View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by RERO DOC Digital Library

doi:10.1093/brain/awn263 *Brain* (2008), **131**, 3421–3431

Locomotion in Parkinson's disease: neuronal coupling of upper and lower limbs

V. Dietz and J. Michel

Spinal Cord Injury Center, Balgrist University Hospital, Forchstrasse 340, CH – 8008 Zurich, Switzerland

Correspondence to: Prof. Dr V. Dietz, Spinal Cord Injury Center, Balgrist University Hospital, Forchstrasse 340, CH – 8008 Zürich
E-mail: volker.dietz@balgrist.ch

Quadrupedal limb coordination during human walking was recently shown to be upregulated during obstacle stepping. An anticipatory activity of coupled cervico-thoraco-lumbar interneuronal circuits is followed by an appropriate executory activation of leg and arm muscles during task performance. This mechanism was studied in subjects with Parkinson's disease and age-matched controls walking on a treadmill with a randomly approaching obstacle. Spinal reflex (SR) responses, evoked by tibial nerve stimulation during mid-stance, were present in all arm and leg muscles investigated. They were larger before execution of obstacle avoidance compared with normal steps in both subject groups. The performance of obstacle stepping was slightly worse in Parkinson's disease than in control subjects. The anticipatory SR in the arm muscles prior to normal and obstacle steps was larger in Parkinson's disease compared with age-matched subjects, but smaller in the tibialis anterior. The arm and leg muscle activation was stronger during obstacle compared with normal swing but did not differ between Parkinson's disease and age-matched subjects. These observations indicate that quadrupedal limb coordination is basically preserved in Parkinson's disease subjects. Our data are consistent with the proposal that in Parkinson's disease subjects the enhanced anticipatory spinal neuronal activity (reflected in the SR) in the arm muscles is required to achieve an appropriate muscle activation for the automatic control of body equilibrium during the performance of the task. In the tibialis anterior the SR is attenuated presumably because of a stronger voluntary (i.e. cortical) control of leg movements.

Keywords: Parkinson's disease; obstacle stepping; quadrupedal limb coordination; anticipatory spinal neuronal activity

Abbreviations: BB = biceps brachii; Del = deltoideus; SR = spinal reflex; TA = tibialis anterior

Received June 9, 2008. Revised September 16, 2008. Accepted September 18, 2008. Advance Access publication October 17, 2008

Introduction

Movement disorder is a prominent feature of Parkinson's disease (Rogers, 1996; Burleigh-Jacobs *et al.*, 1997; Morris *et al.*, 1998). There are several mechanisms known to contribute to the impaired performance, causing deficits to initiate (Morris *et al.*, 1994), modulate (Majsak *et al.*, 1998) and scale (Jackson *et al.*, 2000) movements. Furthermore, an insufficient activation of leg extensor muscles was suggested to contribute to the increased risk of falling during walking (Dietz and Colombo, 1998). These deficits are present even in subjects with moderate Parkinson's disease and they become more evident in a precision locomotor task such as obstacle avoidance locomotion (van Hedel *et al.*, 2006). This task requires a close interaction between automatically performed locomotor and voluntary goal-directed movements. For the performance of such a precision locomotor task a quadrupedal limb coordination seems to be of relevance in healthy subjects (Michel *et al.*, 2008). It could be shown that in such a condition an enhanced spinal neuronal activity couples upper and lower limb muscles already prior to obstacle swing, in order to prepare for the movement execution.

There are a number of studies dealing with the interlimb coordination in healthy people (for review see Dietz, 2002; Haridas and Zehr, 2003; Swinnen and Duysens, 2004; Zehr *et al.*, 2007), but only a few studies focus on the coupling of upper and lower limbs (Winogrodzka *et al.*, 2005; Carpinella *et al.*, 2007) or the interleg coordination (Plotnik *et al.*, 2007) during locomotion in Parkinson's disease subjects. Accordingly, a defective coordination of upper and lower limbs (Swinnen *et al.*, 1997; Winogrodzka *et al.*, 2005) in combination with reduced arm swing (Carpinella *et al.*, 2007) during locomotion and abnormal postural reactions to voluntary movements (Rogers *et al.*, 1987)

© The Author (2008). Published by Oxford University Press on behalf of the Guarantors of Brain. All rights reserved. For Permissions, please email: journals.permissions@oxfordjournals.org

might contribute to the impaired performance of the obstacle locomotor task (van Hedel *et al.*, 2006). The disturbed interlimb coordination was shown to become improved by L-DOPA application and subthalamic nucleus stimulation (Carpinella *et al.*, 2007).

The aim of this study was to explore to what extent the spinal interneuronal function underlying the quadrupedal limb coordination in healthy subjects (Michel *et al.*, 2008) is preserved during the performance of such a precision locomotor task in Parkinson's disease subjects, or, alternatively, whether this mechanism contributes to the locomotor disorder in Parkinson's disease. For this, the quadrupedal distribution of EMG responses to unilateral tibial nerve stimulation was analysed prior to normal and obstacle swing. Such a stimulation is known to evoke spinal reflexes (SR) in humans, most probably corresponding to cutaneous reflexes (Yang and Stein, 1990). Up to now, only a few studies have investigated the behaviour of cutaneous reflexes in Parkinson's disease subjects (Sandrini *et al.*, 2005).

The following hypotheses were tested: (i) a poorer acquisition and performance of the precision locomotor task occurs in Parkinson's disease compared to age-matched subjects; (ii) an impaired performance is associated with an disturbed neuronal coupling between upper and lower limbs, reflected in abnormal SR preceding the execution of the task; (iii) as a consequence, an insufficient upper limb muscle activation is associated with an impaired task execution.

Methods

This study was approved by the Cantonal Ethics Commission and conformed to standards set by the Declaration of Helsinki. The subjects were informed about the experiment and gave written consent. Twelve patients with Parkinson's disease (four females, see Table 1) and 12 age-matched healthy subjects (three females) participated. All Parkinson's disease subjects included were able to perform the obstacle stepping task. In Table 1 the severity of Parkinson's disease, rated according to established scores, and the actual individual treatment are described for all participating Parkinson's disease subjects.

The average age of the Parkinson's disease patients was 65.3 years (SD = 5.9) and their body height was 175 cm (SD = 8.0). The healthy subjects had an average age of 62.0 years (SD = 4.8) and were 172 cm (SD = 6.1) tall. The patients were on their usual medication during the experiment (Table 1).

General procedures and data recordings

Subjects walked on a split belt treadmill (Woodway, Weil am Rhein, Germany) with both belts running at 2.5 km/h with freely moving arms (arm movements were not recorded, but according to the visual inspection they were small at this walking speed). A custom-built obstacle-device was placed next to the treadmill (Fig. 1A) to study repetitive stepping over the obstacle (Erni and Dietz, 2001; van Hedel *et al.*, 2002). The details of the experiment have been described previously (Michel *et al.*, 2008). In short, the obstacle consists of a foam stick, 14 cm above the treadmill. It is attached to the obstacle machine in such a way that it passively folds back when the subject touches it.

The impact of the right foot, i.e. heel strike (HS1), was recorded by force sensors located underneath the right treadmill belt and randomly triggered the start of the obstacle machine and the measurement (Fig. 1A). After release, the obstacle moved at the same speed as the treadmill and the subjects could step over the obstacle with the right foot without changing their rhythmic walking cadence. After stepping over it, the obstacle folded up at the end of the treadmill and moved back to its starting position at the front of the treadmill.

The subjects were instructed to minimize foot clearance (i.e. the distance between foot and obstacle) during the course of the experiment, without touching the obstacle. An improvement of performance during obstacle stepping was defined by the following criteria (cf. Erni and Dietz, 2001): (i) a lower level of foot clearance; or (ii) a decrease of EMG activity during the swing phase over the obstacle (RMS values).

When subjects stepped over the obstacle, the level of foot clearance was determined by infrared sensors attached to the obstacle machine above the foam stick. In contrast to similar experiments in healthy subjects, described recently (Michel *et al.*, 2008), subjects had full vision in order to facilitate the performance of the task

Table 1 Clinical characteristics of Parkinson's disease subjects

Sex	Age (year)	Duration of parkinson's disease (year)	mHY	UPDRS	LED	Medication
M	65	2	2	19	300	9 mg ropinirole
F	73	10	2.5	28	1340	800 mg L- DOPA retard, 3 mg pramipexole
F	63	10	2.5	22	852	400 mg L- DOPA retard, 400 mg L-dopa
M	63	4	2.5	31	930	600 mg L- DOPA retard, 1.5 mg pramipexol
M	55	12	2	33	1131	800 mg L- DOPA (+ entacapone), 14 mg ropinirole
M	58	12	2.5	58	1140	1000 mg L- DOPA retard, 10 mg ropinirole
M	69	5	2.5	35	1100	600 mg L- DOPA retard, 15 mg ropinirole
M	67	12	2.5	37	1400	900 mg L-DOPA, 16 mg ropinirole
M	61	5	2.5	18	200	6 mg ropinirole
F	67	4	2	27	50	62.5 mg madopar
F	74	7	2.5	13	300	200 mg sinemet, 3 mg ropinirole
M	69	5	2.5	21	200	250 mg madopar

F = Female; M = Male; mHY = modified Hoehn and Yahr scale; UPDRS = Unified Parkinson Disease Rating Scale; LED = Levodopa equivalent doses.

for the Parkinson's disease subjects. In addition, they received an acoustic feedback signal (via earphones) about foot clearance in the form of six different levels defined in 2 cm-intervals between 0 and 12 cm. A higher foot clearance was signalled by a higher pitched feedback tone. At the lowest level (optimal foot clearance, i.e. between 0 and 2 cm), a double-beep of a 125 and 1000 Hz sinusoidal signal (600 ms duration) was given. The other feedback signals consisted of a single beep (176, 250, 354, 500 or 707 Hz rectangular signal of 600 ms duration for the second lowest to the highest level, respectively). Furthermore, every obstacle hit was detected by the obstacle machine.

EMG recordings were made using surface electrodes from the tibialis anterior (TA) of the obstacle crossing leg (i.e. ipsilateral, i), the lateral part of the deltoideus (Del) and the biceps brachii (BB) muscles of both arms (ipsi- and contralateral, i and c) (cf. Michel *et al.*, 2008). The EMG signals were amplified, band-pass filtered (30–300 Hz) and transferred together with the biomechanical signals (impact right foot; foot clearance) to a PC via an analogue-to-digital converter. All signals were sampled at 1000 Hz. The EMG signals were rectified.

Recording protocol

The experiment duration was about 25 min and included 100 trials, with four different experimental conditions. Each condition was recorded 25 times in a randomized order and with a time

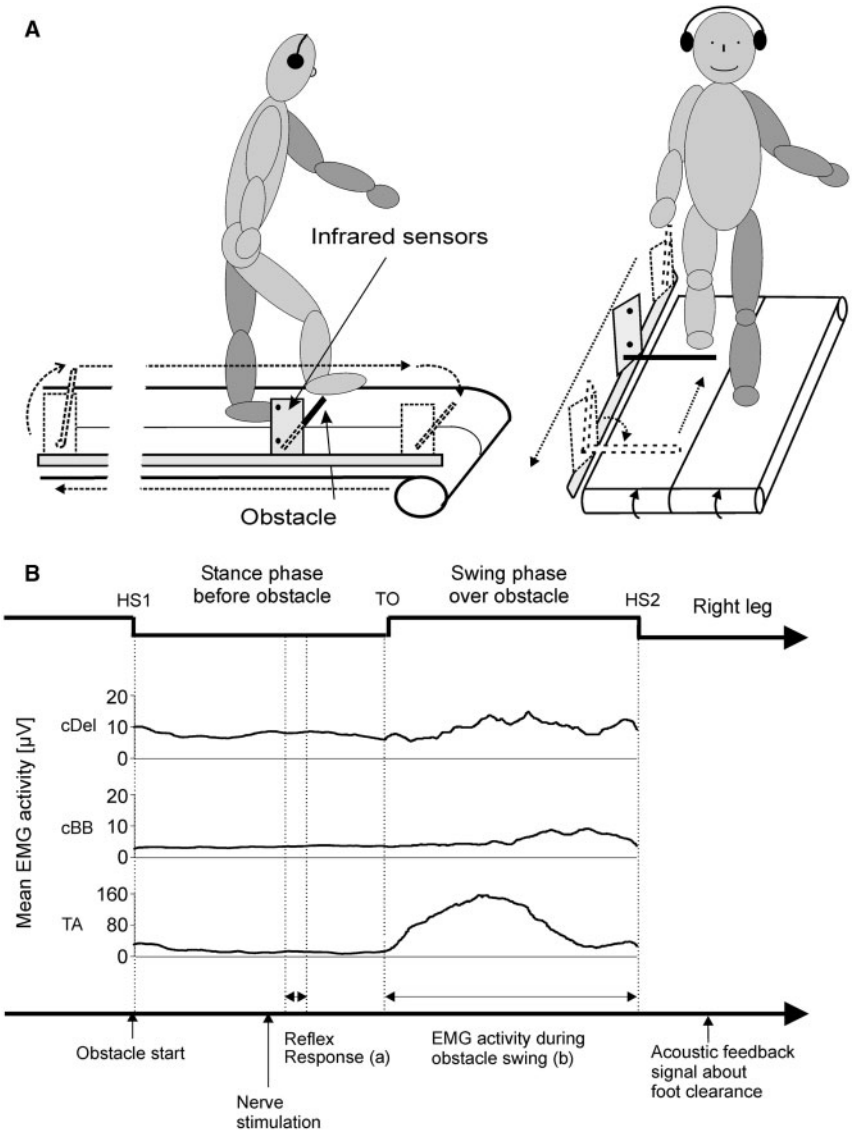

Fig. 1 Experimental setup. (**A**) Schematic experimental setup illustrating a subject on a treadmill stepping over an obstacle with the right leg leading and freely moving arms. (**B**) Illustration of the events during an obstacle step cycle with the mean EMG activity of TA and contralateral arm flexor muscles of all healthy subjects. At heel strike (HSI) the obstacle was randomly released and moved backwards with the treadmill. The SR was evoked at mid-stance before swing over the obstacle. (a) The SR response prior to the obstacle swing was determined. The background EMG activity prior to normal and obstacle swing was calculated for about the same time interval of the step cycle (without nerve stimulation). (b) The EMG activity during the swing phase of an obstacle step was analysed by calculating the RMS during swing phase, i.e. from toe off (TO) to heel strike (HS2). After leg swing over the obstacle, an acoustic feedback signal indicated foot clearance. cDel = contralateral deltoideus; cBB = contralateral biceps brachii.

interval that varied between 11–16 s (i.e. every 6–11 step cycles). The four different measurement conditions were: (i) *normal steps* without tibial nerve stimulation, for the analysis of background EMG activity; (ii) normal steps with nerve stimulation during mid-stance, for the analysis of SR responses; (iii) *obstacle steps* without nerve stimulation, for the analysis of background EMG activity; and (iv) obstacle steps with nerve stimulation during mid-stance, for the analysis of SR responses prior to obstacle steps.

Overall, the subjects had to step over the obstacle 50 times. Before the experiment, subjects adapted to walking on the treadmill without obstacle steps for about 10 min. A habituation of the SR responses was avoided by the introduction of a sufficient time delay between consecutive nerve stimulation (Shahani and Young, 1971).

SR recording

Throughout the experiment, SR were randomly evoked during the mid-stance phase of both normal and pre-obstacle steps. This was at a time when the subject became aware about the approaching obstacle (around 500 ms after the start of the obstacle), but before swing over the obstacle (cf. Fig. 1B). Two stimulation electrodes (Ambu, Ölstykke, Denmark) were placed at the medial side of the right ankle, where the posterior tibial nerve is closest to the skin (Roby-Brami and Bussel, 1987). The electrical stimulus consisted of a train of eight biphasic rectangular pulses (duration of the single stimulus 2 ms, frequency 200 Hz) with a total duration of 40 ms. By such a stimulus, SR responses could reliably be evoked in complete paraplegic (Muller and Dietz, 2006) and healthy (Michel *et al.*, 2008) subjects. In another study (Duysens *et al.*, 1990) the perception threshold was used to standardize the intensity of stimulation to evoke SR. Here the motor threshold (MT) was used, as this might provide a more objective criterion for the stimulus intensity, especially in Parkinson's disease subjects (Hiersemenzel *et al.*, 2000; Dietz *et al.*, 2001; Michel *et al.*, 2008). MT of the abductor hallucis muscle was determined with the subject in a standing condition. After the optimal stimulation site was determined, the electrode was firmly attached by surgical tape. Using this procedure, constant stimulus conditions can be expected (Duysens *et al.*, 1990). MT was determined by increasing the stimulus intensity until a twitch of the abductor hallucis muscle was visible. The stimulation intensity was set at $1.5 \times$ MT. This intensity is known to evoke non-nociceptive cutaneous reflexes (Yang and Stein, 1990).

To yield a net SR response, the average EMG traces of 25 normal and 25 obstacle steps without nerve stimulation were subtracted from each of normal and obstacle steps with stimulation, respectively. The onset and end of the SR response was determined by the EMG activity level that exceeded and returned to twice baseline activity following nerve stimulation. The strength of SR response was analysed by calculating the root mean square (RMS). The SR amplitude was normalized by dividing the SR RMS of each measurement by the average RMS of 25 normal steps (without nerve stimulation).

Obstacle stepping data

The force signal of the leading leg detected toe off, i.e. onset of swing over the obstacle, and heel strike after the obstacle step (HS2).

The RMS of all muscles was calculated during the swing phase over the obstacle (Fig. 1B) to determine the changes of EMG activity required to overcome the obstacle from the first to the last obstacle step. EMG activity during obstacle swing was normalized by dividing the RMS of each measurement by the average RMS during the swing phase of 25 normal steps without preceding nerve stimulation.

Data analysis and statistics

Changes in foot clearance, SR amplitude and EMG activity were analysed by evaluating their course over time. The adaptive rate was analysed by fitting a power function through the averaged data points of all subjects. One characteristic of a power function is that logarithmic transformation of both the number of trials and the performance results in a linear relationship ($y = b_0 + b_1 \times x$). The regression coefficient b_1 provides a quantification of the adaptive rate.

Statistical calculations were performed using a two-way ANOVA (analysis of variance) for repeated measures. To determine differences in SR response amplitudes (normalized RMS of iTA, iDel, iBB, cDel, cBB during mid-stance) between normal and obstacle steps, all SR responses were taken for analysis. The factors measurement condition (levels: normal steps and obstacle steps) and group (Parkinson's disease and age-matched control subjects) and their interaction were included in the model. To get a normal distribution of the data a logarithmic transformation of the data was performed prior to the analysis.

Similar models were used to determine differences in both the background EMG activity during mid-stance (mean values of each subject) and the EMG activity during swing phase.

Differences in foot clearance between Parkinson's disease and control subjects were analysed by taking the first (onset) and last (end) four steps of all subjects for analysis. The factors group (Parkinson's disease and age-matched control subjects) and condition (onset and end) and their interaction were included in the two-way ANOVA. Pair-wise comparisons were performed using Student's *t*-tests, and the *P*-values were adjusted for multiple comparisons using Bonferroni's correction. When an obstacle hit occurred, the data of that trial were removed from further analysis.

The relationship between the averaged reflex amplitudes prior to obstacle steps and EMG activity during swing over the obstacle was quantified using the Pearson's correlation coefficient for each muscle separately.

Results

In steps with tibial nerve stimulation during mid-stance, analysis of the SR behaviour was focused on comparisons between normal and obstacle steps in both subject groups and between Parkinson's disease and control subjects for each muscle separately. The steps without stimulation were taken to calculate the background EMG in normal and obstacle steps in both subject groups. All subjects were walking with free hanging arms. Arm movements, when present, were quite small as far as could be detected by visual inspection during task performance.

Course of task performance

Figure 2 shows the course of mean values of foot clearance (Fig. 2A), of SR amplitude evoked prior to obstacle

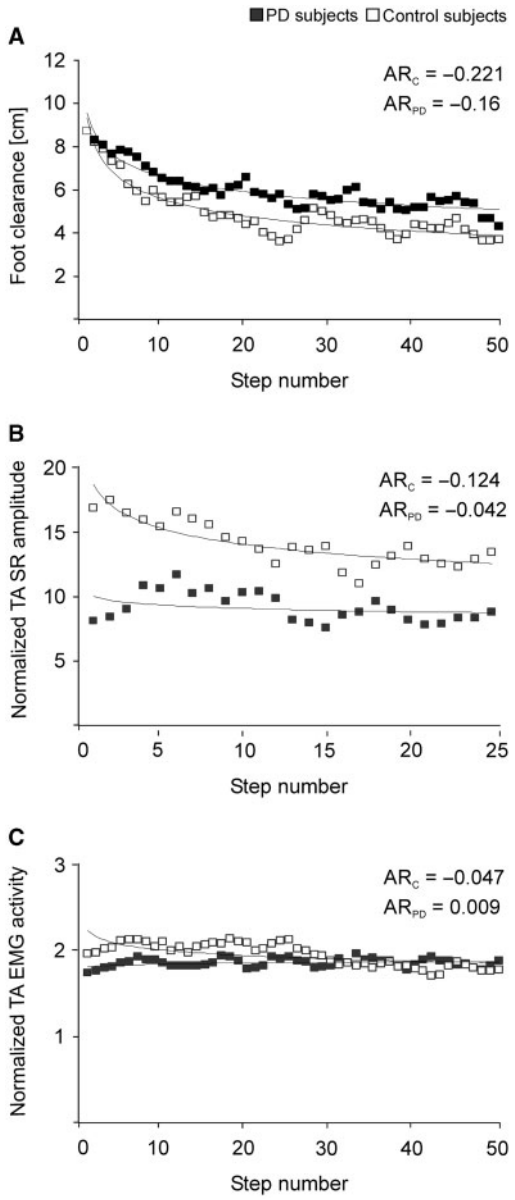

Fig. 2 Course of foot clearance, SR and EMG activity. Course of mean values of (**A**) foot clearance, (**B**) TA SR responses prior to obstacle swing and (**C**) TA EMG activity during obstacle swing for all subjects with Parkinson's disease and age-matched control subjects. The adaptive rates were calculated by fitting a power function through the averaged data points of all subjects over the course of the experiment. AR: adaptive rate; PD: Parkinson's diseases; C: controls.

swing (Fig. 2B), and of TA EMG activity (Fig. 2C) during obstacle swing in the two subject groups.

The mean values of foot clearance at the onset and end of the experiment differed between groups [$F(1,22) = 4.56$, $P = 0.044$]. In Parkinson's disease subjects foot clearance was only slightly higher at the onset, but significantly higher at the end of the experiment compared to age-matched control subjects (Fig. 2A; onset Parkinson's disease: 8.05 cm, controls: 7.97 cm, $P = 1.0$; end Parkinson's disease: 5.25 cm, controls: 3.85 cm, $P = 0.033$).

This was associated with a slightly lower adaptive rate in the Parkinson's disease subjects. The adaptive rates of TA SR amplitude and EMG trajectories (Fig. 2B and C) were also slightly lower in the group of Parkinson's disease subjects. The Del and BB SR amplitudes of both sides showed similar adaptation rates (mean SR adaptive rates of all arm muscles amounted to −0.092 for Parkinson's disease and −0.201 for healthy subjects). No adaptation occurred in the arm muscle activity during obstacle swing (mean EMG activity adaptive rate for all arm muscles amounted to −0.013 for Parkinson's disease and −0.045 for healthy subjects). There was no significant difference in all adaptation rates of the above measures between Parkinson's disease and healthy subjects.

The Parkinson's disease subjects walked with a slightly higher cadence (0.88/s, SD = 0.09) than the age-matched control subjects (0.80/s, SD = 0.08; $P = 0.039$).

The average number of obstacle hits was three (SD = 1.88, range 0–7) for Parkinson's disease and four (SD = 2.97; range 0–9) for age-matched subjects. There was no statistical difference between the groups.

SR activity prior to obstacle swing

Figure 3 shows the mean values of the averaged SR responses to right tibial nerve stimulation in proximal arm muscles of both sides prior (mid-stance) to normal and right leg obstacle swing in the group of Parkinson's disease (Fig. 3A) and age-matched (Fig. 3B) subjects. In both subject groups and in all muscles, reflex amplitudes were significantly greater prior to obstacle stepping compared to normal leg swing (except iDel of control subjects). This was also the case in the iTA ($P < 0.01$; not shown).

The SR onset latencies in the TA muscle were in the range from 80 to 131 ms (mean = 98 ± 15) for Parkinson's disease and from 70 to 115 ms (mean = 88 ± 13) for age-matched subjects. For the SR latencies in the upper limbs, the values of all arm muscles were taken together. The SR onset latencies prior to normal and obstacle steps were in the range from 65 to 125 ms (mean = 100 ± 15) for Parkinson's disease and from 54 to 123 ms (mean = 91 ± 18) for age-matched subjects. There was no significant difference in SR latency between normal and obstacle steps and between Parkinson's disease and healthy subjects.

Figure 4 shows the mean values of the normalized SR responses prior to normal and obstacle swing obtained from the two subject groups. In all arm muscles (except for iBB obstacle and cBB normal steps) the SR amplitude was larger in Parkinson's disease than in the control subjects (cf. see also Fig. 2A). This difference was greatest for the i and cDel prior to obstacle steps. In contrast, in the iTA, the SR was significantly smaller prior to normal and obstacle steps in Parkinson's disease compared with the control subjects.

The difference in SR amplitude between Parkinson's disease and control subjects occurred independent from the background EMG of arm muscles during mid-stance

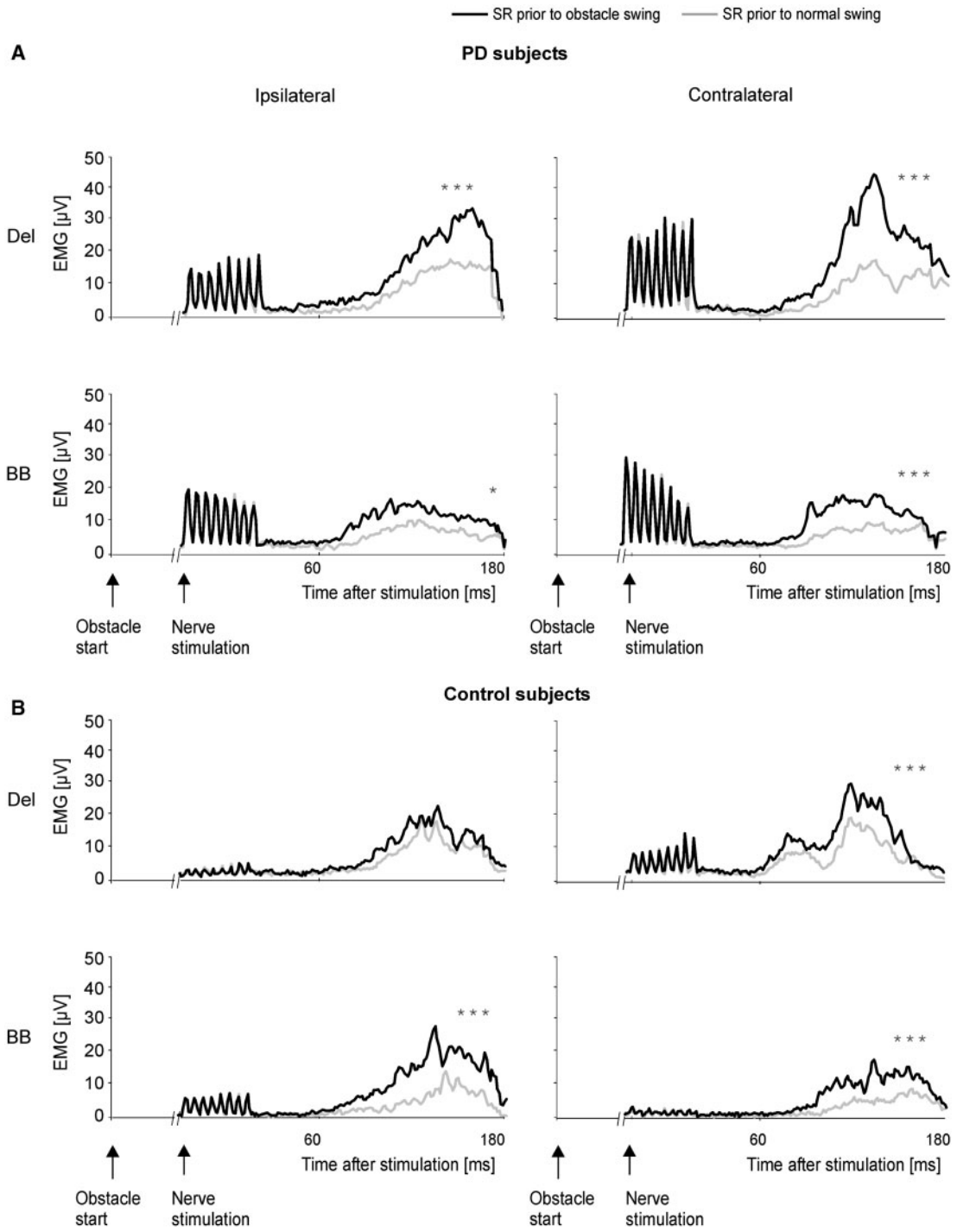

Fig. 3 SR response prior to normal and obstacle steps. Grand means of the rectified and subtracted (from background EMG activity) SR response in the proximal arm flexor muscles prior to normal (thin line) and obstacle (thick line) swing. (**A**) Subjects with Parkinson's disease and (**B**) age-matched control subjects. The reflex was randomly evoked by right tibial nerve stimulation at mid-stance. The SR response was determined by the EMG activity level that exceeded and returned to twice baseline activity following nerve stimulation and was quantified by calculating the RMS. Data of obstacle hits were removed. Significant differences between normal and obstacle steps are indicated by asterisk ($^{*}P \leq 0.05$, $^{***}P \leq 0.001$).

(without stimulation). The background activity differed neither between normal and obstacle steps of both subjects groups nor between Parkinson's disease and control subjects (when the values of all arm muscles were taken together: Parkinson's disease subjects, normal steps: mean 8.9 μV, range 7.3–10.6; obstacle steps: mean 11.1 μV, range 7.9–13.7; control subjects, normal steps: mean 8.7 μV, range 5.8–12.1; obstacle steps mean 9.4 μV, range 6.5–13.4).

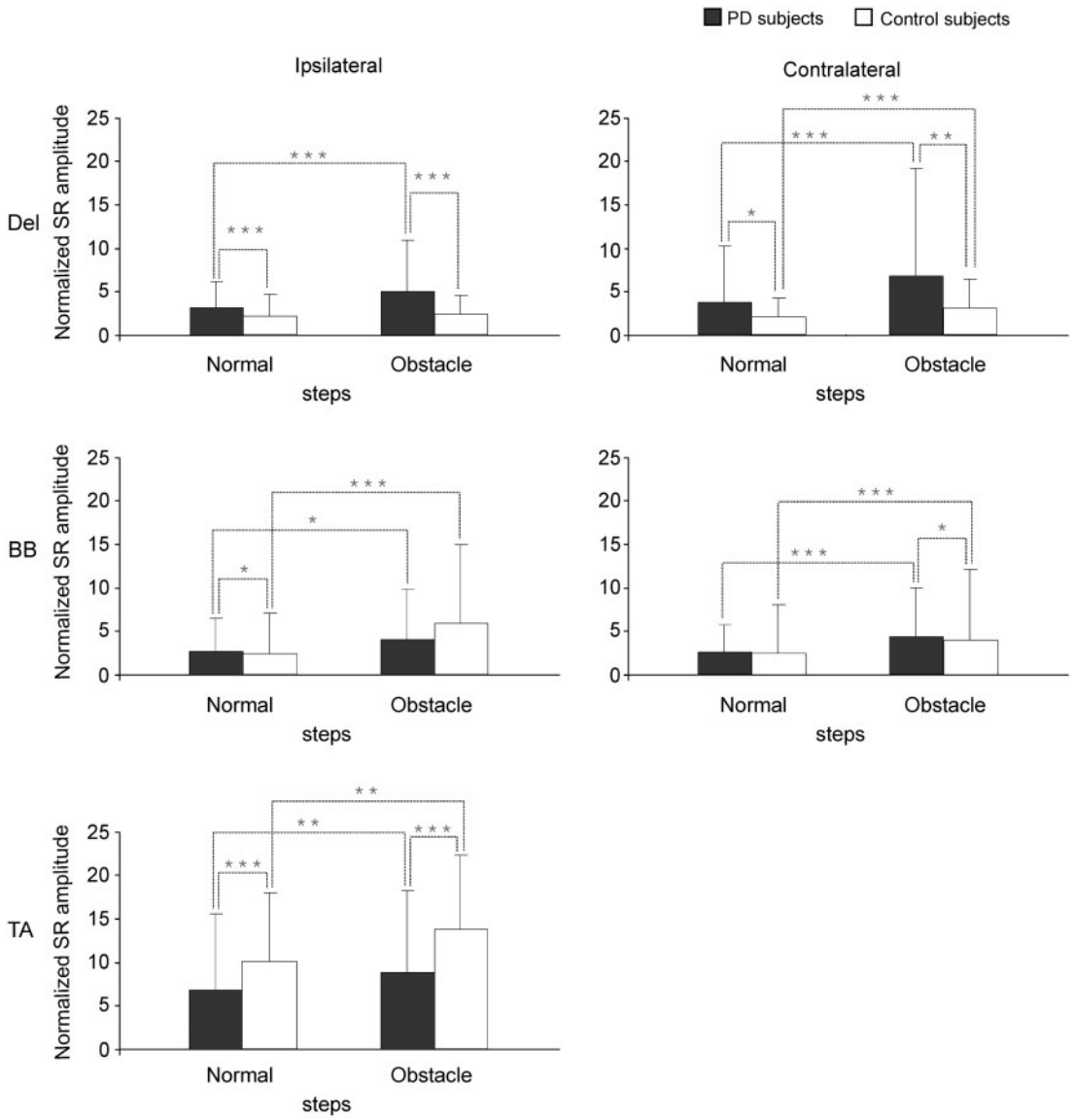

Fig. 4 SR amplitude prior to normal and obstacle swing. Grand mean values of the normalized RMS of the SR amplitude in proximal arm and right leg muscles prior to normal and obstacle swing for subjects with Parkinson's disease and age-matched control subjects. Significant differences are indicated by asterisk ($^{*}P \leq 0.05$, $^{**}P \leq 0.01$, $^{***}P \leq 0.001$).

Muscle activation during obstacle swing

Figure 5 shows the mean values of the EMG activity in the proximal arm and the iTA muscles during normal and obstacle swing in the two subject groups. In all arm and the TA muscles, the EMG activity was significantly larger during obstacle compared with normal swing ($P<0.001$), but did not differ between Parkinson's disease and control subjects (cf. Fig. 2C).

A significant correlation was found between the course of SR responses prior and the EMG activity during obstacle swing during the experiment for the cBB in Parkinson's disease subjects ($r=0.44$; $P=0.026$) and for the cDel in Parkinson's disease and control subjects ($r=0.46$; $P=0.020$ and $r=0.50$; $P=0.01$, respectively). In all other muscles, no significant correlations were found between the course of SR responses prior and the EMG activity during obstacle swing.

Discussion

The aim of this study was to evaluate whether quadrupedal limb coordination is involved in impaired locomotion in Parkinson's disease subjects. The main observations were the following: (i) during obstacle steps, foot clearance was slightly higher and adaptation lower in Parkinson's disease compared with age-matched subjects; (ii) in both subject groups an enhanced activation of spinal interneuronal circuits (mediating the SR) with a quadrupedal distribution

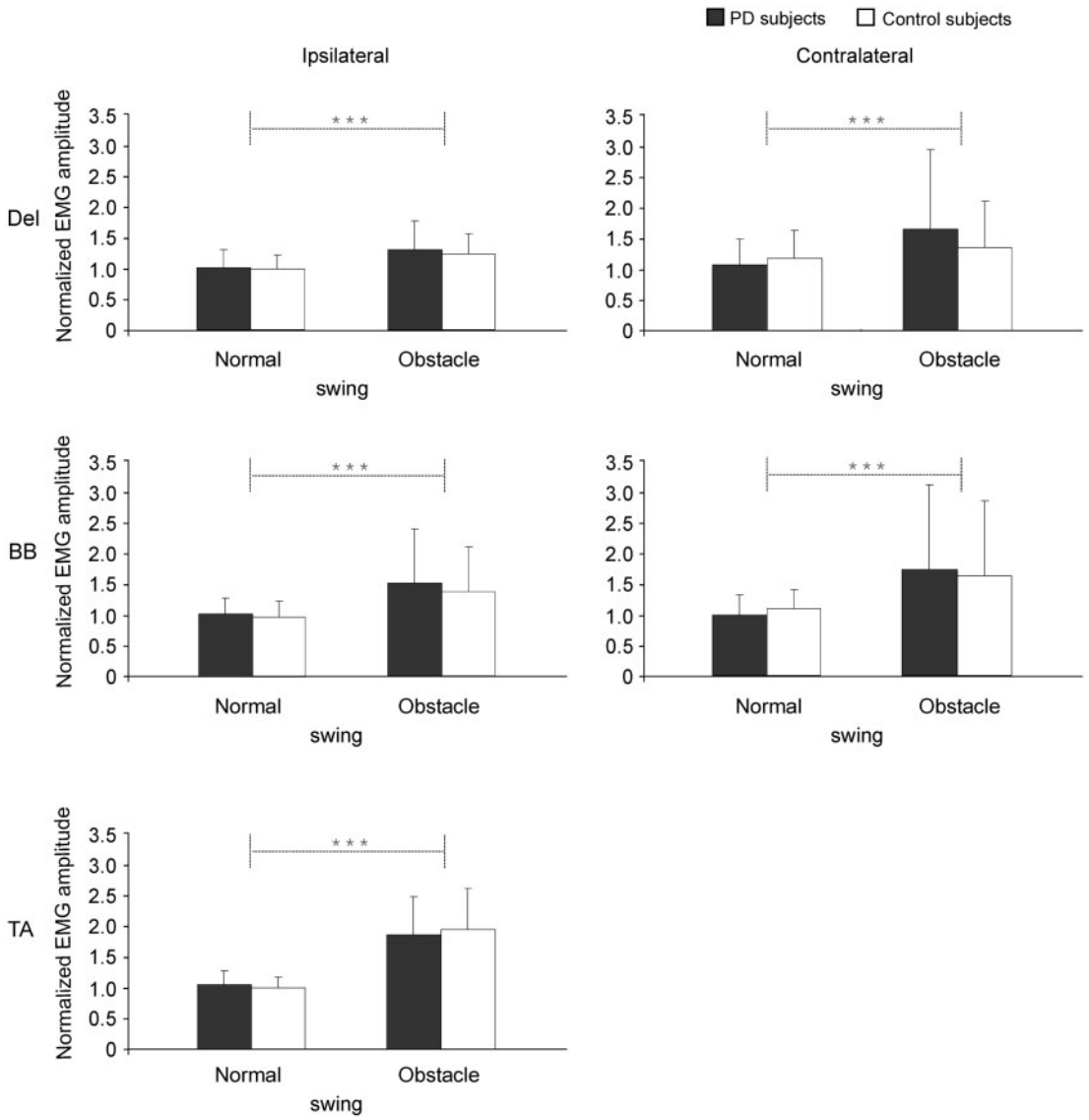

Fig. 5 EMG activity during normal and obstacle swing. Grand mean values of the normalized RMS of the EMG activity in proximal arm and right leg muscles during normal and obstacle swing for subjects with Parkinson's disease and age-matched control subjects. Significant differences are indicated by asterisk ($^{***}P \leq 0.001$).

was present prior to an obstacle step compared with a normal leg swing; (iii) the SR amplitude in the arm flexors was greater in Parkinson's disease compared to age-matched subjects, but smaller in the ipsilateral TA; and (iv) the EMG activity in the arm and TA muscles was greater during obstacle compared with normal swing. However, this did not differ between Parkinson's disease and the control subjects.

Performance of obstacle stepping

In line with earlier reports (van Hedel *et al.*, 2006) subjects with moderate Parkinson's disease perform obstacle stepping almost as well as age-matched healthy subjects, with the exception of a slightly higher foot clearance during obstacle steps and less adaptation. Compared to young subjects (Michel *et al.*, 2007, 2008), elderly healthy subjects also show a poorer performance. This fits with the observation that elderly people have an increased risk of falls (Dietz and Colombo, 1998; Nieuwenhuijzen *et al.*, 2006).

Upper limb muscle involvement

The question underlying this study was to what extent upper limb muscles are involved in keeping body balance during an obstacle stepping task in Parkinson's disease subjects. When balancing over a small support surface it is obvious that upper trunk and limb movements are required to hold the body over the feet. As shown recently in young healthy subjects, this is also the case during obstacle steps (Michel *et al.*, 2008). Especially, contralateral arm flexor muscles are involved in such precision locomotor tasks to

maintain body balance (Grin *et al.*, 2007). An upper limb involvement in the performance of such a task was further supported by the fact that when subjects were partially unloaded during the obstacle task (i.e. when the body was stabilized), no enhanced arm muscle activity occurred (Michel *et al.*, 2008).

In the present study no relevant arm movements were detected (no mechanical recordings). However, proximal arm muscle activation was stronger (especially in the functionally relevant contralateral BB, cf. Grin *et al.*, 2007) during swing over the obstacle but did not differ between Parkinson's disease and elderly control subjects. Therefore, the contribution of upper limb muscle activation to the performance of the precision locomotor task was similar in both subject groups, despite the slightly worse performance of the task by Parkinson's disease subjects. Compared to young healthy subjects (Michel *et al.*, 2008), the increase of arm muscle EMG during obstacle swing was small in both subject groups investigated here. This attenuated modulation of arm muscle activity by the obstacle task (clinically probably reflected in a reduced arm swing) might have contributed to the worse performance compared to the young healthy subjects (Michel *et al.*, 2008).

Anticipatory spinal neuronal activity

Gastrocnemius H-reflex amplitude is only transiently increased during obstacle stepping (Hess *et al.*, 2003). In contrast, the SR in the TA is enhanced throughout the entire experiment when evoked prior to an obstacle compared with normal step swing. It was assumed that this SR facilitation assists in performing but not during learning an obstacle-avoidance task (Michel *et al.*, 2007). SR responses to tibial nerve stimulation appear not only in leg but also in arm muscles during walking but not during standing or writing (Dietz *et al.*, 2001). This suggests a quadrupedal coordination of human locomotion (for review see Dietz, 2002).

The SR paradigm used in the present study assessed the activity of spinal interneurons (presumably long propriospinal neurons) during mid-stance, i.e. prior to normal and obstacle swing. The assumption that an essential part of the reflex responses recorded here is mediated by a spinal pathway rather than a transcortical pathway (cf. Christensen *et al.*, 1999) was discussed in an earlier paper (Michel *et al.*, 2008). A spinal pathway was suggested on the basis of the appearance of corresponding responses in subjects suffering a complete spinal cord injury (Muller and Dietz, 2006). The response latencies corresponded to the SR latencies in the TA and arm muscles found here.

According to the timing of the SR modulation after release of the obstacle, the anticipatory neuronal activity is assumed to be facilitated by a cortico-spinal signal, evoked by the awareness of the approaching obstacle (Michel *et al.*, 2007). Therefore, this anticipatory SR activity resembles the 'readiness brain potentials' preceding voluntary arm movements (Shibasaki and Hallett, 2006). It is assumed that the spinal neuronal activity, reflected in the SR, is enhanced in preparation of ensuing voluntary limb muscle activation during task execution (Michel *et al.*, 2008). In this study, the SR in both subject groups was larger prior to obstacle step compared to normal swing, i.e. this mechanism appears to be basically preserved in Parkinson's disease subjects.

Transformation of anticipatory to executory activity

In Parkinson's disease compared with age-matched subjects the SR activity was enhanced in the arm flexor muscles prior to normal and, more pronounced, obstacle swing. In young healthy subjects, the following muscle activation during obstacle swing took a similar course and strength as the preceding SR (Michel *et al.*, 2008). In this study the course of SR was only reflected in the EMG activity of some arm muscles in both subject groups. However, the strength of EMG activity in arm and leg muscles during normal and obstacle swing was similar in Parkinson's disease and elderly control subjects. It is suggested that Parkinson's disease subjects produce a stronger facilitation of spinal interneuronal activity in the preparatory phase prior to obstacle swing that leads to an enhanced SR. Thus, in contrast to our hypothesis, Parkinson's disease subjects use a quadrupedal limb coordination. The enhanced spinal neuronal activity might be required to achieve an appropriate arm muscle activation during task performance or might be directed to automatically compensate for the inherently reduced arm swing in Parkinson's disease subjects.

In contrast to the arm muscles, the TA SR was smaller in Parkinson's disease compared to age-matched subjects, but was followed by a relatively high TA EMG activity in both normal and obstacle steps. This discrepancy might first be due to a dominance of a cortico-spinal activation of leg flexors (probably due to a defective leg extensor activation) during locomotion of Parkinson's disease subjects (Dietz and Colombo, 1998). Parkinson's disease subjects strongly depend on a visual control of locomotion (Schubert *et al.*, 2005). Therefore, the visuo-motor/cortico-spinal control of leg movements might be more pronounced in Parkinson's disease compared with the control subjects. Second, a higher foot clearance was associated with a strong TA activity in Parkinson's disease subjects. The voluntary command to the prime mover to overcome the obstacle with a high safety margin might override the automatic control by spinal interneuronal circuits (represented by the SR) in the lower limbs. Third, the discrepancy between SR and muscle activity in upper and lower limbs in Parkinson's disease subjects might indicate an unbalance in the coupling of cervico-thoraco-lumbar interneuronal circuits: An enhanced cortical control of the prime movers (reflected in a high TA EMG but relatively low SR amplitude) occurs during obstacle swing, while a more automatic control of upper limbs during stepping remains preserved. A combination of the above mechanisms seems to be most likely.

Quadrupedal limb coordination in Parkinson's disease subjects

There is an increasing evidence for a neuronal coupling of upper and lower limbs during locomotor-like tasks in human beings (Dietz, 2002; Haridas and Zehr, 2003; Zehr *et al.*, 2007). However, only a few studies deal with this aspect in Parkinson's disease (Carpinella *et al.*, 2007). The known mechanisms contributing to the locomotor disorder in elderly people and Parkinson's disease subjects include an insufficient activation of leg extensor muscles (Dietz and Colombo, 1998) and a poor adaptation to environmental influences by a defective proprioceptive feedback (Rogers, 1996). The observations made here indicate that also an impaired quadrupedal neuronal coordination might contribute to the locomotor disorder in Parkinson's disease. Nevertheless, the results do not allow to speculate about their possible contribution to phenomena of Parkinson's disease, such as gait freezing. According to our study, the goal to treat the gait disorder in Parkinson's disease could be to strengthen the quadrupedal coordination of arm/leg muscle activation during the execution of specific locomotor tasks.

Acknowledgements

We would like to thank Dr Martin Schubert and Dr Huub van Hedel for their helpful comments and Rachel Jurd for editorial assistance. Part of the clinical data was provided by the Department of Neurology of the University Hospital Zürich.

Funding

Swiss National Science Foundation (32-105324); the National Center of Competence (NCCR) in Zurich.

References

Burleigh-Jacobs A, Horak FB, Nutt JG, Obeso JA. Step initiation in Parkinson's disease: influence of levodopa and external sensory triggers. Mov Disord 1997; 12: 206–15.

Carpinella I, Crenna P, Marzegan A, Rabuffetti M, Rizzone M, Lopiano L, et al. Effect of L-dopa and subthalamic nucleus stimulation on arm and leg swing during gait in Parkinson's disease. Conference Proceedings: Annual International Conference of the IEEE Engineering in Medicine & Biology Society 2007; 2007. p. 6665–8.

Christensen LO, Morita H, Petersen N, Nielsen J. Evidence suggesting that a transcortical reflex pathway contributes to cutaneous reflexes in the tibialis anterior muscle during walking in man. Exp Brain Res 1999; 124: 59–68.

Dietz V. Do human bipeds use quadrupedal coordination? Trends Neurosci 2002; 25: 462–7.

Dietz V, Colombo G. Influence of body load on the gait pattern in Parkinson's disease. Mov Disord 1998; 13: 255–61.

Dietz V, Fouad K, Bastiaanse CM. Neuronal coordination of arm and leg movements during human locomotion. Eur J Neurosci 2001; 14: 1906–14.

Duysens J, Trippel M, Horstmann GA, Dietz V. Gating and reversal of reflexes in ankle muscles during human walking. Exp Brain Res 1990; 82: 351–8.

Erni T, Dietz V. Obstacle avoidance during human walking: learning rate and cross-modal transfer. J Physiol 2001; 534: 303–12.

Grin L, Frank J, Allum JH. The effect of voluntary arm abduction on balance recovery following multidirectional stance perturbations. Exp Brain Res 2007; 178: 62–78.

Haridas C, Zehr EP. Coordinated interlimb compensatory responses to electrical stimulation of cutaneous nerves in the hand and foot during walking. J Neurophysiol 2003; 90: 2850–61.

Hess F, Van Hedel HJ, Dietz V. Obstacle avoidance during human walking: H-reflex modulation during motor learning. Exp Brain Res 2003; 151: 82–9.

Hiersemenzel LP, Curt A, Dietz V. From spinal shock to spasticity: neuronal adaptations to a spinal cord injury. Neurology 2000; 54: 1574–82.

Jackson GM, Jackson SR, Hindle JV. The control of bimanual reach-to-grasp movements in hemiparkinsonian patients. Exp Brain Res 2000; 132: 390–8.

Majsak MJ, Kaminski T, Gentile AM, Flanagan JR. The reaching movements of patients with Parkinson's disease under self-determined maximal speed and visually cued conditions. Brain 1998; 121 (Pt 4): 755–66.

Michel J, van Hedel HJ, Dietz V. Facilitation of spinal reflexes assists performing but not learning an obstacle-avoidance locomotor task. Eur J Neurosci 2007; 26: 1299–306.

Michel J, van Hedel HJ, Dietz V. Obstacle stepping involves spinal anticipatory activity associated with quadrupedal limb coordination. Eur J Neurosci 2008; 27: 1867–75.

Morris M, Iansek R, Matyas T, Summers J. Abnormalities in the stride length-cadence relation in Parkinsonian gait. Mov Disord 1998; 13: 61–9.

Morris ME, Iansek R, Matyas TA, Summers JJ. Ability to modulate walking cadence remains intact in Parkinson's disease. J Neurol Neurosurg Psychiatry 1994; 57: 1532–4.

Muller R, Dietz V. Neuronal function in chronic spinal cord injury: divergence between locomotor and flexion- and H-reflex activity. Clin Neurophysiol 2006; 117: 1499–507.

Nieuwenhuijzen PH, Horstink MW, Bloem BR, Duysens J. Startle responses in Parkinson patients during human gait. Exp Brain Res 2006; 171: 215–24.

Plotnik M, Giladi N, Hausdorff JM. A new measure for quantifying the bilateral coordination of human gait: effects of aging and Parkinson's disease. Exp Brain Res 2007; 181: 561–70.

Roby-Brami A, Bussel B. Long-latency spinal reflex in man after flexor reflex afferent stimulation. Brain 1987; 110 (Pt 3): 707–25.

Rogers MW. Disorders of posture, balance, and gait in Parkinson's disease. Clin Geriatr Med 1996; 12: 825–45.

Rogers MW, Kukulka CG, Soderberg GL. Postural adjustments preceding rapid arm movements in Parkinsonian subjects. Neurosci Lett 1987; 75: 246–51.

Sandrini G, Serrao M, Rossi P, Romaniello A, Cruccu G, Willer JC. The lower limb flexion reflex in humans. Prog Neurobiol 2005; 77: 353–95.

Schubert M, Prokop T, Brocke F, Berger W. Visual kinesthesia and locomotion in Parkinson's disease. Mov Disord 2005; 20: 141–50.

Shahani BT, Young RR. Human flexor reflexes. J Neurol Neurosurg Psychiatry 1971; 34: 616–27.

Shibasaki H, Hallett M. What is the Bereitschaftspotential? Clin Neurophysiol 2006; 117: 2341–56.

Swinnen SP, Duysens J. Neuro-behavioral determinants of interlimb coordination: a multidisciplinary approach. Boston: Kluwer Academic; 2004.

Swinnen SP, Van Langendonk L, Verschueren S, Peeters G, Dom R, De Weerdt W. Interlimb coordination deficits in patients with Parkinson's disease during the production of two-joint oscillations in the sagittal plane. Mov Disord 1997; 12: 958–68.

van Hedel HJ, Biedermann M, Erni T, Dietz V. Obstacle avoidance during human walking: transfer of motor skill from one leg to the other. J Physiol 2002; 543: 709–17.

van Hedel HJ, Waldvogel D, Dietz V. Learning a high-precision locomotor task in patients with Parkinson's disease. Mov Disord 2006; 21: 406–11.

Winogrodzka A, Wagenaar RC, Booij J, Wolters EC. Rigidity and bradykinesia reduce interlimb coordination in Parkinsonian gait. Arch Phys Med Rehabil 2005; 86: 183–9.

Yang JF, Stein RB. Phase-dependent reflex reversal in human leg muscles during walking. J Neurophysiol 1990; 63: 1109–17.

Zehr EP, Klimstra M, Dragert K, Barzi Y, Bowden MG, Javan B, et al. Enhancement of arm and leg locomotor coupling with augmented cutaneous feedback from the hand. J Neurophysiol 2007; 98: 1810–14.