Life Sciences 245 (2020) 117345

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

The benefits and mechanisms of exercise training for Parkinson's disease

Ya-Shuo Feng[a], Si-Dong Yang[b,c], Zi-Xuan Tan[a], Man-Man Wang[a], Ying Xing[a], Fang Dong[d], Feng Zhang[a,e,*]

[a] Department of Rehabilitation Medicine, The Third Hospital of Hebei Medical University, Shijiazhuang 050051, PR China
[b] Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Brisbane 4072, Australia
[c] Department of Spine Surgery, The Third Hospital of Hebei Medical University, Shijiazhuang 050051, PR China
[d] Department of Clinical Laboratory Medicine, The Third Hospital of Hebei Medical University, Shijiazhuang 050051, PR China
[e] Hebei Provincial Orthopedic Biomechanics Key Laboratory, The Third Hospital of Hebei Medical University, Shijiazhuang 050051, PR China

ARTICLE INFO

Keywords:
Parkinson's disease
Exercise
Motor dysfunction
Dopamine

ABSTRACT

Parkinson's disease (PD) is a significantly progressive neurodegenerative disease characterised by both motor and nonmotor disorders. The main pathological characteristics of PD consist of the loss of dopaminergic neurons and the formation of alpha-synuclein-containing Lewy bodies in the substantia nigra. Currently, the main therapeutic method for PD is anti-Parkinson medications, including levodopa, madopar, sirelin, and so on. However, the effect of pharmacological treatment has its own limitations, the most significant of which is that the therapeutic effect of dopaminergic treatments gradually diminishes with time. Exercise training, as an adjunctive treatment and complementary therapy, can improve the plasticity of cortical striatum and increase the release of dopamine. Exercise training has been proven to effectively improve motor disorders (including balance, gait, risk of falls and physical function) and nonmotor disorders (such as sleep impairments, cognitive function and quality of life) in PD patients. In recent years, various types of exercise training have been used to treat PD. In this review, we summarise the exercise therapy mechanisms and the protective effects of different types of exercise training on PD patients.

1. Introduction

Parkinson's disease (PD), a progressive neurodegenerative disorder, is mainly associated with many factors [1]. First, the strongest genetic risk factor of PD is a mutation in the gene encoding β-glucocerebrosidase [2]. According to previous studies, mutations of the LRRK2 gene have been found in familial and sporadic PD, and mutations of the SNCA gene (the alpha-synuclein gene) are regarded as risk factors for PD [3,4]. Furthermore, the influence of environmental factors on genetically susceptible persons plays a crucial role in the process of PD development [5]. For instance, xenobiotic exposure, such as transitional metal deposits going into vulnerable central nervous system areas, seems to interact with the genes which are regarded as risk factors for PD [5]. In addition, central nervous system infection and craniocerebral trauma, as well as exposure to pesticides and fungicides, such as rotenone and paraquat, seem to be associated with the pathological process of PD [6–8].

PD mainly occurs in adults who are 60 years or older, and its occurrence in men is higher than in women [9,10]. As the second most common neurodegenerative disorder, PD impacts at least 6 million people worldwide [11]. PD patients have motor and nonmotor disorders that prevent them from participating in exercise activities [12]. Motor disorders have received more attention from researchers and clinicians [13] and major motor symptoms include tremor, bradykinesia (hypokinesia or akinesia), plastic-type muscular rigidity and postural instability [14]. PD patients also have other kinds of typical motor disorders, including frozen gait, altered gait patterns and motor coordination dysfunctions [15]. Besides motor symptoms, nonmotor symptoms also influence quality of life and can include cognitive dysfunction, sleep disorder, anxiety, depression and fatigue [16]. There is an increasing amount of evidence indicating that nonmotor disorders can significantly affect quality of life, lead to disability, and cause more health-associated problems compared with a motor disorder [17]. There are also other types of symptoms that seriously affect the quality of life in PD patients, including loss of energy, negative emotions, and loss of control over one's own health [18,19]. Above all, the dysfunction caused by PD makes patients lose the ability to perform daily life activities and hence lose their independence [20].

* Corresponding author at: Department of Rehabilitation Medicine, The Third Hospital of Hebei Medical University, No. 139 Ziqiang Road, 050051 Shijiazhuang, Hebei, PR China.
E-mail address: ydsyzf@hebmu.edu.cn (F. Zhang).

https://doi.org/10.1016/j.lfs.2020.117345
Received 11 January 2020; Received in revised form 18 January 2020; Accepted 19 January 2020
Available online 22 January 2020

Clinically, there are two types of treatments for PD: surgical therapy (deep brain stimulation) and medication (levodopa, dopamine agonists) [21]. L-dopa, the gold standard medication for PD motor symptoms, is a precursor of dopamine that can easily pass through the blood–brain barrier [14]. Other medications are also available, which are commonly related to L-dopa, and are classified in line with the mechanism of action so as to increase dopamine generation; these medications include catechol-*o*-methyl transferase (COMT) inhibitors, monoamine oxidase-B (MAO-B), and dopaminergic agonists for instance pramipexole (amantadine) [22]. Pharmacological therapy can improve PD patients' motor symptoms, but over time, the effect of dopaminergic treatments gradually diminishes, and several characteristics of motor control are resistant to pharmacological therapy [23]. Additionally, the existing medication treatments can only relieve symptoms and hence are unable to stop disease progression [24]. In recent years, two novel treatments for PD patients have emerged, including neurotrophic factor treatment and cell transplantation, but these two strategies mainly depend on highly invasive stereotaxic surgery that is accompanied by safety problems and side effects [25]. Under these circumstances, exercise, as a complementary and nonpharmacological therapy, is gaining more and more attention for the treatment of PD [26].

In 1992, Sasco et al. first reported a link between exercise and PD, and they found that exercise intervention in adulthood significantly reduced the risk of developing PD for the rest of one's lifetime [27]. Subsequently, several large-scale epidemiological research studies confirmed this beneficial role of exercise for PD [28,29]. Furthermore, Lau et al. indicated that exercise can potentially decrease the risk of worsening neurological deficits in PD [30]. As a complementary and alternative treatment, exercise can both improve the motor and nonmotor symptoms of PD patients [31]. In clinical studies, various types of exercise training, such as aerobic exercise, gait training, balance training, progressive resistance training and complementary exercise, have been used. In this review, we summarise the roles of different types of exercise training for PD patients and the related mechanisms in providing PD patients with an optimised exercise therapy and how this can delay disease progression and improve quality of life, thus benefiting the increasing number of PD patients.

2. Dysfunctions and pathophysiology of PD

2.1. Dysfunctions of PD

PD patients have both motor and nonmotor dysfunctions that prevent them from performing normal daily activities, and four of these dysfunctions are most common, including postural instability, gait disorder, freezing of gait, and cognitive impairments.

2.1.1. Postural instability

Postural instability is a prominent movement disability in people with PD [32]. The major reasons for postural instability in PD patients are decreased muscle strength in the hips, spine and ankles, along with damaged proprioception, visual dysfunction and a smaller base of support [33]. With the aggravation of PD, postural instability tends to worsen, resulting in balance dysfunction and an increased risk of falls [32,34]. Balance dysfunction often occurs in the early phase of PD and becomes progressively worse with disease development [35]. The pathophysiology of balance disorders in PD patients integrates with numerous subsystems, such as sensation, movement and cognition [36,37]. For instance, sensory disorders can affect balance function, especially because of impaired proprioception and dysfunction in integrating various sensory patterns into the body's frame of reference [37]. Falling is very common for PD patients, and it is estimated that approximately 18 to 65% of PD patients are frequent fallers, which is mainly associated with gait and postural control dysfunctions [38–40]. Generally speaking, the mechanism of falls is complex, and it is related to motor and non-motor dysfunctions specific to PD patients, comorbidity and age-related risk factors [41]. As frequent fallers, PD patients tend to have a high degree of activity restriction in their daily lives; therefore, they have a limited capacity to perform daily activities and a significant fear of falling [42]. If balance disorders and the fear of falls persist or even worsen, it may prevent PD patients from increasing their physical activities, even if they want to perform these activities [43].

2.1.2. Gait disorder

Gait disorder is a significant clinical manifestation of PD and is one of the most serious disabling symptoms of the disease [44]. The main reason behind gait disturbance is gait hypokinesia [45]. Gait hypokinesia is related to the decrease of stride height and length, reduction of stride frequency and extended double limb support [46]. Another reason is the impairment of gait automaticity, which is in charge of walking without attention or cognitive effort [47]. A decrease of gait automaticity in PD patients is related to the degeneration of dopamine in the sensorimotor area of the basal ganglia, which disrupts the habitual control of PD patients [46,48].

2.1.3. Freezing of gait

Freezing of gait (FOG) is a brief episodic absence or significant decrease in forward progression of the feet, which commonly occurs in more advanced stages of PD patients [49,50]. PD patients with FOG often feel their feet are stuck to the ground even though they are trying to force themselves to walk [51]. There are two common types of FOG: shuffling and tremble in place [52]. The possible triggers for FOG include abnormal gait, such as asymmetry and arrhythmicity [53]. FOG not only affects gait function, but it also causes some nonmotor disorders including social isolation, anxiety and depression, which significantly influence PD patients' quality of life [54].

2.1.4. Cognitive impairments

Approximately 25% of newly diagnosed nondementia PD patients demonstrate several cognitive impairments, including memory, attention, executive and visuospatial dysfunction [55,56]. Dual-tasking dysfunction is primarily an attention-based cognitive disorder and is a major cognitive impairment that directly affects motor function, especially gait function [57,58]. In addition, impaired dual-tasking has a considerable impact on PD patients' daily activities and is connected with an increased risk of falls [59]. It is well-known that in PD patients, cognitive dysfunctions are closely related to motor disorders and motor learning disabilities [60,61]. For instance, Poletti et al. revealed that bradykinesia is a risk factor for mild cognitive disorders in individuals with PD [62].

2.2. Pathophysiology of PD

PD is mainly caused by the existence of Lewy bodies, decreased striatal dopamine and the progressive deficiency of dopaminergic neurons within the substantia nigra pars compacta [63]. Nearly 80% of dopaminergic neurons can be damaged before a patient shows obvious symptoms of PD [64]. In the development process of PD, the early and preferential reduction of dopamine results in decreased automatic and enhanced cognitive control of one's movements [65,66]. As a result, PD patients need to handle and maintain a greater cognitive load to complete motor tasks [67]. Although the dopaminergic system is the one that is the most commonly involved in PD, other neurological systems are also implicated, including the glutaminergic, cholinergic, noradrenergic and GABAergic pathways [68–70]. Neuroinflammation is also a major cause of the neurodegenerative changes in the brain of PD patients, and this is activated via immune and microglia cells [71]. For instance, the levels of interleukin (IL)-1β and tumour necrosis factor (TNF)-α in PD patients are higher than healthy people [72]. In addition, the pathogenesis of PD is also related to a variety of cellular mechanisms, such as oxidative stress, mitochondrial dysfunction and protein

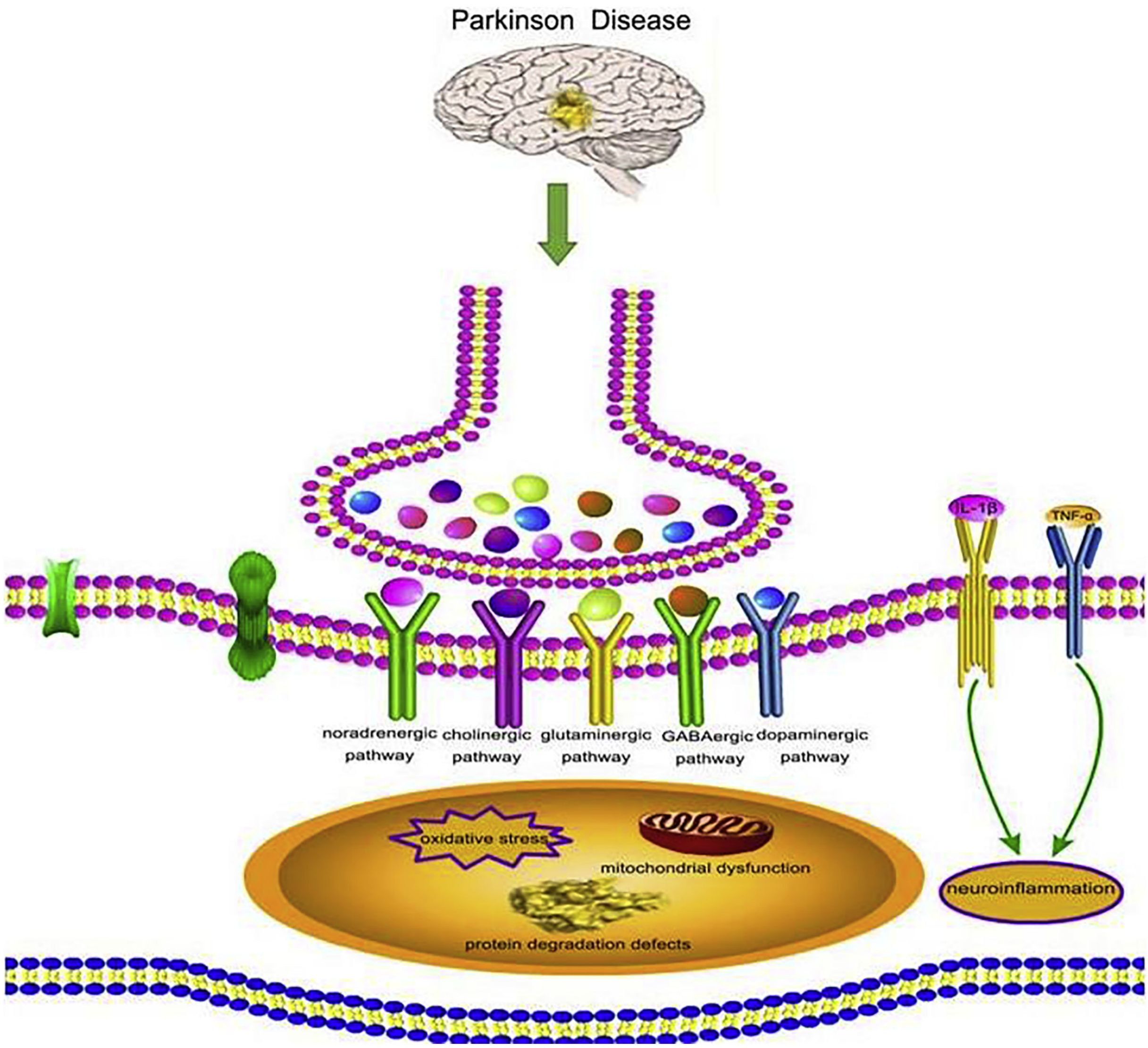

Fig. 1. The pathophysiology of PD.
In the pathophysiology of PD, there are various neurotransmitter system dysfunctions, involving dopaminergic, glutaminergic, cholinergic, noradrenergic, and GABAergic system. Besides, other mechanisms also play a crucial role in the degeneration of PD, such as neuroinflammation, mitochondrial disorder, oxidative stress, and protein degradation defects.

degradation defects [73,74]. As shown in Fig. 1, PD is a complex pathophysiological process that includes multiple neurotransmitter system disorders, cellular dysfunction and neuroinflammation.

3. Exercise training

3.1. The involved mechanisms of exercise training in animal experiments

In recent years, researchers have conducted a series of studies to investigate the mechanisms of exercise training for PD. According to animal research, aerobic exercise exerts neurorestorative and neuroprotective effects, possibly through regulating neurotrophic factors to support synapse formation and angiogenesis, inhibiting oxidative stress and improving mitochondrial function [75]. For instance, exercise on a treadmill can increase the level of brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF) in the striatum in rat PD models [76]. The therapeutic effect of a running wheel exercise in a mouse transgenic model of PD has been associated with the activation of Hsp70, DJ-1 and BDNF and the suppression of α-synuclein aggregation [77]. Treadmill exercise training and strength training increase neuroprotection in PD animals, most likely by stimulating the activity of Sirt1, which may in turn modulate neuronal inflammation and mitochondrial function through NF-κB p65 deacetylation [78]. Furthermore, treadmill exercise can increase the levels of Nrf2 and γGCLC and inverse the upregulation of HO-1, downregulation of Nrf2/γGCLC/glutathione and nigrostriatal dopaminergic neurodegeneration in PD animal models [79].

Neuroplasticity also plays an important role in exercise treatments for PD. Functional connectivity magnetic resonance imaging findings have shown that a high-rate stationary bicycle could increase the thalamo-cortical connectivity in PD patients [80]. Fisher et al. reported that treadmill training for eight weeks increased dopamine D2 receptor binding potential, indicating that the therapeutic effect of exercise is related to neuroplasticity in the dopaminergic pathway [81]. Furthermore, the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and GluR2 subunit play an important role in the neuroplasticity that is induced by high-intensity treadmill exercise in mice PD models [82].

Exercise training has protective effects on the central nervous system as well. Treadmill exercise exerts therapeutic effects for PD rat models via the inhibition of the nigrostriatal formation of Lewy bodies and preservation of nigrostriatal dopaminergic neurons and fibres [83]. Indeed, four weeks of treadmill training was shown to improve the motor impairment in a PD rat model by regulating the mGluR2/3-mediated glutamatergic transmission [84]. Furthermore, long-term treadmill training could decrease the loss of dopaminergic cells and transmission and reduce the oxidation of proteins caused by neurotoxins in PD animal models [30,85].

Other mechanisms after aerobic exercise that occur in the molecular and systems level were also explored, and these include promoted cerebral blood flow and arousal, activated corticospinal excitability and reduced intracortical inhibition [86]. High-intensity weight-supported treadmill training is beneficial for normalising corticomotor excitability for PD patients per an evaluation using transcranial magnetic stimulation [87].

Except for the abovementioned factors, there are other mechanisms whereby exercise can help prevent neurodegeneration and improve function in PD patients. For instance, treadmill training can inhibit the activation of reactive astrocytes and microglia and suppress the apoptosis of cerebellum induced by rotenone in PD rats [88]. Jang et al. demonstrated that treadmill-training-induced neuroprotective function in PD animal models is related to an increase of autophagy-associated proteins, such as LC3-II, P62, Beclin1 and BNIP3, and the inhibition of apoptosis by increasing BCL-2 and decreasing caspase-3 and BAX [89]. Liu et al. suggested that the adaptive mechanism of regular aerobic exercise in treating neurodegenerative diseases was because aerobic exercise could activate miR-3557/324 to regulate its downstream CaMKs signalling pathway [90]. CaMKs coordinates with the gene expression of the mTOR pathway, regulating uch-l1 levels, which is conducive for improving the pathogenesis or alleviating the neurodegeneration of PD rat models [90].

In summary, exercise training exerts beneficial effects on PD patients by increasing neuroplasticity, protecting neuronal cells against from brain damage and regulating neurotrophic factors, autophagy and apoptosis (as shown in Fig. 2).

3.2. Different types of exercise training for PD

3.2.1. Aerobic exercise training

Among the different types of exercise programmes, aerobic exercise training (AET) is considered to be the best choice for improving the health of people throughout their entire life span [91]. Stationary bicycle aerobic exercise training is not only safe, but it also improves aerobic ability, motor performance and cognitive function for early-stage PD patients [92]. Mehmet et al. reported that 14 patients with mild to moderate PD who received high speed–low resistance interval training on a stationary recumbent bicycle showed an improvement of disease severity, balance, functional mobility, upper extremity movement function and cognitive function [93]. Besides, it is reported that aerobic exercise is the most effective method for alleviating depression in PD patients when compared with other types of exercise, such as Qigong, Tai Chi, and so forth [94]. Additionally, cycling is undoubtedly an interesting choice for people with FOG, but safety problems need to be considered [95]. Alexandra et al. conducted a study where for 12 weeks, PD patients took part in AET with stationary bicycle, showing improved gait and cognitive function independently; the improvement of gait is related to the type of motor activity used in the exercise (i.e., pedalling) [96]. Further, the effects of acute aerobic exercise for improving cognitive function depended on exercise intensity based on a comparison between high-intensity interval training (HIIT) and continuous moderate intensity training (MICT) to promote cognitive performance in PD patients [97].

As an effective nondrug therapy, AET does not only promote the physical health of patients with early PD, but it also improves the motor learning ability in daily activities by enhancing the plasticity of motor-related structures [98]. Simon et al. enrolled 17 PD individuals to explore the beneficial effects of moderate intensity AET for PD, and the results indicated that a single moderate intensity AET was effective in promoting motor skills consolidation in participants with PD, demonstrating that acute exercise may be an effective therapy for increasing the motor memory formation for PD patients [99]. In addition, Anson et al. reported that AET for eight weeks (cycling exercise, 60 min, three times per week) may alter various signalling pathways in the central nervous system, regulating the cognitive or physiological processes and controlling olfaction in PD patients [100]. Another animal experiment showed that when compared with nonskilled aerobic exercise in PD rat models, skilled aerobic exercise can increase the improvement of motor functions controlled by cerebellum and prefrontal cortex [101]. In summary, aerobic exercise is a very popular treatment for the function recovery, and it has positive effects on motor, quality of life, cognition and the emotions of PD patients and even animals.

3.2.2. Gait training

3.2.2.1. Treadmill training. Treadmill training is a promising therapeutic method that can provide PD patients with the intensive training of complex gait cycle (high repetition) [102]. It is reported that treadmill training can effectively improve the gait and mobility of PD patients, such as stride length and gait speed [103,104]. A pilot randomised controlled trial demonstrated that treadmill training for eight weeks could obviously improve the motor functions in PD patients, particularly gait and postural stability [105]. Earhart et al. reported that a rotating treadmill could be an effective training method for PD patients who have difficulties with turning [106]. Cheng et al. designed a new turning-based treadmill training, and the turning-based treadmill training could improve the turning ability of PD patients [107]. Furthermore, treadmill training can increase neuroplasticity, protect dopaminergic neurons and fibres in central nervous system, and regulate many signalling pathways [82,83,89]. In brief, treadmill training is regarded as an effective treatment to alleviate gait dysfunction in patients with PD, especially for those with turning impairment.

3.2.2.2. Body weight–supported treadmill training. Body weight–supported treadmill training (BWSTT) may be an option for PD patients who cannot receive traditional ground gait training because of severe postural instability, orthostatic hypotension or balance disorders [108]. BWSTT is commonly well tolerated, but subjects with anxiety and chronic pain need to be cautious when using BWSTT [108]. BWSTT provides more repetitions, a higher intensity and task-oriented practice for the same amount of time than traditional treatments [109]. It was reported that BWSTT is a promising rehabilitative method for improving gait impairment, balance dysfunction and postural instability in patients with PD [110,111]. Miyai et al. indicated that BWSTT had a greater positive effect on ambulation, motor performance and daily living activities when compared with conventional physical treatment [112]. Moreover, Fisher et al. suggested that high intensity BWSTT has positive effects on normalising corticomotor excitability for PD patients [87]. Taken together, BWSTT plays an important role in improving the motor function of PD patients, such as postural stability, gait and balance function.

3.2.2.3. Robot-assisted gait training. Robot training is a safe and feasible rehabilitation therapy for mild PD patients [113]. Robot-assisted gait therapy (RAGT) could improve bradykinesia, motivation, freezing, rigidity, gait, leg agility and posture in PD patients, per an assessment using the Unified Parkinson's Disease Rating Scale [114]. Compared with treadmill treatment, RAGT contributes to a greater improvement in mean velocity, step length and stride length in PD patients [113]. Similarly, Galli et al. demonstrated that RAGT is more beneficial than intensive treadmill therapy, leading to a larger improvement in gait kinematics [115]. In 2013, Picelli et al. reported that the effect of RAGT

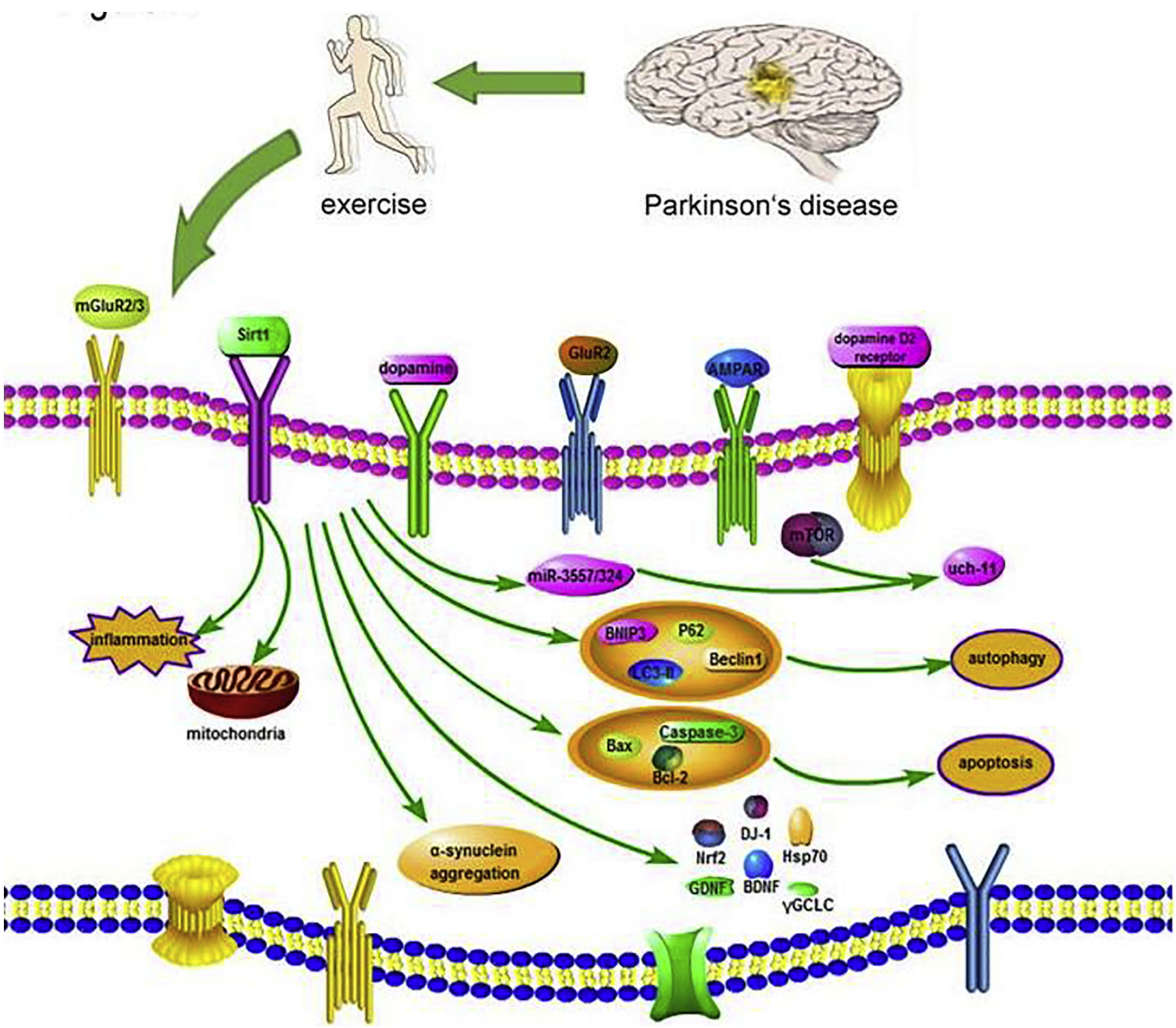

Fig. 2. The benefits of exercise for PD and related mechanisms.
Exercise training exerts beneficial effects on improving degeneration of central nervous system by regulating glutamatergic and dopaminergic system. Besides, the beneficial effects of exercise therapy are related to the regulation of autophagy, apoptosis, inflammation, α-synuclein aggregation, and mitochondrial function. Additionally, exercise training can regulate multiple factors for improving the pathophysiology of PD, such as Sirt1, uch-11, Hsp70, DJ-1, BDNF, GDNF, Nrf2, and γGCLC.

for increasing walking function is not better than equal intensity treadmill training in mild to moderate PD patients [116]. Because of these contradictory results, Kang et al. conducted a randomised controlled trial to investigate whether RAGT training should be recommended instead of treadmill training for gait functional training in PD patients [46]. This research will end in December 2019 and show the impact of RAGT on gait automaticity, gait speed, fall risk, balance function, disease severity and quality of life [46]. The study will also provide new insights into the mechanism of RAGT by assessing changes in the brain's functional networks and gait automaticity [46]. In a word, RAGT is an effective therapy programme for improving gait dysfunctions in PD patients, but its therapeutic efficacy compared with treadmill training needs to be studied further.

3.2.2.4. Virtual reality. Virtual reality (VR) is an adjust to the physical exercise that provides visual, somatosensory and auditory stimulation to improve the gait function of PD patients [117]. VR can provide real-time multiple sensory interactions by offering different virtual environments of real and daily life tasks to promote task changes and enhance motivation and motor learning ability in the process of rehabilitation therapy [118,119]. To obtain a natural and immersive experience, simulations are typically generated via a head-mounted display (HMD), for instance, the HTC VIVE® [120]. VR can provide dual-tasking training and require patients to conduct attention transfer, information processing, sensory integration and motion planning together [121,122]. A systematic review demonstrated that VR dual-task gait therapy should be used in the rehabilitation programmes for PD patients [123]. Indeed, all studies showed that VR training was effective in improving the gait function of PD patients [123]. Compared with traditional physical therapy, a 12-week VR training programme led to more significant progress in the gait and balance of PD patients [117]. Furthermore, a review reported that short-term VR training has positive effects on step and stride length in individuals with PD, but the evidence is low quality [124]. In summary, VR technology can simulate different virtual environments in real life, improving gait disorder and functional independence in PD patients.

3.2.3. Balance training

In general, balance training is an exercise that challenges a person to control the center of gravity of the body during destabilizing movements and/or reduces the size of a person's support base [125]. Shen et al. reported that balance and gait training has positive effects on improving balance and gait function in PD patients and reduce their short- and long-terms fall rates [126]. They also suggested that balance and gait training in the facility may help improve the effectiveness of training [126]. Besides, a meta-analysis showed that highly challenging balance training had a greater impact on the performance of balance-related activities than interventions that did not, or whose content of balance training was unclear [125]. In addition, Wong et al. demonstrated that multi-dimensional outdoor and indoor balance training can improve balance function and dual-task gait performance in PD patients at 12-month follow-up [127]. Further, it has been indicated that balance training could improve posture control in PD patients via improving sensory integration, especially when patients were lack of sensory redundancy [128].

HiBalance is a progressive and highly challenging training programme aimed at treating balance control dysfunction in mild to moderate PD patients [129]. Compared with general care, HiBalance has been show to markedly improve gait and balance function [130]. As for the long-term effects of HiBalance, it was reported that the training benefits decreased within six months following the intervention, indicating that regular repetition of the therapy may be required to maintain the therapeutic effect of HiBalance [131]. Therefore, HiBalance can significantly improve a PD patient's balance disorder, but it requires regular repetition.

Besides, more intensive training via computer games (exercise + games = exergames) has been used for balance training and motor rehabilitation in PD patients [132]. Exergames designed specifically for PD deficits may help increase player motivation, enjoyment and efficiency [133]. The advantage of exergames is their ability to combine cognition therapy and motor training through the application of video games; in these games, PD patients need to perform cognitive exercises while conducting physical movements, which could generate a better therapeutic effect than monotherapy [63]. The reason why simultaneous training of cognition and motor function could exert better effects is because the combination training of both the motor and cognitive aspects is suited for coping with the dual-tasking required in the changing situations of everyday life [58]. Moreover, the wide range of auditory and visual stimuli induced by exergames may act as external cues, minimising motor deficits caused by internal cues because of dopamine depletion [134]. In 2014, a systematic review demonstrated that exergames could improve the motor dysfunctions of PD patients, but there is still little evidence of its safety and clinical effectiveness [133]. Compared with traditional balance therapy, the balance-based exergames training using an XBOX Kinect sensor caused a larger improvement in the posture stability in PD patients [135]. Using the Wii Fit with balance board – a home-based balance programme – also increases the dynamic and static balance, mobility and functional abilities in PD individuals [136]. Furthermore, Wii Fit games can improve motor and cognitive skills, such as weight transfer, symmetric foot stepping, controlling movement around stability limit, memory, attention and decision making [137,138]. In recent years, new exergames systems without the need for a raised platform have emerged, such as the XBOX Kinect,™ which may improve patient safety [133].

In summary, various kinds of balance training is beneficial for improving the balance function and gait performance in PD patients.

3.2.4. *Progressive resistance training*

Progressive resistance training (PRT) is a form of exercise training that includes repetitious movement in a small number until fatigue, allowing adequate rest between repetitions to recover, and increasing additional resistance as the capacity to produce muscle strength increases [139]. It was reported that PRT could exert positive effects on muscle strength, motor function and endurance in PD patients [34,140]. In 2013, Corcos et al. performed a large randomised controlled study to investigate the effects of two-year whole-body PRT without medication in 38 PD patients; this study demonstrated the clinically and statistically significant benefits in unified Parkinson's disease rating scale (UPDRS) scores, indicating that PRT is an effective treatment for improving PD motor symptoms [141]. In addition, resistance training is considered an adjunctive therapy for improving sleep quality in patients with moderate PD [142]. In another study, PRT showed improvement in cardiovascular autonomic dysfunction in PD patients [143]. Additionally, incorporating other functional practices, for example, balance training, into PRT can reduce the risk of falls and postural instability, improving the quality of life of PD patients [144]. Moreover, high-intensity resistance exercise can be safely performed by PD patients, increasing muscle strength, reducing bradykinesia and improving quality of life and walking velocity [145]. However, a systematic review and meta-analysis demonstrated that there was no evidence that PRT was superior to other therapies or to usual activities in the recovery of idiopathic PD [139]. Taken together, these results suggest that PRT has beneficial effects when it comes to improving motor symptoms, sleep dysfunctions and quality of life, especially the muscle strength, of PD patients.

3.2.5. *Complementary exercise*

3.2.5.1. Tango. As a therapeutic method for PD, Tango consists of self-generated and external prompted strategies, as well as music, leading to emotional and social recovery for patients with PD [146]. During the process of Tango training, each participant needs to pay enough attention to his/her own partner's every movement, stepping strategy, and general-body coordination [147]. Tango may improve spatial cognition in PD patients because patients need to remember simple paths and spatial postures in the process of dance learning, and this will be stored, remembered and used again to strengthen cognitive ability [148]. A Bayesian network meta-analysis showed that Tango was the most effective choice for increasing functional mobility in people with PD compared with dance, Qigong, resistance training, Tai Chi and Yoga [149]. A qualitative study on adapted Tango training in 16 PD patients indicated that Tango, when in a structured environment with professional instruction, could improve the activities of daily life and the quality of life for the participants [150]. In addition, Tango can also improve one's sense of body self-efficacy, well-being and outcome expectations [151]. Further, a randomised controlled trial reported that the effect of a 10-week Tango training on emotional health was greater than Tai Chi [152]. Taken together, Tango can effectively improve emotional disorders, cognitive impairment and functional mobility ability for PD patients.

3.2.5.2. Qigong. Qigong is a conventional Chinese exercise that integrates meditation, mental adjustment and breathing patterns [153]. Originating from conventional Chinese medicine, Qigong controls the movement of Qi via the meridian system of the human body [154]. There are many types of Qigong, such as Baduanjin, Wuqinxi, Liuzijue and Yijinjing. The movements of Qigong consist of closed-chain movement of the lower extremities, which are helpful to correct the deficiency of knee extension and heel stride in the process of gait cycle [155,156]. Qigong can result in positive effects on muscle hardness, timed ‘up and go’, balance and hand-eye coordinative ability, which makes Qigong an effective rehabilitation therapy for PD patients [155]. A systematic review and meta-analysis implied that practising Qigong can result in improvements of posture control and balance and decrease the risk of falls in PD patients [157]. Moreover, Baduanjin, a type of Qigong, showed an improvement in the functional mobility, gait outcome and sleep quality of PD patients during a six-month follow-up, indicating that this kind of Qigong is a suitable family practice programme for the elderly PD patients [158]. In summary, Qigong can play a crucial role in alleviating balance dysfunction, sleep disorder and gait impairment.

3.2.5.3. Tai Chi. Tai Chi is composed of a variety of dance-like movements that are linked together in a continuous sequence, moving smoothly and slowly from one movement to the next, emphasising a shift in weight and body movement, which provides benefits for flexibility, posture, well-being, relaxation and mental concentration [159,160]. Mild or moderate PD patients who received Tai Chi and who focused on a multidirectional shift from bilateral to unilateral weights to improve balance capability saw an improvement in dynamic postural stability in PD [161]. Tai Chi training for 16 weeks in patients with PD improved psychological well-being and cognitive function [162]. In addition, a randomised controlled pilot trial showed that group-based Tai Chi training resulted in a greater positive impact on global nonmotor and sleep disorders, which is regarded as a beneficial and labour-saving treatment in clinical settings; PD patients tend to have higher compliance rates in home treatment [163]. In summary, Tai Chi is a very promising therapeutic method for improving balance, cognitive and sleep disorders for PD patients.

3.2.5.4. Yoga. Yoga, which originated in ancient India, is a collection of mental and physical movements [164]. Through a series of mindfulness exercises using breathing exercises, posture and meditation, Yoga practitioners can raise and maintain cognition and attention to the mind, body and present moment [165]. Yoga consists of stretching and lengthening the body postures that activate the stretch receptors in muscles, ligaments and joints and that the stretches the major muscle groups, thus improving body flexibility and strength [166,167]. Following mindfulness Yoga exercises, participants can redefine the sensations of pain, difficulty or disability, thereby enhancing one's acceptance of continued functioning and disability beyond fragile conditions and physical limitations [165]. Additionally, Yoga can integrate the body and mind, and markedly increase the overall balance ability of people with balance dysfunction [168,169]. A series of studies demonstrated that Yoga can improve balance, relaxation, agility, physical alignment, strength, flexibility, mental and emotional health, endurance and general well-being [166,167,170]. Corjena et al. investigated the effects of Hatha Yoga for 12 weeks in PD patients, and they concluded that Yoga is feasible and can be used as a complementary treatment to improve motor performance [171]. Therefore, PD patients can effectively improve their psychological and balance disorders through Yoga training.

4. Conclusion

Overall, various types of exercise therapy have been reported as having therapeutic effects on motor disorders and nonmotor disorders in patients with PD. Among the different kinds of exercise interventions, aerobic exercise is the most widely studied treatment and has positive effects on motor, quality of life, cognition and emotion. In addition, some new types of techniques have been used in the treatment of PD. For instance, VR technology provides patients with visual, auditory and somatosensory stimulation for dual-tasking training to improve the symptoms of the patients.

Furthermore, personalised exercise therapy programmes need to be provided for patients with dysfunction while considering patient safety. Additionally, larger scale clinical research and more rigorous experiments are needed to confirm the effects of exercise therapy on PD patients and further explore the exercise therapy–related mechanisms to carry forward the exercise therapy for PD.

Declaration of competing interest

The authors declare no conflicts of interest.

References

[1] J.T. Greenamyre, T.G. Hastings, Biomedicine. Parkinson's–divergent causes, convergent mechanisms, Science (New York, N.Y.) 304 (2004) 1120–1122.
[2] E. Sidransky, et al., Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease, N. Engl. J. Med. 361 (2009) 1651–1661.
[3] D. Berg, et al., Type and frequency of mutations in the LRRK2 gene in familial and sporadic Parkinson's disease, Brain: a journal of neurology 128 (2005) 3000–3011.
[4] K. Kalinderi, S. Bostantjopoulou, L. Fidani, The genetic background of Parkinson's disease: current progress and future prospects, Acta Neurol. Scand. 134 (2016) 314–326.
[5] J. Aaseth, P. Dusek, P.M. Roos, Prevention of progression in Parkinson's disease, Biometals 31 (2018) 737–747.
[6] F. Fang, et al., Head injury and Parkinson's disease: a population-based study, Movement disorders: official journal of the Movement Disorder Society 27 (2012) 1632–1635.
[7] F. Fang, et al., CNS infections, sepsis and risk of Parkinson's disease, Int. J. Epidemiol. 41 (2012) 1042–1049.
[8] C.M. Tanner, et al., Rotenone, paraquat, and Parkinson's disease, Environ. Health Perspect. 119 (2011) 866–872.
[9] L.V. Kalia, A.E. Lang, Parkinson's disease, Lancet (London, England) 386 (2015) 896–912.
[10] J.J. Annesi, Effects of a group protocol on physical activity and associated changes in mood and health locus of control in adults with Parkinson disease and reduced mobility, Perm J 23 (2019) 18–128.
[11] K. Wirdefeldt, H.O. Adami, P. Cole, D. Trichopoulos, J. Mandel, Epidemiology and etiology of Parkinson's disease: a review of the evidence, Eur. J. Epidemiol. 26 (Suppl. 1) (2011) S1–58.
[12] E.L. McGough, et al., A tandem cycling program: feasibility and physical performance outcomes in people with Parkinson disease, Journal of Neurologic Physical Therapy: JNPT 40 (2016) 223–229.
[13] S. Moon, et al., Effects of qigong exercise on non-motor symptoms and inflammatory status in Parkinson's disease: a protocol for a randomized controlled trial, Medicines (Basel) 6 (2019) 13.
[14] A. Oliveira de Carvalho, et al., Physical exercise for Parkinson's disease: clinical and experimental evidence, Clin. Pract. Epidemiol. Ment. Health 14 (2018) 89–98.
[15] J. Jankovic, Parkinson's disease: clinical features and diagnosis, J. Neurol. Neurosurg. Psychiatry 79 (2008) 368–376.
[16] Moon, S. et al., Effects of Qigong Exercise on Non-Motor Symptoms and Inflammatory Status in Parkinson's Disease: A Protocol for a Randomized Controlled Trial, Medicines (Basel) 6(2019).
[17] K.L. Sullivan, C.L. Ward, R.A. Hauser, T.A. Zesiewicz, Prevalence and treatment of non-motor symptoms in Parkinson's disease, Parkinsonism Relat. Disord. 13 (2007) 545.
[18] G.W. Duncan, et al., Health-related quality of life in early Parkinson's disease: the impact of nonmotor symptoms, Movement Disorders: Official Journal of the Movement Disorder Society 29 (2014) 195–202.
[19] D.A. Gallagher, A. Schrag, Psychosis, apathy, depression and anxiety in Parkinson's disease, Neurobiol. Dis. 46 (2012) 581–589.
[20] M.E. Morris, et al., Quantifying the profile and progression of impairments, activity, participation, and quality of life in people with Parkinson disease: protocol for a prospective cohort study, BMC Geriatr. 9 (2009) 2.
[21] A. Nadeau, et al., A 12-week cycling training regimen improves upper limb functions in people with Parkinson's disease, Front. Hum. Neurosci. 12 (2018) 351.
[22] S.H. Fox, et al., The Movement Disorder Society evidence-based medicine review update: treatments for the motor symptoms of Parkinson's disease, Movement Disorders: Official Journal of the Movement Disorder Society 26 (Suppl. 3) (2011) S2–41.
[23] B. Galna, S. Lord, D.J. Burn, L. Rochester, Progression of gait dysfunction in incident Parkinson's disease: impact of medication and phenotype, Movement Disorders: Official Journal of the Movement Disorder Society 30 (2015) 359–367.
[24] F.I. Tarazi, Z.T. Sahli, M. Wolny, S.A. Mousa, Emerging therapies for Parkinson's disease: from bench to bedside, Pharmacol. Ther. 144 (2014) 123–133.
[25] E.K. Crowley, Y.M. Nolan, A.M. Sullivan, Exercise as a therapeutic intervention for motor and non-motor symptoms in Parkinson's disease: evidence from rodent models, Prog. Neurobiol. 172 (2019) 2–22.
[26] N.M. van der Kolk, L.A. King, Effects of exercise on mobility in people with Parkinson's disease, Movement Disorders: Official Journal of the Movement Disorder Society 28 (2013) 1587–1596.
[27] A.J. Sasco, R.S. Paffenbarger Jr., I. Gendre, A.L. Wing, The role of physical exercise in the occurrence of Parkinson's disease, Arch. Neurol. 49 (1992) 360–365.
[28] Q. Xu, et al., Physical activities and future risk of Parkinson disease, Neurology 75 (2010) 341–348.
[29] F. Yang, et al., Physical activity and risk of Parkinson's disease in the Swedish National March Cohort, Brain: a journal of neurology 138 (2015) 269–275.
[30] Y.S. Lau, G. Patki, K. Das-Panja, W.D. Le, S.O. Ahmad, Neuroprotective effects and mechanisms of exercise in a chronic mouse model of Parkinson's disease with moderate neurodegeneration, Eur. J. Neurosci. 33 (2011) 1264–1274.
[31] V.A. Goodwin, S.H. Richards, R.S. Taylor, A.H. Taylor, J.L. Campbell, The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis, Movement Disorders: Official Journal of the Movement Disorder Society 23 (2008) 631–640.
[32] L.E. Dibble, O. Addison, E. Papa, The effects of exercise on balance in persons with Parkinson's disease: a systematic review across the disability spectrum, Journal of Neurologic Physical Therapy: JNPT 33 (2009) 14–26.
[33] M. Nallegowda, et al., Role of sensory input and muscle strength in maintenance of balance, gait, and posture in Parkinson's disease: a pilot study, American journal of physical medicine & rehabilitation 83 (2004) 898–908.
[34] L.O. Lima, A. Scianni, F. Rodrigues-de-Paula, Progressive resistance exercise improves strength and physical performance in people with mild to moderate Parkinson's disease: a systematic review, J. Phys. 59 (2013) 7–13.
[35] B. Leavy, L. Kwak, M. Hagstromer, E. Franzen, Evaluation and implementation of highly challenging balance training in clinical practice for people with Parkinson's disease: protocol for the HiBalance effectiveness-implementation trial, BMC

Neurol. 17 (2017) 27.
[36] S.D. Kim, N.E. Allen, C.G. Canning, V.S. Fung, Postural instability in patients with Parkinson's disease. Epidemiology, pathophysiology and management, CNS Drugs 27 (2013) 97–112.
[37] J. Konczak, et al., Proprioception and motor control in Parkinson's disease, J. Mot. Behav. 41 (2009) 543–552.
[38] N.E. Allen, A.K. Schwarzel, C.G. Canning, Recurrent falls in Parkinson's disease: a systematic review, Parkinson's Disease 2013 (2013) 906274.
[39] T.A. Boonstra, H. van der Kooij, M. Munneke, B.R. Bloem, Gait disorders and balance disturbances in Parkinson's disease: clinical update and pathophysiology, Curr. Opin. Neurol. 21 (2008) 461–471.
[40] A. Fasano, C.G. Canning, J.M. Hausdorff, S. Lord, L. Rochester, Falls in Parkinson's disease: a complex and evolving picture, Movement Disorders: Official Journal of the Movement Disorder Society 32 (2017) 1524–1536.
[41] C.G. Canning, S.S. Paul, A. Nieuwboer, Prevention of falls in Parkinson's disease: a review of fall risk factors and the role of physical interventions, Neurodegenerative Disease Management 4 (2014) 203–221.
[42] M.S. Bryant, D.H. Rintala, J.G. Hou, E.J. Protas, Relationship of falls and fear of falling to activity limitations and physical inactivity in Parkinson's disease, J. Aging Phys. Act. 23 (2015) 187–193.
[43] H. Nero, E. Franzen, A. Stahle, M. Benka Wallen, M. Hagstromer, Long-term effects of balance training on habitual physical activity in older adults with Parkinson's disease, Parkinson's Disease 2019 (2019) 8769141.
[44] P.S. Myers, M.E. McNeely, K.A. Pickett, R.P. Duncan, G.M. Earhart, Effects of exercise on gait and motor imagery in people with Parkinson disease and freezing of gait, Parkinsonism Relat. Disord. 53 (2018) 89–95.
[45] C.G. Canning, L. Ada, J.J. Johnson, S. McWhirter, Walking capacity in mild to moderate Parkinson's disease, Arch. Phys. Med. Rehabil. 87 (2006) 371–375.
[46] M.G. Kang, et al., Effects of robot-assisted gait training in patients with Parkinson's disease: study protocol for a randomized controlled trial, Trials 20 (2019) 15.
[47] R.A. Poldrack, et al., The neural correlates of motor skill automaticity, J. Neurosci. 25 (2005) 5356–5364.
[48] P. Redgrave, et al., Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease, Nat. Rev. Neurosci. 11 (2010) 760–772.
[49] E. Heremans, A. Nieuwboer, S. Vercruysse, Freezing of gait in Parkinson's disease: where are we now? Current neurology and neuroscience reports 13 (2013) 350.
[50] N. Giladi, F.B. Horak, J.M. Hausdorff, Classification of gait disturbances: distinguishing between continuous and episodic changes, Movement Disorders: Official Journal of the Movement Disorder Society 28 (2013) 1469–1473.
[51] A.C. Lo, et al., Reduction of freezing of gait in Parkinson's disease by repetitive robot-assisted treadmill training: a pilot study, J Neuroeng Rehabil 7 (2010) 51.
[52] J.D. Schaafsma, et al., Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease, Eur. J. Neurol. 10 (2003) 391–398.
[53] M. Plotnik, J.M. Hausdorff, The role of gait rhythmicity and bilateral coordination of stepping in the pathophysiology of freezing of gait in Parkinson's disease, Movement Disorders: Official Journal of the Movement Disorder Society 23 (Suppl. 2) (2008) S444–S450.
[54] O. Moore, C. Peretz, N. Giladi, Freezing of gait affects quality of life of peoples with Parkinson's disease beyond its relationships with mobility and gait, Movement disorders: official journal of the Movement Disorder Society 22 (2007) 2192–2195.
[55] E. Elgh, et al., Cognitive function in early Parkinson's disease: a population-based study, Eur. J. Neurol. 16 (2009) 1278–1284.
[56] E. Mamikonyan, et al., Mild cognitive impairment is common in Parkinson's disease patients with normal mini-mental state examination (MMSE) scores, Parkinsonism Relat. Disord. 15 (2009) 226–231.
[57] J. Spildooren, et al., Freezing of gait in Parkinson's disease: the impact of dual-tasking and turning, Movement disorders: official journal of the Movement Disorder Society 25 (2010) 2563–2570.
[58] E. Schaeffer, et al., Effects of exergaming on attentional deficits and dual-tasking in Parkinson's disease, Front. Neurol. 10 (2019) 646.
[59] S. Heinzel, et al., Motor dual-tasking deficits predict falls in Parkinson's disease: a prospective study, Parkinsonism Relat. Disord. 26 (2016) 73–77.
[60] A.A. Moustafa, et al., Interrelations between cognitive dysfunction and motor symptoms of Parkinson's disease: behavioral and neural studies, Rev. Neurosci. 27 (2016) 535–548.
[61] A. Price, J.C. Shin, The impact of Parkinson's disease on sequence learning: perceptual pattern learning and executive function, Brain Cogn. 69 (2009) 252–261.
[62] M. Poletti, et al., Mild cognitive impairment and cognitive-motor relationships in newly diagnosed drug-naive patients with Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 83 (2012) 601–606.
[63] A. Garcia-Agundez, et al., Recent advances in rehabilitation for Parkinson's disease with Exergames: a systematic review, J Neuroeng Rehabil 16 (2019) 17.
[64] M. Olson, T.E. Lockhart, A. Lieberman, Motor learning deficits in Parkinson's disease (PD) and their effect on training response in gait and balance: a narrative review, Front. Neurol. 10 (2019) 62.
[65] G. Vervoort, et al., Dual-task-related neural connectivity changes in patients with Parkinson' disease, Neuroscience 317 (2016) 36–46.
[66] T. Wu, M. Hallett, Neural correlates of dual task performance in patients with Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 79 (2008) 760–766.
[67] I. Maidan, H. Bernad-Elazari, N. Giladi, J.M. Hausdorff, A. Mirelman, When is higher level cognitive control needed for locomotor tasks among patients with Parkinson's disease? Brain Topogr. 30 (2017) 531–538.
[68] P.T. Francis, E.K. Perry, Cholinergic and other neurotransmitter mechanisms in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies, Movement Disorders: Official Journal of the Movement Disorder Society 22 (Suppl. 17) (2007) S351–S357.
[69] L. Brichta, P. Greengard, M. Flajolet, Advances in the pharmacological treatment of Parkinson's disease: targeting neurotransmitter systems, Trends Neurosci. 36 (2013) 543–554.
[70] P. Calabresi, B. Picconi, L. Parnetti, M. Di Filippo, A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine-acetylcholine synaptic balance, The Lancet. Neurology 5 (2006) 974–983.
[71] Smith, P. F., Inflammation in Parkinson's disease: an update, Current opinion in investigational drugs (London, England: 2000) 9(2008) 478–484.
[72] M. Reale, et al., Peripheral cytokines profile in Parkinson's disease, Brain Behav. Immun. 23 (2009) 55–63.
[73] A. AlDakheel, L.V. Kalia, A.E. Lang, Pathogenesis-targeted, disease-modifying therapies in Parkinson disease, Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics 11 (2014) 6–23.
[74] D.B. Schenk, et al., First-in-human assessment of PRX002, an anti-alpha-synuclein monoclonal antibody, In Healthy Volunteers, Movement Disorders: Official Journal of the Movement Disorder Society 32 (2017) 211–218.
[75] M.J. Zigmond, et al., Triggering endogenous neuroprotective processes through exercise in models of dopamine deficiency, Parkinsonism Relat. Disord. 15 (Suppl. 3) (2009) S42–S45.
[76] N. Tajiri, et al., Exercise exerts neuroprotective effects on Parkinson's disease model of rats, Brain Res. 1310 (2010) 200–207.
[77] W. Zhou, J.C. Barkow, C.R. Freed, Running wheel exercise reduces α-synuclein aggregation and improves motor and cognitive function in a transgenic mouse model of Parkinson's disease, PLoS One 12 (2017) e0190160.
[78] Tuon, T. et al., Physical Training Regulates Mitochondrial Parameters and Neuroinflammatory Mechanisms in an Experimental Model of Parkinson's Disease, Oxid Med Cell Longev 2015(2015) 261809.
[79] Y.H. Tsou, et al., Treadmill exercise activates Nrf2 antioxidant system to protect the nigrostriatal dopaminergic neurons from MPP+ toxicity, Exp. Neurol. 263 (2015) 50–62.
[80] C. Shah, et al., Exercise therapy for Parkinson's disease: pedaling rate is related to changes in motor connectivity, Brain Connectivity 6 (2016) 25–36.
[81] B.E. Fisher, et al., Treadmill exercise elevates striatal dopamine D2 receptor binding potential in patients with early Parkinson's disease, Neuroreport 24 (2013) 509–514.
[82] J.E. VanLeeuwen, et al., Altered AMPA receptor expression with treadmill exercise in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury, J. Neurosci. Res. 88 (2010) 650–668.
[83] M.S. Shin, T.W. Kim, J.M. Lee, E.S. Ji, B.V. Lim, Treadmill exercise alleviates nigrostriatal dopaminergic loss of neurons and fibers in rotenone-induced Parkinson rats, Journal of Exercise Rehabilitation 13 (2017) 30–35.
[84] P. Chen, X. Li, Study on effect of striatal mGluR2/3 in alleviating motor dysfunction in rat PD model treated by exercise therapy, Front. Aging Neurosci. 11 (2019) 255.
[85] T. Tuon, et al., Physical training exerts neuroprotective effects in the regulation of neurochemical factors in an animal model of Parkinson's disease, Neuroscience 227 (2012) 305–312.
[86] M. Taubert, A. Villringer, N. Lehmann, Endurance exercise as an "endogenous" neuro-enhancement strategy to facilitate motor learning, Front. Hum. Neurosci. 9 (2015) 692.
[87] B.E. Fisher, 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 (2008) 1221–1229.
[88] J.-M. Lee, et al., Treadmill exercise improves motor function by suppressing Purkinje cell loss in Parkinson disease rats, Int Neurourol J 22 (2018) S147–S155.
[89] Y.C. Jang, et al., Association of exercise-induced autophagy upregulation and apoptosis suppression with neuroprotection against pharmacologically induced Parkinson's disease, J Exerc Nutrition Biochem 22 (2018) 1–8.
[90] Liu, W. et al., MicroRNA Expression Profiling Screen miR-3557/324-Targeted CaMK/mTOR in the Rat Striatum of Parkinson's Disease in Regular Aerobic Exercise, BioMed research international 2019(2019) 7654798.
[91] Voss, M. W., Nagamatsu, L. S., Liu-Ambrose, T. & Kramer, A. F., Exercise, brain, and cognition across the life span, Journal of applied physiology (Bethesda, Md.: 1985) 111(2011) 1505–1513.
[92] C. Duchesne, et al., Enhancing both motor and cognitive functioning in Parkinson's disease: aerobic exercise as a rehabilitative intervention, Brain Cogn. 99 (2015) 68–77.
[93] M. Uygur, M. Bellumori, C.A. Knight, Effects of a low-resistance, interval bicycling intervention in Parkinson's disease, Physiother Theory Pract 33 (2017) 897–904.
[94] P.L. Wu, M. Lee, T.T. Huang, Effectiveness of physical activity on patients with depression and Parkinson's disease: a systematic review, PLoS One 12 (2017) e0181515.
[95] A.H. Snijders, I. Toni, E. Ruzicka, B.R. Bloem, Bicycling breaks the ice for freezers of gait, Movement Disorders: Official Journal of the Movement Disorder Society 26 (2011) 367–371.
[96] A. Nadeau, et al., A 12-week cycling training regimen improves gait and executive functions concomitantly in people with Parkinson's disease, Front. Hum. Neurosci. 10 (2016) 690.
[97] C.M. Fiorelli, et al., Differential acute effect of high-intensity interval or continuous moderate exercise on cognition in individuals with Parkinson's disease, J. Phys. Act. Health 16 (2019) 157–164.
[98] C. Duchesne, et al., Influence of aerobic exercise training on the neural correlates of motor learning in Parkinson's disease individuals, Neuroimage Clin 12 (2016) 559–569.

[99] S. Steib, et al., A single bout of aerobic exercise improves motor skill consolidation in Parkinson's disease, Front. Aging Neurosci. 10 (2018) 328.
[100] A.B. Rosenfeldt, T. Dey, J.L. Alberts, Aerobic exercise preserves olfaction function in individuals with Parkinson's disease, Parkinson's Disease 2016 (2016) 9725089.
[101] Z. Wang, Y. Guo, K.G. Myers, R. Heintz, D.P. Holschneider, Recruitment of the prefrontal cortex and cerebellum in Parkinsonian rats following skilled aerobic exercise, Neurobiol. Dis. 77 (2015) 71–87.
[102] Mehrholz, J. et al., Treadmill training for patients with Parkinson's disease, The Cochrane database of systematic reviews(2010) Cd007830.
[103] T. Herman, N. Giladi, J.M. Hausdorff, Treadmill training for the treatment of gait disturbances in people with Parkinson's disease: a mini-review, Journal of Neural Transmission (Vienna, Austria: 1996) 116 (2009) 307–318.
[104] J. Mehrholz, et al., Treadmill training for patients with Parkinson disease. An abridged version of a Cochrane review, European Journal of Physical and Rehabilitation Medicine 52 (2016) 704–713.
[105] H. Gassner, et al., Perturbation treadmill training improves clinical characteristics of gait and balance in Parkinson's disease, J. Park. Dis. 9 (2019) 413–426.
[106] G.M. Earhart, M. Hong, Kinematics of podokinetic after-rotation: similarities to voluntary turning and potential clinical implications, Brain Res. Bull. 70 (2006) 15–21.
[107] F.Y. Cheng, et al., Positive effects of specific exercise and novel turning-based treadmill training on turning performance in individuals with Parkinson's disease: a randomized controlled trial, Sci. Rep. 6 (2016) 33242.
[108] E. Berra, et al., Body weight support combined with treadmill in the rehabilitation of Parkinsonian gait: a review of literature and new data from a controlled study, Front. Neurol. 9 (2018) 1066.
[109] Mehrholz, J., Pohl, M. & Elsner, B., Treadmill training and body weight support for walking after stroke, The Cochrane database of systematic reviews(2014) Cd002840.
[110] T. Toole, C.G. Maitland, E. Warren, M.F. Hubmann, L. Panton, The effects of loading and unloading treadmill walking on balance, gait, fall risk, and daily function in Parkinsonism, NeuroRehabilitation 20 (2005) 307–322.
[111] M. Ganesan, T.N. Sathyaprabha, A. Gupta, P.K. Pal, Effect of partial weight-supported treadmill gait training on balance in patients with Parkinson disease, PM & R: The Journal of Injury, Function, and Rehabilitation 6 (2014) 22–33.
[112] I. Miyai, et al., Treadmill training with body weight support: its effect on Parkinson's disease, Arch. Phys. Med. Rehabil. 81 (2000) 849–852.
[113] P. Sale, et al., Robot-assisted walking training for individuals with Parkinson's disease: a pilot randomized controlled trial, BMC Neurol. 13 (2013) 50.
[114] K. Ustinova, L. Chernikova, A. Bilimenko, A. Telenkov, N. Epstein, Effect of robotic locomotor training in an individual with Parkinson's disease: a case report, Disability and rehabilitation. Assistive technology 6 (2011) 77–85.
[115] M. Galli, et al., Robot-assisted gait training versus treadmill training in patients with Parkinson's disease: a kinematic evaluation with gait profile score, Funct. Neurol. 31 (2016) 163–170.
[116] A. Picelli, 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 (2013) 605–610.
[117] H. Feng, et al., Virtual reality rehabilitation versus conventional physical therapy for improving balance and gait in Parkinson's disease patients: a randomized controlled trial, Medical Science Monitor: International Medical Journal of Experimental and Clinical Research 25 (2019) 4186–4192.
[118] E.A. Keshner, J. Fung, The quest to apply VR technology to rehabilitation: tribulations and treasures, Journal of Vestibular Research: Equilibrium & Orientation 27 (2017) 1–5.
[119] M.F. Levin, P.L. Weiss, E.A. Keshner, Emergence of virtual reality as a tool for upper limb rehabilitation: incorporation of motor control and motor learning principles, Phys. Ther. 95 (2015) 415–425.
[120] O. Janeh, et al., Gait training in virtual reality: short-term effects of different virtual manipulation techniques in Parkinson's disease, Cells 8 (2019) 419.
[121] M. van Diest, C.J. Lamoth, J. Stegenga, G.J. Verkerke, K. Postema, Exergaming for balance training of elderly: state of the art and future developments, J Neuroeng Rehabil 10 (2013) 101.
[122] A. Mirelman, I. Maidan, J.E. Deutsch, Virtual reality and motor imagery: promising tools for assessment and therapy in Parkinson's disease, Movement Disorders: Official Journal of the Movement Disorder Society 28 (2013) 1597–1608.
[123] F. Freitag, et al., Is virtual reality beneficial for dual-task gait training in patients with Parkinson's disease? A systematic review, Dement Neuropsychol 13 (2019) 259–267.
[124] Dockx, K. et al., Virtual reality for rehabilitation in Parkinson's disease, The Cochrane database of systematic reviews 12(2016) Cd010760.
[125] N.E. Allen, C. Sherrington, S.S. Paul, C.G. Canning, Balance and falls in Parkinson's disease: a meta-analysis of the effect of exercise and motor training, Movement Disorders: Official Journal of the Movement Disorder Society 26 (2011) 1605–1615.
[126] X. Shen, I.S. Wong-Yu, M.K. Mak, Effects of exercise on falls, balance, and gait ability in Parkinson's disease: a meta-analysis, Neurorehabil. Neural Repair 30 (2016) 512–527.
[127] I.S. Wong-Yu, M.K. Mak, Multi-dimensional balance training programme improves balance and gait performance in people with Parkinson's disease: a pragmatic randomized controlled trial with 12-month follow-up, Parkinsonism Relat. Disord. 21 (2015) 615–621.
[128] C.Y. Yen, et al., Effects of virtual reality-augmented balance training on sensory organization and attentional demand for postural control in people with Parkinson disease: a randomized controlled trial, Phys. Ther. 91 (2011) 862–874.
[129] D. Conradsson, N. Lofgren, A. Stahle, M. Hagstromer, E. Franzen, A novel conceptual framework for balance training in Parkinson's disease-study protocol for a randomised controlled trial, BMC Neurol. 12 (2012) 111.
[130] D. Conradsson, et al., The effects of highly challenging balance training in elderly with Parkinson's disease: a randomized controlled trial, Neurorehabil. Neural Repair 29 (2015) 827–836.
[131] M.B. Wallen, M. Hagstromer, D. Conradsson, K. Sorjonen, E. Franzen, Long-term effects of highly challenging balance training in Parkinson's disease-a randomized controlled trial, Clin. Rehabil. 32 (2018) 1520–1529.
[132] J.E. Pompeu, et al., Feasibility, safety and outcomes of playing Kinect Adventures! for people with Parkinson's disease: a pilot study, Physiotherapy 100 (2014) 162–168.
[133] G. Barry, B. Galna, L. Rochester, The role of exergaming in Parkinson's disease rehabilitation: a systematic review of the evidence, J Neuroeng Rehabil 11 (2014) 33.
[134] H.J. Griffin, et al., The effect of real and virtual visual cues on walking in Parkinson's disease, J. Neurol. 258 (2011) 991–1000.
[135] M.C. Shih, R.Y. Wang, S.J. Cheng, Y.R. Yang, Effects of a balance-based exergaming intervention using the Kinect sensor on posture stability in individuals with Parkinson's disease: a single-blinded randomized controlled trial, J Neuroeng Rehabil 13 (2016) 78.
[136] J.F. Esculier, J. Vaudrin, P. Beriault, K. Gagnon, L.E. Tremblay, Home-based balance training programme using Wii Fit with balance board for Parkinsons's disease: a pilot study, J. Rehabil. Med. 44 (2012) 144–150.
[137] N. Smania, et al., Effect of balance training on postural instability in patients with idiopathic Parkinson's disease, Neurorehabil. Neural Repair 24 (2010) 826–834.
[138] M. Plotnik, N. Giladi, Y. Dagan, J.M. Hausdorff, 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 (2011) 529–538.
[139] M. Saltychev, E. Barlund, J. Paltamaa, N. Katajapuu, K. Laimi, Progressive resistance training in Parkinson's disease: a systematic review and meta-analysis, BMJ Open 6 (2016) e008756.
[140] L.A. Brienesse, M.N. Emerson, Effects of resistance training for people with Parkinson's disease: a systematic review, J. Am. Med. Dir. Assoc. 14 (2013) 236–241.
[141] D.M. Corcos, et al., A two-year randomized controlled trial of progressive resistance exercise for Parkinson's disease, Movement Disorders: Official Journal of the Movement Disorder Society 28 (2013) 1230–1240.
[142] C. Silva-Batista, et al., Resistance training improves sleep quality in subjects with moderate Parkinson's disease, Journal of Strength and Conditioning Research 31 (2017) 2270–2277.
[143] H. Kanegusuku, et al., Effects of progressive resistance training on cardiovascular autonomic regulation in patients with Parkinson disease: a randomized controlled trial, Arch. Phys. Med. Rehabil. 98 (2017) 2134–2141.
[144] M.A. Hirsch, T. Toole, C.G. Maitland, R.A. Rider, The effects of balance training and high-intensity resistance training on persons with idiopathic Parkinson's disease, Arch. Phys. Med. Rehabil. 84 (2003) 1109–1117.
[145] L.E. Dibble, T.F. Hale, R.L. Marcus, J.P. Gerber, P.C. LaStayo, 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 (2009) 752–757.
[146] G. Albani, et al., Feasibility of home exercises to enhance the benefits of tango dancing in people with Parkinson's disease, Complementary therapies in medicine 42 (2019) 233–239.
[147] M.E. Hackney, G.M. Earhart, Effects of dance on balance and gait in severe Parkinson disease: a case study, Disabil. Rehabil. 32 (2010) 679–684.
[148] K.E. McKee, M.E. Hackney, The effects of adapted tango on spatial cognition and disease severity in Parkinson's disease, J. Mot. Behav. 45 (2013) 519–529.
[149] L. Tang, Y. Fang, J. Yin, The effects of exercise interventions on Parkinson's disease: a Bayesian network meta-analysis, J. Clin. Neuropsychol. 70 (2019) 47–54.
[150] W.M. Holmes, M.E. Hackney, Adapted tango for adults with Parkinson's disease: a qualitative study, Adapted Physical Activity Quarterly: APAQ 34 (2017) 256–275.
[151] S.C. Koch, et al., The embodied self in Parkinson's disease: feasibility of a single tango intervention for assessing changes in psychological health outcomes and aesthetic experience, Front. Neurosci. 10 (2016) 287.
[152] Poier, D., Rodrigues Recchia, D., Ostermann, T. & Bussing, A., A Randomized Controlled Trial to Investigate the Impact of Tango Argentino versus Tai Chi on Quality of Life in Patients with Parkinson Disease: A Short Report, Complementary medicine research(2019) 1–6.
[153] Li, Z. et al., Study protocol for a single-blind randomised controlled trial to evaluate the clinical effects of an Integrated Qigong exercise intervention on freezing of gait in Parkinson's disease, BMJ open 9(2019) e028869.
[154] H.W. Tsang, L. Cheung, D.C. Lak, Qigong as a psychosocial intervention for depressed elderly with chronic physical illnesses, International Journal of Geriatric Psychiatry 17 (2002) 1146–1154.
[155] X.L. Liu, S. Chen, Y. Wang, Effects of health qigong exercises on relieving symptoms of Parkinson's disease, Evidence-Based Complementary and Alternative Medicine: eCAM 2016 (2016) 5935782.
[156] Klein, P., Picard, G., Baumgarden, J. & Schneider, R., Meditative Movement, Energetic, and Physical analyses of three qigong exercises: unification of eastern and western mechanistic exercise theory, Medicines (Basel) 4(2017) 69.
[157] S. Chen, Y. Zhang, Y.T. Wang, X.L. Liu, Traditional Chinese mind and body exercises for promoting balance ability of old adults: a systematic review and meta-analysis, Evidence-Based Complementary and Alternative Medicine: eCAM 2016 (2016) 7137362.
[158] C.M. Xiao, Y.C. Zhuang, Effect of health Baduanjin Qigong for mild to moderate

Parkinson's disease, Geriatr Gerontol Int 16 (2016) 911–919.
[159] F. Li, et al., Tai Chi, self-efficacy, and physical function in the elderly, Prevention science: the official journal of the Society for Prevention Research 2 (2001) 229–239.
[160] F. Li, et al., Tai chi and postural stability in patients with Parkinson's disease, N. Engl. J. Med. 366 (2012) 511–519.
[161] H.D. Kim, H.D. Jae, J.H. Jeong, Tai Chi exercise can improve the obstacle negotiating ability of people with Parkinson's disease: a preliminary study, J. Phys. Ther. Sci. 26 (2014) 1025–1030.
[162] J.R. Nocera, S. Amano, S. Vallabhajosula, C.J. Hass, Tai Chi exercise to improve non-motor symptoms of Parkinson's disease, Journal of Yoga & Physical Therapy 3 (2013).
[163] Yang, J. H. et al., The Effects of Group-Based versus Individual-Based Tai Chi Training on Nonmotor Symptoms in Patients with Mild to Moderate Parkinson's Disease: A Randomized Controlled Pilot Trial, Parkinson's disease 2017(2017) 8562867.
[164] Duan-Porter, W. et al., Evidence map of yoga for depression, anxiety, and post-traumatic stress disorder, Journal of physical activity & health 13(2016) 281–288.
[165] J.Y.Y. Kwok, J.C.Y. Kwan, M. Auyeung, V.C.T. Mok, H.Y.L. Chan, The effects of yoga versus stretching and resistance training exercises on psychological distress for people with mild-to-moderate Parkinson's disease: study prxotocol for a randomized controlled trial, Trials 18 (2017) 509.
[166] F.M. Luskin, et al., A review of mind/body therapies in the treatment of musculoskeletal disorders with implications for the elderly, Altern. Ther. Health Med. 6 (2000) 46–56.
[167] M.D. Tran, R.G. Holly, J. Lashbrook, E.A. Amsterdam, Effects of hatha yoga practice on the health-related aspects of physical fitness, Prev. Cardiol. 4 (2001) 165–170.
[168] A.A. Schmid, M. Van Puymbroeck, D.M. Koceja, Effect of a 12-week yoga intervention on fear of falling and balance in older adults: a pilot study, Arch. Phys. Med. Rehabil. 91 (2010) 576–583.
[169] R. Garrett, M.A. Immink, S. Hillier, Becoming connected: the lived experience of yoga participation after stroke, Disabil. Rehabil. 33 (2011) 2404–2415.
[170] M. Van Puymbroeck, L.L. Payne, P.C. Hsieh, A phase I feasibility study of yoga on the physical health and coping of informal caregivers, Evidence-Based Complementary and Alternative Medicine: eCAM 4 (2007) 519–529.
[171] C. Cheung, et al., Effects of yoga on oxidative stress, motor function, and non-motor symptoms in Parkinson's disease: a pilot randomized controlled trial, Pilot Feasibility Stud 4 (2018) 162.