Experimental Neurology 215 (2009) 334–341

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Knee trembling during freezing of gait represents multiple anticipatory postural adjustments

Jesse V. Jacobs [a], John G. Nutt [a,b,c,*], Patricia Carlson-Kuhta [a], Marilee Stephens [a], Fay B. Horak [a,b]

[a] Department of Neurology, Oregon Health & Science University, Portland, OR, USA
[b] Department of Physiology and Pharmacology, Oregon Health & Science University, Portland, OR, USA
[c] Parkinson's Disease Research Education and Clinical Center, Portland Veterans Affairs Medical Center, Portland, OR, USA

ARTICLE INFO

Article history:
Received 14 June 2008
Revised 29 October 2008
Accepted 30 October 2008
Available online 12 November 2008

Keywords:
Freezing of gait
FoG
Parkinson's disease
Balance
Anticipatory postural adjustment
Gait initiation

ABSTRACT

Freezing of gait (FoG) is an episodic, brief inability to step that delays gait initiation or interrupts ongoing gait. FoG is often associated with an alternating shaking of the knees, clinically referred to as knee trembling or trembling in place. The pathophysiology of FoG and of the concomitant trembling knees is unknown; impaired postural adjustment in preparation for stepping is one hypothesis. We examined anticipatory postural adjustments (APAs) prior to protective steps induced by a forward loss of balance in 10 Parkinson's disease (PD) subjects with marked FoG and in 10 control subjects. The amplitude and timing of the APAs were determined from changes in the vertical ground-reaction forces recorded by a force plate under each foot and were confirmed by electromyographic recordings of bilateral medial gastrocnemius, tibialis anterior and tensor fascia latae muscles. Protective steps were accomplished with a single APA followed by a step for control subjects, whereas PD subjects frequently exhibited multiple, alternating APAs coexistent with the knee trembling commonly observed during FoG as well as delayed, inadequate or no stepping. These multiple APAs were not delayed in onset and were of similar or larger amplitude than the single APAs exhibited by the control subjects. These observations suggest that multiple APAs produce the knee trembling commonly associated with FoG and that FoG associated with a forward loss of balance is caused by an inability to couple a normal APA to the stepping motor pattern.

Published by Elsevier Inc.

Introduction

Freezing of gait (FoG) is one of the more dramatic clinical phenomena in neurology. FoG is episodic but typically occurs in several settings. One is so-called "start hesitation": a delay or a complete inability to initiate a step. FoG may also interrupt stepping during walking, particularly while turning (so called "turn hesitation"), or when passing through narrow passages or around obstacles. In all these situations, a 2- to 6-Hz trembling of knees often occurs (Schaafsma et al., 2003). FoG is very common in moderate and severe idiopathic Parkinson's disease (PD) (Schaafsma et al., 2003; Macht et al., 2007) but also occurs with other parkinsonian syndromes, ischemic subcortical white matter disease and hydrocephalus (Yanagisawa et al., 1991; Giladi et al., 1997). FoG is a major cause of disability in the patients who experience it because it limits mobility and frequently causes forward falls onto the knees and outstretched arms (Bloem et al., 2004). Understanding the pathophysiology of FoG is the first step to understanding how to reduce or prevent FoG, which would be a major advance in the treatment of PD and related disorders.

The pathophysiology of FoG is not understood. Many hypotheses exist and most are extensions of motor and sensory abnormalities that have been demonstrated in PD, such as hypokinesia, difficulty with shifting set, impaired automaticity, difficulty with timing sequential actions, dependence upon extrinsic stimuli and impaired postural adjustments (Martin, 1967; Petrovici, 1968; Elble et al., 1996; Hausdorff et al., 2003; Plotnik et al., 2005; Iansek et al., 2006). These hypotheses, however, do not explain the episodic nature of freezing. The episodic occurrence of freezing not only renders its pathophysiology enigmatic, but has also made it difficult to study in the laboratory, indicating a need for more reliable methods of eliciting FoG (Burleigh-Jacobs et al., 1997; Nieuwboer et al., 2001).

One feature of FoG that makes it appear different from other parkinsonian motor abnormalities is the trembling knees that frequently accompany FoG, indicating that FoG is not just akinesia (Hausdorff et al., 2003). This alternating motion of the knees was first recorded by Yanagisawa et al. (1991; Ueno et al., 1993) and has recently been recognized as a common accompaniment of FoG (Hausdorff et al., 2003, Schaafsma et al., 2003; Bloem et al., 2004; Moore et al., 2008). The physiological basis of the knee trembling and its relation to FoG, however, remains unclear.

* Corresponding author. Oregon Health & Science University, Department of Neurology, OP-32, 3181 SW Sam Jackson Park Road, Portland, Oregon 97239-3098, USA. Fax: +1 503 494 9059.
E-mail address: nuttj@ohsu.edu (J.G. Nutt).

0014-4886/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.expneurol.2008.10.019

The postural activity most closely related to initiating gait is the anticipatory postural adjustment (APA) that precedes step initiation to shift the center of mass (CoM) laterally and forward over the stance limb through activation of hip abductors and ankle dorsiflexors prior to foot lift (Burleigh et al., 1994; Elble et al., 1994). We examined the force patterns and electromyographic (EMG) characteristics of the APA during voluntary step initiation and in response to an induced loss of balance in PD subjects with severe FoG compared to healthy control subjects. Protective stepping in response to postural perturbations was frequently associated with FoG and knee trembling in the PD subjects. We present evidence that: (1) the knee trembling accompanying FoG represents multiple APAs, and (2) the characteristics of these APAs suggest that FoG is an inability to couple normal APAs to the motor program for stepping.

Methods

Subjects

Ten subjects, one woman and nine men with mean (±sd) age of 66±6 years (range 57–76 years) with long-standing idiopathic Parkinson's disease (disease duration 14.5±3.9 years, range 8–22 years), and 10 subjects without neurological impairment, matched for sex and age (one woman and nine men, aged 66±6 years, range 53–76 years) gave informed consent to participate in the protocol approved by the Institutional Review Board of the Legacy Health System. The PD subjects were on a mean dose of 1268±454 mg of levodopa per day (calculated with Sinemet CR reduced by 25% and concomitant entecapone increasing the effective dose by 25%). In addition, two subjects were on an anti-cholinergic medication, two on amantadine, two on a dopamine agonist and one on selegiline. One subject had a unilateral pallidotomy one year before participating in the study. All PD subjects exhibited a good response to their anti-parkinsonian medications, with mean (±sd) scores on the motor Unified Parkinson Disease Rating Scale (UPDRS) of 36±7 when "off" after withholding medication overnight, and 17±12 when "on" approximately 1 h after taking anti-parkinsonian medication. The subjects with PD were specifically selected because they were mobile despite marked FoG, which was more prominent when the subjects were "off" but also occurred when they were "on." Tremor-dominant PD subjects were not included; the subjects exhibited a mean (±sd) tremor score of 3±3, range 0–7, out of a possible maximum of 28 on the motor UPDRS. Subjects did not have cognitive deficits that would prohibit their ability to sign an informed consent form or to follow protocol instructions.

Protocol

The subjects stood on a moveable platform with each foot on a separate force plate, looking straight ahead and with their arms at their sides. The subjects performed five trials of voluntary steps initiated by a somatosensory cue consisting of a 1-cm lateral pulse of the force plates that did not elicit any EMG response in the legs. The subjects also performed five trials of protective steps for regaining balance in response to a 21-cm backward translation of the force plates with a peak velocity of 50 cm/s. Voluntary and protective step conditions were imbedded in randomized order with other conditions as part of a larger protocol investigating effects of dual tasking on postural responses (manuscript in preparation). These other conditions included smaller forward and backward surface translations that induced feet-in-place postural responses as well as catch trials without cues or perturbations, and all conditions were performed with and without a concurrent task of verbally listing items within a given category. The subjects were not instructed on a strategy for maintaining balance, but were only told to "try to keep their balance". Only the voluntary stepping task to a small movement cue and the protective stepping task to large, backward translations are presented in this report.

During all tasks, the subjects wore a safety harness attached to the ceiling and an attendant stood beside the subjects to further protect them from falling to the ground. The harness was designed not to provide support in upright stance, but to catch the subjects midway through a fall, and the attendant did not intervene until it was apparent that the subjects could not regain standing equilibrium. The subjects sat intermittently to rest and were instructed to ask for rest whenever needed in order to prevent fatigue. All 10 PD subjects performed the protocol "off" medication, and nine completed a second testing "on" medication.

Data collection and analysis

Examples of the primary dependent measures for the APAs (onset, peak, number) and for the steps (onset) are illustrated in Fig. 1. The figure illustrates the vertical weight under the right and left feet for a representative control subject performing a trial with a single APA and for a subject with PD performing a trial with multiple APAs in response to a backward surface translation (protective step).

APAs

Using MATLAB software (Mathworks, Inc., Natick, MA), the APAs were calculated from the subjects' weight shifts by (1) subtracting the vertical weight loading of the left force plate from that of the right

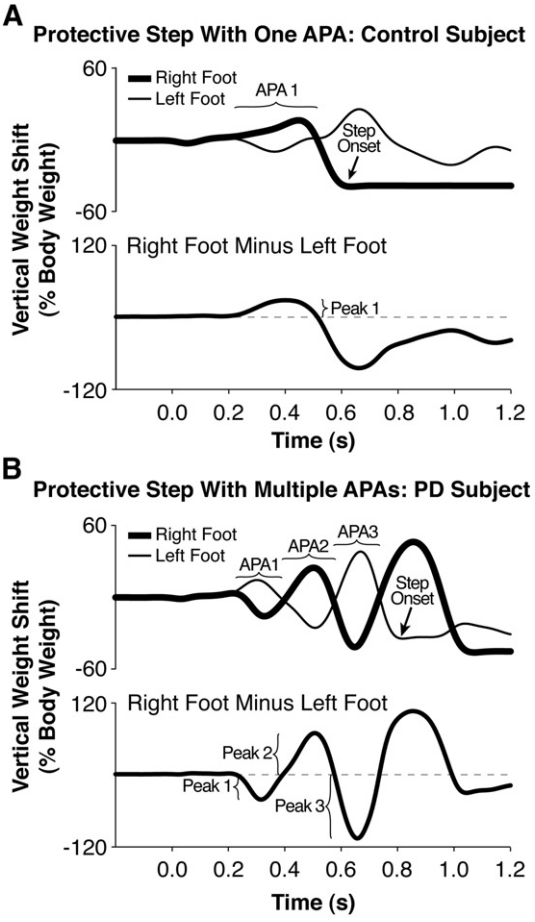

Fig. 1. A representative control subject using a single APA (A) and a PD subject using a multiple APA (B) in response to backward surface translations at time zero, illustrated with vertical forces of the left and right feet (% of body weight). The lower traces in A and B illustrate how APA onset, peak amplitude, and number of APAs were measured from the subtraction of the right- and left-foot forces. Step onset is shown in the top traces of A and B.

force plate, (2) subtracting a baseline position, calculated as the mean value of a subject's difference in weight loading during the first 100 ms of a trial, and (3) normalizing these weight shifts to a subject's total body weight. A weight shift was considered to be an APA if the displacement occurred at least 75 ms after the onset of the perturbation, and if the displacement occurred before the subjects either lifted their foot off the force plate (defined by when the vertical weight of the force plate dropped to a value of zero), or completed their response by either regaining their balance without a step, or by falling (determined by comparing the subjects' weight shift displacements to a video recording of the subjects' performance). To examine whether the PD subjects exhibited disordered or inadequate APAs (i.e., with multiple weight shifts or of late onset or decreased amplitude), we examined the number of APAs exhibited during each trial as well as the onset times and amplitudes of the APAs. The APA onset times were chosen as the moment when the difference in weight loading began to displace from its background level. Peak APA amplitudes were defined as the maximum displacement of a subject's weight shift during an identified APA. To determine whether the frequency of weight shifting during multiple APAs occurred with similar frequency to the weight shifts and trembling previously reported to occur during FoG (Yanagisawa et al., 1991; Hausdorff et al., 2003; Bloem et al., 2004, Moore et al., 2008), we estimated the mean spectral frequency of the PD subjects' weight shifts when exhibiting multiple APAs by calculating the reciprocal of the APA cycle times.

Step characteristics

To identify delayed stepping ("start hesitation"), the onset of the subjects' foot lift (step onset latency) was defined as the time from perturbation onset until the vertical weight on a force plate fell to zero. If the weight under both plates never decreased to zero, then the subject was considered not to have stepped in that trial. Trials with falls were recorded by visual observation during the experiment and were defined as trials in which the subjects required support by the safety harness or by the attendant standing at their side. FoG was functionally defined for the PD subjects as a trial with a step onset that was delayed beyond the latest step onset latency exhibited by the control subjects or lack of a step resulting in a fall.

Muscle activation

To complement the force-plate measures of APA and step behavior, EMG muscle onset latencies activated in response to the surface translations were calculated from differential recordings of surface EMG over the bilateral medial gastrocnemius (for generating step onset), anterior tibialis (for generating the forward APA followed by step onset), and tensor fascia latae (for generating the lateral APA) muscles. The EMG signals were amplified at a gain of 5000–10,000, band-pass filtered from 75–2000 Hz, and full-wave rectified. The latency of each muscle burst was identified as the first sustained activity (lasting at least 25 ms) greater than two standard deviations above the baseline using an interactive graphing function programmed in MATLAB and was occasionally modified by visual inspection (<10% of trials). The latency of each muscle's first activation after translation onset was recorded as well as the latency and duration of the subsequent activation of the tibialis muscle occurring just prior to foot lift.

Statistical analysis

Only descriptive analyses are provided for the voluntary stepping condition because FoG was not evident during this task. Due to violations of the assumptions that underlie parametric statistics, non-parametric statistics were used for all analyses concerning the protective stepping condition. The occurrences of multiple APAs, falls, FoG, and trials without steps were calculated as a percentage of five trials for each subject. The coincidence of these response types was examined by Fisher's exact tests for proportions. Mann–Whitney *U* tests were used to examine differences between the control subjects and the PD subjects on the occurrence of multiple APAs, falls, and trials without steps, as well as on the subjects' average peak APA amplitudes, APA onset latencies, EMG onset latencies, and step onset latencies during the protective stepping task. Wilcoxon signed rank tests were used to examine the effects of anti-parkinsonian medications on the above-named measures of the PD subjects' responses. The APA amplitudes of the first, second, and third APA exhibited in multiple-APA trials of the PD subjects when off medication were compared by a Kruskal–Wallis test. Step onset latencies in trials with one, two, and three or more APAs of the PD subjects when off medication were also compared by a Kruskal–Wallis test. Differences were considered significant if the *P*-value was equal to or less than 0.05.

Results

The following results refer to the PD subjects' performance when they were "off" medication, except in the last section, which describes the effects of anti-parkinsonian medications. All subjects spontaneously exhibited FoG while moving about the laboratory prior to and following the protocol's trials.

Protective stepping

Large, rapid, backward translations of the support surface elicited three patterns of postural preparation (Table 1). The two most common patterns were (1) a single APA followed by a step (Fig. 2A) and (2) two to five (multiple) APAs followed by either a step or by a fall for PD subjects (Fig. 2B). Much less frequently, subjects showed (3) no discernable APA preceding a step or fall (Table 1). The control subjects exhibited a fourth pattern: a single APA followed by a feet-in-place retention of balance in five out of 50 trials.

Control subjects predominantly responded to the backward translation of the platform with a single APA, whereas the PD subjects responded with a single APA much less frequently (Table 1). The prevalence of trials with multiple APAs was significantly higher for the PD subjects than for the control subjects (Table 1) [Mann–Whitney $U=2.94$; $P<0.005$]. The multiple APAs exhibited by the PD subjects were coincident with an alternating trembling of the knees that was apparent in the videos taken during the trials. Multiple APAs significantly delayed step onset in PD subjects [Kruskal Wallis $\chi^2=18.44$; $P=0.0001$] (Fig. 3C). The alternations of the vertical ground-reaction forces during multiple APAs occurred at a mean (±sd) frequency of 2.67±0.95 Hz (illustrated in Fig. 2B). The trembling was not present before the movement of the platform and trembling was initiated by the platform translation at a latency that was consistent with the onset of the APAs (see Supplementary video).

Seven of the 10 PD subjects exhibited FoG for an average (±95% CI) prevalence of 34±27% of trials based on our operational definition of FoG as trials with a step onset delayed beyond that of any control

Table 1
Relationships among APA response types, falls and FoG across groups

Measure	Group	APA response type		
		No APA	Single APA	Multiple APAs
Number of subjects exhibiting each APA response type	Control	1 of 10	10 of 10	5 of 10
	PD off	3 of 10	7 of 10	9 of 10
	PD on	3 of 9	7 of 9	7 of 9
Mean (±95% CI) prevalence of each APA response type	Control	2±4%	86±14%	12±9%
	PD off	6±6%	38±20%	56±20%
	PD on	18±22%	42±21%	40±20%
Percent of fall trials with each APA response type	PD off	6%	25%	69%
	PD on	20%	40%	40%
Percent of FoG trials with each APA response type	PD off	0%	27%	73%
	PD on	0%	20%	80%

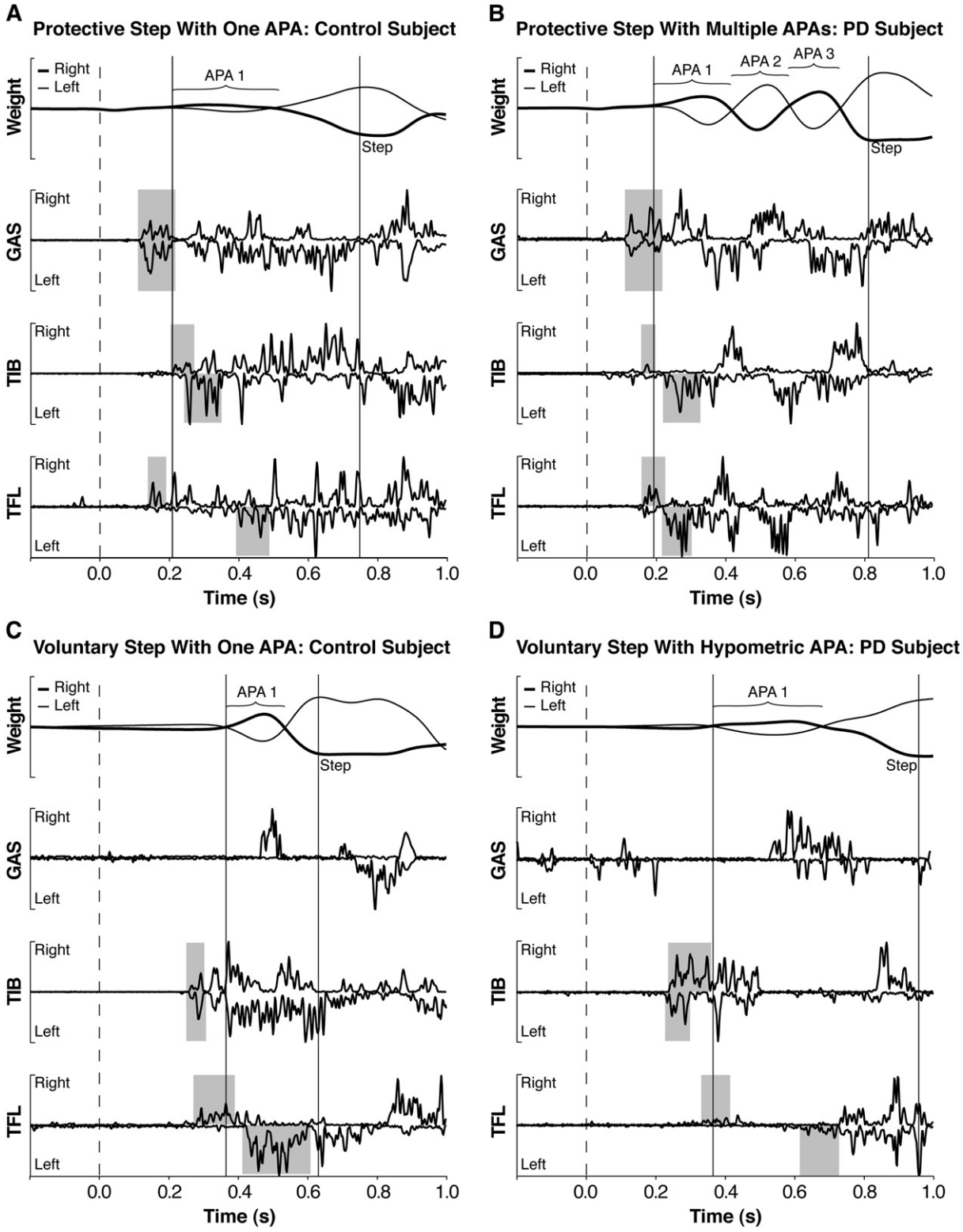

Fig. 2. Examples of APA response patterns during (A) protective step of a control subject, (B) protective step of a PD subject, (C) voluntary step for the same control subject, and (D) voluntary step of the same PD subject. The top graphs of each example illustrate the vertical force exerted under the left (thin line) and right (thick line) feet as a percentage of body weight. Below these graphs are the EMG activity of the gastrocnemius (GAS), tibialis anterior (TIB), and tensor fascia latae (TFL) muscles. The dashed vertical lines denote onset of the fast, backward surface translation for the protective steps and the somatosensory cue for the voluntary steps. The solid vertical lines first denote APA onset based on vertical weight displacements, and the following vertical lines denote step onset. The gray boxes highlight bilateral GAS activity of the feet-in-place automatic postural response for the protective step trials and APA-related activity of the TIB and TFL for all conditions.

subject or no step followed by a fall. Trials with FoG generally occurred when multiple APAs were evident (Table 1). The PD subjects often rose up on their toes but were unable to lift the foot to take a step or the step was delayed. It was as though the toes were glued to the floor, as described in the definition of FoG by Yanagisawa et al. (1991). This phenomenon appeared identical to the FoG spontaneously exhibited by the PD subjects before and after the protocol testing when their center of mass was displaced forward.

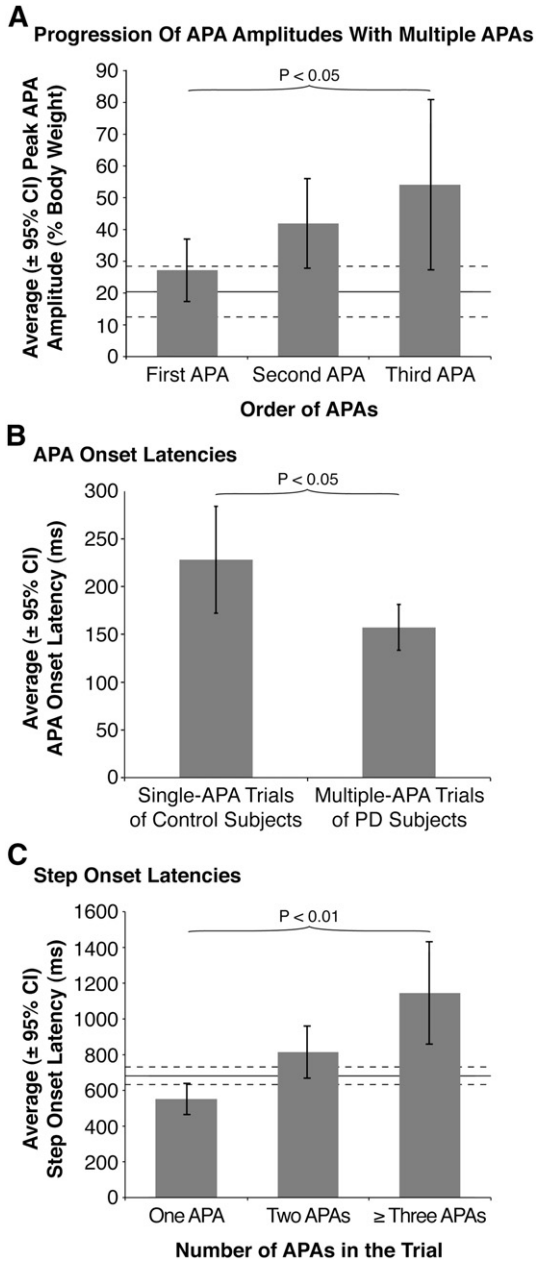

Fig. 3. Characteristics of the PD subject trials with multiple APAs. (A) Average APA amplitudes from the first, second, and third APA of a multiple-APA pattern. (B) Average APA onset latencies of the PD subjects' multiple-APA trials compared to the control subjects' single-APA trials. (C) Average step onset latencies when comparing the PD subject trials with one, two, or ≥three APAs. In (A) and (C), the solid horizontal lines bordered by dashed lines represent the average (±95% CI) onset latencies of the control subjects' single-APA trials.

The control subjects stepped on average (±95% CI) in 84±16% of the trials and regained balance without stepping in the other 16% of the trials. In contrast, the PD subjects stepped in 68±24% of the trials. Failure to step was more commonly associated with multiple APAs. The PD subjects stepped in 57% of trials with multiple APAs compared to 82% of trials with one APA. The six multiple APA trials in control subjects were associated with a step in three trials and with a feet-in-place retention of balance in three trials.

No control subject fell with the forced step paradigm while six of the 10 PD subjects fell, for an average prevalence of 32±28% of trials [Mann–Whitney $U=2.76$; $P<0.02$]. Eighty-eight percent of trials without a step coincided with a fall compared to 6% of trials with a step [$\chi^2=33.31$; $P<0.0001$].

In contrast to what might have been predicted for a hypokinetic motor disorder, the peak amplitudes of the PD subjects' first APA in a multiple-APA pattern tended to be larger than the single APAs of the control subjects: 27±10% of body weight compared to 20±8% of body weight, respectively [Mann Whitney $U=1.35$; $P=0.18$]. In addition, peak APA amplitudes became larger with repetition of APAs in the PD subjects who exhibited multiple APAs [Kruskal Wallis $\chi^2=8.04$; $P<0.05$] (Fig. 3A). Onset of the first APA in a multiple-APA pattern was not delayed for PD subjects, but occurred earlier than in the single-APA trials of the control subjects [Mann–Whitney $U=2.33$; $P<0.05$] (Fig. 3B). Step onset latencies were also similar between the PD subjects who stepped and the control subjects when comparing across all response types [Mann–Whitney $U=0.61$; $P=0.54$]. The PD subjects' step onset latencies, however, increased with multiple APAs [Kruskal Wallis $\chi^2=18.44$; $P=0.0001$] (Fig. 3C).

EMG patterns to initiate APAs prior to protective stepping

The pattern of muscle activation responsible for APAs was similar for voluntary and protective step initiation, except that an additional medium-latency gastrocnemius burst was elicited as part of the automatic postural response to the surface translations prior to protective stepping. Fig. 2 illustrates EMG activity during protective and voluntary stepping for a control subject and a PD subject.

Just as the APA onset latencies measured from forces were earlier for the PD subjects (Fig. 3B), the EMG onset latencies of the tensor fascia latae, responsible for the lateral weight shift of the APA, were earlier for the PD subjects than the control subjects [for the swing limb: $U=2.00$, $P<0.05$; for the stance limb: $U=2.61$, $P<0.01$] (Table 2). In addition, the control subjects tended to activate the tensor fascia latae of the swing limb before that of the stance limb [Wilcoxon signed rank=1.89; $P=0.06$], whereas the PD subjects exhibited similar onset latencies (co-activation) across both limbs [Wilcoxon=0.59; $P=0.55$] (Table 2). The onset latency of the first tibialis anterior activation, responsible for the forward weight shift of the APA, was also earlier for the PD subjects than the control subjects [for the swing limb: $U=2.32$, $P<0.05$; for the stance limb: Mann–Whitney $U=2.29$, $P<0.05$] (Table 2). Multiple APAs were associated with reciprocal activation of right and left leg tibialis anterior (75% of multiple-APA trials), gastrocnemius (50% of multiple-APA trials), and tensor fascia latae (17% of multiple-APA trials) muscles.

Voluntary stepping

Cued voluntary steps elicited similar step initiation patterns in the PD and control subjects, except that the PD subjects exhibited hypometric APAs (Figs. 2C and D) and delayed foot lift, as noted in our former study on voluntary stepping (Burleigh-Jacobs et al., 1997). The mean (±95% CI) APA amplitude was 18±9% body weight for the PD subjects compared to 39±9% body weight for the control subjects. The activation patterns of the tensor fascia latae and tibialis anterior muscles for generating APAs during voluntary step initiation were similar for the PD subjects and the control subjects. The tensor fascia

Table 2
EMG onset latencies to platform translations

Muscle	Limb	Mean (±95% CI) EMG onset latencies (ms after platform translation)	
		Control group	PD group "off"
Medial	Swing limb	108±7.9 ms	103±6.4 ms
Gastrocnemius	Stance limb	115±13.7 ms	98±5.4 ms
Tensor	Swing limb	168±13.6 ms	146±12.0 ms
Fascia latae	Stance limb	198±20.7 ms	145±25.6 ms
Tibialis	Swing limb	188±26.7 ms	136±13.3 ms
Anterior	Stance limb	202±18.1 ms	157±27.2 ms

latae and tibialis anterior muscles tended to activate prior to the onset of the first APA followed by activation of the gastrocnemius and then another tibialis anterior burst just prior to lifting the stepping foot (Figs. 2C and D). With voluntary steps, multiple APAs with delayed step onsets were evident in a total of three trials from two PD subjects. The voluntary stepping trials never elicited clinically apparent FoG or falls in either subject group.

Effects of antiparkinsonian medications on protective steps

Antiparkinsonian medications decreased multiple APAs from 56±20% of trials when "off" to 40±20% of trials when "on" (Table 1). The prevalence of FoG declined from 34±27% of trials occurring in seven of 10 subjects when "off" to 20±27% of trials occurring in three of nine subjects when "on." Neither change reached significance by Wilcoxon signed rank tests. Falls, however, were reduced to a larger extent from 32±28% to 11±21% and failure to step from 32±28% to 15±26% [both $P=0.06$ by Wilcoxon signed rank test]. Thus the antiparkinsonian medications seemed to be more effective in reducing the consequences of multiple APAs and FoG, that is failure to step and falls, than in decreasing the events themselves.

The peak APA amplitudes, APA onset latencies, and the corresponding EMG onset latencies for the tensor fascia latae and the tibialis anterior muscles were not significantly altered by medication. The lack of effect of levodopa on the peak amplitudes and latencies of the APAs associated with the protective steps is not surprising; as described above, peak amplitudes were normal and latencies were not prolonged. In contrast, levodopa augmented the APA amplitude in the voluntary stepping paradigm, as reported previously from our laboratory (Burleigh-Jacobs et al., 1997).

Discussion

Our observations have three major implications. First, trembling of knees during FoG episodes represent multiple APAs, in which several right–left leg loading-unloading cycles occur prior to a delayed step or without a step. Second, the short latency and large amplitude of multiple APAs suggest that FoG during forward disequilibrium is caused by abnormal coupling between the APA and the step motor programs rather than by an impaired ability to generate an APA. Third, protective stepping in response to a loss of balance provides a reliable method for inducing freezing, an otherwise episodic phenomenon that is difficult to capture in the laboratory.

Trembling of knees during FoG represents multiple APAs

Trembling knees are very common during episodes of FoG and present with a frequency spectrum of 2–6 Hz (Yanagisawa et al., 1991; Hausdorff et al., 2003; Schaafsma et al., 2003; Bloem et al., 2004; Moore et al., 2008). Moore et al. (2008) found that trembling of the knees identified 89% of spontaneous FoG episodes in a group of PD subjects. Schaafsma et al. (2003) noted that 84% of their population of PD patients with FoG had "trembling in place." Our videos of the PD subjects' responses to the forced step paradigm appeared identical to the clinical pattern of FoG with "trembling in place." The force and EMG patterns observed in this study during the trembling of the knees were consistent with multiple APAs (Jacobs and Horak, 2007). These multiple APAs are additionally linked to freezing by our observation that they were associated with a delayed or absent step.

In our experimental paradigm, trials with multiple APAs were very rare and FoG was not present during voluntary step initiation, whereas multiple APAs and FoG with bilateral, alternating knee trembling at 2.67 Hz was frequently triggered by backward translations of the support surface that displaced the CoM forward. What explains the difference in the ability of the two types of stepping to elicit FoG and trembling in place? Moore et al. (2008) noted that the knee trembling was more common when subjects exhibited FoG during walking than when initiating gait. Further, FoG more commonly occurred when the patient was moving forward, rather than when standing and initiating gait (Schaafsma et al., 2003). Similar to the situation with a protective step, the CoM is more likely to be forward of the feet when walking than when initiating gait. Thus, we postulate that the forward displacement of the CoM facilitates knee trembling with FoG.

An alternative hypothesis is that the trembling knees associated with FoG are due to a parkinsonian tremor. We, like previous investigators (Hausdorff et al., 2003; Bloem et al., 2004; Moore et al., 2008), think this is unlikely. First, the frequency of APAs was slower than a typical postural tremor of PD subjects (Burleigh et al., 1995) but similar to the leg trembling of freezing episodes reported in previous studies (Yanagisawa et al., 1991; Hausdorff et al., 2003; Bloem et al., 2004, Moore et al., 2008). Second, our PD subjects had little or no rest tremor. Third, the trembling knees were evoked by the platform movement at a latency that is typical for APAs (Burleigh et al., 1994; McIlroy and Maki, 1996). Fourth, early EMG activity of the tensor fascia latae and tibialis anterior muscles was consistent with APAs rather than tremor. Fifth, videos of the subjects during the protective-step trials demonstrated the trembling knees and the rise-to-toes that characterize FoG, consistent with the observations of Yanagisawa et al. (1991). Sixth, multiple APAs were elicited in rare trials from control subjects of this study and have also been elicited from young, healthy subjects when the subjects had to wait to select a stepping foot until the time their CoM was displaced forward or when they had to select a voluntary stepping foot in a complex voluntary reaction-time task (Jacobs and Horak, 2007). Finally, the effects of levodopa in our experimental paradigm are typical for the effects of levodopa on clinically evaluated FoG. As carefully documented by Schaafsma et al. (2003), levodopa reduces "trembling in place" FoG but does not eliminate it. Likewise, in our experimental paradigm, levodopa reduced multiple APAs, trials without steps, and falls. In sum, these observations suggest that the trembling knees with FoG are not parkinsonian tremor but represent repetitive APAs.

Freezing may be due to abnormal coupling of the APA with the step

During voluntary step initiation from upright stance, we and others have observed either akinesia (lack of any muscle activity) or hypometric APAs from subjects with PD or sub-cortical ischemic lesions (Elble et al., 1996; Burleigh-Jacobs et al., 1997; Rocchi et al., 2006). In contrast, the current study demonstrates that the PD subjects' APAs prior to protective stepping were neither delayed nor hypometric. In fact, the PD subjects were faster to initiate an APA (as measured by the latencies of the weight shift and the associated EMG activity) than were the control subjects. The amplitude of the initial APAs in PD subjects was normal in response to surface translations, and the second or third APA often was larger than normal. Therefore, our observations do not suggest that ineffectual (delayed or smaller) APAs were the cause of freezing when steps were initiated in response to forward imbalance. These observations also suggest that the mechanisms for freezing may differ when subjects are in upright equilibrium with their CoM over their feet and when their CoM is forward of their feet.

If the APAs are of normal amplitude and not delayed, why doesn't a step follow? A pathophysiological explanation may be a failure to link the essentially normal APA to a step. A dys-integration of the APA from its associated goal-directed movement (in this case, the swing phase of a step) has been previously suggested for the rise-to-toes task in patients with PD (Frank et al., 2000) and is consistent with a dual-control model for APAs and movement (Brown and Frank, 1987; Nardone and Schieppati, 1988; Massion, 1992; Viallet et al., 1992; Benvenuti et al., 1997; De Wolf et al., 1998; Schepens and Drew, 2003). In a model proposed by Massion (1992), a circuit that includes the

supplementary motor area and basal ganglia generates the APA, whereas a circuit that includes the dorsolateral premotor cortex and primary motor cortex generates the goal-directed movement (e.g., the swing of a step). These parallel circuits are then integrated within the postural and locomotor centers of the brainstem (Massion, 1992; Schepens and Drew, 2004; Takakusaki et al., 2004). Separate groups of spinal projecting neurons of the pontomedullary reticular formation are related to the APA and to the step although the activity of some neurons is related to both the APA and the step (Schepens et al., 2008). We speculate that the dys-integration of the APA and the foot-swing during protective stepping likely results from dysfunction in these neural circuits. Inability of PD subjects to step after a single APA may also be related to the difficulty for PD subjects to simultaneously perform two tasks (Schwab et al., 1954) and to prolonged inter-movement latencies (Benecke et al., 1987).

The results from our study cannot distinguish between the possibility that multiple APAs represent a primary problem with coupling or sequencing the postural and stepping programs versus the possibility that multiple APAs represent a compensatory holding response due to inability to step. In support of the alternative interpretation that multiple APAs are a normal compensation under challenging balance condition, we previously showed that healthy subjects exhibit multiple APAs when compensatory stepping is delayed by withholding information about which foot to step with (Jacobs and Horak, 2007). Further, multiple APAs were occasionally seen in our control subjects. Investigating the set of conditions under which normal subjects show multiple APAs and late steps will lend insight into the nature of coupling between the APA and stepping motor programs so testable hypotheses can be developed for understanding FOG in subjects with PD.

Yanagisawa et al. (1991) and Bloem et al. (2004) present an alternative hypothesis, that trembling knees represent misfiring locomotor oscillators producing ineffective, alternating attempts to initiate a step with each leg. In contrast, we suggest that the trembling knees represent repeated attempts to couple the appropriate preparation for a step (the APA) with the step itself and not misfiring locomotor oscillators.

Forced stepping provides an experimental method to study FoG

Eliciting FoG in the laboratory is often difficult, as seen in this study when examining voluntary gait initiation and in other studies (Burleigh-Jacobs et al., 1997; Nieuwboer et al., 2001; Nieuwboer et al., 2004; Moore et al., 2008). This fact has made FoG hard to study. In contrast, FoG with knee trembling and multiple APAs was elicited in many trials from seven of 10 PD subjects during the protective stepping task, suggesting that inducing a loss of balance may provide a more effective paradigm for acute studies on FoG.

Does this experimental paradigm represent what is occurring when PD patients are normally walking? Steps shorten, cadence increases and speed slows just prior to FoG (Nieuwboer et al., 2001). These changes in step characteristics present a situation in which the CoM may move forward beyond the feet similar to the situation in our paradigm. Clinically, FoG is often associated with a forward CoM position over the feet so that the patients fall forward onto their knees and outstretched arms, suggesting that our experimental paradigm for displacing the CoM relative to the feet provides a representative scenario for FoG. In support of this suggestion, the videos demonstrate the knee trembling that is very characteristic of the phenomenon observed in the clinic when PD patients experience FoG. This visual evidence is supported by the similar frequency of the multiple APAs observed during protective stepping in this study and that of the bilateral trembling observed by other studies on FoG during voluntary gait (Yanagisawa et al., 1991; Ueno et al., 1993; Bloem et al., 2004). In addition, we observed premature activation of tibialis, gastrocnemius and tensor fascia latae muscles in PD subjects compared to control subjects, similar to what was seen just prior to freezing during ongoing locomotion (Nieuwboer et al., 2004). Given the similarities of the freezing episodes described in our study to those described during normal walking, we suggest that the protective step paradigm represents what is occurring when PD patients experience FoG during walking.

In summary, our results suggest that the trembling knees associated with FoG in people with PD represent multiple APAs. The multiple APAs are neither delayed nor hypometric, making inadequate APAs an unlikely primary cause of FoG. Thus, the pathophysiological basis of FoG appears to be a disturbance of coupling a normal postural preparation for a step to the swing phase of a step. Further, the trembling knees produced by the multiple APAs during freezing episodes are not a pathological postural or locomotor response, as multiple APAs can be seen in healthy people under some conditions. The trembling knees and multiple alternating APAs may be a compensatory response while trying to select or access the stepping motor program.

Acknowledgments

We thank the subjects who participated in the protocol. We are grateful for the help with data analysis from Edward King, Michael Amos, and Christine Ryciewcz, and for the technical assistance from Dr. Charles Russell and Edward King. This study was funded by the National Institutes of Health, grant AG06457.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.expneurol.2008.10.019.

References

Benecke, R., Rothwell, J.C., Dick, J.P., Day, B.L., Marsden, C.D., 1987. Disturbance of sequential movements in patients with Parkinson's disease. Brain 110, 361–379.
Benvenuti, F., Stanhope, S.J., Thomas, S.L., Panzer, V.P., Hallett, M., 1997. Flexibility of anticipatory postural adjustments revealed by self-paced and reaction-time arm movements. Brain Res. 761, 59–70.
Bloem, B.R., Hausdorff, J.M., Visser, J.E., Giladi, N., 2004. Falls and freezing of gait in Parkinson's disease a review of two interconnected, episodic phenomena. Mov. Disord. 19, 871–884.
Brown, J.E., Frank, J.S., 1987. Influence of event anticipation on postural actions accompanying voluntary movement. Exp. Brain Res. 67, 645–650.
Burleigh, A.L., Horak, F.B., Malouin, F., 1994. Modification of postural responses and step initiation: evidence for goal-directed postural interactions. J. Neurophysiol. 72, 2892–2902.
Burleigh, A., Horak, F., Nutt, J., Frank, J., 1995. Levodopa reduces muscle tone and lower extremity tremor in Parkinson's disease. Can. J. Neurol. Sci. 22, 280–285.
Burleigh-Jacobs, A., Horak, F.B., Nutt, J.G., Obeso, J.A., 1997. Step initiation in Parkinson's disease: influence of levodopa and external sensory triggers. Mov. Disord. 12, 206–215.
De Wolf, S., Slijper, H., Latash, M.L., 1998. Anticipatory postural adjustments during self-paced and reaction-time movements. Exp. Brain Res. 121, 7–19.
Elble, R.J., Moody, C., Leffler, K., Sinha, R., 1994. The initiation of normal walking. Mov. Disord. 9, 139–146.
Elble, R.J., Cousins, R., Leffler, K., Hughes, L., 1996. Gait initiation by patients with lower-half parkinsonism. Brain 119, 1705–1716.
Frank, J.S., Horak, F.B., Nutt, J., 2000. Centrally initiated postural adjustments in parkinsonian patients on and off levodopa. J. Neurophysiol. 84, 2440–2448.
Giladi, N., Kao, R., Fahn, S., 1997. Freezing phenomenon in patients with parkinsonian syndromes. Mov. Disord. 12, 302–305.
Hausdorff, J.M., Balash, Y., Giladi, N., 2003. Time series analysis of leg movements during freezing of gait in Parkinson's disease: akinesia, rhyme or reason? Physica, A 321, 565–570.
Iansek, R., Huxham, F., McGinley, J., 2006. The sequence effect and gait festination in Parkinson disease: contributors to freezing of gait? Mov. Disord. 21, 1419–1424.
Jacobs, J.V., Horak, F.B., 2007. External postural perturbations induce multiple anticipatory postural adjustments when subjects cannot pre-select their stepping foot. Exp. Brain Res. 179, 29–42.
Macht, M., Kaussner, Y., Möller, J.C., Stiasny-Kolster, K., Eggert, K.M., Krüger, H.P., Ellgring, H., 2007. Predictors of freezing in Parkinson's disease: a survey of 6,620 patients. Mov. Disord. 22, 953–956.
Martin, J.P., 1967. The Basal Ganglia and Posture. Pitman, London.
Massion, J., 1992. Movement, posture and equilibrium: interaction and coordination. Prog. Neurobiol. 38, 35–56.
McIlroy, W.E., Maki, B.E., 1996. Influence of destabilization on the temporal characteristics of stepping. J. Mot. Behav. 28, 28–34.

Moore, S.T., MacDougall, H.G., Ondo, W.G., 2008. Ambulatory monitoring of freezing of gait in Parkinson's disease. J. Neurosci. Methods 167, 340–348.
Nardone, A., Schieppati, M., 1988. Postural adjustments associated with voluntary contraction of leg muscles in standing man. Exp. Brain Res. 69, 469–480.
Nieuwboer, A., Dom, R., De Weerdt, W., Desloovere, K., Fieuws, S., Broens-Kaucsik, E., 2001. Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. Mov. Disord. 16, 1066–1075.
Nieuwboer, A., Dom, R., De Weerdt, W., Desloovere, K., Janssens, L., Stijn, V., 2004. Electromyographic profiles of gait prior to onset of freezing episodes in patients with Parkinson's disease. Brain 127, 1650–1660.
Petrovici, I., 1968. Apraxia of gait and of trunk movements. J. Neurol. Sci. 7, 229–243.
Plotnik, M., Giladi, N., Balash, Y., Peretz, C., Hausdorff, J.M., 2005. Is freezing of gait in Parkinson's disease related to asymmetric motor function? Ann. Neurol. 57, 656–663.
Rocchi, L., Chiari, L., Mancini, M., Carlson-Kuhta, P., Gross, A., Horak, F.B., 2006. Step initiation in Parkinson's disease: influence of initial stance conditions. Neurosci. Lett. 406, 128–132.
Schaafsma, J.D., Balash, Y., Gurevich, T., Bartels, A.L., Hausdorff, J.M., Giladi, N., 2003. Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. Eur. J. Neurol. 10, 391–398.
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.
Schepens, B., Stapley, P.J., Drew, T., 2008. Neurons in the pontomedullary reticular formation signal posture and movement both as an integrated behavior and independently. J. Neurophysiol. 100, 2235–2253.
Schwab, R.S., Chafetz, M.E., Walker, S., 1954. Control of two simultaneous voluntary motor acts in normals and in parkinsonism. A.M.A. Arch. Neurol. Psych. 72, 591–598.
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.
Ueno, E., Yanagisawa, N., Takami, M., 1993. Gait disorders in parkinsonism. A study with floor reaction forces and EMG. Adv. Neurol. 60, 414–418.
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.
Yanagisawa, N., Ueno, E., Takami, M., 1991. Frozen gait of Parkinson's disease and parkinsonism. A study with floor reaction forces and EMG. In: Shimamura, M., Grillner, S., Edgerton, V.R. (Eds.), Neurobiological Basis of Human Locomotion. Japan Scientific Societies Press, Tokyo, pp. 291–304.