of stimulation because (1) despite a high level of variability in this session, the lowest mean of the subjects' swing-phase durations was still evident in the first trial after stimulation (Fig. 4C), (2) the effect was not evident in all of the experimental sessions,

and (3) the PD subjects' clinical motor impairment significantly correlated with the effect of dPMC stimulation on their swing-phase, suggesting a functionally relevant effect.

Safety

Although higher rTMS intensities may have resulted in larger and longer-lasting changes in the subjects' behavior (Fitzgerald et al. 2002; Lang et al. 2006), we chose a low-intensity stimulation in order to maximize the safety of our protocol (Wassermann 1998); PD subjects have been reported to exhibit increased susceptibility to rTMS (Buhmann et al. 2004), with potentially adverse long-term effects (Boylan et al. 2001). Despite using a conservative protocol, one unexpected adverse event was reported: 2 months after completing all 3 sessions of the experiment, one PD subject reported experiencing low-grade headaches 2-3 times per week, despite no previous history of recurring headaches. The headaches were mild, requiring non-prescription medication only once, and the headaches were becoming less frequent at the time of the report. During the first 2 weeks after completing the protocol, the same PD subject also reported twice experiencing phantom sensations that the coil was still pressed against his scalp. These adverse reactions were officially reported to the Internal Review Board of Oregon Health and Science University.

Conclusions

The results support a neural control model for voluntary step initiation in which the APA and swing phase are both coordinated by the pre-SMA, followed by segregated control of the swing phase by the dPMC and of the APA by a circuit that includes the basal ganglia, SMA proper, and M1. The results also suggest that PD subjects exhibit impaired APA *durations* due to dysfunction of the pre-SMA and diminished APA

amplitudes due to dysfunction of the basal ganglia. In addition, the results suggest that, in PD subjects, the dPMC compensates for decreased foot-swing velocity by prolonging swing-phase duration in order to maintain a healthy step length.

CHAPTER 3

Activity of the Cerebral Cortex Correlates with Modifications of Postural Responses Associated with Changes in Central Set

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ABSTRACT

Postural responses to external perturbations of balance are affected by changes in central set – a person's initial neuro-motor state influenced by the environment and expectation – suggesting involvement of the cerebral cortex in preparing for upcoming perturbations. Despite the known influence of central set, the contribution of the cerebral cortex on postural responses is still unclear. We recorded electroencephalographic readiness potentials from healthy subjects before perturbing their balance with backward translations of a platform under their feet. The subjects responded with and without a visual cue that warned them of the upcoming, expected perturbation (the Cue and No Cue conditions, respectively). The subjects were instructed to respond without taking a step. The results showed that the peak amplitudes of the subjects' readiness potentials were larger in the Cue condition than in the No Cue condition. Compared to the No Cue condition, in the Cue condition, the subjects also stepped less often and kept their center of pressure displacements farther from their limits of support. The cue-related difference in the subjects' readiness potentials correlated with the cue-related difference in the number of trials with steps or with the cue-related difference in their center of pressure displacements. This is the first reported neural correlate of central set *prior* to externally triggered postural responses, demonstrating that changes in movement-related neural activity optimize triggered postural responses.

INTRODUCTION

Postural responses to an external perturbation of balance occur quickly: leg and trunk muscles activate 80-120 ms after translating the support surface under a subject's feet (Chan et al. 1979; Nashner and Cordo 1981; Horak and Nashner 1986; Ackermann et al. 1991). These short onset latencies imply that postural responses to external perturbations are controlled automatically by spinal or brainstem mechanisms without involving the cerebral cortex. Although postural responses to sudden perturbations occur quickly, several high-level cognitive processes, such as expectation (Horak et al. 1989; Ackermann et al. 1991; Maki and Whitelaw 1993), intention (McIlroy and Maki 1993a; Burleigh and Horak 1996), and anxiety (Carpenter et al. 2004b), influence how an individual responds to a perturbation that threatens balance, suggesting that the cerebral cortex may be involved in reactive postural control. In anticipation of a sudden postural perturbation, these changes in central set optimize postural responses for an upcoming situation (Horak and Macpherson 1996). Despite the known influence of central set, the contribution of the cerebral cortex to postural responses is still unclear.

Research attempting to characterize the role of the cerebral cortex on triggered postural responses has focused on electroencephalogram (EEG) potentials that occur *after* a perturbation (known as perturbation-evoked potentials; Dietz et al. 1985; Ackermann et al. 1986; Dimitrov et al. 1996; Quant et al. 2004), rather than recording EEG potentials *prior to* a perturbation. These studies have demonstrated that perturbation-evoked potentials become altered with changes in central set, such as with changes in the predictability of a perturbation (Dietz et al. 1985; Quintern et al. 1985; Adkin et al. 2006), or with a secondary motor task (Quant et al. 2004). These perturbation-evoked

potentials occur after the perturbation, however, and are thought to represent cortical processing of sensory input related to the balance disturbance (Dietz et al. 1985). Thus, changes in perturbation-evoked potentials represent the consequence of changes in central set, not the process of central set itself.

As an alternative to studying perturbation-evoked potentials, readiness potentials (slow, negative drifts in EEG amplitude that occur prior to movement), represent pre-movement neural activity related to both anticipation and motor preparation (van Boxtel and Brunia 1994) and, therefore, may provide a neural correlate of central set. Although readiness potentials have been shown to precede voluntary postural movements, such as voluntary stepping and voluntary postural sway (Yazawa et al. 1997; Slobounov et al. 2005), we are not aware of any reports demonstrating the existence of readiness potentials prior to an externally-induced postural perturbation. Such pre-movement cerebral activity, however, may represent the process by which initial mental and environmental states affect postural responses to external perturbations (that is, readiness potentials may represent a neurophysiologic correlate of central set). Therefore, unlike previous studies that relate readiness potentials of the cerebral cortex to voluntary movement, we hypothesized that the cerebral cortex would also exhibit readiness potentials that prepare the body for expected external perturbations of balance to improve externally triggered postural performance.

To test this hypothesis, we performed two experiments on separate subject samples to determine whether changing the predictability of an external perturbation would lead to changes in the subjects' cerebral readiness potentials, and to determine whether these changes in readiness potentials relate to optimizations of the postural

response. To examine these predictions, we recorded the EEG signals of healthy subjects prior to perturbing their balance with backward translations of the support surface under the subjects' feet. The subjects were tested in 3 conditions: (1) the Cue condition, in which the subjects were provided with a visual warning cue and instructed to attempt not to step in response to a challenging perturbation, (2) the No Cue condition, in which subjects attempted not to step in response to the perturbation without a warning cue, and (3) the Step-to-Cue condition, a control condition in which the subjects were provided with a cue and instructed to take a step in response to the perturbation. We predicted that cortical readiness potentials would precede the subjects' responses in every condition because subjects would always prepare for the upcoming anticipated perturbations. We expected, however, that the subjects' average EEG waveforms would exhibit smaller potentials in the No Cue condition because, without the benefit of a warning cue, the subjects would not be able to temporally couple their neuro-motor preparation for a postural response with the onset of the perturbation. That is, over repeated trials in the No Cue condition, cortical readiness potentials would peak at variable times, therefore leading to a smaller average readiness potential than in the conditions with cues. We also postulated that the provision of a warning cue would allow subjects to maintain standing balance with greater stability and without needing to take a step because the cue would prepare the subjects to more effectively couple their response with the onset of the perturbation (Ackermann et al. 1991). In addition, we predicted that improvement in the subjects' performance due to cueing would correlate with cue-related changes in readiness potentials, thereby supporting the hypothesis that activity of the cerebral cortex mediates the optimization of externally triggered postural responses.

Because we hypothesized that readiness potentials represent the *optimization* of a response strategy, rather than representing the *selection* of a response strategy, we also predicted that readiness potentials would not change with a change in the subjects' intentions to step or not to step in response to the perturbation. To ensure changes in readiness potentials relate to the optimizations of the postural response, not to adaptations in initial stance posture (such as anticipatory leaning), we tested a second set of subjects in whom initial posture remained consistent across the experimental conditions. We hypothesized that neuro-motor preparation at the cerebral cortex contributes to the modification of postural responses that occur in reaction to external postural perturbations, not just to anticipatory modifications in initial stance posture that occur prior to the perturbations.

METHODS

This study includes two experiments. In Experiment One, we tested 5 subjects who maintained an initial stance position of their choice and performed 20 trials in each condition, and we examined the cue-related changes in their readiness potentials at only one EEG electrode. In Experiment Two, we tested 12 subjects who maintained a consistent initial stance posture and performed 40 trials in each condition, and we examined their readiness potentials at multiple electrode sites.

Experiment One

Subjects

According to the Helsinki agreement, five healthy males without neurological or neuromuscular impairment gave informed consent to participate in the protocol that was approved by the Institutional Review Board of Oregon Health and Science University,

Portland, OR, USA. Subjects were 26, 31, 36, 36, and 51 years of age. They were 161, 175, 178, 165, and 174 cm tall, and weighed 64, 93, 61, 65, and 68 kg, respectively.

Protocol

Subjects stood with each foot on a moving force plate, with their eyes fixed on a 2x2-cm warning light positioned 1.1 m high and 2.5 m in front of them. Electrodes were attached for EEG and electrooculogram (EOG) recordings. Subjects stood with their feet in a comfortable stance width and with their hands at their sides. No instructions were given to ensure similar initial foot placement or body position across trials or conditions. The perturbations were 18-cm backward translations of the force plates under the subjects' feet, with durations of 548 ms, peak ramp velocities of 35 cm/s, and average initial accelerations of 9 m/s^2. Perturbations of this speed and magnitude naturally elicit a stepping response when subjects respond to the perturbation without any instruction (Mille et al. 2003), and we chose this perturbation based on personal observations that subjects step to this perturbation but could, at times, maintain balance without stepping when challenged to do so.

Without any practice trials, the subjects responded to the perturbations in three blocked conditions that were randomized across subjects: the No Cue condition, the Cue condition, and the control, Step-to-Cue condition. In the No Cue condition, subjects stood on the movable force plates and attempted to keep their balance without taking a step when the force plates were moved backward, without warning, at a variable inter-trial time of 13-20 seconds. In the Cue condition, subjects stood on the force plates and attempted to keep their balance without taking a step in response to the perturbation but were given a warning light that indicated that the platform was going to move backward

2 seconds later. The Step-to-Cue condition was identical to the Cue condition except that the subjects were instructed to take a step when the force plates moved. The Step-to-Cue condition served two purposes: (1) to ensure that the readiness potentials of the Cue and No Cue conditions were not simply a consequence of instructing the subjects to respond with an unusually difficult feet-in-place strategy, and (2) to determine whether readiness potentials relate to the subjects' intended response selection (step or stand) or to the availability of a cue.

Subjects were presented with as many perturbations as necessary to record 20 trials per condition without any eye-movement artifacts in the EEG record. To identify eye movement artifacts, EOGs were monitored by a pair of electrodes placed above and below the left orbital.

EEG Data Collection and Analysis

Previous studies examining readiness potentials associated with voluntary postural tasks have demonstrated that maximal readiness potentials occur over the Cz electrode (Yazawa et al. 1997; Slobounov et al. 2005), so we constrained our EEG analysis to the signals recorded at that electrode. We calculated the peak amplitude of the subjects' readiness potentials at the Cz electrode as the maximum displacement of the EEG signal over 3 seconds immediately preceding the perturbation. To determine cue-related differences in the subjects' readiness potentials, we defined cortical modulation as the peak amplitude of a subject's average readiness potential in the No Cue condition, minus the peak amplitude of the subject's average readiness potential in the Cue condition.

To record the subjects' readiness potentials, scalp EEGs were recorded from an 8-mm diameter, silver/silver-chloride electrode at Cz, as defined by the international 10/20 system of electrode placement (Jasper 1958). The electrode was referred to linked earlobes. Electrode impedance was kept below 5 kΩ. The EEG signals were amplified by 50000 with a BA-1008 amplifier (TEAC Instruments, Japan), and band-pass filtered from 0.05 to 100 Hz. The EOG signals were amplified by 25000 and band-pass filtered from 0.05 to 30 Hz. All signals were sampled at one kHz with 12-bit resolution from 3 seconds before the perturbation to 500 ms after the perturbation. Trials with artifacts due to eye movements were discarded, and the EEG signals from every artifact-free trial were averaged by condition for each subject using EPLYZER II software (Kissei Comtec, Japan). Offline, the subjects' average waveforms for each condition were converted for analysis with Matlab software (MathWorks, USA). The subjects' average EEG signals from each condition were zeroed to their average baseline activity during the first 500 ms of recording. For EEG waveforms recorded in the No Cue condition, subtracting the voltage signal from this time interval may not actually represent a subtraction of baseline activity because, in any given trial, subjects may anticipate the perturbation at different moments within the inter-trial period. Thus, our measure assumes that motor preparation and anticipation occurring immediately before the perturbation contributes more to the subjects' postural responses than any preparation or anticipation occurring more than 3 seconds before the perturbation.

Analysis of Postural Responses

To quantify how subjects modified their postural response when provided with a cue, we calculated the number of trials in which a subject took a step to maintain balance

in the No Cue condition, minus the number of trials in which a subject took a step to maintain balance in the Cue condition. More trials with steps in the No Cue condition than in the Cue condition would signify that, when a cue is provided before the perturbations, the subjects successfully optimize their postural responses to maintain balance without taking a step. This measure assumes, however, that the subjects were motivated to maintain balance without stepping according to our instructions and, therefore, only stepped when they felt it was necessary to maintain standing balance. To provide insight into whether steps taken in the Cue and No Cue conditions didn't represent planned steps and were taken because the subjects felt they required the steps, we recorded the time of step onset. Step onset times were defined as the moment when the vertical weight on one of the force plates reached a value of zero, signifying that a foot came off the plate. If the subjects initiate steps later and at more variable times in the Cue and No Cue conditions than in the Step-to-Cue condition, then the results would suggest that, in the Cue and No Cue conditions, the subjects were attempting to maintain balance without stepping for as long as they could and stepped only when they felt they needed to for maintaining balance (rather than representing a planned step that was initiated well before the perturbation could appreciably displace a subject's body). Unlike in Experiment Two (see below), we could not utilize the CoP data to provide more detailed associations among the subjects' cortical readiness potentials and their postural responses because we did not monitor or control for the subjects' initial stance positions.

Statistical Analyses

For all analyses, decisions to use parametric versus non-parametric statistical tests were based on whether the data satisfied the assumption of normality, as determined by

Shapiro-Wilks tests of normality. In order to determine the effect of cueing on readiness potentials at Cz, a Friedman's ANOVA (followed by pairwise Wilcoxon t-tests) compared peak EEG amplitudes between the experimental conditions. To determine the effect of cueing on the subjects' postural responses, a two-tailed paired t-test compared the number of trials with steps in the Cue condition with the number of trials with steps in the No Cue condition. A two-tailed Spearman's correlation coefficient determined whether cue-related modulation of the Cz readiness potential was associated with a subject's ability to modify postural responses between the Cue and No Cue conditions.

Experiment Two

All conditions and protocols were identical to Experiment One, unless detailed below.

Subjects

According to the Helsinki agreement, 12 healthy subjects (4 males and 8 females) without neurological or neuromuscular impairment gave informed consent to participate in the protocol that was approved by Kanazawa University, Kanazawa, Japan. On average (range), the subjects were 27 (21-32) years of age, 163 (154-174) cm tall, and weighed 55 (45-62) kg.

Protocol

As in Experiment One, the subjects stood on a moving force plate with their eyes fixed on a warning light, and with electrodes attached for EEG and EOG recordings. Unlike in Experiment One, the subjects stood with their arms crossed in front of their torso, and they stood with a consistent stance width of 16.5 cm between the heel centers. The positions of the subjects' feet were outlined by tape and checked between each trial to ensure consistent foot placement across trials and conditions. Before responding to

perturbations, the subjects performed 5 10-s trials of quiet stance in order to record the average position of their CoP. For the ensuing perturbation conditions, the subjects were told to maintain this initial position, and we monitored their CoP position by oscilloscope to ensure they complied with this instruction (we discarded any trials in which the subjects exceeded a threshold of ± 1 cm from their average CoP position recorded during quiet stance).

As in Experiment One, without practice, the subjects then responded to backward translations of the support surface within 3 randomized blocks of experimental conditions: the Cue, No Cue, and Step-to-Cue conditions. To improve the signal-to-noise ratio of the EEG readiness potentials, the subjects were presented with twice as many trials as in Experiment One, responding to as many perturbations as necessary to record 40 trials per condition without any eye-movement artifacts in the EEG record or without any pre-perturbation CoP displacements greater than 1 cm beyond the subjects' average quiet stance position. To prevent fatigue, the subjects were allowed to rest at their request, and they rested, at minimum, after every 20 trials.

EEG Data Collection and Analysis

Unlike in Experiment One, the EEG signals were analyzed from multiple electrode sites, including F3, F4, Fz, Cz, and Pz, as defined by the international 10/20 system of electrode placement (Jasper 1958). The EEG and EOG signals were processed similarly to Experiment One, except that the EEG signals were amplified by 20000 and band-pass filtered from 0.05 to 60 Hz, and the EOG signals were amplified by 4000. All signals were recorded from 3 seconds before the perturbation to 3 seconds after the perturbation. In addition to discarding trials with eye movement artifacts, we also

discarded trials with unacceptable initial CoP positions before averaging each subject's EEG waveforms by condition. In order to evaluate the relative timing and spatial distribution of the subjects' readiness potentials in each condition, we averaged the subjects' EEG waveforms into 500-ms intervals for each condition and electrode site. Once determining the electrode site exhibiting the largest amplitude of readiness potentials in the group average, for that electrode site, we also determined the peak amplitudes of the subjects' readiness potentials in each condition.

Postural Responses and the Center of Pressure

As in Experiment One, as an operational measure of response modification, we calculated the number of trials in which a subject took a step to maintain balance in the No Cue condition, minus the number of trials in which a subject took a step to maintain balance in the Cue condition. To ensure steps taken in the Cue and No Cue conditions didn't represent planned steps and were taken because the subjects felt they required the steps, we recorded the latency of the subjects' step onsets. Step onset latencies were defined to be the time after perturbation onset when a subject's foot accelerated forward. Foot accelerations were recorded from linear accelerometers placed on the subjects' first toes, and they were evaluated after having subtracted the platform's acceleration from the foot accelerations. Data from the linear accelerometers were sampled at one kHz at 12-bit resolution.

In order to provide another measure of response modification, we also recorded the subject's CoP displacements. A subject's CoP position was calculated as previously reported by Fujiwara and colleagues (2003). The data from the force plate were sampled at one kHz with 12-bit resolution. The CoP data were then low-pass filtered offline at 10

Hz. For the Cue and No Cue conditions, we calculated a stability margin as the distance of a subject's peak forward CoP displacement relative to the front edge of that subject's base of support (defined as the position of the front edge of the foot). The distance of the CoP from the edge of the base of support has been previously reported to represent a measure of stability, in which a decreasing distance of the CoP to the limits of the base of support represents decreasing stability (Hayes 1982). As another measure of response modification, then, we calculated the stability margin in the No Cue condition, minus that of the Cue condition. As another measure to ensure steps in the Cue and No Cue conditions were taken because they were required to maintain balance, we calculated each subject's average stability margin at the moment of step onset in the trials with steps. We predicted that, compared to the Step-to-Cue condition, stability margins would be smaller in the Cue and No Cue conditions at the moment of step onset, signifying that the subjects only stepped in the Cue and No Cue conditions when the steps were required to maintain balance.

Statistical Analyses

Within each condition and electrode position, a readiness potential was defined as a significant decrease from the average baseline EEG amplitude of zero μV among the subsequent 500-ms intervals recorded prior to the perturbation. To determine significant potentials, we performed a 3-factor repeated-measures ANOVA testing for differences across the 3 conditions, 5 electrode sites, and 6 interval times. Post-hoc comparisons were then analyzed from 2-factor ANOVAs for each electrode site in order to test for interaction effects among conditions and interval times. The ANOVA statistics were adjusted by Greenhouse-Geisser corrections to remedy any violations of the assumption

of sphericity. For the electrode site found to exhibit the largest group mean potentials, we analyzed the peak amplitudes of the subjects' readiness potentials over the entire 3-second pre-perturbation recording period, using a single-factor ANOVA to test for differences among the three conditions.

To determine the effect of cueing on the subjects' postural responses, two-tailed t-tests compared the subjects' stability margins and the number of trials with steps between the Cue and No Cue conditions.

Two-tailed correlation coefficients determined whether cue-related modulation of the Cz readiness potential (found to be the site with the largest potential) was associated with a subject's ability to modify postural responses between the Cue and No Cue conditions. As an added measure of postural response modification, we calculated the cue-related difference in the subjects' stability margins.

RESULTS

Experiment One

Changes in Readiness Potentials with Cues

The peak amplitude of the subjects' readiness potentials differed significantly at Cz between the conditions [Friedman's $F = 6.0$; $P = 0.050$]. The peak amplitudes of the readiness potentials were, on average, 35% larger in the Cue condition than in the No Cue condition [Wilcoxon $T = 2.02$; $P = 0.04$], whereas readiness potentials were of similar peak amplitude when subjects intended not to step in the Cue condition and when they intended to step in the Step-to-Cue condition [Wilcoxon $T = 0.67$; $P = 0.50$] (Fig. 1A and B).

Trials with Steps

Subjects stepped less often in the Cue condition than in the No Cue condition [T = 3.35; P = 0.03], regardless of the order in which the conditions were presented (Fig. 1C). The subjects who took the most steps in the No Cue condition also improved the most with a cue by reducing the number of trials with steps in the Cue condition. That is, the difference in the number of trials with steps between the Cue and No Cue conditions correlated with the number of trials with steps in the No Cue condition [Pearson r = 0.978; P = 0.004]. When stepping with the intention not to step, every subject lifted a foot off the force plates later and at more variable times in the Cue and No Cue conditions than when intending to step in the Step-to-Cue condition: step onset latencies were, on average (± SD), 423 ± 67 ms after perturbation onset in the Step-to-Cue condition, 1324 ± 666 ms in the Cue condition, and 1202 ± 516 ms in the No Cue condition.

Cortical Modulation and Response Modification

The difference in the subjects' peak readiness potential amplitudes between the Cue and No Cue conditions correlated with the difference in the number of trials with steps between the Cue and No Cue conditions [Spearman rho = 0.87; P = 0.05] (Fig. 1D).

Results of Experiment One

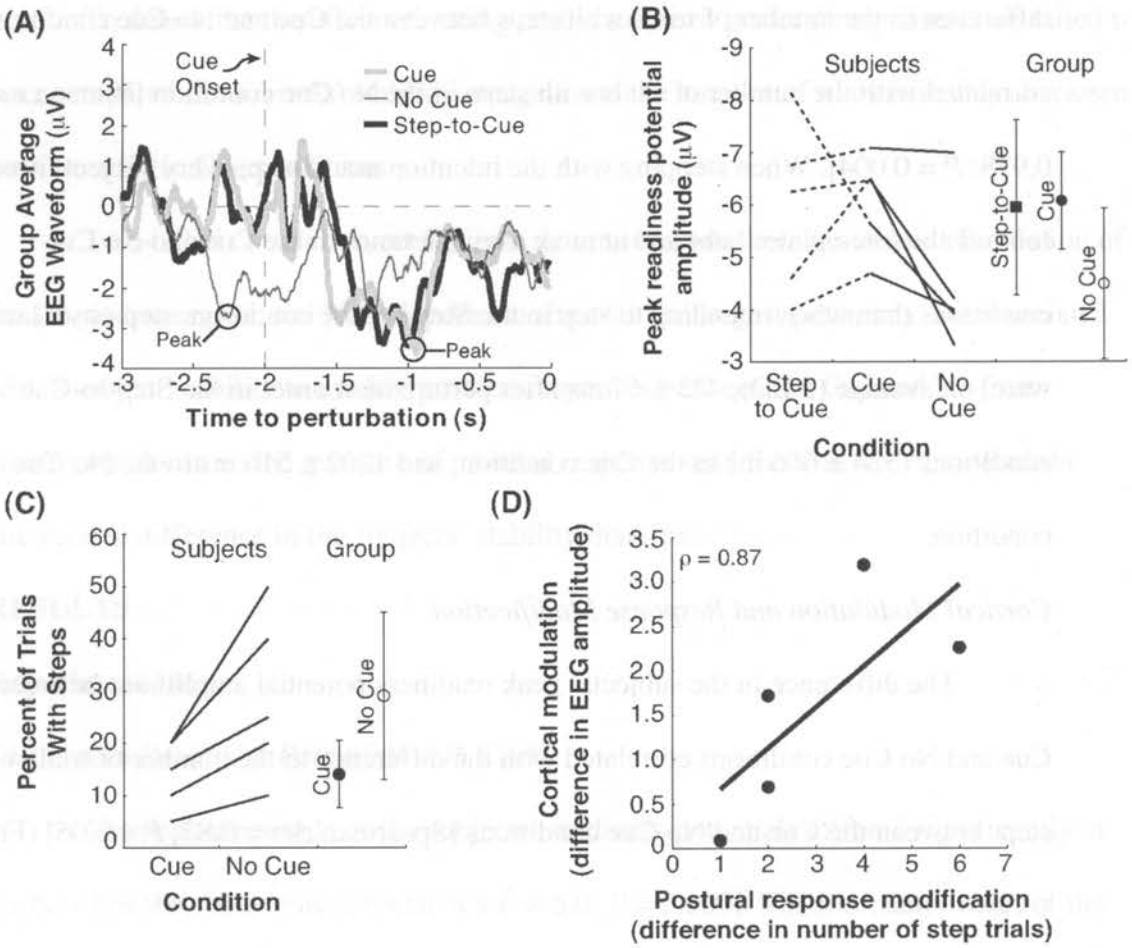

Fig. 1. Results of Experiment One. (***A***) Traces represent the group's average EEG displacement from 20 trials at Cz prior to perturbations in the Cue (thick gray line), No Cue (thin gray line), and Step-to-Cue (thick black line) conditions. The vertical dashed line represents the onset of the cue for the Cue and Step-to-Cue conditions. The horizontal dashed line represents the zeroed baseline activity. The circles highlight that the peak potentials were similar in amplitude and timing in the Cue and Step-to-Cue conditions, whereas in the No Cue condition, the peak potential was smaller and was not constrained to the 2-second period before the perturbation. (***B***) The chart illustrates the peak amplitude of the readiness potential at Cz in each condition. Lines represent peak amplitudes of individual subjects, and the circles represent the group mean (SD) peak amplitudes in the Step-to-Cue (filled squares), Cue (filled circles), and No Cue (open circles) conditions. (***C***) For the Cue and No Cue conditions, the chart shows the percent of trials in which subjects took a step to maintain balance in response to the perturbations. Lines represent the counts of individual subjects, and the circles represent the group mean (SD) percent of trials with steps in the Cue (filled circles) and No Cue (open circles) conditions. (***D***) The scatter plot compares the cue-related difference in the number of trials with steps (postural response modification) with the cue-related difference in the peak amplitude of the average readiness potential at Cz (cortical modulation). The circles represent subject averages, and the diagonal line represents the best-fit line.

Experiment Two

Changes in Readiness Potentials with Cues

Significant negative displacements in the average EEG signals were evident prior to perturbations in the Cue and Step-to-Cue conditions at the Cz and Pz electrodes, and maximal displacements were evident at Cz (consistent with previous studies on voluntary postural tasks; Yazawa et al. 1997; Slobounov et al. 2005). A 3-factor ANOVA testing for differences across electrode sites, conditions, and time intervals demonstrated a significant 3-way interaction effect [$F = 6.48$, $P < 0.0005$]. Post-hoc tests for differences across conditions and time intervals for each individual electrode site demonstrated: (1) significant negative displacements from baseline in the EEG waveforms of the Cue and Step-to-Cue conditions, compared to the No Cue condition, (2) that these significant negative displacements occurred during the 1000 ms immediately preceding perturbation onset (intervals 5 and 6), and (3) that these displacements occurred at Cz [F values range from 9.81 to 15.50, $P < 0.01$] and at Pz [F values range from 5.86 to 21.36, $P < 0.05$]. Significant potentials were not evident at the frontal electrodes [F values range from 0.01 to 3.28, $P > 0.1$], except at Fz, which exhibited a significantly more negative displacement in the EEG waveform in the Step-to-Cue condition than in the No Cue condition during the interval from 1000 ms to 500 ms before perturbation onset [$F = 5.72$, $P < 0.05$]. Consistent with Experiment One, readiness potentials in the Cue condition were similar to those of the Step-to-Cue condition at both Cz and Pz [F values range from 0.06 to 2.76, $P > 0.12$]. The subjects' average EEG waveforms did not exhibit significant readiness potentials in the No Cue condition. Qualitatively, the readiness potentials of Experiment Two (representing the average of 40 trials) exhibited a more

continuous negative drift than those observed in Experiment One (representing the average of 20 trials). Fig. 2A and Fig. 2B illustrate an individual's and the group's average readiness potentials, respectively, at the Cz electrode.

Consistent with Experiment One, the peak amplitudes of the subjects' readiness potentials were, on average, about 300% larger in the Cue condition than in the No Cue condition. At Cz, a significant main effect of condition was evident [$F = 16.34$, $P < 0.001$], and post-hoc comparisons determined that the peak potentials in the No Cue condition were significantly less than those in the Cue [$F = 14.55$, $P < 0.005$] and Step-to-Cue conditions [$F = 21.53$, $P < 0.001$], whereas peak potential amplitudes were similar between the Cue and Step-to-Cue conditions [$F = 1.09$, $P = 0.32$] (Fig. 2C).

Changes with Cues in the Number of Trials with Steps and in Stability Margins

Trials with steps were rare in Experiment Two compared to in Experiment One, suggesting that the perturbation was not as challenging to the subjects in Experiment Two: in the No Cue condition, the subjects in Experiment One stepped in 10%-50% of the trials, whereas 8 of the 12 subjects in Experiment Two stepped in less than 10% of the trials (Figure 2D). Nevertheless, 8 of the 12 subjects in Experiment Two stepped less often in the Cue condition than in the No Cue condition, leading to a trend for fewer trials with steps in the Cue condition [Wilcoxon $T = 1.90$; $P < 0.06$] (Fig. 2D). Only one subject stepped more often in the Cue condition than in the No Cue condition, and 3 subjects did not exhibit any steps in either condition. Similar to Experiment One, the subjects who took the most steps in the No Cue condition also improved the most with a cue by reducing the number of trials with steps in the Cue condition. That is, the difference between the Cue and No Cue conditions in the number of trials with steps

correlated with the number of trials with steps in the No Cue condition [Spearman's rho = 0.84; $P < 0.001$].

As found in Experiment One, the subjects initiated their steps later and at more variable times in the Cue and No Cue conditions than in the Step-to-Cue condition: step onset latencies were, on average (± SD), 474 ± 91 ms after perturbation onset in the Step-to-Cue condition, 1237 ± 540 ms in the Cue condition, and 1050 ± 451 ms in the No Cue condition. In addition, when stepping, the subjects' stability margins were smaller at step onset in the Cue and No Cue conditions than in the Step-to-Cue condition: for the 5 subjects who stepped in the Cue condition, their stability margins were 2.6 ± 0.9 cm in the Cue condition and 4.2 ± 1.7 cm in the Step-to-Cue condition [$T = 3.23$; $P < 0.05$], and for the 9 subjects who stepped in the No Cue condition, their stability margins were 2.5 ± 0.8 cm in the No Cue condition and 4.5 ± 1.6 cm in the Step-to-Cue condition [$T = 3.44$; $P < 0.01$].

Although we counterbalanced the order of the conditions across the subjects, we performed two analyses to ensure that the order of the conditions did not contribute to the difference in the number of trials with steps between the Cue and No Cue conditions. First, we determined that the relative order of the Cue and No Cue conditions did not significantly contribute to the result that more steps were observed in the No Cue condition: after splitting the 12 subjects into two groups of 6 subjects based on the order that they performed the Cue and No Cue conditions, a two-sided t-test determined that the cue-related difference in the subjects' number of trials with steps was not significantly different between the subjects who performed the Cue condition before the No Cue condition and those who performed the Cue condition after the No Cue condition

[$T = 0.45$, $P = 0.67$]. In a second analysis on condition order, we determined that inserting the Step-to-Cue condition did not bias the subjects toward taking more steps in the condition performed immediately after the Step-to-Cue condition: after splitting the number of trials with steps according to whether the steps occurred in a condition immediately preceding or following the Step-to-Cue condition, a two-tailed t-test determined that there was no significant difference in the number of trials with steps between the condition that preceded the Step-to-Cue condition and the condition that followed the Step-to-Cue condition [$T = 0.59$, $P = 0.57$]. A graphical analysis of the group's total number of steps exhibited in each trial (data not shown) suggested that there were more steps in the first five trials of a condition than in the subsequent 5-trial blocks, and that this trial-related effect was more evident in the No Cue condition than in the Cue condition. Nevertheless, the number of steps remained consistently greater in the No Cue condition than in the Cue condition throughout all 40 trials, and trial-related changes in the number of steps taken by the group were not evident after the first 5 trials.

During the 500 ms immediately preceding the perturbations, the subjects' initial CoP positions were similar between the Cue and No Cue conditions: the subjects' initial CoP positions (relative to the position of their heels) were, on average (± SD), held at 10.7 ± 1.3 cm in the Cue condition and at 10.6 ± 1.3 cm in the No Cue condition [$T =$ 1.66, $P = 0.13$]. The subjects' stability margins were significantly smaller in the No Cue condition than in the Cue condition [$T = 3.81$, $P < 0.005$] (Fig. 2E), and this effect remained after excluding trials with steps from the analysis [$T = 3.79$, $P < 0.005$]. Graphical analysis (data not shown) suggested that stability margins were similar across all 40 trials within a condition.

Cortical Modulation and Response Modification

The difference in the subjects' peak readiness potential amplitudes between the Cue and No Cue conditions correlated with the difference in the stability margins between the Cue and No Cue conditions [Pearson r = 0.59; $P < 0.05$] (Fig. 2F). Unlike in Experiment One, however, the difference in the subjects' peak readiness potential amplitudes between the Cue and No Cue conditions did not significantly correlate with the difference in the number of trials with steps between the Cue and No Cue conditions [Spearman rho = 0.45; $P = 0.15$].

Experimental Observations

One subject stepped more often in the Cue condition than in the No Cue condition, and this subject was also the only subject to exhibit a larger readiness potential in the No Cue condition than in the Cue condition. Taking notice of these results during the experiment, we asked the subject whether she was paying attention to the cue, and the subject reported that she did not pay attention to the cue. Although we report the subject's original data, directly after completing the experiment, the subject performed the Cue condition a second time with explicit instructions to pay close attention to the cue. Compared to the first performance in the Cue condition, the subject's readiness potential became more negative in the second performance, and the number of trials with steps also decreased in the second performance.

As another experimental observation, it may be worthy to note that many of the Asian subjects tested in Experiment Two reported and performed a very different preferred response strategy than what was reported and performed by the American and

Results of Experiment Two

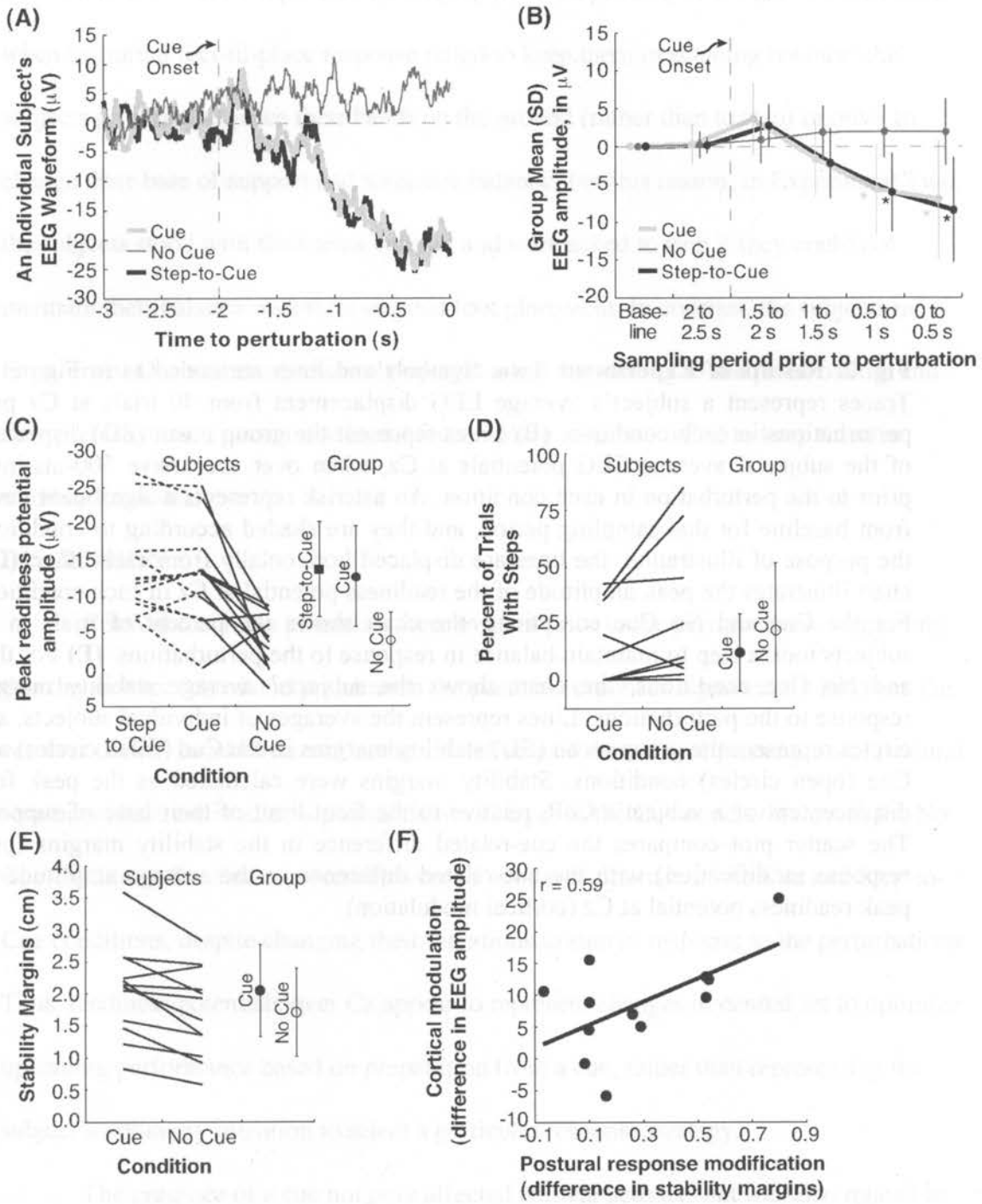

Fig. 2. Results of Experiment Two. Symbols and lines are coded as in Figure 1. **(A)** Traces represent a subject's average EEG displacement from 40 trials at Cz prior to perturbations in each condition. **(B)** Lines represent the group mean (SD) displacements of the subjects' average EEG potentials at Cz, taken over successive 500-ms intervals prior to the perturbation in each condition. An asterisk represents a significant deviation from baseline for that sampling period, and they are shaded according to condition. For the purpose of illustration, the lines are displaced horizontally from each other. **(C)** The chart illustrates the peak amplitude of the readiness potential at Cz in each condition. **(D)** For the Cue and No Cue conditions, the chart shows the percent of trials in which subjects took a step to maintain balance in response to the perturbations. **(E)** For the Cue and No Cue conditions, the chart shows the subjects' average stability margins in response to the perturbations. Lines represent the averages of individual subjects, and the circles represent the group mean (SD) stability margins in the Cue (filled circles) and No Cue (open circles) conditions. Stability margins were calculated as the peak forward displacement of a subject's CoP, relative to the front limit of their base of support. **(F)** The scatter plot compares the cue-related difference in the stability margins (postural response modification) with the cue-related difference in the average amplitude of the peak readiness potential at Cz (cortical modulation).

European subjects tested in Experiment One. Specifically, the subjects in Experiment Two exhibited a very deep flexion at the hip when responding to the perturbations and, when the initial feet-in-place response failed to keep them in standing balance, the subjects preferred to place their hands on the ground (rather than to step) in order to change their base of support and reacquire balance. For this reason, in Experiment Two, the subjects stood with their arms crossed and were asked to step if they could not maintain their balance with their original foot placement. In contrast, the subjects in Experiment One remained relatively upright when responding to the perturbation, and they preferred to step when the initial feet-in-place response failed to keep them in standing balance.

DISCUSSION

Cortical readiness potentials were evident prior to the perturbations, suggesting that the anticipation of and preparation for postural responses significantly involves the cerebral cortex. In addition, at Cz, the cue influenced the cortical preparation of postural responses, because readiness potentials were larger in the Cue condition than in the No Cue condition. Readiness potentials were of similar magnitude in the Cue and Step-to-Cue conditions, despite changing their intentions to step in response to the perturbations. Thus, readiness potentials over Cz appear to represent changes in central set to optimize upcoming performance based on preparation from a cue, rather than representing the subject's voluntary intention to select a particular response strategy.

The presence of a cue not only affected cortical activity, but was also related to how successful the subjects were to withstand the perturbation: compared to the No Cue condition, the subjects stepped less often and exhibited larger stability margins in the Cue

condition. These cue-related effects were evident regardless of the order in which the conditions were presented, suggesting that the cue itself – not the order in which the conditions occurred – mediated the subjects' ability to maintain balance. The subject group did exhibit a trial-by-trial decrease in the number of steps taken (particularly in the first 5 trials and in the No Cue condition), without a trial-by-trial change in stability margins, suggesting that the subjects changed their perceived need to step during the initial trials of a condition, but the group exhibited smaller stability margins and more trials with steps in the No Cue condition than in the Cue condition, regardless of trial number. Therefore, no effects of condition order were evident in the number of trials with steps, despite trial-by-trial learning being primarily evident in the No Cue condition, because the trial-by-trial learning peaked early within the 40-trial condition and was related only to stepping, not to stability margin.

In addition, subjects with the biggest difference in the number of trials with steps between the Cue and No Cue conditions were also the subjects with the largest number of trials with steps in the No Cue condition. Thus, in the No Cue condition, subjects who were least capable of withstanding the perturbation without a step improved the most in the Cue condition. Steps in the Cue and No Cue conditions likely represented the subjects' inability to withstand the perturbation, rather than representing a choice to step before becoming unstable, because steps in the Cue and No Cue condition occurred later (well after the perturbation ended) and only after the subjects reached significantly smaller stability margins compared to the steps taken in the Step-to-Cue condition (which were initiated at larger margins of stability when the platform was still moving). Taken together, the results suggest that the subjects used the temporal signal provided by the cue

to optimize their postural response, if needed, in such a way as to maximize stability margins and decrease the need to step for balance recovery.

Furthermore, the optimized performance exhibited by the subjects in the Cue condition cannot be explained by anticipatory changes in their initial posture, because the cue-related improvements in the subjects' postural responses were evident in both experiments, despite constraining the subjects' initial stance positions in Experiment Two. Thus, improvements in the subjects' performance likely represent modifications to the postural response itself.

These cue-related optimizations in the postural responses were related to the cue-related changes in cerebral activity: in Experiment One, the difference in the peak readiness potential between the Cue and No Cue conditions correlated with the difference in the number of trials with steps between these conditions and, in Experiment Two, the cue-related difference in the peak readiness potential correlated with the cue-related difference in the stability margins. That is, between the Cue and No Cue conditions, the subjects' cortical modulations at Cz significantly correlated with the subjects' modifications of their postural responses. Because readiness potentials occur before the postural perturbation and represent motor preparation (van Boxtel and Brunia 1994), these correlations suggest that the cerebral cortex mediates the optimization of postural responses.

Despite similarities among the results of Experiment One and Experiment Two, some notable differences were evident. First, in the No Cue condition, the average EEG waveforms demonstrated no evidence of a readiness potential in Experiment Two, whereas in Experiment One, the waveforms still exhibited negative deviations in the

signal (albeit of smaller amplitude and more variable timing than the readiness potentials observed when the subjects were provided with a cue). In addition, for the conditions with cues, the readiness potentials were of greater amplitude and exhibited a more consistent negative drift in Experiment Two than in Experiment One. We speculate that these differences were due to doubling the number of trials performed in Experiment Two. That is, we suspect that the subjects always attempted to anticipate the onset of the perturbation, but without the benefit of the warning cue in the No Cue condition, the subjects were unable to temporally couple their response preparation with the perturbation. Thus, over separate trials, the subjects' cerebral potentials would occur at different times prior to the perturbation and, over repeated trials, these potentials would progressively offset each other in the average EEG waveform. This speculation is consistent with previous studies demonstrating that decreased potential amplitudes correspond to an increased difficulty in predicting response timing when testing subjects under different preparatory periods (McAdam et al. 1969; Maeda and Fujiwara 2006). In contrast, during the conditions with cues, the subjects could consistently couple their response preparation with the perturbation and, consequently, their average EEG potentials progressively increased with repeated trials.

In addition to differences in the shape of the subjects' readiness potentials, the results of the two experiments differed in whether the cue-related difference in the number of trials with steps significantly correlated with the cue-related difference in the readiness potential. We suspect that the relationship between step trials and cortical potentials was lost in Experiment Two because trials with steps were relatively rare in Experiment Two.

The subjects in Experiments One and Two also differed in their preferred response to this perturbation, and this observation may underscore a potentially important cultural difference in strategies used to maintain balance in response to an external postural perturbation. The subjects in Experiment Two were Asian, while the subjects in Experiment One were primarily American or European, and studies have demonstrated significant differences in the propensity to fall between these cultures (Fujiwara et al. 1993; Aoyagi et al. 1998; Davis et al. 1999). In this study, we observed that the Asian subjects responded to the perturbations with deep hip flexions, and they preferred to place their hands on the floor if their initial feet-in-place responses were not sufficient to maintain standing balance. In contrast, the American and European subjects remained upright in response to the perturbations, and they preferred to step if their initial feet-in-place responses failed to keep them in standing balance. In addition, the subjects in Experiment Two were able to withstand the perturbations without stepping in a higher percentage of trials than the subjects in Experiment One, suggesting that the perturbation was easier for the subjects in Experiment Two. Cross-cultural studies examining response strategies to external perturbations of balance, therefore, may provide insight into optimal control strategies for the prevention of falls.

Despite different ethnicities, characteristics, and postural behaviors, however, the two subject groups both demonstrated cue-related changes in cortical activity that were correlated to cue-related changes in postural responses. Thus, the concept of utilizing anticipatory cortical activity to modify postural responses through changes in central set represents a robust neuro-motor behavior and does not appear to be dependent on an individual's ethnicity or preferred response strategy.

The cerebral cortex may influence postural responses only when actively attending to postural preparation. We observed one subject who performed more trials with steps in the Cue condition than in the No Cue condition, and this subject's peak readiness potential was also larger in the No Cue condition than in the Cue condition. With explicit instructions to pay attention to the cue, however, the subject stepped less often and increased her readiness potential compared to the first performance of the Cue condition. This observation highlights the notion that attention contributes to the production of cued cerebral readiness potentials (Tecce 1972) and to the performance of postural responses (Norrie et al. 2002).

The role of attention on postural modification emphasizes a major methodological consideration when extrapolating our results to postural behavior outside a laboratory setting. Our studies only tested subjects in conditions in which the subjects expected a perturbation. Because readiness potentials prior to cued responses are dependent on attention to the cue (Tecce 1972), the results suggest that the activation of cortical circuits to optimize postural responses can only occur in situations where a loss of balance is anticipated. In addition, our study only examined responses to a single type of perturbation, requiring further study to determine whether activity at the cerebral cortex can optimize postural responses when perturbation characteristics are unpredictable. Therefore, the cerebral cortex may play a more limited role in shaping reactive postural responses to unexpected or unpredictable perturbations.

In summary, our study demonstrated that the cerebral cortex influences postural responses to external perturbations of balance through changes in anticipatory central set, suggesting that movements once considered automatic might be susceptible to voluntary

control. Because the cerebral cortex may similarly influence both the modification of voluntary movements and the modification of postural responses, techniques that are used to train voluntary movements (e.g., repetitive training and visualization techniques) may also be useful to train postural responses. Thus, individuals with impaired balance may benefit from cognitive training of their postural responses to optimize balance control (Rogers et al. 2003b; Jobges et al. 2004; Woollacott et al. 2005; Maffiuletti et al. 2005).

CHAPTER 4

Pre-Selection of Postural Responses Prior to Unpredictable External Perturbations

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ABSTRACT

Previous research on human balance recovery suggests that, prior to an externally triggered postural perturbation, healthy subjects can pre-select their postural response based on the environmental context, but it is unclear whether this pre-selection includes the selection of a stepping leg when performing compensatory steps. We sought to determine how pre-selecting a stepping limb affects the compensatory steps and stability of young, healthy subjects when responding to postural perturbations. Nine healthy subjects (24-37 years of age) stepped in response to backward translations of a platform under their feet when, prior to the perturbations, the subjects either knew whether they were to step with their left or right leg to a visual target (the Predictable condition) or did not know whether to step with their left or right leg until one of two targets appeared at perturbation onset (the Unpredictable condition). The Unpredictable condition also included randomly inserted trials of toes-up rotations and catch trials, consisting of backward translations without targets. The results showed that, in the Predictable condition, the subjects consistently exhibited one anticipatory postural adjustment (APA; a lateral weight shift) before stepping accurately to the target with the correct leg. In the Unpredictable condition, the subjects either exhibited (1) multiple APAs, late step onsets, and forward center-of-mass (CoM) displacements that were farther beyond their base of support, or (2) an early step with only one APA and kept their CoM closer to the base of support, but also stepped more often with the incorrect leg. Thus, when the subjects had to select a stepping leg at perturbation onset, they either became more unstable and used multiple APAs to provide enough time to select the correct stepping leg, or they stepped earlier to remain stable but often stepped with the incorrect leg. In addition, responses to

catch trials in the Unpredictable condition included distorted step placements that resembled steps to anticipated targets, despite allowing the subjects to step with a leg of their choice and to a location of their choice. Lastly, the subjects' voluntary stepping latencies to visual targets presented without perturbations were twice as long as their stepping latencies to the backward platform translations. Therefore, healthy subjects appear to pre-select their stepping limb, even when the perturbation characteristics are unpredictable, because relying on visual input provided at perturbation onset requires a delayed response that leads to greater instability.

INTRODUCTION

The ability of individuals to recover from a sudden loss of balance is essential for preventing falls and their resulting injuries. Balance recovery depends on the selection of a postural response that is appropriate for the environmental context. For example, when a person slips while crossing a stream along a path of mossy rocks, that person must quickly step to the next available stone in order to prevent falling into the water, thereby requiring the rapid selection of the proper stepping limb and an appropriate step trajectory. Because voluntary visual reaction times are slow relative to the onset of a compensatory step (McIlroy and Maki 1996), it is likely that a subject utilizes visual input to pre-select a stepping foot and step trajectory in advance of a perturbation, rather than online during the impending fall (Zettel et al. 2005).

Studies have shown that healthy subjects pre-select their postural response strategy prior to externally triggered perturbations by accounting for pre-existing environmental or situational cues. For example, healthy subjects modify their postural responses based on (a) the predictability of perturbation characteristics (Burleigh and

Horak 1996; Rogers et al. 2003a), (b) instruction to change their intended response from a feet-in-place strategy to a stepping strategy (McIlroy and Maki 1993a,b; Burleigh et al. 1994; Burleigh and Horak 1996), (c) previously seen obstacles that constrain the step trajectory (Zettel et al. 2002a,b, 2005), and (d) a secondary motor task, such as holding an object in their hands (Bateni et al. 2004).

The literature also suggests that a certain level of response pre-selection may be possible even when the characteristics of a perturbation are unpredictable. For example, Burleigh and Horak (1996) demonstrated that healthy subjects successfully perform a postural response according to their pre-selected intent to either step or to remain with their feet in place, even when the perturbation onset and velocity varied unpredictably. In addition, Zettel et al. (2005) demonstrated that, when healthy subjects responded to anticipated perturbations of unpredictable timing and direction, in the majority of trials, the subjects were able to take a compensatory step over an obstacle without redirecting their gaze to the floor. This result suggests that healthy subjects do not require online visual input to avoid an obstacle during balance recovery because they pre-select the stepping strategy, their stepping limb, and their step trajectory prior to the perturbation. That is, in anticipation of an impending loss of balance and with knowledge of an obstacle placed in front of them, the subjects seemed to prime their postural response with a contingency plan such that, if a perturbation caused them to fall forward, then they would maintain balance and avoid the obstacle by taking a step with a specific foot and trajectory. In addition, when responding to perturbations with unpredictable velocities, directions, and amplitudes, subjects step consistently with a dominant foot and can readily change their choice of stepping foot when instructed to do so in advance of an

upcoming perturbation (unpublished data, see Appendix 1 and Results for confirmation of these personal observations). In general, then, previous studies suggest that a subject may prime a response by pre-selection prior to anticipated, unpredictable perturbations, and then the characteristics of the perturbation would trigger and further shape the primed response (Horak 1996). Previous research, however, has not explicitly tested the hypothesis that the stepping limb is pre-selected for compensatory stepping responses to unpredictable perturbations.

In addition to the above observations, our hypotheses and predictions for this study were motivated and defined by our observations that abnormal response selection may underlie postural instability during balance recovery in patients with Parkinson's disease (Horak et al. 1992; Jacobs et al. 2005a,b). For example, whereas healthy subjects respond to anticipated backward surface translations with one anticipatory postural adjustment (APA; a lateral weight shift preceding a step) before taking a forward compensatory step to recover their balance, subjects with Parkinson's disease often respond to these surface translations with multiple APAs and a less consistent choice of stepping limb, or they often fall after exhibiting multiple APAs because they fail to initiate a compensatory step (Jacobs et al. 2005b, see Appendix 1). Because the APA represents a preparatory process that is specific for the movement that it precedes (Massion 1992), the direction of an APA (toward either the left or right leg) provides information about which leg a subject originally intended to step with before initiating the swing phase of a step. Multiple APAs and an inconsistent choice of stepping limb, therefore, may be related to an inability to pre-select a single stepping limb. If patients with Parkinson's disease exhibit multiple APAs prior to compensatory stepping because

they select their stepping limb online, then requiring online selection of a stepping limb in healthy subjects should also result in multiple APAs and instability.

To test the hypotheses that healthy subjects can pre-select a compensatory stepping limb prior to unpredictable postural perturbations and that online response selection impairs stability when responding to a postural perturbation, nine healthy subjects stepped to maintain standing balance in response to backward translations of a platform under their feet. The subjects responded to the platform translations in 3 conditions: (1) when stepping naturally with a predetermined leg, (2) when stepping to a known target location with a predetermined leg, and (3) when stepping to one of two target locations that determined the subjects' stepping leg at perturbation onset. We hypothesized that subjects normally pre-select which leg they will step with in advance of an anticipated postural perturbation such that, when subjects are forced to select their stepping leg at perturbation onset, postural stability becomes compromised. Thus, we predicted that, with online response selection, subjects initiate their APAs later and exhibit multiple APAs during the selection process, thereby increasing the latency of the step's swing phase. We further predicted that this late response then causes the subjects to become unstable because their center of mass (CoM) continues to fall forward, away from their base of support, as they select their stepping limb. To further support our hypothesis that subjects can pre-select a postural response when the perturbation characteristics are unpredictable, we predicted that, when subjects respond to perturbations without being required to step to a target (amidst the possibility of having to step to a target), the subjects would exhibit response characteristics that suggest they had

pre-selected their step characteristics by stepping with an APA and step trajectory that are similar to those of pre-planned steps taken to a predictably presented target.

METHODS

Subjects and Protocol

Nine healthy subjects (7 males and 2 females) with no neurological or neuromuscular impairment gave written informed consent to participate in the protocol, consistent with the Helsinki agreement. The Institutional Review Board of Oregon Health & Science University approved the protocol. On average, subjects were 31 years old (range = 24-37 yr) and 1.73 m tall (range = 1.61-1.83 m), and weighed 71 kg (range = 53-93 kg).

The task was for the subjects to stand on a movable platform with each foot on a force plate and then take forward compensatory steps to recover balance in response to backward translations of the platform. The subjects stood in a stance width that equaled 11 % of their body height as measured from the center of one heel to the center of the other. The perimeters of the subjects' feet were marked with tape to ensure that stance width remained consistent throughout the experiment. We monitored the force distribution of the 2 force plates under the subjects' feet by an oscilloscope to ensure that the subjects stood with an equal amount of weight under each foot. To prevent the subjects from falling to the ground, they were harnessed to a ceiling-mounted track that did not provide any support during the task unless they began to fall. The subjects also held a small, lightweight wooden dowel (2 cm in diameter, 66 cm long, and 113 g in weight) behind their back with both hands to prevent their arms from swinging in response to the platform movement (Zettel et al. 2002a,b).

The task involved 3 blocked and ordered conditions: first, the No Target condition, second, the Predictable condition, and third, the Unpredictable condition. In the No Target condition, the subjects knew that the platform would translate backward, and they stepped "naturally" (i.e., without specific instructions about where to place their step) with a predetermined leg in response to the perturbation. In the Predictable condition, the subjects knew that the platform would translate backward, and they stepped with a predetermined leg so that their big toe landed on a known visual target that turned on at perturbation onset. The Unpredictable condition was designed to require the subjects to select their stepping limb online, after the onset of the perturbation. Thus, in the Unpredictable condition, the subjects responded to randomized combinations of perturbations and target presentations that included (1) toes-up rotations of the platform without a target, (2) backward platform translations with a target presented in front of the left leg, (3) backward platform translations with a target presented in front of the right leg, and (4) catch trials, consisting of backward translations without a target. Prior to performing the Unpredictable condition, the subjects were instructed to either (1) respond naturally if the platform rotates their toes upward and forces them to sway backward, (2) step naturally with a leg of their choice if a target light does not turn on and the platform translates backward, (3) step with their right leg so that their big toe lands on the target if a target appears in front of their left leg when the platform translates backward, or (4) step with their left leg so that their big toe lands on the target if a target appears in front of their right leg when the platform translates backward. Thus, because we randomized the perturbation characteristics and the presentation of the targets, unlike in the No Target and Predictable conditions, the subjects were not informed about which leg they were to

step with, where they were to step to, or to which perturbation they'd respond. The catch trials were included to enable us to observe whether the subjects were pre-selecting a stepping limb and step trajectory because, if subjects step with the right limb toward the left target or step with the left limb toward the right target, then the results would suggest that, in anticipation of having to step to a target, the subjects pre-selected a targeted step even with no target and no step constraints actually present.

In the Predictable and Unpredictable conditions, the target consisted of a point of green light (0.5 cm in diameter) from a ceiling-mounted laser source shining on the ground. The target was uniquely positioned directly in front of the big toe of the subject's stance limb and at 125% of the average anterior-posterior length of each subject's compensatory steps, as calculated from the compensatory steps taken in the No Target condition (Fig. 1). The light was positioned in front of the stance limb and beyond the subjects' natural step length to accentuate the subjects' APAs because long, narrow compensatory steps are associated with larger APAs (Zettel et al. 2002a,b), and we wanted to increase the probability of generating an APA in order to determine precisely when the subjects selected a particular stepping response. The target placement also forced the subjects to step to a position that was different from their preferred step placement (as evidenced in the No Target condition), as though the subjects were made to recover their balance around obstacles that prevent natural step placement. In addition, altering the subjects' step trajectory allowed us to observe whether the subjects pre-selected a targeted step during the catch trials in the Unpredictable condition. For trials with targets, the target turned on 2 ms prior to when the platform began moving, and the

target remained on until after a trial was complete. The room was well lit, and all subjects reported that the green-light targets were readily visible.

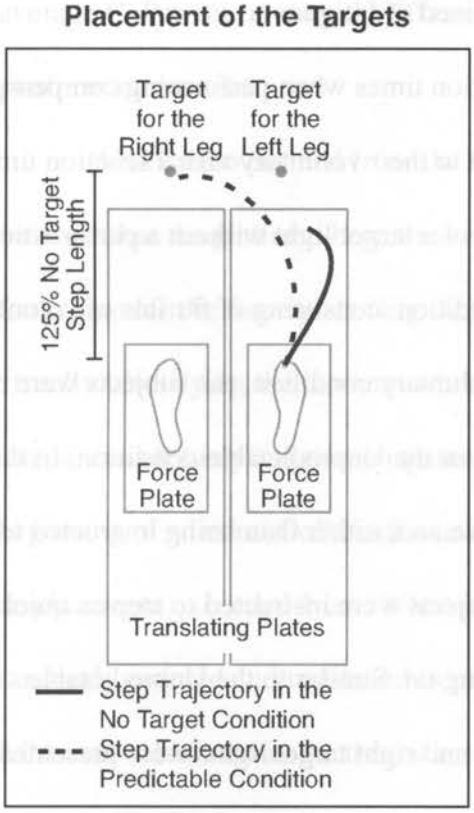


Fig. 1. Description of the compensatory stepping task. The gray circles denote the positions of the targets at 125% of each subject's step length, as recorded in the No Target condition, and in front of the big toe of the stance limb. The dashed curve shows the trajectory of a step taken with the right foot in the Predictable condition; and the solid curve, in the No Target condition. The subjects were instructed to step to the target that was positioned in front of their stance limb, leading to a longer, narrower step placement. Only one target was turned on for each trial.

For all conditions, the backward platform translations consisted of a 435-ms, 24-cm ramp displacement of the support surface that reached a peak velocity of 55 cm/s in 34 ms, leading to an average initial acceleration of 16 m/s^2. In the Unpredictable condition, the toes-up rotations consisted of a 150-ms, 7° rotation around the ankle axis at a peak velocity of 70 °/s. The No Target and Predictable conditions each consisted of 10 trials, corresponding to 5 compensatory steps with each leg. The Unpredictable condition consisted of a total of 60 trials: 20 trials of backward platform translations with targets (10 trials each for the targets presented in front of the left and right legs), 30 trials of toes-up rotations without targets, and 10 catch trials of backward platform translations without

targets. At a minimum, all subjects were given a rest after each condition and, in addition, were allowed to rest whenever they requested. When resting, the subjects rested until they felt ready to continue; no subject complained of fatigue.

In order to compare the subjects' reaction times when performing compensatory steps in response to the platform perturbations to their voluntary visual reaction times when stepping in response to the presentation of a target light without a perturbation, 5 of the 9 subjects also completed a Voluntary condition, consisting of 5 trials of voluntary steps with each foot (10 trials total). In the Voluntary condition, the subjects were cued to step by the same 2 targets that were presented in the Unpredictable condition. In the Voluntary condition, the platform did not move and, rather than being instructed to step in response to the platform movement, the subjects were instructed to step as quickly as they could in response to the target light turning on. Similar to the Unpredictable condition, in the Voluntary condition, the left and right target lights were presented in random order, the subjects initial weight loading was monitored to ensure a symmetrical weight distribution under both legs, and the subjects were instructed to step with their left foot to the target presented in front of their right foot and to step with their right foot to the target presented in front of their left foot.

Data Collection and Statistical Analyses

To capture the subjects' APAs, we recorded the lateral displacements of the subjects' center of pressure (CoP) from two force plates, one under each of the subjects' feet. Each force plate was equipped with 4 vertical and 2 horizontal strain gauge transducers mounted on the movable platform. Force signals were amplified and sampled at 480 Hz. Total-body lateral CoP was calculated from the difference in loading of the

right and left force plates as previously reported by Henry et al. (1998). Lateral CoP displacements were calculated from an initial CoP position, which was defined as the average CoP position over the 500 ms that immediately preceded the onset of the platform movement.

APAs were defined from the lateral CoP displacements that occurred within the moment that the platform began moving to the moment when the big toe of the stepping foot came off the force plate (Fig. 2). The onset of an APA was defined manually, by visually identifying the moment when the CoP began to displace laterally, using an interactive plotting function programmed in Matlab software (Mathworks, Inc.). The beginning of a lateral CoP displacement was only identified as the onset of an APA if the displacement exceeded 1 cm. When identifying APA onsets, the CoP plots were randomly ordered and unlabeled to prevent biased identifications. The onset latency of an APA was calculated as the time when an APA began, minus the time when the platform began to move. The duration of an APA was calculated as the time when the lateral CoP displacement came back to its initial position just prior to when a subject lifted a foot off the force plate, minus the time when the APA began (Fig. 2b). We defined multiple APAs to occur if, after an initial APA, the subject did not lift a foot off the ground and, instead, exhibited another reversal in his or her lateral CoP displacement, such that the CoP displaced more than 1 cm beyond the initial CoP position in the opposite direction from the preceding APA (Fig. 2b).

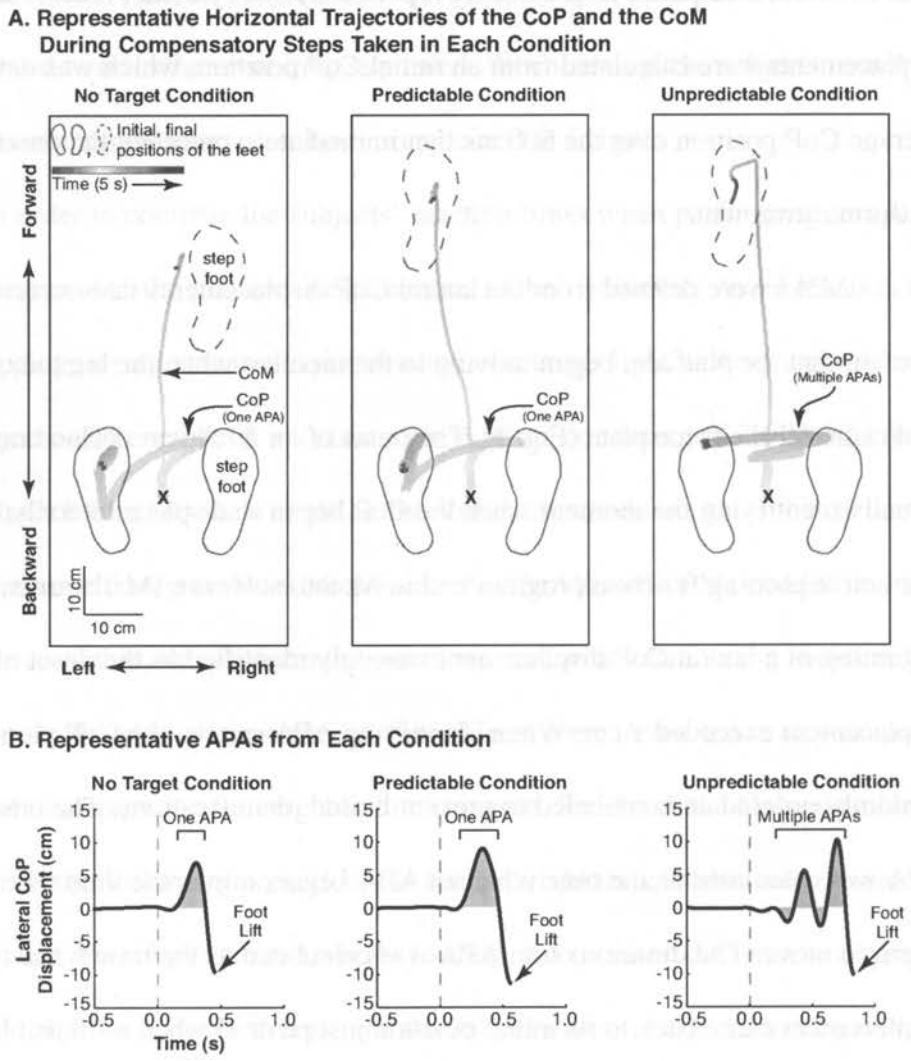


Fig. 2. Examples of APA characteristics. (A) The relationships among CoP displacements, CoM displacements, and step displacements in the horizontal plane for compensatory steps from a representative subject in each condition. Solid footprints represent the subject's initial foot positions before taking a compensatory step, and dashed footprints represent the subject's final foot positions after taking a compensatory step. Steps were taken with the right leg in these representative trials. The thick, shaded lines represent CoP displacement, and the thin, shaded lines represent CoM displacement. Time is represented by the shaded scale over a 5-second period, and the "X" marks the initial locations of the CoP and the CoM. Note how the subject exhibits APAs, characterized by a lateral shift of the CoP toward the swing limb, which moves the CoM toward the stance limb for support. **(B)** Representative lateral displacements of the CoP between perturbation onset (the dashed vertical lines) and step onset (the arrows) to show how we defined an APA (the gray-shaded regions) and how the experimental conditions modified APAs.

To capture the subjects' movements, reflective markers were positioned bilaterally at various locations on the side of the body. Specifically, markers were placed at the approximate center of joint rotation for the fifth metatarsals, ankles, knees, hips, shoulders, elbows, and wrist joints, and markers were also placed on the tip of the first toe, as well as above the eyes, in front of the ears, and on the platform. A high-resolution Motion Analysis System (Santa Rosa, CA) with 8 video cameras sampling at 60 Hz provided 3-dimensional spatial coordinate information about the displacement of body segments.

Using the marker placed on the stepping foot's big toe, we quantified the length of the subjects' steps, their foot-lift latencies, and their peak step velocities. Step length was defined by the anterior-posterior and lateral distances between the location of the toe when it left the ground (at the beginning of the step) and the location of the toe when it subsequently reached the ground (at the end of the step). The toe was defined to have left the ground when the vertical displacement of the toe marker exceeded 2 standard deviations of the initial mean position taken during the 500 ms that immediately preceded the onset of the platform movement. The latency of foot lift was defined as the time when the toe left the ground, minus the time when the platform began to move. The toe was considered to have reached the ground at the end of the step when the vertical position of the toe marker crossed back over the value that was 2 standard deviations above the initial mean position. The peak velocity of a subject's step was determined from the derivative of the big toe marker's anterior-posterior displacement (after subtracting the platform's displacement) during the swing phase of the step (i.e., between the moment

when the big toe left the ground and the moment when it subsequently reached the ground).

To determine the subjects' stability after perturbing their balance, we quantified their post-perturbation forward and lateral CoM displacements relative to the edges of the base of support. To determine each subject's CoM, we collected 26 anthropometrical measures of length, width, and circumference for the head, limbs, and trunk, as well as each subject's body height and weight (Chandler et al. 1975). These measures, in addition to the kinematic data, were used to calculate the CoM position for each segment in the anterior-posterior and lateral directions. Total-body CoM was calculated as a weighted sum of the CoM position for each segment (Vaughan et al. 1991). The position of CoM for each subject was calculated at 3 moments: (1) prior to the perturbation, during a 950-ms baseline period beginning 1 second prior to the perturbation and ending 50 ms prior to the perturbation, (2) after the perturbation but before step onset, when the CoM reached its peak forward displacement between the moment when the platform began moving and the moment when the subject lifted a foot off the ground, and (3) after the compensatory step, when the CoM reached its peak forward or lateral displacement after the subject placed the foot on the ground. The sagittal CoM positions were calculated relative to the position of the front limit of a subject's base of support. The location of the front limit of a subject's base of support was defined to be the location of the marker placed on the big toe of the forward-most foot at the moments of the subject's peak CoM displacements (i.e., the toe position at the moment of the peak CoM displacement before step onset and the toe position at the moment of the peak CoM displacement after the step). The initial lateral CoM positions were calculated relative to the midpoint between the markers

placed on the subjects' left and right fifth metatarsals. The peak lateral CoM displacement occurring after the compensatory step was calculated relative to the position of the marker placed on the fifth metatarsal of the subjects' swing limb in order to represent how close the CoM traveled toward the lateral edge of the subjects' base of support.

When statistically comparing the effects of the experimental conditions on the subjects' postural responses, from the Unpredictable condition, we did not include results from the toes-up rotations or the catch trials without targets. Thus, from the Unpredictable condition, we included only those trials in which the subjects took compensatory steps to a target. We also excluded any trials in which the subjects stepped with the incorrect leg (e.g., if they stepped with the right leg when the target appeared in front of their right leg) because we wanted to characterize the subjects' correct responses. Separate analyses were performed to correlate the subjects' propensity for making an incorrect response with their foot-lift latencies and incidence of trials with multiple APAs. In addition to these statistical comparisons, we also report descriptive statistics regarding the subjects' response characteristics in the Voluntary condition, as well as when responding to the catch trials in the Unpredictable condition.

Results from each subject's trials were averaged for each experimental condition. We compared the percent incidence of subjects exhibiting zero, one, or multiple APAs in each experimental condition with separate, single-factor repeated-measures ANOVAs. Within these ANOVAs, the factor for CONDITION was defined by 3 levels that corresponded to the No Target, Predictable, and Unpredictable conditions. Because multiple APAs were almost entirely unique to the Unpredictable condition (see Results;

Fig. 3a), we split the subject averages in the Unpredictable condition according to whether the subjects exhibited 0-1 APA or multiple APAs. Therefore, when analyzing the effects of the experimental conditions on all other response variables (e.g., APA latency, foot-lift latency, step length, peak step velocity, and peak CoM displacements) the single-factor repeated-measures ANOVAs were calculated with CONDITION as a 4-level (not a 3-level) factor. For each variable, we applied a Greenhouse-Geisser epsilon correction to the ANOVA statistic, which adjusts the degrees of freedom applied to the F statistic according to the level at which the data did not meet the assumption of sphericity (Greenhouse and Geisser 1959). Significance was defined as a corrected *P*-value of less than or equal to 0.05.

RESULTS

Effects of Conditions on the Subjects' APAs

Multiple APAs were most common when the subjects could not respond with a pre-selected stepping leg (Fig. 3a). The percentage of trials with multiple APAs varied significantly across the experimental conditions [$F_{(1.0, 8.4)} = 5.96$; $P = 0.04$]. Post-hoc contrasts showed that trials with multiple APAs occurred most often in the Unpredictable condition compared to the No Target [$F_{(1, 8)} = 7.12$; $P = 0.03$] and Predictable [$F_{(1, 8)} = 5.16$; $P = 0.05$] conditions. In all conditions, the subjects most often exhibited just one APA prior to taking a compensatory step in response to the backward platform movements (Fig. 3a). However, forcing the subjects to take longer, narrower compensatory steps in the Predictable and Unpredictable conditions, in contrast to the No Target condition, significantly decreased the percentage of trials without an APA

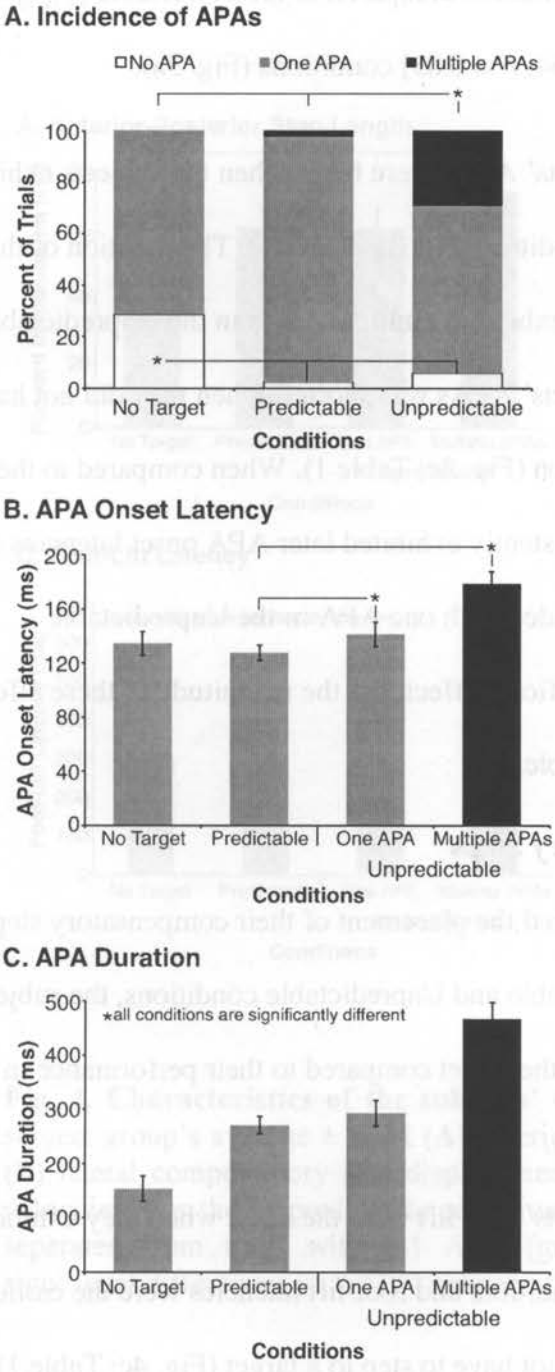


Fig. 3. Characteristics of the subjects' APAs for each condition. (A) For each condition, the subject group's average percent of trials without APAs (white bars), with one APA (gray bars), and with multiple APAs (black bars). **(B)** The subject group's average (± SEM) APA onset latencies and **(C)** APA durations in each condition. For the Unpredictable condition, trials with multiple APAs (black bars) were separated from trials with 0-1 APA (gray bars). The asterisks denote statistically significant differences ($p < 0.05$) between the conditions.

[$F_{(1.2, 9.8)} = 7.51$; $P = 0.02$]: post-hoc contrasts showed that the percentage of trials without an APA was highest in the No Target condition compared to the Predictable [$F_{(1, 8)} = 9.55$; $P = 0.02$] and Unpredictable [$F_{(1, 8)} = 6.54$; $P = 0.03$] conditions (Fig. 3a).

The onset latencies of the subjects' APAs were latest when the subjects exhibited multiple APAs in the Unpredictable condition (Fig. 3b; Table 1). The duration of the subjects' APAs was longest when they exhibited multiple APAs in the Unpredictable condition, and the duration of the subjects' APAs was shortest when they did not have to step to a target in the No Target condition (Fig. 3c; Table 1). When compared to the Predictable condition, the subjects consistently exhibited later APA onset latencies and longer APA durations when they responded with one APA in the Unpredictable condition, leading to a statistically significant effect, but the magnitude of these effects were relatively small (Fig. 3b and c; Table 1).

Effects of Conditions on Compensatory Steps

The subjects successfully modified the placement of their compensatory steps in order to reach the targets. In the Predictable and Unpredictable conditions, the subjects took longer, narrower steps in reaching the target compared to their performance in the No Target condition (Fig. 4a,b; Table 1).

The onset latencies of the subjects' foot lift were the latest when they exhibited multiple APAs in the Unpredictable condition, and foot-lift latencies were the earliest in the No Target condition when they did not have to step to a target (Fig. 4c; Table 1). When compared to the Predictable condition, the subjects consistently exhibited later foot-lift latencies when they responded with one APA in the Unpredictable condition,

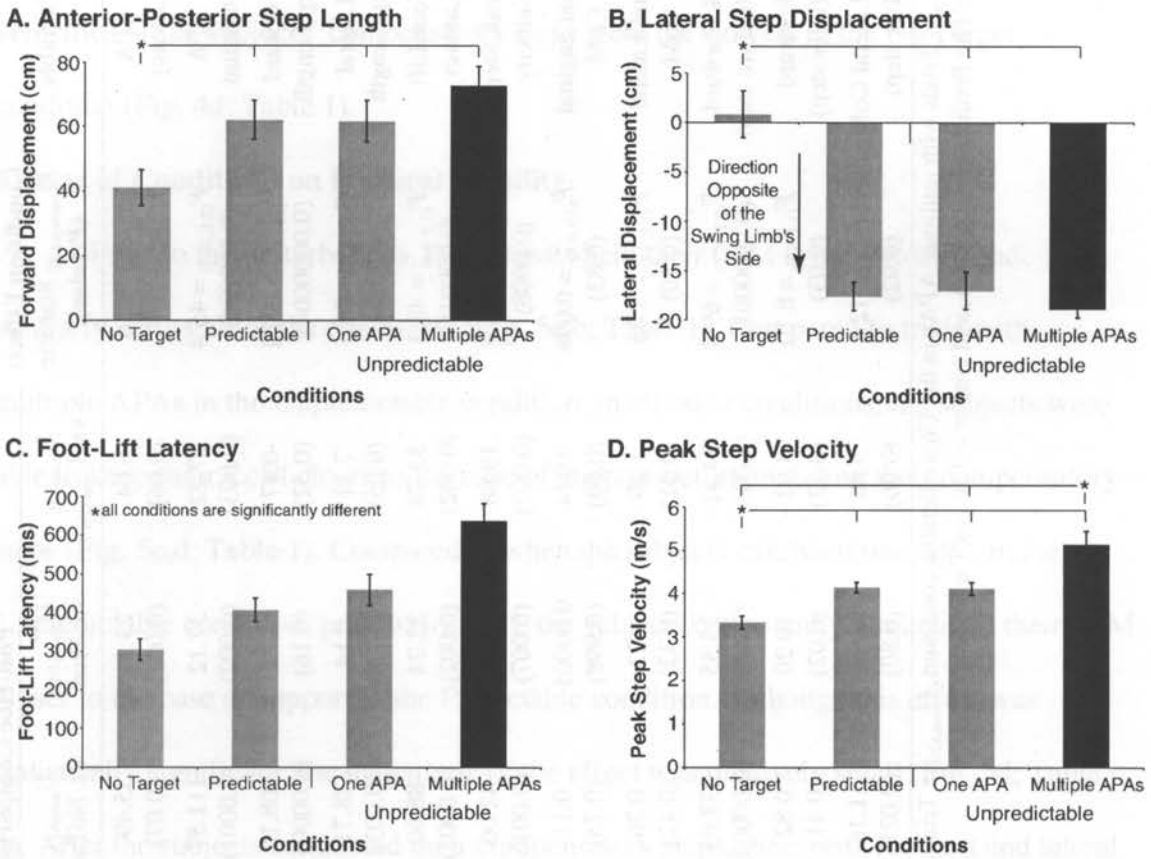


Fig. 4. Characteristics of the subjects' compensatory steps in each condition. The subject group's average ± SEM **(A)** anterior-posterior compensatory step displacements, **(B)** lateral compensatory step displacements, **(C)** foot-lift latencies, and **(D)** peak step velocities. For the Unpredictable condition, trials with multiple APAs (black bars) were separated from trials with 0-1 APA (gray bars). The asterisks denote statistically significant differences ($p < 0.05$) between the conditions.

Variable	Condition Effect: $F_{(\text{corrected df})}$ Statistic (P-value)	Post-Hoc Comparisons: $F_{(1,5)}$ Statistic (P-value)					
		$U_{multAPA}$ vs. U_{oneAPA}	$U_{multAPA}$ vs. Pred	$U_{multAPA}$ vs. NoTar	NoTar vs. U_{oneAPA}	NoTar vs. Pred	U_{oneAPA} vs. Pred
APA Latency	$F_{(1.7, 8.6)} = 7.6$ (0.01)	6.04 (0.06)	23.51 (0.005)	5.49 (0.07)	0.38 (0.56)	2.91 (0.15)	15.76 (0.01)
APA Duration	$F_{(2.1, 10.5)} = 45.4$ (0.000006)	27.22 (0.003)	37.12 (0.002)	111.57 (0.0001)	30.12 (0.003)	21.45 (0.006)	15.42 (0.01)
Forward Step Length	$F_{(1.9, 9.4)} = 104.1$ (0.0000004)	0.47 (0.52)	2.74 (0.16)	208.16 (0.00003)	114.33 (0.0001)	152.64 (0.00006)	0.57 (0.48)
Lateral Step Length	$F_{(1.2, 5.8)} = 25.5$ (0.002)	7.11 (0.05)	0.14 (0.72)	28.71 (0.003)	33.86 (0.002)	20.91 (0.006)	3.53 (0.12)
Foot-Lift Latency	$F_{(1.9, 9.4)} = 48.3$ (0.00001)	33.78 (0.002)	32.24 (0.002)	88.60 (0.0002)	55.89 (0.001)	40.34 (0.001)	9.73 (0.03)
Peak Step Velocity	$F_{(1.8, 8.8)} = 18.9$ (0.0008)	19.88 (0.007)	19.76 (0.007)	42.06 (0.001)	9.04 (0.03)	7.93 (0.04)	5.98 (0.06)
Initial Sagittal CoM	$F_{(1.3, 6.6)} = 0.098$ (0.83)	0.074 (0.80)	0.00001 (0.998)	0.11 (0.75)	0.14 (0.73)	0.59 (0.48)	0.04 (0.85)
Initial Lateral CoM	$F_{(1.5, 7.4)} = 1.35$ (0.30)	1.29 (0.31)	1.22 (0.32)	0.76 (0.42)	0.002 (0.97)	1.49 (0.28)	1.73 (0.25)
Peak Forward CoM (before step)	$F_{(2.2, 11.0)} = 69.4$ (0.0000005)	24.41 (0.005)	35.55 (0.002)	233.95 (0.00003)	72.86 (0.0004)	46.17 (0.002)	12.61 (0.016)
Peak Forward CoM (after step)	$F_{(1.1, 5.7)} = 8.10$ (0.03)	3.62 (0.12)	10.20 (0.02)	0.82 (0.41)	5.00 (0.08)	259.29 (0.00002)	26.67 (0.004)
Peak Lateral CoM (after step)	$F_{(1.1, 5.3)} = 12.1$ (0.02)	5.86 (0.06)	0.07 (0.80)	11.16 (0.021)	13.94 (0.014)	12.10 (0.018)	1.17 (0.33)

$U_{multAPA}$ = Trials with multiple APAs in the Unpredictable condition, U_{oneAPA} = Trials with 0-1 APA in the Unpredictable condition, Pred = The Predictable condition, and NoTar = The No Target condition.

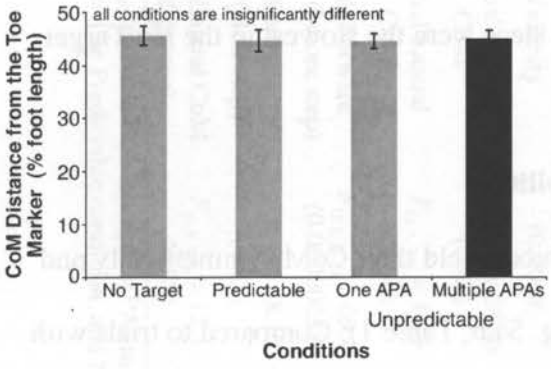
leading to a statistically significant effect, but the magnitude of the effect was relatively small (Fig. 4c; Table 1). The peak velocities of the subjects' compensatory steps were the fastest in the Unpredictable condition when they exhibited multiple APAs, and the peak velocities of the subjects' compensatory steps were the slowest in the No Target condition (Fig. 4d; Table 1).

Effects of Conditions on Postural Stability

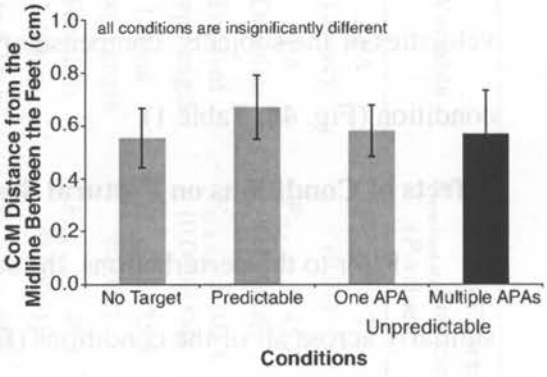
Prior to the perturbations, the subjects held their CoM symmetrically and similarly across all of the conditions (Fig. 5a,b; Table 1). Compared to trials with multiple APAs in the Unpredictable condition, in all other conditions, the subjects were able to keep their CoM closer to the base of support before initiating their compensatory steps (Fig. 5c,d; Table 1). Compared to when the subjects exhibited one APA in the Unpredictable condition, prior to foot-lift, the subjects consistently maintained their CoM closer to the base of support in the Predictable condition. Although this effect was statistically significant, the magnitude of the effect was relatively small (Fig. 5d; Table 1). After the subjects completed their compensatory steps, their peak forward and lateral CoM displacements, on average, remained within their base of support in every condition (Fig. 5d,e). The peak lateral displacements of the subjects' CoM were similar in the Predictable and Unpredictable conditions but were closer to the lateral edge of the base of support compared to the No Target condition (Fig. 5e; Table 1). Multiple steps were not evident in the No Target condition and were rare in the other conditions: multiple steps were evident, on average (± sem), in 3 ± 2% of trials in the Predictable condition and in 6 ± 2% of trials in the Unpredictable condition.

Effects of Conditions on Stability

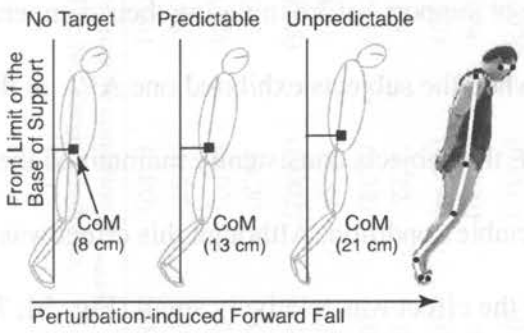
A. Initial Sagittal CoM Position



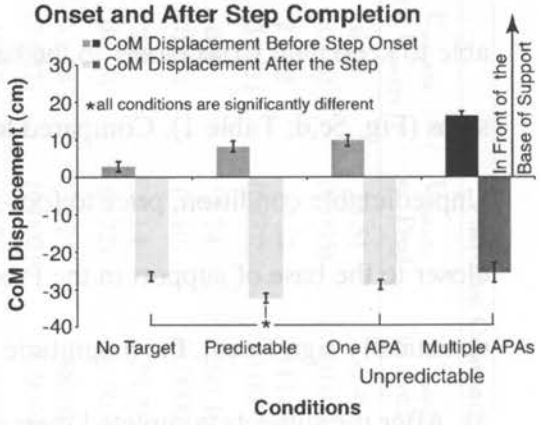
B. Initial Lateral CoM Position



C. Representative Forward CoM Displacement Before Step Onset



D. Peak Forward CoM Displacement Before Step Onset and After Step Completion



E. Peak Lateral CoM Displacement After Step Completion

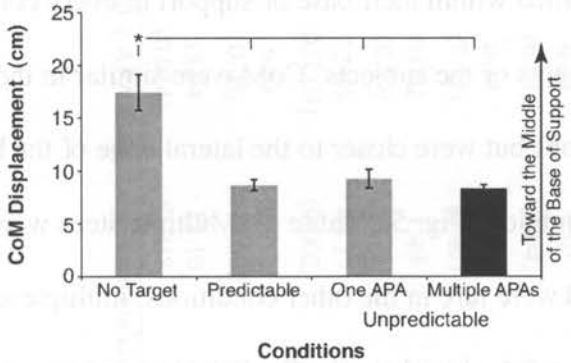


Fig. 5. Effects of conditions on stability. Average initial **(A)** sagittal and **(B)** lateral CoM positions before the perturbation. The initial sagittal CoM equals the distance to the subjects' toes, as a percent of foot length. The initial lateral CoM equals the distance from the midline between the subjects' left and right fifth metatarsals. **(C)** CoM (black square) displacements of a subject prior to step onset from trials in each condition. CoM displacements are relative to the position of the subject's big toes (black vertical line). Representing the subject's body segments, the ovals were placed according to the actual positions of the subject's kinematic markers (connected by gray lines). **(D)** For each condition, the group's average (± SEM) peak forward CoM displacements in response to the platform movement, before and after the subjects' compensatory steps; in **(E)**, the peak lateral CoM displacements after compensatory steps. For the peak forward CoM displacements, positive values represent displacements beyond the front limit of the base of support; negative values, within the base of support. Dark shaded columns represent displacements before lifting the foot off the ground to initiate a compensatory step; lightly shaded columns, after completing a compensatory step. Note that the subjects allowed their CoM to fall beyond their base of support prior to stepping, and the CoM fell farther with each condition, such that the subjects fell the farthest in the Unpredictable condition, while falling the least in the No Target condition. After completing the step, however, the subjects recovered their CoM within the base of support in every condition. For the peak lateral CoM displacements, positive values represent displacements within and toward the middle of the base of support; negative values, beyond the base of support. Note that stepping to a target elicited lateral CoM displacements closer to the lateral limit of the base of support compared to steps taken in the No Target condition. The asterisks denote statistically significant differences ($p < 0.05$) between the conditions.

Incidence and Characteristics of Compensatory Steps Taken with the Incorrect Leg

The subjects did not step with the incorrect leg when they were allowed to respond according to a pre-selected stepping limb (i.e., in the No Target and Predictable conditions), demonstrating that the subjects could readily pre-select their stepping limb based on prior instructions to step with either the left or right leg. In contrast, they stepped with the incorrect leg in 28 % of the trials (range = 10 - 60 %) in the Unpredictable condition. Multiple APAs occurred in just 1 trial for 1 subject when stepping with the incorrect leg. The subjects with the shortest foot-lift latencies stepped the most often with the incorrect leg, and the subjects with the longest foot-lift latencies stepped the least often with the incorrect leg (Fig. 6a). Further, in the Unpredictable condition, the subjects with the highest percentage of multiple-APA trials stepped the least often with the incorrect leg, and the subjects with the lowest percentage of multiple-APA trials stepped the most often with the incorrect leg (Fig. 6b).

Characteristics of Compensatory Steps Taken in Catch Trials in the Unpredictable Condition

Stepping responses to backward translations without targets in the Unpredictable condition (that is, to the catch trials) consisted of longer APA durations and foot-off latencies than those in the No Target condition, and were more similar to the APA durations and foot-off latencies observed in conditions with targets (Table 2). In the catch trials, the incidence of multiple APAs and the length of the subjects' steps were between those observed in the No Target condition and those observed in the Predictable or Unpredictable condition (Table 2).

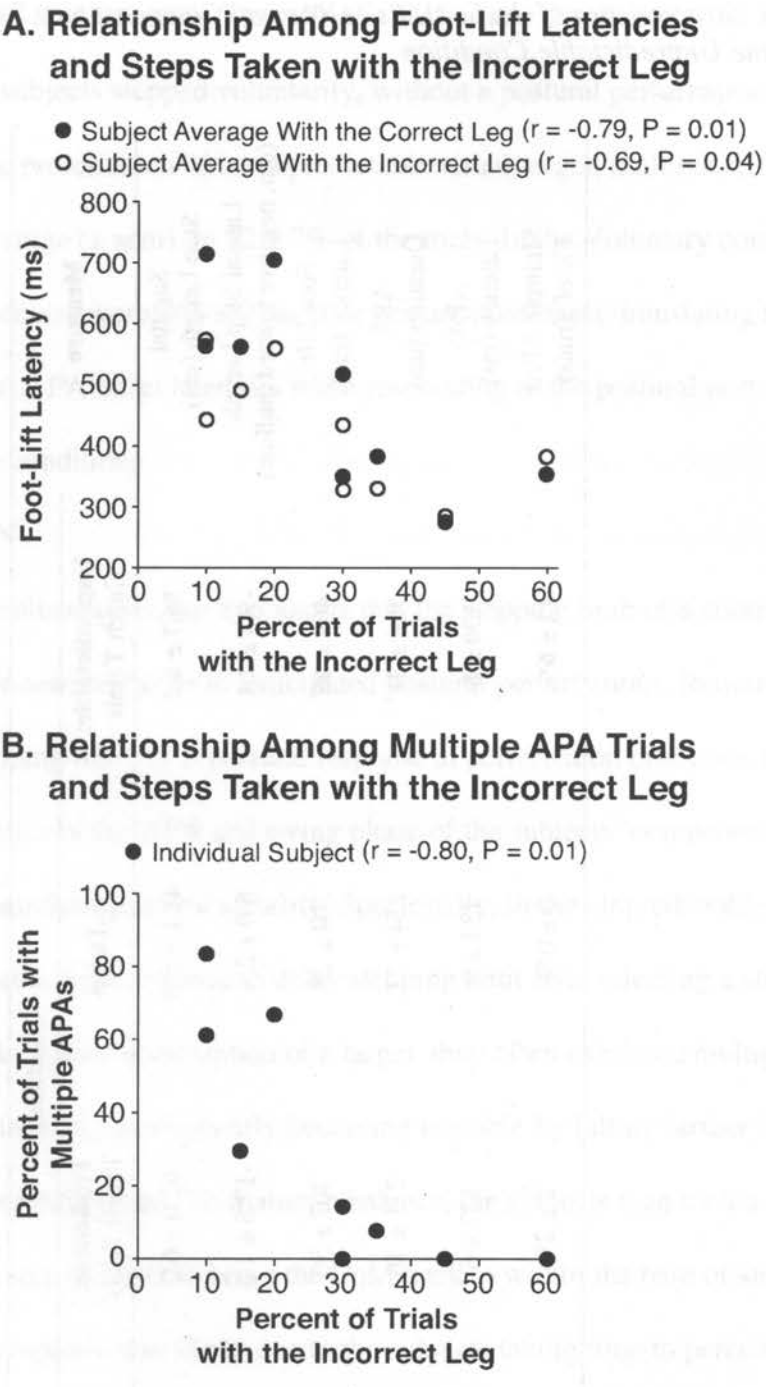


Fig. 6. Behaviors related to stepping with the incorrect leg. Charts illustrate the correlations among the percentage of trials in which the subjects stepped with the incorrect leg and **(A)** the subjects' average step onset latencies when stepping with the correct leg (solid circles) or the incorrect leg (hollow circles), and **(B)** the percentage of trials in which the subjects exhibited multiple APAs in the Unpredictable condition. The reported "r"-values represent Pearson correlation coefficients and the "P"-values, significance of the correlation.

Table 2. *Characteristics of the Subjects' APAs and Compensatory Steps in the No Target Trials of the Unpredictable Condition*

Measure	Condition			
	Unpredictable: Catch Trials	No Target	Predictable: Target Trials	Unpredictable: Target Trials
Sagittal Step Length (cm)	**56.7 ± 6.5**	41.1 ± 5.5	62.0 ± 6.0	61.6 ± 6.3
Lateral Step Length (cm, negative toward midline)	**-9.4 ± 2.1**	8.0 ± 2.4	-17.6 ± 1.5	-15.7 ± 2.0
Foot-Lift Latency (ms)	**469 ± 45**	304 ± 28	407 ± 30	490 ± 54
APA Duration (ms)	**306 ± 31**	154 ± 23	271 ± 16	333 ± 40
APA Latency (ms)	**130 ± 8**	134 ± 9	127 ± 6	149 ± 11
Multiple APAs (% of Trials)	**12 ± 6%**	0 ± 0 %	2 ± 2%	29 ± 11%

Multiple APAs and Reaction Times in the Voluntary Condition

When subjects stepped voluntarily, without a postural perturbation and in response to the presentation of an unpredictable visual target, multiple APAs were evident, on average (± sem), in 22 ± 7% of the trials. In the Voluntary condition, average APA onset latencies were 263 ± 9 ms after perturbation onset, translating to 196 ± 22% of the subjects' APA onset latencies when responding to the postural perturbations of the Unpredictable condition.

DISCUSSION

Our results support the hypothesis that the stepping limb of a compensatory step is normally pre-selected prior to anticipated postural perturbations. Requiring the subjects to select a stepping limb for a postural response at perturbation onset was found to alter the characteristics of the APA and swing phase of the subjects' compensatory steps, as well as to impair their postural stability. Specifically, in the Unpredictable condition, when the subjects were required to delay stepping until after selecting a stepping limb according to the online presentation of a target, they often exhibited multiple APAs and late foot-lift latencies, consequently becoming unstable by falling farther forward before taking a compensatory step. To maintain balance, the subjects then took a faster compensatory step in order to bring the CoM back to within the base of support. This late, unstable response was likely due to the subjects taking time to perceive the visual target and then to select the correct stepping limb, as evidenced by the increased latency and duration of the APA phase when multiple APAs were present.

We are unaware of any other reports of multiple APAs in healthy, young subjects, and we suspect that multiple APAs were evident in this study because they represent a

consequence of requiring online limb selection. According to Donders (1868-1869, translated in 1969), online response selection differentiates choice reaction time tasks from simple reaction time tasks, and the Unpredictable and Voluntary conditions in this study represented choice reaction time tasks to select one of two possible stepping limbs, whereas the No Target and Predictable conditions represented simple reaction time tasks to step with a pre-determined limb. Multiple APAs were generally present only in the choice reaction time tasks of the Unpredictable and Voluntary conditions. Thus, multiple APAs appear to represent a consequence of online limb selection, rather than a consequence of the postural perturbation, because they were also evident in the Voluntary condition that required online limb selection without having to respond to a postural perturbation. Although the choice reaction time task delayed the time to foot off in the Unpredictable condition, the postural response was still triggered by the perturbation, not by the presentation of a visual target, because the subjects' voluntary APA onset latencies in response to the targets were nearly twice as long as their APA onset latencies in response to the postural perturbations.

Presenting a target at perturbation onset to instruct the subjects' stepping foot online, however, did not always elicit a late, unstable response with multiple APAs. Rather, when the subjects could not initiate their foot lift based on a pre-selected stepping limb, there was a tradeoff between whether the subjects stepped with the correct leg and whether they maintained a certain level of stability. Specifically, when the subjects exhibited only one APA in the Unpredictable condition, their steps were initiated quickly, thereby allowing the subjects to preserve their stability by keeping the CoM close to the base of support. However, these early steps with one APA often came at the expense of

stepping with the incorrect leg: stepping with the incorrect leg negatively correlated with foot-lift latencies and the appearance of multiple APAs. Thus, when exhibiting only one APA, the subjects may have initiated the swing phase of their step based on a pre-selected stepping limb, prior to being fully aware of which target they were to step to, thereby increasing the probability of stepping with the incorrect leg.

The results further suggest that the subjects pre-selected their response prior to the perturbation because, when responding to the catch trials in the Unpredictable condition, the subjects' APAs and step placements did not resemble those in the No Target condition but did resemble those when the subjects stepped to targets in the Predictable and Unpredictable conditions. Thus, when the environment potentially constrained the subjects' responses (in this case, by potentially requiring the subjects to step with a specific limb to a target), the subjects pre-selected a response that complied with these potential constraints, even when the constraints weren't actually present. Their steps in response to the catch trials, however, were not precisely similar to their steps in the Predictable condition, suggesting that the subjects exhibited some online mutability of their pre-selected step trajectory once they recognized that a targeted step was not required of them. In addition, the APA onset latencies of the subjects' voluntary steps to unpredictable visual targets were nearly twice as long as those in response to postural perturbations, suggesting that the perturbation triggered their responses prior to being influenced by the target light in the Unpredictable condition. Thus, even when the direction and speed of the postural perturbations were unpredictable, the subjects' pre-selected their stepping limb to comply with potential environmental constraints because, in order to reach the target and still maintain a safer level of stability, the postural

responses had to be selected and initiated before being influenced by online visuo-motor processes.

Other studies have suggested that healthy subjects pre-select their postural response prior to a postural perturbation (Horak and Nashner 1986; Chong et al. 1999; Ghafouri et al. 2004; Zettel et al. 2005), but in doing so, the features of the response may be inappropriate for the environmental context (Horak and Nashner 1986; Chong et al. 1999). For example, Horak and Nashner (1986) reported that when subjects responded to translations of the support surface (1) while standing on a flat surface, they primarily flexed or extended their ankles in order to recover their balance (the ankle strategy), (2) while standing on a narrow beam, they flexed or extended their hips to recover their balance (the hip strategy), and (3) while responding on a flat surface after several trials on the narrow beam, they continued to use the hip strategy, suggesting that the subjects utilized a pre-selected response strategy, but that such a pre-selection led to postural responses that were not appropriate to the perturbation conditions.

Likewise, for the compensatory stepping responses of this study, pre-selecting the stepping limb caused the subjects to step toward targets that weren't actually there and, for those who prematurely initiated the swing phase of their step according to their pre-selected response, the subjects stepped more often with the wrong leg and to the wrong location. In a natural setting, where the environment may be filled with obstacles and incongruities, stepping with the wrong leg or in a wrong direction could result in injury. In our study, however, we did not associate any negative consequences with compensatory steps taken with the incorrect leg (other than knowledge that the response was not in accordance with our instruction), and associating a negative consequence with

incorrect responses may have decreased the number of steps taken with the incorrect leg in favor of the multiple-APA response.

In addition to the consequences associated with the subjects' responses, one must consider the extent to which other aspects of our methods are relevant to postural responses executed outside of the laboratory. In this study, the subjects were aware that their posture would be perturbed, that the perturbations were directed only in the sagittal plane, and they were forced to stand with symmetrical weight. Therefore, our results may only be relevant to situations in which a person anticipates a loss of balance, such as when on a moving bus or train, when crossing a stream along a path of rocks, when stepping onto an escalator, or when standing on an icy surface. Based on our results, we suggest that in these situations, a person can use previous experience and sensory context to ascertain the probability of certain perturbations. Then, upon experiencing a perturbation of semi-unpredictable characteristics, that person would detect, online, the direction of induced body sway and respond according to a pre-selected motor program that was primed by the person's initial anticipation (Horak 1996). Because the subjects expected the perturbations in our study, however, the results may not generalize to situations in which a person experiences an entirely unexpected perturbation. When a subject does anticipate a perturbation, though, that subject may also alter the initial postural alignment before experiencing a perturbation (such as by leaning in a direction that braces for the anticipated perturbation; Horak 1996), thereby further increasing the probability of a specific response and decreasing the latency for that response (for example, stepping with the right leg because it was initially unloaded prior to the perturbation). These pre-perturbation adjustments were not allowed in our protocol and,

had we allowed them, these adjustments may have affected the subjects' postural stability and their choice of stepping limb.

Implications for Clinical Balance Impairment

Our results provide insight into the balance impairments of patients with Parkinson's disease. When responding to postural perturbations, patients with Parkinson's disease exhibit postural instability and fall more easily than healthy control subjects (Horak et al. 2005; Jacobs et al. 2005a, see Appendix 1). This postural instability may be related to an inability to rapidly select a postural response (Horak et al. 1992; Jacobs et al. 2005b). For example, compared to healthy control subjects, subjects with Parkinson's disease exhibit more compensatory steps with multiple APAs, are less apt to select a dominant stepping limb, and are more likely to fall in trials with multiple APAs (Jacobs et al. 2005b, see Appendix 1). Similarly, when subjects with Parkinson's disease respond to small translations of the support surface that do not require steps, they select a response that is non-specific to their stance posture or to the characteristics of the perturbation, failing to coordinate the ankle and hip strategies (Horak et al. 1992, 2005; Chong et al. 2000; Dimitrova et al. 2004a,b; Jacobs et al. 2005a). Taken together, these reports suggest that the postural instability of patients with Parkinson's disease may partly be due to an inability to select appropriate motor programs for a specific environmental context. Because basal ganglia degeneration primarily characterizes the neuropathology associated with PD (Bernheimer et al. 1973; Damier et al. 1999), this hypothesis is consistent with the view that the basal ganglia act to facilitate the automated selection of environmentally appropriate motor programs (Grillner et al. 2005). With an impaired ability to automatically select an appropriate response, then, subjects with

Parkinson's disease seem to resort to online response selection, which is known to activate executive, motor, and sensory association areas of the cerebral cortex (Schluter et al. 2001; van Eimeren et al. 2006). Appendix 1 illustrates that subjects with Parkinson's disease exhibit increased falls and a less consistent choice of stepping limb when having to perform a secondary verbal recall task. We, therefore, speculate that subjects with Parkinson's disease exhibit impaired automatic postural response selection, more common use of online response selection, and that their postural instability becomes influenced more by cognitive tasks because selecting their postural responses online requires the activity of competing cognitive-motor neural resources.

Conclusions

Healthy subjects commonly pre-select a compensatory stepping leg prior to anticipated postural perturbations, even when the perturbation characteristics are unpredictable, but initiating a pre-selected response can lead to a tradeoff between speed and stability on the one hand, and an environmentally appropriate response on the other. In addition, combining this study's results with our previous observations on Parkinson's disease, we suggest that subjects with Parkinson's disease exhibit impaired postural response selection, leading to a higher propensity to select their response online, thereby causing their responses to be influenced more by secondary cognitive-motor tasks.

APPENDIX 1: Patients with Parkinson's Disease Exhibit Multiple APAs

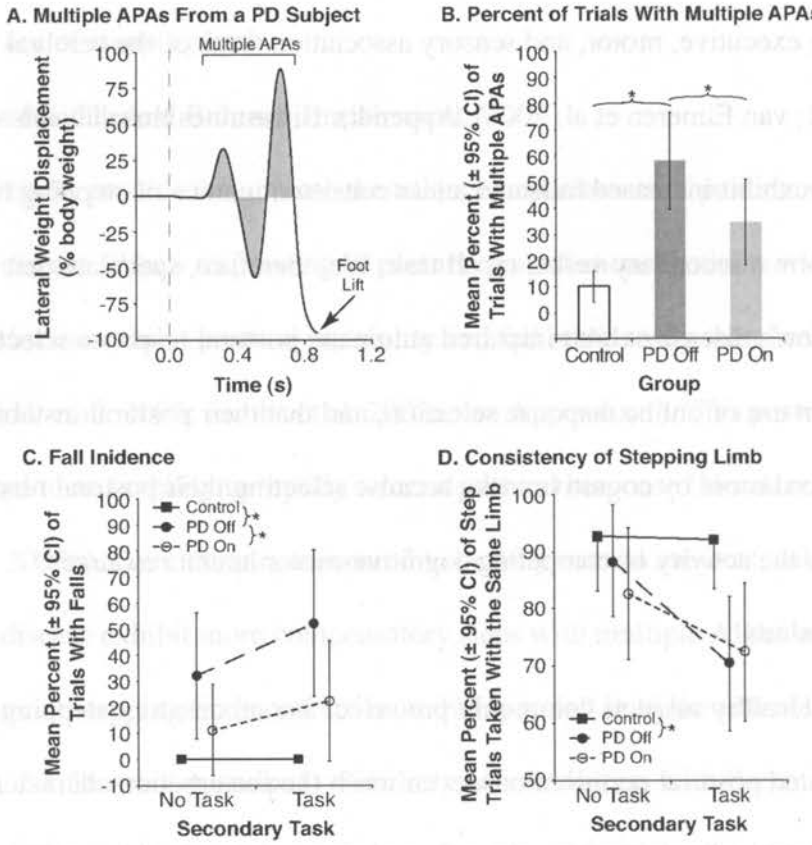


Fig. A1. PD subjects exhibit multiple APAs. The figures depict the results from another experiment examining the compensatory steps of 10 patients with Parkinson's disease (PD) and 10 age- and gender-matched healthy control subjects. Every PD subject exhibited postural instability and had a history of freezing, as determined by the Unified Parkinson's Disease Rating Scale. The PD subjects were evaluated after withholding their anti-Parkinson's medication overnight and approximately one hour after having taken their medication. Compensatory steps were taken in response to fast, backward translations of a platform under the subjects' feet, amidst randomly inserted forward translations of equal size, and smaller, slower forward and backward translations that did not require steps to maintain balance. The subjects also performed compensatory steps with and without performing a secondary verbal recall task. The subjects were not instructed about how they should respond and were only told to keep their balance.

When off their medication, the PD subjects exhibited more trials with multiple APAs than the control subjects or when on medication, and the secondary task had no effect on the incidence of multiple APAs. Although the control subjects never fell in response to these perturbations, the PD subjects fell in response to the perturbations more than the control subjects or when on medication, and the secondary task significantly increased the number of trials with falls. The PD subjects were also less consistent than the control subjects to step with a dominant limb, and the secondary task decreased the consistency of limb choice for the PD subjects, but not for the control subjects.

CHAPTER 5

Patients with Parkinson's Disease Can Use Visual Targets to Modify Compensatory Steps in Response to External Postural Perturbations

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ABSTRACT

Subjects with Parkinson's disease (PD) exhibit abnormally short compensatory steps in response to external postural perturbations. We examined whether: (1) PD subjects exhibit short compensatory steps due to abnormal central proprioceptive-motor integration, (2) this proprioceptive-motor deficit can be overcome by visual-motor neural circuits using visual targets, (3) the proprioceptive-motor deficit relates to the severity of PD, and (4) the dysfunction of central dopaminergic circuits contributes to the PD subjects' proprioceptive-motor deficit. Ten PD subjects and 10 matched control subjects performed compensatory steps in response to backward surface translations in 5 conditions: with eyes closed, with eyes open, to a remembered visual target, to a target without seeing their legs, and to a target while seeing their legs. PD subjects were tested OFF and ON their dopamine medication. PD subjects exhibited shorter compensatory steps than did the control subjects, but all subjects increased their step length when stepping to targets. The severity of the PD subjects' lower-body motor symptoms (as determined by the Unified Parkinson's Disease Rating Scale) significantly correlated with their accuracy errors when stepping to targets. Thus, PD subjects exhibited short compensatory steps due to abnormal proprioceptive-motor integration and used visual input to take longer compensatory steps when a target was provided. With increasingly severe PD, however, visual input did not fully compensate, because the most severely affected PD subjects exhibited poor step accuracy when stepping with full vision to a target. Medication did not consistently improve the length and accuracy of the PD subjects' compensatory steps, suggesting that degeneration of dopamine circuits within

the basal ganglia is not responsible for the proprioceptive-motor deficit that degrades compensatory steps in PD subjects.

INTRODUCTION

Patients with Parkinson's disease (PD) often suffer from postural instability, leading to falls and a decreased quality of life (Bloem et al. 2001; Wood et al. 2002; Keranen et al. 2003). PD subjects often fall because they respond to a sudden loss of balance with abnormally short (hypometric) steps that are inadequate for them to recover equilibrium (Fahn and Elton 1987; Jacobs and Horak 2004; Rocchi et al. 2004; Maki and McIlroy 2005). Steps taken to maintain upright stance after a sudden loss of balance (compensatory steps) represent an important strategy for preventing a fall (Maki and McIlroy 2005). Although it is known that PD subjects exhibit abnormally short compensatory steps, the neurological deficits that underlie their shortened compensatory steps have not been characterized.

Despite the lack of research on compensatory stepping in PD subjects, research on voluntary movement suggests that PD subjects may exhibit hypometria (abnormally short movements) because they over-estimate the length of their movement due to abnormally integrated proprioceptive input (Demirci et al. 1997; Contreras-Vidal and Gold 2004). This abnormal integration of proprioceptive input represents a central dysfunction within the primary and secondary sensorimotor regions of the cerebral cortex (Boecker et al. 1999; Seiss et al. 2003), not a peripheral dysfunction of the proprioceptive receptors (Delwaide and Gonce 1993). Therefore, PD subjects exhibit a central impairment of proprioceptive-motor integration – that is, abnormal central processing of proprioceptive input to form an internal representation of the body's motion for accurately guiding

movement. Studies on PD that assess abnormal proprioceptive-motor integration commonly utilize indirect behavioral measures of proprioceptive-motor function by comparing the subjects' movement in a condition which allows them to see their movement versus in a condition which does not allow them to see their movement in order to force them to rely on proprioceptive-motor integration for guiding their movement (Moore 1987; Klockgether et al. 1995; Demirci et al. 1997; Jobst et al. 1997; Adamovich et al. 2001; Byblow et al. 2003; Maschke et al. 2003; Contreras-Vidal and Gold 2004; Almeida et al. 2005; Keijsers et al. 2005). For example, when PD subjects try to duplicate an active or passive movement of their upper limb without being able to see that limb, they do not move their limb far enough to reach its desired position (Moore 1987; Klockgether et al. 1995; Seiss et al. 2003). PD subjects also fail to reach far enough when reaching to visual targets without being able to see their pointing finger (Adamovich et al. 2001; Keijsers et al. 2005), or when walking toward a target without being able to see their bodies (Almeida et al. 2005). Further, vibrating muscle tendons to stimulate proprioceptive receptors is less effective at altering wrist and ankle movements in PD subjects (Rickards and Cody 1997; Khudados et al. 1999). If abnormal proprioceptive-motor integration leads to hypometric voluntary movements in PD subjects, abnormal proprioceptive-motor integration may also underlie the hypometric compensatory steps that PD subjects exhibit during a sudden loss of balance.

With impaired proprioceptive-motor integration, PD subjects depend more on visual input than on proprioceptive input when performing a motor task. For example, altering the motion of the surrounding visual scene during treadmill walking changes the stride length of PD subjects more than the stride length of control subjects (Schubert et al.

2005). In addition, when stepping voluntarily without a visual target, PD subjects take abnormally short steps, but when stepping to a visual target, they increase their step length (Martin 1967; Bagley et al. 1991; Morris et al. 2005). Because explicit visual cues (such as targets) increase the length of voluntary steps of PD subjects, we hypothesize that PD subjects may also be able to increase their compensatory step length in response to a loss of balance through the use of explicit visual targets, because an explicit target will allow a PD subject to shift from an impaired proprioceptive sensorimotor set to an intact visual sensorimotor set.

Although proprioceptive-motor impairments have been characterized in PD subjects during passive and voluntary arm movements (Moore 1987; Klockgether et al. 1995; Demirci et al. 1997; Adamovich et al. 2001; Seiss et al. 2003; Keijsers et al. 2005) and during voluntary gait (Almeida et al. 2005), impaired proprioceptive-motor control has never been investigated when PD subjects take compensatory steps in response to external perturbations of standing balance. Compensatory steps differ from voluntary movements, such as gait or arm reaching, because compensatory steps are triggered through somatosensory inputs by perturbations of standing posture (Do et al. 1990; Do and Roby-Brami 1991; Perry et al. 2000), and the time it takes to lift the foot off the ground for a compensatory step is half of that for a cued voluntary step (Burleigh et al. 1994; McIlroy and Maki 1996). However, although compensatory steps occur quickly in response to a loss of balance, compensatory steps are not simply unalterable reflexes since they can be modified voluntarily: the onset of a compensatory step can be modified with changes in perturbation velocity or with intention (Burleigh and Horak 1996), and the swing of a compensatory step can be modified by environmental obstacles (Zettel et

al. 2002a,b) or by multiple perturbations occurring in a sequence (Tripp et al. 2004). Therefore, compensatory steps represent a unique behavior that may be controlled by unique neural circuits and, by investigating proprioceptive-motor and visual-motor function during compensatory stepping in PD subjects, we can determine the extent that these triggered postural responses are similar to voluntary movement and also determine the underlying causes of the compensatory step deficits that occur in PD.

We hypothesized that (1) abnormal proprioceptive-motor integration contributes to the shortened compensatory steps of PD subjects during balance recovery, and (2) PD subjects can use visual-motor neural circuits to lengthen their compensatory steps. To test these hypotheses, we exposed PD subjects and healthy subjects to backward translations of the support surface in different visual conditions that required different levels of visual and proprioceptive feedback. We predicted that PD subjects would exhibit abnormally short compensatory steps, and they would increase their compensatory step length when instructed to step to a visual target (Jacobs and Horak 2004; Maki and McIlroy 2005). We also predicted that when the view of their legs was blocked while they step toward a visual target, PD subjects would demonstrate larger accuracy errors than healthy subjects because, without their legs being visible, PD subjects would utilize abnormally integrated proprioceptive input to direct their feet to the target.

We also sought to determine the extent that central dopaminergic circuits directly influence the length of compensatory steps by testing PD subjects after their dopamine medication was withdrawn (the "OFF" state) and after they took their dopamine medication (the "ON" state). Assuming PD subjects exhibit both impaired compensatory steps and impaired voluntary gait due to the same underlying proprioceptive-motor

dysfunction, similar to the results reported by Almeida et al. (2005) during targeted voluntary gait, we predicted that medication would not significantly improve step length and step accuracy during compensatory stepping. Therefore, if we could establish that PD subjects exhibit short compensatory steps due to impaired proprioceptive-motor integration and that dopamine medication has little effect on the length of the PD subjects' compensatory steps, then the results would support the hypothesis that dopaminergic circuits within the basal ganglia do not directly contribute to the postural instability and underlying proprioceptive-motor impairments that are evident in PD subjects. Valkovic et al. (2006) recently supported this hypothesis when testing the postural sway of PD subjects during quiet stance in response to neck vibration, but compensatory steps represent a unique, more complex behavior which may recruit additional, and potentially dopaminergic, neural circuits. Therefore, we tested our PD subjects in the OFF and ON medication states to confirm the hypothesis for compensatory stepping.

METHODS

Subjects

In accordance with the Declaration of Helsinki, 10 subjects with idiopathic PD and 10 control subjects (2 females and 8 males in each group) gave informed consent to participate in the protocol approved by the Institutional Review Board of Oregon Health & Science University. All subjects were right-handed and right leg-dominant. Subjects with neurological, muscular, or psychiatric disorders besides PD were excluded (e.g., subjects with diabetes, peripheral neuropathies, uncorrected visual problems, vestibular problems, hearing problems, joint pain, arthritis, fracture, stroke, and seizure). PD

subjects were included if they exhibited bradykinesia and rigidity and if their neurological history had no evidence of an alternative diagnosis. Subjects were included if they predominantly exhibited hypometria and bradykinesia because our hypotheses sought to understand the neural mechanisms underlying these symptoms during balance recovery. Consequently, tremor-dominant patients were not included in this study. A neurologist with specialized training in movement disorders determined the PD subjects' diagnosis and eligibility. PD subjects were tested in the OFF medication state, at least 12 hours after their last dose of anti-Parkinson's medication, and in the ON state, about one hour after taking their anti-Parkinson's medication. To increase the level of dopamine in their nervous systems, all PD subjects received carbidopa/levodopa, 1 PD subject received pramipexole, 3 PD subjects received ropinirole, and 3 PD subjects received amantadine.

Because compensatory stepping requires control by the axial and lower-limb musculature, we assumed that compensatory step deficits would be worse for those PD subjects with more advanced lower body symptoms. Thus, to determine the severity of the PD subjects' lower body symptoms, we calculated a sub-score of the Unified Parkinson's Disease Rating Scale's (UPDRS) motor exam, summing the items of the exam that assess lower body motor function. Specifically, the lower-body score was defined as the sum of the UPDRS items of leg tremor, leg rigidity, leg agility, arise from chair, posture, postural stability, gait, and body bradykinesia. The symptoms included in the lower-body UPDRS score significantly improved after the PD subjects received their dopamine medications [T=4.34; P=0.002] (Table 1). Qualitatively, these medication-related improvements translate into less rigidity in the legs, an ability to perform faster

sequential leg taps, an improved ability to arise from a chair with fewer attempts or without assistance, improved standing posture due to less hip and knee flexion and, in some cases, improved gait. When the PD subjects were asked to rate their symptoms on a scale of 0-10 (0 meaning that their symptoms were as bad as can be, and 10 meaning that they feel as good as can be), on average, they rated their symptoms with a score of 2.4 when in the OFF state and 8 when in the ON state. Thus, by clinical observation and by subjective assessment, the PD subjects exhibited noticeable symptom improvement after taking their dopamine medications. All PD subjects in the OFF state exhibited some postural instability, as rated by item 30 of the UPDRS motor exam (the Pull Test): on an ordinal scale of 0-4, scores ranged from 1-3, corresponding to retropulsion (multiple, short compensatory steps) and/or falling into the examiner's hands. Two-sided t-tests showed that the PD subjects and control subjects were of similar age, height, and weight [for all comparisons, $T<0.84$; $P>0.41$] (Table 1).

Table 1. *Characteristics of Subject Groups*

Subject Group	Age (yr) mean (range)	Height (cm) mean (range)	Weight (kg) mean (range)	Lower Body UPDRS Score mean (range)		Total Motor UPDRS Score mean (range)	
				OFF	ON	OFF	ON
Control	66 (52-78)	173 (157-188)	75 (54-94)	-	-	-	-
PD	66 (49-78)	171 (150-185)	71 (46-93)	18 (8-29)	13 (6-21)	42 (19-63)	29 (9-46)

Procedure

The task was for the subjects to stand on a moveable platform and then take forward compensatory steps in response to backward movements of the platform. The task involved 5 conditions that forced the subjects to vary their use of visual and

proprioceptive input while taking forward compensatory steps. The conditions were blocked and ordered as follows to gradually increase the level of visual information provided to the subjects: (1) the subjects' eyes were closed and there was no visual target; the Eyes Closed condition, (2) the subjects' eyes were open and there was no visual target; the Eyes Open condition, (3) the subjects' eyes were open, looking at the ground where a visual target had been earlier displayed; the Remembered Target condition, (4) the subjects' eyes were open while they looked at a visual target, but they wore a vest that prevented them from seeing their legs; the No Leg condition, and (5) the subjects' eyes were open while they looked at a visual target and could see their legs; the Target condition.

In the No Leg condition, subjects wore a lightweight vest (0.86 kg; the Xvest from Xtreme Worldwide Athletic Equipment, Katy, TX, USA) that blocked their view of their legs (Fig. 1). The vest consisted of two adjustable flaps worn over the shoulders that covered the chest and back. When the flap was turned up at the front of the vest, as shown in Fig. 1, the flap extended 20 cm forward from the subjects' chest, thus blocking the subjects' view of their legs but not blocking their view of the visual target.

In the Remembered Target, No Leg, and Target conditions, the visual target consisted of a point of green light (0.5 cm in diameter) on the ground, uniquely positioned (a) 130% of the average anterior-posterior length of each subject's compensatory steps as determined in the Eyes Open condition and (b) 10 cm to the right of the force plates (Fig. 1). The green light came from a laser source that was mounted on a ceiling rail and was placed to ensure that the subjects were not forced to step to an unstable position when the platform moved. The visual target was not placed on the

moving plates in order to prevent the subjects from being confused about whether to step to the light on the ground (which would not change position during the platform movement) or to the location on the platform that the light covered before the platform moved (which would change position during the platform movement). In addition, with the visual target 10 cm to the right of the force plates, the subjects could see the visual target when wearing the vest for the No Leg condition (Fig. 1). Although the room was well lit, all subjects reported that the target was readily visible.

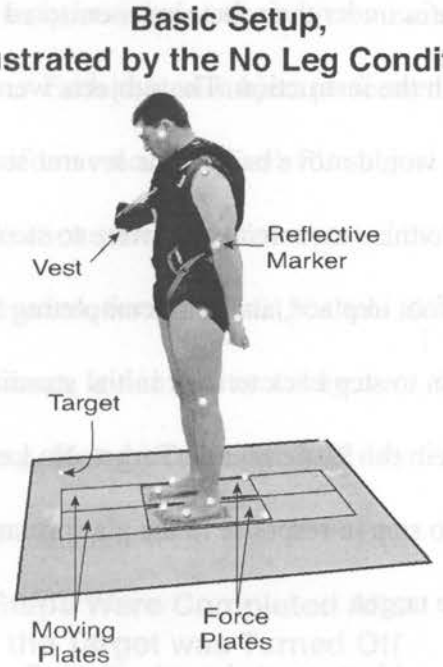

Fig. 1. The basic experimental setup, illustrated by the No Leg condition. For the No Leg condition, subjects wore a vest to block vision of their legs and feet, while the vest allowed the subjects to see the visual target when they stood in their initial position with each foot on a moveable force plate. For all conditions, subjects also wore reflective markers that were placed at the approximate center of joint rotation for the fifth metatarsals, ankles, knees, hips, wrists, and shoulders, as well as on the first toes, above the eyes, in front of the ears, and on the moving platform. In this study, our analysis utilized the data from the toe markers. The additional markers were used to test hypotheses that are beyond the scope of this study. For the Remembered Target, No Leg, and Target conditions, the position of the visual target was uniquely located at 130% of each subject's anterior-posterior step length (determined from the Eyes Open condition) and 10 cm to the right of the moving force plates.

Subjects stood with each foot on a separate, moveable force plate. They stood in a comfortable stance width, and their feet were marked with tape to ensure stance width remained consistent throughout the experiment. A two-sided t-test confirmed that average (± the standard deviation) stance widths were similar among PD subjects (12.7 ± 2.9 cm)

and control subjects (13.2 ± 2.9 cm) [T=0.38; P=0.71]. To prevent the subjects from falling to the ground, they were harnessed to a ceiling-mounted track, and an assistant stood behind them at their left side to help if they fell into the harness. The subjects held a small, lightweight wooden dowel (2-cm diameter, 66 cm long, and 113 g in weight) behind their back with both hands to prevent their arms from swinging in response to the platform movement (Zettel et al. 2002a,b).

The subjects were instructed to stand with an equal amount of weight under each foot. The force distribution of the 2 force plates under their feet was monitored by an oscilloscope to ensure subjects complied with the instruction. The subjects were told that we would say "ready" and then the platform would move backwards several seconds later. They were instructed that in response to this movement, they were to step forward with their right foot while holding their left foot in place, and after completing this step, to hold their position until we instructed them to step back to their initial standing position. When stepping to the visual targets in the Remembered Target, No Leg, and Target conditions, subjects were instructed to step in response to the platform movement so that the tip of their great toe landed on the target.

For all conditions, within 7-10 s after subjects were given the "ready" cue, the platform translated 18 cm backward at 3 randomized ramp velocities (35, 40, and 45 cm/s). Randomizing the platform velocity prevented the subjects from taking stereotyped steps from memory and required that they use online sensory information to initiate their response (Burleigh and Horak 1996). For the Remembered Target, No Leg, and Target conditions, the target light turned on several seconds before the platform moved, and the subjects were allowed to study the visual target during this period. For the No Leg and

Target conditions, to the extent possible in the well-lit room, we prevented subjects from knowing the accuracy of their steps by turning off the target light 200 ms after the platform began to move, thereby ensuring that the light was off when the subjects completed their step (Fig. 2). For the Remembered Target condition, the light was turned off 3 seconds before the platform began to move. Thus, in the Remembered Target condition, subjects were also provided with an implicit temporal cue that gave information about the timing of perturbation onset, but this information was never explicitly revealed to the subjects during the experiment.

Each control subject performed 75 trials: 5 trials for each condition at each of the 3 platform velocities. Each PD subject performed these same 75 trials while in the OFF medication state, and then repeated the 75 trials about one hour after taking their medication, for a total of 150 trials. All subjects were given a rest after every 15 trials at minimum, and in addition, they were allowed to rest whenever they requested. When resting, the subjects rested until they felt ready to continue; no subject complained of fatigue.

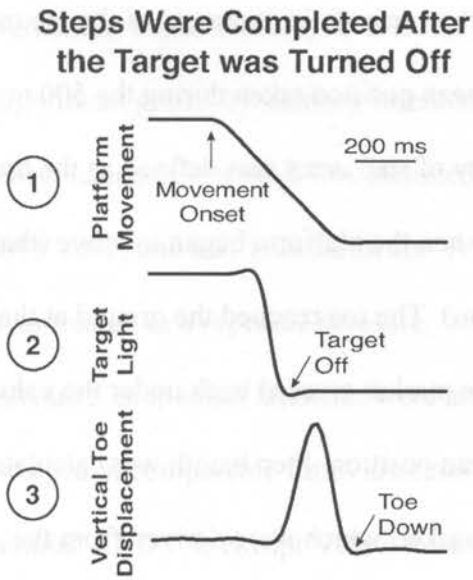

Fig. 2. Timeline of events during trials in the No Leg and Target conditions. The target light was turned off before the subjects completed their step to prevent them from knowing their step accuracy. Lines illustrate the relative timing of when (1) the platform began to move, (2) the target light was turned off, and (3) a severe PD subject with the fastest average step latency of all of the subjects completed a compensatory step in response to a 45 cm/s translation.

Data Analysis and Statistics

Reflective markers were positioned bilaterally on the side of the body at the approximate center of joint rotation for the fifth metatarsal joints, ankles, knees, hips, shoulders, elbows, and wrist joints, and markers were also placed bilaterally on the tip of the first toe, as well as above the eyes, in front of the ears, and on the platform (Fig. 1). A high-resolution Motion Analysis System (Santa Rosa, CA) with 8 video cameras sampling at 60 Hz provided 3-dimensional spatial coordinate information about the displacement of body segments. In this study, our analysis utilized the data from the toe markers. The additional markers were used to test hypotheses that are beyond the scope of this study.

Using the marker placed on the right first toe, we quantified the subjects' step lengths, step onset latencies, and, for the conditions with the visual target, the distance of their steps from the target (step errors). Step length was defined as the distance between the location of the toe when it left the ground (at the beginning of the step) and the location of the toe when it subsequently reached the ground (at the end of the step). The toe was defined to have left the ground when the vertical displacement of the toe marker exceeded 2 standard deviations of the initial mean position taken during the 500 ms prior to the onset of platform translation. The latency of step onset was defined as the time when the toe left the ground, minus the time when the platform began to move (that is, when the platform displacement exceeded 0 cm). The toe reached the ground at the end of the step when the vertical position of the toe marker crossed back under the value that was 2 standard deviations above the initial mean position. Step length was calculated from the horizontal displacements of the toe marker, which were derived from the

anterior-posterior (AP) and the medial-lateral (ML) displacements of the marker: step length = $\sqrt{(AP\_DISPLACE^2 + ML\_DISPLACE^2)}$. Step error was defined by the horizontal distance between the visual target's location and the toe's location at the end of the step: error = $\sqrt{(AP\_ERROR^2 + ML\_ERROR^2)}$, where AP_ERROR = AP_TOEposition – AP_TARGETposition, and ML_ERROR = ML_TOEposition – ML_TARGETposition. Although studies on targeted voluntary movements commonly report the standard deviation of the error (termed the 'variable error'; Adamovich et al. 2001; Almeida et al. 2005; Keijsers et al. 2005), we do not report the variable error in this study because the balance constraints of our task limited how much this measure differed across the experimental conditions.

Results from the individual trials were averaged by visual condition for each subject, and these averages were analyzed by separate mixed-model ANOVAs to determine differences in step lengths and step errors between the subject groups, between the ON and OFF medication states, and across the visual conditions. We collapsed subject averages into the visual conditions, without considering the different platform velocities, because the ANOVAs that included the effects of velocity showed no significant group-by-velocity interactions. Thus, when we compared step lengths and step onset latencies, the ANOVA included a 2-level factor for GROUP (control and PD in the OFF state) and a 5-level factor for VISION that included each test condition. VISION was treated as a repeated measure, whereas GROUP was treated as a between-groups measure. Step onset latencies were analyzed to ensure that the different subject groups stepped at comparable times after the perturbation. Step errors were analyzed with a similar ANOVA, except VISION was defined by a 3-level factor, including only the

Remembered Target, No Leg, and Target conditions. For PD subjects, when we analyzed the effects of dopamine medication on compensatory step length and step error, the repeated-measures ANOVA included a 5- or 3-level factor for VISION (5 levels for step length, 3 levels for step error), and a 2-level factor for MEDICATION (OFF and ON). The ANOVA (F) statistics of the within-subjects factors were corrected by a Greenhouse-Geisser epsilon, which adjusts the degrees of freedom to remedy any violations on the assumption of sphericity. All reported F- and P-values represent the corrected statistic. Significance was defined as a P-value ≤ 0.05.

In addition to these ANOVAs, we utilized Spearman's correlations to relate: (1) the severity of the PD subjects' lower-body symptoms to their step length and error, (2) the effect of dopamine medication on the PD subjects' step length and error to their initial step length and error while in the OFF state, and (3) compensatory step length in the conditions without visual targets to step errors in the conditions with visual targets. Non-parametric correlations were chosen because, with every comparison, a Shapiro-Wilks test for normality showed that at least one variable did not exhibit a normal distribution.

RESULTS

Compensatory Step Length

A significant main effect for GROUP [F=14.83; P<0.002] revealed that PD subjects exhibited shorter step lengths than did control subjects (Fig. 3). In addition, a significant main effect for VISION [F=72.76; P<0.00001] revealed that, for both subject groups, step lengths were longer in conditions with visual targets than in those without visual targets (Fig. 3). The PD subjects and control subjects similarly altered their step

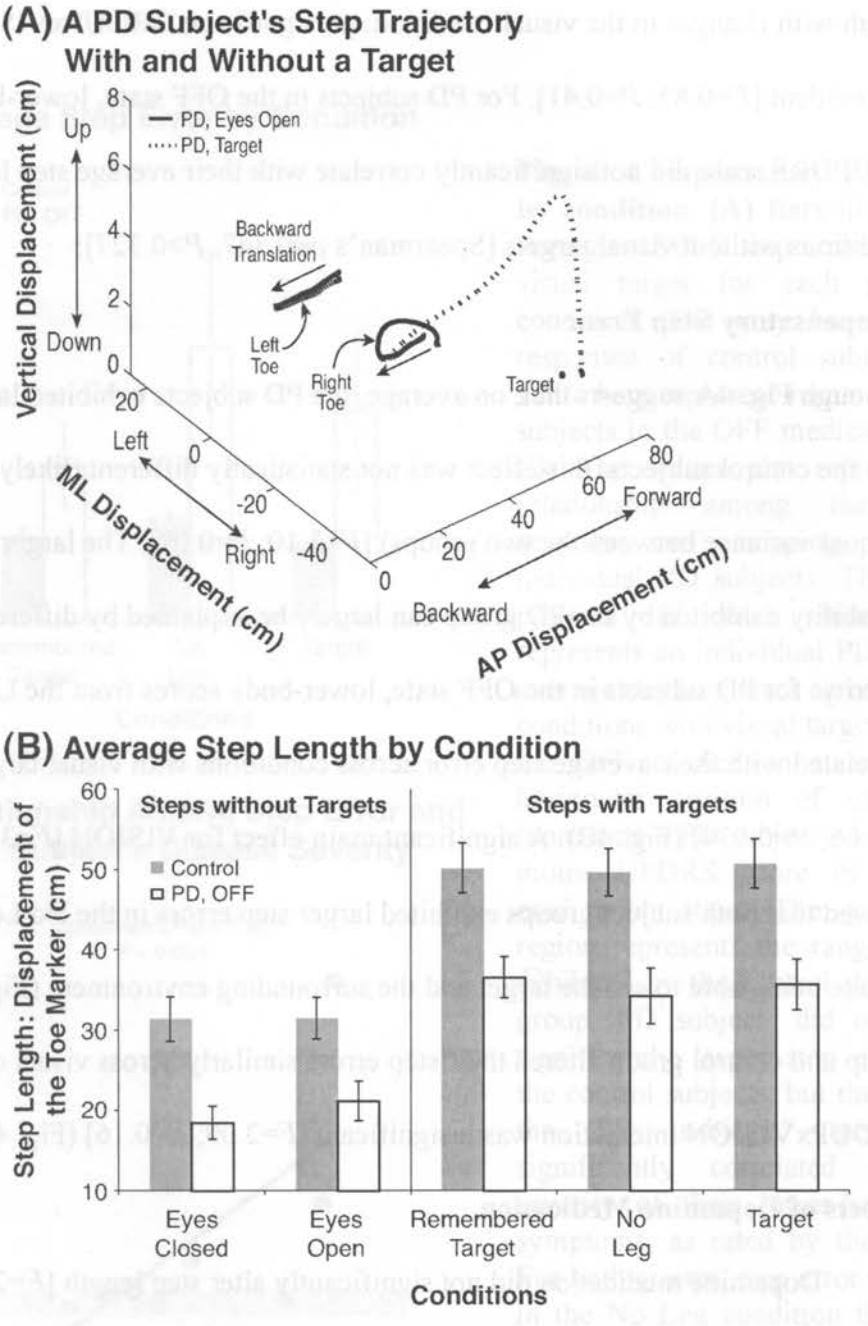

Fig. 3. Compensatory step length by condition. (A) Lines illustrate the three-dimensional trajectories of a PD subject's toe markers for a step taken in the Eyes Open condition (solid line) and a step taken in the Target condition (dashed line). The toe marker initially moved backward with the platform translation until the right foot began lifting off the platform at the onset of a forward compensatory step. **(B)** Bars illustrate the average (±SEM) lengths of compensatory steps for each group by condition. The gray bars represent the responses of control subjects. The white bars represent responses of PD subjects in the OFF medication state. Step length was significantly different between PD and control subjects, as well as between conditions with and without targets.

length with changes in the visual condition: no significant GROUPxVISION interaction was evident [F=0.85; P=0.41]. For PD subjects in the OFF state, lower-body scores from the UPDRS scale did not significantly correlate with their average step length in the conditions without visual targets [Spearman's $\rho \leq 0.347$; $P > 0.327$].

Compensatory Step Error

Although Fig. 4A suggests that, on average, the PD subjects exhibited larger step errors than the control subjects, this effect was not statistically different (likely due to the unequal variance between the two groups) [F=3.10; P=0.09]. The larger inter-subject variability exhibited by the PD group can largely be explained by differences in disease severity: for PD subjects in the OFF state, lower-body scores from the UPDRS scale correlated with their average step error across conditions with visual targets [Spearman's ρ=0.66; P=0.034] (Fig. 4B). A significant main effect for VISION [F=3.86; P=0.05] showed that both subject groups exhibited larger step errors in the No Leg condition, despite being able to see the target and the surrounding environment (Fig. 4A). The PD group and control group altered their step errors similarly across visual conditions: the GROUPxVISION interaction was insignificant [F=2.09; P=0.16] (Fig. 4A).

Effects of Dopamine Medication

Dopamine medication did not significantly alter step length [F=2.63; P=0.14] or error [F=1.42; P=0.26] (Fig. 5). Although dopamine medication appeared to have no statistical effect on the compensatory steps of PD subjects as a group, dopamine medication affected the compensatory steps of many individual PD subjects, but in very diverse ways: some PD subjects exhibited no effects from their medication, others

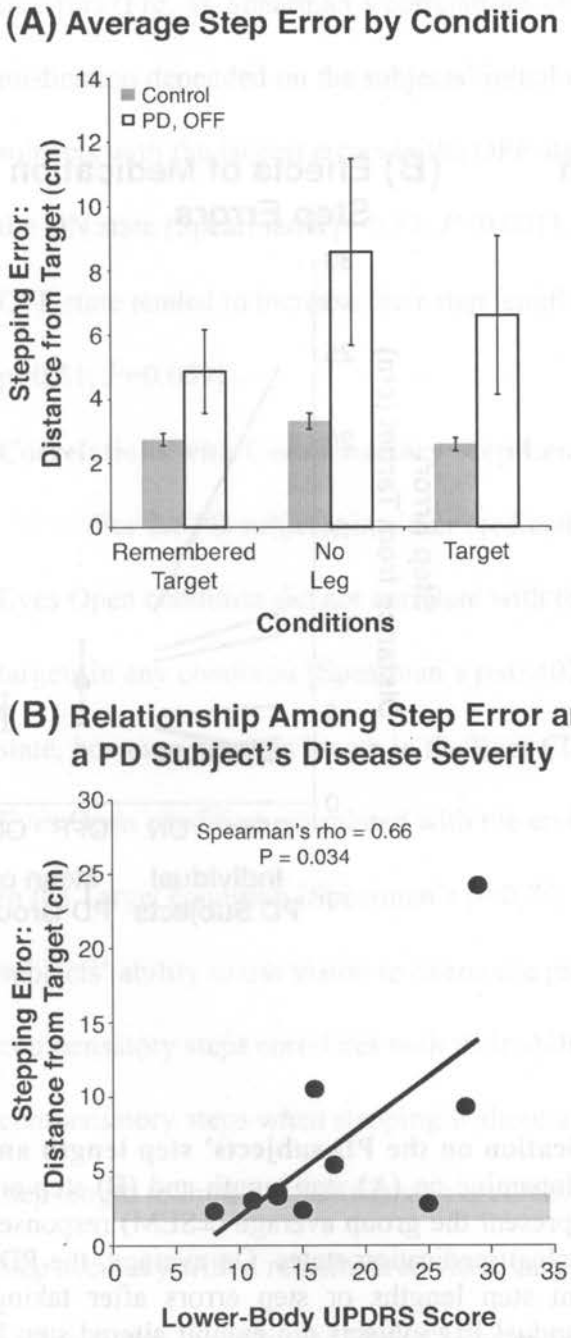

Fig. 4. Compensatory step errors by condition. (A) Bars illustrate the average (±SEM) step errors from the visual target for each group by condition. The gray bars represent responses of control subjects. The white bars represent responses of PD subjects in the OFF medication state. **(B)** The scatter plot represents the relationship among the disease severity and stepping error of individual PD subjects. The vertical position of each black circle represents an individual PD subject's average stepping error across all three conditions with visual targets when in the OFF medication state, and the horizontal position of each circle represents a PD subject's lower-body motor UPDRS score in the OFF medication state. The gray-shaded region represents the range of error exhibited by the control group. As a group, PD subjects did not exhibit significantly larger step errors than the control subjects, but the extent of the PD subjects' step errors significantly correlated with the severity of their lower-body motor symptoms, as rated by the UPDRS. For both groups, step error was larger in the No Leg condition than in the other conditions.

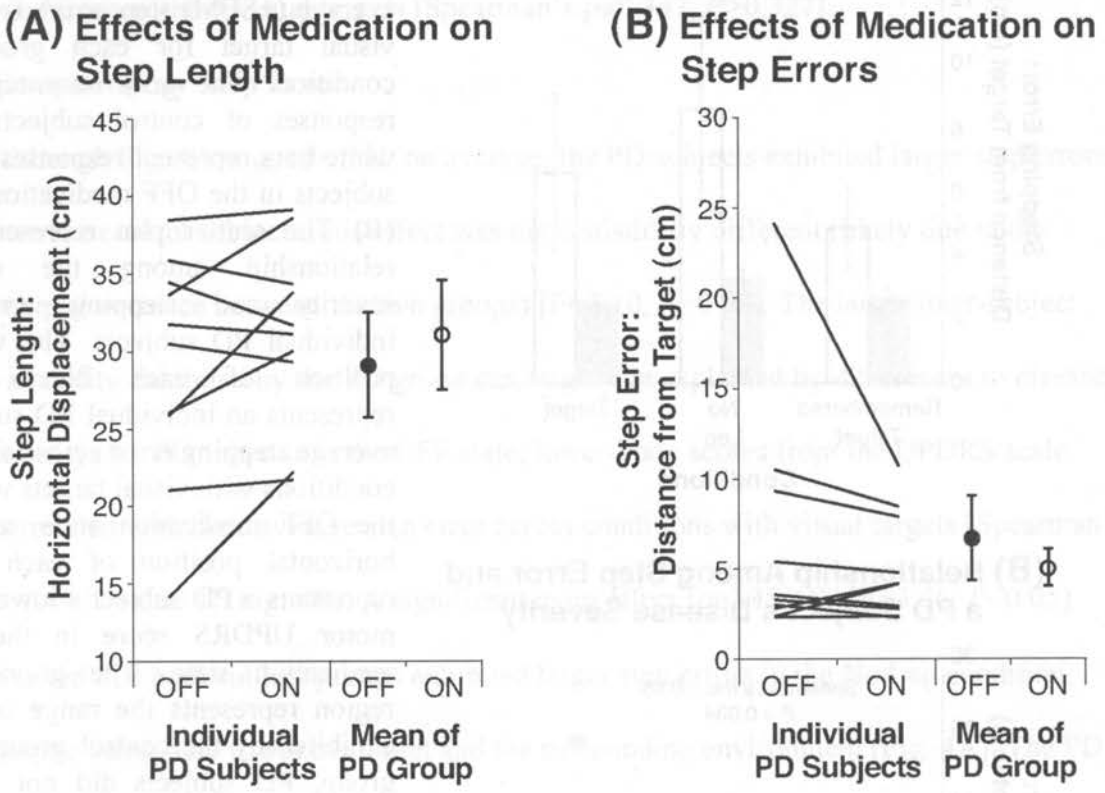

Fig. 5. The effect of dopamine medication on the PD subjects' step length and step error. Lines represent the effects of dopamine on **(A)** step length and **(B)** step error for individual PD subjects. The circles represent the group average (±SEM) response in the OFF (filled circles) and ON (open circles) medication states. On average, the PD group did not exhibit significantly different step lengths or step errors after taking their dopamine medications, but some individual PD subjects did exhibit altered step lengths and step errors after taking their medication.

exhibited decreased step lengths or errors, and still others exhibited increased step lengths or errors (Fig. 5). Spearman's correlations determined that the effect of dopamine medication depended on the subjects' initial error and step length while in the OFF state: subjects with the largest errors in the OFF state decreased their errors the most when in the ON state [Spearman's ρ=0.88; P<0.001], and subjects with the shortest steps in the OFF state tended to increase their step length the most when in the ON state [Spearman's ρ=0.61; P=0.059].

Correlations with Compensatory Step Length and Step Error

For the PD subjects in either medication state, step length in the Eyes Closed or Eyes Open condition did not correlate with their errors when they stepped to visual targets in any condition [Spearman's $\rho \leq 0.407$; P>0.242]. For PD subjects in the OFF state, however, the step length in the Eyes Closed condition, minus the step length in the Eyes Open condition, correlated with the error in the No Leg condition, minus the error in the Target condition [Spearman's ρ=0.70; P<0.05]. This finding suggests that the PD subjects' ability to use vision to overcome proprioceptive impairments during targeted compensatory steps correlates with their ability to use vision to overcome short compensatory steps when stepping without a visual target. Unlike the correlation relating step length to improvements in step accuracy due to vision of the legs, improvements in step accuracy with a remembered visual target did not correlate either with the PD subjects' step length in the Eyes Closed or Eyes Open condition [Spearman's $\rho \leq 0.273$; P>0.445] or with the change in step length from the Eyes Closed condition to the Eyes Open condition [Spearman's ρ=0.273; P>0.445]. Thus, the improved step accuracy exhibited by the PD subjects due to the implicit temporal cue provided in the

Remembered Target condition did not relate to the length of the PD subjects' compensatory steps.

Onset Latencies of the Compensatory Steps

The onset latencies of the compensatory steps were similar across subject groups [F=0.26; P=0.62]: step onset latencies averaged (± the standard deviation) 401 ± 68 ms for the control subjects and 387 ± 76 ms for the PD subjects. In addition, there were no significant group-by-condition interactions [F=0.54; P=0.63], suggesting that visual input affected step onset latencies similarly across the subject groups. A nearly significant main effect for condition showed that step onset latencies were later in the Target condition (412 ± 67 ms) compared to in the Eyes Closed condition (375 ± 68 ms) [F=2.83; P=0.057].

To compare these compensatory step onset latencies with those of cued voluntary steps, other studies have shown that the onset latency of a cued voluntary step is about 650 ms when healthy subjects step in response to a somatosensory cue (a 10 mm displacement of the surface under the subjects' feet, Burleigh et al. 1994), and over 900 ms when healthy subjects step to a visual cue (McIlroy and Maki 1996).

DISCUSSION

Proprioceptive-Motor Integration is Impaired in PD Subjects

The PD subjects exhibited abnormally short compensatory steps when stepping without a visual target but increased their step length when stepping to a visual target. Although these behavioral measures represent only indirect evidence for impaired proprioceptive-motor integration, our results support the hypotheses that abnormal proprioceptive-motor integration contributes to the hypometric compensatory steps of PD

subjects and that a visual-motor reference frame allows PD subjects to overcome their hypometria when taking compensatory steps to visual targets. Thus, although compensatory steps are rapidly triggered by a sudden loss of balance, PD subjects and control subjects altered their compensatory steps with voluntary intent, as has been shown previously in younger groups of healthy subjects (Zettel et al. 2002a,b; Tripp et al. 2004).

In addition, our results suggest that PD subjects who depend on visual input to guide their compensatory steps to a visual target also use visual input to guide step placement when taking compensatory steps without visual targets because the PD subjects' improvement in step accuracy from the No Leg condition to the Target condition correlated with their increase in step length from the Eyes Closed condition to the Eyes Open condition. However, compared to the Eyes Closed condition, PD subjects did not increase their step length in the Eyes Open condition to the same degree as when stepping to an explicit visual target. The need for an explicit visual target, rather than vision alone, to alter compensatory step placement may be because subjects do not usually utilize visual input to guide a compensatory step in an uncluttered, unconstrained environment (such as in the Eyes Open condition). Research has shown that healthy subjects do not divert their gaze to the ground during an unconstrained compensatory step, but when stepping to a visual target, healthy subjects divert their gaze more often to their foot or to the floor in front of them in order to guide their compensatory step (Zettel et al. 2005). In addition, research has shown that PD subjects can increase movement amplitude without explicit visual cues simply by directing their attention to making larger movements (Morris et al. 1996; Oliveira et al. 1997; Farley and Koshland 2005).

Therefore, an explicit visual target may improve step length either because the target facilitated the use of visual input to plan the subjects' step length or because the target focused the subjects' attention on the need to increase their step length. We speculate that the PD subjects could have lengthened their compensatory steps had we explicitly instructed them to attend to doing so (even without a visual target), although this instruction may have led to more variance in the subjects' step placement than when provided with a visual target. Asking a PD subject to take a larger step without providing the subject with a visual target, however, may still activate similar visual-motor neural circuitry as when intending to step to a visual target, because the request to change step length may still elicit visualizations when planning the modified step. Further research is required to determine if PD subjects can similarly modify compensatory step length with visual targets or with instruction alone.

Although our behavioral assessment provides only indirect measures of proprioceptive-motor integration, the inadequate size of the PD subjects' compensatory steps appears to represent an inability to transform proprioceptive input into an appropriately scaled motor output, as has been shown for voluntary gait (Almeida et al. 2005). Both subject groups improved their step accuracy when they could see their legs, suggesting that both groups used visual input to improve step accuracy and that the PD subjects' compensatory step deficits were not likely due to abnormal integration of proprioceptive input with visual input (consistent with Almeida et al. 2005). However, contrary to our prediction that PD subjects would improve step accuracy more than control subjects between the No Leg and Target conditions, there was no significant difference between the PD subjects and control subjects in their ability to improve step

accuracy with vision of their legs. Our data may not have supported our prediction because the PD subjects may have been equally capable as control subjects to pre-plan their step to the explicit visual target prior to the perturbation, thereby eliminating any increased reliance on visual input during the compensatory step.

In addition, because step accuracy improved when PD subjects stepped to a remembered visual target, their impaired compensatory steps likely did not result from a deficit in spatial memory (consistent with Adamovich et al. 2001 and Keijsers et al. 2005). In the Remembered Target condition, the increased ability of the PD subjects to take more accurate compensatory steps than in the No Leg or Target conditions likely reflects their increased dependence on knowing precisely when the perturbation would occur since, in the Remembered Target condition (but not in the other conditions), the visual target was consistently turned off 3 seconds before the perturbation, thereby providing a temporal cue for perturbation onset. It is not likely, however, that the severe PD subjects' dependence on knowing the timing of the perturbation related to their abnormally short compensatory steps because (1) hypometria is evident during self-initiated voluntary movements that do not require PD subjects to couple a response to an external perturbation (Adamovich et al. 2001; Almeida et al. 2005; Keijsers et al. 2005), and (2) improved step accuracy in the Remembered Target condition did not correlate with any measure of step length.

In addition, we suggest that the hypometric steps of the PD subjects represent a central proprioceptive-motor dysfunction, rather than a pure motor coordination disorder, because the PD subjects were capable of improving their step length when provided with a visual target, suggesting that the motor dysfunction is dependent on the PD subjects'

sensory-motor context. The ability of a PD subject to step accurately to the target, however, depended on the severity of their motor symptoms: the PD subjects' lower-body motor UPDRS scores correlated with their step errors. Thus, the ability to overcome hypometric compensatory steps with visual targets diminishes as the symptoms of PD progress.

Potential Neural Correlates for Proprioceptive-Motor Impairment in PD

By examining the effects of dopamine medication and disease severity on the PD subjects' compensatory steps, we can gain insight into the neural circuitry underlying deficits in their compensatory steps. The effects of dopamine medication on step accuracy and step length were dependent on the PD subjects' initial compensatory step impairments. That is, PD subjects with the largest accuracy errors and shortest step lengths in the OFF state improved their step accuracy and increased their step length the most when in the ON state, whereas PD subjects with the largest and most accurate steps in the OFF state benefited the least from dopamine medication, with some PD subjects actually exhibiting larger errors and smaller steps in the ON state. While a floor effect may have contributed to the effect of medication on step error, and PD subjects with larger step lengths would not be expected to improve as much as those with smaller step lengths, it does not seem likely that a ceiling effect contributed to the PD subjects' inability to increase their step length from the OFF state to the ON state, because the PD subjects could increase their step length to a significantly greater length when stepping to the target compared to when stepping without a target in the ON medication state, and the healthy subjects (of similar height and weight to the PD subjects) were able to step farther than the PD subjects. Therefore, if the basal ganglia are directly responsible for

proprioceptive-motor deficits that degrade compensatory stepping in PD, we would have expected the effect of dopamine medication to be relatively homogenous for all of the PD subjects since the loss of nigro-striatal dopaminergic cells ought to have been robust for all PD subjects, regardless of the degree of disease severity (Bernheimer et al. 1973; Damier et al. 1999). Thus, the complex interaction between the effects of dopamine medication and the PD subjects' ability to take large, accurate compensatory steps suggests that dopaminergic dysfunction within the basal ganglia is not primarily responsible for the proprioceptive-motor deficit that degrades compensatory steps in PD subjects.

Instead, the neural locus for the proprioceptive-motor impairment in PD subjects more likely involves a region of the brain outside the basal ganglia where the activity of this other region: (1) degrades secondarily with PD (such that the degeneration of this region is not homogenous for all PD subjects), (2) responds to dopamine medication if activity in the region becomes impaired by PD, (3) is involved in both the processing of proprioceptive input as well as in motor planning and motor execution, and (4) is associated with the motor symptoms of PD. The supplementary motor area (SMA) represents a region in the cerebral cortex with all of these characteristics: in the SMA, degeneration occurs only in the late stages of PD (Braak et al. 2002), and in PD subjects, hypo-activity of the SMA occurs at rest and during limb movements (Jenkins et al. 1992; Playford et al. 1992; Rascol et al. 1992; Jahanshahi et al. 1995; Kikuchi et al. 2001). Furthermore, the hypo-activity of the SMA is related to the motor symptoms of PD (Jenkins et al. 1992; Rascol et al. 1992; Escola et al. 2003; Strafella et al. 2003). In addition, the SMA exhibits dense dopaminergic innervations (Williams and Goldman-

Rakic 1993), and for those PD subjects whose SMA is hypo-active, dopamine medication increases SMA activity (Jenkins et al. 1992; Rascol et al. 1992; Haslinger et al. 2001). Pre-movement and movement-related activity is also evident in the SMA (Halsband et al. 1994; Ball et al. 1999; Toma et al; 1999; Ohara et al. 2000; Cunnington et al. 2003), suggesting that the SMA is important for the planning and execution of movement. Furthermore, activity in the SMA preferentially increases for proprioception-guided movements that are executed without external sensory cues (Debaere et al. 2003), and activity in the SMA increases when proprioceptive afferents are stimulated by tendon vibration (Radovanovic et al. 2002). In a non-human primate model of PD, the responses of SMA neurons to passive joint displacements (thus, likely representing afferent sensory processing, rather than motor processing) become less specific for the joint being moved and for the direction of the displacement (Escola et al. 2002). Therefore, the SMA likely processes proprioceptive input to plan and to execute movements without the benefit of external sensory cues. With these observations, combined with the results of this study, we speculate that PD subjects likely exhibit undersized compensatory steps due to abnormal proprioceptive-motor integration caused by impaired activity of a neural circuit that includes the SMA, thereby biasing the motor control system toward hypometric movement.

Potential Neural Correlates for Compensatory Step Improvements with Visual targets

Visual targets increased the compensatory step length of PD subjects, resembling the phenomenon of paradoxical kinesis that occurs with voluntary stepping, in which PD subjects increase their voluntary step length when provided with explicit visual targets

(Martin 1967; Bagley et al. 1991; Morris et al. 2005). For voluntary movement in PD subjects, paradoxical kinesis may represent a compensatory neural "switch" from impaired neural circuits that include the SMA to intact neural circuits that include the dorso-lateral premotor cortex (dPMC; Hanakawa et al. 1999a; Cunnington et al. 2001). Because dPMC activity increases the most during sensory-cued movements and activity in the SMA increases the most for movements without sensory cues (Mushiake et al. 1991; Halsband et al. 1994; Debaere et al. 2003), the compensatory use of the dPMC by PD subjects may require the availability of explicit visual targets (or, perhaps, explicit intent to lengthen the step) in order to shift their sensorimotor set from a proprioceptive-motor circuit that includes the SMA to a visual-motor circuit that includes the dPMC. In our study, vision alone had only a mild effect on the compensatory step length of some severe PD subjects, whereas explicit visual targets significantly increased the compensatory step length of every PD subject. Therefore, we speculate that PD subjects may have been capable of increasing their compensatory step length with visual targets because the targets facilitated the use of the dPMC, rather than the SMA, to control the placement of their compensatory steps. Thus, although the initiation and timing of compensatory steps differ from the initiation and timing of voluntary steps, the underlying neural circuits that control triggered compensatory steps may be, in some ways, similar to the neural circuits that control voluntary steps (Rocchi et al. 2004).

Although our study did not directly record the activity of proprioceptive-motor or visual-motor neural circuits, our results suggest that PD subjects may use visual-motor neural circuits to compensate for their proprioceptive-motor deficits, but this compensatory mechanism becomes less efficacious as the PD subjects' symptoms

become more severe (consistent with Keijsers et al. 2005). The more severely affected PD subjects in our study exhibited larger errors than less affected PD subjects or control subjects, despite full vision of their movement in the Remembered Target and Target conditions. These results suggest that in PD subjects with moderate lower-body motor symptoms (including postural instability), the SMA circuit degrades, leaving the dPMC circuit intact. In the most advanced stages of PD, however, either (1) use of visual input via the dPMC circuit becomes insufficient to overcome other progressing symptoms, (2) subjects become unable to switch neural control pathways, or (3) the dPMC circuit may also degrade as SMA functions degrade further, thereby causing severely affected PD subjects to become increasingly dependent on a progressively dysfunctional visual-motor circuit.

CHAPTER 6: Conclusions

Summary of Findings

In this dissertation, we found that the cerebral cortex and basal ganglia contribute to anticipatory postural control during voluntary step initiation and in anticipation of external postural perturbations. Specifically, for voluntary step initiation, the results of CHAPTER 2 suggest that the pre-supplementary motor area (pre-SMA) coordinates the duration of both the anticipatory postural adjustment (APA) and the swing phase of a step. The dorso-lateral premotor cortex (dPMC), however, regulates only the duration of the swing phase, and the primary motor cortex (M1) regulates APA amplitudes. Compared to control subjects, subjects with Parkinson's disease (PD) exhibited diminished APAs of more variable duration as well as slower foot-swing velocities, and our results suggested that PD subjects exhibit impaired control of APA duration due to dysfunction of the pre-SMA, while compensating their steps' swing phase through activity of the dPMC.

In CHAPTER 3, we identified for the first time that anticipatory activity of the cerebral cortex mediates the optimization of postural responses with changes in central set (specifically, when subjects are provided with prior warning of a postural perturbation). In addition, CHAPTER 4 demonstrated (1) that anticipatory selection of a postural response strategy can occur even when responding to perturbations with unpredictable characteristics, (2) such pre-selection helps maximize stability but may result in contextually inappropriate responses if the anticipated strategy does not correctly predict the environmental context of the perturbation, and (3) that PD subjects are less able than healthy subjects to execute a pre-selected response strategy, thereby requiring

online response selection and rendering them more susceptible to falls and indecision (particularly when performing a secondary cognitive motor task). Lastly, despite PD subjects exhibiting an impaired ability to perform a context specific postural response to external perturbations, in CHAPTER 5 we demonstrated that PD subjects can use anticipatory response modification to change the length of their compensatory steps when provided with an explicit visual target.

Based on these results, the remainder of this chapter will serve to integrate our findings with current literature in order to develop models of neural control for voluntary step initiation and for responses to external postural perturbations.

The Neural Control of Voluntary Step Initiation

Before detailing this summary on the contributions the cerebral cortex and basal ganglia to step initiation, this section begins with a very brief mention of other neural centers known to participate in the generation of stepping movements so as to provide a basis for a neural control model of voluntary step initiation.

Beginning at the spinal cord, research has shown that, with postural support and external stimulation, de-afferented, spinalized cats exhibit stepping reflexes (Brown 1911). This isolated preparation led to the notion of a complex neural network in the spinal cord, now called the central pattern generator (CPG), and research on infants or on spinal-injured subjects suggests its existence in humans as well (reviewed by Dietz 2003). Action of the CPG alone does not elicit willed locomotion with appropriate postural control, nor the ability to adapt stepping in anticipation of dynamic environments, but the spinal cord does provide a neural center for generating coordinated flexor-extensor patterns of leg movement that are the basis for stepping.

Based on studies in the cat utilizing chemical and electrical stimulation to elicit locomotion and changes in posture, a network of postural and locomotor centers in the brainstem and midbrain have been shown to act on the spinal CPG, including the mesencephalic locomotor region, the pedunculo-pontine nucleus, and the ventral and dorsal tegmentum of the ponto-medulary junction (Mori 1987; Whelan 1996). In humans, activation of midbrain-brainstem sites has been recorded during gait using single-photon emission computed tomography (SPECT, Hanakawa et al. 1999b), and a lesion to the meso-pontine junction leads to an inability to stand or step (Masdeu et al. 1994). Postural orientation and the stepping rhythm are thought to be linked at these supra-spinal levels because stimulation or lesion of these sites affects both postural orientation and stepping (Mori 1987; Masdeu et al. 1994). In addition, neuronal recordings at the ponto-medullary reticular formation reveal that individual neurons can exhibit activity linked to both the anticipatory postural adjustment (APA) and the lifting of a limb (Schepens and Drew 2004).

Moving along the neural axis, cellular activity in the cerebellum of animal preparations, and lesions of the cerebellum in both animals and humans, demonstrate that the cerebellum provides an essential influence on movement patterning and amplitude regulation for both the posture and foot-swing of a step, with a particular authority on adapting posture and stepping with practice (Morton and Bastian 2004). The basal ganglia have also been shown to communicate with brainstem centers for posture and locomotion, regulating postural tone and movement velocity, and providing a dynamic interchange between the cortex and brainstem for the automatization of stepping: in humans, Parkinson's disease (PD) produces abnormal muscle tone, bradykinesia, and

difficulty with the automated execution of movement (including stepping) and, in animals, concomitant stimulation of the substantia nigra modifies the effectiveness of stimulation at the pedunculo-pontine nucleus or mesencephalic locomotor region for altering locomotion or spinal moto-neuronal activity (Takakusaki et al. 2004).

The cerebral cortex acts in concert with each of these sub-cortical regions in order to regulate several fundamental aspects of stepping. First and foremost, the cerebral cortex provides the neural substrate required to efficiently modify step characteristics according to environmental constraints. In cats, neurons in the primary motor cortex (M1) exhibit phase-dependent modulation during locomotion on a flat surface and this activity becomes enhanced when stepping over obstacles or on horizontal ladder rungs. In addition, lesions of the M1 or transections of the pyramidal tract lead to inadequate dorsiflexion and an inability to modify steps for obstacle avoidance or ladder-rung stepping (Liddell and Phillips 1944; Adkins et al. 1971; Armstrong and Drew 1984; Drew 1988; Beloozerova & Sirota 1993, 1998; Widajewicz et al. 1994; Drew et al. 1996; Beloozerova et al. 2003).

In humans, SPECT, near-infrared spectroscopy (NIRS), and functional magnetic resonance imaging (fMRI) reveal activation of a large network of cortical and sub-cortical structures when performing or imagining stepping tasks, including the pre-SMA, SMA proper, dPMC, M1, primary and multimodal sensory cortex, as well as the basal ganglia, cerebellum, and brainstem (Fukuyama et al. 1997; Hanakawa et al. 1999a,b; Miyai et al. 2001; Malouin et al. 2003). In addition, when adapting step placement to visual targets, SPECT imaging reveals enhanced activity within the dPMC, cerebellum, and parietal cortex (and this enhancement is greater in PD subjects than in healthy

subjects, Hanakawa et al. 1999a). Further, transcranial magnetic stimulation (TMS) of human M1 during voluntary stepping demonstrates phase-dependent modulation of cortico-spinal excitability (Petersen et al. 1998; Capaday et al. 1999; Schubert et al. 1999). Thus, even the highest levels of the neural axis participate in human stepping.

Now, after itemizing the known contributions of individual neural structures to stepping and locomotion, what about the coordination of posture and foot-swing during step initiation? As noted earlier, studies suggest that an APA and its associated prime movement are regulated by separate neural circuits, and that the SMA, M1, and basal ganglia contribute to generating the APA (Massion 1979, 1992; Brown and Frank 1987; Gurfinkel and Elner 1988; Nardone and Schieppati 1988; Viallet et al. 1992; Saitou et al. 1996; Benvenuti et al. 1997; de Wolf et al. 1998; Schepens and Drew 2003). The studies that identified an influence of the cerebral cortex on the APA, however, did not evaluate voluntary step initiation, nor did they specify the precise roles of isolated cortical loci for coordinating the APA with a prime movement.

In CHAPTER 2, our study elaborates on previous models of neural control by providing some detail regarding the specific contributions of the pre-SMA, dPMC, M1, and basal ganglia to human voluntary step initiation (although not specific to step initiation, for models on the neural integration of an APA with its prime movement, see Massion 1992, and Schepens and Drew 2004; for a model on the control of locomotion and for neural adaptations associated with PD, see Hanakawa 2006). Using repetitive TMS (rTMS), our study demonstrated that 1-Hz, sub-threshold rTMS over the pre-SMA shortens the duration of both the APA and the swing-phase of a step, but that the effects of pre-SMA stimulation on each step phase were not correlated. These results suggest

that the pre-SMA acts as a central coordinator for sequencing both step phases as two separate motor programs. Stimulation of the dPMC, however, only shortened swing-phase durations without affecting the APA, whereas stimulation over the M1 only decreased APA amplitude. Thus, after being coordinated by the pre-SMA, the neural control of a step's APA and swing-phase diverge into separate neural circuits. Based on the previous models mentioned above, these circuits then converge at the midbrain and brainstem to facilitate the activation of the CPG and elicit a coordinated movement that includes both an APA and a step (see Fig. 1A).

When analyzing the step initiation of PD subjects (who primarily present with neuropathology of the basal ganglia: Bernheimer et al. 1973; Damier et al. 1999), we confirmed previous reports that PD subjects exhibit more variable APA durations with diminished amplitude, as well as decreased foot-swing velocity, when compared to healthy control subjects (Martin 1967; Bazalgette et al. 1987; Viallet et al. 1987; Crenna et al. 1990; Lee et al. 1995; Gantchev et al. 1996; Burleigh-Jacobs et al. 1997; Frank et al. 2000; Rocchi et al. 2006). In addition, whereas the severity of the PD subjects' motor symptoms correlated with the extent to which pre-SMA stimulation affected their APA durations, their disease severity did not correlate with the extent that M1 stimulation affected APA amplitudes, nor did rTMS to any site affect foot-swing velocity. Thus, PD subjects likely exhibit impaired APA durations due to a progressive dysfunction of the pre-SMA, whereas their diminished APA amplitude and foot-swing velocity are likely due to dysfunction of basal ganglia circuits that do not include the pre-SMA, dPMC, or M1. Further, the severity of the PD subjects' motor symptoms also correlated with the extent that dPMC stimulation affected their swing-phase duration. Given that the PD

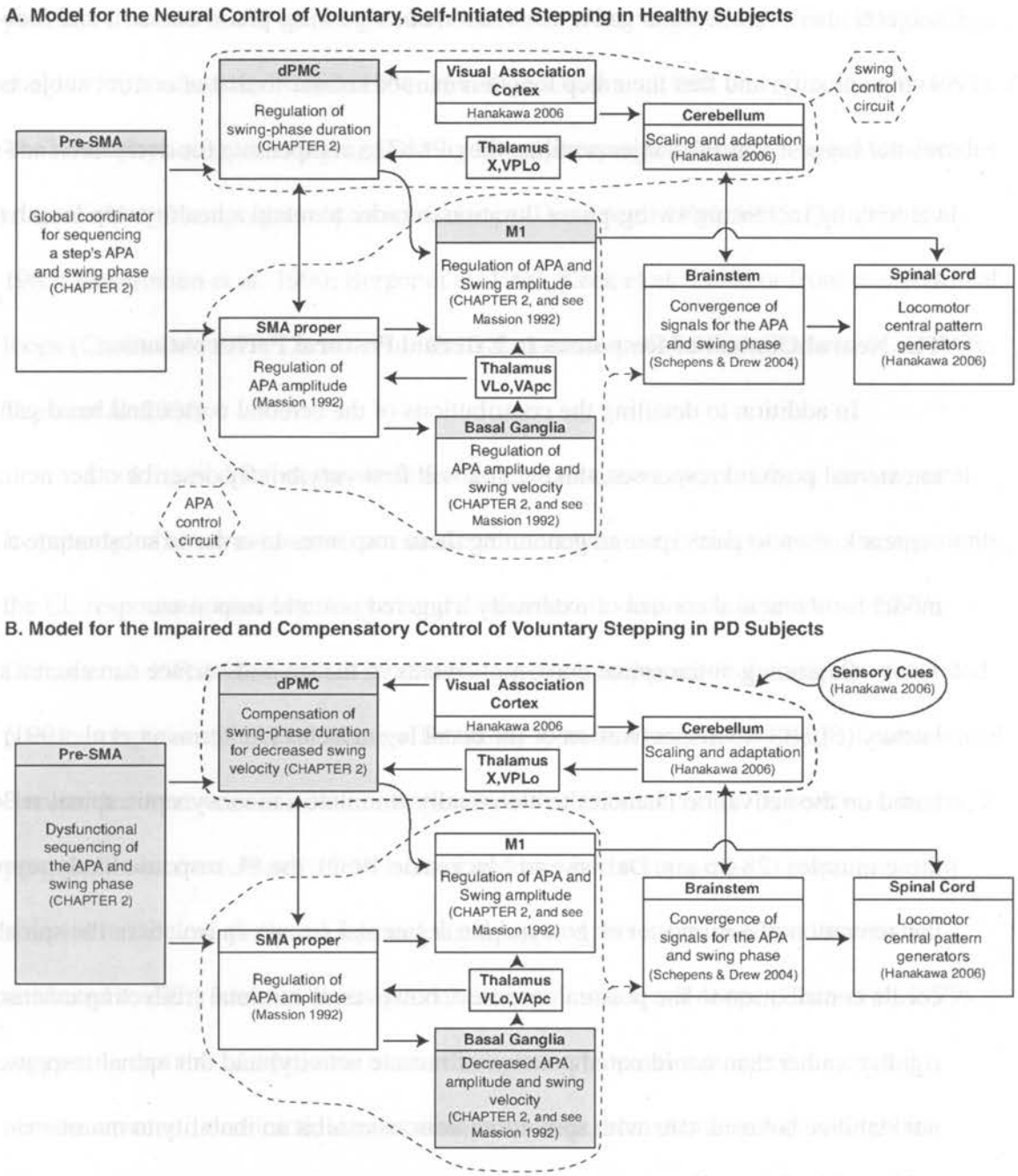

Fig. 1. Neural control models of voluntary step initiation for **(A)** healthy subjects, and **(B)** PD subjects. These models represent elaborations on models previously presented by Massion (1992), Schepens and Drew (2004), and Hanakawa (2006). Although these neural loci may exhibit more afferent and efferent connectivity than illustrated, many arrows were purposefully omitted to focus the illustration on information flow that is most pertinent to voluntary step initiation. Abbreviations: SMA, supplementary motor area; dPMC, dorso-lateral premotor cortex; M1, primary motor cortex; APA, anticipatory postural adjustment; VLo, ventral lateral nucleus pars oralis; VPLo, ventral posterior lateral nucleus pars oralis; VApc, parvicellular ventral anterior nucleus; X, nucleus X.

subjects also exhibited a negative correlation among swing-phase duration and foot-swing velocity, and that their step length remained similar to that of control subjects, the results suggest that PD subjects utilize the dPMC to compensate for decreased foot-swing velocity by increasing swing-phase duration in order to retain a healthy step length (Fig. 1B).

The Neural Control of Responses to External Postural Perturbations

In addition to detailing the contributions of the cerebral cortex and basal ganglia to external postural responses, this section will first very briefly describe other neural centers known to participate in generating these responses in order to substantiate a model for the neural control of externally triggered postural responses.

Beginning at the spinal cord, movements of the support surface can elicit a short-latency (SL; 33-45 ms) activation of the distal leg muscles (Ackermann et al. 1991) and, based on the activation latencies to electrically stimulate a monosynaptic spinal reflex at these muscles (28-35 ms, DeLisa and Mackenzie 1982), the SL response likely represents the activation of a mono- or oligo-synaptic segmental circuit. In isolation, the spinal cord's contribution to the postural response, however, is minimal (reflecting extensor rigidity, rather than coordinated patterns of muscle activity) and this spinal response does not stabilize balance: cats with spinal transections exhibit an inability to maintain unsupported stance or to maintain balance when exposed to postural perturbations (Fung and Macpherson 1999; Macpherson and Fung 1999).

Following the SL response, the feet-in-place postural response continues with functionally stabilizing long-latency (LL) activations in the muscles of the leg and trunk (Nashner 1976). The onset of the LL responses varies considerably with different

perturbations and initial conditions, but common values range between 80-120 ms (Chan et al. 1979; Nashner and Cordo 1981; Horak and Nashner 1986; Ackermann et al. 1991). The neurophysiology underlying the long-latency response has been debated for decades to arise either from poly-synaptic spinal loops (Dietz et al. 1984, 1985; Quintern et al. 1985; Ackermann et al. 1990; Berger et al. 1990; Keck et al. 1998) or from trans-cortical loops (Chan et al. 1979; Diener et al. 1985; Ackermann et al. 1986; Petersen et al. 1998; Taube et al. 2006).

Looking in detail at the evidence for each assertion, support for a trans-cortical loop partly relies on evidence from stroke patients with cerebral lesions. In these patients, the LL response is severely delayed and diminished in amplitude (Chan et al. 1979; Diener et al. 1985). Rather than representing a direct impairment of cortically generated postural responses, however, these effects may represent impaired activity of sub-cortical circuits that were once in communication with the lesioned cortex. In healthy subjects, a progressive increase in activation latency occurs when comparing LL responses from muscles in the arm, proximal leg, and distal leg, and this increase is too large to be attributed to differences in the lengths of the segmental spinal loops (Chan et al. 1979), suggesting that the LL response routes through supra-spinal regions of the central nervous system. In addition, intra-cranial recordings from standing cats and rabbits demonstrate that projection neurons and inter-neurons of the primary motor cortex modulate their activity in response to tilts of the support surface (Beloozerova et al. 2003, 2005). Furthermore, although in a condition that did not require subjects to re-establish postural equilibrium, Petersen et al. (1998) reported that ankle stretch elicited a LL response in the tibialis anterior muscle, and that (1) its latency was sufficiently long to

substantiate a trans-cortical pathway, (2) magnetic stimulation of the motor cortex selectively facilitated the LL response, but not the SL response, and (3) electrical stimulation of the cortico-spinal tract (thought to bypass trans-synaptic stimulations of the motor cortex) did not facilitate the LL response, as did the magnetic stimulation (which does involve trans-synaptic stimulation of cortical neurons). Taube and colleagues (2006) also recently demonstrated that TMS-evoked responses in the soleus muscle become enhanced only during the LL response to a postural perturbation.

Despite these observations, a significant amount of evidence suggests that the LL response to a postural perturbation does not represent the activity of a trans-cortical loop. For instance, studies in the cat indicate that the LL response likely arises from the brainstem: spinalized cats do not exhibit LL responses and cannot maintain equilibrium when exposed to postural perturbations (Macpherson and Fung 1999), but decerebrate cats (despite many functional limitations) can maintain balance and exhibit intact, perturbation-specific muscular synergies during the LL response when exposed to multiple directions of postural perturbations (Honeycutt and Nichols 2005). As further evidence against a trans-cortical loop, in humans, changes in the LL response of the distal leg muscles do not correspond to changes in the perturbation-evoked cortical potentials that represent the sensory processing of the balance disturbance (Quintern et al. 1985; Ackermann et al. 1990, 1991; Berger et al. 1990). In addition, muscular activations evoked by TMS remain unchanged just prior to a perturbation and at varying intervals before or after a perturbation (Ackermann et al. 1991; Keck et al. 1998). These studies, however, did not specifically test cortical excitability during the LL response period, as did Taube and colleagues (2006). Further, while it has been argued that the latency of the

LL response is sufficient for a trans-cortical loop (Chan et al. 1979; Petersen et al. 1998), others have argued that the onset latency of the afferent perturbation-evoked cortical potential is only slightly shorter than that of the LL response and, therefore, the efferent path of the LL response is not properly timed with the afferent cortical potential in order to signify a trans-cortical loop (Dietz et al. 1984, 1985).

Therefore, it remains unclear whether a direct trans-cortical loop generates the LL response to postural perturbations. Given that the LL response lasts for several hundred milliseconds, it may be that brainstem circuits initiate its response, and then the LL response subsequently becomes modified by cortical circuits during its later phases. Studies have found that performing a concurrent cognitive-motor task or the intention to step when responding to a postural perturbation (thought to represent cortical influence) only affects the later phases of the LL response (Burleigh and Horak 1996; Norrie et al. 2002).

The cerebral cortex may also influence postural responses in a more indirect fashion, by altering the circuits that generate the postural response through anticipatory postural control. Thus, rather than viewing the generation of a postural response as being either spinal or cortical in origin, it may be necessary to view the generation of the postural response as a dynamic and context-dependent interplay between all levels of the neural axis. Specifically, the cerebral cortex may act to prime postural responses accommodated within the brainstem (including the LL response), thereby optimizing postural responses for a given environmental context, while still allowing for the early response latencies that are necessary to recover equilibrium. Evidence does support such a role for the cerebral cortex. For example, in cats, pyramidal tract neurons modulate

their activity in response to a postural perturbation, and this perturbation-associated activity becomes altered with changes in the cats' initial postural alignment (a change in central set) but does not clearly correlate with the cats' postural responses (Beloozerova et al. 2005). Thus, cortical activity alters with changes in central set, but the descending cortical output does not directly influence the postural response via cortical-spinal-motoneuronal pathways.

In humans, the study presented in CHAPTER 3 of this dissertation, in combination with studies examining cortico-spinal excitability just prior to postural perturbations, support the hypothesis that cortical activity modifies postural responses with changes in central set, but not via the cortico-spinal tract. Specifically, as reported in CHAPTER 3, feet-in-place responses were shown to change based on changes in central set so as to maximize postural stability during the feet-in-place response. In addition, we found that changes in pre-perturbation cortical activity (observed by electroencephalographic readiness potentials) correlated with these response modifications. Taking into account that visual warning cues do not alter cortico-spinal excitability just prior to a perturbation (as measured by TMS-evoked muscle activity; Ackermann et al. 1991), the cerebral cortex likely influences postural responses with changes in central set via indirect cortico-brainstem pathways. Although not a focus of this dissertation, the cerebellum needs to be mentioned as contributing to set-dependent scaling of postural responses based on prior experience (Timmann and Horak 1997) and, therefore, may be involved in the cortico-brainstem circuit responsible for modifying responses with changes in central set.

The basal ganglia are also likely included in the cortico-brainstem pathway that is activated by changes in central set. Indeed, dysfunction of basal ganglia due to PD leads to an inability to alter postural responses with changes in (1) stance configuration, (2) the intention to respond with different strategies, or (3) when transitioning between perturbations with opposing characteristics (Horak et al. 1992; Beckley et al. 1993; Bloem et al. 1995; Chong et al. 2000; Horak et al. 2005). In addition, in CHAPTER 4 we demonstrated that, compared to healthy subjects, PD subjects more often utilize online response selection when responding to unpredictable perturbations because of an impaired ability to execute a pre-selected response strategy. Therefore, the results suggest that the basal ganglia act as an intermediary between the cerebral cortex and brainstem for automating the selection and execution of a context-specific postural response (Takakusaki et al. 2004; Grillner et al. 2005).

Despite exhibiting bradykinetic and hypometric postural responses, as well as an impaired ability to modify postural responses with changes in central set, in CHAPTER 5, we demonstrated that PD subjects can increase the size of their compensatory stepping responses when provided with a visual target before an expected perturbation. This paradoxical movement (Souques 1921) is remarkably similar to a PD subject's ability to improve voluntary stepping with external sensory cues, which has already been reported to be related to compensatory activity of a circuit that includes the parietal cortex, dorso-lateral premotor cortex, and cerebellum (Hanakawa et al. 1999a). In addition, animals with lesions of the cerebral cortex fail to generate compensatory steps (Rademaker 1931; Bard 1933; Brooks 1933; Magoun and Ranson 1938). Thus, cortical centers influence compensatory steps, rendering it feasible that similar cortical circuits govern both

compensatory and voluntary stepping, and it is also feasible that PD subjects utilize the parietal-premotor-cerebellar circuit to prompt set-mediated priming of a postural response.

Based on the discussion above, Fig. 2 illustrates a model for the neural control of externally triggered postural responses, and it becomes noticeable that remarkably similar neural loci seem responsible for voluntary stepping (Fig. 1) and triggered postural responses. These similarities are supported by reports that repetitive training of externally triggered postural responses also improves voluntary gait in elderly and PD subjects with impaired balance (Rogers et al. 2003b; Jobges et al. 2004). Although an exact overlap of the neural systems governing these two behaviors would allow for the efficient use of neural resources, this simple case obviously cannot be entirely true because both the feet-in-place and change-in-support postural responses occur more quickly than a similar movement performed voluntarily in response to a cue that does not threaten balance, and voluntary response latencies are too slow to effectively recover from a postural perturbation (Diener et al. 1984; Burleigh et al. 1994; McIlroy and Maki 1996; CHAPTER 4).

The answer may lie in the different dynamics and context-dependence of how neural loci are recruited for a voluntary step versus for a triggered postural response. During voluntary step initiation, context-appropriate anticipatory postural control is integrally related to the neural control of the prime movement at the level of the cerebral cortex and at the moment when a step is generated, whereas the use of the cerebral cortex for anticipatory postural control of externally triggered postural responses does not occur during the preliminary generation of the response. Instead, the cerebral cortex provides its

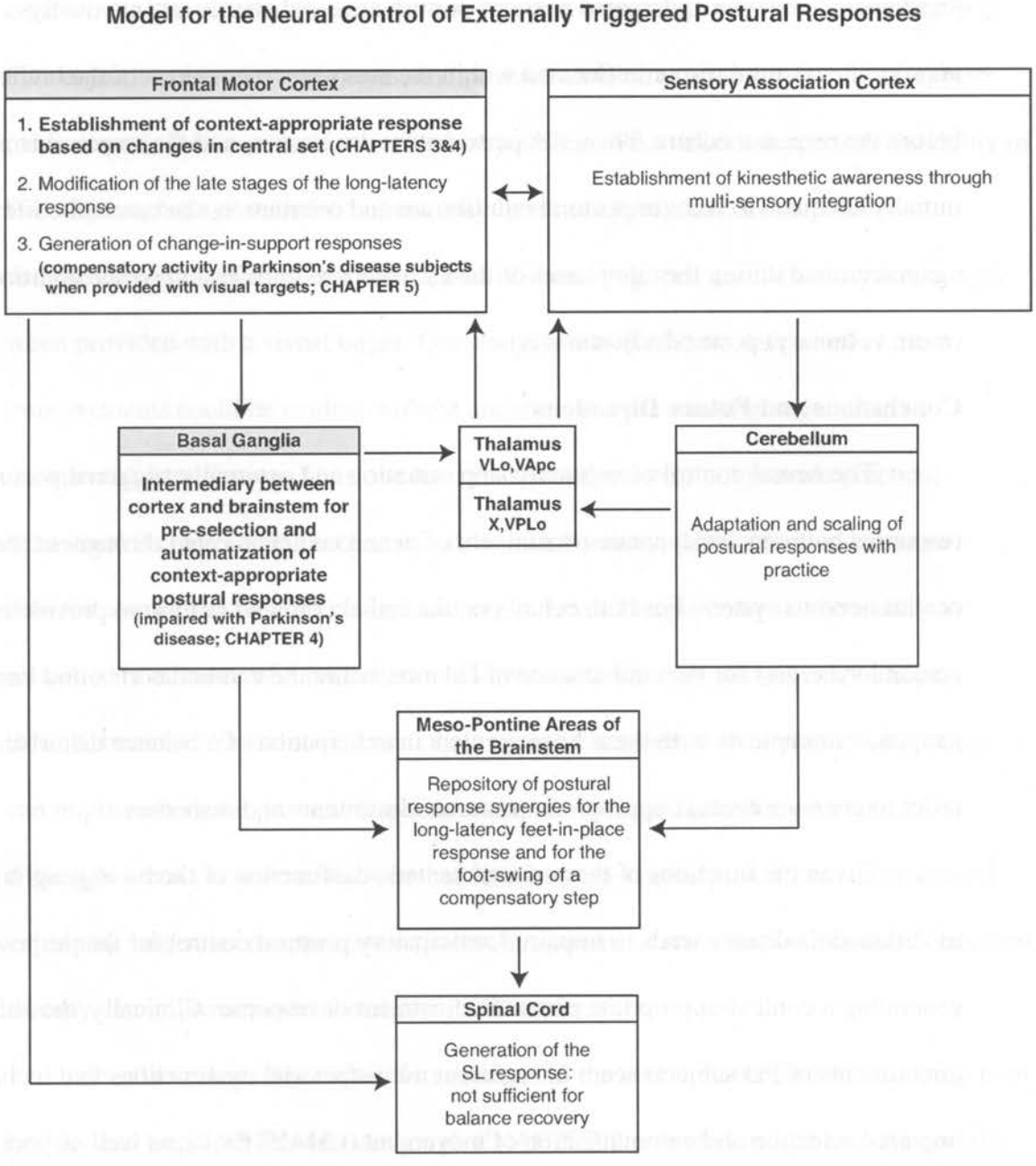

Fig. 2. Neural control model of externally triggered postural responses. This model was generated by combining the results of this dissertation with a review of the literature. Although these neural loci may exhibit more afferent and efferent connectivity than illustrated, many arrows were purposefully omitted to focus the illustration on information flow that is most pertinent to externally triggered postural responses. Abbreviations are defined as in Fig. 1.

"best guess" about an anticipated postural perturbation and primes a contextually appropriate postural response (located within the meso-pontine regions of the brainstem) before the response occurs. Then, if a perturbation does occur, and the response is not initially adequate to recover postural equilibrium and orientation, the cerebral cortex is again recruited during the late phases of the LL response in order to provide additional (more voluntary) postural adjustments.

Conclusions and Future Directions

The neural control of voluntary step initiation and externally triggered postural responses both require dynamic recruitment of neural centers located throughout the central nervous system. For both behaviors, the spinal cord and brainstem provide basic postural synergies for the maintenance of balance, while the cerebral cortex and basal ganglia communicate with these lower centers in anticipation of a balance disturbance in order to generate context-appropriate postural adjustments and responses.

Given the functions of these neural centers, dysfunction of the basal ganglia due to Parkinson's disease leads to impaired anticipatory postural control for the purpose of generating a context-appropriate postural adjustment or response. Clinically, the balance impairments of PD subjects seem to represent multi-factorial dysfunctions that include impaired selection and automatization of movement (CHAPTER 4), as well as poor proprioceptive-motor integration for establishing internal representations of movement (CHAPTER 5). Whereas dopaminergic circuits of the basal ganglia seem to govern response selection (multiple APAs decreased with dopamine-acting medications), dysfunction of both dopamine and non-dopamine circuits residing outside the basal ganglia seem to underlie impaired proprioceptive-motor integration for postural

equilibrium (the effects of dopamine-acting medications depended on the severity of a PD subject's postural impairments, and postural instability often persists despite these medications). Because medication has not yet been able to alleviate postural instability in PD subjects, behavioral interventions may be more appropriate. CHAPTER 5 demonstrated that PD subjects are capable of increasing their compensatory step length when provided with a visual target. Our study, however, did not test whether these improvements could be evident without attention to a pre-existing target or to an unexpected perturbation. Thus, the use of visual targets may not provide practical behavioral therapy for PD subjects outside the laboratory, when attention becomes directed away from balance control and explicit visual targets may not be readily identified in advance of a perturbation. Patients with PD may not be without hope, though, because research has shown that repetitive training of their postural responses can improve both the postural response and their voluntary gait (Jobges et al. 2004). Although it has yet to be tested whether visual targets can help facilitate the process of entraining larger, more appropriate postural responses, it remains possible that behavioral therapy can improve postural stability in PD patients.

Further research is required to understand the neural mechanisms underlying both healthy and impaired balance. Although CHAPTER 2 provided insight into the specific contributions of particular cortical loci to human voluntary step initiation, we still require a deeper understanding for how the APA is coordinated with the foot-swing of a step. Specifically, we require further identification of the influence of other neural centers involved in step initiation, such as the SMA proper. Second, neuropharmacologic and

neurophysiologic studies are required in both animals and humans to clarify how different neural loci communicate to generate a voluntary step.

For externally triggered postural perturbations, CHAPTERS 3-5 provided insight into the neural control of postural responses to anticipated postural perturbations. Although external postural perturbations can be anticipated in many natural situations (for example, when standing on or approaching slippery or compliant surfaces, when on an escalator, bus, or metro, or when engaged in sport), the neural control of postural responses to entirely unexpected perturbations remains untested. When responding to an unexpected loss of balance, context-appropriate postural responses may be generated by (1) the cerebral cortex being activated online, (2) the cerebral cortex constantly updating sub-cortical structures, allowing for optimized responses at all times, without involving online activation during balance recovery, or (3) the cortex only becomes involved late in a response that was selected from unprimed default sub-cortical synergies, thereby risking an environmentally inadequate initial response. The occurrence of either of these options may further depend on the postural capability of the individual (e.g., a person with impaired balance may be incapable of online selection and, instead, may use a default strategy to facilitate the speed of a response). Thus, in addition to identifying the neural substrates of postural orientation and equilibrium, further research is required to understand the roles and communication of these neural loci in varying contexts: such as any changes that occur with dual tasking, while altering the predictability of postural perturbations and/or the intentions of the subject, and with age or disease. To answer these questions, experiments should be directed to both animal and human models, with direct recordings of neural activity during postural tasks in varying contexts. Altogether,

our understanding of the physiology that underlies postural orientation and equilibrium is still in its infancy, particularly with regard to the role of the cerebral cortex. Thus, with current advances in cellular recording and neural imaging techniques, more attention should be paid to this topic in order to better direct physical, pharmacological, and surgical therapies for those with impaired posture control.

REFERENCES

Ackermann H, Dichgans J, Guschlbauer B (1991) Influence of an acoustic preparatory signal on postural reflexes of the distal leg muscles in humans. Neurosci Lett 127:242-246.

Ackermann H, Dichgans J, Guschlbauer B, Scholz E (1990) Postural modulation of evoked cortical and motor potentials and its relationship to functional adaptation of postural reflexes. In: Brandt T, Paulus W, Bles W, Dieterich M, Krafczyk S, Straube A (eds) Disorders of posture and gait. Verlag, New York, pp 86-89.

Ackermann H, Diener HC, and Dichgans J (1986) Mechanically evoked cerebral potentials and long-latency muscle responses in the evaluation of afferent and efferent long-loop pathways in humans. Neurosci Lett 66:233-238.

Adamovich SV, Berkinblit MB, Hening W, Sage J, Poizner H (2001) The interaction of visual and proprioceptive inputs in pointing to actual and remembered targets in Parkinson's disease. Neuroscience 104:1027-1041.

Adkin AL, Quant S, Maki BE, McIlroy WE (2006) Cortical responses associated with predictable and unpredictable compensatory balance reactions. Exp Brain Res 172:85-93.

Adkins RJ, Cegnar MR, Rafuse DD (1971) Differential effects of lesions of the anterior and posterior sygmoid gyri in cats. Brain Res 30:411–414.

Allum JH (1983) Organization of stabilizing reflex responses in tibialis anterior muscles following ankle flexion perturbations of standing man. Brain Res 264:297-301.

Almeida QJ, Frank JS, Roy EA, Jenkins ME, Spaulding S, Patla AE, Jog MS (2005) An evaluation of sensorimotor integration during locomotion toward a target in Parkinson's disease. Neuroscience 134:283-293.

Aoyagi K, Ross PD, Davis JW, Wasnich RD, Hayashi T, Takemoto T (1998) Falls among community-dwelling elderly in Japan. J Bone Miner Res 13:1468-1474.

Armstrong DM, Drew T (1984) Discharges of pyramidal tract and other motor cortical neurones during locomotion in the cat. J Physiol 346:471-495.

Babinski J (1899) De l'asynergie cerebelleuse. Rev Neurol 7:806-816.

Bagley S, Kelly B, Tunnicliffe N, Turnbull GI, Walker GM (1991) The effect of visual cues on the gait of independently mobile Parkinson's disease patients. Physiotherapy 77:415–420.

Ball T, Schreiber A, Feige B, Wagner M, Lucking CH, Kristeva-Feige R (1999) The role of higher-order motor areas in voluntary movement as revealed by high-resolution EEG and fMRI. Neuroimage 10:682-694.

Bard P (1933) Studies on the cerebral cortex I. Localized control of placing and hopping reactions in the cat and their normal management by small cortical remnants. Arch Neurol Psychiatr 30:40-74.

Barra J, Chauvineau V, Ohlmann T, Gresty M, Perennou D (2006) Perception of longitudinal body axis in stroke patients: a pilot study. J Neurol Neurosurg Psychiatry, Electronic Publication: July 25.

Bateni H, Zecevic A, McIlroy WE, Maki BE (2004) Resolving conflicts in task demands during balance recovery: does holding an object inhibit compensatory grasping? Exp Brain Res 157:49-58.

Bazalgette D, Zattara M, Bathien N, Bouisset S, Rondot P (1987) Postural adjustments associated with rapid voluntary arm movements in patients with Parkinson's disease. Adv Neurol 45:371-374.

Beckley DJ, Bloem BR, Remler MP (1993) Impaired scaling of long latency postural reflexes in patients with Parkinson's disease. Electroencephalogr Clin Neurophysiol 89:22-28.

Beloozerova IN, Sirota MG (1993) The role of the motor cortex in the control of accuracy of locomotor movements in the cat. J Physiol 461:1-25.

Beloozerova IN, Sirota MG (1998) Cortically controlled gait adjustments in the cat. Ann N Y Acad Sci 860:550-553.

Beloozerova IN, Sirota MG, Orlovsky GN, Deliagina TG (2005) Activity of pyramidal tract neurons in the cat during postural corrections. J Neurophysiol 93:1831-1844.

Beloozerova IN, Sirota MG, Swadlow HA (2003) Activity of different classes of neurons of the motor cortex during locomotion. J Neurosci 23:1087-1097.

Benvenuti F, Stanhope SJ, Thomas SL, Panzer VP, Hallett M (1997) Flexibility of anticipatory postural adjustments revealed by self-paced and reaction-time arm movements. Brain Res 761:59-70.

Berger W, Horstmann GA, Dietz V (1990) Interlimb coordination of stance in children: divergent modulation of spinal reflex responses and cerebral evoked potentials in terms of age. Neurosci Lett 116:118-122.

Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F (1973) Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. J Neurol Sci 20:415-455.

Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J (2005) BOLD MRI responses to repetitive TMS over human dorsal premotor cortex. Neuroimage 28:22-29.

Bloem BR, Beckley DJ, Remler MP, Roos RA, van Dijk JG (1995) Postural reflexes in Parkinson's disease during 'resist' and 'yield' tasks. J Neurol Sci 129:109-119.

Bloem BR, Grimbergen YA, Cramer M, Willemsen M, Zwinderman AH (2001) Prospective assessment of falls in Parkinson's disease. J Neurol 248:950-958.

Boecker H, Ceballos-Baumann A, Bartenstein P, Weindl A, Siebner HR, Fassbender T, Munz F, Schwaiger M, Conrad B (1999) Sensory processing in Parkinson's and Huntington's disease: investigations with 3D H(2)(15)O-PET. Brain 122:1651-1665.

Boecker H, Dagher A, Ceballos-Baumann AO, Passingham RE, Samuel M, Friston KJ, Poline J, Dettmers C, Conrad B, Brooks DJ (1998) Role of the human rostral supplementary motor area and the basal ganglia in motor sequence control: investigations with H2 15O PET. J Neurophysiol 79:1070-1080.

Bouisset S, Richardson J, Zattara M (2000) Are amplitude and duration of anticipatory postural adjustments identically scaled to focal movement parameters in humans? Neurosci Lett 278:153-156.

Boylan LS, Pullman SL, Lisanby SH, Spicknall KE, Sackeim HA (2001) Repetitive transcranial magnetic stimulation to SMA worsens complex movements in Parkinson's disease. Clin Neurophysiol 112:259-264.

Braak H, Del Tredici K, Bratzke H, Hamm-Clement J, Sandmann-Keil D, Rub U (2002) Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). J Neurol 249:III/1-III/5.

Brandt T, Dieterich M, Danek A (1994) Vestibular cortex lesions affect the perception of verticality. Ann Neurol 35:403-412.

Brauer SG, Woollacott M, Shumway-Cook A (2002) The influence of a concurrent cognitive task on the compensatory stepping response to a perturbation in balance-impaired and healthy elders. Gait Posture 15:83-93.

Brooks CM (1933) Studies on the cerebral cortex II. Localized representation of hopping and placing reactions in the rat. Arch Neurol Psychiatr 30:162-171.

Brown JE, Frank JS (1987) Influence of event anticipation on postural actions accompanying voluntary movement. Exp Brain Res 67:645-650.

Brown LA, Shumway-Cook A, Woollacott MH (1999) Attentional demands and postural recovery: the effects of aging. J Gerontol A Biol Sci Med Sci 54:M165-M171.

Brown TG (1911) The intrinsic factors in the act of progression in the mammals. Proc Roy Soc 84:308-319.

Brunt D, Santos V, Kim HD, Light K, Levy C (2005) Initiation of movement from quiet stance: comparison of gait and stepping in elderly subjects of different levels of functional ability. Gait Posture 21:297-302.

Buchanan JJ, Horak FB (2003) Voluntary control of postural equilibrium patterns. Behav Brain Res 143:121-140.

Buhmann C, Gorsler A, Baumer T, Hidding U, Demiralay C, Hinkelmann K, Weiller C, Siebner HR, Munchau A (2004) Abnormal excitability of premotor–motor connections in de novo Parkinson's disease. Brain 127:2732–2746.

Burleigh A, Horak F (1996) Influence of instruction, prediction, and afferent sensory information on the postural organization of step initiation. J Neurophysiol 75:1619-1628.

Burleigh AL, Horak FB, Malouin F (1994) Modification of postural responses and step initiation: evidence for goal-directed postural interactions. J Neurophysiol 72:2892-2902.

Burleigh-Jacobs A, Horak FB, Nutt JG, Obeso JA (1997) Step initiation in Parkinson's disease: influence of levodopa and external sensory triggers. Mov Disord 12:206-215.

Byblow WD, Lewis GN, Stinear JW (2003) Effector-specific visual information influences kinesthesis and reaction time performance in Parkinson's disease. J Mot Behav 35:99-107.

Capaday C, Lavoie BA, Barbeau H, Schneider C, Bonnard M. 1999. Studies on the corticospinal control of human walking: I. Responses to focal transcranial magnetic stimulation of the motor cortex. J Neurophysiol 81(1):129–39.

Carpenter MG, Allum JH, Honegger F, Adkin AL, Bloem BR (2004a) Postural abnormalities to multidirectional stance perturbations in Parkinson's disease. J Neurol Neurosurg Psychiatry 75:1245-1254.

Carpenter MG, Frank JS, Adkin AL, Paton A, and Allum JH (2004b) Influence of postural anxiety on postural reactions to multi-directional surface rotations. J Neurophysiol 92:3255-3265.

Chan CWY, Melvill Jones G, Kearney RE, Watt DGD (1979) The 'late' electromyographic response to limb displacement in man. I. Evidence for supraspinal contribution. Electroencephalogr Clin Neurophysiol 46:173-181.

Chandler RF, Clauser CE, McConville JT, Reynolds HM, Young JW (1975) Investigation of inertial properties of the human body. In: Aerospace Medical Research Laboratory. Washington D.C., pp 1-162.

Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohen LG (1997) Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 48:1398-1403.

Chen WH, Mima T, Siebner HR, Oga T, Hara H, Satow T, Begum T, Nagamine T, Shibasaki H (2003) Low-frequency rTMS over lateral premotor cortex induces lasting changes in regional activation and functional coupling of cortical motor areas. Clin Neurophysiol 114:1628-1637.

Chong RK, Horak FB, Woollacott MH (1999) Time-dependent influence of sensorimotor set on automatic responses in perturbed stance. Exp Brain Res 124:513-519.

Chong RK, Horak FB, Woollacott MH (2000) Parkinson's disease impairs the ability to change set quickly. J Neurol Sci 175:57-70.

Clement G, Gurfinkel VS, Lestienne F, Lipshits MI, Popov KE (1984) Adaptation of postural control to weightlessness. Exp Brain Res 57:61-72.

Contreras-Vidal JL, Gold DR (2004) Dynamic estimation of hand position is abnormal in Parkinson's disease. Parkinsonism Relat Disord 10:501-506.

Cordo PJ, Nashner LM (1982) Properties of postural adjustments associated with rapid arm movements. J Neurophysiol 47:287-302.

Crenna P, Frigo C, Giovannini P, Piccolo I (1990) The initiation of gait in Parkinson's disease. In: Berardelli A, Benecke M, Manfredi M, Marsden CD (eds) Motor Disturbances II. Academic Press, London, pp 161-173.

Cunnington R, Iansek R, Thickbroom GW, Laing BA, Mastaglia FL, Bradshaw JL, Phillips JG (1996) Effects of magnetic stimulation over supplementary motor area on movement in Parkinson's disease. Brain 119:815-822.

Cunnington R, Lalouschek W, Dirnberger G, Walla P, Lindinger G, Asenbaum S, Brucke

T, Lang W (2001) A medial to lateral shift in pre-movement cortical activity in hemi-Parkinson's disease. Clin Neurophysiol 112:608-618.

Cunnington R, Windischberger C, Deecke L, Moser E (2003) The preparation and readiness for voluntary movement: a high-field event-related fMRI study of the Bereitschafts-BOLD response. Neuroimage 20:404-412.

Damier P, Hirsch EC, Agid Y, Graybiel AM (1999) The substantia nigra of the human brain. II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. Brain 122:1437-1448.

Davis JW, Nevitt MC, Wasnich RD, Ross PD (1999) A cross-cultural comparison of neuromuscular performance, functional status, and falls between Japanese and white women. J Gerontol A Biol Sci Med Sci 54:M288-M292.

De Wolf S, Slijper H, Latash ML (1998) Anticipatory postural adjustments during self paced and reaction-time movements. Exp Brain Res 121:7-19.

Debaere F, Wenderoth N, Sunaert S, Van Hecke P, Swinnen SP (2003) Internal vs external generation of movements: differential neural pathways involved in bimanual coordination performed in the presence or absence of augmented visual feedback. Neuroimage 19:764-776.

DeLisa JA, Mackenzie K (1982) Manual of Nerve Conduction Velocity Techniques. Raven, New York.

Delwaide PJ, Gonce M. Pathophysiology of Parkinson's signs. In: Jankovic, J, Tolosa, E, eds. Parkinson's Disease and Movement Disorders. Baltimore: Williams & Williams: 1993. p 77–92.

Demirci M, Grill S, McShane L, Hallett M (1997) A mismatch between kinesthetic and visual perception in Parkinson's disease. Ann Neurol 41:781-788.

Diedrichsen J, Hashambhoy Y, Rane T, Shadmehr R (2005) Neural correlates of reach errors J Neurosci 25:9919-9931.

Diener HC, Ackermann H, Dichgans J, Guschlbauer B (1985) Medium- and long-latency responses to displacements of the ankle joint in patients with spinal and central lesions. Electroencephalogr Clin Neurophysiol 60:407-416.

Diener HC, Dichgans J, Bootz F, Bacher M (1984) Early stabilization of human posture after a sudden disturbance: influence of rate and amplitude of displacement. Exp Brain Res 56:126-134.

Diener HC, Horak FB, Nashner LM (1988) Influence of stimulus parameters on human

postural responses. J Neurophysiol 59:1888-1905.

Dietz V (2003) Spinal cord pattern generators for locomotion. Clin Neurophysiol 114:1379-1389.

Dietz V, Quintern J, Berger W (1984) Cerebral evoked potentials associated with the compensatory reactions following stance and gait perturbation. Neurosci Lett 50:181-186.

Dietz V, Quintern J, Berger W, and Schenck E (1985) Cerebral potentials and leg muscle e.m.g. responses associated with stance perturbation. Exp Brain Res 57:354-384.

Dimitrov B, Gavrilenko T, Gatev P (1996) Mechanically evoked cerebral potentials to sudden ankle dorsiflexion in human subjects during standing. Neurosci Lett 208:199-202.

Dimitrova D, Horak FB, Nutt JG (2004a) Postural muscle responses to multidirectional translations in patients with Parkinson's disease. J Neurophysiol 91:489-501.

Dimitrova D, Nutt J, Horak FB (2004b) Abnormal force patterns for multidirectional postural responses in patients with Parkinson's disease. Exp Brain Res 156:183-195.

Do MC, Bussel B, Breniere Y (1990) Influence of plantar cutaneous afferents on early compensatory reactions to forward fall. Exp Brain Res 79:319-324.

Do MC, Roby-Brami A (1991) The influence of a reduced plantar support surface area on the compensatory reactions to a forward fall. Exp Brain Res 84:439-443.

Donders (1969) On the speed of mental processes. Acta Psychol 30:412-431.

Drew T (1988) Motor cortical cell discharge during voluntary gait modification. Brain Res 457:181-187.

Drew T, Jiang W, Kably B, Lavoie S. 1996. Role of the motor cortex in the control of visually triggered gait modifications. Can J Physiol Pharmacol 74(4):426–42.

Eckert T, Peschel T, Heinze HJ, Rotte M (2006) Increased pre-SMA activation in early PD patients during simple self-initiated hand movements. J Neurol 253:199-207.

Englander F, Hodson TJ, Terregrossa RA (1996) Economic dimensions of slip and fall injuries. J Forensic Sci 41:733-746.

Escola L, Michelet T, Douillard G, Guehl D, Bioulac B, Burbaud P (2002) Disruption of the proprioceptive mapping in the medial wall of parkinsonian monkeys. Ann

Neurol 52:581-587.

Escola L, Michelet T, Macia F, Guehl D, Bioulac B, Burbaud P (2003) Disruption of information processing in the supplementary motor area of the MPTP-treated monkey: a clue to the pathophysiology of akinesia? Brain 126:95-114.

Fahn S, Elton R. Unified Parkinson's disease rating scale (1987) In: Fahn S, Marsden D, Calne D (eds) Recent developments in Parkinson diseases. Macmillan, London, pp 153-163.

Farley BG, Koshland GF (2005) Training BIG to move faster: the application of the speed-amplitude relation as a rehabilitation strategy for people with Parkinson's disease. Exp Brain Res 167:462-467.

Fitzgerald PB, Brown TL, Daskalakis ZJ, Chen R, Kulkarni J (2002) Intensity-dependent effects of 1 Hz rTMS on human corticospinal excitability. Clin Neurophysiol 113:1136–1141.

Fitzgerald PB, Fountain S, Daskalakis ZJ (2006) A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol, Electronic Publication: August 3.

Frank JS, Horak FB, Nutt J (2000) Centrally initiated postural adjustments in parkinsonian patients on and off levodopa. J Neurophysiol 84:2440-2448.

Fujiwara K, Maeda K, Toyama H (2003) Influences of illusionary position perception on anticipatory postural control associated with arm flexion. J Electromyogr Kinesiol 13:509-517.

Fujiwara NK, Marti B, Gutzwiller F (1993) Hip fracture mortality and morbidity in Switzerland and Japan: a cross-cultural comparison. Soz Praventivmed 38:8-14.

Fukuyama H, Ouchi Y, Matsuzaki S, Nagahama Y, Yamauchi H, Ogawa M, Kimura J,Shibasaki H (1997) Brain functional activity during gait in normal subjects: a SPECT study. Neurosci Lett 228:183–186.

Fung J, Macpherson JM (1999) Attributes of quiet stance in the chronic spinal cat. J Neurophysiol 82:3056-3065

Gantchev N, Viallet F, Aurenty R, Massion J (1996) Impairment of posturo-kinetic co-ordination during initiation of forward oriented stepping movements in parkinsonian patients. Electroencephalogr Clin Neurophysiol 101:110-120.

Gerschlager W, Siebner HR, Rothwell JC (2001) Decreased corticospinal excitability after subthreshold 1 Hz rTMS over lateral premotor cortex. Neurology 57:449-

455.

Geurts AC, de Haart M, van Nes IJ, Duysens J (2005) A review of standing balance recovery from stroke. Gait Posture 22:267-81.

Ghafouri M, McIlroy WE, Maki BE (2004) Initiation of rapid reach-and-grasp balance reactions: is a pre-formed visuospatial map used in controlling the initial arm trajectory? Exp Brain Res 155:532-536.

Greenhouse SW, Geisser S (1959) On methods in the analysis of profile data. Psychometrika 24:95-112.

Grey MJ, Ladouceur M, Andersen JB, Nielsen JB, Sinkjaer T (2001) Group II muscle afferents probably contribute to the medium latency soleus stretch reflex during walking in humans. J Physiol 534:925-933.

Grillner S, Hellgren J, Menard A, Saitoh K, Wikstrom MA (2005) Mechanisms for selection of basic motor programs--roles for the striatum and pallidum. Trends Neurosci 28:364-370.

Gurfinkel VS, Elner AM (1988) Participation of the secondary motor area of the frontal lobe of the brain in organizing postural components of human voluntary movement. Neirofiziologiia 20:7-15.

Halsband U, Matsuzaka Y, Tanji J (1994) Neuronal activity in the primate supplementary, pre-supplementary and premotor cortex during externally and internally instructed sequential movements. Neurosci Res 20:149-155.

Hanakawa T (2006) Neuroimaging of standing and walking: Special emphasis on Parkinsonian gait. Parkinsonism Relat Disord, Electronic Publication: July 7.

Hanakawa T, Fukuyama H, Katsumi Y, Honda M, Shibasaki H (1999a) Enhanced lateral premotor activity during paradoxical gait in Parkinson's disease. Ann Neurol 45:329-336.

Hanakawa T, Katsumi Y, Fukuyama H, Honda M, Hayashi T, Kimura J, Shibasaki H (1999b) Mechanisms underlying gait disturbance in Parkinson's disease: a single photon emission computed tomography study. Brain 122:1271-1282.

Haslinger B, Erhard P, Kampfe N, Boecker H, Rummeny E, Schwaiger M, Conrad B, Ceballos-Baumann AO (2001) Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. Brain 124:558-570.

Hayes KC (1982) Biomechanics of postural control. Exerc Sport Sci Rev 10:363-391.

Henriksson M, Hirschfeld H (2005) Physically active older adults display alterations in gait initiation. Gait Posture 21:289-296.

Henry SM, Fung J, Horak FB (1998) Control of stance during lateral and anterior/posterior surface translations. IEEE Trans Rehabil Eng 6:32-42.

Henry SM, Fung J, Horak FB (2001) Effect of stance width on multidirectional postural responses. J Neurophysiol 85:559-570.

Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17:427-442.

Honeycutt CF, Nichols TR (2005) Contribution of cutaneous and proprioceptive feedback on muscle activation patterns during postural perturbation in decerebrate cats. Program No. 868.1.2005 Abstract Viewer / Itinerary Planner. Washington, DC: Society for Neuroscience.

Horak FB (1996) Adaptation of Automatic Postural Responses (1996) In: Bloedel JR, Ebner TJ, Wise SP (eds) The acquisition of Motor Behavior in Vertebrates. Bradford Books, The MIT Press, Cambridge London, pp 57-85.

Horak FB, Diener HC, Nashner LM (1989) Influence of central set on human postural responses. J Neurophysiol 62:841-853.

Horak FB, Dimitrova D, Nutt JG (2005) Direction-specific postural instability in subjects with Parkinson's disease. Exp Neurol 193:504-521.

Horak FB, Macpherson JM (1996) Postural orientation and equilibrium. In: Rowell LB, Shepherd JT (eds) Handbook of Physiology, Sec 12, Exercise: regulation and integration of multiple systems. Oxford University Press, New York, pp 255-292.

Horak FB, Nashner LM (1986) Central programming of postural movements: adaptation to altered support-surface configurations. J Neurophysiol 55:1369-1381.

Horak FB, Nutt JG, Nashner LM (1992) Postural inflexibility in parkinsonian subjects. J Neurol Sci 111:46-58.

Howland J, Lachman ME, Peterson EW, Cote J, Kasten L, Jette A (1998) Covariates of fear of falling and associated activity curtailment. Gerontologist 38:549-555.

Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ (1992) What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. Neurology 42:1142-1146.

Jacobs JV, Dimitrova DM, Nutt JG, Horak FB (2005a) Can stooped posture explain

multidirectional postural instability in patients with Parkinson's disease? Exp Brain Res 166:78-88.

Jacobs JV, Horak FB (2004) The effect of visual targets during compensatory stepping in subjects with Parkinson's disease. Program No. 1011.1. 2004 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience.

Jacobs JV, Horak FB (2006) Abnormal proprioceptive-motor integration contributes to hypometric postural responses of subjects with Parkinson's disease. Neuroscience 141:999-1009.

Jacobs JV, Horak FB, Nutt JG (2005b) Compensatory step deficits in Parkinson's disease: an inability to select motor programs. Gait Posture 21: S94-S95.

Jahanshahi M, Jenkins IH, Brown RG, et al. (1995) Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. Brain 118:913-933.

Jasper HH (1958) The Ten Twenty Electrode System of the International Federation. Clin Neurophysiol 10:371-375.

Jenkins IH, Fernandez W, Playford ED, Lees AJ, Frackowiak RS, Passingham RE, Brooks DJ (1992) Impaired activation of the supplementary motor area in Parkinson's disease is reversed when akinesia is treated with apomorphine. Ann Neurol 32:749-757.

Jobges M, Heuschkel G, Pretzel C, Illhardt C, Renner C, Hummelsheim H (2004) Repetitive training of compensatory steps: a therapeutic approach for postural instability in Parkinson's disease. J Neurol Neurosurg Psychiatry 75:1682-1687.

Jobst EE, Melnick ME, Byl NN, Dowling GA, Aminoff MJ (1997) Sensory perception in Parkinson disease. Arch Neurol 54:450-454.

Johannsen L, Broetz D, Naegele T, Karnath HO (2006) "Pusher syndrome" following cortical lesions that spare the thalamus. J Neurol 253:455-463.

Karnath HO, Baier B, Nagele T (2005a) Awareness of the functioning of one's own limbs mediated by the insular cortex? J Neurosci 25:7134-7138.

Karnath HO, Johannsen L, Broetz D, Kuker W (2005b) Posterior thalamic hemorrhage induces "pusher syndrome". Neurology 64:1014-1019.

Keijsers NL, Admiraal MA, Cools AR, Bloem BR, Gielen CC (2005) Differential progression of proprioceptive and visual information processing deficits in

Parkinson's disease. Eur J Neurosci 21:239-248.

Keck ME, Pijnappels M, Schubert M, Colombo G, Curt A, Dietz V (1998) Stumbling reactions in man: influence of corticospinal input. Electroencephalogr Clin Neurophysiol 109:215-223.

Kennerley SW, Sakai K, Rushworth MF (2004) Organization of action sequences and the role of the pre-SMA. J Neurophysiol 91:978-993.

Keranen T, Kaakkola S, Sotaniemi K, et al. (2003) Economic burden and quality of life impairment increase with severity of PD. Parkinsonism Relat Disord 9:163-168.

Khedr EM, Rothwell JC, Shawky OA, Ahmed MA, Hamdy A (2006) Effect of daily repetitive transcranial magnetic stimulation on motor performance in Parkinson's disease. Mov Disord, Electronic Publication: September 21, 2006.

Khudados E, Cody FW, O'Boyle DJ (1999) Proprioceptive regulation of voluntary ankle movements, demonstrated using muscle vibration, is impaired by Parkinson's disease. J Neurol Neurosurg Psychiatry 67:504-510.

Kikuchi A, Takeda A, Kimpara T, Nakagawa M, Kawashima R, Sugiura M, Kinomura S, Fukuda H, Chida K, Okita N, Takase S, Itoyama Y (2001) Hypoperfusion in the supplementary motor area, dorsolateral prefrontal cortex and insular cortex in Parkinson's disease. J Neurol Sci 193:29-36.

Klockgether T, Borutta M, Rapp H, Spieker S, Dichgans J (1995) A defect of kinesthesia in Parkinson's disease. Mov Disord 10:460-465.

Lang N, Harms J, Weyh T, Lemon RN, Paulus W, Rothwell JC, Siebner HR (2006) Stimulus intensity and coil characteristics influence the efficacy of rTMS to suppress cortical excitability. Clin Neurophysiol 117:2292-2301.

Lee RG, Tonolli I, Viallet F, Aurenty R, Massion J (1995) Preparatory postural adjustments in parkinsonian patients with postural instability. Can J Neurol Sci 22:126-135.

Lewis GN, Byblow WD, Walt SE (2000) Stride length regulation in Parkinson's disease: the use of extrinsic, visual cues. Brain 123:2077-2090.

Liddell EGT, Phillips CG (1944) Pyramidal section in the cat. Brain 67:1–9.

Lou JS, Benice T, Kearns G, Sexton G, Nutt J (2003) Levodopa normalizes exercise related cortico-motoneuron excitability abnormalities in Parkinson's disease. Clin Neurophysiol 114:930-937.

MacDonald V, Halliday GM (2002) Selective loss of pyramidal neurons in the pre-supplementary motor cortex in Parkinson's disease. Mov Disord 17:1166-1173.

Maeda K, Fujiwara K (2006) Effects of preparatory period on anticipatory postural control and contingent negative variation associated with rapid arm movement in standing posture. Gait Posture, Electronic Publication: February 24.

Maffiuletti NA, Agosti F, Proietti M, Riva D, Resnik M, Lafortuna CL, Sartorio A (2005) Postural instability of extremely obese individuals improves after a body weight reduction program entailing specific balance training. J Endocrinol Invest 28:2-7.

Magnus R (1926) Physiology of posture. Lancet September 11:531-585.

Magoun HW, Ranson SW (1938) The Behavior of cats following bilateral removal of the rostral portion of the cerebral hemispheres. J Neurophysiol 1:39-44.

Maki BE, McIlroy WE (2005) Change-in-support balance reactions in older persons: an emerging research area of clinical importance. Neurol Clin 23:751-783.

Maki BE, Whitelaw RS (1993) Influence of expectation and arousal on center-of-pressure responses to transient postural perturbations. J Vestib Res 3:25-39.

Maki BE, Zecevic A, Bateni H, Kirshenbaum N, McIlroy WE (2001) Cognitive demands of executing postural reactions: does aging impede attention switching? Neuroreport 12:3583-3587.

Malouin F, Richards CL, Jackson PL, Dumas F, Doyon J (2003) Brain activations during motor imagery of locomotor-related tasks: a PET study. Hum Brain Mapp 19:47-62.

Martin JP (1967) The basal ganglia and posture. Pitman, London.

Maschke M, Gomez CM, Tuite PJ, Konczak J (2003) Dysfunction of the basal ganglia, but not the cerebellum, impairs kinaesthesia. Brain 126:2312-2322.

Masdeu JC, Alampur U, Cavaliere R, Tavoulareas G (1994) Astasia and gait failure with damage of the pontomesencephalic locomotor region. Ann Neurol 35:619-621.

Massion J (1979) Role of motor cortex in postural adjustments associated with movements. In: Asanuma H, Wilson VJ (eds) Integration in the nervous system. Igaku-Shoin, Tokyo, pp 239-260.

Massion (1992) Movement, posture and equilibrium: interaction and coordination. Prog Neurobiol 38:35-56

Mayka MA, Corcos DM, Leurgans SE, Vaillancourt DE (2006) Three-dimensional locations and boundaries of motor and premotor cortices as defined by functional brain imaging: a meta-analysis. Neuroimage 31:1453-1474.

McAdam DW, Knott JR, Rebert CS (1969) Cortical slow potential changes in man related to interstimulus interval and to pre-trial prediction of interstimulus interval. Psychophysiology 5:349-358.

McIlroy WE, Maki BE (1993a) Changes in early 'automatic' postural responses associated with the prior-planning and execution of a compensatory step. Brain Res 631:203-211.

McIlroy WE, Maki BE (1993b) Task constraints on foot movement and the incidence of compensatory stepping following perturbation of upright stance. Brain Res 616:30-38.

McIlroy WE, Maki BE (1996) Influence of Destabilization on the Temporal Characteristics of Stepping. J Mot Behav 28:28-34.

McIlroy WE, Norrie RG, Brooke JD, Bishop DC, Nelson AJ, Maki BE (1999) Temporal properties of attention sharing consequent to disturbed balance. Neuroreport 10:2895-2899.

Mille ML, Rogers MW, Martinez K, Hedman LD, Johnson ME, Lord SR, Fitzpatrick RC (2003) Thresholds for inducing protective stepping responses to external perturbations of human standing. J Neurophysiol 90:666-674.

Miyai I, Tanabe HC, Sase I, Eda H, Oda I, Konishi I, Tsunazawa Y, Suzuki T, Yanagida T, Kubota K (2001) Cortical mapping of gait in humans: a near-infrared spectroscopic topography study. Neuroimage 14:1186-1192.

Moore AP (1987) Impaired sensorimotor integration in parkinsonism and dyskinesia: a role for corollary discharges? J Neurol Neurosurg Psychiatry 50:544-552.

Mori (1987) Integration of posture and locomotion in acute decerebrate cats and in awake, freely moving cats. Prog Neurobiol 28:161-195.

Morris ME, Iansek R, Matyas TA, Summers JJ (1996) Stride length regulation in Parkinson's disease. Normalization strategies and underlying mechanisms. Brain 119:551-568.

Morris M, Iansek R, McGinley J, Matyas T, Huxham F (2005) Three-dimensional gait biomechanics in Parkinson's disease: evidence for a centrally mediated amplitude regulation disorder. Mov Disord 20:40-50.

Morton SM, Bastian AJ (2004) control of balance and locomotion. Neuroscientist 10:247-259.

Mushiake H, Inase M, Tanji J (1991) Neuronal activity in the primate premotor, supplementary, and precentral motor cortex during visually guided and internally determined sequential movements. J Neurophysiol 66:705-718.

Myers AH, Young Y, Langlois JA (1996) Prevention of falls in the elderly. Bone 18:87S-101S.

Nakano K, Kayahara T, Tsutsumi T, Ushiro H (2000) Neural circuits and functional organization of the striatum. J Neurol 247:V1-V15.

Nardone A, Giordano A, Corra T, Schieppati M (1990) Responses of leg muscles in humans displaced while standing. Effects of types of perturbation and of postural set. Brain 113:65-84.

Nardone A, Schieppati M (1988) Postural adjustments associated with voluntary contraction of leg muscles in standing man. Exp Brain Res 69:469-480.

Nashner LM (1976) Adapting reflexes controlling the human posture. Exp Brain Res 26:59-72.

Nashner LM (1977) Fixed patterns of rapid postural responses among leg muscles during stance. Exp Brain Res 30:13-24.

Nashner LM (1982) Adaptation of human movement to altered environments. Trends Neurosci 5:358-361.

Nashner LM, Cordo PJ (1981) Relation of automatic postural responses and reaction-time voluntary movements of human leg muscles. Exp Brain Res 43:395-405.

Norrie RG, Maki BE, Staines WR, McIlroy WE (2002) The time course of attention shifts following perturbation of upright stance. Exp Brain Res 146:315-321.

Obhi SS, Haggard P, Taylor J, Pascual-Leone A (2002) rTMS to the supplementary motor area disrupts bimanual coordination. Motor Control 6:319-332.

Ohara S, Ikeda A, Kunieda T, Yazawa S, Baba K, Nagamine T, Taki W, Hashimoto N, Mihara T, Shibasaki H (2000) Movement-related change of electrocorticographic activity in human supplementary motor area proper. Brain 123:1203-1215.

Oliveira RM, Gurd JM, Nixon P, Marshall JC, Passingham RE (1997) Micrographia in Parkinson's disease: the effect of providing external cues. J Neurol Neurosurg

Psychiatry 63:429-433.

Perry SD, McIlroy WE, Maki BE (2000) The role of plantar cutaneous mechanoreceptors in the control of compensatory stepping reactions evoked by unpredictable, multi-directional perturbation. Brain Res 877:401-406.

Petersen N, Christensen LOD, Nielsen J (1998) The effect of transcranial magnetic stimulation on the soleus H reflex during human walking. J Physiol 513:599–610.

Playford ED, Jenkins IH, Passingham RE, Nutt J, Frackowiak RS, Brooks DJ (1992) Impaired mesial frontal and putamen activation in Parkinson's disease: a positron emission tomography study. Ann Neurol 32:151-161.

Priori A, Bertolasi L, Dressler D, Rothwell JC, Day BL, Thompson PD, Marsden CD (1993) Transcranial electric and magnetic stimulation of the leg area of the human motor cortex: single motor unit and surface EMG responses in the tibialis anterior muscle. Electroencephalogr Clin Neurophysiol 89:131-137.

Prochazka A (1989) Sensorimotor gain control: a basic strategy of motor systems? Prog Neurobiol 33:281-307.

Quant S, Adkin AL, Staines WR, Maki BE, McIlroy WE (2004) The effect of a concurrent cognitive task on cortical potentials evoked by unpredictable balance perturbations. BMC Neurosci. May 17:5:18.

Quintern J, Berger W, Dietz V (1985) Compensatory reactions to gait perturbations in man: short- and long-term effects of neuronal adaptation. Neurosci Lett 62:371-376.

Rademaker GGJ (1931) Das Stehen. Springer, Berlin.

Radovanovic S, Korotkov A, Ljubisavljevic M, Lyskov E, Thunberg J, Kataeva G, Danko S, Roudas M, Pakhomov S, Medvedev S, Johansson H (2002) Comparison of brain activity during different types of proprioceptive inputs: a positron emission tomography study. Exp Brain Res 143:276-285.

Rascol O, Sabatini U, Chollet F, Celsis P, Montastruc JL, Marc-Vergnes JP, Rascol A (1992) Supplementary and primary sensory motor area activity in Parkinson's disease. Regional cerebral blood flow changes during finger movements and effects of apomorphine. Arch Neurol 49:144-148.

Rektor I, Bares M, Kubova D (2001) Movement-related potentials in the basal ganglia: a SEEG readiness potential study. Clin Neurophysiol 112:2146-2153.

Rickards C, Cody FW (1997) Proprioceptive control of wrist movements in Parkinson's

disease. Reduced muscle vibration-induced errors. Brain 120:977-990.

Rocchi L, Chiari L, Mancini M, Carlson-Kuhta P, Gross A, Horak FB (2006) Step initiation in Parkinson's disease: Influence of initial stance conditions. Neurosci Lett 406:128-132.

Rocchi L, Chiari L, Gross A, Horak FB (2004) Voluntary and induced steps in Parkinson's disease, starting from different stance conditions. Mov Disord 19:S257-S258.

Rogers MW, Hedman LD, Johnson ME, Martinez KM, Mille ML (2003a) Triggering of protective stepping for the control of human balance: age and contextual dependence. Brain Res Cogn Brain Res 16:192-198.

Rogers MW, Johnson ME, Martinez KM, Mille ML, Hedman LD (2003b) Step training improves the speed of voluntary step initiation in aging. J Gerontol A Biol Sci Med Sci 58:46-51.

Romero JR, Anschel D, Sparing R, Gangitano M, Pascual-Leone A (2002) Subthreshold low frequency repetitive transcranial magnetic stimulation selectively decreases facilitation in the motor cortex. Clin Neurophysiol 113:101-107.

Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijevic MR, Hallett M, Katayama Y, Lucking CH, Maertens de Noordhout AL, Marsden CD, Murray NMF, Rothwell JC, Swash M, Tomberg C (1994) Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 91:79-92.

Ruohonen J, Ilmoniemi RJ (2002) Physical principles for transcranial magnetic stimulation. In: Pascual-Leone A, Davey NJ, Rothwell J, Wassermann EM, Puri BK (eds) Handbook of transcranial magnetic stimulation. Oxford University Press, New York, pp 18-29.

Rushworth MF, Hadland KA, Paus T, Sipila PK (2002) Role of the human medial frontal cortex in task switching: a combined fMRI and TMS study. J Neurophysiol 87:2577-2592.

Saitou K, Washimi Y, Koike Y, Takahashi A, Kaneoke Y (1996) Slow negative cortical potential preceding the onset of postural adjustment. Electroencephalogr Clin Neurophysiol 98:449-455.

Schepens B, Drew T (2003) Strategies for the integration of posture and movement during reaching in the cat. J Neurophysiol 90:3066-3086.

Schepens B, Drew T (2004) Independent and convergent signals from the pontomedullary reticular formation contribute to the control of posture and movement during reaching in the cat. J Neurophysiol 92:2217-2238.

Schluter ND, Krams M, Rushworth MF, Passingham RE (2001) Cerebral dominance for action in the human brain: the selection of actions. Neuropsychologia 39:105-113.

Schubert M, Curt A, Colombo G, Berger W, Dietz V. 1999. Voluntary control of human gait: conditioning of magnetically evoked motor responses in a precision stepping task. Exp Brain Res 126(4):583–8.

Schubert M, Prokop T, Brocke F, Berger W (2005) Visual kinesthesia and locomotion in Parkinson's disease. Mov Disord 20:141-150.

Seiss E, Praamstra P, Hesse CW, Rickards H (2003) Proprioceptive sensory function in Parkinson's disease and Huntington's disease: evidence from proprioception-related EEG potentials. Exp Brain Res 148:308-319.

Sherrington CS (1910) Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. J Physiol 40:28-121.

Siebner HR, Rothwell J (2003) Transcranial magnetic stimulation: new insights into representational cortical plasticity. Exp Brain Res 148:1-16.

Slobounov S, Hallett M, Stanhope S, and Shibasaki H (2005) Role of cerebral cortex in human postural control: an EEG study. Clin Neurophysiol 116:315-323.

Souques MA (1921) Les syndromes parkinsoniens. Rev Neurol 1:543-573.

Speer AM, Willis MW, Herscovitch P, Daube-Witherspoon M, Shelton JR, Benson BE, Post RM, Wassermann EM (2003) Intensity-dependent regional cerebral blood flow during 1-Hz repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers studied with H215O positron emission tomography: I. Effects of primary motor cortex rTMS. Biol Psychiatry 54:818-825.

Strafella AP, Dagher A, Sadikot AF (2003) Cerebral blood flow changes induced by subthalamic stimulation in Parkinson's disease. Neurology 60:1039-1042.

Suteerawattananon M, Morris GS, Etnyre BR, Jankovic J, Protas EJ (2004) Effects of visual and auditory cues on gait in individuals with Parkinson's disease. J Neurol Sci 219:63-69.

Takakusaki K, Oohinata-Sugimoto J, Saitoh K, Habaguchi T (2004) Role of basal ganglia-brainstem systems in the control of postural muscle tone and locomotion. Prog Brain Res 143:231-237.

Taube W, Schubert M, Gruber M, Beck S, Faist M, Gollhofer A (2006) Direct corticospinal pathways contribute to neuromuscular control of perturbed stance. J Appl Physiol 101:420-429.

Tecce JJ (1972) Contingent negative variation (CNV) and psychological processes in man. Psychol Bull 77:73-108.

Terao Y, Ugawa Y, Sakai K, Uesaka Y, Kohara N, Kanazawa I (1994) Transcranial stimulation of the leg area of the motor cortex in humans. Acta Neurol Scand 89:378-383.

Timmann D, Horak FB (1997) Prediction and set-dependent scaling of early postural responses in cerebellar patients. Brain 120:327-337.

Tjernstrom F, Fransson PA, Hafstrom A, Magnusson M (2002) Adaptation of postural control to perturbations--a process that initiates long-term motor memory. Gait Posture 15:75-82.

Toma K, Honda M, Hanakawa T, Okada T, Fukuyama H, Ikeda A, Nishizawa S, Konishi J, Shibasaki H (1999) Activities of the primary and supplementary motor areas increase in preparation and execution of voluntary muscle relaxation: an event-related fMRI study. J Neurosci 19:3527-3534.

Touge T, Gerschlager W, Brown P, Rothwell JC (2001) Are the after-effects of low frequency rTMS on motor cortex excitability due to changes in the efficacy of cortical synapses? Clin Neurophysiol 112:2138–2145.

Toussaint HM, Michies YM, Faber MN, Commissaris DA, van Dieen JH (1998) Scaling anticipatory postural adjustments dependent on confidence of load estimation in a bi-manual whole-body lifting task. Exp Brain Res 120:85-94.

Tremblay F, Tremblay LE (2002) Cortico-motor excitability of the lower limb motor representation: a comparative study in Parkinson's disease and healthy controls. Clin Neurophysiol 113:2006-2012.

Tripp BP, McIlroy WE, Maki BE (2004) Online mutability of step direction during rapid stepping reactions evoked by postural perturbation. IEEE Trans Neural Syst Rehabil Eng 12:140-152.

Tsuji T, Rothwell JC (2002) Long lasting effects of rTMS and associated peripheral sensory input on MEPs, SEPs and transcortical reflex excitability in humans. J Physiol 540:367-376.

Valkovic P, Krafczyk S, Saling M, Benetin J, Botzel K (2006) Postural reactions to neck

vibration in Parkinson's disease. Mov Disord 21:59-65.

van Boxtel GJ, Brunia CH (1994) Motor and non-motor aspects of slow brain potentials. Biol Psychol 38:37-51.

van der Fits IB, Klip AW, van Eykern LA, Hadders-Algra M (1998) Postural adjustments accompanying fast pointing movements in standing, sitting and lying adults. Exp Brain Res 120:202-216.

van Eimeren T, Wolbers T, Munchau A, Buchel C, Weiller C, Siebner HR (2006) Implementation of visuospatial cues in response selection. Neuroimage 29:286-94.

Vaughan CL, Davis BL, O'Connor JC (1991) Dynamics of Human Gait. Human Kinetics Publishers, Champaign.

Vernazza-Martin S, Martin N, Cincera M, Pedotti A, Massion J (1999) Arm raising in humans under loaded vs. unloaded and bipedal vs. unipedal conditions. Brain Res 846:12-22.

Verwey WB, Lammens R, van Honk J (2002) On the role of the SMA in the discrete sequence production task: a TMS study. Transcranial Magnetic Stimulation. Neuropsychologia 40:1268-1276.

Viallet F, Massion J, Massarino R, Khalil R (1987) Performance of a bimanual load-lifting task by parkinsonian patients. J Neurol Neurosurg Psychiatry 50:1274-1283.

Viallet F, Massion J, Massarino R, Khalil R (1992) Coordination between posture and movement in a bimanual load lifting task: putative role of a medial frontal region including the supplementary motor area. Exp Brain Res 88:674-684.

Vidailhet M, Stocchi F, Rothwell JC, Thompson PD, Day BL, Brooks DJ, Marsden CD (1993) The Bereitschaftspotential preceding simple foot movement and initiation of gait in Parkinson's disease. Neurology 43:1784-1788.

Walsh V, Rushworth M (1999) A primer of magnetic stimulation as a tool for neuropsychology. Neuropsychologia 37:125-135.

Ward NS (2005) Neural plasticity and recovery of function. Prog Brain Res 150:527-535.

Wassermann EM (1998) Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalogr Clin Neurophysiol 108:1-16.

Werhahn KJ, Fong JK, Meyer BU, Priori A, Rothwell JC, Day BL, Thompson PD (1994) The effect of magnetic coil orientation on the latency of surface EMG and single motor unit responses in the first dorsal interosseous muscle. Electroencephalogr Clin Neurophysiol 93:138-146.

Whelan PJ (1996) Control of locomotion in the decerebrate cat. Prog Neurobiol 49:481 515.

Widajewicz W, Kably B, Drew T (1994) Motor cortical activity during voluntary gait modifications in the cat. II. Cells related to the hindlimbs. J Neurophysiol 72:2070-2089.

Williams SM, Goldman-Rakic PS (1993) Characterization of the dopaminergic innervation of the primate frontal cortex using a dopamine-specific antibody. Cereb Cortex 3:199-222.

Winter DA (1995) A. B. C. of balance during standing and walking. Waterloo Biomechanics, Waterloo.

Wood BH, Bilclough JA, Bowron A, Walker RW (2002) Incidence and prediction of falls in Parkinson's disease: a prospective multidisciplinary study. J Neurol Neurosurg Psychiatry 72:721-725.

Woollacott M, Shumway-Cook A, Hutchinson S, Ciol M, Price R, Kartin D (2005) Effect of balance training on muscle activity used in recovery of stability in children with cerebral palsy: a pilot study. Dev Med Child Neurol 47:455-461.

Woollacott MH, von Hosten C, Rosblad B (1988) Relation between muscle response onset and body segmental movements during postural perturbations in humans. Exp Brain Res 72:593-604.

Yazawa S, Shibasaki H, Ikeda A, Terada K, Nagamine T, and Honda M (1997) Cortical mechanism underlying externally cued gait initiation studied by contingent negative variation. Electroencephalogr. Clin Neurophysiol 105:390-399.

Zernicke RF, Smith JL (1996) Biomechanical insights into neural control of movement. In: Rowell LB, Shepherd JT (eds) Handbook of Physiology, Sec 12, Exercise: regulation and integration of multiple systems. Oxford University Press, New York, pp 293-330.

Zettel JL, Holbeche A, McIlroy WE, Maki BE (2005) Redirection of gaze and switching of attention during rapid stepping reactions evoked by unpredictable postural perturbation. Exp Brain Res 165:392-401.

Zettel JL, McIlroy WE, Maki BE (2002a) Can stabilizing features of rapid triggered stepping reactions be modulated to meet environmental constraints? Exp Brain Res 145:297-308.

Zettel JL, McIlroy WE, Maki BE (2002b) Environmental constraints on foot trajectory reveal the capacity for modulation of anticipatory postural adjustments during rapid triggered stepping reactions. Exp Brain Res 146:38-47.