Parkinson's disease patients compensate for balance control asymmetry

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Boonstra TA, Schouten AC, van Vugt JP, Bloem BR, van der Kooij H. Parkinson's disease patients compensate for balance control asymmetry. *J Neurophysiol* 112: 3227–3239, 2014. First published September 24, 2014; doi:10.1152/jn.00813.2013.—In Parkinson's disease (PD) subtle balance abnormalities can already be detected in early-stage patients. One feature of impaired balance control in PD is asymmetry: one leg produces more corrective joint torque than the other. We hypothesize that in mild to moderately affected PD patients, the least impaired leg compensates for the more impaired leg. Twenty PD patients and eleven healthy matched control subjects participated. Clinical asymmetry was determined by the difference between the left and right body side scores on the Unified Parkinson's Disease Rating Scale. Balance was perturbed with two independent continuous multisine perturbations in the forward-backward direction. Subsequently, we applied closed-loop system identification, which determined the spectral estimate of the stabilizing mechanisms, for each leg. Balance control behavior was similar in PD patients and control subjects at the ankle, but at the hip stiffness was increased. Control subjects exhibited symmetric balance control, but in PD patients the balance contribution of the leg of the clinically least affected body side was higher whereas the leg of the clinically most affected body side contributed less. The ratio between the legs helped to preserve a normal motor output at the ankle. Our results suggest that PD patients compensate for balance control asymmetries by increasing the relative contribution of the leg of their least affected body side. This compensation appears to be successful at the ankle but is accompanied by an increased stiffness at the hip. We discuss the possible implications of these findings for postural stability and fall risk in PD patients.

Parkinson's disease; multisegmental balance control; compensation; asymmetry; ankle and hip strategy

PATIENTS WITH Parkinson's disease (PD) have an increased risk of falling, especially in later disease stages (Pickering et al. 2007; Stolze et al. 2004). Subtle balance impairments, such as an increased body sway, have been detected in "de novo" PD patients (Chastan et al. 2008; Mancini et al. 2011). In these earlier disease stages, actual falls are perhaps prevented because PD patients can compensate for such mild balance impairments. Indeed, functional imaging studies in PD patients during a hand task have suggested that preserved brain areas can take over the role of other brain areas that are affected by the disease process. Such compensatory mechanisms appeared to help in maintaining normal performance (van Nuenen et al. 2009, 2012). Compensatory mechanisms can also help to maintain gait. For example, external visual or auditory cues can help to improve gait and alleviate freezing episodes (Keus et al. 2007; Nieuwboer et al. 2007). A recent paper showed that PD patients increased their cadence and decreased swing and cycle time to maintain walking velocity (Panyakaew and Bhidayasiri 2013). Whether compensatory mechanisms are also at play during a postural task has not yet been investigated.

PD is a neurodegenerative disorder that typically presents with asymmetric motor symptoms (Djaldetti et al. 2006). Recent work suggests that balance control is no exception (Boonstra et al. 2014; Geurts et al. 2011; Rocchi et al. 2002; van der Kooij et al. 2007). Therefore, a possibility for assessing postural compensation in PD patients is to investigate the balance responses of each leg separately. Patients might compensate for balance control asymmetries by augmenting the relative contribution of the least affected leg. This approach has been fruitfully applied in stroke patients, who compensate for the paretic leg by increasing muscle activation in the nonparetic leg (de Haart et al. 2004; Garland et al. 2003; Kirker et al. 2000).

It is unknown whether the least affected side in PD patients could compensate for the most affected side, and to what extent (partially or fully). Also, it is not clear whether postural compensation might differ between the ankle and the hip joints. Previous work showed that PD patients have increased postural stiffness (Grimbergen et al. 2004; Kim et al. 2009; Termoz et al. 2008), especially at the hip (Carpenter et al. 2004; Colnat-Coulbois et al. 2011; Maurer et al. 2003). Also, the hips are controlled by axial muscles (e.g., m. psoas major), and the axial musculature seems to be more affected in PD patients compared with the appendicular (i.e., ankle) muscles (Carpenter et al. 2004; Kim et al. 2009). Furthermore, axial symptoms of PD (tested by rising from a chair, turning, pull test) respond less to dopaminergic treatment, suggesting that appendicular (i.e., limb control) and axial symptoms of PD are caused by dysfunction in different brain areas (Boonstra et al. 2008; Maurer et al. 2003). We hypothesized that this could affect the relative ability to develop a compensation strategy at the ankle versus the hip joint.

To investigate how and to what extent PD patients can compensate for their balance control asymmetries, and to investigate the hypothesized differences between the ankle and hip joints, we applied closed-loop system identification techniques that separate the balance control contribution of the left and right ankles and hip joints (Boonstra et al. 2013).

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MATERIALS AND METHODS

The methods are described in detail elsewhere (Boonstra et al. 2013) but are described briefly below. A small part of the data has been reported before, although in a different form and focusing on a different research question (see Boonstra et al. 2014).

Experimental Approach

We approached upright stance as a 2-degrees of freedom (DoF) closed-loop multivariate system. The human body is modeled as a double-inverted pendulum, consisting of a leg, a head-arms-trunk (HAT) segment, and an ankle and hip joint (see Fig. 1). This double inverted pendulum is inherently unstable, and therefore without proper corrective action the pendulum will fall over. In our approach, we assume that the stabilizing mechanisms [located in the central nervous system (CNS)] generate stabilizing ankle and hip joint torques (i.e., the 2 outputs) based on the sensed ankle and hip joint angles (i.e., the 2 inputs). Hence, the system is a multiple-input multiple-output (MIMO) closed-loop system. In such a closed-loop system, it is difficult to determine the dynamics of the different components (i.e., the body and the stabilizing mechanisms) separately, as the dynamics of these components show up in both the input (joint angles) and output (joint torques) signals. In other words, joint torques can compensate for body movement but can also initiate body movement. Therefore, to "open" the loop and to separate the dynamics of the different components, the balance system needs to be perturbed (Fitzpatrick et al. 1996; van der Kooij et al. 2005).

In a pendulum with more than one segment, movements from one segment will influence the movements of the other segment and vice versa, because of mechanical coupling (Nott et al. 2010; Zajac 2002). This has consequences for the stabilizing mechanisms, as they have to correct for deviations from upright stance at both the ankle and the hip joint and compensate for the mechanical interaction. In our approach, this is expressed in the direct terms ($C_{\theta_A \to T_A}$ and $C_{\theta_H \to T_H}$), correcting for joint angle deviations by generating corrective joint torques, and the indirect terms ($C_{\theta_A \to T_H}$ and $C_{\theta_H \to T_A}$), correcting for the mechanical effects of the coupled segments, resulting in a 2×2 matrix of the stabilizing mechanisms (see also Fig. 1). Therefore, when estimating the dynamics in a MIMO system with two inputs, two perturbations (e.g., a translation and a force) need to be applied (Boonstra et al. 2013; Pintelon and Schoukens 2001). Using only one perturbation yields erroneous estimates of the stabilizing mechanisms (Boonstra et al. 2013).

In healthy subjects, both feet exert even amounts of force to counteract the destabilizing effect of gravity or other perturbations, so lumping the corrective actions of both legs together in one stabilizing mechanism is justified. However, in neurological populations, such as stroke (Geurts et al. 2005; Roerdink et al. 2009) and PD (Boonstra et al. 2014; Geurts et al. 2011; van der Kooij et al. 2007), balance control can be asymmetric. Therefore, in this report we define two parallel MIMO stabilizing mechanisms, one for each leg, comparable to van Asseldonk et al. (2006). Hence, we assumed that the left joint angles did not have a mechanical or neural effect on the right joint torques. Both stabilizing mechanisms produce corrective torques, which sum up to the total corrective torque required to stabilize the body.

With this approach, we can describe the behavior of the left and right stabilizing mechanisms in a quantitative way.

Participants

Twenty PD patients and eleven healthy matched control subjects were included (Table 1). Patients were assessed in the morning, at least 12 h after intake of their last dose of dopaminergic medication (practically defined OFF state). Disease severity was determined with the Hoehn and Yahr stages and the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz et al. 2008). Clinical asymmetry was defined as the difference between the summed UPDRS scores of the left and right body sides (items 3.3–3.8 and 3.15–3.17). The most affected body side was defined as the side with the highest UPDRS score. Participants with visual, vestibular, orthopedic, psychiatric, or other neurological diseases or with marked cognitive dysfunction (Mini Mental State Examination < 24 or Frontal Assessment Battery < 13) were excluded (Cohen et al. 2012; Crum et al. 1993; Royall 2001). All participants gave written informed consent prior to the experiment, which was approved by the local medical ethics committee and was in accordance with the Declaration of Helsinki.

Apparatus and Recording

Perturbations in the forward-backward direction were applied with a computer-controlled 6-DoF motion platform (Caren, Motek, Am-

Fig. 1. Experimental approach. The stabilizing mechanisms represent the dynamics of the combination of active and passive feedback pathways and generate joint torques to correct for the deviation of upright stance. The direct terms ($C_{\theta_A \to T_A}$ and $C_{\theta_H \to T_H}$) represent the corrective torques of the ankle (T_A) and the hip (T_H), based on the ankle (θ_A) and hip joint (θ_H) angle. Note that movements from the lower segments will influence the movements of the upper segments because of the mechanical coupling; therefore the stabilizing mechanisms have to compensate for the mechanical coupling, which is expressed in coupling terms between ankles and hips (i.e., $C_{\theta_A \to T_H}$ and $C_{\theta_H \to T_A}$). The system is perturbed with 2 independent mechanical perturbations, administered by a movement platform (S_x) and an actuated backboard (F_{ex}), called the pusher.
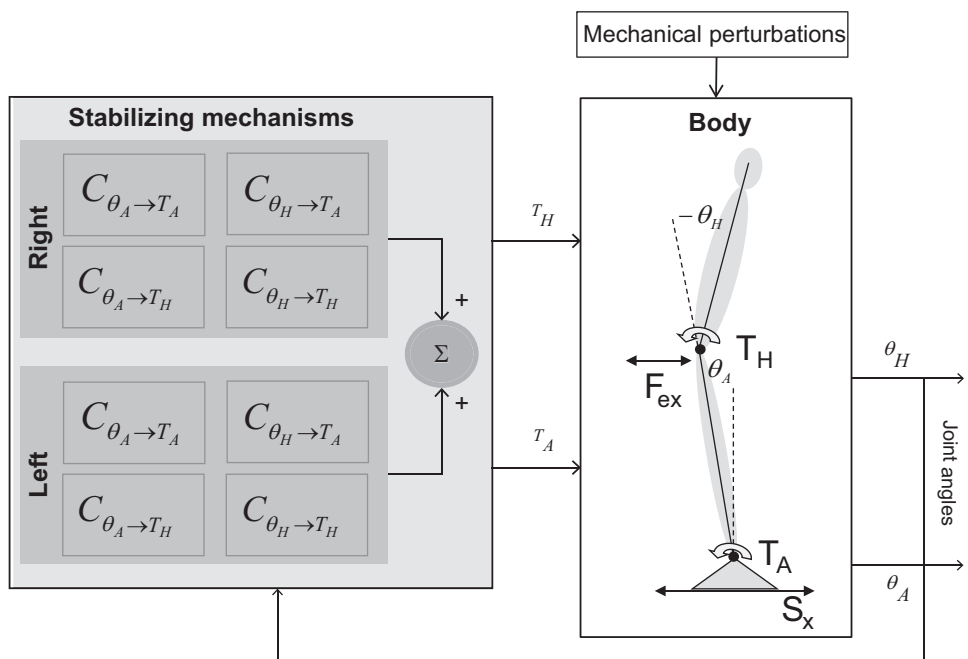
Table 1. *Participant characteristics*

	Patients ($n = 20$)	Control Subjects ($n = 11$)	Group Differences
Age, yr	63.3 (8.35)	64.2 (7.95)	NS
Women/men, %	30/70	37/63	NS
Weight, kg	84.13 (12.20)	78.12 (8.77)	NS
Height, m	1.74 (0.04)	1.75 (0.04)	NS
Disease duration, yr	5.21 (3.11)		
MMSE	28.25 (1.86)		
FAB	15.55 (2.46)		
H&Y (1/2/3)	3/15/2		
Total UPDRS III	27.55 (10.44)		
Left UPDRS III	10.95 (6.53)		
Right UPDRS III	8.45 (3.84)		

Data are means (SD) for *n* subjects, Patients were tested OFF medication. MMSE, Mini Mental State Examination; FAB, Frontal Assessment Battery; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr (1, unilateral signs; 2, bilateral signs without balance impairments; 3, mild to moderate involvement, physically independent but needs assistance to recover from pull test). NS, not significant.

sterdam, The Netherlands) and a custom-built actuated device (called the pusher) attached to the platform. Specifically, the motion platform administered a translational perturbation, whereas the pusher applied a force perturbation at the participant's sacrum. Body kinematics and platform movements were measured by motion capture (Vicon Ox-

ford Metrics, Oxford, UK) at a sample frequency of 120 Hz. Reflective spherical markers were attached to the first metatarsal, calcaneus, medial malleolus, sacrum, manubrium, and the last vertebrae of the cervical spine (C_7). In addition, a cluster of three markers was attached to both anterior superior iliac spines on the pelvis. Also, markers were attached just below the lateral epicondyle and in front of the acromion, and an additional marker was attached to each foot and lower leg. Three markers were attached to the platform. Reactive forces and torques from both feet were measured with a dual force-plate (AMTI, Watertown, MA) and were sampled at 600 Hz together with the perturbation of the pusher.

Procedure

Participants were instructed to maintain their balance without moving their feet while independent multisine platform movements and multisine force perturbations were applied simultaneously in the forward-backward direction. They were not explicitly instructed to distribute their body weight evenly over both feet.

The perturbation signal was a sum of sines, i.e., multisine with a period of 34.13 s, and contained power at 112 frequencies in the range of $0.06-4.25$ Hz (Boonstra et al. 2013; van Asseldonk et al. 2006; van der Kooij and de Vlugt 2007; see also Fig. 3). A multisine has the advantage that it is unpredictable for participants, because the signal consists of many sinusoids (de Vlugt et al. 2003). In addition, compared with pseudorandom ternary sequence (PRTS) (Pasma et al. 2012; Peterka 2002) or white noise signals (Kiemel et al. 2011),
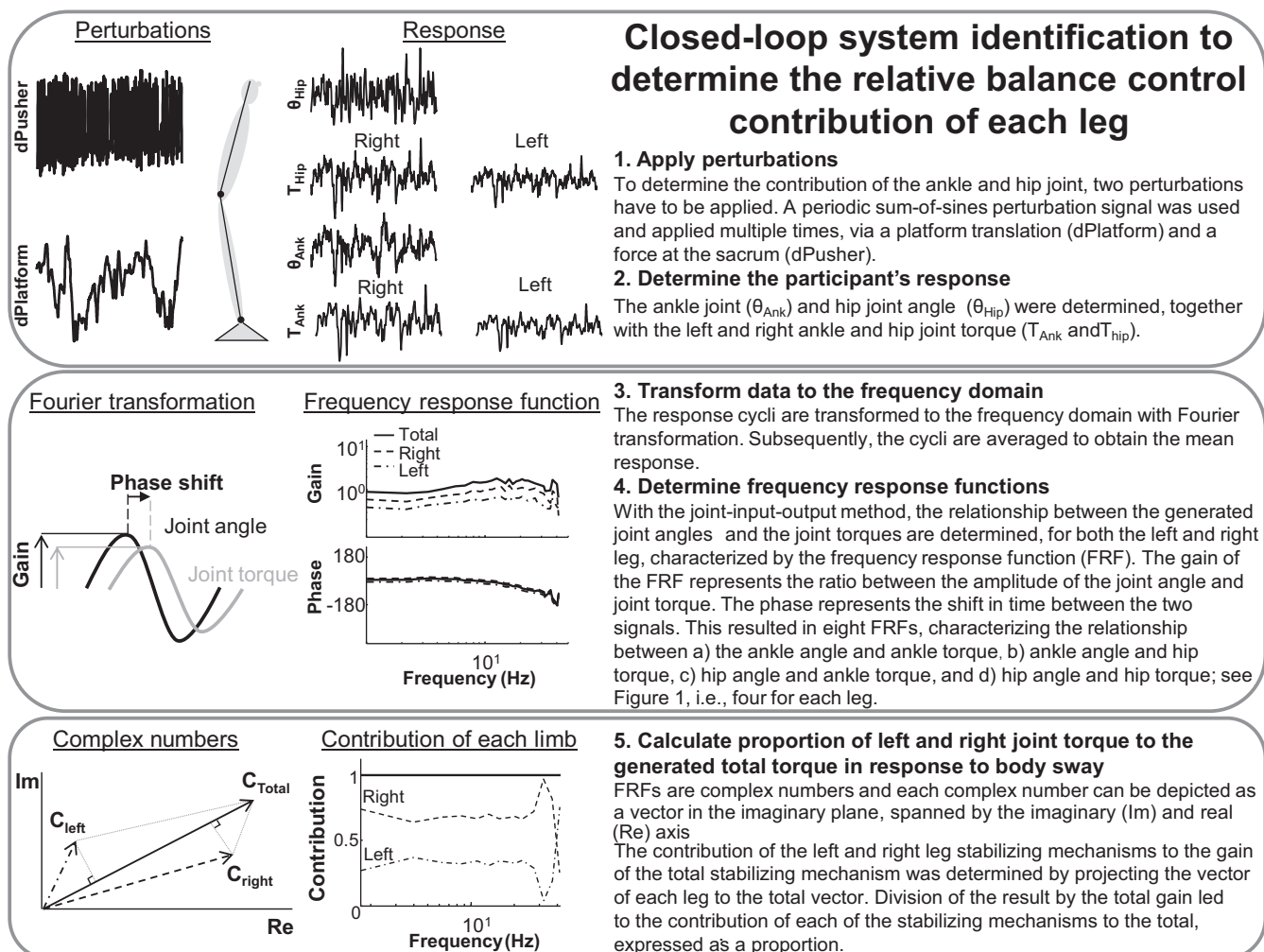

Fig. 2. Explanation of closed-loop system identification techniques to determine the relative balance control contribution of each leg.
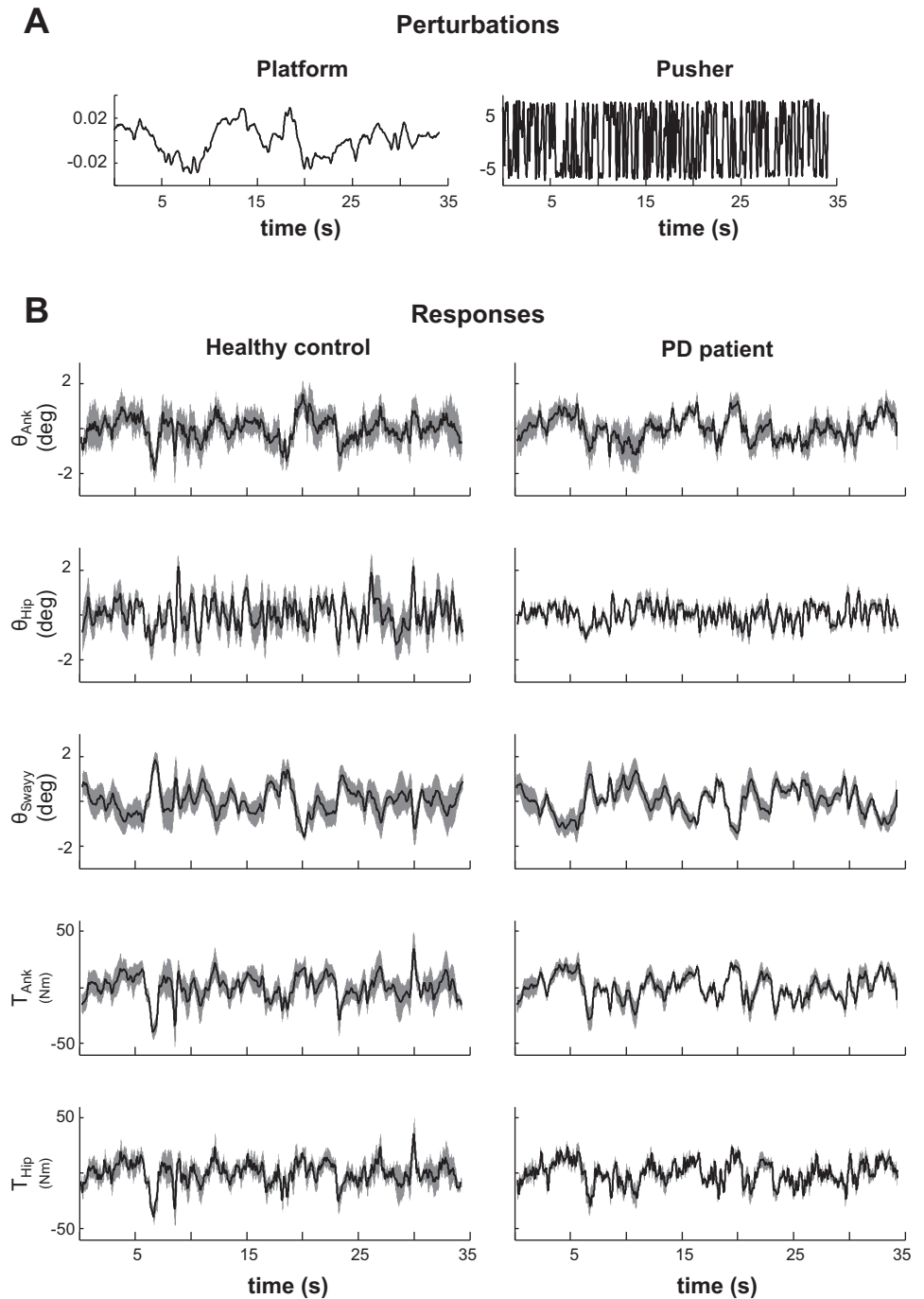
Fig. 3. *A*: time series of the platform and pusher perturbations. *B*: joint angles, sway angle, and joint torques in response to the applied perturbations of a representative healthy control subject (*left*) and Parkinson's disease (PD) patient (*right*). The average over the 8 perturbation cycles is indicated by the black line; the gray area depicts the SD. Perturbation amplitudes and phase of the perturbation cycle were the same for the healthy control subject and the PD patient.

multisines can be designed to have a desired power at specific frequencies, decreasing measurement time and increasing the reliability of the estimate of the stabilizing mechanisms.

For the platform the power of the perturbation decreased with increasing frequency, whereas the signal for the pusher had a flat power spectrum (Boonstra et al. 2013). We aimed to use as large as possible perturbation amplitudes for each individual participant, to optimize the ratio between external and internal destabilizing torques, thereby increasing the reliability of the estimated stabilizing mechanisms (van der Kooij et al. 2005).

The average root mean square (RMS) of platform amplitude was 0.012 m for healthy control subjects and for PD patients [i.e., they were similar, $t_{(60)} = -0.12$; $P = 0.90$]. The pusher's RMS of the amplitude was 4.5 Nm for healthy control subjects and 4.9 Nm for PD

patients [$t_{(60)} = -1.20$; $P = 0.20$]. Participants stood with eyes open and arms folded in front of their chest on the dual forceplate, strapped to the pusher, and wore a safety harness to prevent falling. The harness did not constrain movements or provide support or orientation information in any way. Four trials of 180 s were recorded, and, if needed, the participants were allowed to rest between trials.

Data Analysis

To determine the balance control contribution of each leg, we determined the corrective joint torques of each leg separately. Subsequently, we related the joint angles to the joint torques, by applying MIMO closed-loop system identification techniques to determine both the total contribution of the ankle and hip joint and their interactions,

as well as the contribution of the left and right joints separately. The method is described in detail below and summarized in Fig. 2.

Joint angles and joint torques. From the recorded movement trajectories of the markers, the position of the center of mass (CoM) and the joint angles (i.e., left and right ankle and hip angle) were estimated by custom-written software (Koopman 1989; Koopman et al. 1995) similar to van Asseldonk et al. (2007). Specifically, from the 29 body markers and with regression equations, the mass, the CoM position and the inertia tensor moment of the predefined rigid coupled segments (i.e., 2 feet, 2 legs, and HAT), and the joint positions in 3D were determined (Brand et al. 1982; Chandler et al. 1975) with an optimization algorithm. Movements from the knee were ascribed to the movements of the leg, and movements from the pelvis were incorporated in the movements of the HAT. The position of the HAT was first optimized and the legs and feet subsequently branched off. The joints were modeled as ball hinges with three independent DoFs, and the range of motion was constrained. The total body CoM was determined as the weighted sum of the separate segment CoM positions. From the static trial, the average distance in the sagittal plane from the ankle to the total body CoM [i.e., the length of the pendulum (l_{CoM})] was determined. Subsequently, the sway angle was calculated by taking the inverse sine of the ratio between the horizontal distance from the CoM to the mean position of the ankles and l_{CoM}. The applied platform perturbation was calculated based on platform marker movement.

Kinematic and kinetic data were filtered with a Butterworth filter (4th order low pass; cutoff 8 Hz) and subsequently resampled to 120 Hz. The recorded forces and torques were corrected for the inertia and mass of the top cover of the forceplate (Preuss and Fung 2004).

On the basis of the corrected forces and torques and the recorded body kinematics, ankle and hip joint torques of the left and right leg were calculated with inverse dynamics (Koopman et al. 1995). The joint torques were calculated in a bottom-up approach: first the ankle torques were determined and then the hip torques. The forces and accelerations of one body side were not part of the calculations for the other body side. To check the accuracy of our calculations, we compared the CoM-acceleration product with the sum of the forces (Newton's 2nd law), where the CoM position and acceleration were determined by the model and the forces were recorded with the forceplate.

As there were no differences between RMS of the joint angles of the left and right body sides, both in the control subjects [ankle: $t_{(22)} = 0.22$, $P = 0.82$; hip: $t_{(22)} = 0.13$, $P = 0.89$] and in the PD patients [ankle: $t_{(78)} = 0.36$, $P = 0.71$; hip: $t_{(78)} = 0.036$, $P = 0.97$], in the subsequent analysis "joint angle" refers to the average joint angle of the left and right body sides. The total joint torque is obtained by adding the joint torques of the left and right body sides.

Furthermore, as we perturbed in the forward-backward direction, we only analyzed the responses in the sagittal plane. Inspection of the data showed that this was also the direction in which the largest response could be detected.

Frequency response functions. To reliably identify the stabilizing mechanisms that generate ankle and hip torques based on sensory information of the joint angles (see Fig. 1), we applied linear, time-invariant MIMO system identification techniques, described in detail elsewhere (Boonstra et al. 2013; Koopman et al. 2010; Pintelon and Schoukens 2001), and calculated the frequency response functions (FRFs).

In short, the data of each of the four trials were segmented in response periods of the perturbation signal, yielding five periods of 34.13 s per trial, resulting in a total of 16 perturbation cycles for the estimation of the stabilizing mechanisms (the first cycle was discarded). Offsets and trends were removed from the data; hence possible differences in postural alignment did not influence our analysis. The data were Fourier transformed and averaged over the periods. Subsequently, the cross-spectral densities (CSDs) were calculated by multiplying the obtained Fourier coefficients of the pertur-

bations (i.e., complex numbers) with the complex conjugate of the joint angle or joint torque Fourier coefficients. The CSDs were then smoothed by averaging over four adjacent frequency points (Jenkins and Watts 1969). The stabilizing mechanisms were estimated with the joint input-joint output approach (van der Kooij et al. 2005):

$$\hat{C}_{\theta Tc}(f) = -\hat{G}_{pTc}(f)\hat{G}_{p\theta}^{-1}(f) \qquad (1)$$

with $\hat{G}_{pT_C}(f)$ and $\hat{G}_{p\theta}^{-1}$ the estimated CSD from the perturbations to the corrective torques of one body side and from the perturbations to the joint angles, respectively. Note that C is a 2×2 matrix (see also Fig. 1), p is a vector with the two disturbances, $\theta(f)$ is a vector with ankle and hip joint angles, and $T_c(f)$ is a vector with ankle and hip joint torques for each frequency f, expressed as Fourier coefficients. This resulted in eight FRFs, relating the ankle angle to the ankle torque ($C_{\theta_A \to T_A}$), the ankle angle to the hip torque ($C_{\theta_A \to T_H}$), the hip angle to the ankle torque ($C_{\theta_H \to T_A}$), and the hip angle to the hip torque ($C_{\theta_H \to T_H}$), for the left and right legs. The FRFs represent the multivariate stabilizing mechanisms of the participants.

The FRFs were normalized for the gravitational stiffness (mgl; m is total body mass, l is CoM height, and g is gravitational constant) because the exerted corrective torque depends on gravity. The average FRF over all participants was obtained by taking the mean over the individual normalized FRFs. Note that, as we used a dual forceplate, the obtained Fourier coefficients of the left and right FRFs were added to obtain the total FRFs.

FRF characteristics. The determined FRFs consist of two components: the gain that represents the normalized ratio between the joint angle and the joint torque relative to the pull of gravity and the phase representing the relative timing between these two signals (see Fig. 2). In our approach, the FRFs can be determined over the frequency range of the perturbation signal (0.06–4.25 Hz). Up to 1 Hz, the gain of the FRF is dominated by the stiffness of the system (i.e., reaction to change in joint angle; position feedback), between 1 and 2.5 Hz the gain is dominated by the damping of the system (i.e., reaction to change in joint angle velocity; velocity feedback), and above 2.5 Hz the inertia (i.e., the mass) determines the shape of the FRF (Schouten et al. 2008, 2011).

Balance contribution of left and right body sides. The relative contribution of the left and right legs to the total amount of generated corrective torque to resist the perturbations was determined by calculating the contribution of the gain and phase of each MIMO FRF to the gain and phase of the total MIMO FRF per frequency (Boonstra et al. 2013; van Asseldonk et al. 2006):

$$\text{Contribution}_{l,r}(f) = \frac{\text{FRF}_{l,r}(f) \cdot \text{FRF}_t(f)}{\|\text{FRF}_t(f)\|^2} \qquad (2)$$

with $\text{FRF}_{l,r}$ the left or right FRF and FRF_t the total FRF; the · indicates the dot product of the FRFs. The calculation is graphically depicted in Fig. 2: the gain and phase of the FRF can be represented in the imaginary plane, where the gain of the FRF is represented by the length of the vector and the phase by the angle of the vector with the horizontal real axis. In the imaginary plane, the vectorial sum of the left and right stabilizing mechanisms yields the total stabilizing mechanism (van Asseldonk et al. 2006). The contribution of the left and right legs to the total stabilizing mechanism is then determined by projecting the vector of the stabilizing mechanisms of the left and right legs on the vector of the total stabilizing mechanism. By dividing the result by the total gain, the contribution of the left or right leg to the total balance control is expressed as a proportion. For example, a proportion of 0.8 for the left leg means that the left leg contributed 80% of the total body stabilization at that specific frequency of the perturbation signal. This was done for each separate MIMO FRF (see *Eq. 1*).

The weightbearing and balance control asymmetry values of the healthy control subjects were considered as normative in this study and were expected to fall within an interval of 0.43–0.57 (Dickstein

et al. 1984; Sackley and Lincoln 1997). Furthermore, for the PD patients, we defined the most-contributing leg as the leg with the highest balance control contribution and we calculated the average FRFs of the most- and least-contributing legs by taking the mean over the FRFs of each PD patient.

Statistics

Perturbation amplitudes and the amplitude of the concurrent responses (i.e., sway angle, joint angles, and joint torques) were compared between PD patients and healthy control subjects with independent t-tests. Specifically, the average response of each perturbation round for each participant was first determined. Subsequently, the average RMSs of the responses over both perturbation rounds of the PD patients and healthy control subjects were calculated and compared.

The gain of each MIMO FRF was log transformed to make the data normally distributed. Subsequently, the gains were averaged within three frequency bands (<1 Hz, 1–2.5 Hz, and 2.6–4.2 Hz) and compared with either a paired t-test (within groups) for each frequency band or an independent t-test (between groups).

To test for asymmetries, we first determined the normalized absolute balance control contribution in the following way:

$$\text{NABContr}(f) = |\text{Contribution}_l(f) - 0.5| \qquad (3)$$

This was done for each MIMO FRF.

Subsequently, we grouped the normalized absolute balance control contribution of the MIMO FRFs into low, middle, and high frequency bands. Then we compared the NABContr of the patients with the healthy control subjects with independent t-tests for each frequency band, both for the whole group and for individual PD patients. Hence, we classified PD patients as having asymmetric balance control when their balance contribution was significantly different from healthy control subjects.

To compare the UPDRS scores of the different body sides, we used the Wilcoxon matched-pair signed-rank test. α was set at 0.05, and to correct for multiple comparisons the confidence level was adjusted with Bonferroni correction. For the comparison of the MIMO FRFs, we adjusted the confidence level per sub-FRF, i.e., the confidence level decreased to 0.05/3 (number of frequency bands) = 0.017. For all statistical analysis we used IBM SPSS statistics, version 20.0.

RESULTS

Both patients and control subjects were able to maintain their balance in the face of the applied perturbations. Furthermore, the response could be treated as linear and time invariant, as indicated by low noise-to-signal ratios (data not reported, but see Boonstra et al. 2013), justifying the application of linear time-invariant closed-loop system identification techniques (Boonstra et al. 2013; van der Kooij and de Vlugt 2007).

Time Series

Figure 3 shows the joint angles and torques of a representative healthy control subject and PD patient in response to the perturbations. PD patients tended to have smaller hip joint angle excursions, compared with healthy control subjects ($P < 0.05$; for RMS values see Table 2), and this was accompanied by a smaller exerted total ankle and hip joint torque. On the group level, the RMS amplitudes of the joint angles of the left and right body sides did not differ significantly, both for healthy control subjects [ankle: $t_{(22)} = 0.22$, $P = 0.82$; hip: $t_{(22)} = 0.13$, $P = 0.89$] and for PD patients [ankle: $t_{(78)} = 0.36$, $P = 0.71$; hip: $t_{(78)} = 0.036$, $P = 0.97$]. Comparing the joint angles of the left and right body sides on an individual basis

Table 2. *Average root-mean-square values of joint angles and joint torque responses of healthy control subjects and PD patients*

	Healthy Control Subjects		PD Patients		Group Difference, P†
	Mean	SD	Mean	SD	
Ankle angle, °	0.61	0.18	0.61	0.15	0.82
Hip angle, °	0.59	0.20	0.51	0.15	<0.05
Sway angle, °	0.57	0.05	0.59	0.11	0.55
Ankle torque (total), Nm	9.81	2.85	8.80	2.68	$<0.001*$
Ankle torque (left), Nm	4.90	1.42	4.40	1.58	0.22
Ankle torque (right), Nm	5.02	1.50	6.35	1.56	$<0.002*$
Hip torque (total), Nm	9.02	2.66	8.09	2.51	0.30
Hip torque (left), Nm	4.51	1.33	4.05	1.63	0.26
Hip torque (right), Nm	4.72	1.29	6.17	1.59	$<0.001*$

PD, Parkinson's disease. *Significant difference. †P values are uncorrected; the significance level decreased to 0.006 because of Bonferroni correction.

yielded similar results. Hence in the PD patients asymmetry in joint torques was accompanied by symmetry of joint angles.

Sway amplitude did not differ significantly between PD patients and healthy control subjects. In addition, compared with healthy control subjects, PD patients, on average, had smaller joint torques at the left body side compared with the right side, while healthy control subjects exerted the same amount of torque at each body side (see Table 2).

Multiple-Input Multiple-Output Frequency Response Functions

Figure 4 shows the average MIMO FRFs of the stabilizing mechanisms of the healthy control subjects and PD patients. In general, the gain of the stabilizing mechanism of the ankle increased with frequency until 2 Hz; above 2 Hz the gain decreased. The gain of the hip stabilizing mechanism was flat until 0.7 Hz, decreased until 2 Hz, and subsequently increased. The stabilizing mechanism from hip to ankle remained roughly constant over the frequency range, whereas the stabilizing mechanism from ankle to hip increased above 2 Hz. At the lower frequencies (<1 Hz), the gain was always at least 1, indicating that the participants produced enough corrective torque to resist the perturbations. The phase of all the stabilizing mechanisms decreased with frequency (i.e., a phase lag), indicating the presence of a neural time delay.

There were no significant differences in FRF gain between healthy control subjects and PD patients at the ankle joint or at the cross-coupling from hip joint angle to ankle torque. However, in the cross-coupling from ankle angle to hip torque, there was a trend [$F_{(26)} = 3.85$; $P = 0.08$; uncorrected P value] toward a higher gain at the lower frequencies for the PD patients. Furthermore, the FRF gain of the hip below 1 Hz was significantly higher in PD patients compared with healthy control subjects [$t_{(30)} = -0.53$; $P = 0.01$; uncorrected P value]. Note that the significance level decreased to 0.02 because of the Bonferrroni correction. Hence, PD patients produced relatively more corrective hip torque in response to body movement. As the gain of the FRF at lower frequencies is dominated by stiffness (Schouten et al. 2011), this result indicates a higher hip stiffness in PD patients.
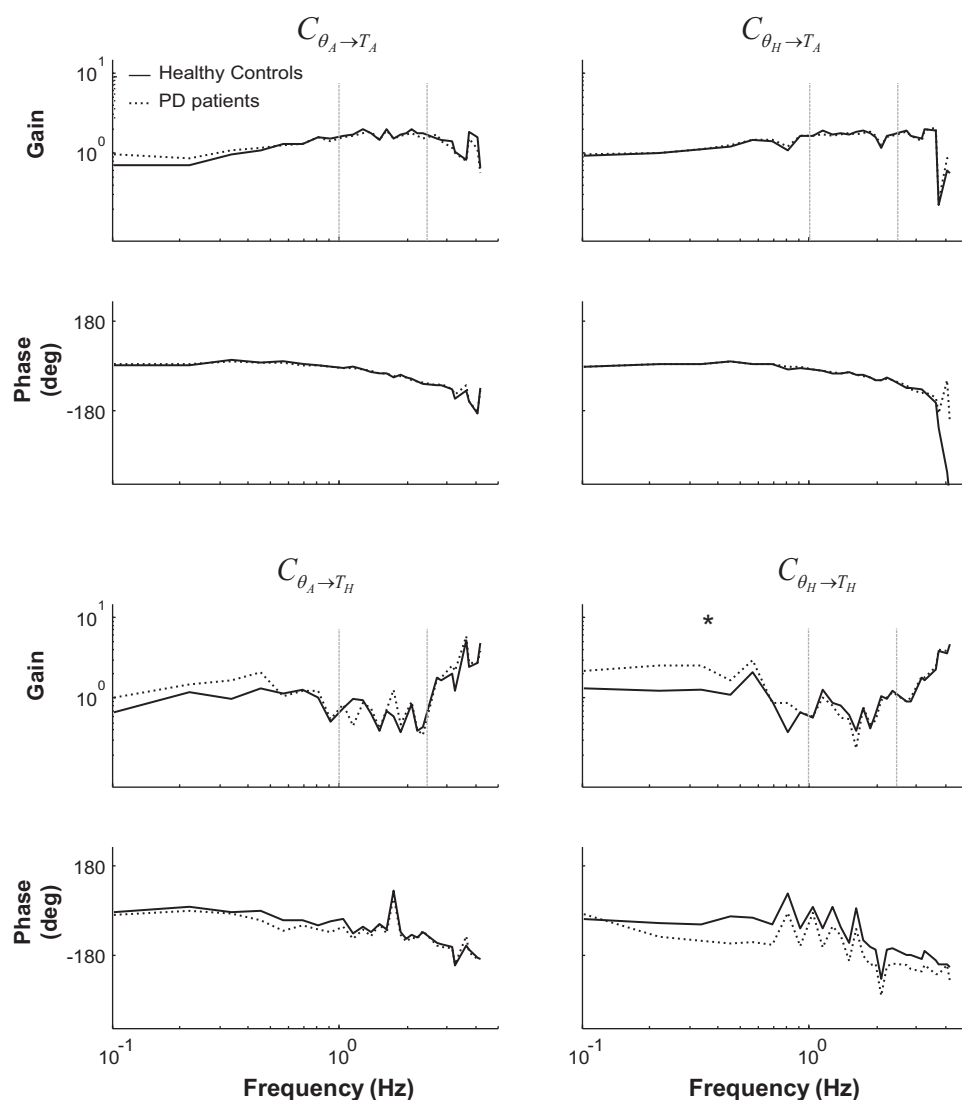
Fig. 4. Multisegmental frequency response functions (FRFs) of the total stabilizing mechanisms (i.e., both legs added together). The healthy control subjects are depicted with the solid line and the PD patients with the dashed line. The vertical dashed lines indicate the borders of the frequency bands (i.e., low, middle, high) used in the statistical analysis. *Significant difference. There were no differences between the healthy control subjects and the PD patients for the $C_{\theta_A \to T_A}$, $C_{\theta_H \to T_A}$, and $C_{\theta_A \to T_H}$ FRFs. For the $C_{\theta_H \to T_H}$ FRF there was a significant difference of gain in the lower frequency band, indicating a higher hip stiffness in PD patients.

Balance Control Contribution of Legs

PD patients exerted different amounts of torque with the left and right legs, i.e., there were asymmetries in balance (see Table 2). Figure 5 indicates the balance control contribution of the right leg of the PD patients, calculated on the basis of the MIMO FRFs (see Fig. 2). The healthy control subjects had average absolute (a)symmetries of 0.06, 0.07, and 0.09 for the low, middle, and high frequencies, whereas the PD patients had absolute asymmetries of 0.14, 0.16, and 0.17, respectively. Comparing the absolute balance control asymmetry values of the PD patients against the normative values of the healthy control subjects showed that ~15 patients controlled their balance asymmetrically (see Table 3); hence one leg was contributing more (i.e., the most-contributing leg) to upright stabilization than the other leg. As can be seen from Fig. 5, in our sample most patients used their right leg the most to control their balance. The asymmetries were evident at both the ankle and the hip joint and in the joint interaction terms. Furthermore, the asymmetries were most evident in the low (<1 Hz) and middle (1–2.5 Hz) frequency bands and were smaller (or absent) at the higher frequencies (>2.5 Hz) (see Table 3).

Balance Control Behavior of Most- and Least-Contributing Legs

Figure 6 depicts the average FRFs of the most- and least-contributing legs of the group of PD patients together with the right leg of the healthy control subjects. The average gains of the least- and most-contributing legs of the PD patients differed significantly for all FRFs and all frequency bands (all $P < 0.01$). This indicates that both stiffness and damping of one leg were increased. The left and right legs of the healthy control subjects contributed equally to upright stabilization.

The body side of the most-contributing leg had a lower total UPDRS score (7.25) compared with the least-contributing leg (11.05; $P = 0.02$), indicating that the larger balance control contribution (i.e., a higher gain) coincided with the clinically least affected body side. Hence, the leg of the less symptomatic body side was stiffer than the most symptomatic leg but also had an increased damping, as determined with our MIMO method. Furthermore, the most-contributing leg also had a lower UPDRS leg score (1.85) compared with the least-contributing leg (2.55), but this difference was not significant ($P = 0.12$). Also, we did not find a difference between the leg rigidity (as tested with item 3.3
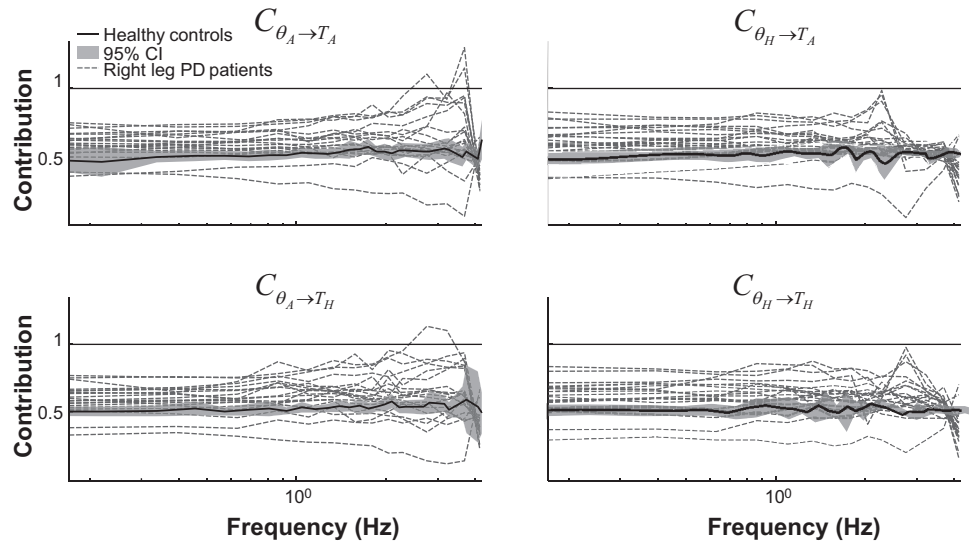
Fig. 5. Balance control contribution of the right leg of the healthy control subjects (average depicted by solid black line, with 95% confidence interval in gray) and of the individual PD patients (indicated by dashed gray lines). Healthy control subjects controlled their balance symmetrically, whereas in PD patients one leg contributed more to upright stabilization than the other leg.

of the motor part of the UPDRS) of the most (0.95)- and least (0.85)-contributing legs ($P = 0.63$).

Bear in mind that the results in Fig. 4 depicted that the total gains of the ankle FRFs over the whole frequency were similar for PD patients and healthy control subjects for all MIMO FRFs, except the FRF that related the hip angle to the hip torque. Hence, at the ankle the decreased balance control contribution (most pronounced at the lowest frequencies) of one leg was canceled out by the increased balance control contribution of the other leg. This pattern was also observed at the hip, but here there was an imbalance between the balance contribution of the least- and most-contributing legs, resulting in a total increased hip stiffness.

Table 3. *Comparison of absolute asymmetry index of PD patients with normative values of healthy control subjects*

	Frequency Band		
PD Patient	Low	Mid	High
1	<0.001*	<0.001*	0.13
2	0.05	0.32	0.47
3	0.001*	0.14	0.66
4	0.42	0.41	0.59
5	0.91	0.06	0.12
6	0.006*	0.01*	0.50
7	<0.001	<0.001*	0.006*
8	<0.001*	<0.001*	0.003*
9	<0.001*	<0.001*	0.02
10	<0.001*	0.37	0.93
11	<0.001*	0.005*	0.05
12	<0.001*	<0.001*	0.02
13	0.19	0.16	0.82
14	0.006*	0.05	0.66
15	<0.001*	0.001*	0.003*
16	<0.001*	<0.001*	0.66
17	<0.001*	<0.001*	0.24
18	0.001*	0.002*	0.16
19	<0.001*	<0.001*	0.002*
20	0.04	0.21	0.17
Group	<0.001*	0.007*	0.02*

Low: < 1 Hz; Mid: 1–2.5 Hz; High > 2.5 Hz. Data are uncorrected *P* values; note that the *P* value decreased to 0.017 because of Bonferroni correction. Comparison was made in low, middle, and high frequency bands for each individual PD patient, averaged for all frequency response functions (FRFs). *Statistically significant difference.

DISCUSSION

In this study, we determined the balance control responses of PD patients and control subjects for each leg separately, by applying mechanical perturbations in the sagittal plane. Our results demonstrate that PD patients had marked asymmetries in their balance control; the leg of the clinically least affected body side contributed more to upright stabilization compared with the leg of the clinically most affected body side. The ratio between the most and least affected legs helped to preserve a normal motor output at the ankle; the total contribution (summed for the left and right ankles) equaled the total balance response of control subjects. However, at the hip, the same strategy was associated with a total increased joint stiffness.

Leg of Clinically Least Affected Body Side Contributes Most to Upright Stabilization in PD Patients

PD is an asymmetric disease; one side of the body is affected first, and this asymmetry is preserved throughout the disease (Djaldetti et al. 2006). In addition, the motor asymmetry corresponds to the asymmetric loss in dopamine-producing cells in the substantia nigra (Djaldetti et al. 2006). Recent work suggested that balance control (which intuitively appears to be a very symmetric task) can also be affected asymmetrically in mild to moderately affected PD patients (Boonstra et al. 2014; Geurts et al. 2011; van der Kooij et al. 2007). The present results confirm these findings, showing that PD patients controlled their balance asymmetrically. Specifically, we demonstrated that the leg of the clinically least affected body side (as determined with the UPDRS) contributed most to balance control. This greater balance contribution of the leg of the clinically least affected body side was reflected by higher stiffness (resistance to movement) and higher damping (resistance to speed) compared with the leg of the clinically most affected body side. The increased stiffness could not be attributed to an increase in rigidity, as we did not find differences in rigidity scores between the most- and least-contributing legs. We therefore think it is more likely that PD patients increased their dynamical response. In addition, whether rigidity (as determined clinically with the UPDRS) is related to our measure of stiffness has not been investigated, that is, it is not clear
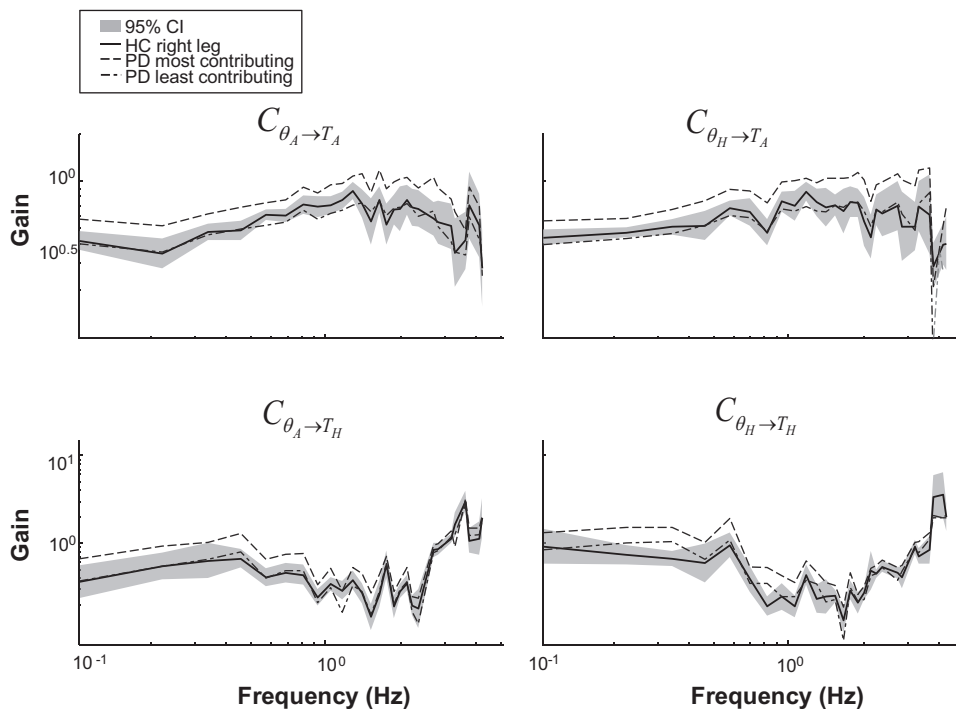
Fig. 6. Gains of the multiple-input multiple-output FRFs of the right leg of the healthy control subjects (average indicated by solid black line, with 95% confidence interval in gray) and of the most (dashed line)- and least (dot-dashed line)-contributing legs of the PD patients. For all FRFs the most-contributing leg of the PD patients had a higher gain than the least-contributing leg ($P < 0.001$). In healthy control subjects there were no differences between the left and right legs for all FRFs. For the $C_{\theta_A \to T_A}$ and the $C_{\theta_H \to T_A}$ FRFs the least-contributing leg had a smaller gain than the right leg of the healthy control subjects, whereas at the hip ($C_{\theta_A \to T_H}$ and $C_{\theta_H \to T_H}$) the least-contributing leg had a similar gain compared with the healthy control subjects. Note that the scale of the y-axis label of the *top* panels is different from that of the *bottom* panels.

whether rigidity and stiffness can be ascribed to the same pathophysiological mechanism.

PD Patients Compensate for Balance Control Asymmetries

For PD patients, the balance control contribution of both legs added together equaled that of healthy control subjects, except at the hip joint. Hence these results show that the balance control contribution of the leg of the clinically least affected body side canceled out the decreased balance control contribution of the leg of the clinically most affected body side, resulting in generation of a sufficient amount of corrective torque. That is, the PD patients did not fall or step more often compared with the healthy control subjects in this study. In the PD patients, this can only be achieved (assuming that before disease onset the PD patients behaved the same as the control subjects) if the leg of the clinically least affected body side increased its balance control contribution. We therefore hypothesize that the clinically least affected body side compensated for the most affected body side, possibly by increasing the common neural input. The ability to compensate for an impaired body side has been shown previously in stroke survivors (Garland et al. 2003; Kirker et al. 2000); these patients increased their muscle activity at the nonparetic side to counteract postural perturbations.

In this study, we investigated one specific form of (postural) compensation, namely, whether one leg can compensate for impaired balance control of the other leg, by determining the balance control actions of each leg separately. This approach has not yet been applied yet in human PD patients; however, an animal study showed similar results (Woodlee et al. 2008). That is, inducing hemiparkinsonism in rats (by unilateral infusion of 6-hydroxydopamine) resulted in postural instability in their impaired forelimb. Interestingly, the unimpaired limb showed enhanced functioning over the course of time, suggesting that the unimpaired body side compensated for the im-

paired body side. The enhanced functioning of the nonimpaired body side was associated with cerebral reorganization and probably involved nondopaminergic pathways. Neuroimaging studies in stroke patients showed similar results: the unlesioned hemisphere became more active after a stroke (Grefkes and Ward 2014). Furthermore, connectivity between the affected and nonaffected hemispheres decreased, and this was positively correlated with functional recovery.

While stroke patients generally have only one hemisphere that is damaged, in PD patients the substantia nigra of both hemispheres become affected, although the initial body side typically remains the most affected (Djaldetti et al. 2006; Hughes et al. 1992). Therefore, whether the compensatory mechanisms found in stroke patients can be generalized to PD is not clear. However, recent studies show that the latency between cell loss and symptom onset [PD manifests itself clinically after loss of 60–80% of dopaminergic neurons (Lloyd 1977)] can be explained by compensatory mechanisms in the brain (Bezard et al. 2003; van Nuenen et al. 2009). These remain active when the disease symptoms are manifested (Helmich et al. 2007). Furthermore, a study by Schieppati and colleagues (Nardone et al. 2012) showed that although sway was normal in de novo PD patients (compared with control subjects and without any apparent asymmetries), asymmetric medium-latency responses were present. Future studies should therefore investigate whether between-hemisphere compensation is also possible in human PD subjects.

Increasing the corrective forces at one body side effectively aggravates balance asymmetries; therefore, the observed asymmetries are most likely due to the balance impairment (asymmetry) caused by the disease itself plus the compensation strategy. This compensation strategy could possibly explain why we did not find any differences in previous self-reported falls between patients with and without asymmetric balance control (unpublished results), as it leads to a sufficient amount of correc-

tive torque to resist the pull of gravity. From this perspective, asymmetric balance control might paradoxically be a good phenomenon in certain stages of the disease, possibly preventing falls. Results of a recent animal study actually point in this direction: in a primate injected with MPTP to induce parkinsonism, an additional unilateral lesion in the nigrostriatal projection (effectively introducing an asymmetry between the brain hemispheres) improved clinical signs (Blesa et al. 2011).

Balance Control Contribution of Leg of Clinically Least Affected Body Side Leads to Increased Hip Stiffness in PD Patients

At the hip, a pattern similar to that at the ankle was observed: the balance control contribution of the leg of the most affected body side was lower compared with the contribution of the leg of the clinically least affected body side. This resulted in a significant increased total hip stiffness. We speculate that the compensation strategy (i.e., increasing the balance control contribution of the leg of the least affected body side) had a different effect at the ankle compared with the hip because of the increased axial stiffness of the PD patients (Boonstra et al. 2008; Carpenter et al. 2004; Maurer et al. 2003; Wright et al. 2007). Apparently, the PD patients were not able to separate the effect of the compensation strategy for the separate joint stiffness of the ankle and the hip. This hypothesis is confirmed by other studies that showed that PD patients are unable to uncouple the control actions of the ankle and hip joints (Horak et al. 1992; Maurer et al. 2003), perhaps because of decreased structural connectivity between locomotor pathways (Fling et al. 2013).

However, it has also been suggested that increasing axial stiffness could be a compensation strategy, as it locks an extra DoF and thereby simplifies the problem of maintaining an upright posture (Grimbergen et al. 2004). This stiffening strategy has also been detected in healthy control subjects when standing on an elevated platform that induced a fear of falling (Carpenter et al. 2001).

In sum, we speculate that the observed higher hip stiffness in PD patients is the result of the primary disease processes (i.e., increased axial stiffness) and the compensation strategy (increased balance control contribution of the leg of the least affected body side, including increased joint stiffness). Our results point in this direction but cannot directly prove this theory.

Future studies should therefore focus on whether increased axial stiffness is a direct effect of the disease, a compensatory strategy, or a combination of both, by, e.g., prospectively following newly diagnosed PD patients. However, another possibility could be to artificially increase or decrease axial stiffness in healthy control subjects (Gruneberg et al. 2004) and PD patients (also for the left and right leg separately) and assess the effects on balance control.

Balance Control is Disturbed in PD Patients Because of Increased Hip Stiffness

Our results indicated that the total gain at the lower frequencies for the hip angle to hip torque was significantly higher in PD patients compared with healthy control subjects. In this study we applied system identification techniques and performed the analysis in the frequency domain, which has the advantage that it can assess the dynamics over a broad frequency range where the low frequencies (<1 Hz) are dominated by stiffness. Hence it can be concluded that the PD patients in our study had an increased total hip stiffness.

Increased hip stiffness in PD patients has been reported before in mild to moderately affected patients (Carpenter et al. 2004; Kim et al. 2009; Termoz et al. 2008). Our results confirm these findings, and this shows that this finding is robust across applied methodologies. For example, Carpenter et al. (2004) used platform rotations, whereas Kim et al. (2009) used platform translations. An increased ankle stiffness in PD has also been proposed (Carpenter et al. 2004; Lauk et al. 1999), but there also have been reports of a decreased ankle stiffness (Colnat-Coulbois et al. 2011; Kim et al. 2009). Our results indicate that the total ankle stiffness in PD patients was similar to that in healthy control subjects.

Intersegmental Balance Control in PD Patients

We found a trend toward an increased intersegmental coordination in PD patients. An increased intersegmental coupling has also been proposed by Maurer and colleagues (Maurer et al. 2003), but they studied a much smaller group of only eight patients that differed markedly from the patients in our sample: their patients were more severely affected and had been treated with subthalamic nucleus deep brain stimulation (STN-DBS). Another study by Horak and colleagues also reported higher intersegmental feedback gains (Kim et al. 2009), and, together with our results, this suggests that PD patients have a higher intersegmental stiffness. Other studies have shown that increased hip and intersegmental stiffness is probably due to excessive cocontraction and a larger background muscle activity (Burleigh et al. 1995; Carpenter et al. 2004; Horak et al. 1996). The above-mentioned studies used either no external balance perturbations (Termoz et al. 2008) or only one perturbation (Carpenter et al. 2004; Colnat-Coulbois et al. 2011; Kim et al. 2009; Maurer et al. 2003), whereas we used two perturbations. This methodological approach, instead of differences in patient characteristics, could also explain why our results differed from previous work. That is, it has been shown that healthy subjects react differently (i.e., other feedback gains) to a platform translation compared with a force perturbation (Kim et al. 2012).

Methodological Limitations

We determined the average healthy control FRFs on the postural responses of only 11 healthy control subjects, which is a relatively small group. However, the FRFs of this control group had a small variation, as reflected by the tight standard deviations. Furthermore, the control group also controlled their balance very symmetrically, and the symmetry values found in this study are comparable with reported values of a large study ($n = 403$), also for the age group investigated here (Sackley and Lincoln 1991). It must be noted, though, that these studies only investigated weight distribution, whereas we investigated joint torques. However, in healthy control subjects balance control and weight distribution are tightly interrelated (van Asseldonk et al. 2006), and therefore we assume that the symmetry values here are representative for healthy control subjects.

As pointed out in *Experimental Approach*, movements from one segment influence the movements of another segment, and a neural controller should take this coupling into account. We, however, assumed a simplified controller, as left body side movements were not used to calculate right body side torques and vice versa. This could potentially have influenced our results, by masking or aggravating balance control asymmetries. We think that the influence of this simplification is small, though, as left and right body side angles were similar, signaling virtually nonexisting movements in the transverse plane. Moreover, if one wants to identify the left-right coupling, another two perturbations are necessary, which would have complicated the experimental design.

It must also be noted that we only investigated balance control with a static, re-active balance control task. PD patients do have difficulties with maintaining balance during static situations but are especially impaired when they have to change their behavior (De Nunzio et al. 2007; Visser and Bloem 2005; Winogrodzka et al. 2005) or prepare or initiate a movement (Kim et al. 2013). Therefore, how our findings relate to anticipatory balance control, walking, or fall risk in PD patients warrants further investigation.

Finally, in order to investigate multisegmental balance control with our applied method, the patient must be able to withstand postural perturbations. This could be a potential problem in patients who have marked balance control instability, making the method less suitable for more severely impaired patients.

Future Perspectives

Our results indicate that multisegmental balance control is altered in PD patients because of an increased hip stiffness and suggest that PD patients can partly compensate for their balance control asymmetries with the leg of the least affected body side, by increasing the exerted force. Future studies should follow PD patients over the course of their disease to monitor the progression of asymmetric balance control. Does the least affected leg compensate for the most affected leg already from symptom onset? When is the least affected leg no longer able to compensate, and does this correlate with a worsening of clinical signs (greater postural instability) and onset of falls? What is the effect of levodopa on the overall balance control and on balance control asymmetries? Can we positively influence postural compensation? What is the origin of balance control asymmetry—could it be a proprioceptive problem (Carpenter and Bloem 2011)? In healthy control subjects postural compensation could be tested by manipulating the balance control ability of one leg, with, e.g., a cuff or tendon vibration. With this knowledge, interventions to stimulate postural compensation can be designed and evaluated.

AUTHOR CONTRIBUTIONS

Author contributions: T.A.B., J.P.P.v.V., B.R.B., and H.v.d.K. conception and design of research; T.A.B. performed experiments; T.A.B. and H.v.d.K. analyzed data; T.A.B., A.C.S., B.R.B., and H.v.d.K. interpreted results of experiments; T.A.B. prepared figures; T.A.B. and H.v.d.K. drafted manuscript; T.A.B., A.C.S., J.P.P.v.V., B.R.B., and H.v.d.K. edited and revised manuscript; T.A.B., A.C.S., J.P.P.v.V., B.R.B., and H.v.d.K. approved final version of manuscript.

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