Long-term effects of exercise and physical therapy in people with Parkinson disease

Margaret K. Mak[1], Irene S. Wong-Yu[1], Xia Shen[2] and Chloe L. Chung[1]

Abstract | Parkinson disease (PD) is a progressive, neurodegenerative movement disorder with symptoms reflecting various impairments and functional limitations, such as postural instability, gait disturbance, immobility and falls. In addition to pharmacological and surgical management of PD, exercise and physical therapy interventions are also being actively researched. This Review provides an overview of the effects of PD on physical activity — including muscle weakness, reduced aerobic capacity, gait impairment, balance disorders and falls. Previously published reviews have discussed only the short-term benefits of exercises and physical therapy for people with PD. However, owing to the progressive nature of PD, the present Review focuses on the long-term effects of such interventions. We also discuss exercise-induced neuroplasticity, present data on the possible risks and adverse effects of exercise training, make recommendations for clinical practice, and describe new treatment approaches. Evidence suggests that a minimum of 4 weeks of gait training or 8 weeks of balance training can have positive effects that persist for 3–12 months after treatment completion. Sustained strength training, aerobic training, tai chi or dance therapy lasting at least 12 weeks can produce long-term beneficial effects. Further studies are needed to verify disease-modifying effects of these interventions.

[1]Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, 11 Yuk Choi Road, Hung Hom, Kowloon, Hong Kong.
[2]Department of Sports Sciences and Physical Education, The Chinese University of Hong Kong, Kwok Sports Building, University Avenue, Shatin, New Territories, Hong Kong.

Correspondence to M.K.M. margaret.mak@polyu.edu.hk

doi:10.1038/nrneurol.2017.128
Published online 13 Oct 2017

Parkinson disease (PD) is the second most common neurodegenerative disease globally, with a prevalence of 400–1,900 cases per 100,000 people worldwide[1,2]. PD results from the interplay of genetic and environmental risk factors acting on an ageing brain[3,4]. Pharmacological treatment is the mainstay of management[5]. However, gait and balance impairments persist in patients with PD despite optimal medication, and frequently lead to falls resulting in potentially severe complications[6]. The suboptimal pharmacological and surgical management of PD prompted the Movement Disorder Society Evidence-Based Medicine Panel to recommend exercise and physical therapy as an efficacious adjunct to levodopa[7]. In the past 20 years, numerous high-quality clinical trials have investigated the role of exercise and physical therapy in the treatment of patients with PD[8–10]. Meta-analyses of these data have demonstrated short-term and, to a lesser extent, long-term benefits of exercise interventions on various physical outcomes. In this Review, we focus on the long-term effects of exercise and physical therapy: that is, studies with a training duration lasting at least 12 weeks or with a minimum of 12 weeks of follow-up after treatment has ended. We group these studies by the focus of the exercises: muscle strength, aerobic capacity, balance or gait. In addition, we review the effects of complementary exercises such as tai chi and dance therapy. We also assess the evidence indicating whether exercise training can induce neuroplasticity, and discuss the possible risks of exercise training. Finally, we make recommendations on the basis of the available evidence and highlight new approaches to treatment.

Impairments and limitations in PD

Muscle weakness has been observed in various muscle groups in patients with PD[11–14]. In particular, reduced lower-limb strength has attracted the most research owing to its association with postural instability[15], poor physical function and walking performance[11,16,17], and increased risk of falls[18,19]. Muscle weakness and bradykinesia have been suggested to share some aspects of their pathophysiology; for example, reduced cortical output to muscles and impaired recruitment of motor units can cause abnormal muscle activation patterns, altered agonist burst frequency and intensity, and a reduced torque generation rate, which can all result in bradykinesia and muscle weakness[20,21]. However, some differences in the pathogenesis of these symptoms also

Key points

- Most progressive strength and aerobic endurance training programmes have positive effects that last for 12 weeks
- Extended progressive strength training improves muscle strength for up to 24 months and aerobic endurance training increases walking capacity at 6–16 months
- Balance training improves balance, gait and mobility, and reduces falls for up to 12 months after completion of treatment
- Gait training improves gait performance and walking capacity for up to 6 months after training
- Tai chi and dance improve balance and tai chi reduces fall frequency up to 6 months after training
- A training period of at least 6 months is effective for achieving clinically meaningful improvement in UPDRS-III scores

exists; for example, bradykinesia can occur because of muscle co-contraction, excessive reciprocal inhibition and altered agonist burst duration[22].

Cardiopulmonary fitness, as quantified by maximal oxygen consumption (VO_2max), was reported to be 20–25% lower in patients with PD than in healthy age-matched controls, as assessed by a treadmill-based walking test[23]. By contrast, other studies have reported near-normal fitness levels in patients with PD as measured by a cycle ergometer[24,25]. The discrepancy in these results might be due to the substantial heterogeneity in testing methodologies and in the severity of PD among participants. Severity of PD is likely to have a substantial effect on cardiopulmonary fitness, as VO_2max is reduced in moderate to severe PD[25] but not in mild PD[24,26].

Compromised physical fitness manifests in patients with PD as a reduction in walking economy[27] (measured using the rate of oxygen consumption (VO_2 uptake); TABLE 1)and walking capacity[28] (measured using the 6 min walk test; TABLE 1). One contributor to reduced walking capacity is decreased physical fitness owing to lower physical activity in individuals with PD than in healthy controls[28]. Lord *et al.*[29] reported that people with PD walked significantly fewer steps per day, and that this suboptimal ambulatory pattern was established in an early stage of PD (Hoehn and Yahr rating scale stage 1). This physical inactivity can lead to reduced VO_2max[24]. Conversely, higher levels of activity in patients with PD are associated with a greater ability to maintain cardiopulmonary fitness and walking capacity[28].

Gait impairments are very common and disabling for individuals with PD. The abnormal walking pattern observed in people with PD is characterized by short, shuffling steps[30]. In addition, individuals with PD have a slower gait speed and a longer double-support phase than those of healthy controls[31]. Other gait deviations resulting from PD include reduced rotation of the trunk and pelvis[32], higher stride-to-stride variability[33]; and turning that involves more, and smaller, steps[34]. These hypokinetic, inflexible gait patterns might contribute to tripping and falling[35], and about 50% of all falls in people with PD are estimated to occur during walking[36].

The impairments in gait are exacerbated when people with PD perform concurrent tasks while walking in daily life. Compared with the sole activity of walking, undertaking an additional task while walking (such as talking or backward counting) results in further reductions in gait speed and stride length and increased stride-to-stride variability in individuals with PD[37,38]. In addition, people with PD commonly experience freezing of gait (FOG), an episodic cessation of walking with a subjective feeling of the feet being glued to the ground[39], most often during gait initiation, turning, passing through narrow pathways or in dual-task walking. A number of pathophysiological mechanisms are proposed to underlie FOG, such as loss of automatic coupling between gait and posture, visuoperceptual impairment, response inhibition and/or motor set-shifting[40].

Postural instability or balance impairment can start in Hoehn and Yahr stages 1.5–2.0 (REF. 41) and gradually worsen as the disease progresses. PD-specific balance impairment is manifested as abnormal postural sway in stance[42,43], gait instability[44], slow turns[45], reduced trunk rotation[45], reduced limit of stability[46], abnormal anticipatory postural adjustments[47] and poor reactive postural responses[48]. A decreased limit of stability is quantified by a reduction in ability to maintain an inclined posture in reaching tasks[49]. The reduced velocity and decreased amplitude of anticipatory postural adjustments in individuals with PD affects postural stability during gait initiation, reaching, and transitioning from sitting to standing[50,51]. Furthermore, abnormal reactive postural responses, including reduced compensatory stepping reactions in multiple directions, increase the risk of falling upon perturbation[52,53].

Fall incidence in PD is a function of the inverted-U relationship between disease severity and activity[54], which reaches a maximum near Hoehn and Yahr stage 3 and decreases in later disease stages, probably owing to immobility and an increasingly sedentary lifestyle[55]. A number of prospective studies with 3 months to 12 months of follow-up have found high overall fall rates (35–70%) and high recurrent fall rates (25–50%) in people with PD[54,56–59]. Alarmingly, 52% of patients sustain their first fall within the 3 years after diagnosis of PD[60]. Two or more falls in the previous year is the strongest, non-modifiable predictor of falls in PD[56,57]. Other non-modifiable risk factors for falls include high disease severity, long disease duration and high levodopa dosages[19,35,58,61]. The major modifiable risk factors for falls are low limit of stability, poor knee and ankle strength, poor anticipatory postural adjustments and reactive postural responses, gait disturbances, deficits in dual-tasking and FOG[58,61–65]. Low gait speed and short one-leg-stance time were found to be significant predictors of the first fall[60]. In a study that had a 20-year follow-up period, falls occurred in 87% of people with PD, with 35% of these individuals sustaining a fracture[66]. Other negative consequences include fear of falling[61], immobility, deconditioning, increased institutionalization risk[67] and high mortality[68]. Clearly, postural instability and falls in PD result in considerable health-care and economic burdens[69], and thus require exercise interventions targeted at ameliorating these impairments, preferably early in the PD disease course[6,60].

Walking economy
The steady-state aerobic demand for a given sub-maximal speed of walking, as measured by VO_2 uptake.

Walking capacity
The distance a person is capable of walking over a period of time, typically measured by 6-min walk distance.

Hoehn and Yahr rating scale
A commonly used scale (from stages 1 to 5) for describing how the symptoms of Parkinson disease progress.

Double-support phase
A phase in the gait cycle when the body weight is supported by both legs.

Set-shifting
The ability to move back and forth between tasks in response to changing goals or environmental experiences.

Limit of stability
A measurement of the maximum centre of pressure displacement with respect to a person's base of support.

Anticipatory postural adjustments
The automatic feedforward postural activities to counteract the destabilizing effects of voluntary movements.

Reactive postural responses
The automatic postural responses against external perturbation with or without a change in a person's base of support.

Physical therapy and exercise

Systematic reviews and clinical guidelines define physical therapy for patients with PD as interventions that are focused on the enhancement of muscle strength, aerobic capacity, balance, gait and functional mobility by means of cueing, cognitive movement strategies and physical exercises[10,70,71]. In this Review, we also use this definition of physical therapy management, and complementary exercises, such as tai chi and dance, are considered separately.

A review by Tomlinson *et al.*[10] evaluated the results of randomized controlled trials (RCTs) that assessed the short-term benefits of physical therapy on balance and gait performance. However, the investigators could not determine which physical therapy approach is the most effective, as comparisons of the protocols found no evidence that the treatment effects differed across the interventions[72]. Most clinical trials and review articles to date have considered only the short-term benefits of physical therapy and exercise interventions[10,71,72]. Owing to the progressive nature of PD, understanding the long-term benefits of these therapies is important; these are, therefore, the main focus of the present Review.

We define the long-term effects of exercise and physical therapy to be those lasting at least 12 weeks. Hence, in this Review, we have included RCTs with an intervention period of at least 12 weeks or with a follow-up period of at least 12 weeks; in total, 46 RCTs were included, 25 of which have an active exercise control group. The key outcomes of these studies are summarised in TABLES 2–4, and details of the treatment protocols and an overview of measurement tools are presented in Supplementary information S1 (table) and TABLE 1.

Multimodal physical therapy interventions. Only a few studies have reported the long-term effects of multimodal physical therapy (BOX 1). In one 6-week supervised programme, overseen by physiotherapists, multimodal physical therapy improved the gait speed and Unified PD Rating Scale Activities of Daily Living subscale (UPDRS-II) scores and UPDRS total scores of patients with PD. The effects lasted for 3 months[73]. In another study, supervised physical therapy comprising either balance and mobility training or aerobic exercise was given to groups of patients with mild PD three times per week for 4 months, followed by one session per month for 12 months[74]. After the first 4 months, improvements were observed in UPDRS-II and UPDRS Motor subscale (UPDRS-III) scores in the balance and mobility training group, and in the walking economy of the aerobic group, compared with an active control group; however, only the improvements in walking economy were maintained at 16 months. Frazzitta *et al.*[75] delivered a 4-week intensive intervention focused on physical therapy, followed by another 4-week period of training in the 13th month, to patients who were newly diagnosed with PD. At the end of the second year, the training had improved the UPDRS-II and UPDRS-III scores in these individuals and enabled the levodopa-equivalent dose to be reduced, suggesting a possible neuroprotective effect. In summary, multimodal supervised physical therapy has long-term beneficial effects on PD motor signs, activities of daily living, and PD disease severity. The efficacy of each physical therapy component is unclear, and is discussed in the following sections.

Progressive resistance training. A few meta-analyses support the use of progressive resistance training (PRT; BOX 1) in PD rehabilitation owing to its moderate short-term benefits[76–78]; however, the long-term benefits of this intervention are unclear. Ten RCTs will be discussed in this Review. In most of these, machines were used for concentric resistance training[64,79–85] or an ergometer was used for eccentric resistance training[86,87]. Exercise dosages for the participants were progressed using the concept of repetitive maximum (that is, 40–80% of the amount of force that can be generated in one maximal muscle contraction)[64,79–81,83], ratings of perceived exertion[86–88], or the number of repetitions to fatigue[89,90]. Most of the studies investigated the treatment effects after 12 weeks of training[64,79,80,82,83,86,87], except for two studies that lasted for 24 months[81,91]. No study examined carry-over effects after treatment ended.

PRT significantly increased muscle strength[64,81–83,86] as well as muscle power[64,84] in the participants. Two studies evaluated off-medication muscle strength[81,87]: Dibble *et al.*[86] reported no significant increase in muscle strength after 3 months of PRT, but Corcos *et al.*[81] found increased peak torque after 12 months and 24 months of PRT. A training period longer than 3 months might, therefore, be required to improve off-medication muscle strength. 12 weeks of PRT enhanced physical capacity in individuals with PD, as assessed by the 6-min walk test[82,87] and the 2-min step test[80] immediately after training. However, Prodoehl *et al.*[91] demonstrated significant gains in 6-min walk test performance after 6 months but not after 24 months of PRT. Additional task-specific training aimed at improving cardiopulmonary fitness might be required to produce a lasting effect on walking endurance.

PRT increased gait speed in patients with PD in two trials[85,86] but another study found no such effect[64]. Additionally, PRT led to modestly improved performance in the Timed Up and Go (TUG) test, a timed test involving a standing, walking and turning task[86]. One study reported that PRT improved balance performance (as measured by Berg Balance Scale (BBS) score, Mini Balance Evaluation Systems Test (miniBEST) score and functional reach distance)[85]. PRT and balance training were found to yield comparable gains in gait speed[79,90,92] and TUG performance[89,90]. Muscle weakness contributes to postural instability; therefore, increased muscle strength could improve some aspects of postural stability and gait performance in individuals with PD. Two of seven studies found that PRT produced a significant improvement in UPDRS-III scores during on-medication[85] and off-medication states[81]. Two studies measured quality of life (QoL) using the 39-Item Parkinson Disease Questionnaire (PDQ-39) and both reported a significant improvement after PRT[85,86].

In summary, the positive effects of PRT on muscle strength, balance, functional mobility, and QoL lasted for 12 weeks. One 24-month study of PRT also

Supervised programme
Any training that was supervised by either a physical therapist or exercise trainer in a one-to-one or small-group basis.

Progressive resistance training.
A style of strength training exercise that involves the steady utilization of resistance via a loading source.

Table 1 | **Overview of measurement tools**

Scale or test	Variable assessed	Description	Ref.
Disease severity			
Unified Parkinson Disease Rating Scale (UPDRS)	Composite score for disease severity	UPDRS scale has 4 subscales: • Part I on mentation, behaviour and mood (4 questions, 0–16 points) • Part II on activities of daily living (13 questions, 0–52 points) • Part III on motor examination (14 items, 0–108 points) • Part IV on motor and other complications of advanced disease (11 items, 0–23 points) Higher scores indicate worse performance	73–75,80–88,90, 93–96,102, 113,117, 119–121, 123–125
Aerobic capacity			
6-min walk test	Walking capacity, walking endurance	Participants are instructed to cover as much distance as possible in 6 min	87,94,95,105, 106,117,120, 121
2-min step test	Physical capacity	Participants are instructed to march on the spot for 2 min. Total number of times of right knee reaches the required height in 2 min	80
VO_2max	Cardiopulmonary fitness	The test involves walking on a treadmill initially at self-selected speed and 0% gradient. The speed and gradient are increased according to a test protocol until participants reach voluntary exhaustion. Peak oxygen consumption (VO_2max) is determined based on the 20 s averages obtained during the final stage of the test	82
VO_2 uptake or walking economy	Cardiopulmonary fitness	The test involves walking on a treadmill for 5 min at 4 speeds (slow to fastest tolerated speed). Oxygen consumption (VO_2 uptake) is measured during the last 2 min of each speed using an automated indirect calorimeter system	74
Stress test duration	Cardiopulmonary fitness	The stress test involves walking on a treadmill with speed and inclination increased every 3 min; stress test duration is the maximum duration tolerated by the participant in the test	97
Balance performance			
Balance Evaluation Systems Test (BESTest)	Balance performance	• 36-item test is scored under 6 subsections (biomechanical constraints; stability limits and verticality; anticipatory postural adjustments; postural responses; sensory orientation; stability in gait) • 3-point ordinal scale (0 = lowest level, 2 = perfect); total score: 0–108 • Higher scores indicate better balance	112
miniBESTest	Balance performance	• 14-item test — short version of BESTest (sit to stand, standing on toes, on inclined surface, on foam, timed up and go test, postural reaction, quality of gait when changing speed, avoiding obstacles and pivot turn) • 3-point ordinal scale (0 = lowest level, 2 = perfect); total score: 0–28 • Higher scores indicate better balance	85,111,120,124
Berg Balance Scale	Balance performance	• 14-item scale (stand with eye closed; stand with feet together; reaching forward; tandem stand; pick up object from ground; obstacles; alternate stepping; single leg stance; 360° turn) • 5-point ordinal scale (0 = unable, 4 = perfect); total score: 0–56 • Higher scores indicate better balance	85,95,113, 116,117,121, 123,125
Functional reach	Limit of stability	• Reach forward while maintaining a fixed base of support in standing • Record the maximum forward reach distance	85,90,109, 118
Five times sit to stand	Balance and leg strength	Time taken to perform sit-to-stand 5 times as quickly as possible	18,95,110
Gait performance			
10 m walk test	• Walking speed (m/s) • Stride length • Cadence (steps/min)	Time taken to walk 10 m at a self-selected and fast walking pace	64,73,79,80,82, 85–87,90–94,96, 100,102,104–106, 112,117,118,120
Freezing of gait questionnaire	Freezing of gait severity	• 6 self-report questions on gait quality and freezing episodes • 5-Point ordinal scale; total scores: 0–24 • Higher scores indicate more severe freezing of gait	18,120,125
Functional mobility			
Timed up and go test (TUG)	Functional mobility, walking ability	Timed taken to get up from a chair, walk for 3 m, turn and sit down on to a chair	83–86,95,113, 117,124
Short physical performance battery	Lower extremity function	• Consists of three parts: The balance test, the gait speed test, fast walking velocity over 4 m; and the chair stand test (5 times sit-to-stand test) • Total scores: 0–12 • Higher scores indicate better performance	110

Table 1 (cont.) | **Overview of measurement tools**

Scale or test	Variable assessed	Description	Ref.
Functional mobility (cont.)			
Modified physical performance test	Physical function	• 7 functional items (lifting a book, putting on and removing a coat, picking up a penny from the floor, performing a 360° turn, walking 50 ft, climbing a flight of stairs, and climbing 4 flights of stairs) with a chair rise and the Romberg test for balance • Score for each task 0–4; total scores: 0–36 • Higher scores indicate better performance	81
Continuous scale–physical functional performance	Functional mobility	• 16 functional items (reaching, picking up object, sweeping the floor, vacuuming, making a bed, unloading groceries, climbing three steps onto a platform while carrying luggage, and getting up and down from the floor, endurance walk, stair climb) • Tasks are scored using an algorithm that takes into account the time taken to complete the task and sometimes distance achieved • Higher scores indicate better performance	74
Balance confidence			
Activities balance confidence scale	Self-perceived balance abilities and fear of fall	• Self-report questionnaire on balance confidence on 16 indoor and outdoor ambulatory activities • 11-point ordinal scale (0% = no confidence to 100% = complete confidence); total score: 0–100% • Higher scores indicate less fear of fall	79,92,112
Fall efficacy scale – international	Self-perceived balance abilities and fear of fall	• Self-report questionnaire to measure the level of concern about falling during social and physical activities (16 items) inside and outside the home • 4-point Likert scale (1 = not at all concerned to 4 = very concerned); total score: 16–64 • Higher scores indicate greater fear of fall	110
Quality of life			
Parkinson disease questionnaire (PDQ-39)	PD-related quality of life	• Self-report questionnaire • 39 questions on 8 discrete dimensions: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, bodily discomfort • 5-point ordinal scale (never, occasionally, sometimes, often or always); total score: 0–100% • Higher scores indicate greater disability	82,85–88,94,96, 100,122,124,125
Parkinson disease questionnaire (PDQ-8)	PD-related quality of life	• A short form of PDQ-39 which contains 8 of the original 39 items of the PDQ-39 from each of the 8 dimensions • Higher scores indicate greater disability	118

reported an improvement in off-medication UPDRS-III scores, suggesting that this type of training has disease-modifying effects[81].

Aerobic endurance training. Eight RCTs that investigated the effects of aerobic endurance training (AET; BOX 1) on patients with PD are discussed here. The AET was restricted to a training intensity of 60–75% of maximum heart rate or 40–50% of heart rate reserve[82]. AET was provided using an elliptical trainer device[74,93], treadmill[80,82,94], Nordic walking[95,96], or walking with music[97]. The training lasted for 12 weeks[80,82,95,97] or 24 weeks[94,96]. Schenkman *et al.*[74] added a monthly training session after 4 months that continued up to 16 months.

AET was superior to general exercise or usual care for enhancing cardiopulmonary fitness in terms of VO_2max[82], walking economy[74] and stress test duration[97] as well as physical capacity as measured by the 6-min walk test[82,94,95] and 2-min step test[80]. In all of these studies, the participants were trained at moderate intensity for at least 40 min per session. By contrast, high intensity training for a shorter duration (30 min per session) did not yield improvement in 6-min walk test performance[82].

Several studies that involved aerobic walking demonstrated improved gait performance in participants in terms of walking speed[82,94,96], stride length[93,94,96] gait stability (as shown by a reduction in gait variability)[94,96] and shortened double-support time[94,96]. However, evidence that AET improves balance and functional mobility is limited. Most studies did not report significant improvements in balance[74,80,96], with one exception[95]. TUG performance improved in one trial[95] but not in another study[93]. UPDRS-III scores improved after Nordic walking[95,96], but other studies found no significant changes after other types of AET[80,82,93]. No study demonstrated significant improvement in QoL after AET[82,94]. Only one study examined the carry-over effects of AET but the improved cardiopulmonary fitness failed to be maintained for 4 weeks post-treatment[97].

To summarise, most of the studies showed that AET improved cardiopulmonary fitness and/or physical capacity for 12 weeks[74,80,82,94,95,97] and one study reported improvement for 24 weeks[94]. One of the studies reported that monthly training following 4 months of treatment sustained the improved walking economy at 16 months[74]. However, no studies show long-term carry-over effects of aerobic training on UPDRS score or cardiopulmonary fitness.

Aerobic endurance training
An exercise training method to improve cardiopulmonary fitness.

Nordic walking
A total body version of walking activity using specially designed walking poles (similar to ski poles).

Cued training. Cueing (BOX 1) has been extensively researched as a training method in PD rehabilitation. Morris *et al.*[98] were the first to report that visual cues, such as floor markers, normalized the gait performance of individuals with PD. Many studies have reported immediate, positive effects resulting from the use of auditory and/or visual cues in patients with PD; however, the long-term benefits are unclear[99].

Here, we discuss four PD rehabilitation studies that used external cues, such as visual cues (in the form of lines or markers on the ground or on a treadmill[100]), rhythmic auditory cues (in the form of metronome beats[101] or music at a pre-set frequency[102]) or somatosensory cues[93]. Patients were trained to perform functional tasks — such as walking, turning, and transferring from sitting to standing — in the presence of these

Table 2 | **Long-term effects of multi-modal physical therapy, progressive resistance training and aerobic training**

Studies	Training period (follow-up duration), weeks	Outcomes (% change from baseline value with between-group difference)				
		Disease severity	Muscle strength	Aerobic capacity	Balance performance and falls	Gait performance and mobility
Multimodal physical therapy						
Ellis *et al.* (2005)[73]	6 (13)	UPDRS-II −14%; UPDRS-total −12%	NA	NS	NA	Speed 11%*
Frazzitta *et al.* (2015)[75]	8 (104)	UPDRS-II −29%; UPDRS-III −47%‡	NA	NA	NA	NS
Schenkman *et al.* (2012)[74]	70 (0)	UPDRS-II: FBF −21%	NA	VO_2 uptake: aerobic exercise 30%	NS	CS-PFP: FBF 9%
Progressive resistance training						
Carvalho *et al.* (2015)[80]	12 (0)	NS	NA	2-min step test 31%	NS	NS
Corcos *et al.* (2013)[81], Prodehl *et al.* (2014)[91]	104 (0)	UPDRS-III (off medication) −21%‡	Elbow (off medication) 19%; elbow (on medication) 12%	NS	NS	NS
Dibble *et al.* (2009)[86]	12 (0)	NS	NS	NA	NA	Speed 12%*; TUG −17%
Dibble *et al.* (2015)[87]	12 (0)	NS	NA	6MWT 5%	NA	NS
Ni *et al.* (2016)[84,85]	12 (0)	UPDRS-III −32.5%‡	Leg press 14–37%	NA	BBS 9%*; miniBEST 19%; functional reach distance 16%	Speed 12%*; TUG −12%
Paul *et al.* (2014)[64]	12 (0)	NS	Shoulder and elbow 8%; hip and knee 23–30%	NA	NS	NS
Shulman *et al.* (2013)[82]	12 (0)	NS	Leg press 16%; leg extension 16%	NS	NA	NS
Silva Batista *et al.* (2016)[83]	12 (0)	NS	Leg press 38%	NA	NA	TUG −20%
Aerobic training						
Bridgewater & Sharp (1996)[97]	12 (4)	NA	NA	NS	NA	NS
Carvalho *et al.* (2015)[80]	12 (0)	NS	NA	2-min step test 37%	NS	NS
Cugusi *et al.* (2015)[95]	12 (0)	UPDRS-III −6.5%‡	NS	6MWT 20%	BBS 15%*	TUG −7%; FTSTS 23%*
Nadeau *et al.* (2013)[94]	24 (0)	NS	NA	6MWT 10%	NA	Double support time −33%; stride length 14%
Reuter *et al.* (2011)[96]	24 (0)	UPDRS-III −28%‡; UPDS-total −20%	NA	NA	NS	speed 25%
Shulman *et al.* (2013)[82]	12 (0)	NS	NS	VO_2 max: high intensity 8.1%; low intensity 6.7%	NA	NS

6MWT, 6-min walk test; BBS, Berg Balance Scale; CS-PFP, Continuous Scale–Physical Functional Performance; FBF, Flexibility, balance and functional training; FTSTS, Five times sit-to-stand; max, maximum; miniBEST, mini Balance Evaluation Systems' Test; NA, data not available; NS, nonsignificant effect; TUG, timed up-and-go; UPDRS, Unified Parkinson Disease Rating Scale; $VO_{2\,max}$, maximum oxygen uptake. *Changes exceeding respective minimal detectable changes (MDC_{95}): BBS 5 points; FTSTS time 1.7 s; speed 0.09 m/s ‡Changes exceeding respective moderate clinical important difference: UPDRS-III 5.2 points; UPDRS-total 9.1 points.

Table 3 | **Long-term effects of cued exercise, gait training and balance training**

Studies	Training period (follow-up duration), weeks	Outcomes (% change from baseline value with between-group difference)			
		Disease severity	Aerobic capacity	Balance performance and falls	Gait performance and mobility
Cued exercise					
de Bruin *et al.* (2010)[102]	13 (0)	UPDRS-III −22%‡	NA	NA	Speed 2%; dual-task speed 6%
Martin *et al.* (2015)[101]	24 (52)	NA	NA	NS	NS
Morris *et al.* (2009)[100]	2 (13)	NS	NS	NS	Speed 11%*
Sage & Almeida (2009)[93]	12 (0)	UPDRS-III: SAFEx −25%‡	NA	NA	Step length: aerobic exercise 8%
Gait training					
Carda *et al.* (2012)[106]	4 (26)	NS	6MWT: robotic 13%; treadmill 18%	NA	• Speed: robotic 10%; treadmill 12% • TUG: robotic −14%; treadmill −13%
Miyai *et al.* (2002)[104]	4 (22)	NS	NS	NA	Step length 10%
Picelli *et al.* (2013)[105]	4 (13)	UPDRS-III: robotic −17%‡	6MWT: robotic 23%; treadmill 24%	BBS: robotic 9%; treadmill 8%;	• Speed: robotic 25%*; treadmill 16%* • Stride length: robotic 15%; treadmill 10% • Double-leg stance: robotic 21%; treadmill 23%
Balance training					
Allen *et al.* (2010)[18]	26 (0)	NA	NA	NS	FOGQ −19%; FTSTS time −20%*
Ashburn *et al.* (2007)[109]	6 (18)	NA	NA	Functional reach distance 2.6%	NS
Canning *et al.* (2015)[110]	26 (0)	NA	NA	Fall rate −69%	SPPB 1.7%; FTSTS (stand/s) 9%
Morris *et al.* (2015)[88]	8 (52)	• UPDRS-II: movement strategy training −21%; PRT −21% • UPDRS-III: movement strategy training −16%	NS	Fall rate: movement strategy training −61.5%; PRT −85%	NS
Palamara *et al.* (2017)[113]	4 (26)	NS	NA	NS	NS
Schlenstedt *et al.* (2015)[89]	7 (13)	NS	NA	NS	NS
Shen & Mak (2014)[92], (2015)[79]	12 (52)	NA	NA	Latency of postural response −6.4%; SLS test 27%; fall rate −81%	Stride length 11.6%
Sparrow *et al.* (2016)[111]	12 (0)	NA	NA	MiniBEST 10%; fall rate −37%	NA
Wong-Yu & Mak (2015)[112]	8 (52)	NA	NA	BEST 11%*	Speed 6%; dual-task TUG −10%

6MWT, 6-min walk test; BBS, Berg Balance Scale; BEST, Balance Evaluation Systems' Test; FOGQ, Freezing of Gait Questionnaire; FTSTS, Five times sit-to-stand; miniBEST, mini Balance Evaluation Systems' Test; NA, data not available; NS, nonsignificant effect; PRT, progressive resistance training; SAFEx, Sensory Attention Focused Exercise; SLS, Single-leg stance; SPPB, Short Physical Performance Battery; TUG, timed up-and-go; UPDRS, Unified Parkinson Disease Rating Scale. *Changes exceeding respective minimal detectable changes (MDC_{95}): BEST total score 6.5%; FTSTS time 1.7 s; speed 0.09 m/s ‡Changes exceeding respective moderate clinical important difference: UPDRS-III 5.2 points.

Table 4 | **Major findings of the long–term effects of complementary exercise**

Studies	Training period (follow–up), weeks	Outcomes (% change from baseline value with between-group difference)				
		Disease severity	Muscle strength	Aerobic capacity	Balance performance and falls	Gait performance and mobility
Tai chi						
Amano *et al.* (2013)[115]	16 (0)	NS	NA	NA	NS	NS
Choi *et al.* (2013)[119]	12 (0)	UPDRS-II −26%	NA	NS	NS	NS
Gao *et al.* (2014)[116]	12 (26)	NS	NA	NA	BBS 9%; fall rate −53%	NA
Hackney & Earhart (2008)[117]	13 (0)	UPDRS-III −6%	NA	6MWT 10%	BBS 7%	Speed 25%; stride length 18%; TUG −10%
Li *et al.* (2012)[90], (2014)[118]	26 (13)	UPDRS-III: tai chi −36%*	Knee: tai chi 12–21%	NA	• Max. excursion: tai chi 13% • Functional reach distance: tai chi 17% • Fall rate: tai chi −69%; PRT −60%	Speed: tai chi 7%; stride length: tai chi 9%
Dance						
Duncan *et al.* (2012)[120]	52 (0)	MDS-UPDRS III (off medication) −29%	NA	6MWT 2%	MiniBEST 16%	Speed 7%; dual-task speed 13%; FOGQ −10%
Hackney *et al.* (2007)[123]	13 (0)	NS	NA	NA	BBS 8%	NS
Hackney & Earhart (2009)[121,122]	13 (0)	NS	NA	6MWT 12%	BBS 8%	NS
Romenets *et al.* (2015)[124]	12 (0)	NS	NA	NA	MiniBEST 2%	TUG −18%
Volpe *et al.* (2013)[125]	24 (0)	UPDRS-III −29%*	NA	NA	BBS 28%	FOGQ −57%

6MWT, 6-min walk test; BBS, Berg Balance Scale; FOGQ, Freezing of Gait Questionnaire; max, maximum; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson Disease Rating Scale; miniBEST, mini Balance Evaluation Systems' Test; NA, data not available; NS, nonsignificant effect; PRT, progressive resistance training; TUG, timed up-and-go; UPDRS, Unified Parkinson Disease Rating Scale. *Changes exceeding respective moderate clinical important difference: UPDRS-III 5.2 points.

external cues. Two of the four studies had 2–24 weeks of training and follow-ups at 3–6 months[100,101], and the other two had a training period of 12–13 weeks[93,102] but no follow-up. Cued training yielded greater improvements in gait speed, UPDRS-II scores and UPDRS-III scores of participants than did general exercise or non-cued training[93,100,102]. Other studies reported that visually cued treadmill training[103] and auditory-cued walking training[18] reduced FOG severity as measured by FOG questionnaire. An extended 24-week intervention period yielded no significant improvements after training, probably owing to inadequate supervision of the home-based training[101].

One study reported that the improved gait speed[100] was sustained for 3 months post-training whereas another study found no carry-over effect[101]. In healthy individuals, the basal ganglia are thought to generate internal cues to enhance movement initiation and execution. By contrast, research has suggested that individuals with PD use external cues as a compensatory strategy to facilitate movement by bypassing the defective basal ganglia circuit and instead rely on frontal cortical and cerebellar mechanisms[98]. The long-term carry-over effects from cued training might, therefore, be inconsistent, owing to the possibility that participants with PD could have relied on external cues to enhance their movement initiation and/or continuation.

Gait training. Here we review three studies in which gait training (BOX 1) was provided with a treadmill[104,105], with a treadmill and partial body-weight support[104], and/or with a robotic gait trainer and partial body-weight support[105,106]. The belt speed of the treadmill or robotic gait trainer was progressively increased in all studies. All interventions lasted for 4 weeks and patients were followed up for 3–6 months[104–106].

Most of the studies demonstrated that the intervention improved gait performance in terms of speed[105,106], stride or step length[104,105] and ratio of single to double leg stance time[105], and increased walking capacity as measured by the 6-min walk test[105,106]. Robotic and treadmill training had comparable benefits in the improvement of gait speed[105], stride length[105], and 6-min walk test performance[105,106]. Only one study[105] reported an improvement in UPDRS-III score; the others reported no such improvement[104,106]. Furthermore, no positive effect on QoL was found[106].

Encouragingly, all the improvements were maintained during follow-up[105,106], with the exception of the gain in gait speed reported in one study[104]. The participants with PD in this study had more-advanced disease (Hoehn and Yahr stage 2.9 versus 2.2), which might have reduced the retention of abilities from their learnt tasks. Robotic training and treadmill training produced a comparable maintenance of all gains during follow-up[105,106]. The effectiveness of these therapies could be attributed to the many repetitions of the rhythmic gait cycle provided by the robotic gait trainer and treadmill and to the stepwise increase in walking speed. These findings corroborate the results of a 2010 Cochrane review, which found that treadmill training has probable short-term beneficial effects on gait hypokinesia[107]. Furthermore, the findings of these three studies support the existence of 3–6 months of positive carry-over effects in gait performance. More studies are needed to confirm the long-term effects of gait training on UPDRS-III scores and QoL.

Box 1 | Physical therapy and exercise interventions

Multimodal intervention
The use of three or more combined exercise modalities — including flexibility, strength, balance, coordination and/or aerobic training — to improve physical and motor fitness.

Progressive resistive training
Training that loads sufficient resistance on the targeted muscle(s) in a progressive manner. Most studies prescribe resistance using the concept of repetitive maximum and progress from 40–70% of one repetitive maximum. Examples include:
- Machine or ergometer for concentric or eccentric training
- Exercise with weighted vest
- Functional training

Aerobic endurance training
Training that involves the use of large muscle groups and a training intensity of 60–75% maximum heart rate or 40–50% heart rate reserve. Examples include:
- Elliptical trainer device training
- Stationary bicycle training
- Walking training with treadmill
- Walking with music
- Nordic walking

Balance training
Exercises prescribed to challenge various PD-specific components of impaired balance including stability limits, anticipatory postural adjustment, reactive postural response and dynamic stability during gait and movements. Training involves balance and mobility training with or without progressive strength training. Examples include:
- Technology-assisted training
- Motor–cognitive training
- Exercise training
- Aquatic therapy
- Movement strategy training
- Fall prevention programme

Gait training
Exercises prescribed to improve gait parameters such as velocity and/or stride length. Examples include:
- Treadmill training with or without body-weight support
- Robotic trainer with or without body-weight support
- Overground training

Cueing strategies
External cues are provided to facilitate movement initiation and/or continuation. Patients are instructed to pay attention to the cues and to step on the line or markers, or to step in time with an auditory or somatosensory cue. Examples include:
- Visual cues — lines or markers on the ground and treadmill
- Rhythmic auditory cues — metronome beats or music at a preset frequency
- Somatosensory cues — tactile sensation given to a body part

Tai chi
A martial art with repetitive body weight shifting from one foot to the other, stepping and turning in different directions.

Dance
Sequenced movements performed to music.

PD, Parkinson disease.

Balance training. A previous meta-analysis suggested that, overall, exercise has beneficial effects on balance, gait speed, motor function and QoL that are retained for 2–6 months after completion of the intervention in people with PD[108]. A subsequent review reported similar positive long-term effects after balance and gait training, as well as a 26–85% reduction in fall rates at 1–12 months of follow-up[9].

Here we review ten RCTs of multicomponent balance training (BOX 1)[18,79,88,89,92,109–113]. The balance training included balance, mobility and/or PRT training, which was provided with a computerized dancing system and Balance Master[79,92], weighted vest resistive exercises[18,110], movement strategy training[88], anticipatory and reactive balance activities[89,109,111], blended indoor and outdoor exercises[112] or aquatic therapy[113]. In some of the studies, cueing strategies[18,88,110], attentional strategies[88], motor–cognitive training[112], and fall prevention education[18,88,110] were also provided. In seven studies, the training lasted for 4–12 weeks and follow-up lasted for 3–12 months[79,88,89,92,109,112,113]. Three of the studies investigated the effects of the training immediately after 12 weeks or 26 weeks of treatment[18,110,111].

Balance training lasting 4–12 weeks significantly improved balance (as measured by miniBEST scores[111] and BEST scores[112], latency of postural response[79], single-leg-stance performance[79] and functional reach distance[109]), gait velocity[112], stride length[79,92], dual-task TUG performance[112] and balance confidence[92]. Interestingly, land-based therapy plus aquatic therapy was as effective as land-based rehabilitation alone in the improvement of BBS scores for people with moderate PD[113]. 26 weeks of minimally supervised, home-based balance training, was found to improve sit-to-stand time[18,110], balance confidence and QoL[110]. Alleviation of FOG was observed in some of these studies[18] but not others[110]. Encouragingly, after a minimum 8 weeks of training, improvements in balance, gait, functional mobility and balance confidence persisted for up to 12 months after treatment completion[79,92,112]. Two studies examined UPDRS-III scores[88,89], one of which reported an improvement in this score during 12 months of follow-up[88].

Significant reductions in fall rates were reported immediately after training completion (−37%)[111], at 3 months of follow-up (−81%)[79] and at 12 months of follow-up (−62%)[88]. The long-term reduction in fall rates could be attributed to the enhanced balance and gait performance[79,111], improved balance confidence[92] and alleviation of motor symptoms[88]. Morris *et al.*[88] found a reduced fall rate of 85% in their PRT group, which was probably due to the functional nature of their PRT (that is, sit-to-stand, step-ups and heel raises) and the inclusion of fall education. Canning *et al.*[110] reported that the fall rate was reduced (by 69%) only in participants with mild PD, suggesting that a minimally supervised fall prevention programme could be beneficial in this subgroup.

To summarize, a minimum of 8 weeks of supervised balance training improves balance and gait performance and reduces fall rates; these effects can be maintained for up to 12 months after treatment ends. The effects of balance training on UPDRS-III scores and QoL are currently unclear.

Complementary exercises

Tai chi. The martial art most commonly performed by individuals with PD is tai chi[90] (BOX 1). A 2014 meta-analysis reported positive effects of tai chi on UPDRS scores, balance, gait and mobility, but long-term benefits have not yet been found[114].

We found six RCTs in which the participants practised Yang-style tai chi[115–117] or a self-integrated style[90,118,119] in groups for 12–24 weeks. Two of the studies had 3 months of follow-up[90,118] and one had 6 months of follow-up[116]. Tai chi practice by individuals with PD generated beneficial effects on BBS scores[116,117], functional reach distance and maximum excursion of whole body centre-of-mass[90]. Improvements were also observed in gait velocity and stride length[90,117], TUG performance[90,117], and UPDRS-III score[90,117,119]. Tai chi involves rhythmic weight shifting, controlled movement to stability limits, stepping, and turning: all of these aspects could have contributed to the improvements observed in the participants. The tai chi training led to reduced fall rates during the follow-up periods[90,116]. A longer training programme, lasting 24 weeks, also resulted in maintenance of the gains in balance, gait, and UPDRS-III scores[108]. In a subsequent study, Li *et al.*[118] found that tai chi participants had improved QoL that was associated with greater exercise compliance.

Dance. The use of dance (BOX 1) in therapy for patients with PD has also been actively researched. Six RCTs of dance therapy in groups are included here, in which tango was the most common dance style[120–124], but one study also examined the effects of Irish dancing[125]. In most of the studies the training lasted for 12–13 weeks[121–124], but two studies included considerably longer training that lasted 6–12 months[120,125]. Compared with no training or waltz dancing, tango dancing is more effective in improving BBS scores[121,123] and 6-min walk test performance[121]. Tango dancing led to improved QoL in one trial[122] but not in another[124]. A longer training period of 6–12 months reduced FOG[120,125] and improved UPDRS-III scores[120,125]. Rhythmic music could serve as an external cue to facilitate movement initiation and/or continuation, and the repetitive practice of dynamic postural control, stepping and turning can improve balance, mobility functions and motor signs. Furthermore, dancing with a partner can be enjoyable and enhance QoL[122]. Sustained practice of Irish dancing and tango dancing for 6–12 months[120,125] enhanced balance, reduced FOG and modified disease progression.

Physical therapy recommendations in PD

In the PRT and AET studies considered in this Review, participants had early PD (Hoehn and Yahr stages 1–2). Most of the studies reported that the beneficial effects of the intervention lasted for 12 weeks. Maintenance of these benefits for longer than 12 weeks could be achieved by sustained PRT training for 12–24 months, which increased muscle strength and decreased off-medication UPDRS-III scores[81]. Other studies found that 6 months of AET[94] and 16 months of multimodal physical therapy (BOX 1) with an AET component[74] improved walking capacity. Physiological studies of healthy adults found a reduction of the beneficial effects of PRT and AET over time, as a result of long-term exercise detraining[126]. However, the benefits of training could be sustained by maintenance programmes, in which supervision was tapered off after the initial training phase and the participants continued to practice as assigned[74,127]. Given the progressive nature of PD, which is compounded by age-associated functional decline, either sustained training or maintenance exercise following an intensive training programme is recommended. The cost-effectiveness of different training modes warrants further exploration.

For most of the studies of balance and gait training, patients with mild to moderate PD (Hoehn and Yahr stage 2–3) were recruited. The beneficial effects of balance and gait training continued for up to 12 months and 6 months after these interventions ended, respectively. Balance training and tai chi reduced falls for up to 12 months and 6 months after training, respectively. Cueing strategies and dance therapy were effective in reducing FOG. Notably, the improvements in balance resulting from balance training[112] exceeded the minimal detectable change (MDC_{95})[41]; increased gait speed also exceeded MDC_{95}[128] after cued training[100] and after robotic or treadmill-based gait training[105] (TABLE 3). Owing to the limited response of postural and gait impairments to pharmacological and surgical treatments, balance and gait rehabilitation are of great benefit and importance for people with PD. We recommend that patients receive task-specific and context-specific training with high levels of repetitive practice, so as to achieve long-term positive effects[129].

UPDRS-III, which documents PD motor performance and disability level, is an important outcome measure for the examination of long-term training benefits. All the multimodal physical therapy programmes resulted in improved UPDRS-II, UPDRS-III and/or UPDRS-total scores. The results of programmes using a single modality were inconsistent. However, extended training periods — ranging from 6 months of AET[96], tai chi[90] or dance[125] to 24 months of PRT[81] — are associated with increased efficacy for achieving clinically meaningful improvement in UPDRS-III scores[130] (TABLES 2–4). UPDRS-III scores are expected to deteriorate over time in patients with PD, so the improvements found in the UPDRS-III scores suggest possible disease-modifying effects.

Notably, in patients with early stage PD, training enabled the reduction of their levodopa dosages[75]. Furthermore, a reduction of falls was found only in patients with mild disease (that is, motor UPDRS score ≤26)[110]. In addition, patients with advanced PD (that is, Hoehn and Yahr stage ≥2.9) failed to maintain

Minimal detectable change
A statistical estimate of the smallest amount of change that can be detected by a measure that corresponds to a noticeable change in ability.

exercise-driven gains in gait speed at follow-up[104]. Severity of PD, therefore, seems to have an effect on treatment outcome, and patients with early PD could be a potential target population for treatment to delay disease progression. More study is needed to explore this area.

Training-induced neuroplasticity

The long-term improvement following physical therapy and exercise training in individuals with PD could indicate the presence of neuroplasticity in motor-related and cognitive-related circuitry as the brain learns new behaviours through modification of existing neural networks[131]. In mouse models of PD, the possible benefits of exercise can be explained by the elevated expression of anti-inflammatory cytokines, the reduced levels of pro-inflammatory cytokines and activated microglia[132], and the reduced levels of mitochondrial dysfunction resulting from decreased α-synuclein expression[133]. Moreover, the positive effects of exercise might be mediated by increased antioxidant defences against neurotoxins[134,135] and a reduction in glutamatergic drive hyperactivity, leading to reduced dopaminergic cell loss[136].

The presence of exercise-induced neuroplasticity in PD is further supported by human studies. High-intensity treadmill training led to increased corticomotor excitability, which was associated with improved gait parameters[137]. Aerobic training of this kind was found to elevate striatal dopamine D2 receptor binding potential in individuals with early stage PD[131]. In line with findings in animal models of PD, a significant increase in serum levels of brain-derived neurotrophic factor (BDNF), which protects against a loss of dopamine transporter binding, was found as early as 10 days after intensive training, and this change was maintained throughout 4 weeks of treatment[138]. Another study showed improved motor function in people with PD after 4 weeks of multidisciplinary intensive rehabilitation treatment, as well as decreased symptom progression (attributed to enhanced BDNF-tyrosine receptor kinase B signalling in lymphocytes)[139]. Learning-dependent changes in grey matter volume that correlated with improved performance were found in participants with PD after 6 weeks of dynamic balance training[140]. In addition, 12 weeks of aerobic training in participants with PD generated functional changes in motor-learning-related brain structures consistent with improved aerobic fitness[141]. Hence, the between-study differences observed in exercise-dependent neuroplastic changes probably depend on the intensity, repetition, specificity and complexity of the exercise regimen[142].

Risks and adverse effects

Risks and adverse effects of long-term exercise were examined in 25 of 46 clinical studies included in this Review[18,64,73–75,80–85,88,90,91,94–96,100,105,106,110–112,124,125], 10 of which reported injuries sustained during training[18,64,74,90,96,106,110,111,124,125] (TABLE 5). The interventions assessed in these studies included multimodal physical therapy[74], PRT[64], balance training[18,110,111], gait training[96,106], tai chi[90] and Nordic walking[96]. Furthermore, 28 studies noted falls and minor injuries that did not require medical attention. Given the total number of participants in the 25 studies ($n = 792$), the overall risk of adverse effects is low, and hence both physical therapy and group exercise training can be considered safe and well tolerated.

Table 5 | **Exercise-related risks and adverse effects**

Adverse effects	Number of studies	Type of training	Number of participants affected	Mean age of participants (years)
Fall without injury or medical attention	6	Balance[74,110], Nordic walking[96], tai chi[90], Irish dance[125], tango[124]	12	62–71
Fall with hospitalization	0	NA	0	NA
Hypotension, lightheadedness or dizziness	2	Progressive resistance training[64], Nordic walking[96]	3	62–66
Joint pain or muscle soreness	5	Balance[18,111], Nordic walking[96], tango[124], tai chi[90]	11	62–69
Injury with medical attention (shoulder pain with nonsteroidal anti-inflammatory medication)	1	Nordic walking[96]	2	62
Fatigue	1	Tango[124]	1	64
Discomfort due to devices (harness)	1	Gait training[106]	1	67
Total studies reporting adverse effects	10 (REFS 18,64,74,90, 96,106,110,111,124,125)	NA	381	62–71
No adverse effects	15 (REFS 73,75,80–85, 88,91,94,95,100,105,112)	NA	411	59–73
Adverse effects not reported	21 (REFS 79,86,87,89, 92,93,97,102,101,104, 109,113,115–123)	NA	NA	NA

NA, not applicable.

Exergaming
A term used for video games that are also a form of exercise.

Compliance and behavioural changes

Studies examining the effects of physical therapy considered in this Review had a low drop-out rate (average: 12%, Supplementary information S1 (table)), suggesting that patients achieved good compliance during the study period. However, adherence to exercise after completion of a training intervention is a challenge for people with chronic illness such as PD. The major barriers to exercise compliance in PD are a low perceived benefit of exercise, lack of time, fear of falling and low self-efficacy[143,144]. Patients who reported a high perceived benefit of exercise were more likely to sustain such exercise after completion of the intervention[118,143]. Education of patients regarding the benefits of exercise, incorporation of exercises into patients' daily routines, and monitoring and feedback by medical professionals or a virtual coach increased patients' problem-solving abilities and improved exercise compliance[145]. Group classes (such as tai chi or dance) that involve interaction with fellow patients[146] and 'exergaming' (REF. 147) at home could enhance motivation and improve exercise compliance. Further studies are needed to examine ways of motivating individuals with PD to build up an exercise habit in order to delay deterioration in their mobility.

New approaches and research directions

Long-term preservation of physical function in people with PD is important to delay disease progression and age-related decline, and published studies confirm that physical therapy and exercise therapy can have long-term benefits for people with PD. Future research is needed to establish the efficacy and dose–response effect of exercise in patients with newly diagnosed PD in order to prescribe exercise as an add-on therapy. A multicentre futility trial is currently underway to test the feasibility of using high-intensity exercise to modify symptoms of people with early stage PD who are naive to medication[148]. New neuroimaging biomarkers[141,149] and serum levels of BDNF[150] are useful tools for investigating the neural mechanisms of exercise and its influence on neuroplasticity.

New cueing devices and techniques — such as laser-guided shoes[151] and Google Glass[152] for combating FOG — warrant further investigation. Wearable sensor technology that enables continuous real-time remote monitoring of patients outside clinical settings could facilitate the development of tailor-made interventions[5,153]. In addition, online communication portals could offer virtual coaching to improve patient engagement and treatment compliance[154].

Non-motor symptoms have a substantial negative effect on the QoL of people with PD and their caregivers[155]. The effectiveness of pharmacological interventions is mainly limited to treatment of depression and psychosis[156], and thus exercise also plays an important part in treating non-motor symptoms such as apathy, fatigue, depression, sleep disturbance and cognitive impairment[157–159]. A long-term study 'Park-in-Shape', which is currently under way, aims examine the effects of aerobic exercise training and exergaming on motor and non-motor symptoms, QoL and exercise compliance[160].

Conclusions

Physical therapy and exercise training can modify long-term motor symptoms and physical functioning in PD. Balance training has the longest carry-over effects of all of these interventions, followed by gait and tai chi training. Balance training improves balance, gait and mobility, and reduces falls for up to 12 months after completion of treatment. Gait training is effective for the improvement of gait performance and walking capacity up to 6 months after training completion. Tai chi reduces falls for up to 6 months after treatment has ended. Most progressive resistive training and aerobic training programmes yield positive effects that last for 12 weeks. A training period longer than 12 weeks is needed to achieve clinically meaningful improvements in UPDRS-III scores. Physical therapy and exercise interventions have the potential to increase the efficacy of pharmacological treatment and delay disease progression in individuals with PD.

1. European Parkinson's Disease Association. What is Parkinson's? *EPDA* http://www.epda.eu.com/en/pd-info/about-parkinsons/ (2015).
2. Pringsheim, T., Jette, N., Frolkis, A. & Steeves, T. D. The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Mov. Disord.* **29**, 1583–1590 (2014).
3. Gasser, T. Mendelian forms of Parkinson's disease. *Biochim. Biophys. Acta* **1792**, 587–596 (2009).
4. Wirdefeldt, K., Adami, H. O., Cole, P., Trichopoulos, D. & Mandel, J. Epidemiology and etiology of Parkinson's disease: a review of the evidence. *Eur. J. Epidemiol.* **26**, 1–58 (2011).
5. Curtze, C., Nutt, J. G., Carlson-Kuhta, P., Mancini, M. & Horak, F. B. Levodopa is a double-edged sword for balance and gait in people with Parkinson's disease. *Mov. Disord.* **30**, 1361–1370 (2015).
6. van der Marck, M. A. *et al.* Consensus-based clinical practice recommendations for the examination and management of falls in patients with Parkinson's disease. *Parkinsonism Relat. Disord.* **20**, 360–369 (2014).
7. Fox, S. H. *et al.* The Movement Disorder Society Evidence-Based Medicine review update: treatments for the motor symptoms of Parkinson's disease. *Mov. Disord.* **26**, S2–S41 (2011).
8. Allen, N. E., Sherrington, C., Paul, S. S. & Canning, C. G. Balance and falls in Parkinson's disease: a meta-analysis of the effect of exercise and motor training. *Mov. Disord.* **26**, 1605–1615 (2011).
9. Shen, X., Wong-Yu, I. S. & Mak, M. K. Effects of exercise on falls, balance, and gait ability in Parkinson's disease: a meta-analysis. *Neurorehabil. Neural Repair.* **30**, 512–527 (2016).
10. Tomlinson, C. L. *et al.* Physiotherapy intervention in Parkinson's disease: systematic review and meta-analysis. *BMJ* **345**, e5004 (2012).
11. Allen, N. E., Canning, C. G., Sherrington, C. & Fung, V. S. Bradykinesia, muscle weakness and reduced muscle power in Parkinson's disease. *Mov. Disord.* **24**, 1344–1351 (2009).
12. Bridgewater, K. J. & Sharpe, M. H. Trunk muscle performance in early Parkinson's disease. *Phys. Ther.* **78**, 566 (1998).
13. Kakinuma, S., Nogaki, H., Pramanik, B. & Morimatsu, M. Muscle weakness in Parkinson's disease: isokinetic study of the lower limbs. *Eur. Neurol.* **39**, 218–222 (1998).
14. Koller, W. & Kase, S. Muscle strength testing in Parkinson's disease. *Eur. Neurol.* **25**, 130–133 (1986).
15. Nallegowda, M. *et al.* 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 (2004).
16. Inkster, L. M., Eng, J. J., MacIntyre, D. L. & Stoessl, A. J. Leg muscle strength is reduced in Parkinson's disease and relates to the ability to rise from a chair. *Mov. Disord.* **18**, 157–162 (2003).
17. Nocera, J. R., Buckley, T., Waddell, D., Okun, M. S. & Hass, C. J. Knee extensor strength, dynamic stability, and functional ambulation: are they related in Parkinson's disease? *Arch. Phys. Med. Rehabil.* **91**, 589–595 (2010).
18. Allen, N. E. *et al.* The effects of an exercise program on fall risk factors in people with Parkinson's disease: a randomized controlled trial. *Mov. Disord.* **25**, 1217–1225 (2010).
19. Latt, M. D., Lord, S. R., Morris, J. G. L. & Fung, V. S. Clinical and physiological assessments for elucidating falls risk in Parkinson's disease. *Mov. Disord.* **24**, 1280–1289 (2009).
20. Berardelli, A., Rothwell, J. C., Thompson, P. D. & Hallett, M. Pathophysiology of bradykinesia in Parkinson's disease. *Brain* **124**, 2131–2146 (2001).
21. David, F. J. *et al.* Progressive resistance exercise and Parkinson's disease: a review of potential mechanisms. *Parkinsons Dis.* **2012**, 124527 (2012).
22. Glendinning, D. S. & Enoka, R. M. Motor unit behavior in Parkinson's disease. *Phys. Ther.* **74**, 61–70 (1994).
23. Katzel, L. I. *et al.* Repeatability of aerobic capacity measurements in Parkinson disease. *Med. Sci. Sports Exerc.* **43**, 2381 (2011).

24. Canning, C. G., Alison, J. A., Allen, N. E. & Groeller, H. Parkinson's disease: an investigation of exercise capacity, respiratory function, and gait. *Arch. Phys. Med. Rehabil.* **78**, 199–207 (1997).
25. Saltin, B. & Landin, S. Work capacity, muscle strength and SDH activity in both legs of hemiparetic patients and patients with Parkinson's disease. *Scand. J. Clin. Lab. Invest.* **35**, 531–538 (1975).
26. Protas, E. J., Stanley, R. K., Jankovic, J. & MacNeill, B. Cardiovascular and metabolic responses to upper-and lower-extremity exercise in men with idiopathic Parkinson's disease. *Phys. Ther.* **76**, 34–40 (1996).
27. Christiansen, C. L., Schenkman, M. L., McFann, K., Wolfe, P. & Kohrt, W. M. Walking economy in people with Parkinson's disease. *Mov. Disord.* **24**, 1481–1487 (2009).
28. Canning, C. G., Ada, L., Johnson, J. J. & McWhirter, S. Walking capacity in mild to moderate Parkinson's disease. *Arch. Phys. Med. Rehabil.* **87**, 371–375 (2006).
29. Lord, S. *et al.* Ambulatory activity in incident Parkinson's: more than meets the eye? *J. Neurol.* **260**, 2964–2972 (2013).
30. Rogers, M. W. Disorders of posture, balance, and gait in Parkinson's disease. *Clin. Geriatr. Med.* **12**, 825 (1996).
31. Morris, M. E., Iansek, R., Matyas, T. A. & Summers, J. J. The pathogenesis of gait hypokinesia in Parkinson's disease. *Brain* **117**, 1169–1181 (1994).
32. Van Emmerik, R. E., Wagenaar, R. C., Winogrodzka, A. & Wolters, E. C. Identification of axial rigidity during locomotion in Parkinson disease. *Arch. Phys. Med. Rehabil.* **80**, 186–191 (1999).
33. Hausdorff, J. M., Cudkowicz, M. E., Firtion, R., Wei, J. Y. & Goldberger, A. L. Gait variability and basal ganglia disorders: stride-to-stride variations of gait cycle timing in Parkinson's disease and Huntington's disease. *Mov. Disord.* **13**, 428–437 (1998).
34. Willems, A. M. *et al.* Turning in Parkinson's disease patients and controls: the effect of auditory cues. *Mov. Disord.* **22**, 1871–1878 (2007).
35. Dennison, A. C. *et al.* Falling in Parkinson disease: identifying and prioritizing risk factors in recurrent fallers. *Am. J. Phys. Med. Rehabil.* **86**, 621–632 (2007).
36. Ashburn, A., Stack, E., Ballinger, C., Fazakarley, L. & Fitton, C. The circumstances of falls among people with Parkinson's disease and the use of Falls Diaries to facilitate reporting. *Disabil. Rehabil.* **30**, 1205–1212 (2008).
37. Rochester, L. *et al.* Attending to the task: interference effects of functional tasks on walking in Parkinson's disease and the roles of cognition, depression, fatigue, and balance. *Arch. Phys. Med. Rehabil.* **85**, 1578–1585 (2004).
38. Yogev-Seligmann, G., Hausdorff, J. M. & Giladi, N. Do we always prioritize balance when walking? Towards an integrated model of task prioritization. *Mov. Disord.* **27**, 765–770 (2012).
39. Giladi, N., Horak, F. B. & Hausdorff, J. M. Classification of gait disturbances: distinguishing between continuous and episodic changes. *Mov. Disord.* **28**, 1469–1473 (2013).
40. Nutt, J. G. *et al.* Freezing of gait: moving forward on a mysterious clinical phenomenon. *Lancet Neurol.* **10**, 734–744 (2011).
41. Leddy, A. L., Crowner, B. E. & Earhart, G. M. Utility of the mini-BESTest, BESTest, and BESTest sections for balance assessments in individuals with Parkinson disease. *J. Neurol. Phys. Ther.* **35**, 90–97 (2011).
42. Mancini, M. *et al.* Postural sway as a marker of progression in Parkinson's disease: a pilot longitudinal study. *Gait Posture* **36**, 471–476 (2012).
43. Beuter, A., Hernández, R., Rigal, R., Modolo, J. & Blanchet, P. J. Postural sway and effect of levodopa in early Parkinson's disease. *Can. J. Neurol. Sci.* **35**, 65–68 (2008).
44. Švehlík, M. *et al.* Gait analysis in patients with Parkinson's disease off dopaminergic therapy. *Arch. Phys. Med. Rehabil.* **90**, 1880–1886 (2009).
45. Zampieri, C., Salarian, A., Carlson-Kuhta, P., Nutt, J. G. & Horak, F. B. Assessing mobility at home in people with early Parkinson's disease using an instrumented Timed Up and Go test. *Parkinsonism Relat. Disord.* **17**, 277–280 (2011).
46. Mancini, M., Rocchi, L., Horak, F. B. & Chiari, L. Effects of Parkinson's disease and levodopa on functional limits of stability. *Clin. Biomech. (Bristol, Avon)* **23**, 450–458 (2008).
47. Vaugoyeau, M., Viallet, F., Mesure, S. & Massion, J. Coordination of axial rotation and step execution: deficits in Parkinson's disease. *Gait Posture* **18**, 150–157 (2003).
48. Boonstra, T. A., van Kordelaar, J., Engelhart, D., van Vugt, J. P. & van der Kooij, H. Asymmetries in reactive and anticipatory balance control are of similar magnitude in Parkinson's disease patients. *Gait Posture* **43**, 108–113 (2015).
49. Stack, E. L., Ashburn, A. & Jupp, K. Postural instability during reaching tasks in Parkinson's disease. *Physiother. Res. Int.* **10**, 146–153 (2005).
50. Roemmich, R. T. *et al.* Spatiotemporal variability during gait initiation in Parkinson's disease. *Gait Posture* **36**, 340–343 (2012).
51. Rogers, M. W. *et al.* Postural preparation prior to stepping in patients with Parkinson's disease. *J. Neurophysiol.* **106**, 915–924 (2011).
52. King, L. A. & Horak, F. B. Lateral stepping for postural correction in Parkinson's disease. *Arch. Phys. Med. Rehabil.* **89**, 492–499 (2008).
53. Peterson, D. S. & Horak, F. B. The effect of levodopa on improvements in protective stepping in people with Parkinson's disease. *Neurorehabil. Neural Repair* **30**, 931–940 (2016).
54. Pickering, R. M. *et al.* A meta-analysis of six prospective studies of falling in Parkinson's disease. *Mov. Disord.* **22**, 1892–1900 (2007).
55. Bloem, B. R., Grimbergen, Y. A., Cramer, M., Willemsen, M. & Zwinderman, A. H. Prospective assessment of falls in Parkinson's disease. *J. Neurol.* **248**, 950–958 (2001).
56. Ashburn, A., Stack, E., Pickering, R. M. & Ward, C. D. Predicting fallers in a community-based sample of people with Parkinson's disease. *Gerontology* **47**, 277–281 (2001).
57. Gray, P. & Hildebrand, K. Fall risk factors in Parkinson's disease. *J. Neurosci. Nurs.* **32**, 222–228 (2000).
58. Kerr, G. K. *et al.* Predictors of future falls in Parkinson disease. *Neurology* **75**, 116–124 (2010).
59. Wood, B. H., Bilclough, J. A., Bowron, A. & Walker, R. W. Incidence and prediction of falls in Parkinson's disease: a prospective multidisciplinary study. *J. Neurol. Neurosurg. Psychiatry* **72**, 721–725 (2002).
60. Lord, S. *et al.* Predicting first fall in newly diagnosed Parkinson's disease: insights from a fall-naïve cohort. *Mov. Disord.* **31**, 1829–1836 (2016).
61. Mak, M. K. & Pang, M. Y. Fear of falling is independently associated with recurrent falls in patients with Parkinson's disease: a 1-year prospective study. *J. Neurol.* **256**, 1689–1695 (2009).
62. Matinolli, M., Korpelainen, J. T., Sotaniemi, K. A., Myllylä, V. V. & Korpelainen, R. Recurrent falls and mortality in Parkinson's disease: a prospective two-year follow-up study. *Acta Neurol. Scand.* **123**, 193–200 (2011).
63. Paul, S. S. *et al.* Three simple clinical tests to accurately predict falls in people with Parkinson's disease. *Mov. Disord.* **28**, 655–662 (2013).
64. Paul, S. S., Canning, C. G., Song, J., Fung, V. S. & Sherrington, C. Leg muscle power is enhanced by training in people with Parkinson's disease: a randomized controlled trial. *Clin. Rehabil.* **28**, 275–288 (2014).
65. Plotnik, M., Giladi, N., Dagan, Y. & Hausdorff, J. M. Postural instability and fall risk in Parkinson's disease: impaired dual tasking, pacing, and bilateral coordination of gait during the "ON" medication state. *Exp. Brain Res.* **210**, 529–538 (2011).
66. Hely, M. A., Reid, W. G., Adena, M. A., Halliday, G. M. & Morris, J. G. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov. Disord.* **23**, 837–844 (2008).
67. Idjadi, J. A. *et al.* Hip fracture outcomes in patients with Parkinson's disease. *Am. J. Orthop. (Belle Mead NJ)* **34**, 341–346 (2005).
68. Bloem, B. R., Hausdorff, J. M., Visser, J. E. & Giladi, N. Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. *Mov. Disord.* **19**, 871–884 (2004).
69. Melton, L. J. *et al.* Fracture risk after the diagnosis of Parkinson's disease: influence of concomitant dementia. *Mov. Disord.* **21**, 1361–1367 (2006).
70. Keus, S. H., Munneke, M., Nijkrake, M. J., Kwakkel, G. & Bloem, B. R. Physical therapy in Parkinson's disease: evolution and future challenges. *Mov. Disord.* **24**, 1–14 (2009).
71. Keus, S. *et al. European Physiotherapy Guideline for Parkinson's Disease*. (KNGF/ParkinsonNet, 2014).
72. Tomlinson, C. L. *et al.* Physiotherapy for Parkinson's disease: a comparison of techniques. *Cochrane Database Syst. Rev.* **6**, CD002815 (2014).
73. Ellis, T. *et al.* Efficacy of a physical therapy program in patients with Parkinson's disease: a randomized controlled trial. *Arch. Phys. Med. Rehabil.* **86**, 626–632 (2005).
74. Schenkman, M. *et al.* Exercise for people in early- or mid-stage Parkinson disease: a 16-month randomized controlled trial. *Phys. Ther.* **92**, 1395 (2012).
75. Frazzitta, G. *et al.* Intensive rehabilitation treatment in early Parkinson's disease: a randomized pilot study with a 2-year follow-up. *Neurorehabil. Neural Repair.* **29**, 123–131 (2015).
76. Chung, C. L., Thilarajah, S. & Tan, D. Effectiveness of resistance training on muscle strength and physical function in people with Parkinson's disease: a systematic review and meta-analysis. *Clin. Rehabil.* **30**, 11–23 (2016).
77. Lima, L. O., Scianni, A. & Rodrigues-de-Paula, F. Progressive resistance exercise improves strength and physical performance in people with mild to moderate Parkinson's disease: a systematic review. *J. Physiother.* **59**, 7–13 (2013).
78. Lamotte, G. *et al.* Effects of endurance exercise training on the motor and non-motor features of Parkinson's disease: a review. *J. Parkinsons Dis.* **5**, 21–41 (2015).
79. Shen, X. & Mak, M. K. Technology-assisted balance and gait training reduces falls in patients with Parkinson's disease: a randomized controlled trial with 12-month follow-up. *Neurorehabil. Neural Repair.* **29**, 103–111 (2015).
80. Carvalho, A. *et al.* Comparison of strength training, aerobic training, and additional physical therapy as supplementary treatments for Parkinson's disease: pilot study. *Clin. Interv. Aging* **10**, 183 (2015).
81. Corcos, D. *et al.* A two-year randomized controlled trial of progressive resistance exercise for Parkinson's disease. *Mov. Disord.* **28**, 1230–1240 (2013).
82. Shulman, L. M. *et al.* Randomized clinical trial of 3 types of physical exercise for patients with Parkinson disease. *JAMA Neurol.* **70**, 183–191 (2013).
83. Silva-Batista, C. *et al.* Resistance training with instability for patients with Parkinson's disease. *Med. Sci. Sports Exerc.* **48**, 1678–1687 (2016).
84. Ni, M., Signorile, J. F., Balachandran, A. & Potiaumpai, M. Power training induced change in bradykinesia and muscle power in Parkinson's disease. *Parkinsonism Relat. Disord.* **23**, 37–44 (2016).
85. Ni, M. *et al.* Comparative effect of power training and high-speed yoga on motor function in older patients with Parkinson disease. *Arch. Phys. Med. Rehabil.* **97**, 345–354. e15 (2016).
86. Dibble, L. E., Hale, T. F., Marcus, R. L., Gerber, J. P. & LaStayo, P. C. High intensity eccentric resistance training decreases bradykinesia and improves quality of life in persons with Parkinson's disease: a preliminary study. *Parkinsonism Relat. Disord.* **15**, 752–757 (2009).
87. Dibble, L. E., Foreman, K. B., Addison, O., Marcus, R. L. & LaStayo, P. C. Exercise and medication effects on persons with Parkinson disease across the domains of disability: a randomized clinical trial. *J. Neurol. Phys. Ther.* **39**, 85 (2015).
88. Morris, M. E. *et al.* A randomized controlled trial to reduce falls in people with Parkinson's disease. *Neurorehabil. Neural Repair.* **29**, 777–785 (2015).
89. Schlenstedt, C. *et al.* Resistance versus balance training to improve postural control in Parkinson's disease: a randomized rater blinded controlled study. *PLoS ONE* **10**, e0140584 (2015).
90. Li, F. *et al.* Tai chi and postural stability in patients with Parkinson's disease. *N. Engl. J. Med.* **366**, 511–519 (2012).
91. Prodoehl, J. *et al.* Two-year exercise program improves physical function in Parkinson's disease the PRET-PD randomized clinical trial. *Neurorehabil. Neural Repair.* **29**, 112–122 (2015).
92. Shen, X. & Mak, M. K. Balance and gait training with augmented feedback improves balance confidence in people with Parkinson's disease: a randomized controlled trial. *Neurorehabil. Neural Repair.* **28**, 524–535 (2014).
93. Sage, M. D. & Almeida, Q. J. Symptom and gait changes after sensory attention focused exercise versus aerobic training in Parkinson's disease. *Mov. Disord.* **24**, 1132–1138 (2009).

94. Nadeau, A., Pourcher, E. & Corbeil, P. Effects of 24 weeks of treadmill training on gait performance in Parkinson disease. *Med. Sci. Sports Exerc.* **46**, 645–655 (2013).
95. Cugusi, L. *et al.* Effects of a Nordic walking program on motor and non-motor symptoms, functional performance and body composition in patients with Parkinson's disease. *NeuroRehabilitation* **37**, 245–254 (2015).
96. Reuter, I. *et al.* Effects of a flexibility and relaxation programme, walking, and Nordic walking on Parkinson's disease. *J. Aging Res.* **2011**, 232473 (2011).
97. Bridgewater, K. J. & Sharpe, M. H. Aerobic exercise and early Parkinson's disease. *J. Neurol. Rehabil.* **10**, 233–241 (1996).
98. Morris, M. E., Iansek, R., Matyas, T. A. & Summers, J. J. Stride length regulation in Parkinson's disease. *Brain* **119**, 551–568 (1996).
99. Spaulding, S. J. *et al.* Cueing and gait improvement among people with Parkinson's disease: a meta-analysis. *Arch. Phys. Med. Rehabil.* **94**, 562–570 (2013).
100. Morris, M. E., Iansek, R. & Kirkwood, B. A randomized controlled trial of movement strategies compared with exercise for people with Parkinson's disease. *Mov. Disord.* **24**, 64–71 (2009).
101. Martin, T., Weatherall, M., Anderson, T. J. & MacAskill, M. R. randomized controlled feasibility trial of a specific cueing program for falls management in persons with Parkinson disease and freezing of gait. *J. Neurol. Phys. Ther.* **39**, 179–184 (2015).
102. de Bruin, N. *et al.* Walking with music is a safe and viable tool for gait training in Parkinson's disease: the effect of a 13-week feasibility study on single and dual task walking. *Parkinsons Dis.* **2010**, 483530 (2010).
103. Frazzitta, G., Maestri, R., Uccellini, D., Bertotti, G. & Abelli, P. Rehabilitation treatment of gait in patients with Parkinson's disease with freezing: a comparison between two physical therapy protocols using visual and auditory cues with or without treadmill training. *Mov. Disord.* **24**, 1139–1143 (2009).
104. Miyai, I. *et al.* Long-term effect of body weight–supported treadmill training in Parkinson's disease: a randomized controlled trial. *Arch. Phys. Med. Rehabil.* **83**, 1370–1373 (2002).
105. Picelli, A. *et al.* Robot-assisted gait training versus equal intensity treadmill training in patients with mild to moderate Parkinson's disease: a randomized controlled trial. *Parkinsonism Relat. Disord.* **19**, 605–610 (2013).
106. Carda, S. *et al.* Robotic gait training is not superior to conventional treadmill training in Parkinson disease: a single-blind randomized controlled trial. *Neurorehabil. Neural Repair.* **26**, 1027–1034 (2012).
107. Mehrholz, J. *et al.* Treadmill training for patients with Parkinson's disease. *Cochrane Database Syst. Rev.* **1**, CD007830 (2010).
108. Goodwin, V. A., Richards, S. H., Taylor, R. S., Taylor, A. H. & Campbell, J. L. The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. *Mov. Disord.* **23**, 631–640 (2008).
109. Ashburn, A. *et al.* A randomised controlled trial of a home based exercise programme to reduce the risk of falling among people with Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* **78**, 678–684 (2007).
110. Canning, C. G. *et al.* Exercise for falls prevention in Parkinson disease: a randomized controlled trial. *Neurology* **84**, 304–312 (2015).
111. Sparrow, D. *et al.* Highly challenging balance program reduces fall rate in Parkinson disease. *J. Neurol. Phys. Ther.* **40**, 24–30 (2016).
112. Wong-Yu, I. S. & Mak, M. K. Multi-dimensional balance training programme improves balance and gait performance in people with Parkinson's disease: a pragmatic randomised controlled trial with 12-month follow-up. *Parkinsonism Relat. Disord.* **21**, 615–621 (2015).
113. Palamara, G. *et al.* Land plus aquatic therapy versus land-based rehabilitation alone for the treatment of balance dysfunction in Parkinson disease: a randomized controlled study with 6-month follow-up. *Arch. Phys. Med. Rehabil.* **98**,1077–1085 (2017).
114. Ni, X., Liu, S., Lu, F., Shi, X. & Guo, X. Efficacy and safety of Tai Chi for Parkinson's disease: a systematic review and meta-analysis of randomized controlled trials. *PLoS ONE* **9**, e99377 (2014).
115. Amano, S. *et al.* The effect of tai chi exercise on gait initiation and gait performance in persons with Parkinson's disease. *Parkinsonism Relat. Disord.* **19**, 955–960 (2013).
116. Gao, Q. *et al.* Effects of tai chi on balance and fall prevention in Parkinson's disease: a randomized controlled trial. *Clin. Rehabil.* **28**, 748–753 (2014).
117. Hackney, M. E. & Earhart, G. M. Tai chi improves balance and mobility in people with Parkinson disease. *Gait Posture* **28**, 456–460 (2008).
118. Li, F. *et al.* A randomized controlled trial of patient-reported outcomes with tai chi exercise in Parkinson's disease. *Mov. Disord.* **29**, 539–545 (2014).
119. Choi, H. J. *et al.* Therapeutic effects of tai chi in patients with Parkinson's disease. *ISRN Neurol.* **2013**, 548240 (2013).
120. Duncan, R. P. & Earhart, G. M. Randomized controlled trial of community-based dancing to modify disease progression in Parkinson disease. *Neurorehabil. Neural Repair.* **26**, 132–143 (2012).
121. Hackney, M. E. & Earhart, G. M. Effects of dance on movement control in Parkinson's disease: a comparison of Argentine tango and American ballroom. *J. Rehabil. Med.* **41**, 475–481 (2009).
122. Hackney, M. E. & Earhart, G. M. Health-related quality of life and alternative forms of exercise in Parkinson disease. *Parkinsonism Relat. Disord.* **15**, 644–648 (2009).
123. Hackney, M. E., Kantorovich, S., Levin, R. & Earhart, G. M. Effects of tango on functional mobility in Parkinson's disease: a preliminary study. *J. Neurol. Phys. Ther.* **31**, 173 (2007).
124. Romenets, S. R., Anang, J., Fereshtehnejad, S.-M., Pelletier, A. & Postuma, R. Tango for treatment of motor and non-motor manifestations in Parkinson's disease: a randomized control study. *Complement. Ther. Med.* **23**, 175–184 (2015).
125. Volpe, D., Signorini, M., Marchetto, A., Lynch, T. & Morris, M. E. A comparison of Irish set dancing and exercises for people with Parkinson's disease: a phase II feasibility study. *BMC Geriatr.* **13**, 1 (2013).
126. Mujika, I. & Padilla, S. Detraining: loss of training-induced physiological & performance adaptations. Part I: short term insufficient training stimulus. *Sports Med.* **30**, 79–87 (2000).
127. Garber, C. E. *et al.* American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med. Sci. Sports Exerc.* **43**, 1334–1359 (2011).
128. Steffen, T. & Seney, M. Test-retest reliability and minimal detectable change on balance and ambulation tests, the 36-item short-form health survey, and the unified Parkinson disease rating scale in people with Parkinsonism. *Phys. Ther.* **88**, 733 (2008).
129. Muslimoviç D., Post, B., Speelman, J. D. & Schmand, B. Motor procedural learning in Parkinson's disease. *Brain* **130**, 2887–2897 (2007).
130. Shulman, L. M. *et al.* The clinically important difference on the unified Parkinson's disease rating scale. *Arch. Neurol.* **67**, 64–70 (2010).
131. Fisher, B. E. *et al.* Treadmill exercise elevates striatal dopamine D2 receptor binding potential in patients with early Parkinson's disease. *Neuroreport* **24**, 509–514 (2013).
132. Svensson, M., Lexell, J. & Deierborg, T. Effects of physical exercise on neuroinflammation, neuroplasticity, neurodegeneration, and behavior: what we can learn from animal models in clinical settings. *Neurorehabil. Neural Repair.* **29**, 577–589 (2015).
133. Koo, J. H., Cho, J. Y. & Lee, U. B. Treadmill exercise alleviates motor deficits and improves mitochondrial import machinery in an MPTP-induced mouse model of Parkinson's disease. *Exp. Gerontol.* **89**, 20–29 (2017).
134. Monteiro-Junior, R. S. *et al.* We need to move more: neurobiological hypotheses of physical exercise as a treatment for Parkinson's disease. *Med. Hypotheses* **85**, 537–541 (2015).
135. Zigmond, M. J. & Smeyne, R. J. Exercise: is it a neuroprotective and if so, how does it work? *Parkinsonism Relat. Disord.* **20**, S123–S127 (2014).
136. Petzinger, G. *et al.* The effects of exercise on dopamine neurotransmission in Parkinson's disease: targeting neuroplasticity to modulate basal ganglia circuitry. *Brain Plast.* **1**, 29–39 (2015).
137. Fisher, B. E. *et al.* The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinson's disease. *Arch. Phys. Med. Rehabil.* **89**, 1221–1229 (2008).
138. Frazzitta, G. *et al.* Intensive rehabilitation increases BDNF serum levels in Parkinsonian patients: a randomized study. *Neurorehabil. Neural Repair.* **28**, 163–168 (2014).
139. Fontanesi, C. *et al.* Intensive rehabilitation enhances lymphocyte BDNF–TrkB signaling in patients with Parkinson's disease. *Neurorehabil. Neural Repair.* **30**, 411–418 (2016).
140. Sehm, B. *et al.* Structural brain plasticity in Parkinson's disease induced by balance training. *Neurobiol. Aging* **35**, 232–239 (2014).
141. Duchesne, C. *et al.* Influence of aerobic exercise training on the neural correlates of motor learning in Parkinson's disease individuals. *Neuroimage Clin.* **12**, 559–569 (2016).
142. Abbruzzese, G., Marchese, R., Avanzino, L. & Pelosin, E. Rehabilitation for Parkinson's disease: current outlook and future challenges. *Parkinsonism Relat. Disord.* **22**, S60–S64 (2016).
143. Speelman, A. D., van Nimwegen, M., Bloem, B. R. & Munneke, M. Evaluation of implementation of the ParkFit program: a multifaceted intervention aimed to promote physical activity in patients with Parkinson's disease. *Physiotherapy* **100**, 134–141 (2014).
144. Ellis, T. *et al.* Barriers to exercise in people with Parkinson disease. *Phys. Ther.* **93**, 628 (2013).
145. Cress, M. E. *et al.* Best practices for physical activity programs and behavior counseling in older adult populations. *J. Aging. Phys. Act.* **13**, 61–74 (2005).
146. Rosser, B. A., Vowles, K. E., Keogh, E., Eccleston, C. & Mountain, G. A. Technologically-assisted behaviour change: a systematic review of studies of novel technologies for the management of chronic illness. *J. Telemed. Telecare* **15**, 327–338 (2009).
147. Barry, G., Galna, B. & Rochester, L. The role of exergaming in Parkinson's disease rehabilitation: a systematic review of the evidence. *J. Neuroeng. Rehabil.* **11**, 33 (2014).
148. Moore, C. G. *et al.* Study in Parkinson disease of exercise (SPARX): translating high-intensity exercise from animals to humans. *Contemp. Clin. Trials* **36**, 90–98 (2013).
149. Earhart, G. M., Duncan, R. P., Huang, J. L., Perlmutter, J. S. & Pickett, K. A. Comparing interventions and exploring neural mechanisms of exercise in Parkinson disease: a study protocol for a randomized controlled trial. *BMC Neurol.* **15**, 9 (2015).
150. Angelucci, F. *et al.* The effects of motor rehabilitation training on clinical symptoms and serum BDNF levels in Parkinson's disease subjects. *Can. J. Physiol. Pharmacol.* **94**, 455–461 (2016).
151. Ferraye, M. U., Fraix, V., Pollak, P., Bloem, B. R. & Debû, B. The laser-shoe: a new form of continuous ambulatory cueing for patients with Parkinson's disease. *Parkinsonism Relat. Disord.* **29**, 127 (2016).
152. Zhao, Y. *et al.* Feasibility of external rhythmic cueing with the Google Glass for improving gait in people with Parkinson's disease. *J. Neurol.* **263**, 1156–1165 (2016).
153. Horak, F. B., King, L. & Mancini, M. Role of body-worn movement monitor technology for balance and gait rehabilitation. *Phys. Ther.* **95**, 461–470 (2015).
154. Ekker, M. S., Janssen, S., Nonnekes, J., Bloem, B. R. & de Vries, N. M. Neurorehabilitation for Parkinson's disease: future perspectives for behavioural adaptation. *Parkinsonism Relat. Disord.* **22**, S73–S77 (2016).
155. Hely, M. A., Morris, J. G., Reid, W. G. & Trafficante, R. Sydney multicenter study of Parkinson's disease: non L-dopa responsive problems dominate at 15 years. *Mov. Disord.* **20**, 190–199 (2005).
156. Seppi, K. *et al.* The Movement Disorder Society Evidence-Based Medicine review update: treatments for the non-motor symptoms of Parkinson's disease. *Mov. Disord.* **26**, S42–S80 (2011).

157. Cusso, M. E., Donald, K. J. & Khoo, T. K. The impact of physical activity on non-motor symptoms in Parkinson's disease: a systematic review. *Front. Med. (Lausanne)* **3**, 35 (2016).
158. Duchesne, C. *et al.* Enhancing both motor and cognitive functioning in Parkinson's disease: aerobic exercise as a rehabilitative intervention. *Brain Cogn.* **99**, 68–77 (2015).
159. Reynolds, G. O., Otto, M. W., Ellis, T. D. & Cronin-Golomb, A. The therapeutic potential of exercise to improve mood, cognition, and sleep in Parkinson's disease. *Mov. Disord.* **31**, 23–38 (2016).
160. Van der Kolk, N. M. *et al.* Design of the Park-in-Shape study: a phase II double blind randomized controlled trial evaluating the effects of exercise on motor and non-motor symptoms in Parkinson's disease. *BMC Neurol.* **15**, 56 (2015).

Author contributions
All authors contributed equally to the researching, discussion writing and review of this manuscript.

Competing interests statement
The authors declare no competing interests.

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Review criteria
We conducted an extensive search of the literature up to 15 May 2017, using electronic databases, including the CINAHL database, MEDLINE, PubMed, Academic Search Premier via EbscoHost, and Cochrane Library. The keywords used to conduct the literature search were combined with the following English terms: (Physical therapy OR physiotherapy OR rehabilitation OR training OR exercise OR movement) AND Parkin* AND (balance OR postural stability OR gait OR fall OR aerobic OR endurance OR strength OR resistance). A total of 4,116 papers were identified after removal of duplicates. Other studies were added from other sources, including reviews, reference lists of relevant publications, and a search of the authors' own reference libraries. We selected randomized controlled trials with at least 12 weeks of training period or 12 weeks of follow-up, and with high-quality methodology (judged by the Cochrane risk-of-bias tool to have three or more bias domains with low risk). Finally, 46 articles were taken into account for this Review.

SUPPLEMENTARY INFORMATION
See online article: S1 (table)
ALL LINKS ARE ACTIVE IN THE ONLINE PDF