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

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

Running title: Interlimb coordination in Parkinson's disease

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Abstract

Quadrupedal limb coordination during human walking was recently shown to be up-regulated 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 (PD) 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 PD than in control subjects. The anticipatory SR in the arm muscles *prior* to normal and obstacle steps was larger in PD compared to age-matched subjects, but smaller in the tibialis anterior (TA). The arm and leg muscle activation was stronger *during* obstacle compared to normal swing but did not differ between PD and age-matched subjects. These observations indicate that quadrupedal limb coordination is basically preserved in PD subjects. Our data are consistent with the proposal that in PD 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 TA the SR is attenuated presumably because of a stronger voluntary (i.e. cortical) control of leg movements.

Introduction

Movement disorder is a prominent feature of Parkinson's disease (PD) (Burleigh-Jacobs *et al.*, 1997; Morris *et al.*, 1998; Rogers, 1996). 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 PD 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 (Carpinella *et al.*, 2007; Winogrodzka *et al.*, 2005) or the interleg coordination (Plotnik *et al.*, 2007) during locomotion in PD 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) 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 PD subjects, or, alternatively, whether this mechanism contributes to the locomotor disorder in PD. For this, the quadrupedal distribution of electromyographic (EMG) responses to unilateral tibial nerve stimulation was analyzed *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 PD subjects (Sandrini *et al.*, 2005).

The following hypotheses were tested: 1. A poorer acquisition and performance of the precision locomotor task occurs in PD compared to age-matched subjects; 2. 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. 3. 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 PD (4 females, see table I) and 12 age-matched healthy subjects (3 females) participated. All PD subjects included were able to perform the obstacle stepping task. In table I the severity of

PD, rated according to established scores, and the actual individual treatment are described for all participating PD subjects.

The average age of the PD patients was 65.3 years (standard deviation (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 I).

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 (figure 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 (figure 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 obsta-

cle. An improvement of performance during obstacle stepping was defined by the following criteria (cf. Erni and Dietz, 2001): (1) a lower level of foot clearance or (2) 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 for the PD subjects. In addition, they received an acoustic feedback signal (via earphones) about foot clearance in the form of 6 different levels defined in 2 cm-intervals between 0 and 12 cm. A higher foot clearance was signaled 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 tibials 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 minutes and included 100 trials, with 4 different experimental conditions. Each condition was recorded 25 times in a randomized order and with a time interval that varied between 11 to 16 seconds (i.e. every 6 to 11 step cycles). The four different measurement conditions were: (1) *normal steps* without tibial nerve stimulation, for the analysis of background EMG activity, (2) normal steps with nerve stimulation during mid-stance, for the analysis of SR responses, (3) *obstacle steps* without nerve stimulation, for the analysis of background EMG activity and (4) 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 minutes. A habituation of the SR responses was avoided by the introduction of a sufficient time delay between consecutive nerve stimulation (Shahani and Young, 1971).

Spinal reflex recording

Throughout the experiment, spinal reflexes (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 PD subjects (Dietz *et al.*, 2001; Hiersemenzel *et al.*, 2000; 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 x 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 (TO), 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 (see 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 2-way analysis of variance (ANOVA) 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 (PD 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 PD and control subjects were analysed by taking the first (onset) and last (end) 4 steps of all subjects for analysis. The factors group (PD and age-matched control subjects) and condition (onset and end) and their interaction were included in the 2-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 PD 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 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 PD 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 PD: 8.05 cm, controls: 7.97 cm, $P = 1.0$; end PD: 5.25 cm, controls: 3.85 cm, $P=0.033$).

This was associated with a slightly lower adaptive rate in the PD subjects. The adaptive rates of TA SR amplitude and EMG trajectories (fig. 2 B and C) were also slightly lower in the group of PD 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 PD 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 PD and -0.045 for healthy subjects). There was no significant difference in all adaptation rates of the above measures between PD and healthy subjects.

The PD 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 3 (SD = 1.88, range, 0 – 7) for PD and 4 (SD = 2.97; range, 0 – 9) for age-matched subjects. There was no statistical difference between the groups.

Spinal reflex 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 PD (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 PD 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 PD 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 PD 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 PD than in the control subjects (cf. 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 PD compared to the control subjects.

The difference in SR amplitude between PD and control subjects occurred independent from the background EMG of arm muscles during mid-stance (without stimulation). The background activity differed neither between normal and obstacle steps of both subjects groups nor between PD and control subjects (when the values of all arm muscles were taken together: PD 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).

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 to normal swing ($P < 0.001$), but did not differ between PD 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 PD subjects ($r = 0.44$; $P = 0.026$) and for the cDel in PD 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 PD subjects. The main observations were the following: 1. During obstacle steps, foot clearance was slightly higher and adaptation lower in PD compared to age-matched subjects. 2. In both subject groups an enhanced activation of spinal interneuronal circuits (mediating the SR) with a quadrupedal distribution was present *prior* to an obstacle step compared to a normal leg swing. 3. The SR amplitude in the arm flexors was greater in PD compared to age-matched subjects, but smaller in the ipsilateral TA. 4. The EMG activity in the arm and TA muscles was greater during obstacle compared to normal swing. However, this did not differ between PD and the control subjects.

Performance of obstacle stepping

In line with earlier reports (van Hedel *et al.*, 2006) subjects with moderate PD 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; Michel *et al.*, 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 PD 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 PD 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 PD 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 to 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). This corresponds 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 PD subjects.

Transformation of anticipatory to executory activity

In PD compared to 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 only the course of SR was 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 PD and elderly control subjects. It is suggested that PD 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, PD 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 PD subjects.

In contrast to the arm muscles, the TA SR was smaller in PD 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 PD subjects (Dietz and Colombo, 1998). PD 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 PD compared to the control subjects. Second, a higher foot clearance was associated with a strong TA activity in PD 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 PD 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 PD 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 PD (Carpinella *et al.*, 2007). The known mechanisms contributing to the locomotor disorder in elderly people and PD 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 PD. Nevertheless, the results do not allow to speculate about their possible contribution to phenomena of PD, such as gait freezing. According to our study, the goal to treat the gait disorder in PD could be to strengthen the quadrupedal coordination of arm/leg muscle activation during the execution of specific locomotor tasks.

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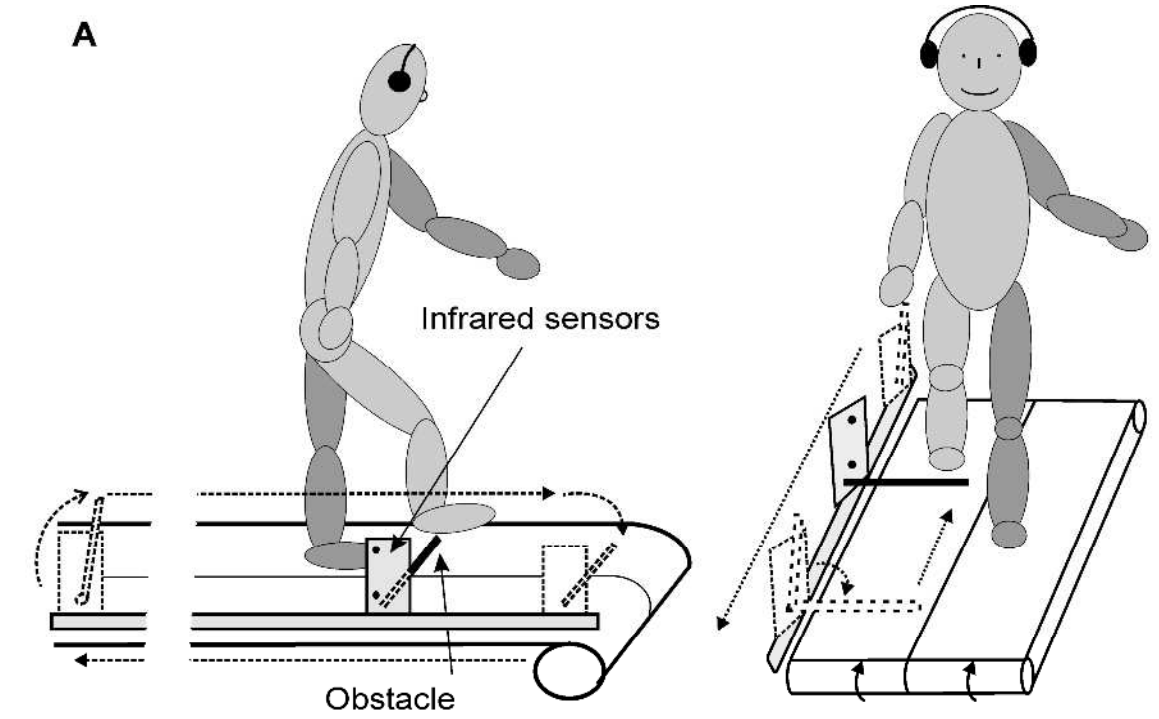
Table I. Clinical characteristics of PD subjects

Sex	Age (y)	Duration of PD (y)	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; PD = Parkinson's disease; mHY = modified Hoehn and Yahr scale; UPDRS = Unified Parkinson Disease Rating Scale; LED = Levodopa equivalent doses


A
Infrared sensors
Obstacle

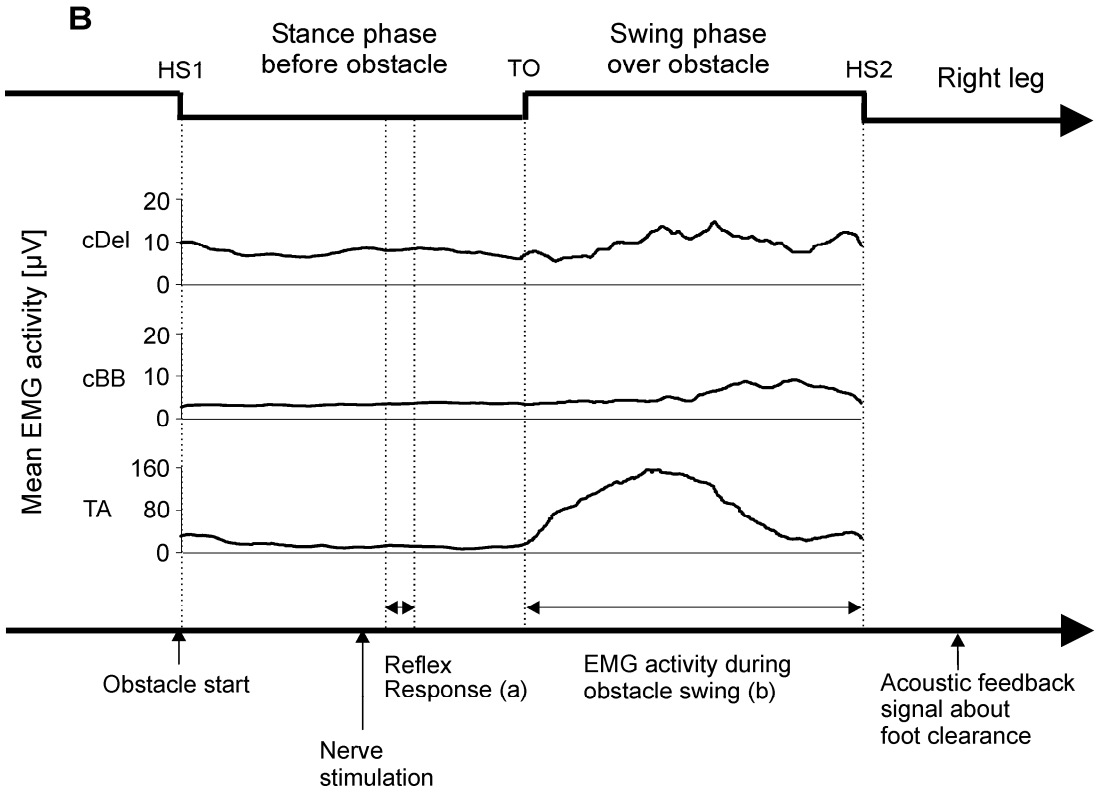

B
Stance phase
before obstacle
Swing phase
over obstacle
HS1
TO
HS2
Right leg
Mean EMG activity [µV]
cDel
cBB
TA
20
10
0
160
80
Obstacle start
Reflex
Response (a)
Nerve
stimulation
EMG activity during
obstacle swing (b)
Acoustic feedback
signal about
foot clearance

Figure 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 (HS1) the obstacle was randomly released and moved backwards with the treadmill. The spinal reflex (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.

Abbreviations: cDel = contralateral deltoideus, cBB = contralateral biceps brachii, TA = tibialis anterior muscle.

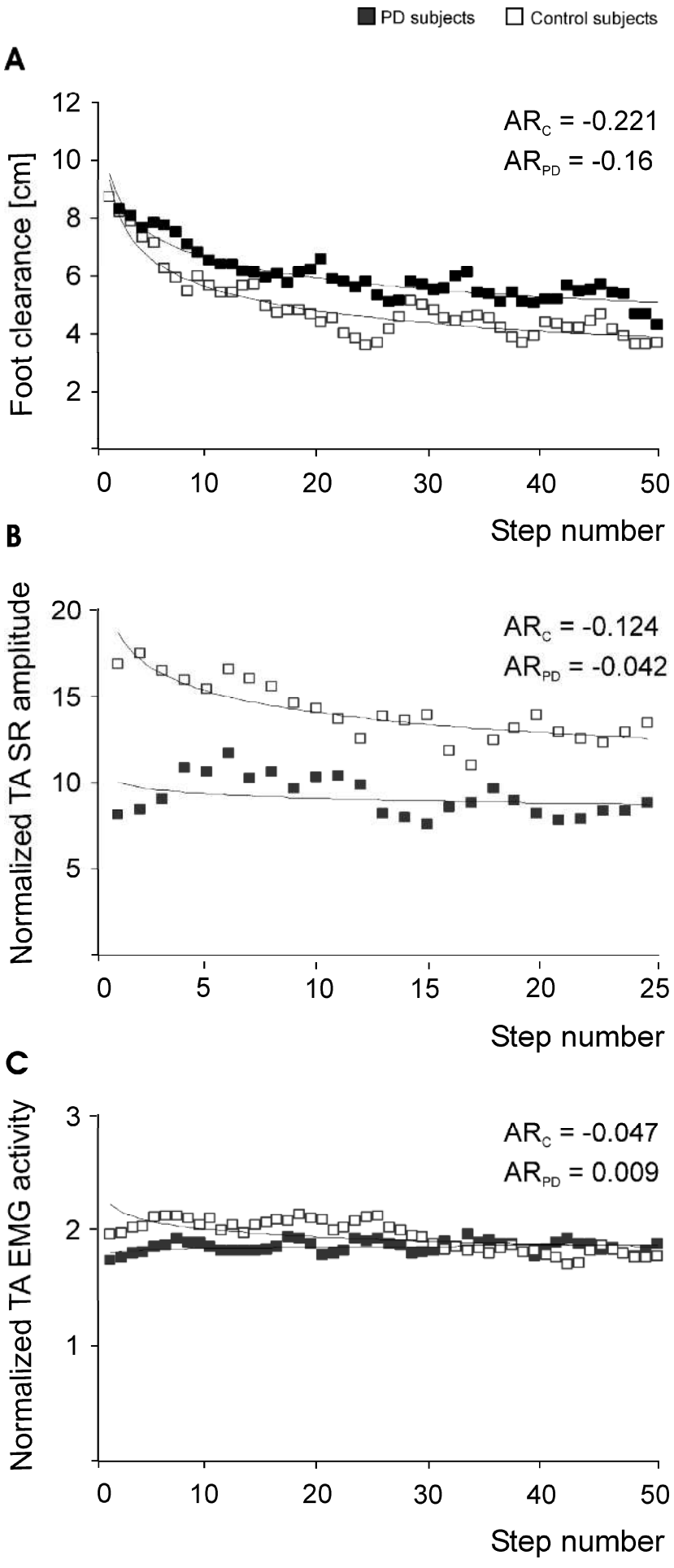
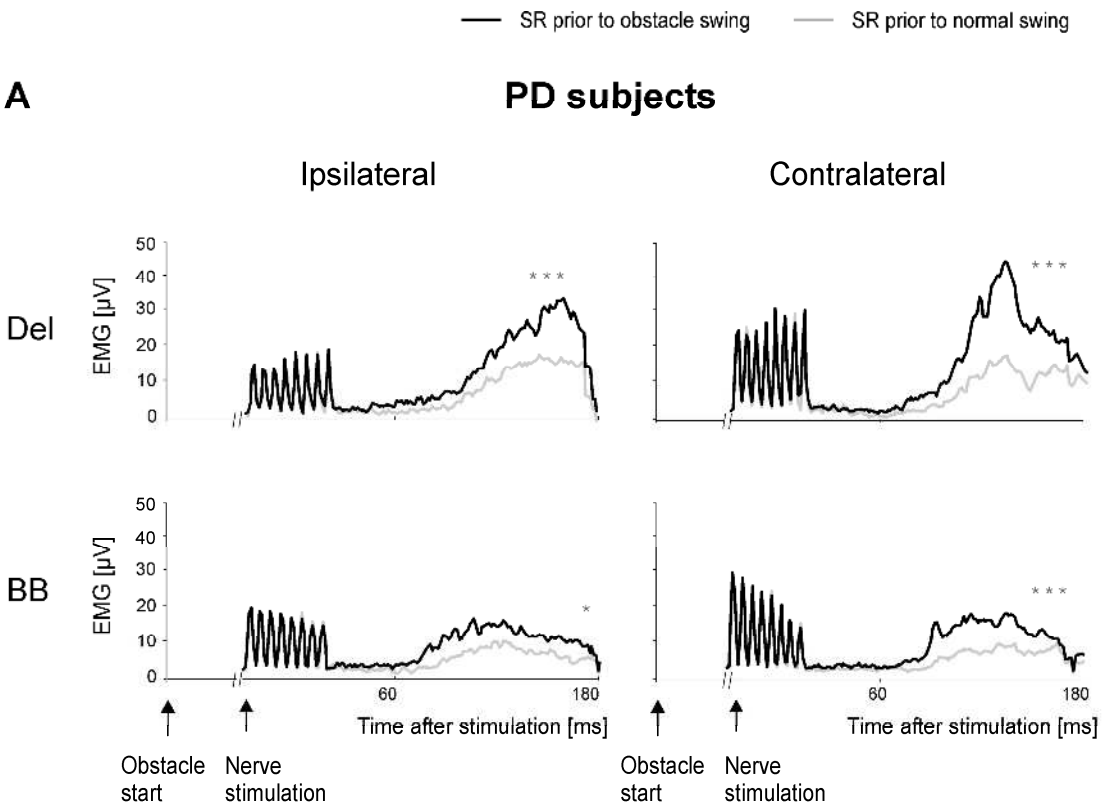

PD subjects
Control subjects
A
Foot clearance [cm]
AR_C = -0.221
AR_PD = -0.16
Step number
B
Normalized TA SR amplitude
AR_C = -0.124
AR_PD = -0.042
Step number
C
Normalized TA EMG activity
AR_C = -0.047
AR_PD = 0.009
Step number

Figure 2. Course of foot clearance, spinal reflex and EMG activity

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


SR prior to obstacle swing
SR prior to normal swing
A
PD subjects
Ipsilateral
Contralateral
Del
BB
EMG [µV]
50
40
30
20
10
0
* * *
*
60
180
Time after stimulation [ms]
Obstacle start
Nerve stimulation

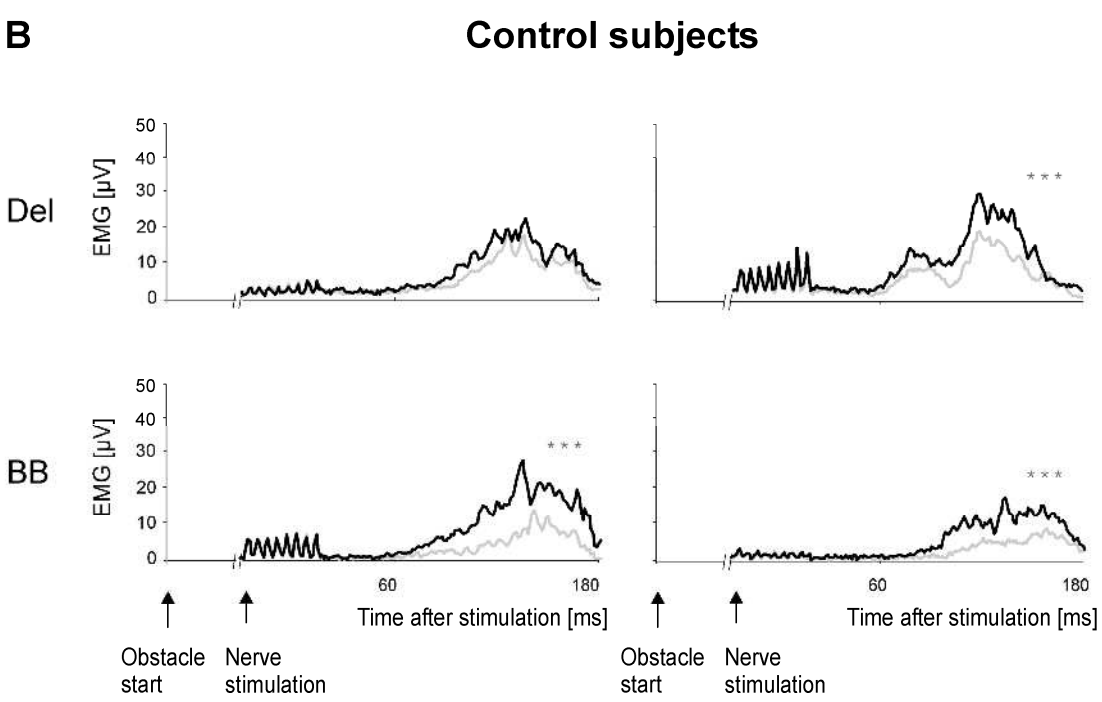

B
Control subjects
Del
BB
EMG [µV]
50
40
30
20
10
0
* * *
60
180
Time after stimulation [ms]
Obstacle start
Nerve stimulation

Figure 3. Spinal reflex response *prior to* normal and obstacle steps

Grand means of the rectified and subtracted (from background EMG activity) spinal reflex (SR) response in the proximal arm flexor muscles *prior to* normal (thin line) and obstacle (thick line) swing. **A,** subjects with Parkinson's disease (PD) 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 root mean square (RMS). Data of obstacle hits were removed. Significant differences between normal and obstacle steps are indicated by asterisk (* $P \leq 0.05$, *** $P \leq 0.001$). Abbreviations: Del = deltoideus, BB = biceps brachii muscle.

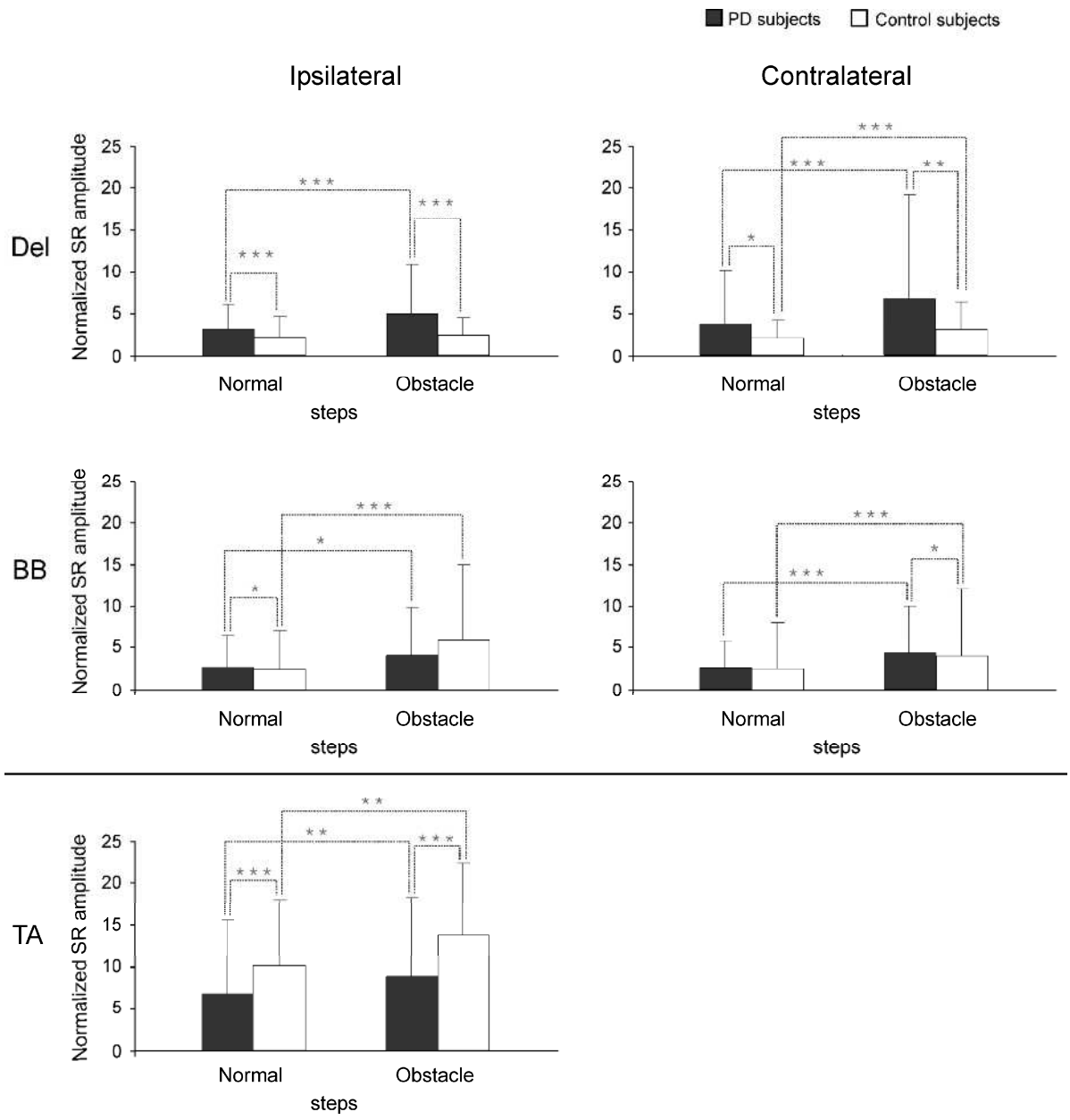


Figure 4. SR amplitude *prior to* normal and obstacle swing

Grand mean values of the normalized root mean square (RMS) of the spinal reflex (SR) amplitude in proximal arm and right leg muscles *prior to* normal and obstacle swing for subjects with Parkinson's disease (PD) and age-matched control subjects. Significant differences are indicated by asterisk (* $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$). Abbreviations: Del = deltoideus, BB = biceps brachii, TA = tibialis anterior muscle.

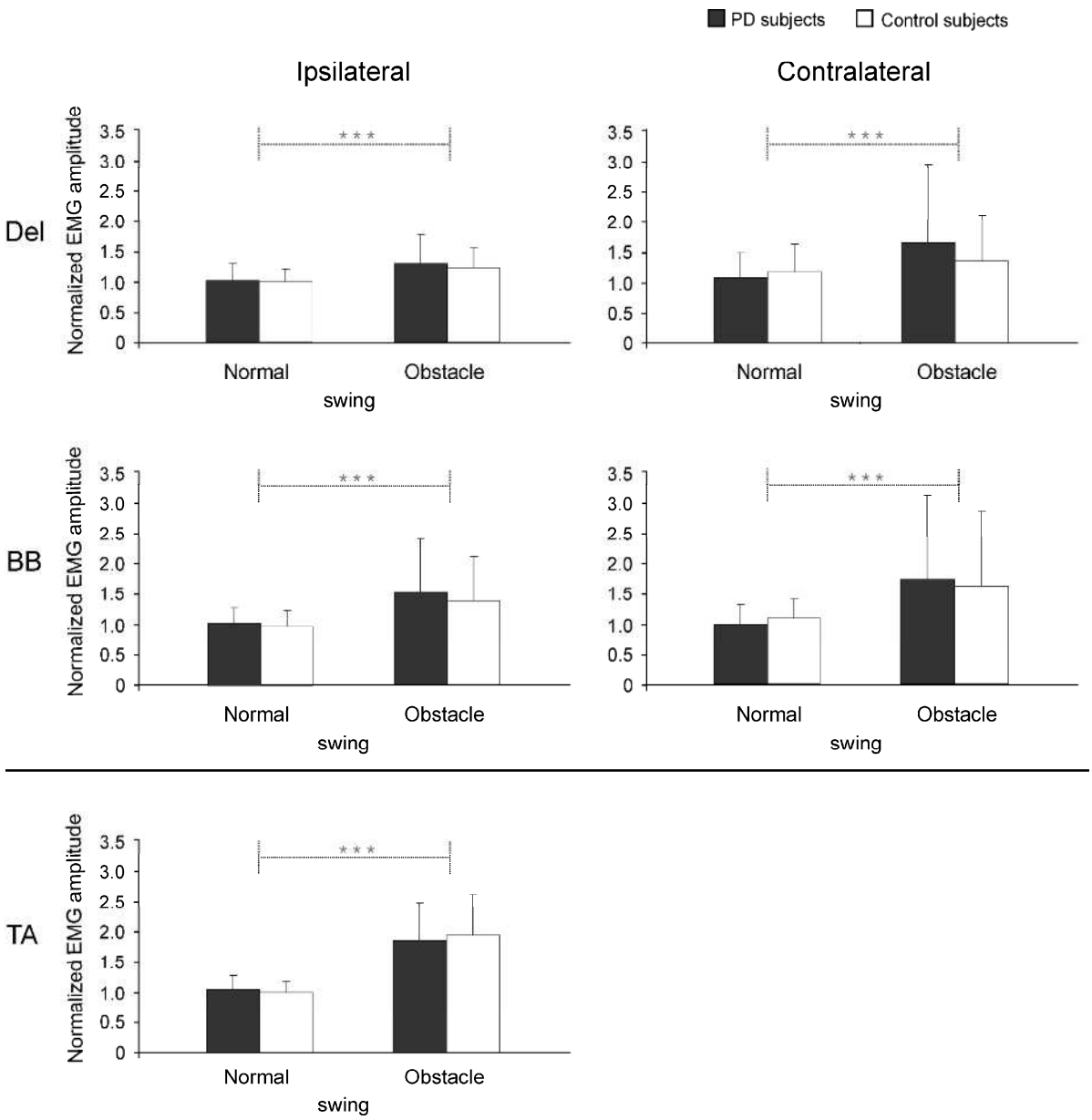


Figure 5. EMG activity *during* normal and obstacle swing

Grand mean values of the normalized root mean square (RMS) of the EMG activity in proximal arm and right leg muscles *during* normal and obstacle swing for subjects with Parkinson's disease (PD) and age-matched control subjects. Abbreviations and asterisk see figure 4.