

# Postural control learning dynamics in Parkinson's disease: early improvement with plateau in stability, and continuous progression in flexibility and mobility

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## Research

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## Abstract

**Background:** Balance training improves postural control in Parkinson's disease (PD). However, a systematic approach for the development of individualized, optimal training programs is still lacking, as the learning dynamics of the postural control in PD, over a training program are poorly understood.

**Methods:** We explored the learning dynamics of the postural control in PD, during a balance-training program, in terms of the clinical, posturographic, and novel model-based measures. Twenty patients with PD participated in a balance-training program, 3 days a week, for 6 weeks. Clinical tests assessed functional balance and mobility pre-training, mid-training, and post-training. Center-of-pressure (COP) was recorded at four time-points during the training (pre-, week 2, week 4, and post-training). COP was used to calculate the sway measures and to identify the parameters of a patient-specific postural control model, at each time-point (stability and flexibility degree). The posturographic and model-based measures constituted the two sets of stability- and flexibility-related measures.

**Results:** Mobility- and flexibility-related measures showed a continuous improvement during the balance-training program. In particular, mobility improved at mid-training and continued to improve to the end of the training, whereas flexibility-related measures reached significance only at the end. The progression in the balance- and stability-related measures was characterized by early improvements over the first three to four weeks of training, and reached a plateau (did not change) for the rest of the training.

**Conclusions:** The progression in balance and postural stability is achieved earlier and susceptible to plateau out, while mobility and flexibility continues to improve during balance training.

## 1. Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder, which is traditionally managed by symptomatic treatments [1]. Among motor and non-motor manifestation of PD, axial (gait and posture) symptoms evolve more rapidly [2]. As PD progresses, non-dopaminergic motor circuits are also involved, exacerbating the axial motor features that do not usually respond to standard antiparkinsonian medication [3, 4]. Gradual deterioration of muscle strength, balance, and gait, causes postural instability and immobility [5], which considerably diminish quality of life, and are known as risk factors for fall [6, 7]. Several studies suggested rehabilitation as an adjuvant to pharmacological and surgical treatments [1, 8], which is proven to slow down the progression of PD and act as a neuroprotective strategy [9–11].

Although it is well evidenced that the physical exercises counteract the motor degradation (especially balance and gait) in patients with PD [12, 13], still many open questions remain regarding the optimal intervention. Training programs are prescribed based on empirical experiences [1] and a definite rationale for development of individualized and impairment-based interventions is still lacking [14, 15]. Several studies compared different training programs (e.g. resistance, balance, treadmill training) [4, 13], or investigated the effects of specific training modality on various clinical outcomes [16, 17]. In addition, numerous reviews and meta-analysis were carried out on randomized controlled clinical trials (RCT) to recommend evidence-based exercise guidelines [1, 12, 18–22]. However, these reviews all indicate that there is a broad heterogeneity in RCTs regarding the optimal delivery (dosage, frequency, duration), and content of exercises (specificity, complexity, needed modalities) for each targeted stage of the disease. Apart from heterogeneity among RCTs, most RCTs used multicomponent training programs as well as insensitive and multidimensional assessments, which further caused these reviews to be inconclusive [4, 8, 23]. These studies highlight the need for disclosing the dose-response relationship for improvement of postural control as a result of different training modalities and exercise components [8, 22]. Furthermore, the most sensitive and well-defined clinical measures to assess the effect of trainings on postural control is still undetermined [2, 4].

The further we gain knowledge about the learning dynamics of postural control during a training program, and in particular, balance training, the closer we come to an answer for an optimal patient-specific training regimen. Nonetheless, the dynamics of the postural control motor learning is relatively unknown due to the paucity of longitudinal studies with multipoint assessments, over a course of training. The majority of RCTs are designed with assessments at baseline and follow-up after intervention; and only a few used intermediate assessments during a training program [24–26]. Multipoint-assessment design is generally used to evaluate the follow-up lasting effects of an applied surgical [3] or physical [6, 27] therapy, or to investigate the natural progression of L-dopa treated PD [2, 7]. To the best of our knowledge, there is no study which investigated the learning dynamics in postural control during a balance-training program. Some studies suggest that the learning rates in dual-tasking or in upper extremities functions in PD patients are reduced compared to healthy subjects [1, 13, 28]. Peterson et al. [28] also found that people with PD have different learning dynamics and retention pattern when exposed to translational perturbation in one day and re-exposed the next day for assessment. Yet, these patients

were not involved in a training program. Therefore, a longitudinal study of postural control learning dynamics on the basis of sensitive and quantitative measures, is highly demanded.

Given the many contributing factors to postural control (e.g. flexibility, strength, balance) as well as the inefficiency of clinimetric measurements provided yet, inconsistent results may arise in the investigations of postural control learning dynamics. In our previous study, we proposed a computational framework, which disentangles the 'stability' and 'flexibility' degree – denoted by  $K_p$  and  $K_n$ , respectively – in patients with PD. The framework was based on general postural sway measures, which were earlier shown to be sensitive to different types of training programs [23]. Furthermore, the framework showed to be sufficiently sensitive to balance-training programs [29, 30], and as such paved the path for future studies of postural control learning dynamics, using unidimensional and meaningful assessment measures.

In this study, we investigated the learning dynamics of postural control, using our previously proposed postural control model for PD, during a balance-training program. For this purpose, a representative PD cohort receiving a 6-week balance-training program was assessed clinically and experimentally at multiple time points during training. Finally, the patterns for all experimental measures were addressed in conjunction with correspondent patterns in clinical measures; thereby providing recommendations for future prospect of exercise guidelines for PD.

## **2. Results**

### **2.1. Clinical outcomes**

The results of the clinical assessments at pre-, mid-, and post-training are provided in Table 1, including the statistical results.

Table 1  
– Clinical outcomes of patients with PD at pre-, mid-, and post-training

Clinical measure	PD Patients (n = 20)			ANOVA P-value (F-value)	Effect size	Tukey P-value for post hoc comparisons			Change Pattern
	pre-training	mid-training	post-training			pre to mid	mid to post	pre to post	
Functional Balance									
Functional reach test (cm)	23.5 ± 7.9	32.8 ± 6.7*	37.6 ± 6.1†*	< 0.0001 (43.1)	0.694	< 0.0001	< 0.0005	< 0.0001	Continuous
Step test (taps in 15 sec)	13.2 ± 3.5	15.9 ± 4.0*	17.3 ± 3.6*	< 0.0001 (23.9)	0.557	< 0.0001	0.063	< 0.0001	Saturation
Tinetti balance score	14.7 ± 1.5	15.6 ± 0.9*	15.9 ± 0.2*	< 0.0003 (10.3)	0.351	0.015	0.239	0.004	Saturation
Tandem stance <sup>a</sup> – EO (sec)	93.0 ± 27.6	113.7 ± 12.6*	118.3 ± 5.7*	< 0.0001 (16.3)	0.461	0.002	0.102	0.001	Saturation
Tandem stance <sup>a</sup> – EC (sec)	35.4 ± 26.8	54.8 ± 29.1*	72.7 ± 30.2†*	< 0.0001 (23.2)	0.549	0.004	0.012	< 0.0001	Continuous
Functional Mobility									
TUG (sec)	9.1 ± 2.7	7.4 ± 1.6*	6.5 ± 1.4*†	< 0.0001 (23.5)	0.553	0.0007	0.004	0.0001	Continuous
6MWT (m)	226.0 ± 67	254.1 ± 61*	305.5 ± 62*†	< 0.0001 (19.8)	0.510	0.040	0.002	0.0001	Continuous
Tinetti gait score	10.5 ± 1.4	11.5 ± 0.6*	11.8 ± 0.4*†	< 0.0001 (15.3)	0.446	0.007	0.006	0.001	Continuous
Values are reported as mean ± standard deviation.									
Abbreviations: EO, eyes open; EC, eyes closed; TUG, Timed Up and Go test; 6MWT, Six-minute walk test; FRT, Functional reach test; Continuous, continuously improving with significant difference between all time points; Saturation, improvements with saturation at the end – i.e. significant change in the first half of the training (from pre- to mid-training), but then non-significant from mid- to post-training points.									
Post-hoc Tukey tests for pairwise comparisons between time points: *significantly different from pre-training (P < 0.05); †significantly different from mid-training (P < 0.05).									
Significant P-values are in bold.									
<sup>a</sup> Timed tandem stance was performed with the right and left leg in the front position, and then the time of both legs was summed as one scale (with maximum score of 120 sec, considering that the maximum time to complete each stance test was set to 60 sec).									

Table 1 to be inserted here

All measures of functional balance and mobility improved after balance training. The improvement pattern was either continuous with significant difference between all time points (Continuous) or the improvement was observed only at the first part of the training (significant from pre- to mid-training), and came to a saturation for the rest, i.e. non-significant from mid- to post-training (Saturation). All the mobility tests (TUG, 6MWT, Tinetti gait score) exhibited a continuous improvement. In contrast, most of balance tests (i.e. Step test, Tinetti balance score, Tandem stance – EO) presented the Saturation pattern. A few balance tests (i.e. FRT and Tandem stance – EC), however, presented the Continuous pattern.

## 2.2. Experimental and model-based outcomes

The pattern of improvements for the sway measures (RMS, MV, f95,  $\Delta t_c$ ) and model parameters ( $K_p$ ,  $K_n$ ,  $\tau_d$ ) are presented in Fig. 1 and Table 2 (for R-tasks: RO, RC), and Fig. 2 and Table 3 (for F-tasks: FO, FC). The first time point at which each measure achieved

significant change, and further time points if maintained that level of change, are marked with asterisk.  $K_D$  and  $K_I$  did not significantly change in any tasks and were excluded from the figures (see Additional File 1, Fig. S1, for patterns of  $K_D$  and  $K_I$ ).

Table 2

– Sway measures and model parameters of patients with PD, at pre-, week 2, week 4, and post-training, in R-tasks (RO and RC).

Task	PD Patients (n = 20)				ANOVA P-value (F- value)	Effect size	Tukey P-value for post hoc comparisons					
	pre (T1)	week 2 (T2)	week 4 (T3)	post (T4)			T1- T2	T1- T3	T1- T4	T2- T3	T2- T4	T3- T4
RO												
RMS (mm)	5.99 ± 1.80	7.21 ± 2.90	6.78 ± 2.38	6.56 ± 1.98	0.186 (1.66)	0.080	0.346	0.562	0.381	0.842	0.716	0.970
MV (mm/sec)	10.04 ± 3.25	10.22 ± 3.75	11.20 ± 3.41	12.31 ± 4.30†	0.010 (4.13)	0.179	0.994	0.468	0.052	0.266	0.019	0.541
f95 (Hz)	1.14 ± 0.39	1.12 ± 0.35	1.26 ± 0.42	1.37 ± 0.58	0.106 (2.13)	0.101	0.998	0.712	0.243	0.373	0.260	0.792
$\Delta t_c$ (sec)	1.59 ± 0.54	1.75 ± 0.57	1.70 ± 0.41	1.76 ± 0.49	0.531 (0.742)	0.038	0.686	0.821	0.452	0.983	1.000	0.935
$K_p$ (N.m/deg)	16.43 ± 3.78	16.84 ± 3.65	16.96 ± 3.51	18.42 ± 4.88	0.062 (2.58)	0.120	0.958	0.750	0.192	0.998	0.079	0.383
$K_D$ (N.m.sec/deg)	5.87 ± 1.84	5.22 ± 1.93	5.47 ± 1.54	5.94 ± 2.20	0.370 (1.07)	0.053	0.309	0.802	1.000	0.931	0.372	0.788
$K_I$ (N.m/deg/sec)	1.46 ± 0.82	1.09 ± 0.74	1.56 ± 0.65	1.31 ± 0.76	0.125 (2.00)	0.095	0.192	0.971	0.916	0.187	0.690	0.436
$K_n$	446.9 ± 215	462.3 ± 214	543.3 ± 211	568.9 ± 197*	0.022 (3.48)	0.155	0.989	0.278	0.036	0.132	0.085	0.956
$\tau_d$ (ms)	135.3 ± 33.0	115.7 ± 44.0	117.1 ± 28.6	109.3 ± 28.5	0.059 (2.63)	0.122	0.339	0.294	0.058	0.999	0.914	0.768
RC												
RMS (mm)	6.64 ± 2.11	7.13 ± 3.09	7.23 ± 2.42	6.63 ± 2.10	0.463 (0.868)	0.044	0.827	0.428	1.000	0.998	0.850	0.201
MV (mm/sec)	11.94 ± 5.37	11.73 ± 5.37	13.81 ± 5.08	14.92 ± 6.12*	0.034 (3.09)	0.140	0.999	0.109	0.047	0.360	0.216	0.725
f95 (Hz)	1.37 ± 0.51	1.47 ± 0.53	1.56 ± 0.52	1.74 ± 0.70	0.085 (2.31)	0.109	0.802	0.472	0.215	0.903	0.389	0.599
$\Delta t_c$ (sec)	1.51 ± 0.59	1.22 ± 0.37	1.23 ± 0.35	1.34 ± 0.47	0.093 (2.24)	0.105	0.180	0.246	0.676	0.998	0.780	0.637
$K_p$ (N.m/deg)	19.64 ± 6.57	18.91 ± 4.62	19.49 ± 5.91	21.13 ± 5.53	0.148 (1.85)	0.089	0.874	0.999	0.354	0.914	0.061	0.474
$K_D$ (N.m.sec/deg)	6.06 ± 2.26	5.84 ± 1.28	6.45 ± 1.72	6.69 ± 2.12	0.110 (2.10)	0.100	0.958	0.637	0.463	0.214	0.199	0.865
$K_I$ (N.m/deg/sec)	1.83 ± 1.37	1.60 ± 0.87	1.66 ± 0.94	2.05 ± 1.09	0.264 (1.36)	0.067	0.831	0.934	0.866	0.991	0.166	0.199

Values are reported as mean ± standard deviation. Significant P-values are in bold.

T1 to T4 refer to pre-, week 2, week 4, and post-training, respectively.

\*significantly different from pre-training ( $P < 0.05$ ); †significantly different from week 2 ( $P < 0.05$ ).

Task	PD Patients (n = 20)				ANOVA P-value (F- value)	Effect size	Tukey P-value for post hoc comparisons						
	pre (T1)	week 2 (T2)	week 4 (T3)	post (T4)			T1- T2	T1- T3	T1- T4	T2- T3	T2- T4	T3- T4	
Sway measures/ Model parameters													
$K_n$	547.1 ± 314	568.8 ± 303	652.1 ± 321	718.0 ± 344	0.035 (3.07)	0.139	1.000	0.575	0.120	0.238	0.071	0.486	
$\tau_d$ (ms)	121.9 ± 40.4	129.8 ± 40.3	127.6 ± 38.1	117.0 ± 41.1	0.428 (0.939)	0.047	0.876	0.907	0.929	0.993	0.456	0.290	
Values are reported as mean ± standard deviation. Significant P-values are in bold.													
T1 to T4 refer to pre-, week 2, week 4, and post-training, respectively.													
*significantly different from pre-training (P < 0.05); †significantly different from week 2 (P < 0.05).													

Table 3

– Sway measures and model parameters of patients with PD, at pre-, week 2, week 4, and post-training, in F-tasks (FO and FC).

Task	PD Patients (n = 20)				ANOVA P- value (F- value)	Effect size	Tukey P-value for post hoc comparisons					
	pre (T1)	week 2 (T2)	week 4 (T3)	post (T4)			T1- T2	T1- T3	T1- T4	T2- T3	T2- T4	T3- T4
FO												
RMS (mm)	10.72 ± 2.89	9.20 ± 2.47	9.73 ± 2.21	9.37 ± 1.98	0.041 (2.94)	0.134	0.105	0.397	0.227	0.674	0.987	0.840
MV (mm/sec)	19.80 ± 6.52	19.17 ± 6.30	19.89 ± 5.82	18.51 ± 4.70	0.616 (0.603)	0.031	0.944	1.000	0.631	0.933	0.937	0.629
f95 (Hz)	1.05 ± 0.24	1.12 ± 0.22	1.31 ± 0.33*†	1.32 ± 0.35*	0.0001 (8.11)	0.299	0.549	0.016	0.020	0.026	0.059	0.996
$\Delta t_c$ (sec)	1.58 ± 0.44	1.43 ± 0.45	1.21 ± 0.25*	1.31 ± 0.28*	0.003 (5.35)	0.220	0.648	0.006	0.043	0.116	0.666	0.308
$K_p$ (N.m/deg)	18.52 ± 4.34	18.69 ± 5.21	20.49 ± 5.78	19.75 ± 5.21	0.021 (3.50)	0.156	0.992	0.123	0.276	0.237	0.397	0.299
$K_D$ (N.m.sec/deg)	5.23 ± 1.65	5.12 ± 1.46	5.34 ± 1.17	5.49 ± 1.33	0.602 (0.625)	0.032	0.990	0.990	0.844	0.824	0.088	0.868
$K_I$ (N.m/deg/sec)	1.93 ± 1.21	1.96 ± 1.36	1.88 ± 0.82	1.89 ± 1.17	0.986 (0.048)	0.003	1.000	0.992	0.999	0.983	0.995	1.000
$K_n$	803.6 ± 262	787.5 ± 259	804.8 ± 172	817.5 ± 208	0.920 (0.164)	0.009	0.988	1.000	0.983	0.981	0.934	0.980
$\tau_d$ (ms)	134.8 ± 34.8	125.1 ± 27.2	123.8 ± 31.7	111.9 ± 23.8	0.032 (3.15)	0.142	0.554	0.680	0.072	0.998	0.053	0.295
FC												
RMS (mm)	14.14 ± 2.83	13.40 ± 3.34	12.46 ± 2.33*	12.40 ± 2.81*	0.013 (3.90)	0.170	0.636	0.018	0.039	0.532	0.427	0.999
MV (mm/sec)	29.15 ± 7.83	26.56 ± 7.57	28.07 ± 8.34	26.40 ± 7.22	0.096 (2.22)	0.105	0.128	0.845	0.171	0.548	0.999	0.670
f95 (Hz)	1.23 ± 0.34	1.21 ± 0.24	1.42 ± 0.34†	1.44 ± 0.43	0.002 (5.81)	0.234	0.974	0.065	0.106	0.014	0.076	0.988
$\Delta t_c$ (sec)	1.43 ± 0.40	1.27 ± 0.26	1.18 ± 0.17	1.11 ± 0.15*	0.001 (6.59)	0.258	0.221	0.061	0.016	0.488	0.091	0.576
$K_p$ (N.m/deg)	18.82 ± 4.43	18.69 ± 5.10	20.34 ± 4.82*	20.12 ± 5.30	0.046 (2.84)	0.130	0.999	0.042	0.105	0.277	0.415	0.971
$K_D$ (N.m.sec/deg)	5.17 ± 1.54	5.29 ± 1.93	5.27 ± 1.57	5.80 ± 1.43	0.120 (2.03)	0.097	0.950	0.967	0.051	1.000	0.580	0.256

Values are reported as mean ± standard deviation. Significant P-values are in bold.

T1 to T4 refer to pre-, week 2, week 4, and post-training, respectively.

\*significantly different from pre-training ( $P < 0.05$ ); †significantly different from week 2 ( $P < 0.05$ ).



Task	PD Patients (n = 20)				ANOVA P-value (F-value)	Effect size	Tukey P-value for post hoc comparisons					
	pre (T1)	week 2 (T2)	week 4 (T3)	post (T4)			T1-T2	T1-T3	T1-T4	T2-T3	T2-T4	T3-T4
<b>Sway measures/ Model parameters</b>												
$K_f$ (N.m/deg/sec)	2.14 ± 1.19	2.14 ± 1.08	1.97 ± 1.07	2.51 ± 1.54	0.317 (1.20)	0.060	1.000	0.935	0.614	0.934	0.652	0.248
$K_n$	1273 ± 499	1113 ± 493	1153 ± 415	1145 ± 372	0.298 (1.26)	0.062	0.510	0.290	0.608	0.967	0.969	1.000
$\tau_d$ (ms)	122.8 ± 37.8	124.6 ± 62.8	125.1 ± 48.5	125.1 ± 46.5	0.994 (0.026)	0.001	0.998	0.996	0.995	1.000	1.000	1.000
Values are reported as mean ± standard deviation. Significant P-values are in bold.												
T1 to T4 refer to pre-, week 2, week 4, and post-training, respectively.												
*significantly different from pre-training (P < 0.05); †significantly different from week 2 (P < 0.05).												

In R-tasks (Fig. 1, Table 2), only MV (RO: P = 0.010, F = 4.13; RC: P = 0.034, F = 3.09) and  $K_n$  (RO: P = 0.022, F = 3.48; RC: P = 0.035, F = 3.07) improved (increased significantly) after balance training (Fig. 1, bold plots). MV and  $K_n$  increased by 22.6% and 27.3%, in RO; and by 25% and 31.3% in RC, respectively. The improvement in flexibility-related measures,  $K_n$  and MV, achieved late, at the end of the training program at week 6. In general, the statistical significance in  $K_n$  and MV was stronger in RO than in RC. As for measures related to stability, f95 (RO: P = 0.106, RC: P = 0.085) and  $K_p$  (RO: P = 0.062, RC: P = 0.148) present a modest monotonic increment via balance training (marked with † in Fig. 1). Yet, RMS and  $\Delta t_c$  remained unchanged after training in R-tasks. Patients also showed a trend toward gradual decline in time delay ( $\tau_d$ ) in task RO (P = 0.059).

Table 2 to be inserted here

Figure 1 to be inserted here

In F-tasks (Fig. 2, Table 3),  $K_p$  significantly increased (FO: 6.6%, P = 0.021, F = 3.50, FC: 6.9%, P = 0.046, F = 2.84), which reached significant changes from baseline, at week 4 (FC: P = 0.042). However,  $K_p$  ceased further improvements after week 4 and slightly returned to the baseline level. Likewise, f95 significantly increased (FO: 25.7%, P = 0.0001, F = 8.11; FC: 17%, P = 0.002, F = 5.81), with similar early emergence of improvements at week 4 (FO: P = 0.016; FC: P = 0.014), which further remained at a steady level. Major improvements in f95 achieved from week 2 to week 4 (Table 3).  $\Delta t_c$ , the other stability-related measure, showed decline after training in both F-tasks (FO: 17%, P = 0.003, F = 5.35; FC: 22.4%, P = 0.001, F = 6.59).  $\Delta t_c$  in FO achieved improvements before the cessation of the training program (at week 4, P = 0.006), and did not further decrease; while in FC, it continued progression to the end of the balance-training program (at week 6, P = 0.016). Time delay, as in task RO, generally reduced in FO (P = 0.032, F = 3.15). In view of the developed balance performance as well as reduced  $\tau_d$ , abnormally large RMS in patients significantly decreased (FO: 12.6%, P = 0.041, F = 2.94; FC: 12.3%, P = 0.013, F = 3.90). RMS had an overall reduction in FO; yet in FC, RMS showed a significant early drop at week 4 (P = 0.018), which similar to f95, did not further change and remained at that attained level. The flexibility-related measures,  $K_n$  and MV, in contrast to R-tasks, did not change in F-tasks.

Table 3 to be inserted here

Figure 2 to be inserted here

None of the measures, neither in R-tasks nor in F-tasks, changed in the first two weeks of training (non-significant from pre to week 2). In fact, MV and  $K_n$  in R-tasks, and  $K_p$  and f95 in F-tasks displayed a delay (the steady interval between pre to week 2) before rising to a new level (Fig. 1, 2). On the other hand, although changes in RMS and  $\Delta t_c$  (in F-tasks, Fig. 2), as well as  $\tau_d$  (in RO and FO, Fig. 1, 2), in the first two weeks, was statistically non-significant; they embarked on a quick change in their average values since the onset of the training program.

### 3. Discussion

This study investigated the motor learning dynamics of the postural control in people with PD, using the unidimensional measures of stability and flexibility degree that we proposed in a previous study [30]. The pattern of improvements during a 6-week balance-training program in people with PD was assessed. The evaluated outcomes comprised clinical measures of functional balance and mobility, posturography measures, and parameters of a patient-specific postural control model (particularly, the stability –  $K_p$  –, and flexibility degree –  $K_n$ ). Findings demonstrated that the balance-training program resulted in continuous improvements in mobility- and flexibility-related measures such as TUG, 6MWT, Tinetti gait score; as well as MV and  $K_n$  (flexibility degree), which changed significantly in R-tasks. Furthermore, balance- and stability-related measures – timed tandem stance with eyes open, step test, Tinetti balance score as clinical measures;  $f_{95}$ ,  $\Delta t_c$ , RMS on foam,  $K_p$  (stability degree) as posturographic and model-based measures – showed an early improvement, in F-tasks, and reached a plateau before the end of the training program. The present study proposed a systematic approach to study the impact of specific training programs on postural disabilities in PD; and as such facilitates the design of new individualized and optimal interventions.

The found improvement at mid-training, and from mid- to post-training for clinical measures of functional mobility implies a relatively constant improvement in mobility. Esculier et al. [24] also observed a continuous reduction in TUG for people with PD, at mid-training (week 3) and post-training (week 6) during an 18-session balance training. Improved TUG even after short-term interventions [31, 32], supports the possibility that TUG (i.e. mobility) in PD can improve rapidly. Furthermore, the abrupt and ongoing improvement of gait performance in people with PD was documented with excessively short gait trainings, besides long-term trainings with multi-assessment design. For instance, a minimum of 2-week gait training promoted walking speed and gait performance [15, 33]. In addition, continuing increase in walking capacity – 6MWT –, using multiple assessments during 24 weeks of treadmill training in PD was observed [26]. This improvement, however, was not restricted to gait trainings; rather, short-term strength training [17] or resistance training [34] also caused increase in 6MWT in PD. At the same time, there exist studies, which found no improvement in mobility measures, even after long-term interventions due to high initial values that measures had at baseline or the unfocused, non-specific type of training that was applied [35, 36]. Considering the pivotal role that additional factors like type and duration of interventions play, the above-mentioned conjecture cannot be generalized.

Our findings on clinical balance tests suggest an early improvement (at mid-training) in postural stability, with subsequent plateaued behavior for the rest of the balance-training program. Such behavior – Saturation pattern – was in part, consistent with the results of a few studies, which included a mid-training assessment during a training program [24, 25]. For instance, Esculier et al. [24] reported improvements at mid-training for Tinetti total score, which remained almost the same to the end of the balance training. Unfortunately, none of these articles clearly reported whether a statistically significant change occurred from mid- to post-training; hence, complicating the differentiation between Saturation and Continuous pattern in the second half of program. In the same manner, Ganesan et al. [25] found improvements at mid- (session 8) and post-training (session 16) in Tinetti balance score. However, this improvement was 24.5% up to mid-training and merely 12% from mid- to post-training; suggesting a plateauing form in the second half of the training program (again not statistically tested). As a more objective test of balance, Stankovic [37] asserted that step test and tandem/one-leg stance more precisely discriminate the balance disorder in PD. We found no previous study, which investigated the mid-training changes in either step test or timed tandem stance. However, in a study by Nieuwboer et al. [38], Tandem-EO improved almost to its maximum score, following a minimum of 9 sessions (3 weeks) cueing training (as equal duration and sessions as our mid-training), which favors our results on early improvement of balance scores at mid-training. One may suspect that the Saturation pattern seen in these clinical scales might be the consequence of a natural ceiling effect. However, as for step test, a capability of up to 25 taps was recorded for healthy subjects (not shown here), implying that saturation in step test at 17 taps for PD patients (Table 1) was caused by the limited learning capacity in PD and not the ceiling effect in the assessment measure. Although most balance tests exhibited early-improvement followed by saturation, few balance tests behave differently. FRT showed a Continuous pattern. It is plausible that clinical scales like FRT are in fact assessing multiple tangled aspects of postural control, i.e. balance (or stability) and mobility (or in particular flexibility); considering the proven significant contribution of axial flexibility in FRT [16]. This may reiterate that the commonly used clinical tests have potential shortcomings such as being insensitive [4, 23], being multidimensional in measuring a mixture of contributors to postural control [8, 19], being confined by ceiling effects [39, 40], and being poorly defined in the level of the underlying constructs [8]. All these facts highlight the need to re-define current clinical measures.

Despite the equivocal results that may arise from clinical scales, the consistent set of postural sway measures along with the proposed model-based measures (stability and flexibility degree), provided clear conforming results. Findings revealed a constant improvement in

flexibility-related measures, and early-progressed with plateaued behavior for stability-related measure. The increment in MV and  $K_n$  (flexibility degree) in R-tasks was characterized by a continuous improvement throughout sessions; nevertheless, it appeared significant almost late – only at week 6. Esculier et al. [24] also reported late improvement in MV, only at the end of the 6-week balance-training program. Interestingly, similar to our finding, MV in EC condition hardly improved as compared to EO condition [24]. Moreover, PD patients showed an accumulating capacity to improve the upper extremity movement velocity over a longer course of training (two-year progressive resistance training – PRE) [41]; suggesting the potential in flexibility and range-of-motion (ROM) features to improve continuously. Although both mobility- and flexibility-related measures exhibited a continuous progression, results indicated that flexibility, in contrast to mobility, reached significant changes at later times. Mobility advances sooner, likely because commuting to the rehabilitation center and participating in trainings, in turn, develop the physical and psychological well-being. In fact, the early improvement in mobility may be attributed to leaving the sedentary lifestyle; but its further improvement may be due to the gradual progression in other root factors such as flexibility. Nicely, Shen et al. [42] noticed that patients who dropped out a training program had lower mobility in comparison to non-dropout ones. Whilst usual exercise guidelines (e.g. by American College of Sport Medicine – ACSM) emphasize on longer exercise duration to achieve sustained improvements in flexibility [4] (at least 6 weeks [15]), a minimum of two [33] to four weeks [23] intervention turned out to be sufficient to enhance mobility. It is noteworthy that flexibility-related measures were mainly reflected in R-tasks, although other stability-related measures (such as  $f_{95}$  and  $K_p$ ) also showed modest improvement in R-tasks. Conversely, improved stability in the patients was mainly reflected in stability-related measures in F-tasks since these tasks challenge the stability more intensively.

The pattern of stability-related measures ( $f_{95}$ ,  $\Delta t_c$ ,  $K_p$ , RMS) in F-tasks was characterized by two main features: first, an early improvement during the first four weeks of training, and then a plateaued behavior in the remaining two weeks of the training. As for the early improvement of balance, one potential reason may be that fast strength gain occurs in muscles, during the first weeks of training, due to the neural adaptation and muscle fiber recruitment [17, 21, 39, 43]. Nonetheless, the neural adaptation appears as a transient response, during the first two weeks of training [21], which is shown to have transient central manifestation as well [11]. Apparently, after two weeks of training, the neural changes grow to physiological changes and muscular hypertrophy [44, 45]; which in turn translates to enough strength to significantly influence postural stability at week four. It is well evidenced that enough muscular strength directly contributes to postural stability [9, 39, 46]. The developed stability over a short time span of four weeks, is also in agreement with other studies which noticed improvements in balance performance (such as Berg balance scale, sensory organization test, limit of stability) by minimum of four weeks of training [23, 43, 47]. Furthermore, results revealed that the proposed model-based measures are more conservative than the postural sway measures, considering the smaller value of significance for  $K_p$  (or  $K_n$ ) as compared to  $f_{95}$  and  $\Delta t_c$  (or MV). This is because model-based measures are expressing some more subtle underlying neurophysiology of postural control.

The plateaued behavior in stability-related measures after some early rise was observed in some previous studies. Corcos et al. [41] noted such plateaued behavior in mean elbow flexion torque after 6 months, in favor of the PRE group compared to non-progressive control group which was even worsened over the two-year training program. This is while both PRE and control group had shown similar strength gain during the first 6 months of training; indicating that strength gain is achievable to some extent, regardless of the training program. However, regarding the chronic feature of PD [8, 21], further strengthening demands more focused progressive programs. This observation supports the impression that the attainable strength, and as such the learning capacity for postural stability in PD patients may be limited and has tendency to stop after a while. Likewise, Peterson et al. [28] claimed that people with PD may exhibit early, but not continued improvement in balance performance by training. In their study, the postural responses to translational perturbations in one-day practice were investigated in PD and healthy controls. Unlike healthy controls, improvements in people with PD occurred primarily in the first blocks of trials and then plateaued; whereas healthy controls gradually improved over all blocks of trials [28]. Other possible explanations for such behavior may be the insufficiency of the challenges and stimulus provided in the exercises, or the induced fatigue and detraining effects during the two closing weeks of the program [14, 39, 48]. However, it is less probable in our study since we employed a progressive difficulty level for the exercises throughout sessions. Interestingly, unlike RMS and  $f_{95}$ , which plateaued at a steady level,  $K_p$  and  $\Delta t_c$ -FO relatively reverted back to baseline. There are also studies that addressed such regress-to-baseline pattern in postural sway measures during a training program [48, 49]. However, these results should be interpreted cautiously, given the inherent bounds, or the maximum/minimum normal value that any measure such as  $K_p$ ,  $f_{95}$ , etc. can attain and may stagnate at that level.

As an intriguing finding, our results revealed that improvements in some measures (e.g. MV,  $K_n$ ,  $\Delta t_c$ ,  $f_{95}$ ) occurred sooner (or with stronger significant difference) in EO condition than the EC condition, likely because EC tasks are more difficult. From this perspective,

the continuous improvement in Tandem-EC and  $\Delta t_c$ -FC, compared to the saturated improvement in Tandem-EO and  $\Delta t_c$ -FO is explained. Similarly,  $\tau_d$  showed decline only in EO tasks (RO and FO).

This study had limitations. The inclusion of a PD control group as well as a healthy control group as to limit the placebo effects is lacking. Furthermore, it is intriguing for future studies to design longer interventions with more assessment times during the intervention, as well as during the follow-up inspection. As such, future studies can discover an analytical formula for learning dynamics and dose-response relationships of postural control. Using longer training programs may also reveal the change patterns for other measures such as  $K_I$  and  $K_D$ , which was non-significant in the current study. Future studies also can employ targeted exercises to define the exact added value of each modality.

## 4. Conclusions

The balance-training program resulted in early improvement of postural stability with plateaued behavior, in PD. On the other hand, flexibility-related measures took longer time to show improvement, yet exhibited a continuous progression during the training. Furthermore, improvement in mobility was achieved early at mid-training, and continued to improve to the end of the training. Taken together, the proposed framework provides a basis for the systematic analyses of motor learning dynamics of postural control in PD, and can be used for future studies to design optimal training programs.

## 5. Methods

### 5.1. Participants and Balance-training Program

Twenty patients with PD, diagnosed as outlined by the UK Parkinson's Disease Society Brain Bank Criteria [50] (Hoehn and Yahr  $\leq 3$ , Mini-Mental State Examination score  $\geq 24$ ), who had no other comorbidities (e.g. neurological, musculoskeletal disorders, etc.) were included in the study (Table 4). Patients were eligible if they were able to walk independently for 10 m, and were on stable dopaminergic therapy. All patients provided written informed consent according to the Declaration of Helsinki. The study was approved by the local ethics committee.

Table 4 – Patients' characteristics

Characteristic	PD Patients (n = 20)
	Mean $\pm$ Standard deviation
Age (years)	63.3 $\pm$ 7.5
Gender (male : female)	15 : 5
Height (m)	1.67 $\pm$ 0.08
Weight (kg)	69.7 $\pm$ 14.7
Disease duration (years)	8.15 $\pm$ 4.8
Most affected side (right : left)	14 : 6
Disease severity (Hoehn & Yahr)	1.8 $\pm$ 0.7

The patients received 18 sessions of balance exercises (3 days/week for 6 weeks) in an outpatient rehabilitation center. Each session lasted for 60–90 min, with 10 min warm-up followed by 20 min of conventional rehabilitation (such as stretching, range-of-motion exercise, body-weight strengthening of hip and ankle, volitional/large stepping, forward/backward/sideways walking), and 30–60 min of balance exercises. The balance exercises included 8-directional reaching at different speeds, to different distances, and on different surfaces (on rigid or foam surfaces). Also, maintaining balance in response to unexpected toe-down/up tilt perturbations and in different stance conditions (e.g. quiet standing, tandem standing, semi-tandem standing), while receiving sensory stimulations (e.g. on foam, with closed eyes, with movements of the head), or while performing upper extremity tasks (e.g. throwing ball, reaching, etc.). The exercises were designed based on the task difficulty, which progressed through sessions in order to remain challenging, while considering the patients' safety. All patients completed the balance-training program and none of them reported any side effects.

## 5.2. Testing Procedure and Outcome Measures

Multipoint-assessment design: The clinical assessments were performed three times, at baseline (pre-training), mid-training (i.e. week 3), and after the completion of the training program (post-training, week 6). Additionally, experimental assessments were performed, using static posturography, at four time points: pre-training, post-training (week 6), and two time points during the training program (at week 2 and week 4). All assessments and training sessions were held while patients were ON-medicated, i.e. about 1–2 hour(s) after taking their usual dopaminergic medication.

Clinical assessment [20, 40]: Clinical assessments consisted of functional reach test (FRT), Tinetti performance-oriented assessment tool (balance section), timed tandem stance with eyes open (Tandem stance – EO) and closed (Tandem stance – EC), and step test [37] in order to examine functional balance; as well as Timed Up and Go test (TUG), six-minute walk test (6MWT), and Tinetti performance-oriented assessment tool (gait section), for the assessment of functional mobility. Tandem stance was performed with the right and then left leg, in the front position and until patients reached a maximum of 60 sec in each test; and then the time of both legs was summed as one scale (with maximum score of 120 sec).

Experimental assessment (The whole experimental assessment procedure is completely similar to the method of our previous study and is described in detail in our previous article [30]):

For static posturography, the center-of-pressure (COP) of patients was recorded for 70 sec at 1 kHz, while standing on a force-plate (type 9260AA6, Kistler Instrument AG, Winterthur, Switzerland) in eight trials: quiet stance on rigid surface with eyes open and closed (RO, RC); and on 10.5 cm-thick foam with eyes open and closed (FO, FC); each in two repetitions. The order of tasks were randomized for each patient to avoid any bias caused by learning effects. Patients were allowed to have sufficient rest intervals between the trials, if they needed.

Four postural sway measures were calculated from the COP data for each patient and each task (5–65 sec of each trial and averaged for each task): root mean square (RMS) of the COP displacement, mean velocity (MV), the frequency associated with the 95% of the total power frequency ( $f_{95}$ ), and the time coordinate of the critical point in the stabilogram diffusion function (SDF) diagram ( $\Delta t_c$ ) [51]. RMS provides a measure of sway amplitude, which is normally larger in PD patients [52]. MV also reflects the degree to which patients regulate the spontaneous sway in a flexible manner [30, 53]. Higher MV reflects higher flexibility.  $f_{95}$  and  $\Delta t_c$ , as frequency-domain measures, are associated with the ankle stiffness. Greater  $f_{95}$  (smaller  $\Delta t_c$ ) indicates higher stiffness. However, these measures are the overall outcome of interconnected underlying neurophysiological mechanisms, and therefore were projected onto a postural control model to separate stability and flexibility degree [30].

Based on the COP-based sway measures, the parameters of a patient-specific postural control model of PD (Fig. 3) were estimated through an optimization algorithm (i.e.  $K_p$ ,  $K_D$ ,  $K_I$ ,  $K_n$ ,  $\tau_d$ ) [30]. The model consists of an inverted pendulum, which is defined by body mass  $m_B$  at height  $h$ ; a PID controller ( $K_p$ ,  $K_D$ ,  $K_I$ ) representing the central nervous system (CNS) control performance; and a time delay  $\tau_d$ , which corresponds to the time delay that CNS takes to respond. A disturbance torque ( $T_d$ ) in form of a Gaussian noise (filtered by a low-pass filter with time constant  $\tau_f = 100$  s) is injected into the control loop to mimic the spontaneous sway – scaled by gain  $K_n$ . The output of the model is the COP displacement  $y_p$ , calculated from the body sway angle ( $\theta$ ) [30].

Figure 3 to be inserted here

From the model point of view,  $K_p$  and  $K_n$  exclusively quantify the stability and flexibility degree, respectively, that contribute to the spontaneous sway.  $K_D$  expresses the ankle damping, and  $K_I$  denotes the amount of effort from the CNS to correct for undesired steady deviation from the upright position. Three parameters  $K_p$ ,  $K_D$ , and  $K_I$  adjust the amount of the corrective ankle torque ( $T_a$ ). Accordingly,  $K_p$  is an estimate of the ankle stiffness and therefore greater  $K_p$  is associated with larger  $f_{95}$  (smaller  $\Delta t_c$ ). On the other hand,  $K_n$  adjusts sway amplitude and mainly affects MV and RMS (greater  $K_n$  – more flexibility – manifests in larger MV). Postural sway measures reflect an overall performance of the postural control. As an instance, RMS is simultaneously adjusted by  $K_p$  (stability degree),  $K_n$  (flexibility degree), and  $\tau_d$ . Therefore, we used these model-based measures to prevent misinterpretation of simple postural sway measures like RMS [30, 54]. The model-based measures are sensitive enough to detect improvements after a balance-training program [29, 30].

The sway measures and model parameters constituted the two sets of stability-related ( $f_{95}$ ,  $\Delta t_c$ ,  $K_p$  – stability degree) and flexibility-related measures ( $MV$ ,  $K_n$  – flexibility degree). Improvement in flexibility-related measures ( $MV$ , and  $K_n$ ) is significant on tasks with stance on rigid surface (R-tasks); conversely, improvement in measures related to stability ( $f_{95}$ ,  $\Delta t_c$ , and  $K_p$ ) is significant in foam standing tasks (F-tasks) [17, 30, 55].

All sway measures and model parameters were calculated for each patient in each task, and at each time point of experimental assessment (i.e. pre-, week 2, week 4, and post-training).

## 5.3. Statistical Analysis

The temporal improvements for each of the clinical and experimental outcomes were studied individually in each task. For this purpose, repeated measure analysis of variance (ANOVA) with one factor (Time) was performed for each of the clinical and postural sway measures, as well as the model parameters in each task. Factor Time includes three levels for the clinical measures (pre, mid, post); and four levels for the sway measures and model parameters (pre, week 2, week 4, post). The Tukey test was used for post-hoc multiple pairwise comparisons between time points. Statistical significance was set at  $P < 0.05$ .

## 6. Abbreviations

Parkinson's disease (PD), Center-of-pressure (COP), Root mean square (RMS), Mean velocity (MV), Eyes open (EO), Eyes closed (EC), Rigid surface with eyes open task (RO), Rigid surface with eyes closed task (RC), Foam surface with eyes open task (FO), Foam surface with eyes closed task (FC), Rigid-surface tasks (R-tasks), Foam-surface tasks (F-tasks), Timed Up and Go test (TUG), Functional reach test (FRT), Six-minute walk test (6MWT), Progressive resistance exercise (PRE)

## 7. Declarations

**Ethics approval and consent to participate:** The Ethics committee of Iran University of Medical Sciences approved all protocols. All participants provided written confirmed consent according to the Declaration of Helsinki.

**Consent for publication:** Not applicable.

**Availability of data and material:** The data used during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare no competing interests.

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**Authors' contributions:** ZR designed and partially performed the experiments, performed the mathematical modeling, analysis and interpretation of the data, drafted and revised the manuscript. ACS, SB, and GT substantially contributed to the methodology development, and revising the manuscript. GT critically contributed to the conception and design of the experiment, statistical analysis, and interpretation of the data. KF and SB contributed to the design of the study. All authors read and approved the final manuscript.

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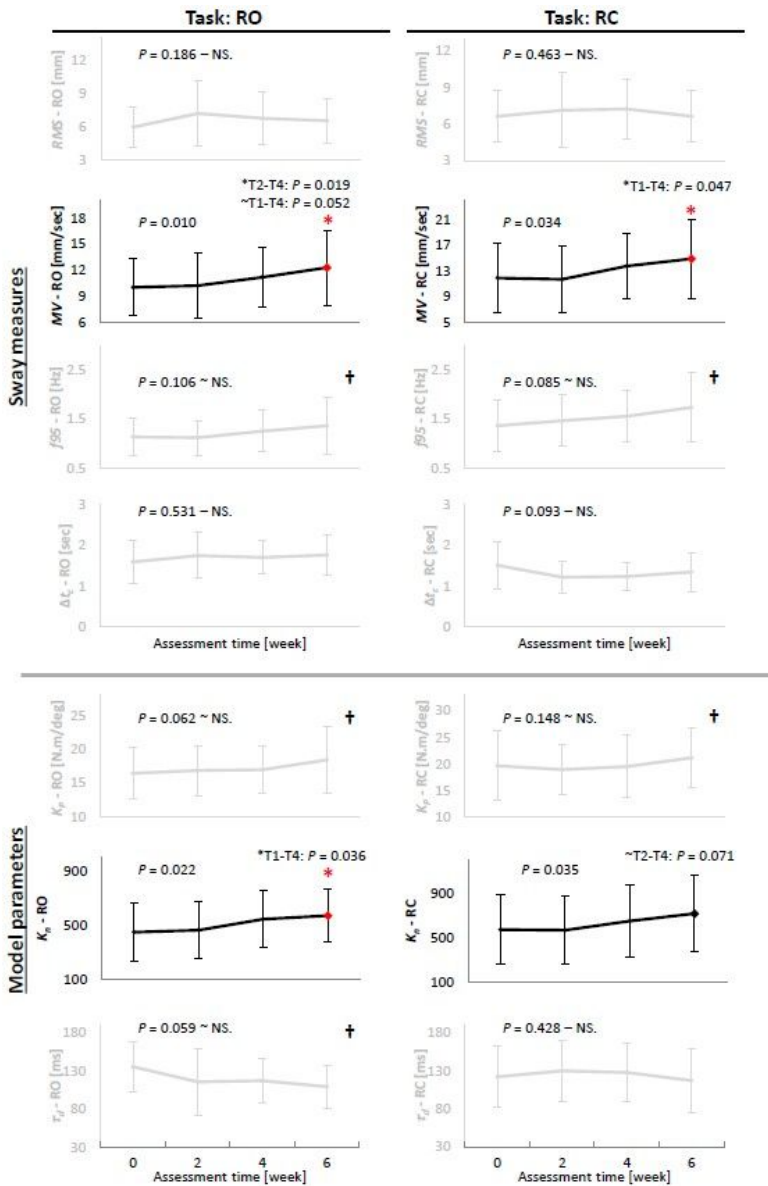
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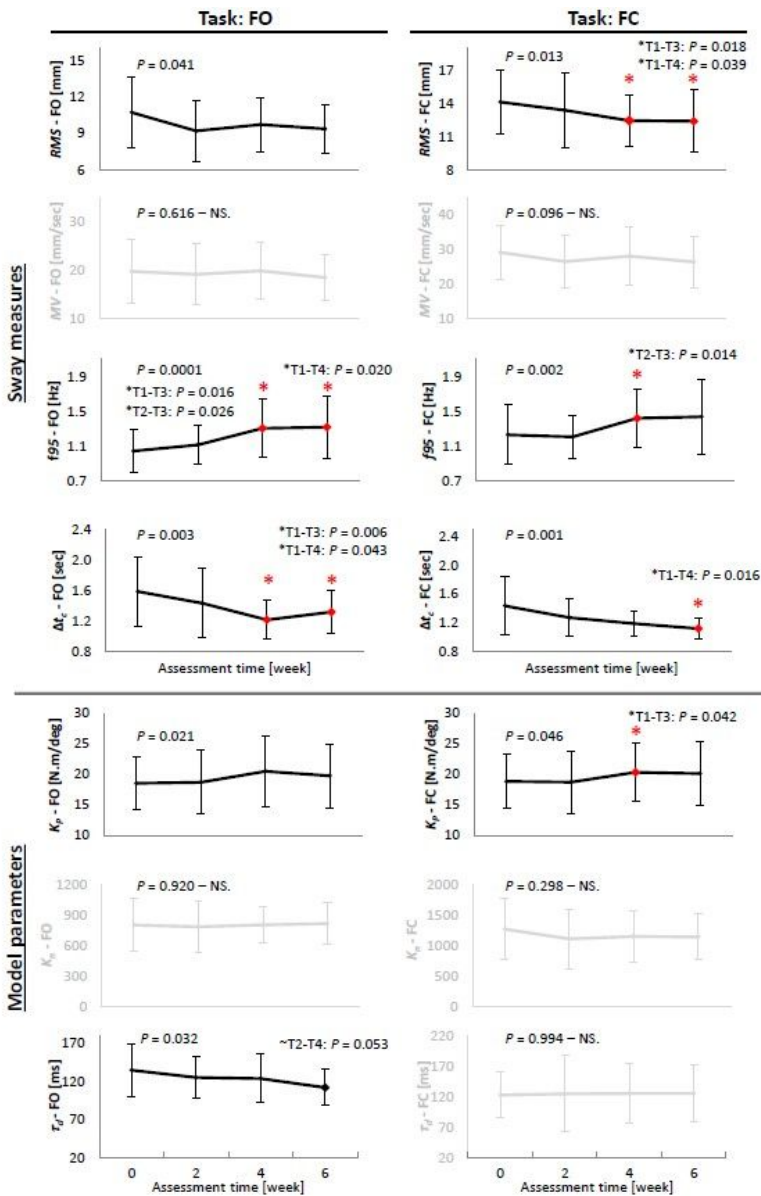
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## Figures



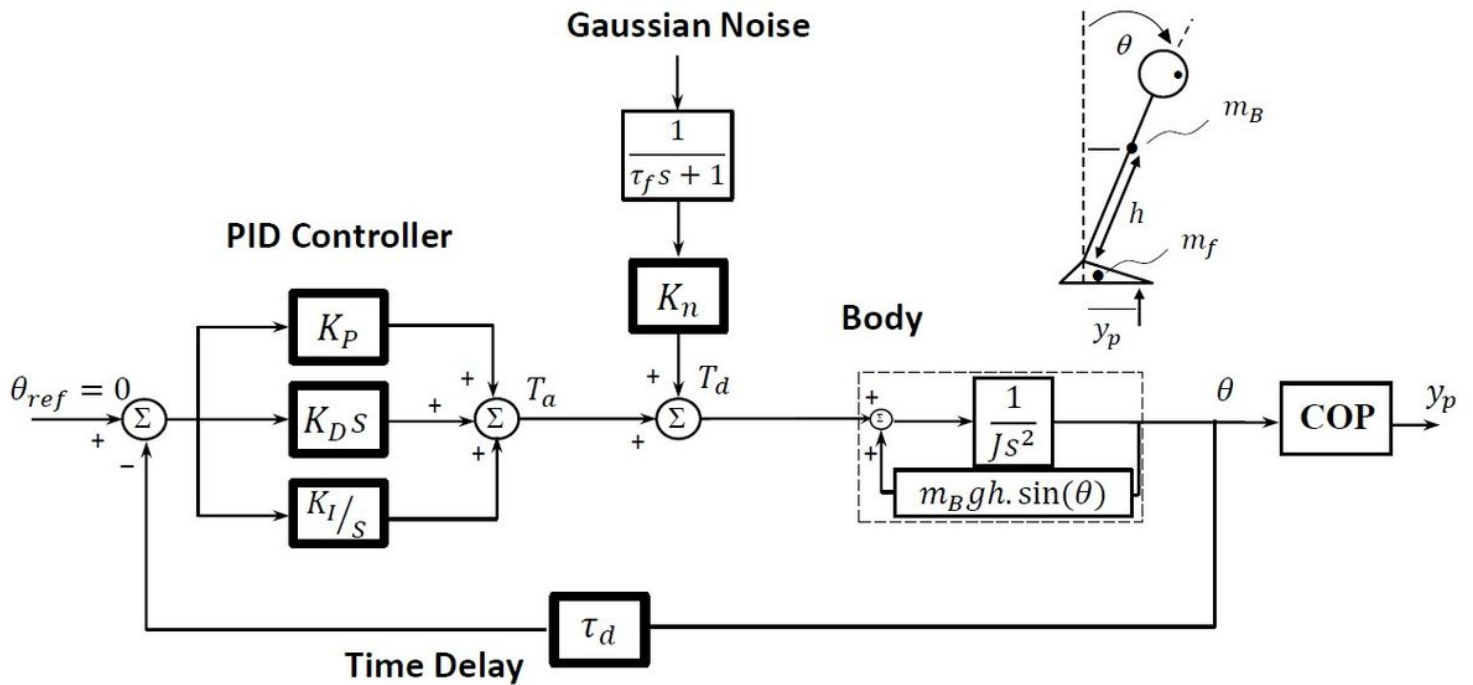
**Figure 1**

The pattern of improvements for sway measures (RMS, MV, f95, Δtc) and model parameters (K<sub>p</sub>, K<sub>n</sub>, τ<sub>d</sub>) for patients with PD, at four time points (i.e. pre-, week 2, week 4, and post-training) during the balance-training program, in tasks with stance on rigid surface with eyes open (RO), and eyes closed (RC). Significant measures are in bold. Measures close to significance are marked with †. Tukey P-values are reported for post hoc pairwise comparisons. The first time point at which significant change appeared, and further time points if that level of improvement retained, are marked with asterisk.



**Figure 2**

The pattern of improvements for sway measures (RMS, MV, f95,  $\Delta t_c$ ) and model parameters ( $K_p$ ,  $K_n$ ,  $\tau_d$ ) for patients with PD, at four time points (i.e. pre-, week 2, week 4, and post-training) during the balance-training program, in tasks with stance on foam with eyes open (FO), and eyes closed (FC). Significant measures are in bold. Tukey P-values are reported for post hoc pairwise comparisons. The first time point at which significant change appeared, and further time points if that level of improvement retained, are marked with asterisk.



**Figure 3**

The patient-specific postural control model of PD. The model consisted of human 'Body', CNS in form of a PID controller, and time delay ( $\tau_d$ ). The 'Body' was modeled by an inverted pendulum with all mass ( $m_B$ ) centered at the height of  $h$  (which were adjusted patient-specifically).  $J$ , moment of inertia of body around ankle axis. The COP displacement ( $y_p$ ) was calculated from the body sway angle ( $\theta$ ) considering the feet mass ( $m_f = 2.01$  kg), which is fully described in [30]. The CNS was modeled by a PID controller:  $K_P$  (proportional gain – quantifies the stability degree),  $K_D$  (derivative gain),  $K_I$  (integral gain).  $T_a$ , corrective ankle torque;  $T_d$ , disturbance torque;  $K_n$ , internal disturbance torque gain which quantifies the flexibility degree;  $\tau_f = 100$  s, time constant for low-pass filter.

## Supplementary Files

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