Full length Article

Asymmetries in reactive and anticipatory balance control are of similar magnitude in Parkinson’s disease patients

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Many Parkinson’s disease (PD) patients show asymmetries in balance control during quiet stance and in response to perturbations (i.e., reactive balance control) in the sagittal plane. In addition, PD patients show a reduced ability to anticipate to self-induced disturbances, but it is not clear whether these anticipatory responses can be asymmetric too. Furthermore, it is not known how reactive balance control and anticipatory balance control are related in PD patients. Therefore, we investigated whether reactive and anticipatory balance control are asymmetric to the same extent in PD patients.

14 PD patients and 10 controls participated. Reactive balance control (RBC) was investigated by applying external platform and force perturbations and relating the response of the left and right ankle torque to the body sway angle at the excited frequencies. Anticipatory postural adjustments (APAs) were investigated by determining the increase in the left and right ankle torque just before the subjects released a force exerted with the hands against a force sensor.

The symmetry ratio between the contribution of the left and right ankle was used to express the asymmetry in reactive and anticipatory balance control; the correlation between the two ratio’s was investigated with Spearman’s rank correlation coefficients.

PD patients were more asymmetric in anticipatory (p = 0.026) and reactive balance control (p = 0.004) compared to controls and the symmetry ratios were significantly related (ρ = 0.74; p = 0.003) in PD patients.

These findings suggest that asymmetric reactive balance control during bipedal stance may share a common pathophysiology with asymmetries in the anticipation of voluntary perturbations during, for instance, gait initiation.

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1. Introduction

In patients with PD, motor symptoms (e.g., rigidity) typically manifest themselves asymmetrically [1,2]. Recent studies have shown that balance control can also be asymmetrical in PD patients [3–6]. Consequently, PD patients may be less able to control the torques needed to shift the body’s center of mass in the lateral and sagittal directions; which is essential for the planning and preparation of actions such as gait initiation [7,8].

Several studies have indicated that anticipatory postural adjustments (APAs), i.e. changes in postural muscle activity or joint torques prior to self-inflicted postural actions, are preserved in patients with PD, although slower and less pronounced in magnitude [8,9]. It is unclear however, whether APAs in PD can also be asymmetric [8,9].

Crucial for maintaining an upright posture is a) reactive balance control (the ability to respond to unpredictable perturbations), b) the ability to anticipate to a perturbation and c) the ability to make a step. It has been suggested that the coupling between posture
(i.e., anticipatory balance control) and actual stepping, as normally seen in healthy subjects is disturbed in PD patients [11,12]. It is however not clear whether reactive balance control and anticipatory balance control are abnormally related in PD patients.

Therefore, we investigated whether reactive and anticipatory balance control are asymmetric to the same extent in PD patients. We investigated, in a group of patients with PD, the asymmetries in APAs prior to a self-inflicted perturbation (i.e., anticipatory) and dynamic balance control during continuous unpredictable mechanical perturbations (i.e., reactive). A control group was included to investigate if asymmetries in the patient group were significantly larger than in healthy subjects.

2. Methods

The part of the experimental set-up, data analysis and results describing reactive balance control (Experiment 1) presented here has been published before [3,13]. Below, we briefly describe the data analysis and we shortly report the results, in order to be able to relate asymmetries in reactive balance control with asymmetries in anticipatory balance control.

All measurements were conducted while the subjects maintained their balance without moving their feet during normal bipedal stance (feet were about 14 cm apart). Both tasks were performed on the same day, as part of one experimental session. Subjects wore a safety harness to prevent falling, but it did not constrain movements or provide support or orientation information in any way.

2.1. Subjects

14 PD patients (two female; 63.9 ± 7.3 years) and 10 healthy aged-matched controls (four female; 66.0 ± 8.1 years) participated, see Tables 1 and 2. These subjects were a subset of a larger study that investigated asymmetries in balance control in PD patients [3,13]. This subset comprised the subjects who were physically able to participate in a set of additional trials necessary for this study. Patients were measured in their OFF state, i.e. at least 12 h after their last dopaminergic medication intake. Disease severity was determined with the Hoehn–Yahr stage [14] and clinical asymmetry was defined as a difference between the summed UPDRS scores [14] of the left and right extremities (items 3.3–3.8 and 3.15–3.17; UPDRS<sub>R</sub>–<sub>L</sub>) and for the legs separately (items 3.3, 3.7 and 3.8; UPDRS<sub>RLL</sub>–<sub>L</sub>}). The research proposal was approved by the Ethics committee of the Medical Spectrum Twente in Enschede, The Netherlands, in accordance with the Declaration of Helsinki. All subjects provided written informed consent prior to participation.

2.1.1. Data-recording

Body kinematics and platform movements were measured using motion capture (Vicon Oxford Metrics, Oxford, UK) at a sample frequency of 120 Hz. Reflective spherical markers were attached to the first metatarsal, calcaneus, medial malleolus, the sacrum, the manubrium, the most caudal vertebrae of the cervical spine (C7), the knee and shoulder joints. A cluster of three markers was attached to the anterior superior iliac spines on the pelvis. One additional marker was attached to the foot and two markers were attached to the lower leg; three markers were attached to the platform. Reactive forces from both feet were measured with a dual forceplate (AMTI, Watertown, USA), embedded in the motion platform. A 1 DoF force sensor was used to measure the exerted hand force of the subjects. Force plate data as well as 1 DoF force data was sampled with a frequency of 360 Hz, resampled to 120 Hz, and subsequently filtered with a recursive fourth order Butterworth filter with a cut-off frequency of 10 Hz.

2.2. Experiment 1: reactive balance control

2.2.1. Task

Subjects were instructed to maintain their balance (eyes open) without moving their feet, while continuous, multisine platform translations and continuous, multisine force perturbations were applied simultaneously in the forward–backward direction [3,15]. The perturbations were unpredictable for the participants, ruling out the use of effective anticipatory strategies [16].

The two independent perturbations were administered with a computer-controlled six-degrees-of-freedom motion platform (Caren, Motek, Amsterdam, The Netherlands) and a custom-built actuated device that was able to apply perturbing forces at the sacrum. The perturbation amplitudes were as large as possible to increase the reliability of the estimated stabilizing mechanisms [17].

2.2.2. Data analysis

From the recorded movement of the markers, the position of the center-of-mass (CoM) of the whole body and of the segments (i.e., feet, legs, the head–arms–trunk (HAT)) was estimated [18,19]. The sway angle was calculated from the body height and the horizontal distance from the CoM to the mean position of the ankles. Forces and torques of the force plate were corrected for the inertia and mass of the top cover [19]. Based on the corrected forces and torques and recorded body kinematics, the ankle joint torques were calculated with inverse dynamics [18].

2.2.3. Frequency response functions

The time series of the perturbations, sway angle, and the ankle torques were separated into data blocks of 34.14 s (i.e., length of the perturbation signal). The responses were Fourier transformed at the 112 frequencies of the perturbation signal using the fast Fourier transform in Matlab and subsequently averaged over the cycles. The average Fourier coefficients of the platform perturbation and the responses (sway angle and left and right ankle torques) were used to calculate the power spectral density (PSD).

Table 1

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT&lt;sub&gt;hand&lt;/sub&gt;</td>
<td>Reaction time ankle torque</td>
<td>Left ankle torque − Right ankle torque</td>
</tr>
<tr>
<td>RT&lt;sub&gt;ankle-force&lt;/sub&gt;</td>
<td>Reaction time ankle torque</td>
<td>Right ankle torque − Left ankle torque</td>
</tr>
<tr>
<td>%APA</td>
<td>Percentage of APAs found</td>
<td>100% × number of APAs/total (number of force drop actions)</td>
</tr>
<tr>
<td>APA&lt;sub&gt;L&lt;/sub&gt;</td>
<td>Length APA of left leg</td>
<td>(t₀ + 50 ms) − t&lt;sub&gt;peak&lt;/sub&gt;</td>
</tr>
<tr>
<td>APA&lt;sub&gt;R&lt;/sub&gt;</td>
<td>Length APA of right leg</td>
<td>(t₀ + 50 ms) − t&lt;sub&gt;peak&lt;/sub&gt;</td>
</tr>
<tr>
<td>APA&lt;sub&gt;both&lt;/sub&gt;</td>
<td>Length APA of both legs</td>
<td>(t₀ + 50 ms) − t&lt;sub&gt;peak&lt;/sub&gt;</td>
</tr>
<tr>
<td>APA&lt;sub&gt;L&lt;/sub&gt;</td>
<td>Magnitude APA left leg</td>
<td>Left ankle torque at (t₀ + 50 ms) − Right ankle torque at (t₀ + 50 ms)</td>
</tr>
<tr>
<td>APA&lt;sub&gt;R&lt;/sub&gt;</td>
<td>Magnitude APA right leg</td>
<td>Right ankle torque at (t₀ + 50 ms) − Total ankle torque at (t₀ + 50 ms)</td>
</tr>
<tr>
<td>APA&lt;sub&gt;total&lt;/sub&gt;</td>
<td>Magnitude APA both legs</td>
<td>Total ankle torque at (t₀ + 50 ms) − Total ankle torque at (t₀ + 50 ms)</td>
</tr>
</tbody>
</table>
and cross spectral densities (CSDs) between a) the average Fourier coefficients of the platform perturbation and the sway angle and b) the platform perturbation and the left and right ankle torques. Lastly, the frequency response function (FRF) of the stabilizing mechanism (with joint angle as input and joint torque as output) was estimated with a Single-Input Single-Output joint-input-joint-output system-identification technique [17,20].

The FRFs were calculated from sway angle to left and right ankle torques separately and were normalized by the mass and length of the participants, to compensate for differences in the subjects’ mass and pendulum length [21].

2.2.4. Symmetry ratio of reactive balance control

To determine the relative contribution of each ankle joint to the total amount of generated corrective torque to resist the perturbations, the contribution of the gain and phase of the FRFs of each leg to the gain of the total body was calculated [20]. Subsequently, the contributions were averaged over the frequencies of the perturbation signal to obtain the reactive balance contribution (RBC) for each leg:

\[
SR_{RBC} = \frac{1}{n_{freq}} \left( \sum_{f=1}^{f_{max}} \frac{\text{FRF}(f; \text{frf})}{||\text{FRF}(f)||^2} \right)
\]  

(1)

With FRF, the left FRF and FRF, the total FRF; \( n_{freq} \) is the amount of frequencies in the signal (i.e., 112). The \( \cdot \) indicates the dot product of the FRFs. This resulted in the contribution of the left ankle to the total balance control, expressed as a proportion [20].

2.3. Experiment 2: anticipatory balance control

2.3.1. Task

Subjects were instructed to push with two hands against the 1 DoF force sensor as soon as an acoustic signal sounded (see Fig. 1), while standing as still as possible. They had to reach a force level of 10 N and visual feedback with regard to the force that was provided to keep the level of error as small as possible. When the force level was maintained within a margin of 1 N for 2 s, a second acoustic signal indicated that the subjects had to stop pushing, but, they maintained light finger contact with the force sensor. This cycle of actions was repeated 10 times in each trial. When subjects were able to participate in a second trial, an additional trial (i.e. 20 pushes as well as 20 releases; see Tables 2 and 3) was recorded.

2.3.2. Data-analysis

Anticipatory postural adjustments (APAs) were investigated during the episodes in which subjects stopped pushing. This induced a reduction of plantar flexion torque around the ankles. Therefore, subjects had to increase plantar flexion torque around the ankle joint in order to maintain upright posture. An APA was defined as an increase in the plantar flexion ankle torque, starting before the drop in force exerted by the hands plus a time delay of 50 ms, because the time-delay within the proprioceptive feedback loops is at least 50 ms [9,22]. Therefore, ankle torque changes before this time instant are by definition anticipatory, and can be considered an APA.

To estimate the onset of the force drop (\( t_0 \)) the mean \( \pm 2.57^* \) standard deviation of the 1 DoF hand force signal was calculated over the time interval of 2 s directly before the acoustic signal (\( t_{freq} \)). \( t_0 \) was defined as the first time instant after the acoustic signal at which the force signal fell below the lower bound of this range. Similarly, to define the onset of the ankle torque increase (\( t_{torque} \)), the mean \( \pm 2.57^* \) standard deviation of the ankle torque during the 2 s directly before the acoustic signal was calculated. \( t_{torque} \) was defined as the first time instant after the acoustic signal at which the ankle torque exceeded the upper bound of this interval. This time instant was calculated for the left, right and both legs.

The percentage of APAs observed in the total number of force drop actions (%APA) was calculated for each subject. If an APA was detected based on the total torque, the reaction time of the hand force (\( RT_{hand\_force} \)) and the reaction time of the ankle torque (\( RT_{ankle\_torque} \)) as well as the length (APA) and the magnitude (\( APA_m \)) of the APA were determined. A short comprehensive overview of the definitions of these outcome parameters is provided in Table 1.

2.3.3. Symmetry ratio of anticipatory balance control

A symmetry ratio (\( SR_{ABC} \)) was calculated to quantify the contribution of the left leg and the right leg to \( APA_{m\_tot} \):

\[
SR_{ABC} = \frac{APA_{m\_left}}{APA_{m\_tot}}
\]

where a value of 0/1 means that all torque contributing to the total APA is generated by the right/left leg.

2.4. Statistics

We investigated differences in gender and age between groups with Fisher’s exact test and the Mann–Whitney U test. To compare asymmetries in RBC and APAs between healthy subjects and PD patients, the absolute \( SR_{ABC} \) and \( SR_{RBC} \) was determined, i.e. \( [SR - 0.5] \). Differences between healthy subjects and PD patients with regard to \( APA: RT_{ankle\_torque}: RT_{hand\_force}: APA_{m\_tot}: APA_{m\_left}, \) absolute SRs were assessed using independent t-tests. In addition, Spearman’s rank correlation coefficients between \( SR_{ABC} \) and \( SR_{RBC} \) of the left leg were calculated for both groups separately. For the PD patients, Spearman’s rank correlation coefficients were also calculated between the clinical asymmetry (UPDRS) and balance control asymmetry ratios. For all statistical tests, level of significance was set at \( p < 0.05 \). Lastly, we used linear regression analysis with the method of least squares to obtain the slope and intercept of the regression line that optimally explains the relationship between reactive and anticipatory balance control.

3. Results

The difference in APAs between a typically performing PD patient and healthy control subject is represented in Fig. 1. The outcome measures of the individual subjects are shown in Tables 2 and 3. PD patients and healthy controls did not differ with respect to gender (\( p = 0.192 \)), age (\( U = 48.5; p = 0.217 \)), the percentage of APAs that were observed (%APA; PD: 91 ± 12%, healthy: 91 ± 12%, \( t = -0.18, p = 0.986 \)) and reaction time of ankle torque increase (\( RT_{ankle\_torque} \); PD: 0.35 ± 0.08 s, healthy: 0.31 ± 0.05 s, \( t = -1.399, p = 0.176 \)).

PD patients had significantly slower reaction times of hand force drops (\( RT_{hand\_force} \); PD: 0.44 ± 0.11, healthy: 0.36 ± 0.07, \( t = -2.199, p = 0.039 \)), longer APA times (\( APA_{m\_tot} \); PD: 0.137 ± 0.051, healthy: 0.095 ± 0.038, \( t = -2.195, p = 0.039 \)) and smaller APA magnitudes (\( APA_{m\_tot} \); PD: 0.40 ± 1.40, healthy: 6.26 ± 2.84, \( t = 2.54, p = 0.019 \)). In addition, PD patients were significantly more asymmetric in their APAs than healthy controls (\( SR_{RBC} \); PD: 0.25 ± 0.15, healthy: 0.12 ± 0.10, \( t = -2.39, p = 0.026 \)) and their reactive balance control (\( SR_{ABC} \); PD: 0.17 ± 0.12, healthy: 0.06 ± 0.04, \( t = -3.32, p = 0.004 \)).

Spearman’s rank correlation analysis showed that the relation between \( SR_{ABC} \) and \( SR_{RBC} \) was significant in PD patients (\( p = 0.74, p = 0.003 \)), see Fig. 2. \( SR_{RBC} \) (\( p = 0.59, p = 0.03 \)) and \( SR_{ABC} \) (\( p = 0.53, p = 0.05 \)) were also significantly related to UPDRS\_al, but not with UPDRS\_T.A. (\( SR_{ABC} \); \( p = 0.46, p = 0.10, SR_{RBC} \); \( p = 0.41, p = 0.15 \)).
4. Discussion

Our results showed that PD patients can have asymmetries in anticipatory balance control (in the sagittal plane) compared to healthy subjects; that is, one leg made a larger APA compared to the other leg, in response to a self-inflicted perturbation. Furthermore, the asymmetries in anticipatory balance control were of the same magnitude as those found during a reactive balance control task. Although to a lesser extent, these asymmetries were also related to clinical asymmetry between the left and right body side.

4.1. Anticipatory postural adjustments are slower, smaller and asymmetric in PD patients

PD patients were able to produce an APA in response to a self-inflicted disturbance; however, their responses were slower and smaller compared to the healthy controls. This is in accordance with previous research [8]. It has been hypothesized that deficits in anticipatory postural adjustments in people with PD are characterized by underscaling of the preparation of the planned action [23], similar to the underscaling during voluntary movements.

Table 2

Characteristics and the APA outcome measures and the symmetry ratios of the healthy controls.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th># of actions</th>
<th># APA's Total/Left/ Right</th>
<th>Reaction time/force drop (s)</th>
<th>Reaction time/torque increase (s)</th>
<th>Mean APA\textsubscript{1,just} (s)</th>
<th>Mean APA\textsubscript{1,just} (Nm)</th>
<th>Mean APA\textsubscript{1,just} (Nm)</th>
<th>Mean APA\textsubscript{1,just} (Nm)</th>
<th>SR\textsubscript{WB}</th>
<th>SR\textsubscript{ABC}</th>
<th>SR\textsubscript{ABBC}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>61 20</td>
<td>17/17/17</td>
<td>0.47</td>
<td>0.43</td>
<td>0.093</td>
<td>4.81</td>
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<td>0.46</td>
<td>0.40</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>65 18</td>
<td>13/14/12</td>
<td>0.26</td>
<td>0.26</td>
<td>0.059</td>
<td>5.82</td>
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<tr>
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<tr>
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<td>5</td>
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<td>0.081</td>
<td>4.06</td>
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<tr>
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<td>0.096</td>
<td>6.11</td>
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<td>6.09</td>
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<td>0.36</td>
</tr>
<tr>
<td>10</td>
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<td>74 9</td>
<td>6/6/5</td>
<td>0.32</td>
<td>0.33</td>
<td>0.040</td>
<td>3.22</td>
<td>1.72</td>
<td>1.49</td>
<td>0.49</td>
<td>0.54</td>
<td>0.55</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>66 ± 8</td>
<td></td>
<td>0.36 ± 0.07</td>
<td>0.31 ± 0.05</td>
<td>0.095 ± 0.038</td>
<td>6.26 ± 2.64</td>
<td>3.66 ± 1.57</td>
<td>2.60 ± 1.69</td>
<td>0.54 ± 0.08</td>
<td>0.59 ± 0.13</td>
<td>0.49 ± 0.07</td>
</tr>
</tbody>
</table>

\# of actions: the amount of force drops that could be analyzed. \#APA's: total, left and right amount of APA's. s: seconds; WB: weight bearing; APA: anticipatory postural adjustment; RBC: reactive balance control; ABC: anticipatory balance control; SR: symmetry ratio.
Table 3
Characteristics and the APA outcome measures and the symmetry ratios of the PD patients.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (yrs)</th>
<th>H&amp;Y</th>
<th>UPDRS -RL</th>
<th>UPDRS -L</th>
<th># of actions</th>
<th># APA’s total/Left/Right</th>
<th>Reaction time force drop (s)</th>
<th>Reaction time torque increase (s)</th>
<th>Mean APA Left (Nm)</th>
<th>Mean APA Right (Nm)</th>
<th>Mean APA Left/Right</th>
<th>Mean APA Right/Left</th>
<th>Mean APA right</th>
<th>SRWB</th>
<th>SRABC</th>
<th>SRABC</th>
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Mean ± SD: 64 ± 7


4.2. Asymmetry in reactive balance is related to asymmetry in anticipatory balance in PD patients.

Our results indicated that the asymmetries in reactive balance control were of the same magnitude as the asymmetries in anticipatory balance control. For individual PD patients, the balance control was differentially affected (e.g., head/leg asymmetry). It has been shown that these deficits are mainly mediated by dopaminergic brain pathways that can be symmetrically or asymmetrically affected in PD patients [24]. Furthermore, we showed that PD patients exhibited more corrective, directed movements with one leg compared to the other (e.g., head/leg asymmetry), which is consistent with previous findings [24].

Fig. 2: Linear regression between SRWB and SRRABC. The red line shows the correlation between SRWB and SRRABC. The blue line shows the correlation between SRABC and SRRABC. The green line shows the correlation between SRABC and SRWB. The red line shows the correlation between SRABC and SRRABC. The blue line shows the correlation between SRABC and SRRABC. The green line shows the correlation between SRABC and SRRABC.
Neuroimaging studies have shown that the motor cortex and supplementary motor area are hypoactive in PD [26,27] and a recent study, that investigated the influence of levodopa on asymmetries in activation in the motor cortex [28], showed asymmetrical activity in these areas. The authors concluded that ‘the impact of reduced dopamine in the cortico-striatal system and the action of levodopa is not symmetrical’. Hence, the asymmetry resulted from basal ganglia may influence the motor cortex asymmetrical activity through its projections to this area. Our results confirm these findings for an anticipatory and reactive postural task, suggesting that both the dopaminergic and non-dopaminergic neural systems are asymmetrical affected in PD, see also [29].

4.3. Methodological considerations

Studies investigating APAs in both healthy and patients, usually use EMGs to determine when an anticipatory action is starting [9]. Determining asymmetries from EMGs can be difficult: differences in electrode placements, skin conductivity and background activity can all cause ‘artificial’ asymmetries. Therefore, we determined the occurrence of an APA based on ankle torque responses.

Secondly, we only investigated APAs after the subjects dropped the push force. Inspection of the data showed that the subjects’ behavior was less variable when releasing the force, compared to building up the force. That is, force increases often occurred in an intermittent way, leading to variable postural disturbances, whereas force drops occurred always abruptly and were therefore the most appropriate for our analyses.

Furthermore, subjects were not instructed to perform the task as fast as possible, which reduced the self-inflicted perturbation and may have led to a reduction in the number of APAs we could observe.

Lastly, to investigate the relationship between reactive and anticipatory balance control, which is hypothesized to be abnormal in PD patients [11], we investigated APAs in response to a self-inflicted perturbation. We did not look at gait initiation, which makes it hard to relate our findings to gait initiation in PD patients. We argue however that in order to draw valid conclusions about the pathophysiology underlying reactive and anticipatory balance control, the same task in both conditions should be used, i.e., tasks that both involve feet-in-place responses as conducted in this study.

Acknowledgments

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Conflict of interest

The authors declare no conflicts of interest.

References