Modulation of Cutaneous Reflexes From the Foot During Gait in Parkinson’s Disease

Jacques Duysens, Bart M. H. Van Wezel, and Bouwien Smits-Engelsman

Department of Medical Physics and Biophysics, Radboud University, Nijmegen, The Netherlands

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INTRODUCTION

In healthy subjects, a weak (nonnociceptive) electrical stimulus to a cutaneous nerve, innervating the skin of the foot, evokes reflex responses at a latency of about 80 ms in a wide variety of muscles in both the stimulated and the contralateral leg during walking (De Serres et al. 1995; Duyssens et al. 1990, 1991, 1996; Yang and Stein 1990; Zehr et al. 1997, 1998a,b). These reflex responses are mediated by the low-threshold Aβ fibers (Van Wezel et al. 2000). The gain of these responses is modulated according to the phase of the step cycle such that it generally does not vary in parallel with the background activity (and thus presumably not with motoneuronal excitability), indicating premotoneuronal mechanisms that control the gain of the reflex pathways during the course of a step cycle.

This phase-dependent reflex control is specific for the location of the stimulus (Van Wezel et al. 1997; Zehr et al. 1997) and is thought to be mostly due to actions of spinal locomotor central pattern generators (Duyssens et al. 2004; Zehr and Duyssens 2004). Indeed, in patients with spinal cord injury some elements of the modulation of these responses are largely preserved (Jones and Yang 1994; Knikou et al. 2009). Lesions in the corticospinal tract do not eliminate the phase-dependent modulation but mostly cause an overall reduction in the amplitude of the responses (Duyssens et al. 2004b). Inversely, activation of the cortex through transcranial magnetic stimulation facilitates the reflex responses, indicating that there is convergence of the corticospinal tract and the reflex pathways involved in these responses, in confirmation of evidence obtained in cat studies (Bretzner and Drew 2005). These results prompted the suggestion that the cortical input may act to selectively change the gain in these reflex pathways (Haridas et al. 2005, 2008). It was found that conditions that posed a threat to stability during gait (such as walking with arms crossed when surface translations of the belt of the treadmill could occur) selectively increased the amplitude of responses in contralateral muscles (Haridas et al. 2005). Similar results were obtained when an added postural threat was induced by unexpectedly touching the dorsum of the foot during walking (Haridas et al. 2008). It was speculated that these crossed reflexes were facilitated from the motor cortex to restore balance in case of instability (Haridas et al. 2005, 2008). Down-regulation (decreased response amplitudes) can occur as well. For example, decreased amplitudes of cutaneous reflexes were observed when subjects delivered the stimulation themselves (Baken et al. 2006).

Although there is substantial evidence for a role of the motor cortex in the up- or down-regulation of cutaneous reflexes, the contribution of the basal ganglia in this process is largely unknown. In Parkinson’s disease (PD) there has not yet been a study on the phase-dependent modulation of cutaneous reflexes. However, in a previous study we investigated the phase-dependent modulation of another type of reflexes (startle) in PD and found very few abnormalities either in the overall amplitude or in the phase-dependent modulation of the responses (Nieuwenhuijzen et al. 2005). This result is consistent with the notion that the substantia nigra is not a major element involved in phase-dependent modulation. It is possible, however, that abnormalities are present in this patient group since the gait in PD patients is unstable. Walking on a treadmill can be seen by PD patients as a threat to stability. Thus one might expect an exaggeration of responses, especially on the contralateral side (Haridas et al. 2005, 2008).

An overall effect on the amplitude is also possible. For example, at rest conditions there have been indications for some abnormalities of cutaneous reflexes in the arm (Fuhr et al. 1992). Suppressive cutaneous reflexes in the arm are less pronounced in PD subjects. For other reflexes some abnormalities were reported as well. For example, abnormalities in
postural reflexes have been observed (Beckley et al. 1991; Bloem et al. 1995; Carpenter et al. 2004; Chong et al. 2000; Dietz et al. 1988, 1995; Dimitrova et al. 2004; Schieppati and Nardone 1991). However, these abnormalities did not seem to involve the basic synergies (Dimitrova et al. 2004). The latter authors stated that "the direction of maximum activation for each muscle was similar for PD and control subjects, suggesting that the basal ganglia is not critical for programming externally triggered postural synergies." The present study addresses the same type of question but now in the context of cutaneous reflexes. Are these reflexes abnormal in Parkinson’s disease (either in terms of a general change in amplitude or more specifically with respect to phase-dependent modulation)? To this end, reflex responses to nonnociceptive electrical stimulation of the sural nerve (involving the lateral side of the foot) were elicited during gait of these patients. Responses were studied in the biceps femoris (BF) and tibialis anterior (TA) of both the stimulated (ipsilateral) and unstimulated (contralateral) legs. The ipsilateral BF (iBF) and TA (iTA) were chosen because these muscles exhibit large facilitatory responses to sural nerve stimulation in normal subjects during gait (Baken et al. 2006; De Serres et al. 1995; Duyens et al. 1990, 1996; Van Wezel et al. 1997, 2000; Yang and Stein 1990; Zehr et al. 1998b).

**Methods**

**Subjects**

Experiments were performed on a group of nine patients (eight male, one female) with a clinically diagnosed Parkinson’s disease (Table 1). The same group participated as described in an earlier study (Nieuwenhuijzen et al. 2006). The average age was 53 yr (SD 12; range, 42 to 73 yr). The average disease duration was 9 yr (SD 4; range, 4 to 15 yr). Motor disability was evaluated using the Hoehn–Yahr score. Due to the nature of the task (treadmill walking) only minor affected patients were included in this study, showing in the off stage a Hoehn–Yahr level varying from 3 to 4. The leg function was also evaluated separately by measuring the walking velocity and stride length (velocity range: 1–4 km/h; stride length range: 68–88 cm).

Patients data were compared with those of a group of 10 healthy subjects with no known history of neuromuscular disorder (8 male, 2 female; age range: 19–46 yr). The data from the control subjects were previously published in Van Wezel et al. (1997) and in part additio­nally analyzed. The experiments were carried out in conformity with the Helsinki Declaration for experiments on humans. All subjects had given informed consent and the experiments were performed after approval of the local ethical committee.

**Table 1.** Patient profiles

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Duration, yr</th>
<th>Hoehn–Yahr Scale</th>
<th>Gait Impairment</th>
<th>L-Dopa, mg/day</th>
<th>Pergolide, mg/day</th>
<th>Selegiline, mg/day</th>
<th>Orphenadrine HCl, mg/day</th>
<th>Amantadine, mg/day</th>
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**Experimental setup**

The subjects were asked to walk on a treadmill while wearing a safety-harness fastened to an emergency brake at the ceiling. Very thin custom-made insole foot-switch systems were used to detect foot contact. Bipolar electromyographic (EMG) activity was recorded in both legs by means of surface electrodes over the long head of the biceps femoris (BF) and the tibialis anterior (TA) muscles. The EMG signals were (pre-) amplified (total factor = 10³), high-pass filtered (cutoff frequency at 3 Hz), full-wave rectified, and then low-pass filtered (cutoff frequency at 300 Hz). These signals were sampled along with the foot-switch signals. The data were AD-converted (500 Hz) and stored on hard disk. The electrical stimulus (a train of five rectangular pulses of 1 ms duration given at 200 Hz) was applied by a custom-made constant-current stimulator through a bipolar stimulation electrode (with poles of 0.5 cm and an interpole distance of 2.0 cm) that was positioned over the sural nerve (approximately halfway between the lateral malleolus and the Achilles tendon) of the most affected leg. For each subject the exact position of the stimulation electrode was determined according to the optimal irradiation to the lateral side of the foot (the innervation area of the sural nerve), similar to previously published methods (Baken et al. 2006; Duyens et al. 1996; Van Wezel et al. 1997, 2000) and to those used by others (Yang and Stein 1990; Zehr et al. 1998b).

**Experimental procedures**

The patients were trained to walk at a comfortable, self-selected speed. Prior to each experimental run, during quiet standing, the perception threshold (PT) was determined by gradually increasing (to above PT) and decreasing (to below PT) the stimulus amplitude. Before the start of an experimental run the PT had to be stable before and after a short walking period. During the experimental runs the intensity of the stimuli was 2 PT (Duyens et al. 1996; Van Wezel et al. 1997, 2000). This intensity was chosen because it gives a nonnociceptive sensation on the innervation area of the sural nerve (lateral side of the foot) and reliably elicits reflex responses in healthy subjects. The stimuli were delivered at 16 preprogrammed and equi­distantly distributed points over the whole step cycle. During the same periods control values (i.e., no stimulus) of the EMG were also measured. Both ipsilateral and contralateral footfall served as reference points for the time in the step cycle, each for a half of the total step cycle.

There were 10 stimuli presented in each of the 16 positions in the step cycle and there were 10 nonstimulated sweeps collected for each position in the step cycle, equaling 320 sweeps collected in total. All 320 trials occurred in random order. To avoid predictability of the stimuli and to reduce habituation of the responses as much as possible, successive stimulus conditions were separated by a random interval in the range of 3.5 to 6.5 s. Thus two stimuli were always separated by at least two step cycles without a stimulus. At the end of each experimental run the perception threshold was determined once more.
It was slightly lowered (~8% on average) compared with the measurement taken immediately prior to the experimental run. Because this change was small and systematic no further corrections were deemed essential.

**Data analysis**

Because the present data on PD had to be compared with data from a previous study, a similar analysis to that described in Van Wezel et al. (1997) was used. The overall effect after nerve stimulation was obtained by averaging the 10 trials per condition (16 stimulus phases with and 16 control phases without stimulation) and, subsequently, by subtracting the resulting control data from the corresponding stimulus data. Thus for each muscle 16 subtracted responses were obtained, corresponding to the 16 phases in the step cycle (see Fig. 1). Quantification of the responses occurred by determining a time window over the period in which the responses occurred and by calculating the mean of the EMG data within that window. When a muscle showed little or no response no adequate window could be set. In that case an average window was used, calculated from the time windows used to measure responses (in order of priority) in the other muscle in the same leg or the muscles in the other leg (cf. Tax et al. 1995; Van Wezel et al. 1997). For each trial, the mean EMG value was calculated within the applicable window obtained from the above-cited analysis. Subsequently, for all conditions (i.e., for 16 phases for both control and stimulus conditions), the average and the SE were calculated from these window-averaged trials.

The maximum of the 16 averaged control values was used to normalize the EMG data so that a proper intersubject comparison could be made. The response amplitudes to cutaneous stimulation for a given condition are not normally distributed (as described in Duysens et al. 1996) and therefore it is common in this field to use nonparametric statistics. The same approach was taken here, especially since there was a need to compare the results with previous work on which the present study was built (Van Wezel et al. 1997). To determine whether any given mean subtracted response at a given phase was significantly different from zero the Wilcoxon signed-rank test (significance level $P < 0.05$) was used. The differences in subtracted responses between patients and control subjects were tested using independent-samples Mann–Whitney $U$ tests. To look for similarities in the phase dependence between the two groups, nonparametric correlation coefficients between the phase patterns of the controls and PD groups were calculated.

**RESULTS**

Results of the patients will be presented in relation to the results of the healthy subjects, which have been published elsewhere (Van Wezel et al. 1997). The control subjects were studied at 4 km/h. The patients were asked to determine their preferred walking velocity during a short walking period on the treadmill. On average, the preferred velocity for the patients was 2.8 km/h (SD 0.9; range 1.3–4.0 km/h). An example of the BF EMG and foot contact data during a single step cycle is given in Fig. 1A for single healthy subject and a patient with PD.

The healthy subjects showed two EMG activity bursts in biceps femoris during the step cycle. The largest activity burst was observed during the late swing phase to decelerate the leg in preparation for the stance phase. This activity gradually declined during the stance phase. A second, considerably smaller activity was often observed during the late stance phase. In the patient the activity in BF lasted longer in the stance phase, a change that was consistently observed in the whole population (see the following text).

**Reflex responses: latency and duration**

Results of typical reflex responses are shown in Fig. 1B for iBF of a healthy subject and a patient with PD. In both subjects large facilitatory reflex responses were observed at a latency of about 80–90 ms. The step cycle was subdivided in 16 parts (as described in Van Wezel et al. 1997), with phase 1 being the phase in which the response occurred just after touchdown. The latency of these responses was rather constant over the 16 phases of the step cycle. On average for all subjects, this time window started at 82 ms (SD 9) and ended at 116 ms (SD 12). The window settings were very similar for the two groups. For the control subjects the onset was 84 ms (SD 8) to 115 ms (SD 7), whereas for the patients it was 81 ms (SD 6) to 117 ms (SD 5).
Using these windows, a considerable phase-dependent effect on the magnitude of these responses could be observed. For example, both patients and healthy subjects exhibited large responses during phases 7 to 11, whereas considerably smaller responses were elicited during the succeeding phases 12 to 14. Although phase dependence appeared similar in patients and control subjects there was a tendency for the responses to be larger in the patient group. To quantify the responses a time window was set around the responses in which the mean EMG value was calculated (see METHODS). To examine the overall difference in amplitude the mean amplitude was calculated over the whole step cycle for each subject and then the overall means were calculated for the two populations. The results are shown in Fig. 2.

In all muscles except iTA the responses were larger in the PD group than those in the control group. This was verified using independent-samples Mann–Whitney U tests. The differences were significant for all muscles (iBF, P = 0.003; cBF, P < 0.001; cTA, P = 0.032) except iTA (P = 0.61).

Habituation

In a previous study (Nieuwenhuijzen et al. 2006) it was found that startle responses were larger in PD than those in control subjects, although this effect was due to a decrease in habituation in the PD patients. Since the present cutaneous reflex responses were also found to be exaggerated in PD the question arose whether this difference was also due to a difference in habituations. To examine this, the degree of habituation of the responses was checked for differences between patients and control subjects. For all subjects the subtracted trials of all stimulus phases were averaged in order of delivery and the responses were then normalized to their mean. Subsequently, they were averaged for both patients and healthy subjects and a regression analysis was performed. The habituation did not differ significantly between the two groups. The amount of habituation was 26% for the group of patients and 23% for the group of healthy subjects. These results are consistent with previously reported habituation in comparable experiments on healthy subjects (25%; Tax et al. 1995).

Phase-dependent reflex responses

The overall increase in reflex responses could have been due to an overall increase at all phases or it could be related to the responses being selectively larger in given parts of the step cycle. To examine this question the phase dependence of the responses was examined in detail for the various muscles investigated.

Ipsilateral biceps femoris

The average EMG activation profiles for the whole population of PD patients are shown at the top of all plots in Figs. 3–6 so that an easy comparison can be made with the reflex responses (to judge the presence of premotoneuronal activation present in periods in which reflexes are large despite the background activity being low or absent). In Fig. 3 the results are given for the reflexes in iBF following a format as used in Van Wezel et al. (1997). In this and the following figures the significant responses (subtracted responses different from zero) are indicated by bold data points. The timing can be evaluated by the bars beneath the figures (top is stance ipsilaterally, bottom contralaterally). The method is first illustrated based on the data of a single subject (Fig. 3, top).

The reflex responses were mostly facilitatory over the whole step cycle in iBF. In patient 5 (the same as used for Fig. 1) the responses were large from late stance to early swing (phases 7–11), smaller during midswing (phases 12–15), and again large from late swing into the stance phase (phases 16–4; Fig. 3, top, based on the same data as in Fig. 1). The reflex responses were clearly not strictly related to the background activity in this muscle. For example, the reflex responses from late stance to early swing (phases 7–11) were larger in amplitude than the responses from late swing into the stance phase (phases 16–4), whereas the opposite was observed for the background activity (Fig. 3, top). For the whole population of patients the phase dependence was comparable to the example shown at the top of Fig. 3, although less pronounced (Fig. 3, middle). At the bottom of Fig. 3 the data of the control subjects are shown. The overall amplitude was somewhat smaller, although the phase dependence of the modulation was not basically different between patients and control subjects. Thus the average increased response amplitude that was observed in this muscle (Fig. 2) was not restricted to specific phases. Rather, the average increase of response amplitude was observed across the whole step cycle (Fig. 3, middle vs. bottom).

Ipsilateral tibialis anterior

In tibialis anterior of the healthy subjects most activity was observed during the swing phase (Fig. 4 for iTA).
The greatest activity occurred during the end of the swing phase to prepare the foot for the stance phase. After the foot was set on the ground (phase 1), the activity in TA declined rapidly and during most of the stance phase TA activity was absent. In the patient group comparable TA activity was observed during the swing phase. However, in stance there was a clear difference. In three patients (including patient 5 from the top of the figure), activity was also observed during most of the stance phase (as also seen in the average on top of the population plot; Fig. 4, middle). The reflex modulation was quite similar in patients and control subjects. During the first half of the stance phase no significant responses were observed for iTA in the patients or control subjects. The responses were on average facilitatory during the second half of stance and most of the swing phase, whereas they were suppressive during end swing. Such a combination of facilitations and suppressions was observed in six patients (a typical example is shown in Fig. 4, top). Three patients primarily showed suppressions in these phases. This intersubject variability in the iTA responses during the swing phase is normal for the sural nerve (see also Baken et al. 2006; Duyzens et al. 1990, 1996; Van Wezel et al. 1997; Yang and Stein 1990; Zehr et al. 1997). The main difference in reflex modulation was that significant responses were already observed at midstance (phase 6). In two patients the responses were observed even in the first half of the stance phase (e.g., Fig. 4, top). Note, however, that these patients also tended to show more background TA activity in these periods compared with that in control subjects. Thus the increased responses can be attributed to increased background activity. Overall the patients and the control subjects showed many similarities in phase dependence despite the variability within the populations. This was further quantified by correlating the mean subtracted responses for all phases for the two populations. This yielded a Spearman correlation coefficient of 0.88, well above the correlations found for other muscles (0.36 for iBF; 0.29 for cBF; 0.02 for cTA).

Contralateral biceps femoris

In cBF, the difference between patients and control subjects was most obvious. In fact, the y-scale of the plots in Fig. 5 had to be adjusted to allow for the much larger responses in the patients.

In the control subjects (Fig. 5, bottom) most significant cBF responses occurred in the contralateral stance phase. In the patient group the most significant responses occurred in the

**FIG. 3.** Window-averaged and normalized background activity and subtracted responses of the iBF. Within the 3 panels subtracted data (±SE) are plotted as a function of their appearance in the 16 phases of the step cycle. On top of the panels the background activity is shown. Top: window-averaged data of the same patient as in Fig. 1. Middle: average of the population of patients. Bottom: average of the population of healthy subjects (adapted from Van Wezel et al. 1997). The statistical significance of the reflexes (Wilcoxon signed-rank test, P < 0.05) is indicated by the black dots. Phases 1 and 9 correspond to the onset of ipsilateral and contralateral stance, respectively. The ipsilateral (i) and contralateral (c) stance phases are shown at the bottom (as upper and lower sets of lines, respectively). Note the different vertical scales for the different panels.

The greatest activity occurred during the end of the swing phase to prepare the foot for the stance phase. After the foot was set on the ground (phase 1), the activity in TA declined rapidly and during most of the stance phase TA activity was absent. In the patient group comparable TA activity was observed during the swing phase. However, in stance there was a clear difference. In three patients (including patient 5 from the top of the figure), activity was also observed during most of the stance phase (as also seen in the average on top of the population plot; Fig. 4, middle).

The reflex modulation was quite similar in patients and control subjects. During the first half of the stance phase no significant responses were observed for iTA in the patients or control subjects. The responses were on average facilitatory during the second half of stance and most of the swing phase, whereas they were suppressive during end swing. Such a combination of facilitations and suppressions was observed in six patients (a typical example is shown in Fig. 4, top). Three patients primarily showed suppressions in these phases. This intersubject variability in the iTA responses during the swing phase is normal for the sural nerve (see also Baken et al. 2006; Duyzens et al. 1990, 1996; Van Wezel et al. 1997; Yang and Stein 1990; Zehr et al. 1997). The main difference in reflex modulation was that significant responses were already observed at midstance (phase 6). In two patients the responses were observed even in the first half of the stance phase (e.g., Fig. 4, top). Note, however, that these patients also tended to show more background TA activity in these periods compared with that in control subjects. Thus the increased responses can be attributed to increased background activity. Overall the patients and the control subjects showed many similarities in phase dependence despite the variability within the populations. This was further quantified by correlating the mean subtracted responses for all phases for the two populations. This yielded a Spearman correlation coefficient of 0.88, well above the correlations found for other muscles (0.36 for iBF; 0.29 for cBF; 0.02 for cTA).
same period, although the responses were considerably larger. Furthermore, in the patients some large responses were present during contralateral swing, whereas such responses were absent in the control subjects. In the patient group, the average response amplitude in this part of the step cycle was comparable with the one seen during contralateral mid to late stance, but the variability was considerably larger. This was due to large responses being present in patients 4, 6, and 9 but not in the other patients. In patient 6 the amplitude of the responses reached levels of more than twofold the maximum background activity and in patient 4 the amplitude even reached levels of more than fourfold this level. The latter patient is therefore illustrated separately (Fig. 5, top; note that an adjustment of the y-scale was needed). In these two patients these responses were larger for cBF than those for iBF, whereas in the other patients and all healthy subjects the opposite was the case. The large responses were not correlated with elevated background activity (as is particularly clear for the example of patient 4, illustrated in Fig. 5, top).

Contralateral tibialis anterior

In cTA no clear differences were observed for the responses of the patients compared with those of healthy subjects. The response pattern consisted basically of small facilitations during the contralateral stance phase (phases 1 and 9–16), whereas on average the responses were smaller or absent during contralateral swing (Fig. 6).

DISCUSSION

A major result of the present study was that the responses to sural nerve stimulation are selectively increased in some muscles such as BF in PD patients. Two types of increases were observed. The first was an increase over the whole step cycle, as was found on average over the whole population. The second was a phase-dependent increase in cBF at a specific time of the step cycle and this was present in only a subset of the patients.

Generalized increase

Overall there was some increase in reflex amplitude but there was no basic difference in phase-dependent modulation in patients versus that in control subjects. In iTA the typical phase-dependent reversal was present in both groups. This indicates that deficits in the substantia nigra have little or no effect on this modulation, consistent with the idea that such

FIG. 5. Window-averaged and normalized background activity and subtracted responses of the contralateral biceps femoris (cBF). The same format is used as that in Fig. 3.

FIG. 6. Window-averaged and normalized background activity and subtracted responses of the contralateral tibialis anterior (cTA). The same format is used as that in Fig. 3.
and control subjects, since the largest cBF responses were related to the average age difference between the PD patients pared with that of healthy subjects. The increase was also not habituation since habituation was of the same magnitude compared with that of healthy subjects. The increase was also not related to the average age difference between the PD patients and control subjects, since the largest cBF responses were observed in the youngest patient (see RESULTS). Furthermore, the average age was 53 yr, which does not place these subjects in the group of “elderly.” If anything, one would expect responses to decrease with age since somatosensory medium-latency cutaneous reflex responses were decreased in healthy elderly compared with those in younger subjects (Pijnappels et al. 2005b; Schillings et al. 2005; Tang and Woollacott 1998, 1999). Another possible confound is the difference is walking speed. The patients walked at a comfortable self-selected speed that was on average lower than the speed of the control subjects. Potentially, this could influence the results on the reflex responses. However, previously published studies indicate that there is little effect of speed on these reflex responses. Phase dependencies of the medium-latency cutaneous reflexes at 2.5 km/h walking (Van Wezel et al. 2000), 4 km/h walking (Duyssens et al. 1996; Van Wezel et al. 1997), and 8 km/h running (Tax et al. 1995) are completely comparable. Other studies confirm the low speed dependence on cutaneous reflexes during human gait (Zehr et al. 1997, 1998a,b).

**Phase-dependent increase in cBF in some PD patients**

Although generally the phase-dependent modulation of reflexes was maintained in PD, an additional effect appeared in three of them since the amplitude of the cBF reflex responses was selectively increased during the contralateral swing phase. In such cases the crossed responses were considerably larger than the amplitude of the responses in the iBF. In patient 4 (illustrated in Fig. 5) the amplitude of the subtracted responses were often larger than fourfold the maximum background activation encountered during gait. In control subjects the contralateral medium-latency cutaneous reflex responses are normally smaller than the corresponding ipsilateral responses during gait (Van Wezel et al. 1997) and during nonlocomotor tasks (Burke et al. 1991). Furthermore, in our laboratory such high amplitudes of contralateral reflex responses were never observed in healthy subjects during normal gait (Duyssens et al. 1990, 1991; Van Wezel et al. 1997).

In principle these large responses could have been due to a related increase in background activation. Indeed, for particular muscles such as cBF an increase in response amplitude in some phases of the step cycle (second half of the contralateral step cycle) could be partly related to increased background EMG activity in PD subjects. This additional background activity is consistent with earlier findings since increased EMG activity patterns during parkinsonian gait have been reported for BF by several authors (Cioni et al. 1997; Dietz et al. 1997; Mitoma et al. 2000). However, the changes in reflex amplitudes in cBF were not limited to the phases with increased background. In the beginning of the contralateral swing phase there was no extra background EMG activity in the cBF, yet in three patients very large reflex activations occurred in that period. The fact that these responses occurred without a concomitant increase in background EMG indicates involvement of premotoneuronal gain control of the pathways that mediate these reflexes.

Thus to understand these extremely large cBF reflexes other factors have to be considered. These responses occurred in the contralateral leg, which was the least affected one and thus the limb that is most important in making compensatory movements after a perturbation to the most affected leg. In the case of ipsilateral perturbations (such as stumbling) it is well known that contralateral BF is strongly activated with a latency that is comparable with the one observed for the present responses (Pijnappels et al. 2005a,b). In such instances the cBF responses occur at almost the same latency as that of ipsilateral BF activations (Schillings et al. 2000, 2005). During the crossed stance phase the cBF responses are thought to be important in braking the forward momentum of the upper body (BF is a hip extensor that can tilt the upper body backward; see Pijnappels et al. 2005a,b). During contralateral swing, the cBF may be important because it is a knee flexor. Stumbling (or slipping) is likely to lower the body mass toward the ground surface and the contralateral limb has to flex to make a compensatory step if required. Large crossed responses have been observed in other situations as well. When the support surface is suddenly translated on one side, amplitudes of medium-latency responses in the unperturbed leg occur in contralateral swing and these responses can exceed the responses in the perturbed leg (Berger et al. 1984; Dietz et al. 1984). Similar results can be obtained with mechanical perturbation of the swing phase (Dietz et al. 1986; Schillings et al. 2000). A perceived threat to stability has been shown to affect crossed reflex responses (Haridas et al. 2005, 2008). Thus in agreement with Haridas and colleagues (2005, 2008) it is proposed that the currently described cBF activations reflect the facilitation of reflex pathways that are commonly recruited in cases of perceived instability (such as when ipsilateral perturbations threaten stability). In other words, the results as presented could be due either to the direct effect of the neuronal deficit (e.g., in substantia nigra) or to the indirect effect of having an unstable gait (as a result of the neuronal loss).

An argument in favor of this explanation is that in PD patients there were clear signs of compensation for instability, which were not present in the control subjects. In the present study a clear sign of perceived threat is the iTA background activation in the first part of the stance phase. This TA activity is part of the ankle muscle coactivation frequently seen when subject are walking while feeling unstable. For example, under conditions that resemble limping, TA activity was observed during the stance phase of the more stable leg in both healthy subjects (Dietz et al. 1994; Duyssens et al. 2004b) and patients with PD (Dietz et al. 1995). Under stable conditions, however, there is usually no extra TA activity during the stance phase (Cioni et al. 1997; Dietz et al. 1981, 1995, 1997; Lewis et al. 2000; Mitoma et al. 2000; for
exceptions see Cioni et al. 1997; Dietz et al. 1995). This extra TA activity is not due to the slower speed since the TA does not show extra activity during the stance phase in slow gait (Den Otter et al. 2004). Rather, this activity may reflect the increased instability that is characteristic for patients with PD. On the basis of the present experiments it is reasonable to assume that this TA activation in stance is related to perceived instability. An age effect can be excluded since ankle coactivation is not normally present during walking of this age group (Lamontagne et al. 2000). It follows that one likely explanation for the currently observed increase in facilitatory responses in PD is the instability of the gait, presumably accompanied by feelings of fear. To distinguish between this “fear” effect and a direct contribution of the disease some future experiments are needed with age-matched control subjects walking under “threatening” conditions (imitating situations that produce some threat as experienced by PD patients).

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vusvest 101–bus 01500, BE-3001 Leuven (Heverlee), Belgium.

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