FLEX CEUs

Parkinson's Disease: Exercise Mode Comparison

RESEARCH ARTICLE

Effects of Resistance Training on Measures of Muscular Strength in People with Parkinson's Disease: A Systematic Review and Meta-Analysis

Abstract

Objective

The aim of this systematic review and meta-analysis was to determine the overall effect of resistance training (RT) on measures of muscular strength in people with Parkinson's disease (PD).

Methods

Controlled trials with parallel-group-design were identified from computerized literature searching and citation tracking performed until August 2014. Two reviewers independently screened for eligibility and assessed the quality of the studies using the Cochrane risk-of-bias-tool. For each study, mean differences (MD) or standardized mean differences (SMD) and 95% confidence intervals (CI) were calculated for continuous outcomes based on between-group comparisons using post-intervention data. Subgroup analysis was conducted based on differences in study design.

Results

Nine studies met the inclusion criteria; all had a moderate to high risk of bias. Pooled data showed that knee extension, knee flexion and leg press strength were significantly greater in PD patients who undertook RT compared to control groups with or without interventions. Subgroups were: RT vs. control-without-intervention, RT vs. control-with-intervention, RT-with-other-form-of-exercise vs. control-without-intervention, RT-with-other-form-of-exercise vs. control-with-intervention. Pooled subgroup analysis showed that RT combined with

aerobic/balance/stretching exercise resulted in significantly greater knee extension, knee flexion and leg press strength compared with no-intervention. Compared to treadmill or balance exercise it resulted in greater knee flexion, but not knee extension or leg press strength. RT alone resulted in greater knee extension and flexion strength compared to stretching, but not in greater leg press strength compared to no-intervention.

Discussion

Overall, the current evidence suggests that exercise interventions that contain RT may be effective in improving muscular strength in people with PD compared with no exercise. However, depending on muscle group and/or training dose, RT may not be superior to other exercise types. Interventions which combine RT with other exercise may be most effective. Findings should be interpreted with caution due to the relatively high risk of bias of most studies.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease [1] and affects approximately six million people worldwide [2]. PD is more prevalent in older age groups with a rapid increase of cases after the age of 60 [3,4]. The incidence rate adjusted for age is estimated to be 9.7 to 13.8 cases per 100,000 people per year [5]. It is expected that these numbers will increase further in the next few decades due to an aging population [6].

PD is a chronic and progressive disorder that is thought to be caused by death of dopaminergic neurons in the substantia nigra of the basal ganglia [7]. There is emerging evidence that other non-dopaminergic structures are also involved [8]. PD includes motor and non-motor symptoms [1,9]. Non-motor symptoms include a decline in cognitive function, psychiatric problems such as depression and anxiety, and autonomic, sleep, and sensory disturbances [10]. Common motor symptoms are tremor, bradykinesia (slowness of movement), rigidity, postural instability and a stooped posture, gait difficulties including freezing of gait (inability to initiate movement), and muscle weakness [1,2,11]. These movement difficulties lead to decreased activity levels in people with PD which, in turn, further impairs strength and physical functioning. Impaired muscular strength may be a primary symptom inherent in PD [12], but this remains controversial [13]. Impaired strength may be of central origin [14], as the ability to activate motor neurons of the active muscle might be impaired due to deficient cortical drive to the muscle [15]. Moreover, muscle weakness may contribute to postural instability and gait difficulties [16,17] and has been identified as a secondary cause for bradykinesia in PD [18].

Available treatment options for PD include pharmacological therapy (dopamine replacement), brain surgery (deep brain stimulation (DBS)) and exercise [1,2]. While there is no cure for PD, these therapies aim to provide symptom relief [7]. Medication and surgery are effective in alleviating the cardinal symptoms (tremor, bradykinesia, rigidity). However, pharmacological therapy only insufficiently improves balance- and gait-disorders and can cause disabling side-effects that become more prominent as the disease progresses [19]. DBS can provide improvements in balance and gait to some extent but its effectiveness is dependent on the stimulation site in the brain and medication co-effects, and decreases over time [20].

Exercise has been shown to be beneficial for people with PD [2,21]. In particular, resistance training (RT) has been shown to improve strength, and some measures of physical function and mobility in PD patients [22–25]. Moreover, it has been demonstrated that increases in muscular strength in response to RT are accompanied by cellular adaptative mechanisms like myofiber hypertrophy in people with PD [26]. RT might also have a neuro-protective effect and slow down disease progression [15,27].Yet, evidence for these beneficial effects arises from a broad variety of RT and the overall effect of RT on measures of muscular strength is unknown. Currently, there are few evidence-based guidelines for RT for people with PD [28]. Therefore, this systematic review aims to (1) collate studies that utilized RT to improve muscular strength in people with PD and update previous reviews, (2) determine the overall effect of RT on measures of muscular strength in people with PD, and (3) identify effective RT interventions to increase strength in people with PD in order to provide evidence-based guidelines for health professionals prescribing RT to PD patients.

Methods

Literature Search Strategy

The literature search was performed in MEDLINE, the Cochrane library, CINAHL, EMBASE, and SPORTDiscus. MeSH or keywords and matching synonyms were combined, including Parkinson's disease, resistance training, and controlled clinical trials. Subject headings were modified for use in the other databases. A copy of the full search strategy in each database can be found in the supporting information (S2 Appendix). Each database was searched from their earliest available record up to 2014 August 15th. Reference lists of all relevant articles were also examined for identification of further eligible studies.

Inclusion and Exclusion Criteria

RT was defined as a form of strength training that is designed to improve components of muscular fitness including strength, power and endurance. It involves the activation of motor units against an external resistance which may be applied to whole body movements or isolated muscle groups. A range of equipment can be used to apply external resistance, for instance bodyweight, free weights, machines with additional weights, elastic bands or water pressure. A RT program is designed by adjusting acute training variables such as the choice of exercises, the order of exercises, frequency of exercise sessions, number of sets and repetitions, intensity levels and rest periods [29,30].

Studies meeting the following criteria were considered for the review: 1) participants of the study had to have PD (any age, any concurrent drug therapy, any disease duration or severity); 2) at least one group of the study must have undergone a RT intervention (> 2 weeks of exercise in order to see a physiological strength change not a neurological improvement in muscle fiber recruitment [31]); 3) at least one outcome measure of muscle strength was reported; 4) the study design was a parallel group design of some sort (i.e. it included at least two arms with an intervention group that performed RT and a control group which did not receive treatment other than standard medical practice or underwent another type of intervention that did not include strengthening exercises). RT studies that did not report acute training variables in a detailed manner and studies that applied strengthening exercises to both/all groups (e.g. comparing two different types of resistance training) were not considered. Only fully peer-reviewed articles with full text available in English were considered.

Selection of Studies

The initial search was undertaken by one researcher (LR). Titles and abstracts of publications obtained by the search strategy were screened and only those that were obviously outside the scope of the review were removed. We were over-inclusive at this stage and received the full text for any papers that potentially met the review inclusion criteria. Following title/abstract screening, two authors (LR, IBS) independently selected trials for inclusion; based on the information within the full reports, eligible trials were included in the review. All trials classified as eligible by either author were retrieved. Disagreement between the authors was resolved by consensus, or third-party adjudication (JTC, GKK).

Data Extraction and Management

Data were extracted by two review authors using a customized form (LR, JTC). This was used to extract relevant data on methodological design, eligibility criteria, interventions (including detailed characteristics of the training protocols), participants, comparisons and outcome measures. There was no blinding to study author, institution or journal at this stage.

Risk of Bias

For all included studies, methodological quality was assessed by two authors independently, using the Cochrane risk-of-bias tool [32]. Each study was graded for the following domains: sequence generation, allocation concealment, blinding (participants & personnel, outcome assessors), incomplete outcome data and selective reporting. For each study, the domains were described as reported in the published study report (or if appropriate based on information from related protocols, or published comments) and judged by the review authors as to their risk of bias according to Section 8.5 of the Cochrane handbook [33]. They were assigned a rating of 'low' if criteria for a low risk of bias were met or 'high' if criteria for a high risk of bias were met. The risk of bias was deemed 'unclear' for a domain if insufficient detail of what happened in the study was reported, or if what happened in the study was known, but the risk of bias was unknown. Disagreements between authors regarding the risk of bias for domains were resolved by consensus.

Measures of Treatment Effect

For each study, mean differences (MD) or standardized mean differences (SMD) and 95% confidence intervals (CIs) were calculated for continuous outcomes using the Cochrane Collaboration's software RevMan version 5.2 [34]. As advised in chapter 7.7.3.1 and 9.4.5.2 of the Cochrane handbook [33] treatment effect estimates (MD, SMD) were based on between-group comparisons using post-intervention data (comparison of final values across groups). When values were missing from continuous data, the authors of the article were contacted. There was one case where standard deviation values were missing [35] which were retrieved after correspondence with the authors. In the event that there was no evidence of heterogeneity of effect ($P>0.1$), a fixed-effect model was used for meta-analysis. In cases where there was evidence of statistical heterogeneity, we checked the results using a random-effects mode.

Assessment of Heterogeneity

Assessment of heterogeneity between comparable trials was evaluated visually with the use of forest plots, as well as Chi^2 tests and I^2 statistics, as outlined in chapter 9.5 of the Cochrane handbook [33]. The level of significance for the Chi^2 test was set at $P = 0.1$: a P value for $Chi^2 < 0.1$ was considered to indicate statistically significant heterogeneity between studies. Values of

I^2 were interpreted as follows: 0%to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% may represent considerable heterogeneity.

Subgroup Analysis

Differences in study designs were considered for subgroup analysis. The studies were grouped into four categories as depicted in Table 1: 1) RT vs. control-without-intervention; 2) RT vs. control-with-intervention; 3) RT with other form of exercise vs. control-without-intervention; 4) RT with other form of exercise vs. control-with-intervention. The subgroup analysis was ad hoc and determined by the available literature. The authors decided on the four categories as they were logical and defined the majority of the included studies.

Results

Fig 1 summarizes the search and selection process based on included and excluded studies.

Included studies

Characteristics of included studies are summarized in Table 1. There were nine eligible studies [35–43]. Of the nine included studies, four were randomized controlled trials (RCTs) [36,39,40,42], one study was match-randomized according to disease severity and gender [35], one study was gender-match-randomized [41] and three studies incorporated an intervention group and a control group (parallel group design) without further details on their study design [37,38,43]. Two studies [35,41] compared RT alone with a control group that received standard medical practice; one study (RCT) [40] compared RT with another intervention (Tai Chi or Stretching); four studies [36–38,43] including one RCT [36] compared an intervention that comprised RT combined with another form of exercise (aerobic or balance training) with a control group that received standard medical practice; two studies [39,42] (both RCTs) compared an intervention that comprised RT combined with another form of exercise (balance training or stretching) with another intervention that did not contain any strengthening component.

Study Cohort

The nine included studies comprised a total of 425 participants with PD. Overall, 168 participants followed a RT regime, 257 were part of a control group (standard medical practice) or another intervention (stretching, balance, treadmill training). The sample size was 47 ± 58 [mean ± SD]. Of all participants 254 were male (59.8%), 156 participants (36.7%) were female and the sex of 15 (3.5%) was not reported. All but one study [35] reported the age of their participants; overall, the mean age of participants was 67.7 ± 8.8 years.

PD severity was described using the Hoehn and Yahr scale (H&Y) [44] in all but one study [36]; however, some studies reported means and standard deviations/errors while others reported the range only. The H&Y scale gives an overall estimate of symptom severity from stage 1 (little signs of disease, unilaterally) to 5 (severe disability, wheelchair bound). The majority of studies included participants with low to moderate disease severity according to the H&Y scale (for details see Table 1). The Unified Parkinson's Disease Rating scale (UPDRS) [45], as another measure of PD status, was described in three studies [36,41,42] (see Table 1 for details). The PD duration was reported in five studies [36–38,40,42] and the mean was 7.1 ± 1.7 years.

Table 1. Study Characteristics.

Study	Participants and Groups Number, sex (f;m), age (yrs), disease details (HY, PD dura)	Resistance Training Program (duration, frequency, exercises, volume, intensity, progression)	Outcome Measures of Strength	Results, Findings (WGC: BL vs. post; BGC: post RT group vs. post other group)		
Resistance training vs. control-without-intervention						
Bloomer et al. (2008) *PGS* [35]	1) RT—8 PD (4;4), 61 ± 2, HY n/a (1–2), PD dura n/a	8 wks, 2 days/wk	BILATERAL 1 RM	Strength leg press		
	2) Con PD—8 PD (4;4), 57 ± 3, HY n/a (1–2), PD dura n/a	Machine leg press, knee flx, calf press	machine-based leg press (kg)		WGC	BGC
		3 x 5–8, each set to a momentary failure	Tested/trained ON	RT	↑	→
		5–10% load increase when performance of 3 x 8 successful		Con PD	→	→
Schilling et al. (2010) *PGS* [41]	1) RT PD—8 PD (3;5), 61.3 ± 8.6, HY 2.1 (1–2.5), PD dura n/a, UPDRS total 19.1±7.0	8wks, 2 days/wk	BILATERAL 1 RM	Strength leg press		
	2) Con PD—7 PD (3;4), 57.0 ± 7.1, HY 1.9 (1–2.5), PD dura n/a, UPDRS total 23.3 ± 18.0	Machine leg press, knee flx, calf press	machine-based leg press (kg/kg)		WGC	BGC
		3 x 5–8: initial load established via trial and error, requirement: subject is able to perform 2 x 8 + 1 x 5–8; Conc phase: fast, ecc: slow	Tested ON	RT	↑	→
		load increase of 5–10% when 3 x 8 achieved		Con PD	→	→
Resistance training vs. control-with-intervention						
Li et al. (2012) *RCT* [40]	1) RT—65 PD (27;38), 69 ± 8, HY (1–4), PD dura 8 ± 9, UPDRS motor 15.32±6.04	24 wks, 2days/wk, 60 min./session	BILATERAL ISOKINETIC DYNAMOMETER	Strength knee ext/flx		
	2) Stretch—65 PD (26;39), 69 ± 9, HY (1–4), PD dura 6 ± 5, UPDRS motor 15.06 ±6.17	Forward/side steps, squats, forward/ side lunges, heel/toe raises with weighted vests & ankle weights	Peak torque (Nm)		WGC	BGC
	3) Tai Chi—65 PD (20;45), 68 ± 9, HY (1–4), PD dura 8 ± 9, UPDRS motor 15.28 ±5.59	wk 1–9: 1–3 x 10–15 body weight, wk 10–14: 1–3 x 10–15 weights 1–2% of body weight, wk 15–19: 1–3 x 10–15 weights 2–4% of body weight, wk 20–24: 1–3 x 10–15 weights 3–5% of body weight	1. knee ext at 60°.sec^{-1}, 2. knee flx at 60°.sec^{-1}	RT	↑	↑ (vs. Stretch)
		(increase of resistance every 5th week)	Tested ON	Stretch	→	→ (vs. RT)
				Tai Chi	↑	↑ (vs. Stretch)
Resistance training with other form of exercise vs. control-without-intervention						
Bridge-water et al. (1997) *PGS* [37]	1) Exc–13 PD (4;9), 67.3 ± 3.9, HY 2.1 (1–3), PD dura 4 ±2.4	12 wks, 2 days/wk	MAX. ISOMETRIC DYNAMOMETER	Strength trunk flx/ext/ rotation		
	2) Con–13PD (6;7), 65.9 ± 10.2, HY 2.0 (1–3), PD dura 4 ± 3.2	1x10: 4 abdominal exercises supine	Max & avg torque (Nm)		WGC	BGC
		1x10 of 7s isometric contractions: upper back prone, lower back prone, on-all-fours exercises (as the subjects ability improved they got more advanced exercises, but overall bodyweight only)	1. trunk flx (from neutral), 2. trunk ext (from 10° flx), 3. right trunk rotation (from neutral), 4. left trunk rotation (from neutral)	Exc	↑	↑
		Aerobic training	2x6sec contractions	Con	→	→

(*Continued*)

Table 1. (*Continued*)

Study	Participants and Groups Number, sex (f;m), age (yrs), disease details (HY, PD dura)	Resistance Training Program (duration, frequency, exercises, volume, intensity, progression)	Outcome Measures of Strength	Results, Findings (WGC: BL vs. post; BGC: post RT group vs. post other group)		
Toole et al. (2000) *PGS* [43]	1) RT + Bal—4 PD (2;2), 73, HY n/a (1–3), PD dura n/a	10 wks, 3 days/wk, 60 min./session	UNILATERAL ISOKINETIC DYNAMOMETER	Strength knee ext/flx		
	2) Con—3 PD (1;2), 71, HY n/a (1–3), PD dura n/a	Machine knee flx/ext, theraband ankle inversion, Balance exercises	Peak torque (ft-lb) right leg		WGC	BGC
		3 x 10 at 60% 4 RM, 6s contraction (2conc-4ecc), weekly readjusted	1. knee ext at 90°.sec^{-1} and 180°.sec^{-1}, 2. knee flx at 90°.sec^{-1} and 180°.sec^{-1}, 3. ankle inversion at 120°.sec^{-1}	RT +Bal	→	→
			Tested ON	Con	↓	→
Allen et al. (2010) *RCT* [36]	1) Exc–24 PD (11;13), 66±10, HY n/a, PD dura 7±5, UPDRS motor 29 ±10	6 months, 3 days/wk (1x per month supervised group session, remaining sessions at home), 40–60 min./session	UNILATERAL STRAIN GAUGE	Strength knee ext		
	2) Con–24PD (11;13), 68±7, HY n/a, PD dura 9±6, UPDRS motor 30 ± 15	Standing up and sitting down, heel raises in standing, half squats, forward or lateral step-ups onto a block	(kg), knee ext, weaker leg, stronger leg, average		WGC	BGC
		wk 1: 2 x 10 body weight or weighted vests up to 2% of body weight, 3 exercises only; from wk 1 onwards: 10–15 reps, more exercises		Exc	→	→
		progression (load increase) individually tailored aimed to reach RPE = 15 (“hard”) on Borg Scale, readjusted every 2–4 wks; Balance exercises		Con	→	→
DiFrancisco-Donoghue et al. (2012) *PGS* [38]	1) Exc–9PD (2;7), 68 ±7, HY 2, PD dura 8 ± 5	6 wks, 2 days/wk, 40 min./session	1RM	Strength knee ext/flx/leg press		
	2) Exc+Vit–9PD (5;5), 67 ±6, HY 2, PD dura 7 ± 4	20 min. aerobic training (treadmill), 20 min. machine-based resistance training: knee ext/flx, leg press, arm curl, chest fly	in lb		WGC	BGC
	3) Vit–9PD (4;5), 69 ±7, HY 2, PD dura 9 ± 6	2x8-15 at 50–80% 1RM, 30s rest	1. knee ext, 2. knee flx, 3. leg press	Exc	↑	↑ (vs. Con)
	4) Con–9PD (6;3), 68 ±8, HY 2, PD dura 9 ± 6	5lb load increase when 1x15 successfully performed	Tested ON	Exc +Vit	↑	↑ (vs. Con)
				Vit	→	→ (vs. Con)
				Con	→	→ (vs. Exc)
Resistance training with other form of exercise vs. control-with- intervention						
Hirsch et al. (2003) *RCT* [39]	1) RT+Bal–6 PD, 70.8 ± 2.8, HY 1.8 ± 0.3, PD dura n/a	10 wks, 3 days/wk, 15 min./session	BILATERAL 4 RM,	Strength knee ext/flx/ plantarflx		
	2) Bal–9 PD, 75.7 ± 1.8, HY 1.9 ± 0.6, PD dura n/a	Machine knee flx/ext, plantarflx, Balance exercises	machine-based (kg)		WGC	BGC
		1 x 12 at 60% 4RM wk 1–2, 1 x 12 at 80% 4RM wk 3–10, 6-9s contraction, 2 min. rest between exercises, fortnightly readjusted	1. knee ext (seated, from 90° of knee flx to full knee ext), 2. knee flx (seated, from 170° of knee ext to 90° of knee flx), 3. plantarflx (seated, from 90° of ankle flx to max plantarflx)	RT +Bal	↑	↑
			Tested ON	Bal	→	→

(*Continued*)

Table 1. (*Continued*)

Study	Participants and Groups Number, sex (f;m), age (yrs), disease details (HY, PD dura)	Resistance Training Program (duration, frequency, exercises, volume, intensity, progression)	Outcome Measures of Strength	Results, Findings (WGC: BL vs. post; BGC: post RT group vs. post other group)		
Shulman et al. (2013) *RCT* [42]	1) RT–22PD (4;18), 65.3 ± 11.3, HY ON 2.2 (2–3), PD dura 6.3 ± 4.0, UPDRS total 48.2 ± 15.5; UPDRS motor 34.5 ± 10.7	3 months, 3 days/wk	UNILATERAL 1 RM	Strength leg press/knee ext		
	2) HIT–23PD (7;16), 66.1 ± 9.7, HY ON 2.2 (2–3), PD dura 5.9 ± 3.9, UPDRS total 45.2 ± 12.2; UPDRS motor 30.3 ± 9.8	Machine leg press, knee ext, knee flx	machine-based		WGC	BGC
	3) LIT–22PD (6;16), 65.8 ± 11.5, HY ON 2.2 (2–3), PD dura 6.3 ± 3.5, UPDRS total 46.6 ± 12.6; UPDRS motor 31.6 ± 9.2	2 x 10 at? % 1RM, load increased as tolerated	1. leg press (lb), 2. knee ext (lb)	RT	↑	→
		Stretching: trunk rotation, hip abduction, and stretches of hamstrings, quadriceps, calves, and ankles (1 x 10)		HIT	→	→
				LIT	→	→

↑increase; → no changes; **1RM** = one-repetition maximum; **ab** = abdominal; **avg** = average; **Bal** = balance training; **BGC** = between-group comparison; **BL** = baseline; **Con** = control group; **conc** = concentric; **ecc** = eccentric; **exc** = exercise; **ext** = extension; **f** = female; **flx** = flexion; **HIT** = high-intensity treadmill training; **HY** = mean Hoehn & Yahr score ± SD (range); **lat** = latissimus dorsi; **LIT** = low-intensity treadmill training; **m** = male; **max.** = maximal; **OFF** = patients were on an overnight withdrawal of medication; **ON** = patients had taken parkinsonian medication; **PD** = Parkinson's disease; **PD dura** = mean duration of PD in years ± SD (range) since diagnosis; **PGS** = parallel group study; **post** = post intervention; **RCT** = randomized controlled trial; **RPE** = rating of perceived exertion; **RT** = resistance training; **sc** = standard care; **TMW** = 10 m walk test; **TUG** = timed up and go; **WGC** = within-group comparison; **wk** = week (duration); **Vit** = vitamin supplementation, **yrs** = mean age ± SD (range).

doi:10.1371/journal.pone.0132135.t001

Training Dose

Reporting of acute training variables across all studies was highly variable. Details about training duration, frequency, volume, intensity, progression, resting periods, movement velocity, which muscle groups were targeted, which equipment was used and about supervision arrangements are collated in Table 1. It is important to note, though, that not all studies provided information on all of those training variables.

In summary, the majority of studies targeted the lower limbs in their RT [35,36,39–43], particularly the knee extensors and flexors, hip extensors and plantarflexors and conducted machine-based training [35,38,39,41–43]. Intervention durations ranged from six weeks [38] to six months [36,40]. Exercise frequency was either two [35,37,38,40,41] or three days per week [36,39,42,43]. Training volume ranged from one to three sets with five to 15 repetitions with or without increasing volume over the course of the intervention. Only two studies reported the duration of rest periods between sets or exercises (30s [38] and 120s [39]). Three studies provided some details regarding movement velocity during each repetition [39,41,43].

Intensity levels were specified in only three studies [38,39,43]. Five studies described intensity levels in a more indirect way, such as maximal effort to volitional fatigue [35,41], aim to reach a rating of perceived exertion (RPE) of 15 ('hard') on the Borg Scale [36], or percent of bodyweight used as resistance [37,40]. One study did not report any information on the

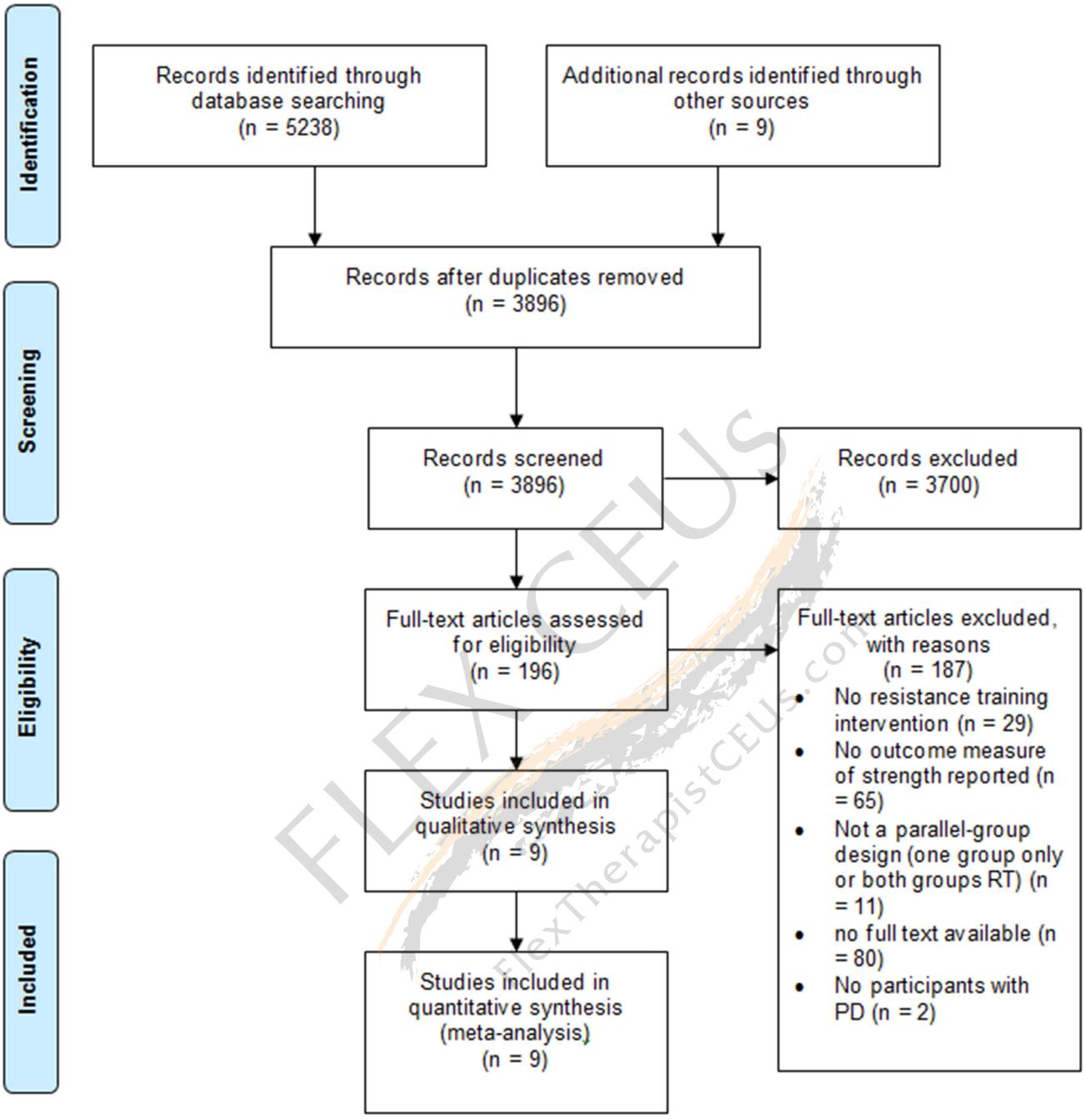

Fig 1. Summary of search and selection process based on included and excluded studies.

doi:10.1371/journal.pone.0132135.g001

intensity of the exercise [42]. All but one study [37] conducted *progressive* resistance training. How progression was implemented was highly heterogeneous in the included studies (Table 1).

Six interventions were supervised [35,37,39–42] and one study was a home-based intervention which included a supervised group session once a month [36].

Details of Outcome

All nine studies recorded muscle strength and all but one study [37] assessed lower limb muscle strength. Knee extensor strength was most commonly reported [36,38–40,42,43]. Four studies [38–40,43] measured knee flexor strength and four studies [35,38,41,42] assessed leg press strength. Two studies recorded ankle muscle strength with plantarflexion [39] and inversion [43] and one study reported strength measures of the trunk (flexion, extension, rotation) [37].

Nonetheless, the ways in which strength was measured was heterogeneous (see Table 1). Some studies conducted strength testing via isokinetic or isometric dynamometry [37,40,43] with different specifications, other studies conducted repetition-maximum (RM) strength tests [35,38,39,41,42] with different testing protocols or used a strain gauge [36]. Units of the strength measurements varied across studies (kg, lb, kg/kg, Nm, ft-lb) and so did reporting of the outcomes (e.g. whether peak torque was reported of mean torque) and of testing protocols (e.g. seat and leg/body position, joint angles, unilateral or bilateral testing, number of sets).

Follow-Up

All studies [35–43] recorded outcomes before and immediately after (pre-post) the RT intervention. Three studies undertook additional outcome assessments at four weeks [37,39] or three months [40] after completion of the intervention. Additionally, one study that ran over six months also undertook outcome assessments midway through the study (at three months) [40].

Risk of Bias

There was a moderate to high risk of bias across all studies (Figs 2 and 3). Due to the nature of the intervention none of the studies utilized blinding of participants or personnel administering the exercises. Blinding of outcome assessors was reported in three studies [36,40,42]. There was a high risk of attrition bias across all studies; only one study [40] provided appropriate information relating to dropouts, exclusions, missing data and approach to analysis (intention-to-treat). Likewise, only one study [38] made any reference to a published protocol. Despite all studies stating that some form of randomization was employed, only four studies [35,36,40,42] provided adequate details on sequence generation and only one study [40] adequately reported allocation concealment.

Muscle Strength

Muscle Strength: Knee Extension. Six studies [36,38–40,42,43] reported knee extensor strength as an outcome. Overall, pooled data revealed significantly higher knee extensor strength in people who had undergone an intervention that contained RT compared to controls-without-intervention (standard medical practice) or controls-with-intervention (i.e. people who had undergone another intervention) (SMD 0.80 [95% CI 0.33, 1.27]; Fig 4). Because there was a significant level of heterogeneity between studies ($P = 0.05$; $I^2 = 56\%$) sensitivity analysis using a random effects model was performed.

Results of the subgroup analysis according to differences in study design are summarized in Fig 5. The largest knee extension strength levels were found in people who performed RT for 24 weeks compared to people who underwent a stretching intervention (MD 41.70 Nm [95% CI 29.33, 54.07]) [40]. Knee extension strength was also significantly higher in people who undertook RT combined with another form of exercise (e.g. aerobic, balance training) compared to people who did not engage in any intervention after 6 weeks [38], 10 weeks [43] or 6 months [36] of training (SMD 0.54 [95% CI 0.05, 1.02]). There was significant heterogeneity

(P = 0.05; I^2 = 75%) in the fourth subgroup analysis (RT with other form of exercise vs. control-with-intervention). Using a random effects model knee extension strength was not significantly higher in people who undertook RT concurrently with balance or stretching exercise for 10 weeks [39] or 3 months [42] than in people who engaged in balance [39] or treadmill training [42] (SMD 0.95 [95% CI -0.54, 2.43]; data not displayed).

Muscle Strength: Knee Flexion. Pooled data from four studies investigating the effects of RT on knee flexor strength [38–40,43] showed significantly higher knee flexion strength in people who had undergone an intervention that contained RT compared to controls-without-intervention or people who had undergone another intervention (SMD 0.59 [95%CI 0.27, 0.90], Fig 6). Although heterogeneity between studies was not statistically significant (P = 0.11) there may be a moderate level of heterogeneity (I^2 = 49%).

Details of the subgroup analysis according to study design are summarized in Fig 7. Also the subgroup analysis revealed significantly higher knee flexion strength in people who had performed an intervention that contained RT. This was observed in people who performed RT for 24 weeks compared to people who engaged in a 24-week stretching intervention (MD 8 Nm [95% CI 1.79, 14.21]) [40], as well as in individuals who undertook simultaneous resistance and balance training over 10 weeks compared with individuals who performed balance training only (MD 16 kg [95% CI 7.48, 24.52]) [39], and in participants who underwent RT combined with aerobic training for six weeks [38] or RT with balance training for 10 weeks [43] compared to controls-without-intervention (SMD 0.97 [95% CI 0.12, 1.83]).

Muscle Strength: Leg Press. Four studies [35,38,41,42] reported leg press strength as an outcome. Overall, pooled data revealed significant higher leg press strength in people who had undergone an intervention that contained RT compared to controls-without/with-intervention (SMD 0.67 [95%CI 0.23, 1.11]; Fig 8).

Details of the subgroup analysis according to study design are presented in Fig 9. There was evidence from a single study [38] that leg press strength was significantly increased after 6 weeks of exercise that contained RT and aerobic exercise in people with PD compared to a control group without-intervention (MD 56.70 lb [95% CI 14.34, 99.06]). In contrast, Shulman et al. [42] found that 3-months RT and stretching did not lead to significantly larger leg press strength compared to treadmill training in people with PD (MD 174.34 lb [95% CI -60.10, 408.78]). Moreover, leg press strength was not significantly higher in participants who undertook RT in isolation for 8 weeks compared to a control group without-intervention [35,41] (SMD 0.69 [95% CI -0.08, 1.47]).

Muscle Strength: Other Outcome Measures. Hirsch et al. [39] found significant higher plantarflexion strength in PD patients who performed RT in combination with balance training over 10 weeks than in individuals who undertook balance training only (MD 23.6 kg [95% CI 13.00, 34.20]). With regards to ankle inversion strength [43] there was no significant difference found between participants who engaged in a 10-week RT-balance intervention and control participants without-intervention (MD 1 ft-lb [95% CI -6.07, 8.07]).

One study [37] reported significantly greater strength values in trunk flexion (MD 15.2 Nm [95% CI 11.79, 18.61]), trunk extension (MD 26.6 Nm [95% CI 22.72, 30.48]), and trunk rotation to the right (MD 8.91 Nm [95% CI 7.28, 10.54]) in people who performed resistance and aerobic training for 12 weeks compared to a control-without-intervention-group. Trunk rotation to the left did not show a significant difference between groups (MD -0.6 Nm [-2.48, 1.28]).

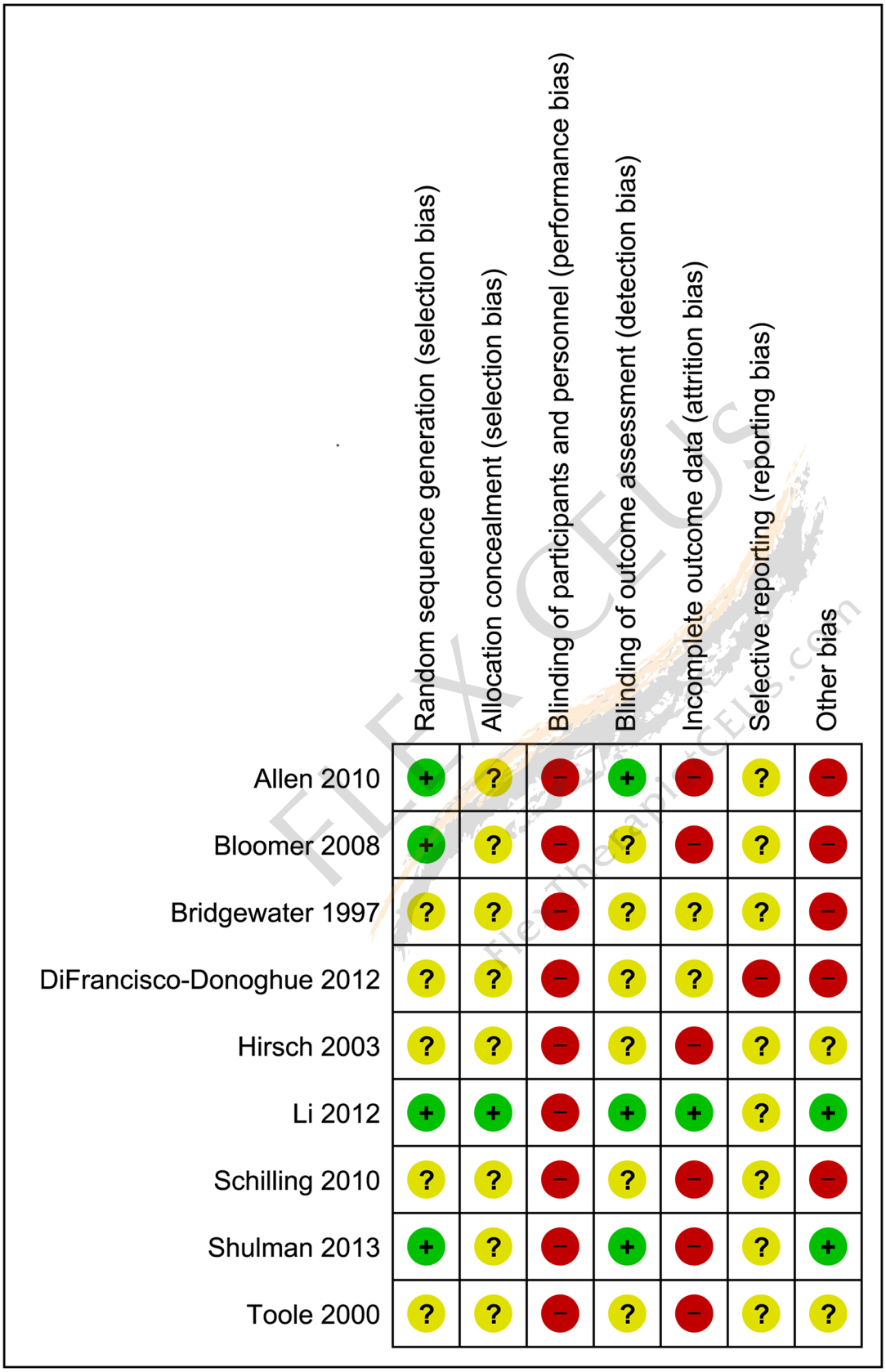

Fig 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

doi:10.1371/journal.pone.0132135.g002

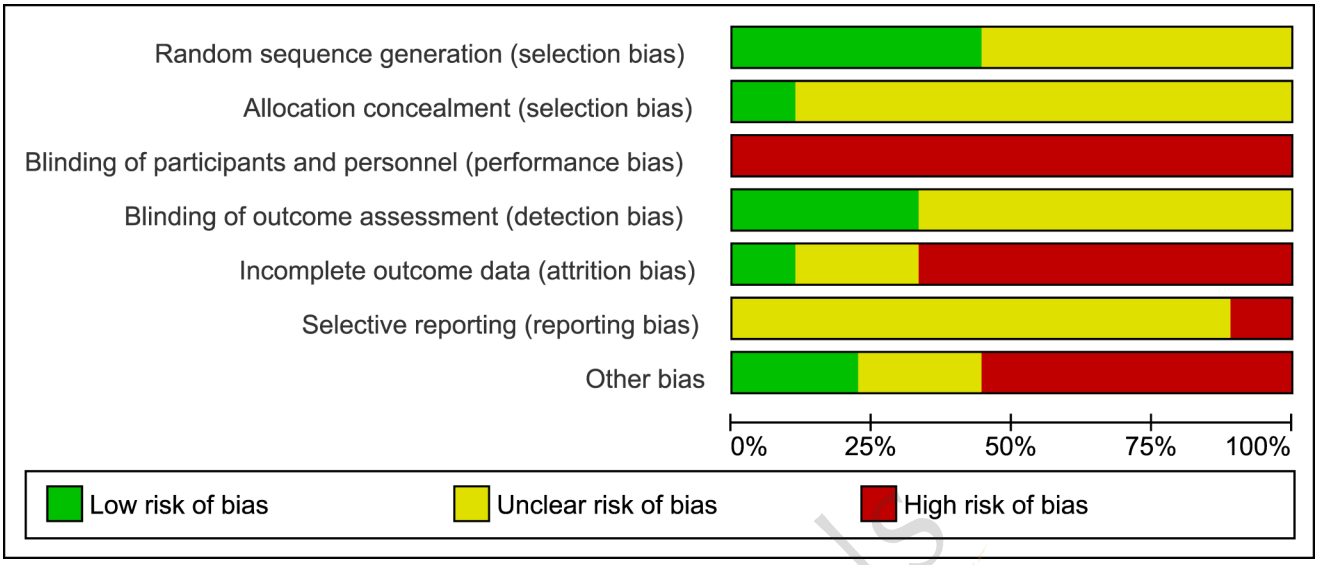

Fig 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

doi:10.1371/journal.pone.0132135.g003

Duration of Effects Post-Intervention

Three studies found that four weeks [37,39] to three months [40] after completion of the intervention, strength values were still significantly larger in the RT-group compared to controls-without-intervention or controls-with-intervention. At the end of a four-week follow-up period, people of the RT group showed higher knee extension strength (MD 16.8 kg [95% CI 4.46, 29.14]) [39], knee flexion strength (MD 11.8 kg [95% CI 1.79, 21.81] [39], plantarflexion strength (MD 15.9 kg [95% CI 3.06, 28.74] [39], trunk flexion strength (MD 4.3 Nm [95% CI 0.89, 7.71]) [37], trunk extension strength (MD 14.9 Nm [95% CI 11.02, 18.78]) [37], and rightwards-trunk-rotation strength (MD 8.37 Nm [95% CI 6.74, 10.00]; leftwards-trunk-rotation strength was not significant MD -2 Nm [95% CI -3.88, -0.12]) [37]. However, Bridgewater and Sharpe [37] noted that 23% of participants in the RT group continued exercising during the follow-up period while the remainder did not; hence, these results should be interpreted with caution. Li et al. [40] reported that the RT group maintained the level of strength during the three-month follow-up period (knee extension MD 15.8 Nm [95% CI 4.93, 26.67]; knee flexion MD 8.6 Nm [95% CI 2.96, 14.24]).

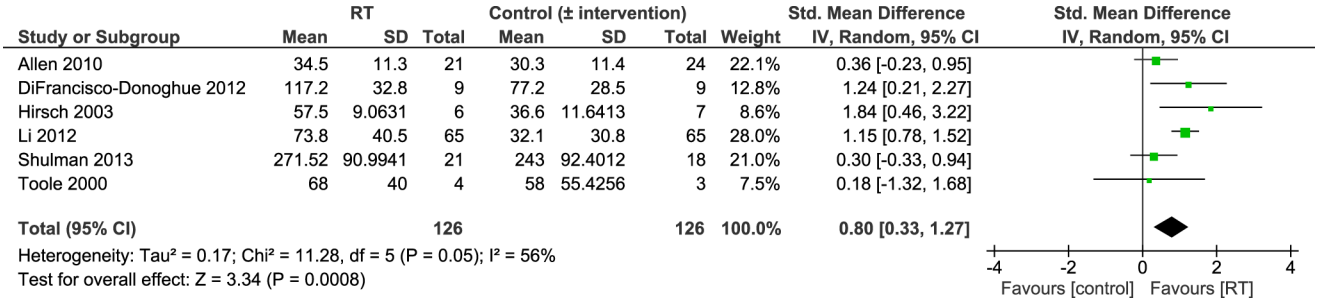

Fig 4. Primary analysis forest plot of comparison: RT vs. control-without/with-intervention, using post-intervention values, outcome: knee extension strength. CI = confidence interval; IV = inverse variance; SMD = standardized mean difference.

doi:10.1371/journal.pone.0132135.g004

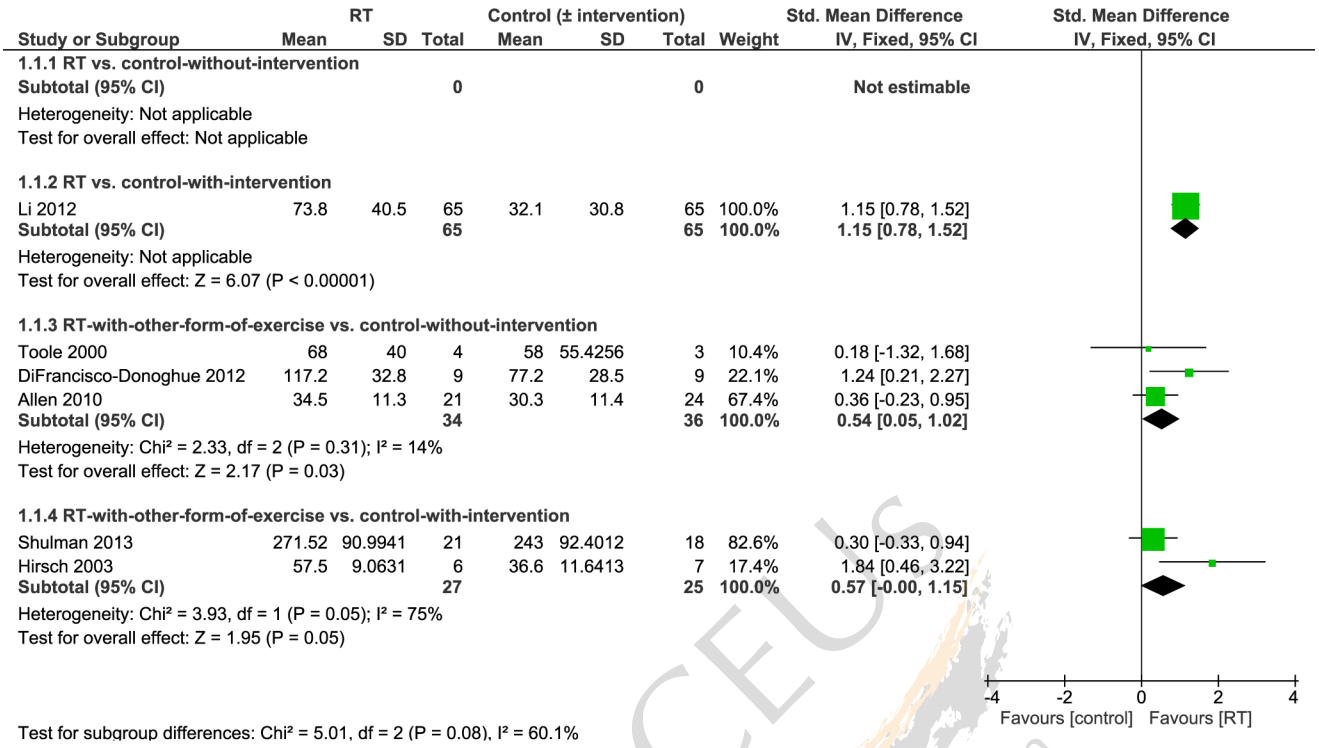

Fig 5. Subgroup analysis forest plot of comparison: RT vs. control-without-intervention, RT vs. control-with-intervention, RT with other form of exercise vs. control-without-intervention, RT with other form of exercise vs. control-with-intervention, using post-intervention values. Outcome: knee extension strength. CI = confidence interval; IV = inverse variance; SMD = standardized mean difference.

doi:10.1371/journal.pone.0132135.g005

Adverse Events

Only three studies [36,40,42] adequately reported exercise-induced complications, side-effects or adverse events. Li et al. [40] provided the greatest level of detail; they recorded adverse events over the course of the intervention (24 weeks) that occurred *during* exercise sessions and *outside* of exercise classes for each of the three intervention groups. *In class* 6.2% RT participants experienced a fall, 6.2% muscle soreness/pain, 4.6% dizziness and 4.6% symptoms of hypotension [40]; overall, the number of incidents per number of participants in the RT group was 0.22 versus 0.14 in the stretching group. *Outside of class*, 47.7% experienced a fall, 6.2% reported lower back pain, and <5% reported ankle sprain, symptoms of hypotension or chest pain [40]; the number of incidents per number of participants in the RT group was 0.63 versus 0.55 in the stretching group. Musculoskeletal damage or injuries following a fall (e.g. fracture) were not

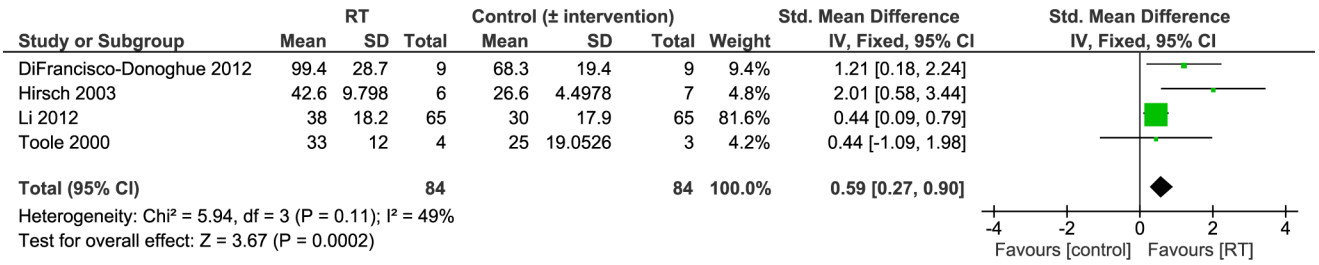

Fig 6. Primary analysis forest plot of comparison: RT vs. control-without/with-intervention, using post-intervention values, outcome: knee flexion strength. CI = confidence interval; IV = inverse variance; SMD = standardized mean difference.

doi:10.1371/journal.pone.0132135.g006

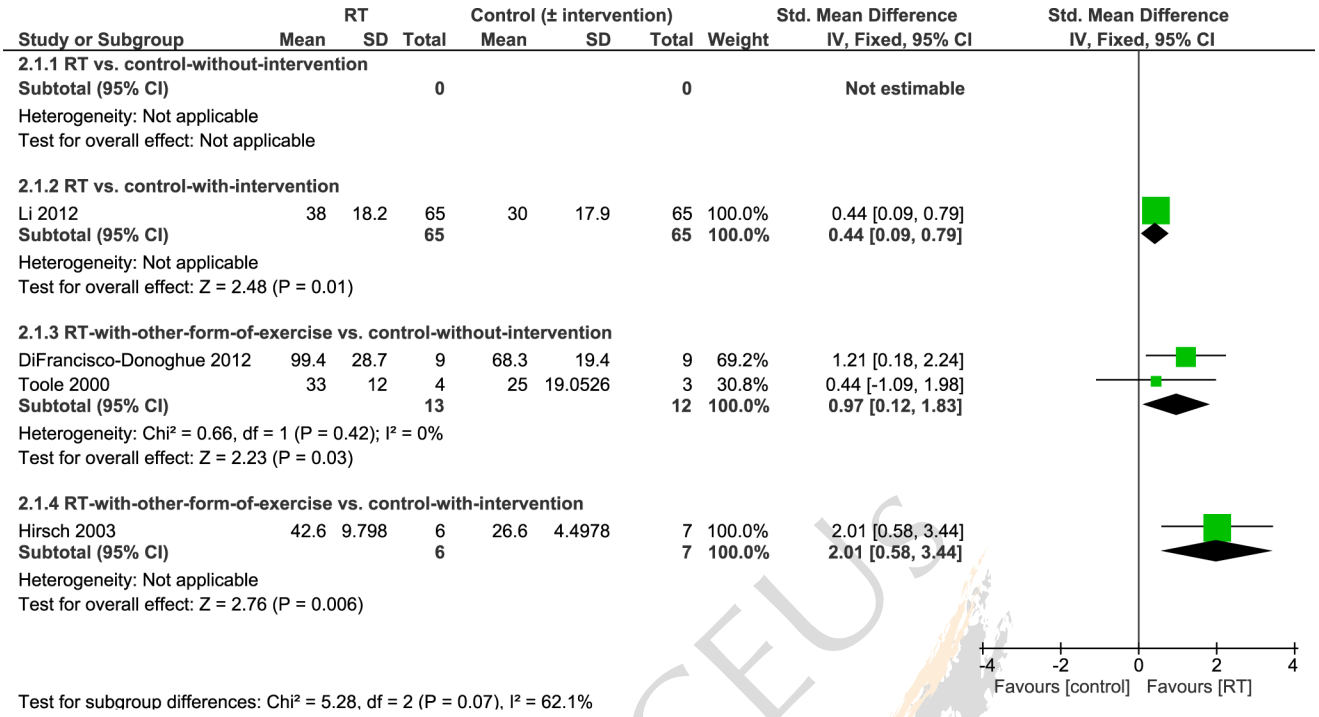

Fig 7. Subgroup analysis forest plot of comparison: RT vs. control-without-intervention, RT vs. control-with-intervention, RT with other form of exercise vs. control-without-intervention, RT with other form of exercise vs. control-with-intervention, using post-intervention values. Outcome: knee flexion strength. CI = confidence interval; IV = inverse variance; SMD = standardized mean difference.

doi:10.1371/journal.pone.0132135.g007

reported, neither was the context of a fall [40]. In the home-based study by Allen et al. [36] none of the participants experienced a fall *during* RT exercise and 14.3% reported back, shoulder or hip pain which appeared unrelated to the RT intervention. In Shulman et al. [42] no adverse events occurred *during* the RT sessions throughout the three-month intervention, however four people (18.2%) dropped out of the RT group due to medical reasons such as hypotension, joint pain and DBS. Although Toole et al. [43] did not report adverse events they stated that in the RT group 44% of trials during the balance pre-test (computerized dynamic posturography) led to a fall while no falls occurred in the post-test. Consequences of these falls and associated injuries were not described.

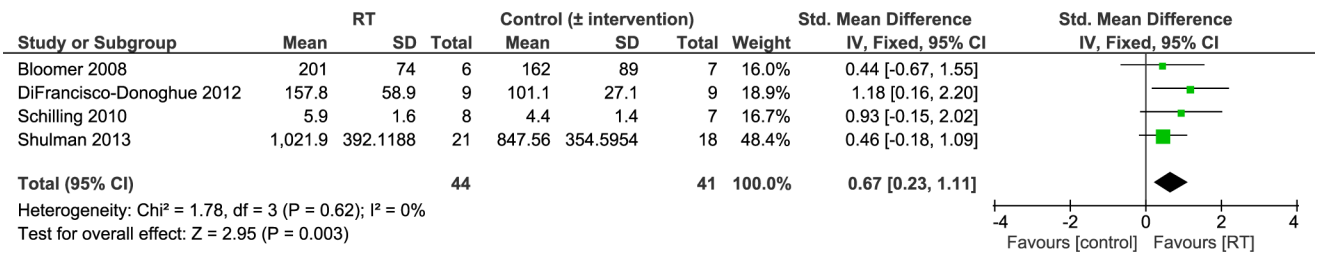

Fig 8. Primary analysis forest plot of comparison: RT vs. control-without/with-intervention, using post-intervention values, outcome: leg press strength. CI = confidence interval; IV = inverse variance; SMD = standardized mean difference.

doi:10.1371/journal.pone.0132135.g008

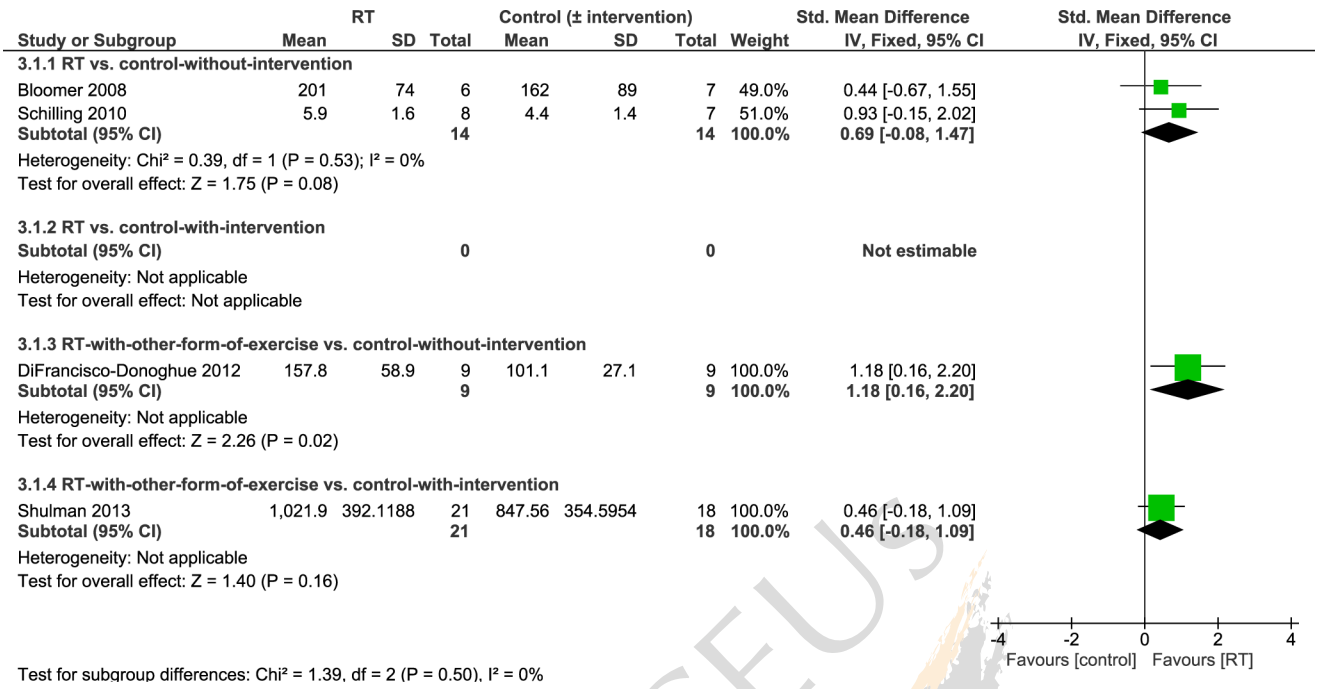

Fig 9. Subgroup analysis forest plot of comparison: RT vs. control-without-intervention, RT vs. control-with-intervention, RT with other form of exercise vs. control-without-intervention, RT with other form of exercise vs. control-with-intervention, using post-intervention values. Outcome: leg press strength. CI = confidence interval; IV = inverse variance; SMD = standardized mean difference.

doi:10.1371/journal.pone.0132135.g009

Discussion

Summary of findings

This systematic review and meta-analysis examines the overall effect of RT on different measures of muscular strength in people with PD. Overall, pooled data (between-group differences) indicated significantly higher muscular strength in people who had undergone an intervention that contained RT compared to controls-without-intervention (standard medical practice) or people who had undergone another intervention. Subgroup analysis according to study design revealed that RT combined with other forms of exercise (balance, aerobic) consistently led to significantly greater strength compared to controls-without-intervention but not compared to controls-with-intervention (balance, treadmill). RT alone did not result in significantly greater strength compared to controls-without-intervention although there was a positive trend. Due to the limited quality of the evidence, and the small sample size of most included studies, the current findings should be interpreted with caution.

Participant Characteristics

The sample cohort included in this review is representative of an early stage PD population with low to moderate disease severity. Generally, it matches that prevalence of PD is higher in older age groups [3,4,46,47]. The majority of participants were male (62%) which reflects higher PD prevalence in men than in women with a male to female ratio of 1.46 [48]. However, a recent meta-analysis [4] identified higher prevalence in males than in females in the 50–59 age-group only. It is currently unknown if findings also apply to more advanced stages of the disease and it is unlikely that RT would be tolerable for patients in advanced stages considering movement and cognitive symptoms of PD.

It should be noted that few studies monitored and reported adverse events and no study described context and consequences of adverse events. Therefore, potential side effects are difficult to determine.

Muscle Strength

Overall, the review suggests that exercise including RT is effective in improving muscle strength in people with PD. Considering that muscle weakness may be a primary symptom of PD [12], contributes to postural instability and gait difficulties [16,17], and has been identified as secondary cause for bradykinesia [18] this is an important insight and it emphasizes the role of RT in the treatment of PD.

However, this evidence arises from a large number of treatment comparisons and subgroup analysis, based on study design, revealed that there may be inconsistent intervention effects on different measures of strength (Figs 5, 7 and 9). It is important to highlight that only two small studies [35,41] have compared RT in isolation to a control group without intervention. All of the other studies have compared RT to other interventions and/or combined RT with another form of exercise (e.g. balance training, stretching, aerobic training). Studies that do not include a 'non-exercise' control group or that combine different interventions do not allow determination of which factors caused strength improvements. Notwithstanding, it may be unrealistic for PD patients to adopt a single form of exercise such as RT and many different types of exercise (treadmill training, dance, cueing, etc.) have shown beneficial effects on a variety of physical function measures [2]. Ultimately, it will be important to design an exercise treatment for people with PD that improves motor and non-motor complications across the disability spectrum and that allows patients to utilize the newly trained skills in their activities of daily living. There may be potential cumulative effects of different exercise treatments on a number of aspects of physical function and future research should focus on determining the most effective combination of interventions. RT should be included in such interventions because, as shown herein, RT is likely to improve muscular strength (see Figs 4, 6 and 8) especially in combination with another form of exercise (as suggested by pooled data of subgroup 3; Figs 5, 7 and 9). Moreover, it has been shown to improve leg muscle power [49], balance control [24,39] and disease severity [24,27,40]. It may also improve some aspects of gait (e.g. gait initiation) [40,50] although this has recently been questioned by two meta-analyses [24,25] which did not find significant gait improvements (gait speed, 6-minute-walking-test, timed-up-and-go-test) in the RT groups.

Interestingly, pooled data from two studies that compared RT in isolation to controls-without-intervention [35,41] (subgroup 1) did not show significantly greater strength in the RT groups (see Fig 9). While there was a positive (non-significant) trend towards greater strength in the RT groups compared to controls-without-intervention, these studies had a small sample size and a moderate to high risk-of-bias.

Differences in the chosen outcome measure, method of assessment, or the muscle group investigated may also play a role in the context of these results. Only one study found significantly greater *leg press* strength in the RT group (Fig 9), whereas pooled data of studies that assessed single-joint knee extension or flexion (Figs 5 and 7) showed significantly higher strength in the RT groups. A leg press strength assessment comprises a multi-joint movement which is more complex and involves more muscles than single-joint movements (e.g. knee extension/flexion). Hence, during a leg press test one does not only assess muscular strength of the quadriceps but also of the hip extensors. This corresponds to suggestions of previous studies that proximal muscles (i.e. hip extensors) show greater strength impairments than distal muscles (i.e. knee extensors/flexors) in people with PD [16,51]. Moreover, it has been observed

that extensor muscles may be more affected by muscle weakness than flexor muscles in PD [13,52]. Taken together, if proximal and extensor muscles show greater strength deficits than distal and flexor muscles it might explain why leg press strength was not significantly higher in the RT groups (Fig 9) as opposed to knee flexor and knee extensor strength (Figs 5 and 7). However, results of this review refer to post-intervention data; muscles have already been trained and one would therefore assume that imbalanced strength deficits across proximal-distal or extensor-flexor muscles may have been evened out. This raises questions whether muscles that are more affected by weakness (extensors and proximal muscles) are as trainable compared to others. It may be necessary to focus a RT program for people with PD on muscle groups that are more prone to weakness in order to balance out the uneven distribution of muscle strength.

Overall though, these reflections are speculative as data available to date are too sparse to draw a definitive conclusion. Nonetheless, results herein show for the first time that strength increases following RT in people with PD may not be as consistent as suggested previously [15,22,23,28], but that they might vary with muscle group or training mode.

In addition, evidence regarding durability of strength improvements in response to RT in people with PD is inconclusive. Available data do not allow assessing whether effects might habituate over time. All studies ran over a short- to medium-term time period of six weeks to six months (see Table 1) and only three studies provided follow-up data [37,39,40] which were not possible to pool. Data from these individual studies [37,39,40] suggest that it is possible to maintain improved strength levels for up to three months after completion of the intervention but potential changes afterwards are unknown to date. Also, it is not clear whether strength increases stagnate over the course of a medium- to long-term intervention. However, since it is clinically of interest to incorporate RT long-term in the treatment of a chronic and progressive condition such as PD, there is a strong need for long-term studies that investigate durability of beneficial effects such as strength and mobility improvements. Corcos and colleagues [27], for example, showed that strength might not increase consistently over the course of a two–year progressive RT intervention in people with PD. Rather, strength increased within the first six months of the intervention and then plateaued for the remaining 18 months. However, these findings need to be confirmed in future RCTs that include a 'non-exercise' control arm [53].

Methodologically, it is important to highlight the heterogeneity in strength measurements utilized in the included studies (testing protocol, muscle groups, reported units) which makes comparability of trials and interpretation of findings difficult. There is certainly need for standardization of strength assessments in future studies in order to improve comparability of studies. We recommend that, where feasible, future RT studies utilize isokinetic dynamometry for strength assessment and that specifications are kept consistent across studies (velocity, seating position, muscle group, unit in Nm). Otherwise, 1RM testing has been shown as an appropriate assessment of strength in people with PD [54] and it might be easier to conduct in a clinical setting. Moreover, it is worthwhile mentioning that all included studies only analyzed maximal voluntary contraction. Future studies should also analyze the effects of RT on other strength related measures such as rate of force development. This would provide valuable information in order to improve future interventions and maximize beneficial effects on other outcomes related to physical function.

Training Dose

In this review, high variation was evident across studies in the training durations, frequencies, modes, volumes, intensities and progression. This makes it difficult to identify characteristics of effective RT interventions and to provide evidence-based guidelines at the present time. It

clearly demonstrates the difficulty in finding a best-practice RT program for people with PD and highlights the need for more research into training dose. As discussed in the paragraphs above, this meta-analysis suggests that a combination of RT with other forms of exercise may be most effective to increase strength in people with PD.

Some guidelines for RT have been provided previously [28] which this meta-analysis generally supports. We also recommend utilizing RT interventions for healthy elderly as a guide for prescribing RT to people with PD. In the elderly, for example, it has been shown that high intensity RT may be more effective in improving strength than low intensity programs whereas training frequency and volume may not be such a crucial factor in influencing the magnitude of strength improvements [55]. However, it has also been shown that the participants' health status and physical function impacts effect size [55] which is important to consider for a PD study population. Moreover, previous findings in a PD population indicate that eccentric RT resulted in greater strength increases than non-eccentric RT in people with PD [56,57]; these findings should be considered for the development of future RCTs.

Finally, it is important to note that *reporting* of acute training variables was heterogeneous across studies as well. Duration, frequency and mode were reasonably well documented in all studies, although more details could be provided for training mode (e.g. seat/body/joint position on machines). However, volume, intensity and progression were reported in distinctly different ways. Often it was not clear in what way the number of repetitions were increased during the intervention or at what intensity levels participants trained and how the program was progressed for each individual. Moreover, some studies also provided details on more variables that are relevant for the overall training dose. These included duration of each training session [36,39,40,43], rest intervals [38,39] and movement velocity [39,41,43]. We suggest that future studies report clearly on each training variable in order to improve comparability between studies.

Comparison to Other Reviews

A number of narrative [15,28] and systematic [22–25] reviews have previously examined the benefits of RT for people with PD. While these previous reviews focused their analyzes on the effects of RT on different health related measures of physical function (e.g. strength, mobility, balance, gait) the current review and meta-analysis investigated the effects of RT on measures of muscular strength in detail and provides a differentiated analysis with respect to various study designs and outcome measures. Generally in agreement with the other RT reviews, our meta-analysis (primary analysis results) also suggests that exercise incorporating RT is effective in improving muscular strength in people with PD. However, subgroup analysis based on study design demonstrated that strength increases following RT may not occur in all muscle groups equally and that not all RT interventions may lead to significant strength improvements in people with PD. This review also emphasizes the lack of studies that compared RT alone with a 'non-exercise' control group.

Quality of Evidence

We found a relatively high risk of bias across all reviewed studies which indicates a limited quality of evidence. Data used in this meta-analysis are mainly from studies with a moderate-high risk of bias (see Figs 2 and 3). However, pooled effect estimates were consistent for all outcome measures with similar magnitudes (see Figs 4, 6 and 8) and generally in agreement with previous reviews [22–25]. Also results of the subgroup analyses showed a positive trend in favor of RT, although they were not statistically significant (e.g. subgroup 4: RT with other form of exercise vs. control-with-intervention). It is important to note that the non-significant

results of our subgroup analysis must not be taken as evidence for no-effect or no-difference between groups. On the contrary, because of the limited evidence, in terms of the quality and the quantity of the included studies, conclusions are not definitive; thus, appropriately powered RCTs that include a non-exercise control arm are required. Our analysis also highlights many areas of methodological uncertainty of RT studies and, therefore, guides the design of future trials.

Limitations and Future Studies

We undertook an exhaustive search based on multiple electronic databases and supplementary sources. Nonetheless, we acknowledge that other relevant studies in the grey literature or in other languages may have been overlooked. Bias from selective reporting of results and from allocation concealment was difficult to determine as the published reports did not provide sufficient details for judgment. Since much was unknown about the quality of most included studies, it impacts on conclusions drawn from this review which are not definitive. We acknowledge that we only investigated effects of RT on strength but not on other outcome measures related to physical function, mobility or non-motor symptoms that may be of interest for treatment of PD (for review see [22–25]). However, we were able to conduct an additional subgroup analysis and this approach suggested that there may be inconsistent effects of RT on measures of muscular strength in people with PD which, in turn, highlights the need for future research.

We recommend that future studies comprise an appropriately powered RCT with adequate sequence generation and allocation concealment, and employ methods to limit detection, attrition and reporting bias. Second, RT interventions should be carefully designed with regards to acute training variables based on a sound physiological rationale (for review see [15,28]) and should aim to investigate a best-practice RT for the treatment of PD over short- and long-term. Third, active monitoring of pre-defined adverse events should be undertaken in future RT studies and reported accordingly. Fourth, measurement of strength should be standardized across studies and strength related measures other than maximal voluntary contraction (e.g. rate of force development) should also be recorded. Fifth, future trials should include participants of all stages of the disease (RT programs will have to be amended accordingly to make it feasible for patients in more advanced stages of the disease) with respect to generalizability of findings towards the overall PD population. Finally, assessment of disease severity should be standardized across studies using the MDS-UPDRS [58] as a subjective, assessor-rated scale; there is a strong need for additional objective measurements of disease severity.

Conclusion

Overall, the current evidence suggests that exercise interventions that contain RT are effective in improving muscular strength in people with PD compared with no exercise. However, depending on muscle group and/or training dose RT may not be superior to other types of exercise (e.g. aerobic). Results indicate that an intervention that combines RT with another form of exercise may be most effective. There are not enough data available yet to confirm evidence-based guidelines for prescribing RT to PD patients.

These conclusions are based on limited methodological quality and relatively small sample sizes in the reviewed studies, and are not definitive. Well reported RCTs in this area are required in order to develop a best-practice RT intervention for people with PD. Until better evidence is available, health professionals are advised to incorporate RT of moderate to high intensity in an exercise treatment that combines different exercise modalities (e.g. aerobic exercise and RT) and that is designed progressively over a mid- to long-term time period.

Supporting Information

S1 Appendix. PRISMA checklist.
(PDF)

S2 Appendix. Search Strategy.
(PDF)

S3 Appendix. Excluded Studies.
(PDF)

Author Contributions

Conceived and designed the experiments: LR JTC SSS IBS GKK. Performed the experiments: LR JTC IBS GKK. Analyzed the data: LR JTC SSS IBS GKK. Contributed reagents/materials/analysis tools: LR JTC SSS IBS GKK. Wrote the paper: LR JTC SSS IBS GKK.

References

1. Nutt JG, Wooten GF (2005) Diagnosis and Initial Management of Parkinson's Disease. New England Journal of Medicine 353: 1021–1027. PMID: 16148287
2. Earhart GM, Falvo MJ (2013) Parkinson disease and exercise. Compr Physiol 3: 833–848. doi: 10.1002/cphy.c100047 PMID: 23720332
3. de Lau LML, Breteler MMB (2006) Epidemiology of Parkinson's disease. The Lancet Neurology 5: 525–535. PMID: 16713924
4. Pringsheim T, Jette N, Frolkis A, Steeves TD (2014) The prevalence of Parkinson's disease: A systematic review and meta-analysis. Movement disorders.
5. World Health Organization (2006) Neurological Disorders: Public Health Challenges. Geneva: WHO Press.
6. Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, et al. (2007) Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology 68: 384–386. PMID: 17082464
7. Schapira AHV (1999) Science, medicine, and the future—Parkinson's disease. British Medical Journal 318: 311–314. PMID: 9924061
8. Bohnen NI, Jahn K (2013) Imaging: What can it tell us about parkinsonian gait? Movement Disorders 28: 1492–1500. doi: 10.1002/mds.25534 PMID: 24132837
9. Chaudhuri KR, Schapira AHV (2009) Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurology 8: 464–474.
10. Park A, Stacy M (2009) Non-motor symptoms in Parkinson's disease. Journal of Neurology 256: S293–S298.
11. Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A (2011) Freezing of gait: moving forward on a mysterious clinical phenomenon. Lancet Neurol 10: 734–744. doi: 10.1016/S1474-4422(11)70143-0 PMID: 21777828
12. Kakinuma S, Nogaki H, Pramanik B, Morimatsu M (1998) Muscle weakness in Parkinson's disease: isokinetic study of the lower limbs. Eur Neurol 39: 218–222. PMID: 9635472
13. Cano-de-la-Cuerda R, Perez-de-Heredia M, Miangolarra-Page JC, Munoz-Hellin E, Fernandez-de-Las-Penas C (2010) Is there muscular weakness in Parkinson's disease? American Journal of Physical Medicine & Rehabilitation 89: 70–76.
14. Stevens-Lapsley J, Kluger BM, Schenkman M (2012) Quadriceps muscle weakness, activation deficits, and fatigue with parkinson Disease. Neurorehabilitation and Neural Repair 26: 533–541. doi: 10.1177/1545968311425925 PMID: 22140196
15. David FJ, Rafferty MR, Robichaud JA, Prodoehl J, Kohrt WM, Vaillancourt DE, et al. (2012) Progressive resistance exercise and Parkinson's disease: A review of potential mechanisms. Parkinson's Disease.
16. Inkster LM, Eng JJ, MacIntyre DL, Jon Stoessl A (2003) Leg muscle strength is reduced in Parkinson's disease and relates to the ability to rise from a chair. Movement Disorders 18: 157–162. PMID: 12539208

17. Nallegowda M, Singh U, Handa G, Khanna M, Wadhwa S, Yadav SL, et al. (2004) Role of sensory input and muscle strength in maintenance of balance, gait, and posture in Parkinson's disease: a pilot study. Am J Phys Med Rehabil 83: 898–908. PMID: 15624568

18. Berardelli A, Rothwell JC, Thompson PD, Hallett M (2001) Pathophysiology of bradykinesia in Parkinson's disease. Brain 124: 2131–2146. PMID: 11673316

19. Poewe W (2009) Treatments for Parkinson disease—past achievements and current clinical needs. Neurology 72: S65–73. doi: 10.1212/WNL.0b013e31819908ce PMID: 19221317

20. St George RJ, Nutt JG, Burchiel KJ, Horak FB (2010) A meta-regression of the long-term effects of deep brain stimulation on balance and gait in PD. Neurology 75: 1292–1299. doi: 10.1212/WNL.0b013e3181f61329 PMID: 20921515

21. Goodwin VA, Richards SH, Taylor RS, Taylor AH, Campbell JL (2008) The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. Movement Disorders 23: 631–640. doi: 10.1002/mds.21922 PMID: 18181210

22. Brienesse LA, Emerson MN (2013) Effects of Resistance Training for People With Parkinson's Disease: A Systematic Review. Journal of the American Medical Directors Association 14: 236–241. doi: 10.1016/j.jamda.2012.11.012 PMID: 23318666

23. Lima LO, Scianni A, Rodrigues-de-Paula F (2013) Progressive resistance exercise improves strength and physical performance in people with mild to moderate Parkinson's disease: a systematic review. Journal of Physiotherapy 59: 7–13. doi: 10.1016/S1836-9553(13)70141-3 PMID: 23419910

24. Chung CL, Thilarajah S, Tan D (2015) Effectiveness of resistance training on muscle strength and physical function in people with Parkinson's disease: A systematic review and meta-analysis. Clin Rehabil.

25. Tillman A, Muthalib M, Hendy AM, Johnson LG, Rantalainen T, Kidgell DJ, et al. (2015) Lower limb progressive resistance training improves leg strength but not gait speed or balance in Parkinson's disease: a systematic review and meta-analysis. Front Aging Neurosci 7: 40. doi: 10.3389/fnagi.2015.00040 PMID: 25852550

26. Kelly NA, Ford MP, Standaert DG, Watts RL, Bickel CS, Moellering DR, et al. (2014) Novel, high-intensity exercise prescription improves muscle mass, mitochondrial function, and physical capacity in individuals with Parkinson's disease. Journal of Applied Physiology 116: 582–592. doi: 10.1152/japplphysiol.01277.2013 PMID: 24408997

27. Corcos DM, Robichaud JA, David FJ, Leurgans SE, Vaillancourt DE, Poon C, et al. (2013) A two-year randomized controlled trial of progressive resistance exercise for Parkinson's disease. Movement Disorders.

28. Falvo MJ, Schilling BK, Earhart GM (2008) Parkinson's disease and resistive exercise: rationale, review, and recommendations. Movement Disorders 23: 1–11. PMID: 17894327

29. American College of Sports Medicine (2010) ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins.

30. American College of Sports Medicine (2013) ACSM's guidelines for exercise testing and prescription. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health.

31. Folland JP, Williams AG (2007) The adaptations to strength training: morphological and neurological contributions to increased strength. Sports Med 37: 145–168. PMID: 17241104

32. The Cochrane Collaboration ([accessed 2014 Mar 03]) Section 8.5 The Cochrane Collaboration's tool for assessing risk of bias. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. Chapter 8 [online]. Available from http://handbook-cochrane.org/.

33. Higgins JPT, Green S, (editors) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

34. Review Manager (RevMan). Version 5.2.10. [Computer program]. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

35. Bloomer RJ, Schilling BK, Karlage RE, Ledoux MS, Pfeiffer RF, Callegari J (2008) Effect of resistance training on blood oxidative stress in Parkinson disease. Medicine & Science in Sports & Exercise 40: 1385–1389.

36. Allen NE, Canning CG, Sherrington C, Lord SR, Latt MD, Close JCT, et al. (2010) The effects of an exercise program on fall risk factors in people with Parkinson's disease: a randomized controlled trial. Movement Disorders 25: 1217–1225. doi: 10.1002/mds.23082 PMID: 20629134

37. Bridgewater KJ, Sharpe MH (1997) Trunk muscle training and early Parkinson's disease. Physiotherapy Theory & Practice 13: 139–153.

38. DiFrancisco-Donoghue J, Lamberg EM, Rabin E, Elokda A, Fazzini E, Werner WG (2012) Effects of exercise and B vitamins on homocysteine and glutathione in Parkinson's disease: a randomized trial. Neurodegenerative Diseases 10: 127–134. doi: 10.1159/000333790 PMID: 22261439

39. Hirsch MA, Toole T, Maitland CG, Rider RA (2003) The effects of balance training and high-intensity resistance training on persons with idiopathic Parkinson's disease. Archives of Physical Medicine & Rehabilitation 84: 1109–1117.

40. Li F, Harmer P, Fitzgerald K, Eckstrom E, Stock R, Galver J, et al. (2012) Tai chi and postural stability in patients with Parkinson's disease. New England Journal of Medicine 366: 511–519. doi: 10.1056/NEJMoa1107911 PMID: 22316445

41. Schilling BK, Pfeiffer RF, Ledoux MS, Karlage RE, Bloomer RJ, Falvo MJ (2010) Effects of moderate-volume, high-load lower-body resistance training on strength and function in persons with Parkinson's disease: a pilot study. Parkinson's Disease: Article no: 824734.

42. Shulman LM, Katzel LI, Ivey FM, Sorkin JD, Favors K, Anderson KE, et al. (2013) Randomized clinical trial of 3 types of physical exercise for patients with Parkinson disease. JAMA Neurology 70: 183–190. doi: 10.1001/jamaneurol.2013.646 PMID: 23128427

43. Toole T, Hirsch MA, Forkink A, Lehman DA, Maitland CG (2000) The effects of a balance and strength training program on equilibrium in Parkinsonism: A preliminary study. Neurorehabilitation 14: 165–174. PMID: 11455079

44. Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17: 427–442. PMID: 6067254

45. Fahn S, Elton R, UPDRS Program Members (1987) Unified Parkinson's disease rating scale. In: Fahn S, Marsden C, Goldstein M, Calne D, editors. Recent developments in Parkinson's disease, Vol. 2. Florham Park, NJ: Macmillan Healthcare Information. pp. 153–163, 293–304.

46. Alves G, Forsaa EB, Pedersen KF, Gjerstad MD, Larsen JP (2008) Epidemiology of Parkinson's disease. Journal of Neurology 255: 18–32. doi: 10.1007/s00415-008-5004-3 PMID: 18787879

47. Fahn S (2003) Description of Parkinson's disease as a clinical syndrome. Ann N Y Acad Sci 991: 1–14.

48. Taylor KS, Cook JA, Counsell CE (2007) Heterogeneity in male to female risk for Parkinson's disease. J Neurol Neurosurg Psychiatry 78: 905–906. PMID: 17635983

49. Paul SS, Canning CG, Song J, Fung VSC, Sherrington C (2014) Leg muscle power is enhanced by training in people with Parkinson's disease: a randomized controlled trial. Clinical Rehabilitation 28: 275–288. doi: 10.1177/0269215513507462 PMID: 24188914

50. Hass CJ, Buckley TA, Pitsikoulis C, Barthelemy EJ (2012) Progressive resistance training improves gait initiation in individuals with Parkinson's disease. Gait & Posture 35: 669–673.

51. Bridgewater KJ, Sharpe MH (1998) Trunk muscle performance in early Parkinson's disease. Physical Therapy 78: 566–576. PMID: 9626269

52. Corcos DM, Chen CM, Quinn NP, McAuley J, Rothwell JC (1996) Strength in Parkinson's disease: relationship to rate of force generation and clinical status. Ann Neurol 39: 79–88. PMID: 8572671

53. Rascol O (2013) Physical exercise in Parkinson disease: moving toward more robust evidence? Movement Disorders 28: 1173–1175. doi: 10.1002/mds.25453 PMID: 23589379

54. Buckley TA, Hass CJ (2012) Reliability in one-repetition maximum performance in people with Parkinson's disease. Parkinson's Disease.

55. Liu C-j, Latham Nancy K (2009) Progressive resistance strength training for improving physical function in older adults. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd.

56. Dibble LE, Hale TF, Marcus RL, Droge J, Gerber JP, LaStayo PC (2006) High-intensity resistance training amplifies muscle hypertrophy and functional gains in persons with Parkinson's disease. Movement Disorders 21: 1444–1452. PMID: 16773643

57. Dibble LE, Hale TF, Marcus RL, Gerber JP, LaStayo PC (2009) High intensity eccentric resistance training decreases bradykinesia and improves Quality Of Life in persons with Parkinson's disease: a preliminary study. Parkinsonism & Related Disorders 15: 752–757.

58. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Movement Disorders 23: 2129–2170. doi: 10.1002/mds.22340 PMID: 19025984

RESEARCH ARTICLE

Resistance versus Balance Training to Improve Postural Control in Parkinson's Disease: A Randomized Rater Blinded Controlled Study

Abstract

Background

Reduced muscle strength is an independent risk factor for falls and related to postural instability in individuals with Parkinson's disease. The ability of resistance training to improve postural control still remains unclear.

Objective

To compare resistance training with balance training to improve postural control in people with Parkinson's disease.

Methods

40 patients with idiopathic Parkinson's disease (Hoehn&Yahr: 2.5–3.0) were randomly assigned into resistance or balance training (2x/week for 7 weeks). Assessments were performed at baseline, 8- and 12-weeks follow-up: primary outcome: Fullerton Advanced Balance (FAB) scale; secondary outcomes: center of mass analysis during surface perturbations, Timed-up-and-go-test, Unified Parkinson's Disease Rating Scale, Clinical Global Impression, gait analysis, maximal isometric leg strength, PDQ-39, Beck Depression Inventory. Clinical tests were videotaped and analysed by a second rater, blind to group allocation and assessment time.

Results

32 participants (resistance training: n = 17, balance training: n = 15; 8 drop-outs) were analyzed at 8-weeks follow-up. No significant difference was found in the FAB scale when comparing the effects of the two training types (p = 0.14; effect size (Cohen's d) = -0.59). Participants from the resistance training group, but not from the balance training group significantly improved on the FAB scale (resistance training: +2.4 points, Cohen's d = -0.46;

Competing Interests: The authors have declared that no competing interests exist.

Abbreviations: BDI, Beck Depression Inventory; BT, Balance Training; CGI-I, Clinical Global Impression–Improvement; FAB, Fullerton Advanced Balance; ICC, intraclass correlation coefficient; LAS, less affected Parkinson's disease side; LSWT, long swing time; MAS, more affected Parkinson's disease side; MDC, minimal detectable change; MMSE, Mini-Mental State Examinaion; MVC, maximal voluntary contraction; PD, Parkinson's disease; PDQ-39, Parkinson's disease Questionnaire; PASE, Physical Activity for the Elderly; RFD, rate of force development; RT, Resistance Training; SSWT, short swing time; TUG, Timed-up-and-go-test; UPDRS, Unified Parkinson's Disease Rating Scale.

balance training: +0.3 points, Cohen's *d* = -0.08). Within the resistance training group, improvements of the FAB scale were significantly correlated with improvements of rate of force development and stride time variability. No significant differences were found in the secondary outcome measures when comparing the training effects of both training types.

Conclusions

The difference between resistance and balance training to improve postural control in people with Parkinson's disease was small and not significant with this sample size. There was weak evidence that freely coordinated resistance training might be more effective than balance training. Our results indicate a relationship between the enhancement of rate of force development and the improvement of postural control.

Trial Registration

ClinicalTrials.gov ID: NCT02253563

Introduction

Postural Instability is one of the major motor symptoms of individuals with Parkinson's disease (PD) and is generally not improved by medication or Deep Brain Stimulation [1–3]. Postural disturbances are one of the independent risk factors for falling [4–6] and fall rates range from 39 to 68% in patients suffering from PD [7,8]. Moderate evidence exists that exercise can improve postural control [9–11]. A study conducted by Canning et al. [12] showed that a combined training targeting balance, strengths and freezing of gait was effective to enhance postural control. Studies have shown that balance training (BT) alone can be effective to improve postural control in people with PD [13,14].

Resistance training (RT) is an effective treatment to improve motor symptoms [15] and strength in PD [16–19]. Reduced muscle strength coincides with an increased risk for falls in PD [4] and is associated with postural impairments [20,21]. Compensatory mechanisms play an important role in PD and the improvement of strength due to resistance training might facilitate the activation of balance related muscle-groups. Accordingly RT might lead to enhanced postural control. Two recently published meta-analysis showed no significant improvement of postural control due to RT in PD [16,17]. The authors report to interpret this result with caution as only 3 studies were analyzed having the assessment of postural control as secondary outcome [22–24]. Furthermore, none of these studies used clinical balance scales to reflect the various dimensions of postural control and the control groups did not received any intervention. Only one study had blinded rating but this study analyzed a combination of training of resistance and balance training [22]. Due to these various limitations, the effect of isolated RT on postural control still remains unclear. Interestingly, a recently published study with healthy elderly showed that RT might be efficacious, as the authors showed better improvement in postural control due to RT in comparison to classical BT [25].

In order to create the most effective exercises, studies often use multidimensional training programs [23,26,27]. These physical therapy techniques are difficult to compare and more specific trials are needed to give further information about which exercise program might be more effective and about the underlying processes leading to the results [9,28].

The aim of the present study was to compare the efficacy of RT with BT to improve postural control in people with PD. BT was chosen because classical BT is widely used in physical therapy to treat individuals with postural instability and further we wanted to pit two typical exercise interventions against each other. In addition, we intended to relate the effects on postural control with changes of several disease associated conditions in order to gain insight which mechanisms play an important role for the improvement of postural control.

Methods

We designed a randomized rater blinded controlled trial to compare the effects of RT with the effects of BT for people with idiopathic PD. The study was registered online at ClinicalTrials.gov (ID: NCT02253563). Registration of the trial was delayed after the enrollment of the first patient due to an administrative error. The authors confirm that all ongoing and related trials for this intervention are registered.

Participants

People were included if they met the following inclusion criteria: (1) diagnosed with idiopathic PD as defined by the UK Brain Bank criteria [29] and by a neurologist specializing in movement disorders, (2) postural instability (Fullerton Advanced Balance (FAB) scale $\leq$ 25 points) [30], (3) able to follow exercise instructions (assessed during a pre-examination during which the FAB scale was performed (see below)). Exclusion criteria were: (1) deep brain stimulation, (2) other diseases that could influence stance- and gait performance, (3) participation in a specific RT or BT program (beside usual physical therapy) during the last 6 months, (4) participation in any other medical, behavioral or exercise treatment (additionally to the usual received therapeutic treatment) during the study period, (5) unstable medication and (6) cardiopulmonary/metabolic diseases that could interfere with the safe conduct of the study protocol. Cognitive impairments (assessed with the Mini-Mental State Examination (MMSE)) were not defined as exclusion criteria so that a representative sample of affected patients could be included.

The study protocol was approved by the local ethics committee (Ethik-Kommission, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Arnold-Heller-Straße 3, 24105 Kiel, Germany, ref. A 146/11) in September 2011 and all participants gave written informed consent prior to participating. All participants had legal capacity to make decisions and patients having a MMSE score<25 gave written informed consent together with their spouse, if applicable. The person of the images in S1 File and S2 File gave written consent to publication.

Screening and Randomization

Participants were screened with a pre-examination prior to inclusion in the study. The FAB scale was performed to determine the level of postural instability. Patients were stratified by gender and level of postural instability and randomized in matched pairs using computer generated random number sequences in a ratio of 1:1. Participants were reassessed for baseline analysis at another day.

Intervention

Participants were randomly assigned into RT or BT (2x/week for 7 weeks). Each session lasted 60 minutes (4–5 participants/group), and consisted of 10 minutes to warm-up followed by 50 minutes RT or BT. Each session was guided by a movement disorders experienced sport

scientist who had experience in neurological rehabilitation and with the help of a sport student (student of kinesiology).

Resistance Training. RT was performed with the aim to improve muscle strength of the lower limbs. The trained muscle groups were hip flexors, extensors and abductors, knee flexors and extensors, ankle dorsiflexors and plantarflexors, as these are muscle groups primary involved in postural control mechanisms [20,21]. The participants' own weight, cuff weights and elasticated bands were used as resistance [31]. Squats, knee extensions, toe/calf raises, hip abductions and other exercises were performed (see S1 File, which shows the performed exercises). In line with training recommendations based on previous studies (e.g. Hass et al. [32]) participants completed three sets of 15–20 repetitions to volitional fatigue of each exercise. With respect to the age of the participants and the stage of disease, exercise intensity was kept on a moderate level in order to avoid injuries. Once participants could complete more than 20 consecutive repetitions of an exercise, they were asked to increase the resistance to a point where they could only complete between 15–20 repetitions in order to keep the training intensity on a consistent level. Resistance was increased by cuff weights, elasticated bands or by the trainer who gave additional resistance. Participants rested for 2 minutes between exercise sets.

Balance Training. BT involved stance- and gait tasks which require feedforward and feedback postural control [13]. Feedforward postural control for example was trained by letting the participants lean forward, backward or sideward, thus letting them control their center of pressure inside the boundaries of their base of support. To practice feedback control one exercise was to perturb the participants by shoulder pulls from the trainer. Training progression during the intervention period was reached by reducing or manipulating sensory information, necessary to obtain balance and by adding movement to make the activity more dynamic. Visual information for example was disturbed by closing the eyes or looking up to the ceiling. Proprioceptive feedback was manipulated by standing on different unstable surfaces instead of normal overground. Each exercise lasted for 45 sec and was performed 3 times, followed by a break of 2 minutes (see S2 File, which shows the performed exercises).

Outcome Measures

Assessments were performed at baseline, 8- and 12-weeks follow-up. Primary outcome measure was the FAB scale [33]. The FAB scale is a 10-item clinical balance scale with a 5-point ordinal scale (0–4) for each item and a maximal score of 40 points (higher values indicate better performance). The FAB scale is validated for individuals with Parkinson's disease with excellent interrater and test-retest reliability [30]. We chose the FAB scale instead of the often used Berg Balance Scale because in contrast to the Berg Balance Scale the FAB scale has less ceiling effect and includes the assessment of reactive postural control [30]. We decided against the frequently used Mini-BESTest as the FAB scale's items are more detailed and it takes less time to perform the FAB scale [30].

Secondary outcome measures: Center of mass (COM) displacement was analyzed during surface perturbations. Participants were asked to maintain their balance without doing steps while standing on a movable platform which shifted unexpectedly towards the anterior or posterior direction (20cm with a velocity of 0.1m/s and an acceleration of $10m/s^2$). Participants were aware neither when the platform would move nor in which direction the surface would change.COM was assessed with an infrared movement analysis system (Qualisys, Gothenburg, Sweden) consisting of six infrared cameras (240 Hz sampling rate). 17 infrared light emitting diodes were placed on anatomic landmarks as described in detail elsewhere [2] and the COM was calculated as the weighted sum of all segments, as adapted from Winter et al. [34]. According to Visser et al. [2] the vector length of three-dimensional COM displacement was

calculated. In order to adapt to different biomechanical requirements due to different sizes of participants, the vector length was normalized to COM height. The average normalized vector length over all backward and forward pulls was calculated, respectively. The area under the curve of the normalized vector length from the beginning until 1 sec after the perturbation was defined as an instability outcome measure (see S3 File, which gives further details about the analysis of the surface perturbations) [2].

The following tests were used additionally: Timed-up-and-go-test (TUG) [35], Clinical Global Impression—Improvement (CGI-I) [36], Unified PD Rating Scale (UPDRS) [37], PD Questionnaire (PDQ-39) [38], Beck Depression Inventory (BDI) [39] and Physical Activity Scale for the Elderly (PASE) [40].

Gait velocity of participants was measured during uninterrupted ground level walking, recorded by light barriers placed at the beginning and at the end of a 5m pathway, which the participants had to cross 5 times. Afterwards, participants were asked to walk 2 min. on a treadmill (Woodway, Weil am Rhein, Germany) with their overground gait velocity. The treadmill comprised two separate belts, each with 4 force transducers (Kistler, Winterthur, Switzerland) (960Hz sampling rate). Contact times (heel strike, toe off) were measured by the force transducers to calculate the following spatio-temporal variables: stride length, double support time, stride time variability, bilateral coordination (Phase Coordination Index (PCI)) [41] and gait asymmetry [41] (see S4 File, which describes in detail the gait analysis).

Maximal isometric leg strength was measured on a custom designed leg press equipped with a force platform (Kistler, Winterthur, Switzerland) (1000Hz sampling rate). Maximal voluntary contraction (MVC) and rate of force development (RFD) was assessed. Results were analyzed for both legs separately according to the less- (LAS) and more (MAS) affected PD side—defined by comparing the sums of the UPDRS items 20–26 for the left and right side separately [42,43] (see S5 File, which describes in detail the strength testing).

All clinical tests were carried out by a rater who was blind to the participant's group allocation. The FAB scale and UPDRS were videotaped and rated by a second rater, blind to participant's group allocation and assessment time.

Testing Procedure

Assessments were performed on two separate days. Participants were tested in the medication ON-state (1 hour after the last intake of antiparkinsonian medication). Each participant performed the baseline, 8- and 12-weeks follow-up measurements at the exact same time of day.

Statistical Analysis

Sample size calculation was performed for the FAB scale as the main outcome. A sample size of 18 participants per group was found to be required to detect a between-group difference of 2 points at the FAB scale from baseline to 8-weeks follow-up (power = 0.9, alpha = 0.05) (G*Power, version 3.1.9 [44]). This predicted difference equate to a large effect size of 0.6 or greater. With an expected 10% drop-out rate we included 20 participants per group.

Between-group differences in demographic and baseline variables were tested using the Mann-Whitney-U-Test. Within group differences were analysed with the Wilcoxon signed rank test.

To compare the effect of treatment between the two training groups, the difference between 8-weeks follow-up and baseline performance was computed for each participant. Both groups were then compared with the Mann-Whitney-U-Test.

Non-parametric statistical tests were used for the demographic, within and between group analyses as some of the outcome variables are ordinal scaled and not all of the variables were normally distributed.

The Mann-Whitney-U-Test was used to compare CGI-I between the groups.

Interrater reliability between the blinded rater and the blinded video rater were analysed by calculating two-way mixed single measure intraclass correlation coefficients (ICC (3,1)).

Cohen's *d* was calculated to evaluate effect sizes.

To analyze the relationship between the magnitude of change in the different outcome variables, Spearman's rank correlation coefficients (Spearman's Rho) were calculated. Those variables which significantly correlated with the changes in the FAB scale were included as independent variables in a multiple linear regression analysis. To analyze the risk of multicollinearity variance inflation factors were calculated for each independent variable. A variance inflation factor > 10 indicates high multicollinearity [45].

Data were analyzed on a per-protocol basis. Participants were excluded if they missed more than two training sessions, if medication was changed or if any other injury which could influence stance- and gait performance occurred during the study period.

Statistical tests were performed with SPSS (version 19, IBM), the α level for significance was set at $P < 0.05$ and all tests were two-sided. Bonferroni correction was used for multiple comparisons for the variables of the gait analysis and strength testing separately.

The study protocol and supporting CONSORT checklist are available as supporting information (S1 Protocol, S2 Protocol, and S1 CONSORT Checklist).

Results

From September 2011 till August 2013 a total of 172 persons were screened for eligibility at the department of Neurology, University Hospital Schleswig-Holstein, Kiel, Germany, among which 40 patients met the inclusion criteria and underwent randomization. Final data collection was February 2014. 8 participants (20%; 3 RT; 5 BT) did not complete the training protocol. For drop-out reasons see Fig 1 which shows the CONSORT flow diagram. All patients were able to follow the instructions during the training sessions.

Baseline data

No significant differences were found in the demographic or baseline variables between the two groups except for the outcome forward pull (Tables 1 and 2).

Agreement between the two blinded raters

The agreement between the blinded rater and the blinded video rater was high with ICCs >0.80 for baseline and 8-weeks follow-up. Since the blinded video rater (the person who rated by videos) not only was blind to group allocation but also to assessment time, results are analysed and interpreted with priority to the blinded video rater.

Effect of intervention from baseline to 8-weeks follow-up

The RT-group significantly improved from baseline to week 8 on average by 2.4 points on the FAB scale ($p = 0.04$; Cohen's $d = -0.46$), whereas the score of the BT-group only increased on average by 0.3 points and that was statistically not significant ($p = 0.526$; Cohen's $d = -0.08$) (Table 2). The higher intervention effect of the RT-group did not differ significantly from the training effect of the BT-group ($p = 0.143$, Cohen's $d = -0.59$).

No significant differences were found when analysing the COM displacement during surface perturbations (an example of the average normalized COM vector length during backward perturbations is shown in Fig 2).

The RT-group but not the BT-group performed the TUG significantly quicker at 8-weeks follow-up in comparison to baseline (on average -1.7sec, $p = 0.033$) but the difference between the training types was not significant ($p = 0.139$).

Fig 3 shows the results of the CGI-I. 65% of the participants from the RT-group reported a clinical global improvement whereas only 40% of the participants from the BT-group indicated amelioration. However, the difference between both groups was not significant ($p = 0.295$).

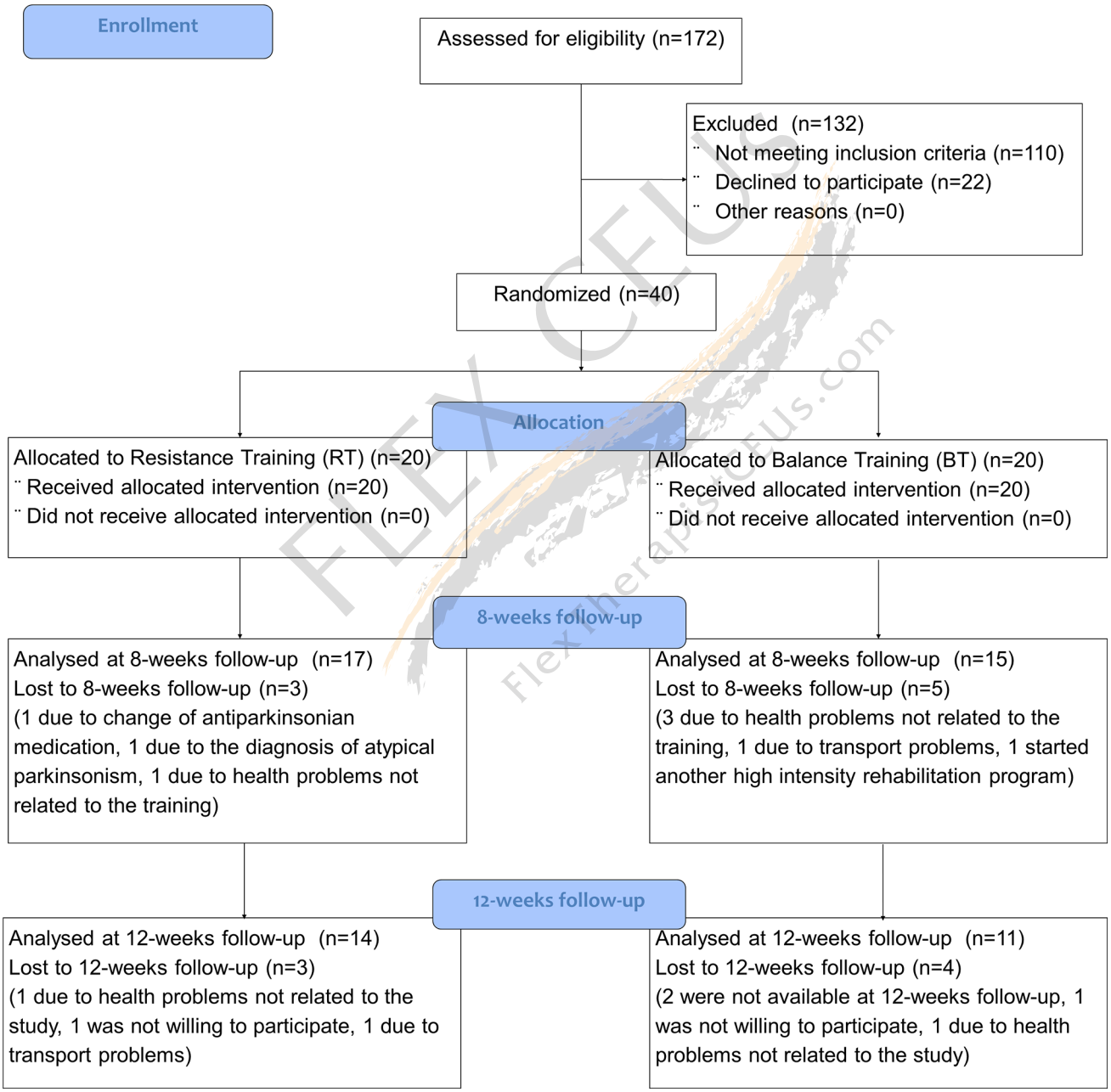

Fig 1. The CONSORT flow diagram for this study.

doi:10.1371/journal.pone.0140584.g001

Table 1. Participant characteristics.

Variable	Resistance (n = 17)	Balance (n = 15)	*p*-value[a]
Age (yr)	75.7 ± 5.5	75.7 ± 7.2	0.882
No. of female subjects	5 (29.4%)	6 (40%)	0.529[b]
Duration of Disease (yr)	10.1 ± 6.0	9.3 ± 7.9	0.455
BMI (kg/m^2)	27.9 ± 5.5	25.5 ± 4.4	0.142
H&Y	2.8 ± 0.26	2.7 ± 0.4	0.216
H&Y (Range)	2.5–3.0	2.5–3.0	n/a
UPDRS total (ON)	40.2 ± 12.5	37.7 ± 13.1	0.455
UPDRS part II (ON)	13.4 ± 5.1	11.1 ± 6.0	0.105
UPDRS part III (ON)	23.6 ± 9.5	22.3 ± 6.1	0.941
FAB scale	22.2 ± 4.8	24.5 ± 4.6	0.123
MMSE	27.3 ± 3.6	27.7 ± 3.0	0.891
MMSE (Range)	17–30	20–30	n/a
PASE score	104.6 ± 87.3	77.2 ± 63.1	0.576
LEDD (mg/day)	817.4 ± 468.0	674.7 ± 294.9	0.318

If not indicated differently, values are either mean ± SD or number and percentage. BMI, Body-Mass-Index; FAB, Fullerton Advanced Balance; H&Y, Hoehn & Yahr; LEDD, levodopa equivalent daily dose; MMSE, Mini-Mental State Examination; PASE, Physical Activity Scale for the Elderly; UPDRS, Unified Parkinson's Disease Rating Scale

[a] unless otherwise indicated *P*-value of independent samples Mann-Whitney-U-Test

[b] *P*-value of Chi-Square Test.

doi:10.1371/journal.pone.0140584.t001

In contrast to the RT-group, a significant improvement was found for the BT-group at the UPDRS total score (on average -4.1 points, $p = 0.033$) without any significant difference between the training types ($p = 0.272$). No significant differences were found for the UPDRS motor score.

The BT-group slightly improved the peak rate of force development of the less affected side from baseline to week 8, but this improvement was statistically not significant after Bonferroni-correction.

No significant differences were found for the PDQ-39 (baseline: RT: 28.5 ±12.7, BT: 28.5 ±17.7; 8-weeks follow-up: RT: 26.5 ±12.0, BT: 30.2 ±17.8) and the BDI (baseline: RT: 9.9 ±5.6, BT: 14.0 ±9.1; 8-weeks follow-up: RT: 8.4 ±5.3, BT: 10.8 ±5.9) for the between group comparison (baseline and differences from baseline to 8-weeks follow-up) and within group comparison ($p<0.05$).

Effect of intervention from baseline to 12-weeks follow-up

Table 3 shows the results of the baseline, 8- and 12 weeks follow-up assessments. The differences within one group from baseline to week 12 and the comparison of changes between the two training groups were statistically not significant.

Correlation between different outcome variables

When correlating the differences from baseline to week 8 of the FAB scale (Δ-FAB scale) with the magnitude of changes of the other test variables, we found significant correlations between Δ-FAB scale and Δ-stride time variability (Spearman's Rho: -0.649, $p = 0.009$) and Δ-RFD (LES) (Spearman's Rho: 0.643, $p = 0.018$) within the RT-group (Table 4). A multiple linear regression analysis showed that 71.6% (adjusted R^2) of the variance of Δ-FAB scale (as dependent variable) can be explained by Δ-stride time variability and Δ-RFD (LES) (as independent

Table 2. Comparison within- and between the two training groups from baseline to 8-weeks follow-up.

Variable		Baseline	8-wk follow-up	Mean change (95% CI) from baseline to 8-wk follow-up	*p*-value[a] (within group comparison)	*p*-value[b] (between group comparison)	Effect size[c] (within group)	Effect size[c] (between group)
FAB scale[d]	RT	22.2 ± 4.8	24.5 ± 5.4	2.4 (0.1; 4.6)	0.04*	0.143	-0.46	-0.59
	BT	24.5 ± 4.6	24.9 ± 5.3	0.3 (-0.8; 1.5)	0.526		-0.08	
Forward pull[e]	RT	2270.3 ± 375.1	2336.7 ± 274.0	66.4 (-138.2; 270.9)	0.311	0.769	-0.20	-0.17
	BT	1807.4 ± 351.8	1836.6 ± 360.9	29.2 (-66.4; 124.9)	0.239		-0.08	
Backward pull[e]	RT	1882.3 ± 326.9	1782.1 ± 373.4	-100.2 (-311.5; 111.0)	0.286	0.332	0.29	0.42
	BT	1844.6 ± 411.4	1917.4 ± 362.7	72.8 (-261.4; 407.0)	0.657		-0.19	
TUG (sec)	RT	11.2 ± 3.2	9.5 ± 2.4	-1.7 (-3.3; -0.1)	0.033*	0.139	0.60	0.69
	BT	9.2 ± 3.0	9.0 ± 1.8	-0.2 (-1.3; 0.9)	0.929		0.08	
UPDRS total score	RT	40.2 ± 12.5	38.5 ± 12.3	-1.7 (-5.1; 1.8)	0.347	0.272	0.14	-0.38
	BT	37.7 ± 13.1	33.6 ± 12.3	-4.1 (-7.3; -0.9)	0.033*		0.32	
UPDRS motor score[f]	RT	22.6 ± 8.8	22.2 ± 8.9	-0.4 (-2.0; 1.2)	0.568	0.911	0.04	-0.51
	BT	20.3 ± 4.9	19.4 ± 6.7	-0.9 (-3.0; 1.1)	0.821		0.49	
gait velocity (cm/sec)	RT	104.3 ± 15.3	106.1 ± 15.0	1.8 (-5.2; 8.7)	0.619	0.692	-0.12	-0.14
	BT	106.9 ± 18.3	106.8 ± 17.7	-0.1 (-7.4; 7.4)	0.776		0.01	
stride length (cm)	RT	80.6 ± 13.0	80.3 ± 11.7	-0.4 (-4.5; 3.7)	0.865	0.097	0.02	0.50
	BT	88.8 ± 15.7	91.5 ± 16.1	2.7 (-0.4; 5.9)	0.131		-0.17	
double support time (msec)	RT	156.6 ± 31.7	156.3 ± 35.5	-0.3 (-8.4; 7.8)	0.532	0.134	0.01	0.45
	BT	149.4 ± 24.9	155.0 ± 32.1	5.6 (-2.1; 13.3)	0.11		-0.19	
stride time variability (%)	RT	3.8 ± 1.0	3.7 ± 1.7	-0.1 (-0.8; 0.6)	0.334	0.413	0.07	-0.53
	BT	3.9 ± 1.8	3.0 ± 0.8	-0.9 (-2.0; 0.3)	0.182		0.65	
PCI (%)	RT	6.6 ± 1.5	6.1 ± 1.8	-0.5 (-1.1; 0.1)	0.061	0.077	0.30	0.75
	BT	6.1 ± 1.4	6.9 ± 2.1	0.8 (-0.7; 2.3)	0.286		-0.45	
Asymmetry Index	RT	5.1 ± 4.1	6.0 ± 4.3	0.9 (-1.1; 0.1)	0.82	0.959	-0.21	-0.22
	BT	4.9 ± 3.7	5.0 ± 5.3	0.1 (-1.6; 1.8)	0.99		-0.02	
leg strength (MVC), LES (N)	RT	393.8 ± 113.5	416.9 ± 91.0	23.0 (-15.5; 61.6)	0.279	0.458	-0.22	-0.43
	BT	416.5 ± 129.6	408.8 ± 138.5	-7.7 (-53.3; 37.8)	0.925		0.06	
leg strength (MVC), MAS (N)	RT	401.8 ± 130.0	399.8 ± 85.7	-2.0 (-48.2; 44.2)	0.807	0.287	0.02	0.33
	BT	407.9 ± 134.4	426.2 ± 131.6	18.3 (-4.4; 41.1)	0.133		-0.14	
peak RFD, LAS (N/msec)	RT	1.5 ± 0.7	1.6 ± 0.8	0.1 (-0.4; 0.4)	0.753	0.223	-0.13	0.50
	BT	1.6 ± 1.0	1.8 ± 0.9	0.3 (0.0; 0.5)	0.028**		-0.21	
peak RFD, MAS (N/msec)	RT	1.5 ± 1.0	1.5 ± 0.7	0.0 (-0.6; 0.5)	0.972	0.503	0.00	0.40
	BT	1.4 ± 0.7	1.7 ± 0.9	0.3 (-0.2; 0.8)	0.308		-0.37	
RFD, LAS (N/msec)	RT	0.8 ± 0.6	0.9 ± 0.6	0.1 (-0.2; 0.5)	0.249	0.627	-0.17	0.31

(*Continued*)

Table 2. (*Continued*)

Variable		Baseline	8-wk follow-up	Mean change (95% CI) from baseline to 8-wk follow-up	*p*-value[a] (within group comparison)	*p*-value[b] (between group comparison)	Effect size[c] (within group)	Effect size[c] (between group)
	BT	0.7 ± 0.5	1.0 ± 0.6	0.3 (0.0; 0.5)	0.056		-0.54	
RFD, MAS (N/msec)	RT	0.8 ± 0.7	0.9 ± 0.6	0.1 (-0.3; 0.5)	0.600	0.939	-0.15	-0.14
	BT	0.9 ± 0.7	0.9 ± 0.7	0.0 (-0.4; 0.4)	0.507		0.00	

FAB, Fullerton Advanced Balance; TUG, Timed-Up-and-Go-Test; LAS, less affected side; MAS, more affected side; MVC, maximal voluntary contraction; PCI, Phase Coordination Index; RFD, rate of force development (0-100ms); UPDRS, Unified Parkinson's Disease Rating Scale

[a] *p*-value of Wilcoxon test

[b] *p*-value of independent samples Mann-Whitney-U-Test

[c] Cohen's d was calculated as effect size

[d] blinded video rating

[e] values represent the area under the curve of the normalized vector length from 0–3 sec after the surface perturbation

[f] blinded video rating, without item 22 (rigidity)

RT, resistance training (n = 17); BT, balance training (n = 15)

*significant different (p<0.05)

**after Bonferroni-adjustment not significant.

doi:10.1371/journal.pone.0140584.t002

variables) and this model was statistically significant (F = 14.9, $p = 0.001$). Stride time variability and average RFD equally contributed to the model (stride time variability: Beta = 0.517, T = 2.98, $p = 0.015$; RFD: Beta = -0.54, T = -3.114, $p = 0.012$).

Within the BT-group significant correlations were found between Δ-FAB-scale and Δ-PCI (Spearman's Rho: -0.608, $p = 0.047$) and Δ-BDI (Spearman's Rho: 0.718, $p = 0.003$) (Table 4). With Δ-PCI and Δ-BDI as predictors for Δ-FAB-scale in the multiple linear regression analysis for the BT-group, the model failed to be significant (adjusted $R^2 = 19.2\%$; F = 2.191, $p = 0.174$).

The independent variables of both models did not correlate (Spearman's Rho<0.6; p<0.05) and the variance inflation factors were below 2.2 indicating a very low risk of mutlicollinearity.

No significant correlation was found when correlating the degree of cognitive impairment (measured by the MMSE) and Δ-FAB scale.

Discussion

No significant differences were found when comparing the effects of RT with the effects of BT to improve postural control in individuals with PD. Within the RT group, participants significantly improved postural control with a medium effect size. The average improvement at the FAB scale of the RT group was beyond the minimal detectable change (MDC) ($MDC_{95} = 2.25$ points, calculated according to [30,46]), indicating a true performance change instead of a change due to variability of performance or measurement error. Participants from the BT group only slightly improved on the FAB scale but this amelioration was not significant and the effect size was small. Within the RT group 7 patients improved beyond the MDC of the FAB scale whereas only 2 of the participants of the BT group showed improvements beyond the MDC. The fact, that the difference between the training effects was not significant, may be due to our small sample size. We conclude that there exists only a small difference between RT and BT. With regard to the large effect size when comparing the effects of the two training interventions, a tendency is given that RT might be more effective than BT to improve postural control in this population.

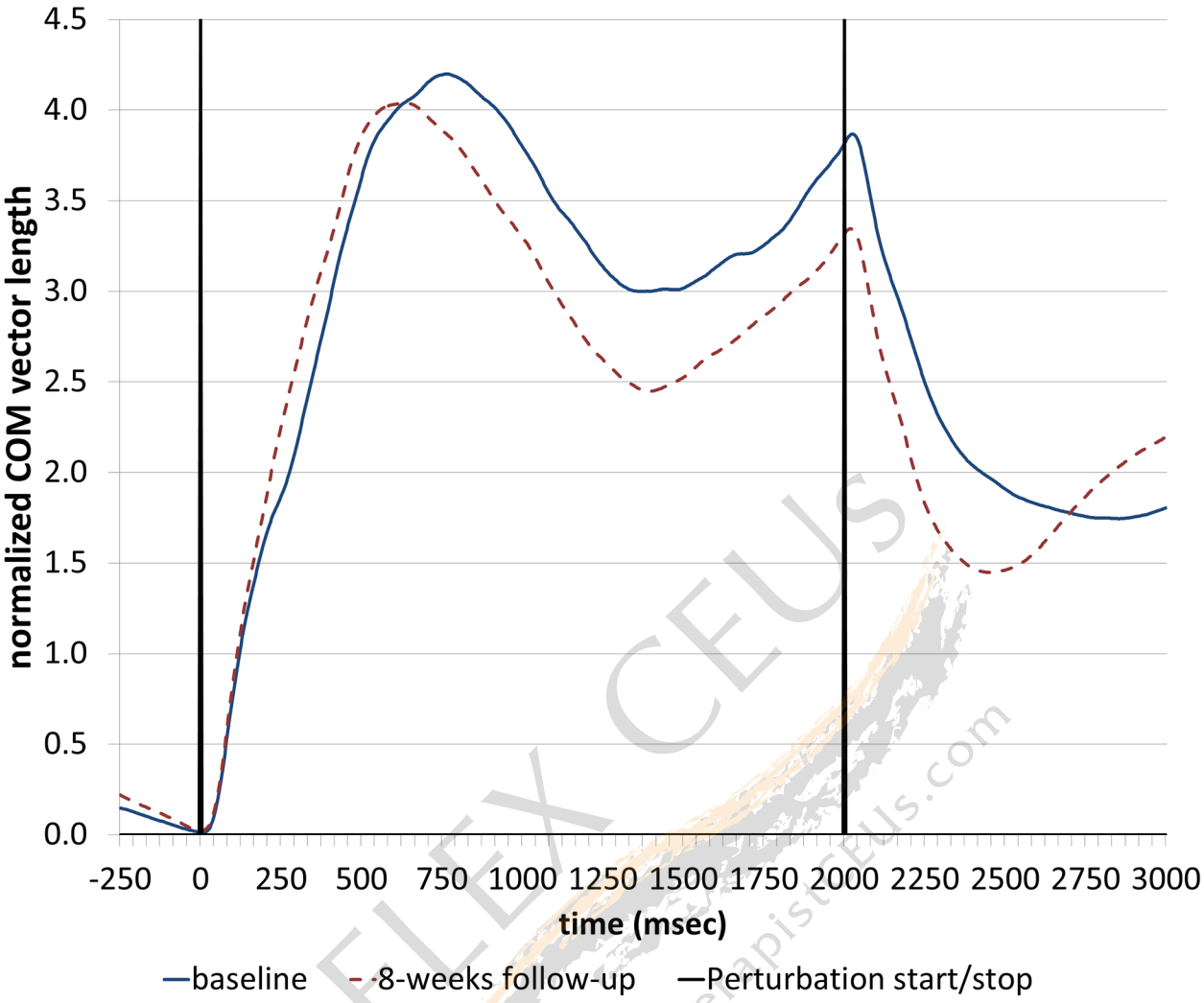

Fig 2. Average normalized center of mass (COM) vector length of one participant during backward perturbations at baseline and 8-weeks follow-up.

doi:10.1371/journal.pone.0140584.g002

It has been shown that balance training can be effective to improve postural control in PD [13,14]. These studies used higher training frequencies which may explain the different findings in comparison to our trial. Furthermore the aim of these studies was not to compare competing training types but to analyse the efficacy of one training type.

The higher training effects of the RT group in comparison to the BT group on the FAB scale is notable, as—in contrast to RT—the items of the FAB scale are closely related to the exercises of the BT. All participants underwent an examination to assess eligibility before participating meanwhile the FAB scale was carried out the first time. At baseline the participants thus performed the scale the second time. This emphasizes to consider the improvement from baseline to week 8 due to training effects and not based on memory effects due to the repetition of the same test.

It has to be taken into account that participants only trained two times per week. Training frequency therefore was low and maybe not high enough to detect significant differences. The pre-intervention level of physical activity of the participants was relatively low but similar to the activity level of healthy age-matched controls. In the study of Joshua et al. [25] who showed

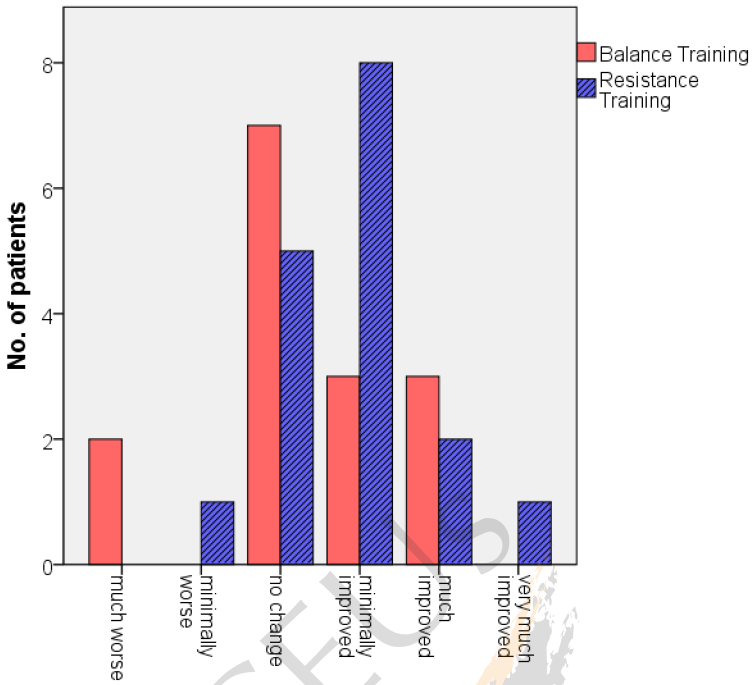

Fig 3. Results of the Clinical Global Impression–Improvement scale (CGI-I).

doi:10.1371/journal.pone.0140584.g003

significant stronger improvement in postural control due to RT in comparison to BT in healthy elderly, training intensity was much higher and participants trained 4x/week for 6 months. As our participants were in an advanced stage of disease (H&Y: 2.5–3.0) and all of them reported to have postural impairments, we considered this training frequency practical feasible as most

Table 3. Comparison of baseline, 8- and 12-weeks follow-up.

Variable	Group	Baseline	8-wk follow-up	12-wk follow-up	Mean change (baseline to 12-wk follow-up) (95% CI)	*p*-value[a] (within group comparison, baseline to 12-wk follow-up)	*p*-value[b] (between group comparison, baseline to 12-wk follow-up)
FAB scale[c]	RT	22.2 ± 5.3	24.4 ± 5.7	22.5 ± 5.1	0.3 (-2.2; 2.8)	0.370	0.767
	BT	24.8 ± 4.2	25.3 ± 4.4	24.0 ± 4.6	-0.8 (-2.6; 1.0)	0.900	
TUG (sec)	RT	11.4 ± 3.6	9.4 ± 2.5	10.0 ± 2.1	-1.4 (-3.2; 0.4)	0.686	0.699
	BT	9.2 ± 3.8	9.0 ± 2.4	8.4 ± 1.9	-0.8 (-3.5; 1.9)	0.139	
UPDRS total score	RT	40.7 ± 15.0	40.7 ± 13.1	39.4 ± 12.0	-1.4 (-9.8; 7.1)	0.183	0.797
	BT	38.8 ± 14.7	32.8 ± 13.5	36.4 ± 15.9	-2.5 (-9.0; 4.1)	0.286	
UPDRS motor score[d]	RT	23.7 ± 10.4	23.4 ± 10.5	22.5 ± 10.2	-1.2 (-3.3; 0.9)	0.183	0.833
	BT	20.8 ± 4.1	19.3 ± 6.6	19.6 ± 5.5	-1.3 (-3.4; 0.9)	0.052	

FAB, Fullerton Advanced Balance; TUG, Timed-Up-and-Go-Test; UPDRS, Unified Parkinson's Disease Rating Scale

[a] *p*-value of Wilcoxon test

[b] *p*-value of independent samples Mann-Whitney-U-Test

[c] blinded video rating

[d] blinded video rating, without item 22 (rigidity)

RT, resistance training (n = 14); BT, balance training (n = 11).

doi:10.1371/journal.pone.0140584.t003

Table 4. Correlation between the differences from baseline to 8-weeks follow-up of the FAB scale with the differences from baseline to 8-weeks follow-up of other outcomes.

	Resistance		Balance	
Variable	**Rho[a]**	***p***	**Rho[a]**	***p***
Forward pull[b]	-0.318	0.289	-0.366	0.241
Backward pull[b]	-0.217	0.420	0.019	0.956
TUG	-0.097	0.754	0.230	0.497
UPDRS total score	-0.413	0.100	0.003	0.992
UPDRS motor score[c]	-0.397	0.115	0.030	0.915
gait velocity	0.148	0.572	0.058	0.837
stride length	0.319	0.246	-0.074	0.828
double support time	0.310	0.260	-0.357	0.281
stride time variability	**-0.649**	**0.009**	0.260	0.440
PCI	-0.152	0.587	**-0.608**	**0.047**
Asymmetry Index	0.215	0.441	-0.153	0.653
Leg Strength (MVC), LAS	0.014	0.964	0.343	0.230
Leg Strength (MVC), MAS	-0.510	0.075	-0.140	0.647
peak RFD, LAS	0.114	0.712	-0.003	0.993
peak RFD, MAS	0.263	0.385	-0.119	0.713
average RFD (0-100ms), LAS	**0.643**	**0.018**	0.276	0.340
average RFD (0-100ms), MAS	0.355	0.235	-0.174	0.569
PDQ-39	0.017	0.948	0.053	0.852
BDI	0.337	0.186	**0.718**	**0.003**

BDI, Beck Depression Inventory; FAB, Fullerton Advanced Balance; TUG, Timed-Up-and-Go-Test; LAS, less affected side; MAS, more affected side; MVC, maximal voluntary contraction; PCI, Phase Coordination Index; PDQ-39, Parkinson's Disease Questionnaire; RFD, rate of force development; UPDRS, Unified Parkinson's Disease Rating Scale

[a] Spearman's rank correlation coefficient

[b] value represents the area under the curve of the normalized vector length from 0–3 sec after the surface perturbation (see Fig 2 and S3 File)

[c] blinded video rating, without item 22 (rigidity).

doi:10.1371/journal.pone.0140584.t004

of the participants were not able to come to the training sessions alone and probably may not be able to train more often.

Gait velocity did not improve due to RT. This is in line with a recently published meta-analysis [16]. Furthermore, we have shown that stride lengths, double support time, gait variability, gait asymmetry and bilateral coordination did not improve due to both training types. To our best knowledge, this is the first study analysing the efficacy of RT and BT on more specific gait features than gait velocity.

The relationship between the improvement in postural control and improvement in rate of force development of the less affected PD site highlights the importance of strength with regard to postural control. The ability to generate force in the early onset of muscle contraction seems to play an important role for postural control mechanisms. By contrast, the changes of overall motor and mobility performance (measured by the UPDRS and TUG) did not correlate with the improvements of balance. The fact that especially the RFD of the less- but not the more affected PD side contributed to better postural control is in accordance with a recent study showing that training the less affected side leads to higher improvements in PD than standard

exercise [47]. This raises the idea that RT may be an effective compensatory strategy to enhance postural control in this population.

RT was not performed with exercise machines; instead, participants' body weight, cuff weights and elasticated bands were used as resistance. This was done as we wanted to perform a training type, which is–as BT–easy and cost-effective to perform without the need of exercise machines which are not always present in physical therapy. We are aware that beside the main aim to improve strength, RT with freely coordinated exercises may train sensorimotor integration as well. However, the primary objective of these kinds of exercises is the improvement of muscle strength.

Three participants had MMSE scores below 25 points. As some tests with multi-step instructions (FAB scale and TUG) and some tests with self-report measures (UPDRS, BDI, PDQ-39 and CGI-I) require cognitive capacity, we reanalyzed our data excluding these three patients for the between group comparison. Results did not change except for the PDQ-39 (significant higher improvement of the RT group in comparison to the BT group).

The following limitations exist. First, one major limitation is that training frequency was low and probably under-dosed to detect significant differences between these two competing training types. Second, we had a 20% drop-out rate, which was larger as we anticipated in the sample size calculation. Our sample size therefore might have been underpowered to detect significant differences. Especially as the correlation- and regression analysis were performed with the RT- and BT-group separately, results have to be interpreted with caution with respect to the small sample size. Furthermore, we did not assess fall rates which would be of interest as strength and balance performance are independent risk factors for falls. Finally, we did not include any control group without any intervention which would allow to further interpret the effects of both training types.

Conclusions

This randomized controlled rater blinded trial shows that the difference between RT and BT to improve postural control in individuals with PD was small and not significant with this sample size. There was weak evidence that freely coordinated RT might be more effective than BT. Our results indicate a relationship between the enhancement of rate of force development and the improvement of postural control within the RT group, but this should be verified in future trials. Future studies should include larger sample sizes to further explore the impact of RT to improve postural control in patients with PD. The comparison of competing training interventions should be analyzed furthermore to gain insight into which exercise program might be most effective and about the underlying processes leading to the results. Concerning long-term attendance the assessment of how much the participants like to participate in a specific training type should be included.

Supporting Information

S1 CONSORT Checklist. CONSORT checklist.
(PDF)

S1 File. Resistance training. Text and figures which describe the resistance training.
(PDF)

S2 File. Balance training. Text and figures which describe the balance training.
(PDF)

S3 File. Surface perturbations. Text which gives further details about the surface perturbations.
(PDF)

S4 File. Gait analysis. Text which gives further details about the gait analysis.
(PDF)

S5 File. Strength testing. Text which gives further details about the strength testing.
(PDF)

S1 Protocol. Study Protocol (English translation).
(PDF)

S2 Protocol. Study Protocol.
(PDF)

Author Contributions

Conceived and designed the experiments: CS JR BW GD. Performed the experiments: CS AK. Analyzed the data: CS SP GD. Contributed reagents/materials/analysis tools: CS JR BW GD. Wrote the paper: CS SP GD.

References

1. Nantel J, McDonald JC, Bronte-Stewart H (2012) Effect of medication and STN-DBS on postural control in subjects with Parkinson's disease. Parkinsonism & related disorders 18: 285–289.
2. Visser JE, Allum JH, Carpenter MG, Esselink RA, Speelman JD, Borm GF, et al. (2008) Subthalamic nucleus stimulation and levodopa-resistant postural instability in Parkinson's disease. J Neurol 255: 205–210. doi: 10.1007/s00415-008-0636-x PMID: 18274810
3. Fasano A, Aquino CC, Krauss JK, Honey CR, Bloem BR (2015) Axial disability and deep brain stimulation in patients with Parkinson disease. Nature reviews Neurology 11: 98–110. doi: 10.1038/nrneurol.2014.252 PMID: 25582445
4. Latt MD, Lord SR, Morris JG, Fung VS (2009) Clinical and physiological assessments for elucidating falls risk in Parkinson's disease. Mov Disord 24: 1280–1289. doi: 10.1002/mds.22561 PMID: 19425059
5. Robinson K, Dennison A, Roalf D, Noorigian J, Cianci H, Bunting-Perry L, et al. (2005) Falling risk factors in Parkinson's disease. NeuroRehabilitation 20: 169–182. PMID: 16340098
6. Kerr GK, Worringham CJ, Cole MH, Lacherez PF, Wood JM, Silburn PA (2010) Predictors of future falls in Parkinson disease. Neurology 75: 116–124. doi: 10.1212/WNL.0b013e3181e7b688 PMID: 20574039
7. Ashburn A, Stack E, Pickering RM, Ward CD (2001) Predicting fallers in a community-based sample of people with Parkinson's disease. Gerontology 47: 277–281. PMID: 11490147
8. Wood BH, Bilclough JA, Bowron A, Walker RW (2002) Incidence and prediction of falls in Parkinson's disease: a prospective multidisciplinary study. J Neurol Neurosurg Psychiatry 72: 721–725. PMID: 12023412
9. Dibble LE, Addison O, Papa E (2009) The effects of exercise on balance in persons with Parkinson's disease: a systematic review across the disability spectrum. J Neurol Phys Ther 33: 14–26. doi: 10.1097/NPT.0b013e3181990fcc PMID: 19265767
10. Allen NE, Sherrington C, Suriyarachchi GD, Paul SS, Song J, Canning CG (2012) Exercise and motor training in people with Parkinson's disease: a systematic review of participant characteristics, intervention delivery, retention rates, adherence, and adverse events in clinical trials. Parkinson's disease 2012: 854–869.
11. Goodwin VA, Richards SH, Taylor RS, Taylor AH, Campbell JL (2008) The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. Movement Disorders 23: 631–640. doi: 10.1002/mds.21922 PMID: 18181210
12. Canning CG, Sherrington C, Lord SR, Close JC, Heritier S, Heller GZ, et al. (2015) Exercise for falls prevention in Parkinson disease: A randomized controlled trial. Neurology 84: 304–312. doi: 10.1212/WNL.0000000000001155 PMID: 25552576

13. Smania N, Corato E, Tinazzi M, Stanzani C, Fiaschi A, Girardi P, et al. (2010) Effect of balance training on postural instability in patients with idiopathic Parkinson's disease. Neurorehabil Neural Repair 24: 826–834. doi: 10.1177/1545968310376057 PMID: 21045119

14. Conradsson D, Lofgren N, Nero H, Hagstromer M, Stahle A, Lokk J, et al. (2015) The Effects of Highly Challenging Balance Training in Elderly With Parkinson's Disease: A Randomized Controlled Trial. Neurorehabilitation and neural repair.

15. Corcos DM, Robichaud JA, David FJ, Leurgans SE, Vaillancourt DE, Poon C, et al. (2013) A two-year randomized controlled trial of progressive resistance exercise for Parkinson's disease. Movement disorders: official journal of the Movement Disorder Society 28: 1230–1240.

16. Tillman A, Muthalib M, Hendy AM, Johnson LG, Rantalainen T, Kidgell DJ, et al. (2015) Lower limb progressive resistance training improves leg strength but not gait speed or balance in Parkinson's disease: a systematic review and meta-analysis. Frontiers in aging neuroscience 7: 40. doi: 10.3389/fnagi.2015.00040 PMID: 25852550

17. Chung CL, Thilarajah S, Tan D (2015) Effectiveness of resistance training on muscle strength and physical function in people with Parkinson's disease: A systematic review and meta-analysis. Clinical rehabilitation.

18. Lima LO, Scianni A, Rodrigues-de-Paula F (2013) Progressive resistance exercise improves strength and physical performance in people with mild to moderate Parkinson's disease: a systematic review. Journal of physiotherapy 59: 7–13. doi: 10.1016/S1836-9553(13)70141-3 PMID: 23419910

19. Brienesse LA, Emerson MN (2013) Effects of resistance training for people with Parkinson's disease: a systematic review. Journal of the American Medical Directors Association 14: 236–241. doi: 10.1016/j.jamda.2012.11.012 PMID: 23318666

20. Nallegowda M, Singh U, Handa G, Khanna M, Wadhwa S, Yadav SL, et al. (2004) Role of sensory input and muscle strength in maintenance of balance, gait, and posture in Parkinson's disease: a pilot study. American journal of physical medicine & rehabilitation 83: 898–908.

21. Nocera JR, Buckley T, Waddell D, Okun MS, Hass CJ (2010) Knee extensor strength, dynamic stability, and functional ambulation: are they related in Parkinson's disease? Arch Phys Med Rehabil 91: 589–595. doi: 10.1016/j.apmr.2009.11.026 PMID: 20382292

22. Allen NE, Canning CG, Sherrington C, Lord SR, Latt MD, Close JC, et al. (2010) The effects of an exercise program on fall risk factors in people with Parkinson's disease: a randomized controlled trial. Movement disorders: official journal of the Movement Disorder Society 25: 1217–1225.

23. Hirsch MA, Toole T, Maitland CG, Rider RA (2003) The effects of balance training and high-intensity resistance training on persons with idiopathic Parkinson's disease. Arch Phys Med Rehabil 84: 1109–1117. PMID: 12917847

24. Schilling BK, Pfeiffer RF, Ledoux MS, Karlage RE, Bloomer RJ, Falvo MJ (2010) Effects of moderate-volume, high-load lower-body resistance training on strength and function in persons with Parkinson's disease: a pilot study. Parkinson's disease 2010: 824734. doi: 10.4061/2010/824734 PMID: 20976096

25. Joshua AM, D'Souza V, Unnikrishnan B, Mithra P, Kamath A, Acharya V, et al. (2014) Effectiveness of progressive resistance strength training versus traditional balance exercise in improving balance among the elderly—a randomised controlled trial. Journal of clinical and diagnostic research 8: 98–102. doi: 10.7860/JCDR/2014/8217.4119 PMID: 24783093

26. Gobbi LT, Oliveira-Ferreira MD, Caetano MJ, Lirani-Silva E, Barbieri FA, Stella F, et al. (2009) Exercise programs improve mobility and balance in people with Parkinson's disease. Parkinsonism Relat Disord 15 Suppl 3: 49–52.

27. Toole T, Hirsch MA, Forkink A, Lehman DA, Maitland CG (2000) The effects of a balance and strength training program on equilibrium in Parkinsonism: A preliminary study. NeuroRehabilitation 14: 165–174. PMID: 11455079

28. Tomlinson CL, Herd CP, Clarke CE, Meek C, Patel S, Stowe R, et al. (2014) Physiotherapy for Parkinson's disease: a comparison of techniques. The Cochrane database of systematic reviews 6: CD002815.

29. Gelb DJ, Oliver E, Gilman S (1999) Diagnostic criteria for Parkinson disease. Archives of neurology 56: 33–39. PMID: 9923759

30. Schlenstedt C, Brombacher S, Hartwigsen G, Weisser B, Moller B, Deuschl G (2015) Comparing the Fullerton Advanced Balance Scale With the Mini-BESTest and Berg Balance Scale to Assess Postural Control in Patients With Parkinson Disease. Arch Phys Med Rehabil 96: 218–225. doi: 10.1016/j.apmr.2014.09.002 PMID: 25261718

31. Martins WR, de Oliveira RJ, Carvalho RS, de Oliveira Damasceno V, da Silva VZ, Silva MS (2013) Elastic resistance training to increase muscle strength in elderly: a systematic review with meta-analysis. Archives of gerontology and geriatrics 57: 8–15. doi: 10.1016/j.archger.2013.03.002 PMID: 23562413

32. Hass CJ, Buckley TA, Pitsikoulis C, Barthelemy EJ (2012) Progressive resistance training improves gait initiation in individuals with Parkinson's disease. Gait Posture 35: 669–673. doi: 10.1016/j.gaitpost.2011.12.022 PMID: 22266107

33. Rose DJ, Lucchese N, Wiersma LD (2006) Development of a multidimensional balance scale for use with functionally independent older adults. Arch Phys Med Rehabil 87: 1478–1485. PMID: 17084123

34. Winter DA, Patla AE, Ishac M, Gage WH (2003) Motor mechanisms of balance during quiet standing. J Electromyogr Kinesiol 13: 49–56. PMID: 12488086

35. Podsiadlo D, Richardson S (1991) The timed "Up & Go": a test of basic functional mobility for frail elderly persons. Journal of the American Geriatrics Society 39: 142–148. PMID: 1991946

36. Guy W (1976) ECDEU assessment manual for psychopharmacology; National Institute of Mental Health. Psychopharmacology Research Branch. Division of Extramural Research P, editor. Rockville, Md: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs. 218–222 p.

37. Fahn S, Elton RL (1987) Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne D, Goldstein M, editors. Recent developments in Parkinson's disease. Florham Park (NJ): MacMillan Health Care Information. pp. 153–163.

38. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N (1997) The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. Age Ageing 26: 353–357. PMID: 9351479

39. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. Archives of general psychiatry 4: 561–571. PMID: 13688369

40. Washburn RA, Smith KW, Jette AM, Janney CA (1993) The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol 46: 153–162. PMID: 8437031

41. Plotnik M, Giladi N, Hausdorff JM (2007) A new measure for quantifying the bilateral coordination of human gait: effects of aging and Parkinson's disease. Experimental brain research 181: 561–570. PMID: 17503027

42. Plotnik M, Hausdorff JM (2008) The role of gait rhythmicity and bilateral coordination of stepping in the pathophysiology of freezing of gait in Parkinson's disease. Mov Disord 23: 444–450.

43. Geurts AC, Boonstra TA, Voermans NC, Diender MG, Weerdesteyn V, Bloem BR (2011) Assessment of postural asymmetry in mild to moderate Parkinson's disease. Gait & Posture 33: 143–145.

44. Faul F, Erdfelder E, Lang AG, Buchner A (2007) G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior research methods 39: 175–191. PMID: 17695343

45. Slinker BK, Glantz SA (1985) Multiple regression for physiological data analysis: the problem of multicollinearity. The American journal of physiology 249: R1–12. PMID: 4014489

46. Haley SM, Fragala-Pinkham MA (2006) Interpreting change scores of tests and measures used in physical therapy. Physical therapy 86: 735–743. PMID: 16649896

47. Ricciardi L, Ricciardi D, Lena F, Plotnik M, Petracca M, Barricella S, et al. (2015) Working on asymmetry in Parkinson's disease: randomized, controlled pilot study. Neurological sciences: official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology.

Adaptive training with full-body movements to reduce bradykinesia in persons with Parkinson's disease: a pilot study

Abstract

Background: Bradykinesia (slow movements) is a common symptom of Parkinson's disease (PD) and results in reduced mobility and postural instability. The objective of this study is to develop and demonstrate a technology-assisted exercise protocol that is specifically aimed at reducing bradykinesia.

Methods: Seven persons with PD participated in this study. They were required to perform whole body reaching movements toward targets placed in different directions and at different elevations. Movements were recorded by a Microsoft Kinect movement sensor and used to control a human-like avatar, which was continuously displayed on a screen placed in front of the subjects. After completion of each movement, subjects received a 0-100 score that was inversely proportional to movement time. Target distance in the next movements was automatically adjusted in order to keep the score around a pre-specified target value. In this way, subjects always exercised with the largest movement amplitude they could sustain. The training protocol was organised into blocks of 45 movements toward targets placed in three different directions and at three different elevations (a total of nine targets). Each training session included a finite number of blocks, fitted within a fixed 40 minutes duration. The whole protocol included a total of 10 sessions (approximately two sessions/week).
As primary outcome measure we took the absolute average acceleration. Various aspects of movement performance were taken as secondary outcome measures, namely accuracy (undershoot error), path curvature, movement time, and average speed.

Results: Throughout sessions, we observed an increase of the absolute average acceleration and speed and decreased undershoot error and movement time. Exercise also significantly affected the relationship between target elevation and both speed and acceleration - the improvement was greater at higher elevations.

Conclusions: The device and the protocol were well accepted by subjects and appeared safe and easy to use. Our preliminary results point at a training-induced reduction of bradykinesia.

Keywords: Parkinson's disease, Bradykinesia, Microsoft kinect

Introduction

Bradykinesia (slow movements) is a common symptom in Parkinson's disease (PD) [1] and has important consequences on daily life activities. As regards the upper limb, it may cause difficulties in dexterous activities such as using work or kitchen tools. It may also contribute to impaired coordination in activities like sport or dressing.

It has been suggested [2] that slow movements are a consequence of a reduced accuracy, which would lead to multiple corrections [3] and therefore to a greater movement time. However, this view is difficult to reconcile with previous observations [4] that movements in PD are characterized by prolonged acceleration phases, not prolonged decelerations as it would have been expected by multiple corrections.

Problems with energy expenditure have often been associated to bradykinesia in PD. Protas et al. [5] and Schenkman et al. [6] suggested that individuals with PD

*Correspondence: susanna.summa@unige.it
[1] Department of Informatics, Bioengineering, Robotics and Systems Engineering, University of Genoa, Genoa, Italy
Full list of author information is available at the end of the article

spend about 20% more energy than healthy people during movements, which points at a poor management of energy expenditure in terms of economy of movement. Canning et al. [7] and Stanley et al. [8] showed that, during motor exercise, the attainment of peak aerobic power occurs at a significantly lower exercise level respect to healthy persons, thus indicating poor metabolic efficiency.

Slower movements in PD have also been associated to a reduced muscle strength and to an inability to generate rapid muscle contraction [9]. However, muscle weakness was not consistently observed in all muscles in persons with bradykinesia.

Alteration in sensory processing is another possible explanation. Persons with PD have an abnormal regulation of proprioception; for instance, lack of vision affects the speed/accuracy trade-off more than in controls [10]. However, it is unclear whether these problems arise from altered peripheral feedback or from abnormal central processing [11].

All the above explanations are hard to reconcile with the observation that persons with bradykinesia may indeed perform fast movements, e.g. to escape from a danger (paradoxical kinesia) [12]. Also, persons with bradykinesia can exceed their preferred moving speed while maintaining a movement accuracy comparable to the one of healthy subjects [13]. This suggests that bradykinesia in persons with PD is not a mere compensatory mechanism for impaired motor control or defective sensory processing. Rather, is may be a consequence of an implicit decision to select movements that have a lower energy expenditure or are characterized by lower force levels. Consistent with the emerging view of the role of the basal ganglia as action 'energizers' - see [14] for a review - Mazzoni et al. [15] suggested that dopaminergic pathways from the substantia nigra to the striatum may regulate the likelihood of moving at higher speeds.

Rehabilitation may have an important impact in the quality of life of persons with PD. Physical exercise might help to reduce the motor symptoms - especially bradykinesia and balance problems - while keeping the levodopa (LD) dose as low as possible. Also, moderate endurance exercises have been reported to augment the efficacy of LD therapy [16].

A recent review [17] compared the effectiveness of physiotherapy intervention in persons with PD. The study took into consideration a number of common treatments (i.e. general physiotherapy, exercise, treadmill training, cueing, dance, or martial arts). Short-term (i.e. <3 months) benefits of physiotherapy were observed in most outcomes, but were significant only for speed, two- or six-minute walk test, Freezing of Gait questionnaire, Timed Up & Go, Functional Reach Test, Berg Balance Scale, and UPDRS. While many treatments resulted in improved performance, no significant difference was observed between treatments, at least for the outcome measures that were taken into consideration. Recently, a technique originally developed for speech rehabilitation (Lee Silverman's Voice Therapy, LSVT) has been extended to specifically address motor bradykinesia (Training BIG, later known as LSVT BIG); see [18]. This technique is based on intensive full-body exercise, specifically aimed at increasing the sensory awareness of the widest range of motion that patients can achieve and encouraging the maximum speed. Farley et al. [18] related this technique to the speed-amplitude relation [19] - speed increases with movement amplitude - and observed that training of large amplitude movements involving the whole body induces a modification of this relation - in high-amplitude movements the speed improves more. In a comparative study [20], the LSVT BIG technique resulted in a greater improvement in motor performance with respect to either nordic walking or non-supervised home exercise.

Here we propose a novel approach for reducing bradykinesia, based on virtual reality, exergaming [21] and the low-cost natural user interface Microsoft Kinect. A few studies have tested safety and feasibility of using this device with persons with Parkinson's disease. Pompeu et al. [22] used a commercial game suite - Microsoft Kinect Adventures™ - to engage the player in a variety of mini games that exploit full body motion. Galna et al. [23] used an exercise protocol specifically designed to train dynamic postural control.

Taking inspiration to the LSVT BIG technique, we designed an exercise protocol that relies on whole body reaching movements with different amplitudes and directions, to induce subjects to increase their movement speed and its sensitivity to movement amplitude. Movements were recorded through the Kinect device and displayed on a screen by an animated avatar in a mirror view, which provided subjects with knowledge of their performance. Depending on the measured movement time, an adaptive regulator continuously adjusted the distance of the targets to keep movement time close to a target value established by the therapist. In this way, the exercise was automatically and continuously adapted to the individual's degree of impairment.

Materials and methods

Experimental set-up

The experimental apparatus included a video projector, displaying a virtual reality environment on a 2 m × 2 m screen. Subjects were required to stand in front of the screen, within a 3 m distance. A markerless motion capture sensor (Microsoft Kinect), placed below the screen, recorded the subjects' full-body movements in 3D space at a 30 Hz sampling rate. The device has a limited accuracy - 1 cm range, see [24] - but allows to reconstruct the trajectories of 'virtual' markers in real-time.

Therefore, it can provide participants an immediate, continuous visual feedback of their movements. In our experiment, the reconstructed trajectories of 13 virtual 'markers' (one head marker, plus shoulder, elbow, hand, hip, knee, and foot, respectively left and right) were used to animate a ten-segments avatar. Estimates of the markers' spatial coordinates from the motion sensor data were obtained through the OpenNI (PrimeSense, Tel-Aviv, Israel, [25]) Application Program Interface (API). A specifically developed software application, based on the H3DAPI (SenseGraphics, Sweden, [26]) software environment and Python, was used to implement the task and the experimental protocol (see below).

Task

The proposed exercise protocol involved full-body movements. While standing, subjects were required to reach one of nine targets, presented in random order. The movement was considered as terminated when the hand first entered the target. Therefore, participants were not required to stop their movement when the target was reached. Target positions were defined in terms of a subject-centered reference frame, as points on the surface of two spheres, centered on each shoulder, at elevation angles of −45° (below shoulder, 'low'), 0° (shoulder level, 'middle') and 45° (above shoulder, 'high'). The targets' horizontal direction (azimuth) with respect to the ipsilateral shoulder marker was 30° (right), 150° (left) and frontal (intersection of the spheres with the sagittal plane); see Figure 1 for details. The radius of the spheres - i.e. the distance between the targets and the shoulder (target distance, TD) - was initially set to 150% of the subject's arm length, and was automatically adjusted during the exercise (see below), within the 50-150% range (of arm length). At the beginning of each session, the difficulty level was reset to its initial value. All movements started from a neutral posture in which both arms were extended downward, so that the hands were placed slightly below the pelvis.

A mirror image of the subject was continuously displayed on the screen as an animated avatar, in which the subject's hands were displayed as ⊘15 cm spheres; see Figure 1 (left). While the subject was in the reference pose, one target (⊘15 cm) appeared on the screen (displayed as either an apple, a star or a bag of money). Subjects were required to reach the target as fast as possible, by using their preferred hand. In other words, subjects were free to choose with which hand to reach the target. In this sense, the task was bilateral. To facilitate reaching, subjects were also allowed to step in all directions.

The task involved movements in three dimensions, but targets were only displayed as projections on the screen placed in front of the subjects. In this way, subjects had a limited information on target location along the 'depth' direction. In fact, all points of the projection line connecting the projection center defined by the virtual environment and the 3D position of the virtual target project to the same point of the screen. The only information on 'depth' was provided by the size of the displayed target (targets, or body segments, that are further away look smaller when projected). As a consequence, the visual feedback on reaching accuracy was largely two-dimensional (on-screen distance between target and subject's hand).

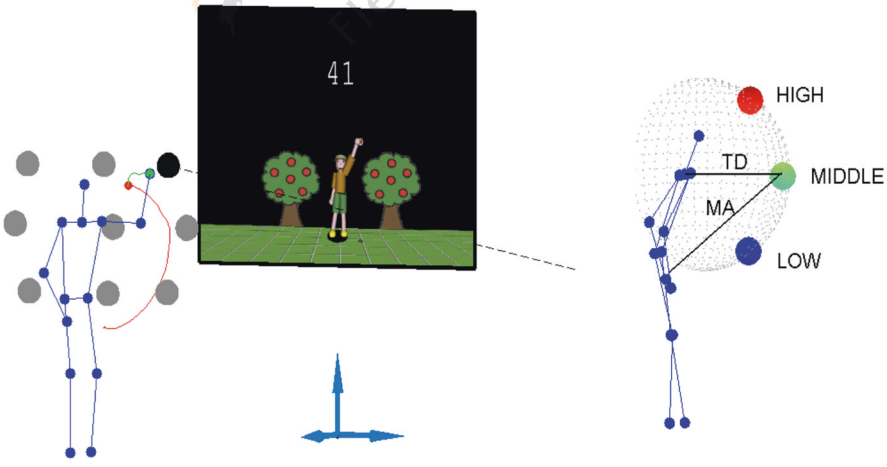

Figure 1 Target arrangement and visual environment. Left: The virtual environment consists of an animated avatar, which is continuously showed to the subject, a target point and a numeric score that is displayed after the end of each movement. Each trajectory can be decomposed into an approach (red) and a correction phase (green). The dashed line denotes the line of projection of the target onto the projection center used by the display. Right: The nine targets were placed at a distance TD from the shoulder, at three different elevations: low (blue), middle (green), high (red). For a given target, movement amplitude (MA) denotes the distance of the target from the start hand position.

The movement was considered completed when either the distance between hand and target was less than the target size, i.e. 15 cm, or movement time was greater than 10 s. After completion of a movement, a $0-100$ score was displayed on the screen, calculated as:

$$\text{score} = 100 \cdot \left\lfloor \frac{1/\text{MT} - 1/\text{MT}_{max}}{1/\text{MT}_{min} - 1/\text{MT}_{max}} \right\rfloor \quad (1)$$

where MT is the total movement time; MT_{max} and MT_{min} are, respectively, the maximum and minimum durations; and $\lfloor x \rfloor$ is the integer value of x. Based on pilot tests with healthy subjects, we set MT_{min} and MT_{max} to, respectively, 0.5 and 10 s. A zero score was assigned to movements whose duration was greater than MT_{max}. Movements whose duration was less than MT_{min} received a maximum (100) score. We did not explicit tell them that the score was related with MT, but they all realized it after a few epochs. We also provided an audio feedback: (i) an unpleasant sound when a zero score was achieved; (ii) a trumpet sound when score was equal to 100, or (iii) a theme-specific 'ok' sound (e.g. a clink if the target was a bag of money) for intermediate score values. In this way, subjects were encouraged to move as fast as possible.

Exercise protocol

The exercise protocol was organized into epochs, each one corresponding to 5 repetitions of a target set - a sequence of all nine targets, in random order (i.e., $5 \times 9 = 45$ movements per epoch). After each epoch, subjects had to rest (sitting if necessary) for at least 1 min. The therapy protocol consisted of a total of 10 training sessions (2 sessions/week), each lasting 40 minutes. Depending on the individual conditions and thus on individual movement speeds, each session could involve a variable number of epochs. At the beginning of each session, an automatic calibration procedure was carried out to initialize the movement tracking algorithm, to estimate the subject's arm length and to establish the subject-centered reference frame with respect to which targets were specified. Each phase of this procedure was guided by vocal messages.

We used a Bayesian procedure [27] to automatically adjust the target distance to the individual movement capabilities, on a per target set basis. After completion of a target set (i.e., nine movements), TD was adjusted in order to get the average score in the next target set as close as possible to a pre-specified target value. Specifically, TD was increased if the average score was greater than the target value, and decreased if the average score was smaller. In other words, if a subject could not reach the target fast enough, the next targets were placed closer to the body. If subjects performed well, targets were placed farther away. In this way, subjects always made movements as wide as they could afford but the score, and therefore the average speed, was kept around the specified target score. In our experiments the target score was set to 25/100, corresponding to MT $=$ 1.74 s. In summary, subjects were required to maintain a target average performance (quantified by the above duration score) within a pre-specified number of consecutive trials (the 'target set') and across different target elevations and movement amplitudes. The adaptive controller automatically adjusted the target distance (i.e., task difficulty) in order to maintain that average score.

Subjects

The study involved a total of seven subjects with idiopathic PD, see the Table 1 for demographic and clinical information, recruited among the outpatients of the National Health System of the municipality of Genoa, Italy (ASL3 'Genovese').

The inclusion criteria were a diagnosis of Parkinson's disease made by a neurologist and the ability to stand up and make a few steps without a walking aid. Presence of serious psychiatric problems, severe receptive aphasia and inability to perform the Timed 'Up and Go' test (TUG) with aids and supervision were taken as exclusion criteria. Presence of early dementia did not in itself constitute an exclusion criterion.

The age of the seven subjects (2M + 5F) was 67 ± 5 years (range $60-76$). Disease duration was 5 ± 4 years (range $2-13$). We quantified subjects' impairment through the Unified Parkinson Disease Rating Scale (UPDRS) - part III (motor) - a 0-56 scale (0: normal; 56: maximally impaired) [28] - 15 ± 10 (range: $5-28$) and the Modified Hoehn and Yahr (H&Y) staging scale [29,30], a 1-5 scale (1: minimal disability, 5: maximum disability) - 3 ± 1 (range 1.5-4). Before the start of the exercise protocol, the subjects' performance with the Timed 'Up and Go' test (TUG) [31] was 15 ± 12 s (range $5-38$ s) and with the 10-Meters-Walk Test (10MWT) [32] was 12 ± 12 s (range: $4-39$ s). In the latter test, subjects were instructed to walk as fast as possible. Two subjects (S1 and S3) exhibited an abnormal forward-flexed posture (camptocormia). All subjects were taking medications at the time of testing and were in their 'ON' phase during training.

The research conforms to the ethical standards laid down in the 1964 Declaration of Helsinki that protects research subjects. Each subject signed a consent form that conforms to these guidelines.

Data analysis

The raw recordings of the 3D trajectories of the 13 virtual markers were smoothed with a 4^{th} order Savitzky-Golay filter with a 0.96 s time window (corresponding to 29 data samples). The same filter was used to estimate all subsequent time derivatives. The filter parameters correspond to a cut-off frequency of approximately 1.5 Hz. Although relatively low with respect to movement analysis

Table 1 Subjects' demographic and clinical information

Subject	Sex	Age [y]	Disease dur. [y]	TUG [s]	10MWT [s]	UPDRS III (motor) (0-56)	H&Y (1-5)
S1	M	69	13	12*	10*	21	3
S2	M	76	2	12	6	5	2
S3	M	60	5	5	4	5	2
S4	F	65	3	24	12	26	4
S5	M	72	4	38	39*	28	4
S6	F	63	4	6	6	11	1.5
S7	M	67	4	7	8	12	1.5
mean ± SD		67 ± 5	5 ± 4	15 ± 12	12 ± 12	15 ± 10	3 ± 1

M: male, F: female; TUG: Timed 'Up and Go' test; 10MWT: 10 Meter Walk Test; UPDRS III (motor): Unified Parkinson's Disease Rating Scale, part III - motor examination (items 18-31); H&Y: Modified Hoehn and Yahr staging scale. (*) with crutch.

standards, this value is necessary to deal with the low accuracy of the Kinect sensor. The Kinect system uses a reconstruction algorithm to estimate the positions of anatomical points (hand centroid etc.). This reconstruction is not 100% accurate, so that the estimated marker positions tend to fluctuate from one sample to the next. As a consequence, the estimated marker trajectories are more irregular and less smooth than in conventional marker-based motion capture systems [33]. Smoothing reduces this problem. In spite of the limited tracking accuracy of this device [24], the smoothed trajectories still allowed to reliably estimate the main spatio-temporal features of the movement (path, duration, speed).

Movement trajectories can be decomposed into an approach phase, in which subjects reach the target projection line, and a correction phase, in which subjects move along the projection line in order to achieve the target. PD subjects with bradykinesia tend to move slowly and to undershoot the target [34], therefore we expected they had problems with both phases.

In the analysis we only considered the movements that achieved a score greater than zero; the others were rejected. For each movement, we first identified the hand that subjects selected to perform the movement by comparing target distance measurements. We then focused on this hand for all subsequent analysis of each single movement.

We then estimated the movement onset as the instant at which movement speed went above 10% of peak speed. The end of the approach phase was identified as the time when the speed went below this same threshold. Finally, movement end was estimated as the instant at which the distance between the hand and the target was smaller than the target size (i.e. 15 cm).

To assess the effect of exercise, we focused on various aspects of movement performance. In addition to target distance, which is a measure of task difficulty and was automatically adjusted at every target set, for each movement we specifically looked at movement path, movement time and the average absolute acceleration (a measure of movement 'effort').

Movement path Movements toward a specific target, placed at distance TD from the shoulder, are characterized by a specific Movement Amplitude (MA), defined as the distance between the start position of the hand selected for the movement (i.e. its reference pose) and the target (see Figure 1). This quantity depends on TD but also on target location, thus it is target-dependent. We quantified the movement path in terms of the undershoot error (US), defined as the projection of the endpoint error - difference from target position and final position at the end of the approach phase - over the direction of the target with respect to the start position. As a measure of path curvature we calculated a Linearity index (LI), defined as the relative increase of path length (PL) with respect to the nominal MA: $\mathrm{LI} = \mathrm{PL}/\mathrm{MA} - 1$. A zero LI would correspond to a perfectly straight hand trajectory.

Movement timing For each movement we calculated the Movement Time (MT) - which determined the movement score as explained above - defined as the time interval between movement onset and movement end. We also looked at the average speed (AS) for each movement.

Movement effort The actual effort that subjects actually devoted to a movement was quantified by taking the average norm of acceleration (AA), calculated as the value of the rectified tangential acceleration, averaged from movement start to movement end (i.e., average of the absolute value of acceleration):

$$\mathrm{AA} = \frac{1}{MT}\int_0^{MT}\left|\frac{dv}{dt}\right| dt \qquad (2)$$

where $v(t)$ is movement speed; see also [15]. In straight-line reaching movements, the average acceleration is proportional to the ratio between path length and the square of movement time, i.e. $\mathrm{AA} \propto \mathrm{PL}/\mathrm{MT}^2$; see [35,36]. We

tentatively assumed that this relation holds in the present task. As a consequence, the score, and thus the reciprocal of movement time, is approximately proportional to the square root of the ratio between the absolute average acceleration and the path length, i.e. $\sqrt{AA/PL}$. Hence AA and PL are two major determinants of movement time and therefore of the movement score. Specifically, increasing PL would require an increase of AA in order to keep MT (and thus the movement score) constant.

Since movements toward targets at different elevations have very different amplitudes, we expect that if they are forced to be of equal duration (i.e., equal score), absolute acceleration should also increase with target elevation. In other words, movements toward 'high' targets should require more effort to achieve the same score. As the controller regulates the average score and the adjusted target distance is common to all targets, irrespective of their elevation, targets at low elevation - requiring less effort - are expected to achieve a greater-than-average score, whereas targets at high elevation - requiring more effort - will achieve a lower-than-average score.

With training, subjects are expected to improve their overall performance. This means that they should be able to achieve the same target score by reaching more distant targets. Furthermore, for a given target distance, they are expected to put more effort in their movements, i.e they should increase their absolute average acceleration.

Statistical analysis

From the recorded hand trajectories, their velocities and their accelerations, we calculated the above indicators for each individual movement. We took the average absolute acceleration as primary outcome measure. All other indicators, which reflect different aspects of task performance, were taken as secondary outcome measures.

To assess the overall effect of exercise on subjects' performance, for each indicator we ran a 2-way repeated-measures ANOVA, with training (pre- vs post-) and elevation (low, middle, high) as within-subject factors. We compared the trials performed under the most challenging condition, represented by the maximum target distance (150% of arm length). For this reason, we took the first epoch of the first session (pre- condition) and the first epoch of the last session (post- condition).

For the indicators that exhibited a significant training and training × elevation effects, we additionally looked at their correlations with disease severity, as measured by the UPDRS - part III and the Modified Hoehn and Yahr staging scale. To do this, for each individual subject and for each indicator we calculated a linear regression over target elevation (low, middle, high), separately for the pre- and post-treatment conditions. We then took: (i) the intercept of the pre-treatment line as pre-treatment performance measure; (ii) the corresponding slope; (iii) the difference in the intercepts of the post- and the pre-treatment lines as a measure of the treatment-related change in performance; and (iv) the difference in the slopes of the post- and pre-treatment lines. For each of the above indicators we took the correlation coefficients with disease severity.

In all cases we took $p = 0.05$ as the threshold for statistical significance. We used Matlab (Mathworks, Natick MA) for all data analysis.

Results

Both the visual environment and the exercise protocol were well accepted by all subjects. Subject S7 exited the study after 5 sessions for health reasons (flu) unrelated to the treatment protocol. This subject was not considered in all further statistical analysis. Although subjects were allowed to step, they very rarely did, likely because they did not feel safe in moving the arm while stepping. In all cases we observed no relevant changes of this behavior as training proceeded. Across sessions, subjects significantly increased ($p = 0.0335$; paired samples t-test) the number of completed blocks of trials (epochs) during the (fixed) duration of each session; see Table 2 for details.

Regulation of target distance

Based on subjects' performance (score), task difficulty - i.e. TD - was adaptively regulated 'as needed' [27]. In this way, the average score over sessions was expected to gradually get closer to this target value, and a concurrent increase in TD is an indirect indication of improved task performance. Figure 2 (left) shows the temporal evolution of score (top) and TD (bottom), averaged over sessions, for each individual subject. With the exception of subjects S1 and S5 who only approached the target score in the later sessions, all other subjects generally managed to keep their score close to the target value. Across sessions, subjects rapidly reduced the fraction of trials per session in which they got a zero score (target not reached within the timeout interval), from 27 ± 9% to 7 ± 1%. The

Table 2 Number of epochs completed on the first (1) and the last treatment sessions (10)

Subject	Session 1	Session 10
S1	5	6
S2	7	10
S3	8	9
S4	7	8
S5	7	8
S6	10	10
S7	7	9*

Each epoch corresponds to 5 × 9 = 45 movements. (*) Subject S7 exited the study after 5 sessions. The reported number of epochs relates to the last completed session (session 5).

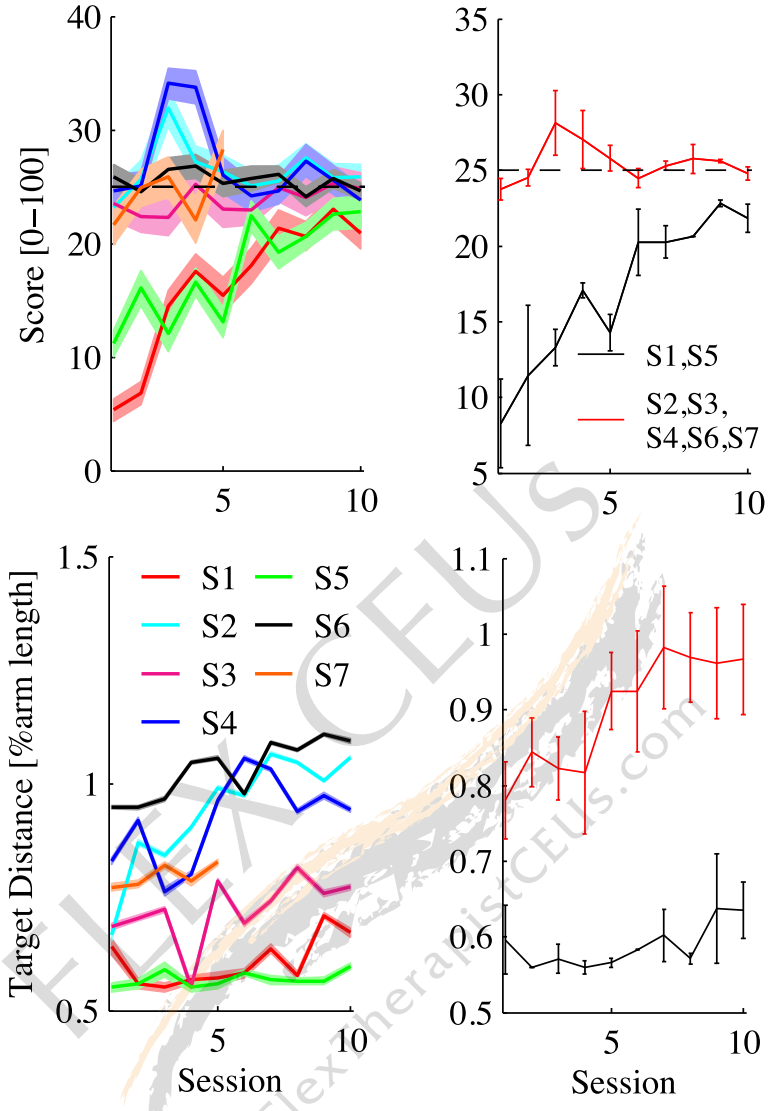

Figure 2 Temporal evolution of score (top) and TD (bottom). Left: Individual subjects. Each color represents a different subject. Right: average over subjects (black: S1 and S5; red: all other subjects). Dashed areas and bars denote the standard error (SE).

effect was not significant due to the large between-subject variability.

With the exception of subjects S1 and S5, for which TD remained close to its minimum value (50% of arm length), all other subjects exhibited a gradual TD increase; see Figure 2 (right). Several subjects exhibit a non-monotonic evolution of target distance over sessions. This is because the difficulty level was set to its initial value at the beginning of each session, so that the temporal evolution of TD across sessions exhibits some variability.

Movement performance

Experimental observations confirmed that subjects generally used a two-step strategy for reaching the targets, consisting of an approach and a correction phase. During the approach phase, subjects reached the line joining the point of view and the actual position in space of the virtual target. All points of this line are projected into the same point on the screen. During the correction phase, subjects moved along this line to achieve the actual 3D target position; see Figure 1 (left).

The results of the 2-way ANOVA are summarized in Table 3.

Movement Path During the approach phase, subjects generally tended to undershoot the target, but the magnitude of the effect did not depend on target elevation (non-significant effect of elevation). We observed a significant training effect on the amount of undershoot ($p = 0.03$) - undershoot decreases with training. This effect

Table 3 Summary of the results of the 2-way analysis of variance (ns: not significant), for undershoot error (US), linearity index (LI), movement time (MT), average speed (AS) and average absolute acceleration (AA)

	Elevation	Training	Training × Elevation
US	ns	0.03	ns
LI	ns	ns	ns
MT	ns	0.002	ns
AS	0.008	0.01	0.005
AA	0.02	0.025	0.014

did not depend on target elevation (non-significant interaction between session and elevation); see Table 3 and Figure 3 (left). In contrast, we found no significant changes in path curvature (linearity index, LI) - curvature neither significantly depends on elevation nor significantly decreases with training.

Movement Effort We assessed movement effort in terms of the average absolute acceleration. We found significant training ($p = 0.025$) and elevation ($p = 0.02$) effects. Figure 4 (right) summarizes the effect of training on movement effort.

In addition, we observed a significant training × elevation effect ($p = 0.014$); see Table 3. Figure 5 summarizes this effect.

Movement timing We observed a significant decrease ($p = 0.002$) of movement time with training; see Figure 3 (right). We did not find significant elevation or elevation × training effects, see Table 3.

As regards average speed, we found a significant elevation effect in the overall movement ($p = 0.008$) - speed increases with target elevation. We also found a significant training effect ($p = 0.01$); see Table 3. Figure 4 (left) summarizes the effect of training on average speed. We also observed a significant training × elevation interaction ($p = 0.005$); see Figure 5.

A look at the relation between MT and elevation - see Figure 5 (left)- suggests that before training MT is significantly greater at high elevation than at low elevation ($p = 0.026$, post-hoc comparison with Bonferroni correction). At the end of the training, MT decreases and also becomes less dependent on MA (elevation effect not significant).

Disease severity

The relation between disease severity of the individual subjects - quantified through the Modified Hoehn and Yahr scale - and the corresponding performance indicators is summarized in Table 4.

We only found a significant correlation with the pre-treatment movement speed (AS; $R = -0.82$, $p = 0.04$) - greater disease severity, less speed. No statistically significant correlations were observed with the UPDRS score.

Clinical scales

To assess whether the training protocol resulted in modifications of the subjects' degree of impairment, we performed clinical tests (TUG, 10MWT) before the start and after the end of the training protocol. The TUG score was 15±12 s (range 5−38 s) before training and 16±15 s (range

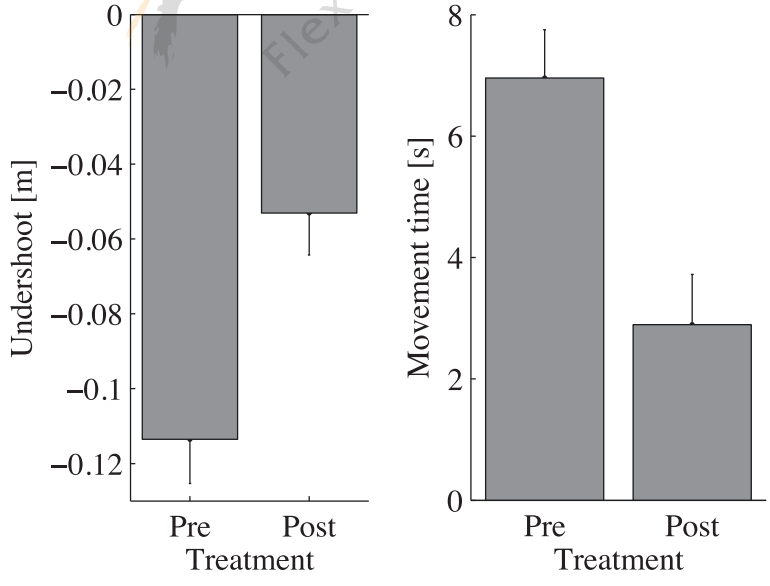

Figure 3 Effect of training on undershoot error and movement time. Undershoot Error (left) and Movement Time (rigth) in the first epoch of the beginning (Pre) and the first epoch at the end of the training protocol (Post). Error bars denote the SE.

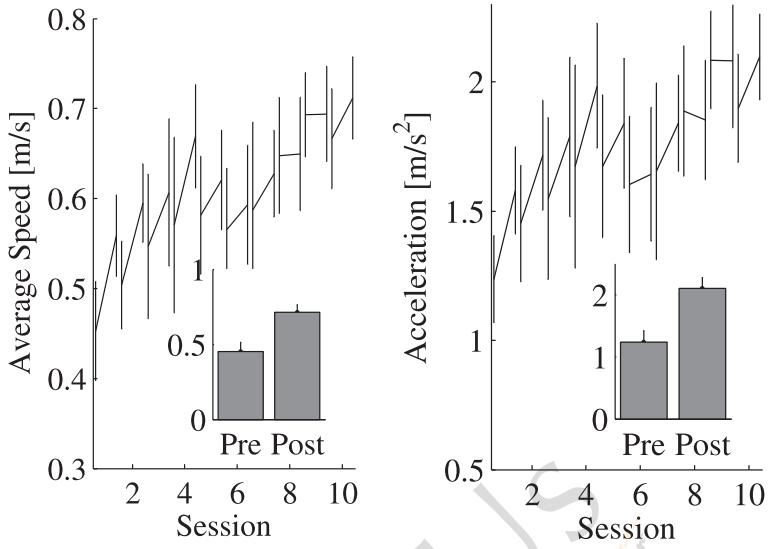

Figure 4 Temporal evolution and effect of training on average speed and average acceleration. Average Speed (left) and Average Acceleration (right) averaged across subjects (first and last epoch of each session). Bar graph of Average Speed and Average Acceleration in the first epoch of the beginning (Pre) and the last epoch at the end of the training protocol (Post). Error bars denote the SE.

4 − 45 s) after training. The 10MWT score, respectively before and after training, was 12 ± 12 s (range: 4 − 39 s) and 12±13 s (range: 3−37.7 s), see Table 5 for details. We found an improvement in, respectively, the TUG and the 10MWT in 3/6 and 5/6 subjects. However, these effects turned out to be non-significant from the statistical point of view (paired-sample t-test).

Discussion

We designed a technology-assisted exercise that specifically aims at increasing movement speed through the repeated practice of large amplitude movements.

Six subjects (out of seven) successfully completed the trial, with the exclusion of S7 who exited the study for reasons unrelated to the treatment. All subjects verbally

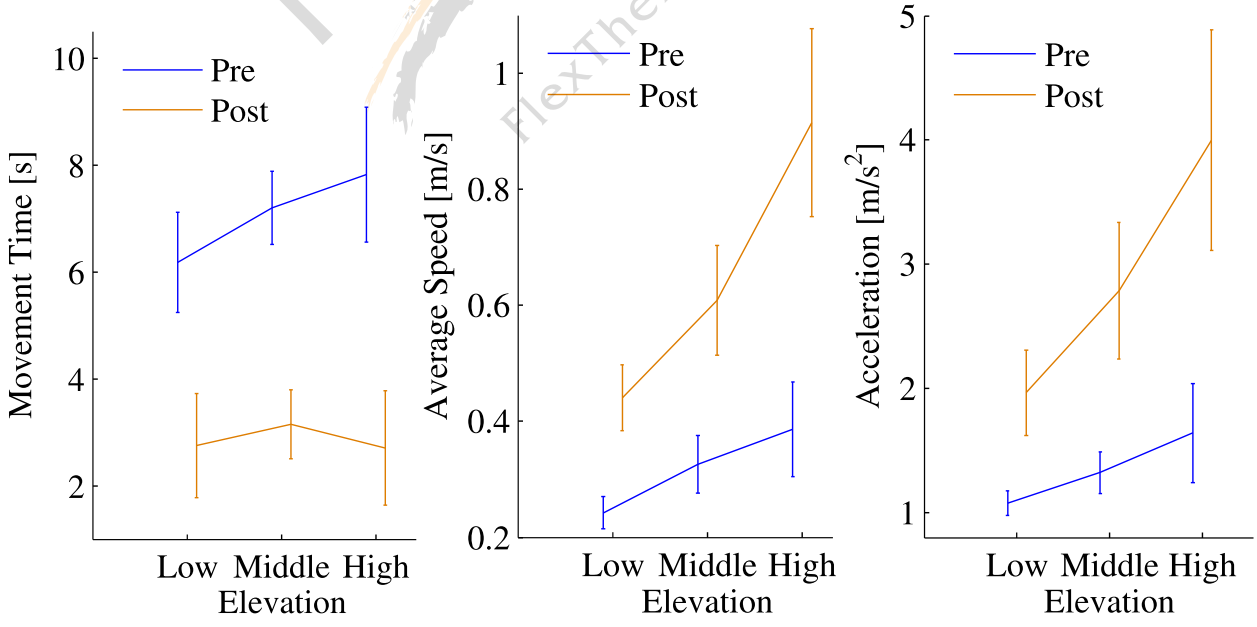

Figure 5 Interaction between training and target elevation. Sensitivity of movement time (left), average speed (middle) and average absolute acceleration (right) to target elevation (low, middle, high), respectively at the beginning (Pre, blue line) and at the end of training (Post, orange line). Error bars denote the SE.

Table 4 Correlation of disease severity (Modified Hoehn and Yahr scale, H&Y) with the regression parameters (slope, intercept) of undershoot error (US), movement time (MT), average speed (AS) and average absolute acceleration (AA) with respect to target elevation

	US		MT		AS		AA	
	R	p	*R*	p	*R*	p	*R*	p
Pre-treatment slope	0.42	0.32	0.36	0.47	-0.82	0.04*	-0.74	0.09
Pre-treatment intercept	-0.13	0.80	0.41	0.41	-0.17	0.74	-0.33	0.52
Δslope	-0.54	0.26	0.35	0.49	0.36	0.47	0.23	0.66
Δintercept	0.17	0.73	-0.31	0.54	-0.66	0.15	-0.18	0.73

For each indicator we report the parameter values pre-treatment and the pre-post change. *R* and *p* denote the correlation coefficient and the p-value.

expressed a high level of acceptance for the treatment and the apparatus. They only reported a difficulty in assessing the 3D location of the targets. This is consistent with a previous study [23] pointing out that, while participants enjoyed the game and could gladly train at home, they exhibited a difficulty to 'discriminate between different types and orientations of visual objects'.

Subjects gradually increased movement amplitude

To encourage subjects to exercise at the maximum amplitude they could sustain, we adaptively regulated target distance (and therefore movement amplitude) so that subjects could achieve and maintain a target movement time [27]. This guaranteed both exercising at maximal effort but also safety and motivation (speed and amplitude were maintained within comfortable levels).

Over the training sessions all subjects - see Figure 2 - exhibited a gradual increase of target distance. At the same time, all managed to maintain the movement score (based on movement time) close to the target value of 25/100. The fraction of trials in which subjects got a zero score also rapidly decreased across sessions. We decided to set the same target score for all subjects. For subjects S1 and S5 this was specially challenging, and they only managed to reach it on the final sessions of the training protocol.

Table 5 TUG and 10MWT tests before and after training

Subject	TUG [s]		10MWT [s]	
	Before	After	Before	After
S1	12	14	10	8.7
S2	12	10	6	4.9
S3	5	4	4	3
S4	24	14	12	10
S5	38	45	39	37.7
S6	6	6	6	7
S7	7	NA	8	NA
mean ± SD	15 ± 12	16 ± 15	12 ± 12	12 ± 13

Post-training scores for subject S7 are not available (NA) as he did not complete the protocol.

To all other subjects, the target appeared to be within easy reach, but they still found the task challenging and motivating.

The proposed approach is similar to the LSVT BIG technique, in which subjects are encouraged to practice large amplitude movements through verbal cues by a therapist [18]. In our case, adaptive control of amplitude, time-based reward and the continuous display of the mirror image of the subject, of his/her movements and of the targets plays a similar role of the verbal cues used by [18], as a way to promote subjects' awareness of the amplitude of their movements. Sensory awareness of movement magnitude is related to the integration of proprioception and vision, which is another essential aspect of the LSVT BIG technique.

Subjects become faster and more accurate

With training, we expected subjects to gradually improve both precision and speed of their movements.

As regards precision, irrespective of target elevation subjects generally tended to undershoot the target. This is a well-documented symptom - hypometria - that has often been related to bradykinesia [2,37]. Specifically, bradykinesia may in part result from a reduced endpoint accuracy. Sheridan and Flowers [38] hypothesized that in order to maintain accuracy within acceptable limits, PD patients are forced to increase the duration of their movements. However, we suspect that in the present experiment the observed undershoot may be at least partly a consequence of a parsimonious strategy (i.e. 'stopping early') to deal with the lack of depth information. In fact, we ran few trials with healthy subjects and they reported similar problems (data not shown). Nevertheless, with training we indeed observed a significant decrease of the undershoot error; see Figure 3 (top).

We also observed a significant decrease in the movement time - see Figure 3 (top) - and a corresponding increase in movement speed and in absolute acceleration - subjects tend to move faster and to put more effort in their movements increasing also their accuracy; see Figure 3 (bottom). A further, more indirect indication that subjects move faster is represented by the significant increase

of the number of movements that subjects managed to complete within each 40-min training session.

Finally, we looked at the relation between the amount of improvement (in motor performance, in motor motivation) and the initial degree of impairment, as measured by the Modified Hoehn and Yahr score and the UPDRS-III scale. We found a weak but significant negative correlation between disease severity and the pre-treatment speed - more severely impaired subjects initially make slower movements. In contrast, no significant relationship was observed between disease severity and performance improvement. These results suggest a simple relation between task-related performance measure and the overall degree of impairment. However, they should be taken cautiously given the small number of subjects that are far from representative of the general PD population.

Reduced bradykinesia or task familiarization?

An improved speed and accuracy of the movement may result from either a true reduction of the bradykinesia symptoms, or mere familiarization with the task.

As mentioned in the Introduction, bradykinesia has been associated to either a difficulty in selecting movements that require greater levels of energy expenditure [15,39,40] or an insensitivity to rewarding outcomes [41]. Formulations based on optimal control - e.g. [40] - emphasize that movements are the result of a trade-off between reward and effort. Response vigor - the bias toward selecting high-speed movements - reflects this trade-off. The notion that the latter is mediated by the basal ganglia has found some empirical confirmation [14,42].

Vigor is difficult to quantify empirically [15]. Some studies have been looking at the observation that movement speed increases with movement amplitude - the amplitude-speed effect, see [18]. This relation has been reported in reaching, in walking, in handwriting and in eye movements. For instance, Choi et al. [43] analyzed saccades of various amplitudes and looked at the relationship between amplitude and speed, and how it depends on the subjects' degree of impulsivity, defined in terms of how long they are willing to wait for a rewarding outcome. Their main finding was that subjects' impulsivity correlated with the slope of the saccade's amplitude-speed relationship. In other studies [44] this effect was quantified in terms of the relationship between movement amplitude and the average acceleration, taken as a measure of effort. These authors reported that the handwriting movements of PD subjects have an abnormal stroke size - acceleration dependence.

Taken together, the above studies suggest that the slope of the amplitude-speed or amplitude-acceleration dependence can be taken as a measure of vigor. In the present study we looked at the slopes of both the amplitude-acceleration and the amplitude-speed relations. We observed a significant effect of elevation (or, equivalently, amplitude) in the average absolute acceleration, which more directly reflects energy expenditure; see Table 3 and Figure 5. A similar effect was observed in the average speed - training led to an increase of the slope of the amplitude-speed relation.

However, one problem with this interpretation is that familiarization with the task would result, by itself, in a generalized increase of movement speed, while not necessarily implying a vigor change.

As regards the amplitude-absolute acceleration relationship, Rigoux et al. [40]'s model predicts that low vigor - i.e. a greater subjective importance given to movement effort - implies a greater sensitivity of MT to MA. To further explore this point, we looked at the empirical relation between MT, elevation (i.e. MA) and training; see Figure 5 (left). We found that before training MT is significantly greater at high elevation than at low elevation. At the end of the training MT not only decreases, but also becomes less dependent on MA (elevation effect no longer significant). Similar findings were reported by van Gemmert et al. [44] in the context of handwriting. They specifically looked at the relationship between the size and the duration of elementary movements (stroke), in healthy subjects and in persons with PD.

Hence, our data exhibit an effect that is consistent with an increased vigor [40]. However, familiarization with the task would lead to a reduced MT in ways that are similar to those induced by vigor change, so that these aspects would be difficult to distinguish. Therefore, a slope increase in the AA vs MA relation may be at least in part a consequence of familiarization with the task. Similar considerations apply to the AS vs MA relation.

In summary, our observed training-induced changes in both the amplitude-speed or the amplitude-acceleration relations are consistent with an increased vigor but are not conclusive in distinguishing between task familiarization and vigor change.

Toward clinical application

Although our findings are far from conclusive and expect confirmation by a larger study, they nevertheless suggest a training-induced improvement of the bradykinesia symptoms.

We observed a modest improvement in some subjects in a variety of clinical scales, but these changes were not statistically significant. In contrast, Ebersbach et al. [20] delivered 1-hour treatment sessions, 4 sessions/week for 4 weeks (a total of 16 hours of treatment) and found a clinically significant reduction of the UPDRS-III score. A lower reduction was observed after a shorter duration (2 weeks) version of the same LSVT protocol [45] (a total of 8 hours of treatment). After a Kinect-based training protocol consisting of fourteen 60-minute sessions with the

Kinect Adventure game suite (a total of 14 hours of treatment), Pompeu et al. [22] also reported an improvement in activity (balance and gait) and participation (quality of life).

It should be noted that our subjects only made 40-minutes treatment sessions, 2 sessions/week for 5 weeks (a total of 6.6 hours of treatment), which is a far lower dose than [20,22] but is similar to [45]. The better outcome of the latter may depend on the different intensity (similar treatment doses administered in half the time) and/or the behavioral training provided in addition to the large amplitude exercise. In all cases we found no evidence of plateau effects in the temporal evolution of performance indicators in Figure 4, which suggests that additional exercise might have resulted in even more improvement.

Another limitation of our proposed approach with respect to the LSVT BIG technique is that, although we provided several forms of feedback on task performance, we did not explicitly stimulate subjects' motivation and we did not explicitly promote transfer of the improved performance to activities of daily living. Using a tangible (monetary) reward and/or directly measuring enjoyment, and possibly modulating them during training might further improve the outcome.

Conclusions

We have explored the potential of the Microsoft Kinect by focusing on two specific symptoms of Parkinson's disease, namely bradykinesia and hypokinesia.

The rationale underlying the study is that bradykinesia can be mitigated by repeated exercise that specifically focuses on high-amplitude movements [18,20].

Although preliminar, our results point at a training-induced reduction of bradykinesia. However, we cannot conclude on whether the observed outcome is the mere effect of familiarization with the task or is a consequence of an increased vigor. Proper discrimination between these two effects is indeed an open issue, which we leave to future developments. To address this, one could possibly focus on more automatic motor activities (e.g. handwriting, speech, etc), for which a familiarization effect can be ruled out, or on comparing the effects of training with a baseline (e.g. healthy subjects, or PD subjects ON vs OFF medication). Another possibility is to use computational models that explicitly address learning and vigor change, to estimate learning-related and vigor change-related contributions to the observed changes of performance. The same arguments on the difficulty of distinguishing between performance improvements related to familiarization and those related to vigor also apply to assessing bradykinesia through clinical scales, none of which specifically address or vigor.

More in general, we wanted to explore the potential of natural user interfaces as rehabilitation devices. Natural interfaces are appealing because subjects can freely move and are not required to wear sensors or markers. This makes their use more intuitive and more comfortable specially for older users. In fact as in other reports the device was well accepted by our subjects and appeared safe and easy to use. In the context of rehabilitation they are increasingly used in conjunction with off-the-shelf video games [22], but they also allow to design exercises that target specific types of impairment [23]. One secondary aspect is the low cost, which makes this treatment particularly affordable by rehabilitation centers and even individual users. Taken together, these aspects suggest that the proposed treatment may be suitable for training with little or no supervision by a therapist, possibly in domestic environments.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
EB, VS, AB and SS conceived the study. SS and AB developed the experimental setup and the software. EB recruited the subjects and made the clinical assessments. SS, AB and EB made the experiments. SS and VS analyzed the results. SS,EB and VS wrote the manuscript. All authors read and approved the final manuscript.

Acknowledgements
This work was partly supported by the EU Grant FP7-ICT- 271724 (HUMOUR), by a grant from the Italian Ministry of University and Research (PRIN 2009) and with the kind contribution of the Italian Ministry of Foreign Affairs, Unit for S/T cooperation.

Author details
[1]Department of Informatics, Bioengineering, Robotics and Systems Engineering, University of Genoa, Genoa, Italy. [2]School of Computer Science, University of Hertfordshire, Hatfield, UK. [3]Functional Recovery and Rehabilitation Service, Hospital 'La Colletta', Arenzano, Italy.

Received: 14 July 2014 Accepted: 4 February 2015
Published online: 14 February 2015

References

1. Berardelli A, Rothwell JC, Thompson PD, Hallett M. Pathophysiology of bradykinesia in Parkinson's disease. Brain. 2001;124(Pt 11):2131–46.
2. Mazzoni P, Shabbott B, Cortés JC. Motor control abnormalities in Parkinson's Disease. Cold Spring Harbor Perspect Med. 2012;2(6):a009282.
3. Pfann KD, Buchman AS, Comella CL, Corcos DM. Control of movement distance in Parkinson's disease. Mov Disord. 2001;16(6):1048–65.
4. Phillips JG, Martin KE, Bradshaw JL, Iansek R. Could bradykinesia in Parkinson's disease simply be compensation? J Neurol. 1994;241(7):439–47.
5. Protas EJ, Stanley RK, Jankovic J, MacNeill B. Cardiovascular and metabolic responses to upper- and lower-extremity exercise in men with idiopathic Parkinson's disease. Phys Ther. 1996;76(1):34–40.
6. Schenkman M, Salay J, Scherer N, Kohrt W. Walking Economy in Patients With Mild to Moderate Parkinsons Disease. J Neurol Phys Ther. 2004;28(4):172–3.
7. Canning CG, Alison JA, Allen NE, Groeller H. Parkinson's disease: An investigation of exercise capacity, respiratory function, and gait. Arch Phys Med Rehabil. 2014;78(2):199–207.
8. Stanley RK, Protas EJ, Jankovic J. Exercise performance in those having Parkinson's disease and healthy normals. Med Sci Sport Exerc. 1999;31(6):761–6.

9. Corcos DM, Chen CM, Quinn NP, McAuley J, Rothwell JC. Strength in Parkinson's disease: relationship to rate of force generation and clinical status. Ann Neurol. 1996;39(1):79–88.
10. Klockgether T, Dichgans J. Visual control of arm movement in Parkinson's disease. Mov Disord. 1994;9(1):48–56.
11. Abbruzzese G, Berardelli A. Sensorimotor integration in movement disorders. Mov Disord. 2003;18(3):231–40.
12. Berardelli A, Dick JP, Rothwell JC, Day BL, Marsden CD. Scaling of the size of the first agonist EMG burst during rapid wrist movements in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 1986;49(11):1273–9.
13. Majsak MJ, Kaminski T, Gentile AM, Flanagan JR. The reaching movements of patients with Parkinson's disease under self-determined maximal speed and visually cued conditions. Brain. 1998;121(Pt 4):755–66.
14. Turner RS, Desmurget M. Basal ganglia contributions to motor control: a vigorous tutor. Current Opin Neurobiol. 2010;20(6):704–16.
15. Mazzoni P, Hristova A, Krakauer JW. Why don't we move faster? Parkinson's disease, movement vigor, and implicit motivation. J Neurosci. 2007;27(27):7105–16.
16. Muhlack S, Welnic J, Woitalla D, Müller T. Exercise improves efficacy of levodopa in patients with Parkinson's disease. Mov Disord. 2007;22(3):427–30.
17. Tomlinson CL, Patel S, Meek C, Herd CP, Clarke CE, Stowe R, et al. Physiotherapy versus placebo or no intervention in Parkinson's disease. Cochrane Database Syst Rev. 2013;9.
18. Farley BG, Koshland GF. Training BIG to move faster: the application of the speed-amplitude relation as a rehabilitation strategy for people with Parkinson's disease. Exp Brain Res. 2005;167(3):462–7.
19. Freund HJ, Büdingen HJ. The relationship between speed and amplitude of the fastest voluntary contractions of human arm muscles. Exp Brain Res. 1978;31(1):1–12.
20. Ebersbach G, Ebersbach A, Edler D, Kaufhold O, Kusch M, Kupsch A, et al. Comparing exercise in Parkinson's disease–the Berlin LSVT®BIG study. Mov Disord. 2010;25(12):1902–8.
21. Barry G, Galna B, Rochester L. The role of exergaming in Parkinson's disease rehabilitation: a systematic review of the evidence. J Neuroeng Rehabil. 2014;11:33.
22. Pompeu JE, Arduini LA, Botelho AR, Fonseca MBF, Pompeu SMAA, Torriani-Pasin C, et al. Feasibility, safety and outcomes of playing Kinect Adventures!™for people with Parkinson's disease: a pilot study. Physiotherapy. 2014;100(2):162–8. Noncommunicable diseases.
23. Galna B, Jackson D, Schofield G, McNaney R, Webster M, Barry G, et al. Retraining function in people with Parkinson's disease using the Microsoft kinect: game design and pilot testing. J NeuroEng Rehabil. 2014;11(1):60.
24. Dutta T. Evaluation of the Kinect™ sensor for 3-D kinematic measurement in the workplace. Appl Ergon. 2012;43(4):645–9.
25. OpenNI User Guide. http://www.primesense.com.
26. H3D.org: Open Source Haptics. http://www.h3dapi.org.
27. Squeri V, Basteris A, Sanguineti V. Adaptive regulation of assistance "as needed" in robot-assisted motor skill learning and neuro-rehabilitation. In: IEEE International Conference on Rehabilitation Robotics; 2011. p. 1–6. http://www.ncbi.nlm.nih.gov/pubmed/22275579.
28. Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Fahn S, et al. The unified Parkinson's disease rating scale (UPDRS): status and recommendations. Mov Disord. 2003;18(7):738–50.
29. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology. 1998;50(2):318.
30. Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, et al. Movement disorder society task force report on the Hoehn and Yahr staging scale: status and recommendations. Mov Disord. 2004;19(9):1020–8.
31. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39(2):142–8.
32. Schenkman M, Cutson TM, Kuchibhatla M, Chandler J, Pieper C. Reliability of impairment and physical performance measures for persons with Parkinson's disease. Phys Ther. 1997;77(1):19–27.
33. van Diest M, Stegenga J, Wörtche HJ, Postema K, Verkerke GJ, Lamoth CJC. Suitability of kinect for measuring whole body movement patterns during exergaming. J Biomech. 2014;47(12):2925–32.
34. Flowers K. Ballistic and corrective movements on an aiming task. Intention tremor and parkinsonian movement disorders compared. Neurology. 1975;25(5):413–21.
35. Nelson WL. Physical principles for economies of skilled movements. Biol Cybern. 1983;46(2):135–47.
36. Nagasaki H. Asymmetric velocity and acceleration profiles of human arm movements. Exp Brain Res. 1989;74(2):319–26.
37. Broderick MP, Van Gemmert AWA, Shill HA, Stelmach GE. Hypometria and bradykinesia during drawing movements in individuals with Parkinson's disease. Exp Brain Res. 2009;197(3):223–33.
38. Sheridan MR, Flowers KA. Movement variability and bradykinesia in Parkinson's disease. Brain. 1990;113(4):1149–61.
39. Shadmehr R, Krakauer JW. A computational neuroanatomy for motor control. Exp Brain Res. 2008;185(3):359–81.
40. Rigoux L, Guigon E. A model of reward- and effort-based optimal decision making and motor control. PLoS Comput Biol. 2012;8(10):1002716.
41. Shiner T, Seymour B, Symmonds M, Dayan P, Bhatia KP, Dolan RJ. The effect of motivation on movement: a study of bradykinesia in Parkinson's disease. PLoS One. 2012;7(10):47138.
42. Pasquereau B, Turner RS. Limited encoding of effort by dopamine neurons in a cost–benefit trade-off task. J Neurosci. 2013;33(19):8288–300.
43. Choi JES, Vaswani PA, Shadmehr R. Vigor of movements and the cost of time in decision making. J Neurosci. 2014;34(4):1212–23.
44. Van Gemmert AWA, Adler CH, Stelmach GE. Parkinson's disease patients undershoot target size in handwriting and similar tasks. J Neurol Neurosurg Psychiat. 2003;74(11):1502–8.
45. Ebersbach G, Grust U, Ebersbach A, Wegner B, Gandor F, Kühn AA. Amplitude-oriented exercise in Parkinson's disease: a randomized study comparing LSVT-BIG and a short training protocol. J Neural Transm. 2014;122(2):253–6.

This course was developed from the document: “Effects of Resistance Training on Measures of Muscular Strength in People with Parkinson’s Disease: A Systematic Review and Meta-Analysis by Luisa Roeder, Joseph T. Costello, Simon S. Smith, Ian B. Stewart, and Graham K. Kerr used under the Creative Commons Attribution License."

This course was developed from the document: “Resistance versus Balance Training to Improve Postural Control in Parkinson's Disease: A Randomized Rater Blinded Controlled Study by Christian Schlenstedt, Steffen Paschen, Annika Kruse, Jan Raethjen, Burkhard Weisser, and Günther Deuschl used under the Creative Commons Attribution License."

This course was developed from the document: “Adaptive Training with Full-Body Movements to Reduce Bradykinesia in Persons with Parkinson’s Disease: A Pilot Study by Susanna Summa, Angelo Basteris, Enrico Betti, and Vittorio Sanguineti used under the Creative Commons Attribution License."