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Review Article

Molecular mechanisms of exercise-induced neuroprotection against Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disease that affects movement and cognitive function, resulting from the loss of the neurotransmitter dopamine due to the death of dopaminergic neurons. It affects nearly one million people in the United States and 8.5 million worldwide. While there are some pharmacological and surgical options available, they only provide symptomatic relief, as there is currently no cure for PD. In contrast, exercise training, a non-pharmacological intervention, has emerged as a powerful strategy to enhance the psychological, cognitive, and physiological (motor) impairments associated with PD. Given that the beneficial effects of exercise differ based on the intensity and type of training, gaining a thorough understanding of the molecular mechanisms underlying exercise-induced protection is crucial for developing innovative therapies that improve the quality of life for PD patients around the globe. This review discusses PD pathogenesis and pathophysiology and provides recent clinical evidence of neuroprotective benefits from various exercise modalities and intensity. Furthermore, the molecular mechanisms of exercise in PD pathogenesis (e.g., modulations on neurotrophic factors, oxidative stress, mitochondria dysfunction, endoplasmic reticulum stress, and autophagy) will be emphasized.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder caused by the loss of dopaminergic neurons, leading to movement impairment (e.g., resting tremor, muscle rigidity, bradykinesia, and postural instability).[1–3] PD is the second most common neurodegenerative disease, affecting 1%–3% of the population aged over 60 years worldwide,[4,5] with the occurrence increased in those over the age of 80.[1] The incidence of PD is 1.5–2 fold higher in men than women, and the age of disease onset also typically occurs earlier in men than women.[6,7]

Aside from motor function degeneration, cognitive impairment (e.g., executive function deficits, loss of memory capacity, visuospatial dysfunction, and attention problems) is also a significant feature of PD.[8–11] Dementia is a general term that describes a decline in cognitive function, which severely interferes with daily life, and a subset of PD patients develop PD-induced dementia (PDD) due to LD-induced death of cholinergic neurons in a region of the nucleus basalis of Meynert.[12–16] Approximately 27%, 50%, and 74% of PD patients develop PDD at 10, 15, and 20 years of disease duration, respectively, showing increases in its risk with disease duration.[17]

Currently, there is no cure for PD, but medications for motor impairment (e.g., levodopa/carbidopa, monoamine oxidase-B inhibitors, catechol-O-methyltransferase inhibitors, and anticholinergic medications) and surgical interventions (e.g., deep brain stimulation) help relieve PD symptoms.[18–20] However, long-term uses of these medications can cause a wearing-off effect after 5–10 years of use, and deep brain stimulation accompanies side effects such as cognitive decline.[18,20] For the treatment of PD-induced cognitive impairment, a cholinesterase inhibitor, which helps prevent the neurotransmitter

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Abbreviations

AIT	Aerobic interval training
BBS	Berg Balance Scale
BFR	Blood flow restriction
ER	Endoplasmic reticulum
fMRI	Functional magnetic resonance imaging
HIIT	High-intensity interval training
HRR	Heart rate reserve
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
METs	Metabolic equivalents
MICT	Moderate-intensity continuous training
PD	Parkinson's disease
PDD	Parkinson's disease-induced dementia
PDQ-39	Parkinson's Disease Questionnaire-39 items
RM	Repetition maximum
ROM	Range of motion
ROS	Reactive oxygen species
SRTE	Stretching resistance training exercises
TUG	Timed up and go test
TWM	Timed walking measure
T30	Timed 30-s chair stand test
UPDRS-III	Unified Parkinson's Disease Rating Scale-III
$\dot{V}O_2$	Oxygen uptake

acetylcholine essential for cognition and memory from being degraded, has been used; however, this medication has been reported to worsen tremors.[21]

Besides surgical interventions and medication options, physical exercises have emerged as potent therapeutic strategies for PD since exercise interventions confer broad, substantial benefits for motor (e.g., flexibility, balance, muscular strength, and gait) and non-motor (memory, attention, depression, anxiety, and apathy) symptoms by delaying the progression of PD, improving lesions from the PD pathologies, and restoring neurogenesis.[22,23] (See Tables 1, 2 and 3). However, despite preclinical and clinical evidence of the neuroprotective effects of exercise, the precise molecular mechanisms underlying these benefits are not yet fully understood. Furthermore, the efficacy and specific impact of different modes and intensities on protection against PD remain unclear. Therefore, this review will begin by providing an overview of PD (potential causes of PD) and clinical evidence of exercise-induced production and finish by illuminating its molecular mechanisms.

2. Mechanisms of voluntary movement and Dopamine's role

To better understand the characteristics of PD, it is important to know the basic interplays (thalamo-cortical-basal ganglia loop) in the brain between the thalamus, motor cortex, and basal ganglia, including the striatum (comprising the caudate nucleus and putamen), globus pallidus interna (GPi) and externa (GPe), substantia nigra pars compacta (SNc), substantia nigra pars reticulata (SNr), and subthalamic nucleus (STN) since they play a critical role in movement initiation, motor control, and cognitive function via two major neural pathways: the direct and indirect pathways. The direct pathway facilitates movement by activating the thalamus-motor cortex-spinal cord-peripheral motor

Table 1
The effect of low-intensity exercise on protection against PD.

Study	Participants	Type of Exercise	Intensity	Duration of Exercise Session	Duration of Training Protocol	Measured Outcomes
Khuzema et al., 2020	60–85 years old (male and female)	Aerobic Exercise: (Tai Chi, Yoga, Conventional balance)	11–15 (light to somewhat hard) on the Borg Rating of Perceived Exertion Scale.	Tai Chi exercise :30–40 min Yoga exercise :30–40 min Conventional balance exercise :40–45 min	5 days/week for 8 weeks	↑Balance (Berg balance scale scores) ↑Timed up and go time ↑10-m Walk test
Ni et al., 2016	60–90 years old	Aerobic Exercise: Yoga	Mild to moderate intensity	60 min/session	2 days/week for 12 weeks	↑Bradykinesia (Upper and lower limbs) ↑Rigidity ↑Strength (kg) ↑Power (Watts)
Rawson et al., 2019	(67.2 ± 8.9) years (42% female)	Aerobic Exercise (Tango, Treadmill, Stretching)	Tango: Basic steps Treadmill Stretching:Gentle stretching	60 min/session	2 days/week for 12 weeks	↑Forward velocity ↑Backward velocity
Gaβner et al., 2022	(60.5 ± 9.1) and (61.7 ± 8.1) (Male and Female)	Aerobic Exercise (Treadmill and Physiotherapy)	Walking speed scale of 4–6	25 min/session	14 days	↑Gait speed ↑Gait parameters ↑UPDRS-III, ↑BBS ↑Walking capacity
Kwok et al., 2019	(63.7 ± 8.7) years (Male)	Mindfulness yoga and Stretching Resistance Training Exercises (SRTE)	–	90 min/session 60 min/session	2 days/week for 8 weeks 1 day/week for 8 weeks	↑MDS-UPDRS ↑Part III motor score ↑Anxiety and Depression
Donahue wt al., 2022	(66.76 ± 8.60) (Male)	Physical activities	light and moderate intensity	62.63 min/day	Seven-day exercise	↑Cognitive function (memory capacity and verbal learning) ↑Visuospatial ability at moderate intensity

Abbreviation: UPDRS-III: Unified Parkinson's Disease Rating Scale-III, BBS: Berg Balance Scale, MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale.

Table 2
The effects of moderate to high-intensity aerobic and resistance exercise on protection against PD.

Study	Participants	Type of Exercise	Intensity	Duration of Exercise Session	Duration of Training Protocol	Measured Outcomes
Kathia et al., 2024	Female	High-intensity interval training (HIIT) moderate-intensity continuous training (MICT)	High intensity: 90% of peak (80%–99% of HRmax) Moderate intensity 60% of peak (55%–65% of HRmax)	10 sessions/day with 1 min intervals 30 min–50 min	3 days/week for 10 weeks	↑MDS UPDRS Part III motor scores ↑Fatigue levels
Fiorelli et al., 2019	53-81 (66.50) years (6 males and 6 females)	HIIT MICT	High intensity: 15–17 on the Borg Rating Low intensity: 11-13 on the Borg Rating	25 min of high-intensity intervals 30 min of high-intensity intervals	–	↑Superior cognitive improvements (e.g., auditory memory and attention) at HIIT
Marusiak et al., 2019	(72 ± 10) years (Male and Female)	Aerobic interval training (AIT)	High intensity (75% of their individualized HRmax)	60 min/session	8 weeks	↑Motor and cognitive function and ameliorates MDS-UPDRS scores ↑Rate of grip force development
Rose et al., 2013	53–75 years	Aerobic Exercise (High-intensive locomotor training)	High intensity (70%–80% of estimated heart rate capacity)	60 min/session	3 days/week for 8 weeks	↑MDS-UPDRS) ↑Parkinson's Disease ↑Questionnaire-39 items (PDQ-39) ↑Six-minute Walk test
van der Kolk et al., 2019	30–75 years	Aerobic Exercise (Home-based and remotely supervised aerobic exercise)	(50%–70% of HRR)	30–45 min/ session	3 days/week for 6 months	↑$\dot{V}O_2$ max, ↑MDS-UPDRS motor score ↑Quality of life
Jansen et al., 2021	40–75 years (Males and Females)	Aerobic Exercise (Stationary tandem bike exercise)	60%–80% HRR	40 min/session	3 days/week for 6 weeks	↑MDS-UPDRS Motor III ↑Motor function (grip strength and movement coordination capacity)
Johansson et al., 2022	58.9 (8.9) years	Aerobic Exercise	50%–80% HRR	30–45 min/ session	3 days/week for 6 months	↑Functional connectivity of the anterior putamen ↑Sensorimotor cortex ↑Restored cognitive function
Sacheli et al., 2019	45–80 years	Aerobic Exercise (stationary bike exercise)	80% of $\dot{V}O_2$ max	40–60 min/ session	3 days/week for 3 months	↑Dopamine release in the caudate ↑Dopaminergic activities in the ventral striatum
Fisher et al., 2008	(63.1 ± 11.5) years (61.5 ± 9.8) years (64.0 ± 14.5) years	Aerobic Exercise (Body weight-supported treadmill)	Low Intensity: ↓ 3.0 METs and ↓ 50% of HR High Intensity: ↑3.0 METs ↑ 75% of HR	45 min	3 days/week for 8 weeks	↑MDS-UPDRS Motor ↑Gait speed, step and stride length, and hip and ankle joint excursion at high intensity ↑Transcranial Magnetic Stimulation
Vieira de Moraes Filho et al., 2020	50–80 years: (64.7 ± 1.8) (Males and Females)	Resistance training (Chest press, knee extension, ham-strings curl, leg press, and seated row)	More than 12 repetitions	50–60 min with 2 sets of 10–12 repetitions	9 weeks	↑Functional tests (TUG, T30, and TWM) ↑Isokinetic muscle strength
Dashtipour et al., 2015	30–90 years	Resistance training (LSVT BIG therapy)	Borg scale of 4–5	60 min/session	4 days/week for 4 weeks	↑MDS-UPDRS motor scores ↑Non-motor function (Depression, anxiety, and fatigue)
David et al., 2015	50–67 years	Resistance training (PRET program)	–	–	2 days/week for 24 months	↑Cognitive outcomes (Digit span task, stroop test, and behavioral test of attention)
Ferreira et al., 2018	Over 60 years	Resistance training (bench press, deadlift, unilateral rowing, standing calf raise, and lower abdominal exercise)	8–12 submaximal repetitions	30–40 min/ session	3 days/week for 6 months	↑Anxiety symptoms and quality of life (cognition, communication, mobility ↑MDS-UPDRS (Emotional well-being) ↑Parkinson's disease questionnaire-39 (PDQ-39)
Marusiak et al., 2019	(29 ± 7) (Males and Females)	Resistance training (Heavy Load) Blood flow restriction	70% of predicted 1 RM 30% of predicted 1 RM	10 reps at 3 sets 10 reps at 4 sets	2 days/week for 8 weeks	↑10 RM strength ↑Isokinetic strength test (knee extension and flexion peak torque) ↑Muscle thickness and pennation angle & = fascicle length ↑Self-reported function ↑Y-balance performance ↑ROM
Douris et al., 2022	66 years	Blood flow restriction (BFR)	20%–30% of 1 RM	15 reps at 3 sets	3 days/week for 6 weeks	↑Muscular strength ↑Mitigated restless legs syndrome ↑Timed up and go test score (Less time)
Douris et al., 2018	65 years (males)	Blood flow restriction (Abe's BFR walk-training protocol)	Upper thigh BFR (120 mmHg–160 mmHg)	50 m/min	3 days/week for 6 weeks	↑Motor function (6-min walk test, timed up and go test, restless legs syndrome, 30-s chair stand test).

(*continued on next page*)

Table 2 (*continued*)

Study	Participants	Type of Exercise	Intensity	Duration of Exercise Session	Duration of Training Protocol	Measured Outcomes
Bane et al., 2024	Over 50 years (Males and Females)	Low-intensity RT with BFR (LIRT-BFR) :leg extensions, seated biceps curls, seated leg curls, seated triceps extensions, seated calf raises and seated handgrips	20% of 1 RM with 60% limb occlusion pressure	20 reps at 3 sets	3 days/week for 4 weeks	↑Orthostatic hypotension ↑Homocysteine levels↑ Peripheral circulation↑ Supine blood pressure ↑Heart rate variability ↑Endothelial function

Abbreviation: MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale, TUG: Timed Up and Go, TWM: Timed walking measure, T30: Timed 30-s chair stand test, ROM: range of motion.

division (autonomic and voluntary movement regulation) axis; in contrast, the indirect pathway undermines movement initiation to fine-tune or avoid unwanted movement.[24–26] A precise modulatory regulation of these two pathways is essential for executing proper movement. As illustrated in Fig. 1, under the direct pathway (blue), the motor cortex (glutamatergic neurons) excitation causes the striatum (GABAergic neurons) to be depolarized and release the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) to the GABAergic GPi and SNr. Since GPi and SNr typically inhibit thalamic activity by releasing GABA upon depolarization, the resultant hyperpolarization of GPi and SNr due to GABA from the striatum allows the thalamus to be disinhibited from the GPi and SNr and to excite the motor cortex to initiate movement execution. Conversely, under the indirect pathway (green), the motor cortex excitation induces the striatum to release GABA onto GPe, which leads to hyperpolarization of GPe. Given the fact that GPe depolarization-induced GABA release to STN inhibits its activity, the resultant hyperpolarization of GPe halts GABA release and allows STN to be disinhibited. Next, the activated STN (glutamatergic neurons) release excitatory neurotransmitter glutamate to excite GPi and SNr, which, upon excitation, release GABA onto the thalamus and suppress the thalamus's excitation input signal to the motor cortex for movement execution.

These two pathways have opposing effects, simultaneously facilitating and inhibiting voluntary movement. Thus, without the intricate reciprocal regulation between them, executing precise motor activities becomes challenging. In this regard, the neurotransmitter dopamine (DA) is crucial for synchronously fine-tuning these pathways. As depicted in Fig. 1, DA released from the substantia nigra pars compacta (SNc) excites the striatum through D1-like dopamine receptors (D1R) via excitatory G-protein-coupled receptors (eGPCRs) to enhance the direct pathway and D2-like receptors (D2R) via inhibitory iGPCRs to suppress the indirect pathway. Consequently, this DA action within the nigrostriatal system allows for the potentiation of thalamocortical activation, leading to smooth, coordinated movement. However, as portrayed in Fig. 1, the absence or deficiency of DA due to Parkinson's Disease (PD), characterized by the accumulation of abnormal α-synuclein (α-syn) aggregates known as Lewy bodies (LBs) in the SNc, results in the inhibition of the direct pathway and excessive activation of the indirect pathway. The resultant incoordination between the basal ganglia and the thalamocortical circuit due to PD prohibits proper autonomic and somatic movement activities.

3. Pathogenesis of PD

3.1. Genetic vulnerability

The *SNCA* gene produces α-syn enriched in presynaptic regions, which plays a crucial role in maintaining an adequate supply of synaptic vesicles in presynaptic terminals by regulating the release of dopamine and sustaining neuronal structure via microtubule modulation.[27] However, mutations in the SNCA gene result in the production of misfolded insoluble α-syn aggregation, which becomes the source of LBs, the primary pathological hallmark of PD.[28–30] Aggregated α-syn interferes with vesicle clustering and alters postsynaptic activities.[31] Consequently, this synaptic anomaly contributes to dysregulation of cellular function and neurodegeneration. Moreover, the aggregated α-syn has been reported to cause mitochondria dysfunction,[32,33] oxidative stress,[34] inflammation,[35] and calcium dysregulation.[36] Dopaminergic neurons in the substantia nigra pars compacta (SNc) are particularly susceptible to α-syn-induced toxicity as the disease progresses.[5,37]

The *PARK2* gene is associated with an E3-ligase PARKIN protein, whose main function is to ligate ubiquitin to lysine residues of targeted (e.g., damaged or misfolded) proteins. Such PARKIN-induced ubiquitination, a posttranslational modification, is essential for proper proteostasis because the polyubiquitinated proteins are subsequently degraded and removed via the ubiquitin-proteasome system (UPS)[38] and autophagy, which is a lysosome-dependent catabolic process.[39,40] Specifically, PARKIN helps maintain mitochondrial turnover by removing dilapidated mitochondria via autophagy (hereafter mitophagy).[41,42] Thus, the loss of function resulting from PARKIN gene mutations renders dysfunctional mitochondria remaining in the cell, which provokes an unfavorable cell environment and subsequently induces dopaminergic cell death.[42–45] The *PARK2* gene mutation is linked to juvenile PD and the late-onset form of PD.[46]

The *PINK1* gene produces the mitochondrial-targeted kinase, named phosphatase, tensin homolog-induced putative kinase 1 (PINK1) located in the mitochondria. Mutations within the kinase domain (loss of PINK1 kinase activity) of PINK1 are associated with the disease initiation.[47,48] Although the critical function of the PINK1 protein remains elusive, it, like PARKIN, appears to play an important role in mitochondrial turnover and oxidative stress appeasement[47,49] by modulating mitophagy adaptor proteins such as mitofusin 2 (MFN2)[50] and marking dysfunctional mitochondria for mitophagy.[51] Importantly, the *PINK1* and *PARK2* genes mutually work to execute mitochondrial quality control since the identification of damaged mitochondria via PINK1 and tagging impaired mitochondria with ubiquitination by PARKIN for degradation are sequential processes for mitochondrial elimination.[52–56] In this regard, mutations in PARK2/PINK1 contribute to impaired mitochondrial removal and, thus, cell death.

The *PARK7* gene produces DJ-1 protein, which has multiple roles, such as an antioxidant and deglycase. For example, DJ-1 is redox-sensitive and thus functions as an atypical peroxiredoxin-like peroxidase that scavenges H_2O_2, possibly due to its conserved cysteine) residue at position 106.[57] Also, DJ-1's chaperone-like function promotes cellular antioxidative capacity by stabilizing a master antioxidant transcription factor, nuclear factor erythroid 2-related factor 2 (NRF2), by evading its degradation.[58,59] Another role of DJ-1 is deglycase, an enzyme that removes glycation adducts from proteins and lipids. Although glycation as post-translational modifications of proteins and lipids is necessary for their proper functions, the formation of advanced glycation end-products (AGEs) caused by excessively accumulated glycation disrupts their functions[60,61] and is linked to various diseases, including neurodegenerative disorders.[62,63] Given the potent multifunctional roles of DJ-1 in neuroprotection, it is not surprising that DJ-1 mutations are

Table 3
The effects of aerobic exercise on protection against PD (pre-clinical studies).

Study	Participants	Type of Exercise	Intensity	Duration of Exercise Session	Duration of Training Protocol	Measured Outcomes
Tung YT et al. (2024)	(6-OHDA) Rat	Endurance exercise (Treadmill)	Low (10 m/min)	15 or 30 min/day	5 days/week for 10 weeks	↑Motor function (Grip Strength, Rota-rod, Beam walking, Catwalk gait analysis) ↑Body composition (Body weight, Fat mass, Muscle mass, Bone mineral density) ↑Dopaminergic neurons (TH) ↓Oxidative stress (GPx, CuZnSOD, MnSOD, CATALASE) ↑Mitochondrial function (OCR, TFAM, PGC-1α, NRF-1) ↑Neurotrophic factors (BDNF, VEGF, FNDC5)
Fallah Mohammadi Z et al. (2019)	(6-OHDA) Rat	Endurance exercise (Treadmill)	Progressive low to moderate (15 m/min)	60 min/day	5 days/week for 4 weeks	↑Neurotrophic factors (MANF, CDNF, NGF)
Hwang DJ et al. (2018)	(MPTP) Mice	Endurance Exercise (Treadmill)	Progressive low to high (6–15 m/min)	40 min/day	5 days/week for 8 weeks	↑Motor function (Rota-rod) ↑Dopaminergic neurons (TH) & ↓α-synuclein ↑Autophagy & Mitophagy (PINK1, Parkin, p62, LC3, LAMP2, CATHEPSIN L)
Naoki Tajiri et al. (2010)	(6-OHDA) Rat	Endurance exercise (Treadmill)	Moderate (11 m/min)	30 min/day	5 days/week for 4 weeks	↑Neurotrophic factors (BDNF, GDNF) ↑Dopaminergic neurons (TH) & ↑Neurogenesis (BrdU, Doublecortin)
Zhuo W et al. (2022)	(6-OHDA) Rat	Endurance exercise (Treadmill)	Moderate (10–30 m/min)	15 min/day	5 days/week for 10 weeks	↑Dopaminergic neurons (TH) ↑Processing-related response accuracy ↑Cognitive flexibility ↑D1R, D3R, D4R, synaptophysin, PSD-95
Koo JH et al. (2017)	(MPTP) Mice	Endurance exercise (Treadmill)	Moderate (12 m/min)	60 min/day	5 days/week for 4 weeks	↑Motor function (Rota-rod) ↑Dopaminergic neurons (TH, DAT) & ↓α-synuclein ↑Mitochondrial function (SIRT1, PGC-1α, NRF-1, TFAM, COX-IV) ↓Oxidative stress (MnSOD, CuZnSOD) ↑Autophagy (Beclin-1, LC3-II, p62)
Naoki Tajiri et al. (2010)	(6-OHDA) Rat	Endurance exercise (Treadmill)	Moderate (11 m/min)	30 min/day	5 days/week for 4 weeks	↑Neurotrophic factors (BDNF, GDNF) ↑Dopaminergic neurons (TH) & ↑Neurogenesis (BrdU, Doublecortin)
Koo JH et al. (2017)	(MPTP) Mice	Endurance exercise (Treadmill)	Moderate (12 m/min)	60 min/day	5 days/week for 4 weeks	↑Motor function (Rota-rod) ↑Dopaminergic neurons (TH, DAT) & ↓α-synuclein ↓Apoptotic cell death (Bcl2, Bax, Caspase-3) ↑Mitochondrial function (COX-I, COX-IV, TOM20, TIM23)
Jang Y et al. (2018)	(MPTP) Mice	Endurance exercise (Treadmill)	Moderate (12 m/min)	60 min/day	5 days/week for 6 weeks	↑Motor function (Pole test) ↑Dopaminergic neurons (TH & DAT) & ↑Neurogenesis (BrdU) ↑Oxidative stress (CuZnSOD, CATALASE, GPX1/2, HO-1, DJ-1, PRXIII, Protein carbonylation, NRF2) ↑Autophagy (LC3, p62, Beclin-1, BNIP3, LAMP2, CATHEPSIN L, TFEB)
Sokouti H et al. (2022)	(6-OHDA) Rat	Endurance exercise (Treadmill)	Moderate (11 m/min)	30 min/day	5 days/week for 8 weeks	↑Motor function (Rota-rod) ↑Dopaminergic neurons & ↓α-synuclein ↑Antioxidant activity (Serum TAC, Brain GPx, Brain MDA)
da Costa RO et al. (2017)	(6-OHDA) Rat	Endurance exercise (Treadmill)	Moderate (20 cm/s)	30 min/day	14 days	↑Motor function (Rotational behavior, Open field, Rota-rod) ↓Loss of dopaminergic neurons (DA, DOPAC, HVA) & ↑Dopaminergic neurons (TH, DAT) ↓NO & ↓Lipid peroxidation (TBARS) ↑Neurotrophic factors (BDNF)
Tuon T et al. (2012)	(6-OHDA) Rat	Endurance exercise (Motor-driven treadmill)	Progressive moderate to high (13–17 m/min)	50 min/day	4 days/week for 8 weeks	↑Motor function (Rotational test) ↑Dopaminergic neurons (TH) & ↓α-synuclein ↑Neurotrophic factors (BDNF) ↑SERCA2 ↓Oxidative stress (TBARS, Carbonyl) ↑Antioxidant enzyme (SOD, CATALASE, Gpx)
Chuang CS et al. (2017)	(6-OHDA) Rat	Endurance Exercise (Treadmill)	High (15 m/min)	30 min/day	5 days/week for 4 weeks	↑Motor function (CatWalk-assisted automated gate analysis, Methamphetamine-induced rotation) ↑Dopaminergic neurons (TH) & ↑Cell viability (Ki67) ↓Oxidative stress (8-OHdG) ↑Mitochondrial function (OPA-1, MFN2, DRP1, PARKIN, PINK1, TOM20)

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Table 3 (*continued*)

Study	Participants	Type of Exercise	Intensity	Duration of Exercise Session	Duration of Training Protocol	Measured Outcomes
Liu W et al. (2019)	(6-OHDA) Rat	Endurance Exercise (Treadmill)	Progressive High (15–22 m/min)	40 min/day	5 days/week for 8 weeks	↑Motor function (Rotational behavior) ↑Dopaminergic neurons (TH) & ↓α-synuclein ↑Autophagy (LC3, Beclin-1) ↑CAMKIIα, CAMK signaling
Liu W et al. (2020)	(6-OHDA) Rat	Endurance Exercise (Treadmill)	Progressive High (15–22 m/min)	60 min/day	5 days/week for 8 weeks	↑Motor function (Rotational behavior) ↑Dopaminergic neurons (TH) & ↓α-synuclein ↑miR-3557 & ↓miR-324 ↑CAMKIIα ↑UCH-L1
Lau YS et al. (2019)	(MPTP) Mice	Endurance exercise (Treadmill)	Progressive high (6–15 m/min)	40 min/day	5 days/week for 18 weeks	↑Dopaminergic neurons (TH) ↓Protein carbonylation ↑Oxidative stress (CuZnSOD, MnSOD) ↑Neurotrophic factors (BDNF, GDNF)

Abbreviation: TH: Tyrosine hydroxylase, GPX: Glutathione peroxidase, CuZnSOD: Copper Zinc superoxide dismutase, MnSOD: Manganese superoxide dismutase, OCR: Oxygen consumption rate, PINK1: PTEN-induced putative kinase 1, LC3-II: Microtubule-associated protein 1A/1B-light chain 3-II, LAMP2: Lysosomal-associated membrane protein 2, BDNF: Brain-derived neurotrophic factor, NGF: Nerve growth factor, D1R: D1 dopamine receptor, DAT: Dopamine transporter, BCL2: B-cell lymphoma 2, Bax: Bcl-2-associated X protein, TAC: Total antioxidant capacity, TBARS: Thiobarbituric Acid Reactive Substances, SERCA2: Sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase isoform 2, 8-OHdG: 8-hydroxy-2′-deoxyguanosine, CAMKIIα: Calcium/calmodulin-dependent protein kinase II alpha, UCH-L1: Ubiquitin C-terminal Hydrolase L1.

linked to the early onset of PD-induced motor impairments like rigidity, tremors, and psychiatric symptoms, such as psychotic disturbance, anxiety, and cognitive decline.

The *LRRK2* gene produces a dardarin protein containing a leucine-rich repeat kinase 2 domain. LRRK2 was characterized as a member of the Ras of complex proteins (Roc) family containing Ras-like GTPase domain.[64] Mutations in the LRRK2 are considered the most common cause of both sporadic and familial PD. Among the mutations, the G2019S mutations of the LRRK2 have been known to hyperactivate its kinase activities. As such, its downstream target proteins, such as mitogen-activated protein kinase (MAPK) and extracellular signaling regulated kinase (ERK), become overactivated and lead to α-syn accumulation and Lewy-type pathology, causing dopaminergic neuronal cell death and impaired dopamine neurotransmission.[65,66] Moreover, one of the most notable effects of the LRRK2 mutation is the dysregulation of the autophagy-lysosomal system, contributing to dopaminergic neuronal cell death due to dysfunctions in mitochondrial turnover.[66,67]

It should be noted that although genetic inheritance appears to be a predominant causative factor, it accounts for only 15% of PD, while approximately 85% of PD is linked to environmental factors, such as pollution, a person's occupation, or exposure to heavy metals.[68] Thus, environmental factors alone or the interaction between genetic and environmental factors seems more critical to PD.

3.2. Environmental factors

Exposure to environmental toxins has been reported to be linked to the etiology of PD. For example, treatments of cells with pesticides (e.g., the herbicide paraquat and insecticide rotenone) induce oxidative stress, endoplasmic reticulum (ER) stress, and alterations in mitochondrial function, facilitate α- α-syn oligomerization and its fibrillation, and thus cause the loss of dopaminergic neurons.[69–72] Paraquat (1,1′-dimethyl-4, 4′-bipyridinium dichloride) possesses a similar molecular structure to the neurotoxin 1-methyl-4-phenyl pyridinium (MPP^+), which is converted from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) by the enzyme monoamine oxidase in astrocytes and transported into dopaminergic neurons by the dopaminergic transporters.[73]

Rotenone is known to inhibit complex I of the mitochondrial electron transport complex and thus provokes oxidative stress, contributing to lipid and protein oxidation of dopaminergic neurons, which is a pivotal causative factor of PD pathogenesis.[74] MPTP, a similar toxicant to rotenone, simulates rotenone-like progressive PD pathology and motor function deficit in rodents, accompanied by injuries of dopaminergic neurons in the nigrostriatal areas.[75–78] These studies confirm that toxicant chemical-induced PD pathologies resemble the manifestation of both sporadic and familial forms of PD. Furthermore, exposure to paraquat causes loss of dopaminergic neurons in the SNc due to increased reactive oxygen species (ROS) and α-syn aggregation.[79,80] Similarly, in a human study, Liou et al. reported that users of paraquat have a higher association with PD than nonusers.[81] Exposure to environmental metals is also thought to be involved in PD. A recent meta-analysis reported that higher levels of magnesium in cerebrospinal fluid, zinc in hair, and lead in bone were associated with PD,[82] although their molecular roles in PD pathogenesis are unclear.

4. Pathophysiology PD

As illustrated in Fig. 2, pathogenesis factors of PD (genetic vulnerability, aging, and environment) contribute to mitochondrial damage, autophagy dysfunction, inflammation, and ER stress, which leads to the accumulation of aggregated α-syn and its insoluble plague as LBs. This initial cellular event triggers a cascade of harmful events that not only induce cell death but also exacerbate further destructive responses to their own cells and neighboring cells. This vicious cycle contributes to the progressive nature of neurodegeneration of PD, where LB formation and neuronal death perpetuate in the SNc and striatum.

Due to the loss of DA in the SNc resulting from PD, atypical movements like resting tremors typically start unilaterally and progressively evolve into bilateral.[83–85] Besides the central command impairment, DA deficiency also deteriorates the excitability (e.g., diminished acetylcholine release) and reflex control of motor neurons in the spinal cord, which subsequently improperly modulates muscular contraction and coordination, as manifested in various movement anomalies. For example, rigidity is PD-related motor dysfunction caused by abnormal corticospinal motor control systems. This dysfunction is featured as a velocity-independent increase in muscle tone/stiffness by enhanced muscle spindle sensitivity or reduced amine neurotransmitters (i.e., end products of dopamine such as norepinephrine and acetylcholine).[86] Examples of rigidity, such as cogwheel jerking or small jerky motions, are seen in almost all cases of PD, causing instability during movements. This symptom manifests later and develops when the neurons in the substantia nigra have depleted by about 50%–70%.[87]

Other forms of movement impairment are Bradykinesia and Akinesia, which are described as slowed movement or the absence of movement, respectively. Examples include decreased gait and reduced amplitude and smoothness of arm swing during walking; thus, the

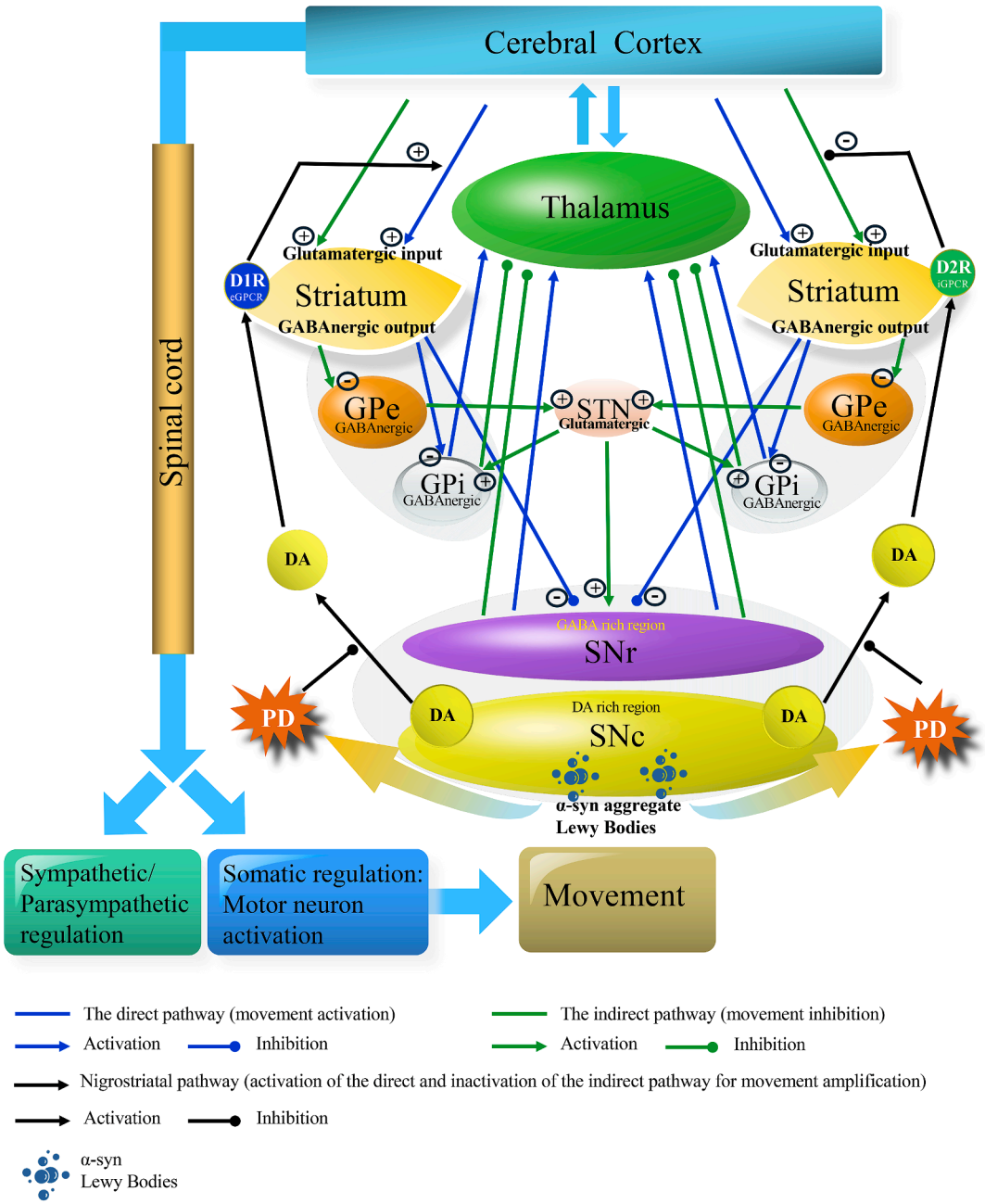

Fig. 1. A schematic overview of the interplays between the thalamocortical and basal ganglia axis associated with movement regulation in the presence and absence of dopamine. Under the direct pathway, neurotransmitter glutamate released from the motor cortex excites the striatum to release the inhibitory neurotransmitter GABA, which inhibits GPi and SNr, which typically suppress thalamic activity by releasing GABA. As a result, the thalamus becomes disinhibited from the GPi and SNr and thus is allowed to excite the motor cortex to initiate movement execution. In contrast, under the indirect pathway, neurotransmitter glutamate released from the motor cortex excites the striatum to release GABA to inhibit GPe, which typically suppresses STN. As a result of GPe inhibition, STN becomes disinhibited from GPe and excites GPi and SNr. Then, the activated GPi and SNr release GABA to the thalami and suppress the thalamus's excitation input to the motor cortex, which results in movement inhibition. These two pathways work in opposite directions; the direct pathway facilitates, but the indirect pathway inhibits voluntary movement. In this movement readiness plan, DA is crucial in synchronously fine-tuning these pathways. DA released from SNc excites the striatum through D1R, an excitatory G-protein coupled receptor, leading to increased cyclic-AMP (cAMP). This results in the activation of the direct pathway. DA also excites D2R, an inhibitory G-protein coupled receptor, leading to decreased cAMP. This results in the inactivation of the indirect pathway. Consequently, this interplay by DA within the nigrostriatal system allows for the potentiation of thalamocortical activation by activating and deactivating the direct and indirect pathways, respectively, leading to smoothly coordinated movement. However, DA absence/deficiency due to the degeneration of dopaminergic neurons by the accumulation of LB and α-syn aggregation in the SNc causes suppression of the direct pathway and excessive activation of the indirect pathway. This results in suppressing thalamocortical activation and inducing unintended irregular synaptic firings, which prohibits proper voluntary movement. Abbreviation: GABA: gamma-aminobutyric acid, GPi: Globus pallidus interna, GPe: Globus pallidus externa, STN: Subthalamus nucleus, DA: Dopamine, SNc: Substantia nigra pars compacta, D1R: D1-like dopamine receptor and D2R: D2-like dopamine receptor, α-syn: α-synuclein, LBs: Lewy Bodies.

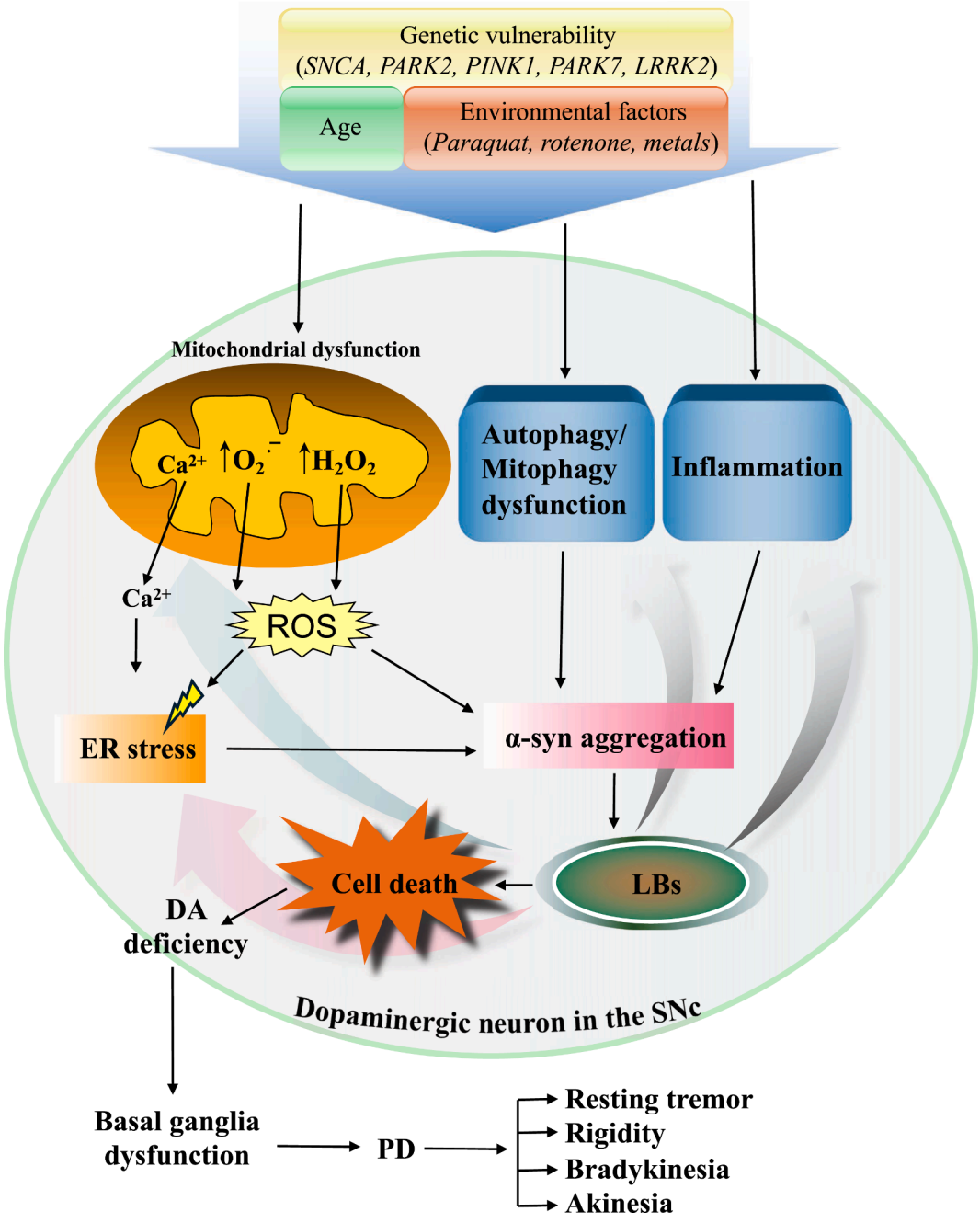

Fig. 2. A schematic overview of the pathophysiology of PD. Genetic vulnerability, age, and environmental factors damage mitochondria, disrupt autophagy/mitophagy, and induce neuroinflammation, producing ROS and ER stress, which become primary sources of misfolded α-syn aggregation and its insoluble plague as LBs. Importantly, the initial cellular event (e.g., toxic element α-syn and LBs generation by mitochondrial impairment, calcium dysregulation, autophagy dysfunction, and inflammation) triggers a cascade of harmful events that not only induce cell death but also exacerbate further destructive responses in neighboring cells. This vicious cycle contributes to the progressive nature of neurodegenerative diseases like PD, where LB formation and neuronal death ensue in perpetuating processes. Loss of DA resulting from dopaminergic cell death in the SNc disrupts nigrostriatal-thalamocortical pathways, leading to movement impairments such as resting tremor, rigidity, bradykinesia, and akinesia. Abbreviation: DA: Dopamine, LBs: Lewy Bodies, SNc: Substantia nigra pars compacta, ER: Endoplasmic reticulum, ROS: reactive oxygen species, α-syn: α-synuclein.

patient's steps get shorter, and the speed becomes slower. These symptoms are unilateral (especially for symptoms caused by spatiotemporal impairments) at first but become bilateral over time.[88] Postural instability is another primary motor-related symptom described as the inability to maintain postural balance, resulting in leaning forward and hunching over with forward movement.[89] This symptom typically occurs during the later stages of PD due to a combination of several issues, including muscle rigidity, impaired coordination, reduced reflexes, and can lead to injuries and falls.[90,91]

Besides its profound role in motor regulations via nigrostriatal interplay, DA is also crucial to orchestrating cognitive function through its neuromodulatortory impact on other regions in the cerebral cortices (e.g., prefrontal, temporal, and parietal cortex) where cholinergic neurons govern higher cognitive functions like memory, attention, and

problem-solving.[92–94] Thus, the loss of DAergic neurons in the SNc can deteriorate normal cognitive functions. Likewise, PD can negatively affect cognitive function not only due to reduced DA signaling input from demised DAergic neurons but also LBs, which spread to the prefrontal, temporal, and parietal cortex and execute cell death.[13,95,96] As illustrated in Fig. 3, LBs can spread to various regions in the brain, such as the prefrontal, temporal, and parietal cortices, where cholinergic neurons preside. Translocated LBs from the SNc and striatum cause cell death in the prefrontal cortex and impair executive functions such as working memory and attention, and LBs-induced cell death in the temporal cortex disrupts memory function. Furthermore, visuospatial function deteriorates when LBs cause cell death in the parietal cortex.

5. Exercise and PD

There is no long-term palliative strategy and cure for PD; moreover, a PD-induced sedentary lifestyle worsens patients' executive function (i.e., the ability to organize, plan, and control physical movements). Conversely, active participation in regular exercise delays the adverse progression of PD and improves the quality of life (e.g., facilitation in walking ability and improvement in cognitive function, muscular strength, cardiovascular fitness, and flexibility).[97,98] According to the exercise guideline from the Parkinson's Foundation in collaboration with the American College of Sports Medicine (ACSM), at least 30 min (min) of moderate to vigorous intensity aerobic exercise 3 days/week and at least 30 min of strength training (10–15 repetitions) for major muscle groups 2–3 non-consecutive days/week along with balance, agility, and flexibility exercises 2–3 days/week or daily if possible.[99]

Exercise studies with PD patients use various combinations of exercise programs (e.g., low, moderate, or high intensity with disparate modalities of exercises such as aerobic or resistance exercise) based on the general guidelines introduced above. Therefore, it is critical to

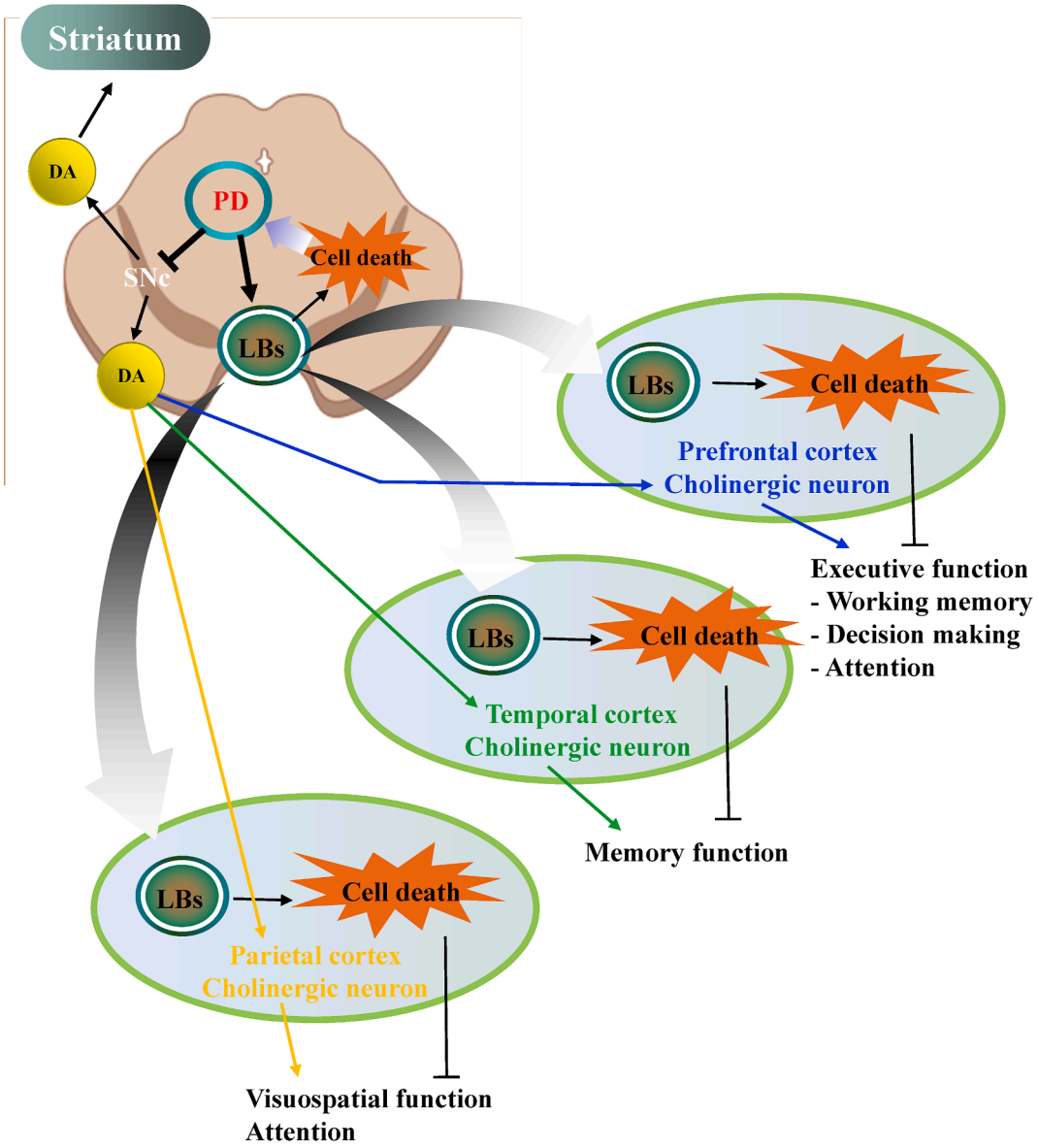

Fig. 3. A schematic overview of cognitive impairment by PD. DA produced from the SNc is critical for movement regulation as a neurotransmitter modulating nigrostriatal activities. It is also crucial for cognitive functions, such as executive function (working memory and attention), memory, and visuospatial function. Thus, PD-induced loss of dopaminergic neurons in the SNc and VTA limits DA availability and undermines cognitive functions. Also, LBs produced from the SNc and VTA can spread to other areas of cerebral cortices and disrupt cell function, leading to death. Specifically, translocated LBs in the prefrontal and temporal cortex impair executive functions such as working memory and attention and disrupt memory function, respectively. Furthermore, LBs deteriorate visuospatial function in the parietal cortex. Abbreviation: DA: Dopamine, LBs: Lewy Bodies, SNc: Substantia nigra pars compacta, PD: Parkinson's disease, VTA: ventral tegmental area.

understand what specific exercise programs are more effective and prophylactic to PD because the extent of exercise efficacy varies depending upon modality (e.g., endurance or resistance) and intensity (e.g., low, moderate, or vigorous). Additionally, understanding its molecular mechanisms is essential for gaining therapeutic insight into developing a potential pharmacological strategy for PD patients who are unable to engage in physical activities due to disease severity or comorbidities. Accordingly, this review describes recent evidence of exercise benefits relative to exercise modalities and intensities and provides potential molecular mechanisms involved.

6. Aerobic exercise and PD

Aerobic exercise is known to improve motor function, alleviate emotional distress, and enhance cognition and language function in individuals with Parkinson's disease (PD). While most studies used a stationary bike exercise as a prevalent modality of exercise due to concerns about patients' limited mobility and safety, other forms of exercise, such as treadmill walking and running, have also been used to examine an exercise effect against PD. The intensity of aerobic exercise is critical, as the body's response to exercise, such as changes in humoral factors, immune function, and neurotrophic factors, varies with exercise intensity. Thus, the following section highlights emerging evidence of neuroprotective effects from aerobic exercise, particularly in relation to exercise intensity.

6.1. Low-intensity aerobic exercise and PD: clinical studies

Low-intensity exercise (e.g., yoga, walking, stationary biking, and some daily living activities) is suited for PD patients with poor balance, stiffness, and significantly limited range of motion (ROM). Three months of Yoga and Tai Chi exercises have been shown to improve balance (Berg balance scale scores), functional mobility (timed up and go time), rigidity, and strength.[100,101] Moreover, treadmill walking exercise (two sessions of 1-h walking per week for 12 weeks) improves motor function (e.g., walking speed).[102] Another study has shown that treadmill walking (25 min per session, 10 sessions over 14 days) improves gait speed and walking capacity (i.e., increased walking distance in a 2-min walk test).[103] Similarly, Yoga exercise (90 min per week for 8 weeks) ameliorates motor dysfunction (Movement Disorder Society Unified Parkinson's Disease Rating Scale [MDS-UPDRS], Part III motor score), as well as anxiety and depression.[104] Interestingly, low-intensity exercise is not enough to reach any significant improvement in cognitive function, such as memory capacity and verbal learning, indicating that higher exercise intensity is necessary to activate brain regions responsible for improvement in executive and cognitive function.[105]

6.2. Moderate and high-intensity aerobic exercise and PD: clinical studies

Moderate-intensity exercises require 3 to 6 metabolic equivalents (METs) or above, which equates to 3 to 6 times above a basal metabolic rate,[106] which has been shown to slow PD progression and provide neuroprotection. For example, cycling exercise at 60% power output for 30–50 min throughout 10 weeks improved MDS UPDRS Part III motor scores and perceived fatigue levels.[107] Besides motor function improvement, combined physical activities (e.g., walking and running) at moderate intensity (3–5.99 metabolic equivalent of task [MET] for 150 min over seven days ameliorated cognitive and memory function and visuospatial ability in mild to moderate PD patients.[105] This study supported an essential concept of the importance of exercise intensity in prescribing exercise for efficacious neuroprotection against PD since no cognitive benefits of exercise were observed when exercise intensity was low (1–2.99 MET).

In addition to the well-established health benefits of moderate-intensity exercise, accumulating evidence suggests that higher exercise intensities beyond moderate levels may confer even more significant benefits for PD patients. For example, 25 min of high-intensity interval training (HIIT), consisting of 1 min of high-intensity cycling followed by 2 min of moderate-intensity cycling, resulted in superior cognitive improvements (e.g., auditory memory and attention) compared to moderate-intensity exercise to 30-min continuous moderate-intensity cycling on a stationary bike.[108] Similarly, 8 weeks of high-intensity stationary bicycle aerobic interval exercise (8 sets of 5 min intervals consisting of 3 min of cycling at 80–90 rpm and 2 min of cycling at 60 rpm), with the heart rate progressively reaching 75%, significantly improved motor and cognitive function and ameliorates MDS-UPDRS scores in mild to moderate PD patients compared to their sedentary counterparts with a similar degree of PD.[109] Consistently, 8 weeks of progressive high-intensity treadmill exercise reaching 70%–80% of estimated heart rate capacity improved both non-motor and motor function as reflected in the MDS-UPDRS scores, the Parkinson's Disease Questionnaire-39 item index (e.g., mobility, levels of activities of daily living, emotional well-being, communication, and sleep quality), and gait capacity.[110] Another study has shown that stationary bike exercise at 80% heart rate reserve (HRR) for 30 min 3 times a week for 6 months improved MDS-UPDRS scores, implying an improvement in both non-motor and motor function.[111] Intriguingly, involuntary assisted exercise as a stationary tandem bike exercise at 60%–80% HRR (e.g., 85 rpm) for 40 min daily, 3 times a week for 8 weeks, alleviated PD symptomology (reduced MDS-UPDRS ratings) and recuperated motor function (grip strength and movement coordination capacity).[112]

The advanced imaging technologies further support the superiority of high-intensity exercise for neuroprotection over low and moderate-intensity exercise. Functional MRI (fMRI) studies have demonstrated that stationary bike exercises at 50%–80% of their HRR for 30–45 min a day three times a week for 6 months restored functional connectivity of the anterior putamen and the sensorimotor cortex and improved cognitive function compared to sedentary PD patients.[113] Furthermore, Sacheli et al., using fMRI and raclopride positron emission tomography (PET) scans, have demonstrated that a high-intensity stationary bike exercise at 60%–80% of maximal aerobic capacity for 30–50 min per day 3 times a week for 3 months elevated dopamine release in the caudate and dopaminergic activities in the ventral striatum area.[114] The benefits of high-intensity exercise are not limited to cycling. Weight-supported treadmill exercise at 75% of maximal heart rate, 45 min per day 3 times a week for 8 weeks, recuperated motor dysfunction (e.g., gait speed, stride length, and step length) and improved corticomotor excitability (neuroplasticity) in early-stage PD patients.[115]

Collectively, clinical studies have demonstrated that high-intensity aerobic exercise is a potent therapeutic strategy for improving motor and cognitive function and psychological symptoms of PD by elevating nigrostriatal plasticity.

7. Resistance training and Parkinson's disease: clinical studies

PD progressively deteriorates motor function due to reduced neural synaptic activities between the spinal cord and motor neurons, and thus, amelioration of motor dysfunction by muscular exercise may delay or prevent poor PD progression. In this regard, resistant training (RT) has emerged as a potential therapeutic means to ameliorate PD-induced falling and attenuate tremors and mobility impairments, such as ROM, gait patterns, speed, and balance.[116] Similarly, 9 weeks of progressive RT targeting major muscle groups (2 sets of 10–12 repetitions of chest press, knee extension, hamstring curl, leg press, and seated row) improved bradykinesia, suggesting resistance exercise can restore neural connectivity and enhance locomotion coordination.[117] Also, rubber band-based resistance exercise targeting large trunk and extremities (e.g., 30 min of a rubber band-based resistance exercise on a Borg scale of 4–5, four sessions per week for four weeks) improved MDS-UPDRS motor scores and non-motor function such as depression, anxiety, and fatigue.[118] Regarding the effect of RT on cognitive function, progressive weight-lifting exercises aimed at large muscle groups twice a week for

24 months improved cognitive outcomes (e.g., digit span task, Stroop test, and behavioral test of attention).[119] Another RT study demonstrated that major muscle exercises such as bench press, deadlift, unilateral rowing, and abdominal exercise (2 sets of 8–12 repetitions, 3 times a week for 24 weeks) assuaged anxiety and regained cognition, communication ability, emotional well-being, and mobility as reflexed in MDS-UPDRS and Parkinson's disease questionnaire-39 (PDQ-39) scores.[120]

Despite promising evidence and new insights into resistance training (RT) as a therapeutic approach to delay or halt Parkinson's disease (PD) progression, a limited body of research still warrants further investigation to establish a consensus on the efficacy of resistive exercise as a critical therapeutic strategy for PD.

8. Blood flow restriction training: clinical studies

Generally, gaining muscular hypertrophy and strength requires multisets of moderate to high-intensity exercises (e.g., 60%–80% of 1 repetition maximum (RM) for hypertrophy and > 80% of 1 RM for strength).[121–123] However, due to poor motor regulation capacity in PD patients, reaching those recommended exercise intensities is difficult or seems infeasible in some advanced PD patients. A potential solution to this impracticality may be blood flow restriction training (BFRT). BFRT is an emerging trend in athletic rehabilitation due to its lower intensity while promoting similar gains in muscular hypertrophy and strength compared to regular resistance training.[124,125] BFRT uses inflatable cuffs to limit blood flow to the exercising muscles in the targeted limbs. This training causes an accumulation of metabolic byproducts (e.g., lactic acid) and facilitates the production of anabolic factors, promoting muscle growth[126,127]; it also improves aerobic capacity and muscle hypertrophy despite performing low-intensity aerobic exercise.[128,129]

Recent studies have applied BFRT to PD patients and provided encouraging results. For instance, low-intensity (20%–30% of 1 RM) leg RT (e.g., leg press, leg curl, leg extension, and calf raise) with upper thigh BFR (160 mmHg pressure) 3 times a week for 6 weeks improved muscular strength, mitigated restless legs syndrome, and reduced timed up and go test score.[130] Intriguingly, aside from motor function, low-intensity RT (20 repetitions at 20% of the 1 RM) with BFRT (60% limb occlusion pressure) was linked to rescuing autonomic function (e.g., ameliorated orthostatic hypotension and poor heart variability) and endothelial function in PD patients.[131] Besides resistive exercise, endurance exercise with BFR also rendered positive outcomes on PD. Likewise, five 2-min bouts of treadmill walking exercise at 50 m/min with upper thigh progressive BFR (120 mmHg pressure at 1–2 weeks, 140 mmHg at week 3–4 weeks, and 160 mmHg at 5–6 weeks) 3 times a week for 6 weeks improved 6-min walk test, timed up and go test, restless legs syndrome, and 30-s chair stand test.[132] on PD-induced autonomic dysfunction. These studies suggest that both RT and aerobic-style exercises with BFR are conducive to recuperating PD-induced motor degeneration. However, a limited body of research necessitates further investigation to establish a clear consensus on the efficacy and safety of BFRT as a therapeutic strategy for PD.

9. Summary of exercise benefits in clinical studies

As shown in Fig. 4, most studies leveraging physical activities as a therapeutic scheme for PD have shown a positive effect in ameliorating motor deterioration (resting tremor, bradykinesia, muscle rigidity, postural instability, and gait changes) and cognitive impairment (memory loss, attention deficit, anxiety, depression, and communication difficulty). Notably, the degree of protection depends on the exercise intensity, with higher intensity offering profound restoration of motor and cognitive function by reconstructing impaired synaptic network circuitry. Nevertheless, most data from clinical studies are descriptive, lacking molecular mechanisms underlying exercise-induced neuroprotection due to the invasiveness of study characteristics (e.g., brain tissue sampling from live human beings).

10. Molecular mechanisms underpinning exercise-induced protection: pre-clinical studies

Consistent with clinical studies, preclinical studies also support the importance of exercise intensity in the physiological and morphological changes required for neuroprotection, with moderate to high-intensity exercise proving more effective. In this section, we will present preclinical studies (e.g., cell and animal models of PD) to elucidate the

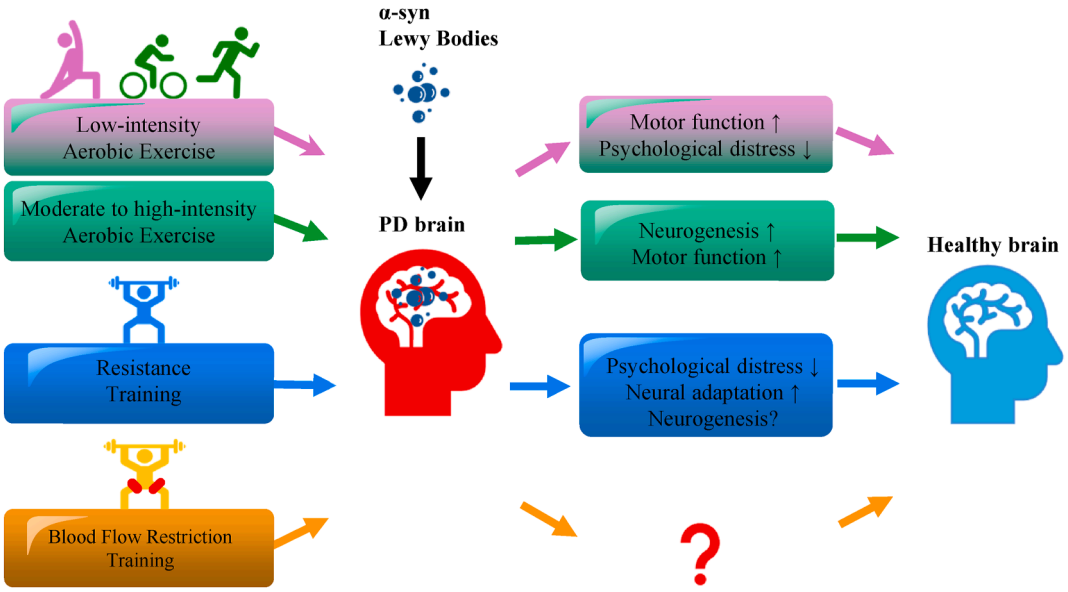

Fig. 4. An overview of protective effects of different types and intensity of exercises on PD brain. Low-intensity exercises (e.g., yoga, walking, and cycling) relieve PD-related motor dysfunction and psychological distress, while moderate and high-intensity endurance exercises (cycling and treadmill running) enhance neuroprotection accompanied by physical modification like neurogenesis. Besides, resistance training subsides PD-induced psychological distress and improves motor function, but whether this protection relates to neurogenesis remains unknown. Resistance training with blood flood restriction has emerged as a potential exercise modality for PD; however, its efficacy and effectiveness as a therapeutic strategy remain to be determined.

cellular and molecular mechanisms behind exercise-induced protection, given the limitations of collecting human brain tissues for clinical studies.

10.1. Neurotrophic factors

Neurotrophic factors, including brain-derived neurotrophic factor (BDNF), neurotrophin-4 (NT-4), nerve growth factor (NGF), glial cell-derived neurotrophic factor (GDNF), GNDF family proteins cerebral dopamine neurotrophic factor (CDNF), and neurturin (NTRN) are proteins that help neuronal cells grow, survive, and differentiate in the brain, which support neuroplasticity by reorganizing or forming existing synapses or new neural synapses.[133,134]

Each neurotrophic factor operates its function by binding to specific receptors. For instance, NGF binds tropomyosin-related receptor tyrosine kinase A (TrkA), which enhances nuclear factor-kappa B (NF-kB) expression to increase anti-apoptotic proteins such as B-cell leukemia/lymphoma 2 protein (BCL2) and B-cell lymphoma-extra large (BCL-xL) in the hippocampal neurons,[135] and BDNF and NT-4 bind TrkB to upregulate proteins associated with synapse density via PI3K-AKT-mTOR signaling nexus.[136–139] In contrast, GDNF binds to the GDNF family receptor α1 (GFRα1) to activate its receptor tyrosine kinase, rearranged during transfection (RET), for the completion of neuroprotective signaling transmission via AKT and extracellular signal-regulated kinase (ERK) in the neuron, including dopaminergic neurons.[140–142] Similarly, CDNF and NRTN bind to the GFRs to activate RET; specifically, CDNF binds to GFRα4, whereas NRTN binds to GFR α2, both of which are known to promote their downstream signaling targets, including mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathways to improve survival of dopaminergic neurons under PD-like stress.[143,144]

These neurotrophic factors play a critical role in maintaining neuronal health by supporting the repair and regeneration of existing neurons.[145,146] However, their levels are significantly reduced in the striatum and SNc of the brain,[147] further endangering poor PD progress. Thus, restoring those crucial neuro-survival factors will be a potent therapeutic approach to reverse or halt PD-induced neuronal cell death, leading to a favorable prognosis of PD. In this regard, regular endurance exercise training has been reported as a potent therapeutic strategy since it increases neurotrophic factors.

A recent study has shown that 4 weeks of moderate-intensity treadmill exercise (11 m/min for 30 min/day, 5 days/week) significantly increased BDNF and GDNF and preserved dopaminergic neurons in 6-OHDA (6-hydroxydopamine)-induced PD rat, evidenced by tyrosine hydroxylase (a dopaminergic neuron marker)-positive neurons in the striatum and substantia nigra (SN), and increased neurogenesis evidenced by increased bromodeoxyuridine (a neurogenesis marker) and doublecortin (a marker of newly formed neurons) positive cells in the lesioned striatum.[148] Another study using a α-*syn*-induced PD model has also shown that 4 weeks of progressive low to moderate-intensity treadmill exercise (a progressive increase in speed from 3 to 11 m/min for 20 min plus 10 min at 11 m/min/day, 5 days/week) enhanced BDNF expression in the striatal tissues, which as linked to improving motor impairments (e.g., a decreased locomotion latency) and restoring striatal plasticity (e.g., an increase in dendritic spine density).[149] Besides BDNF and GDNF, 4 weeks of progressive treadmill running exercise (15 m/min for 60 min twice a day, 5 days/week) increased NGF and CDNF and sustained dopaminergic neurons in the striatum of 6-hydroxydopamine (6-OHDA)-induced PD rats.[150]

In addition to 4-week exercise models, longer duration (8–18 weeks) exercise also reported similar results; for instance, 8 weeks of progressive moderate/high-intensity treadmill running exercise (13–17 m/minfor 50 min/day, 3–4 days/week) restored the BDNF and its receptor TrkB levels in the striatum of 6-OHDA-induced PD mice.[151] Similarly, 10 weeks of progressive low to moderate-intensity treadmill running exercise (gradual increases in speed from 6 to 12 m/min for 40 min/day, 5 days/week) conferred regeneration of dopaminergic neurons in SNc and ventral tegmental area of MPTP-induced PD mice concomitant with elevated BDNF and GDNF levels.[152] Moreover, 18 weeks of long-term progressive high-intensity treadmill exercise (starting from 6 to 15 m/min for 40 min/day, 5 days/week) sustained high levels of BDNF and GDNF levels in the striatal area of MPTP-induced PD mice.[153] These enhanced neurotrophins were associated with recovery of motor coordination capacity (an improved walking ability on a beam) and improved dopamine levels.

Like continuous treadmill running protocol, a progressive increase in moderate-intensity exercise is also effective for neuroprotection against PD. For instance, 12 weeks of progressive treadmill exercise (30 min running at 6–30 m/min, 5 times/week) significantly improved attention and cognitive function in a 6-OHDA-induced rat PD model.[154] This study showed that exercise-induced amelioration in cognitive function was associated with upregulated D1R and D2R, synaptophysin, and post-synaptic density protein 95 in the caudate, suggesting that enhanced dopamine modulation capacity and synaptic connectivity by exercise may be causative factors for restored cognitive functions. Although this study did not provide a causal relationship between neurotrophic factors and the upregulated protein expressions, given that the deficiency in exercise-induced BDNF in the heterozygote ($BDNF^{-/+}$) abolished exercise-induced DA production and compromised motor,[155] the results may imply that exercise-induced BDNF upregulation contributes to increased DA production and its receptors in the striatum to improve cognitive function.

In summary, accumulating evidence supports the key concept that exercise (moderate to high intensity for 30–60 min daily, over 4–18 weeks) reestablishes neurotrophic factors to restore damaged neurons and promote neurogenesis, essential for movement and cognitive function recovery from PD.

10.2. Mitochondrial health

Mitochondria are small organelles in the cell that generate cellular metabolic energy, adenosine triphosphate (ATP), through oxidative phosphorylation; they also contribute to intracellular Ca^{2+} homeostasis and cell signaling.[156,157] However, upon damage, they become strong cell death inducers by spilling pro-apoptotic factors (e.g., cytochrome *c* and apoptosis-inducing factor) and producing reactive oxygen species.[158,159] Thus, they can determine cells' fate: life and death, impacting the normal physiology and pathogenesis of diverse diseases.

In PD, mitochondrial impairment has been manifested and drastically contributes to its pathogenesis.[160–163] As addressed in the pathogenesis of PD, most genetic mutations linked to PD (e.g., PINK1, PARKIN, LRRK2, and DJ-1) are associated with mitochondrial functional defects and oxidative injuries; also, environmental toxins (e.g., MPTP and rotenone) inhibit respiratory function and replicate PD-like symptoms. These findings highlight that the interplay between mitochondrial defects due to genetic mutations and environmental factors may trigger or expedite the onset and progression of PD. Given the convincing association between mitochondrial susceptibility and PD pathogenesis, it seems reasonable to premise that therapeutic strategies targeting appropriate mitochondria turnover via mitochondria biogenesis and selective elimination of damaged mitochondria will prevent or delay the onset of PD and ameliorate PD progression.

In this regard, exercise is a suitable non-pharmacological option since exercise has been known to leverage various molecular signaling networks to enhance mitochondrial biogenesis, morphological adaptation (fission and fusion), and cellular energy production (oxidative phosphorylation).[164–167] An increased adenosine monophosphate (AMP)/adenosine triphosphate (ATP) ratio activates adenosine monophosphate-activated protein kinase (AMPK) to promote mitochondrial biogenesis by activating (phosphorylating) peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a

prime regulator of mitochondrial gene expression including mitochondrial transcription factor A (TFAM), estrogen-regulated receptor alpha (ERRα), and nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase sirtuin 1 (SIRT1).[166,168]

Given the growing literature, the concept that exercise may alleviate PD symptoms through mitochondrial biogenesis and rejuvenation seems tantalizing and encouraging. Growing numbers of studies have shown that 4 weeks of moderate-intensity treadmill exercise (a mouse model: 12 m/min, 60 min/day, 5 days/week),[169] 10 weeks of low-intensity (a rat model: 10 m/min, 15 or 30 min/day, 5 days/week),[170] and 16 weeks of high-intensity treadmill exercise (a rat model: 25 m/min, 50 min/day, 5 days/week)[171] attenuate PD-induced mitochondrial loss and improve mitochondrial biogenesis by AMPK-PGC-1α signaling, which transmits mitochondrial biogenesis signaling by facilitating TAFM, AMPK, and SIRT1. Another study using a mouse model of MPTP-induced PD has shown that treadmill exercise (12 m/min, 60 min/day for 4 weeks)-induced upregulation of mitochondrial biogenesis markers COX-I and COX-IV and the translocase of the outer mitochondrial membrane complex subunit 20 (TOM20) and mitochondrial import inner membrane translocase subunit (TIM23) are associated with improved neuronal death in the striatum and SNc.[172] These studies support that exercise-induced mitigation of mitochondrial loss and improvement in mitochondrial biogenesis is a promising therapeutic target for non-pharmacological PD management.

10.3. Antioxidant capacity

The primary pathophysiologic feature of PD is excessive oxidative stress in the regions of dopaminergic neurons, which results from accumulated α-syn oligomers, a precursor of LBs.[32,173,174] Superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical (•OH) generated by the iron-dependent or independent reaction called the Fenton reaction or Haber-Weiss reaction, respectively, are the most recognized reactive oxygen species (ROS).[175,176] These ROS contribute to the further production of other ROS, such as peroxyl radicals (ROO•), because of ROS-induced lipid peroxidation,[177–179] which is also seen in PD.[32]

Nitric oxide (NO) is an essential element in vascular compliance regulation; however, it has emerged as another potential attributor to PD pathogenesis because NO can become a source of reactive nitrogen species (RNS), a finding noted in post-mortem analysis of dopaminergic neurons (basal ganglia) of PD patients and PD animals.[180–182] Indeed, RNS has been suggested to be a causative factor of PD pathogenesis because the nitration to the phenolic ring of a tyrosine residue of α-syn facilitates α-syn oligomerization and toxicity.[183] Also, a dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) produced from the interaction of dopamine with NO is linked to mitochondrial dysfunction and neurotoxicity.[184]

The sources of dysregulated NO production in the nigrostriatal tissue are neuronal nitric oxide synthase (nNOS) and/or inducible NOS (iNOS), primarily expressed in glial cells.[185,186] The problem with the overexpression of NOS is that overproduced NO becomes the supply of RNS such as peroxynitrite ($ONOO^-$) due to the reaction of $O_2^{\bullet-}$ with NO.[187,188] Also, uncoupled NOS produces $O_2^{\bullet-}$ instead of NO because electrons flowing from the reductase domain of an uncoupled NOS are diverted to oxygen instead of to L-arginine, leading to the formation of $O_2^{\bullet-}$,[189] which further exacerbates ROS and RNS.[190] In addition, elevated nitrite and nitrate were observed in the cerebrospinal fluid of PD patients with levodopa-induced dyskinesia (LID).[191] Therefore, improved antioxidative capacity to reduce ROS and RNS is pivotal in preventing or stagnating PD progression.

Given that oxidative stress is a critical contributor to PD pathogenesis, exercise training has emerged as a promising therapeutic potential since it has been known to upregulate the antioxidative state in the brain of PD, which can neutralize oxidative stress. For example, exercise increases antioxidant enzyme levels such as manganese superoxide dismutase (MnSOD), which neutralizes $O_2\bullet^-$ as H_2O_2 and peroxiredoxin 3 (PRX3) and glutathione peroxidase 4 (GPX4), which subsequently detoxify H_2O_2 into H_2O in mitochondria. Exercise also improves antioxidant enzymes in the cytosol, such as copper/zinc superoxide dismutase (CuZnSOD), which neutralizes $O_2\bullet^-$, and catalase (CAT) and GPX1, which decompose H_2O_2 into H_2O.[76,170,192,193] Accordingly, endurance exercise-induced improvement in antioxidant capacity attenuated lipid peroxidation and minimized neuronal damage in the brains of MPTP-induced PD mice.[77,192,194] Also, in neurotoxin 6-hydroxydopamine (6-OHDA)-induced rat models of PD, moderate-intensity (12 m/min, 30 min/day, 5 days/week for 2 weeks) and progressive high-intensity treadmill exercise (13–17 m/min, 50 min/day, 4 days/week for 8 weeks) suppresses lipid peroxidation in the striatal region as evidenced by reduced lipid peroxidation marker thiobarbituric acid reactive substances (TBARS) levels.[194,195] Furthermore, studies have shown that moderate-intensity treadmill[76] and rotarod exercise[77,192] upregulate antioxidant enzymes heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase in the substantia nigra and improve motor function (improved pole and rotarod test scores) against MPTP-mediated PD.

Besides eliciting protection against PD-induced oxidative injuries, progressive high-intensity treadmill exercises attenuate nitrosative stress-induced damages by dampening NO and nNOS levels in the striatum of PD rats.[196–198] It should be noted that iNOS modulation does not seem necessary for exercise-induced protection against RNS because exercise does not change its levels.[197] Moreover, it was reported that treadmill running exercise (18 m/min for 60 min/day, 5 days/week for 6 weeks) before MPTP administration resulted in reversing impaired non-motor PD symptoms as a result of attenuated oxidative stress inducer receptor advanced glycation end-product (RAGE) and upregulated DJ1, which is a crucial antioxidant and molecular chaperone involved in protecting mitochondria and their proper function.[199]

10.4. Endoplasmic reticulum (ER) stress

The ER is a crucial locus for protein synthesis and quality control in the cell. The ER is a profoundly regulated organelle, and under stressed conditions (e.g., accumulation of unfolded proteins and oxidative stress), it engages in an adaptive response, the unfolded protein response (UPR).[200] The UPR suspends protein translation and synthesis, promotes protein degradation by the ubiquitin-proteasome system to remove misfolded proteins, and modulates cell fate through the activation of apoptosis and ultimate mass cell destruction.[201,202] The UPR regulates three signaling pathways, which have been utilized as ER stress markers in most tissues: Protein kinase RNA-like Endoplasmic Reticulum Kinase (PERK) that activates Eukaryotic Initiation Factor 2α (eIF2α), type I transmembrane protein inositol requiring I (IRE1), and activating transcription factor 6 (ATF6).[203]

While the UPR plays a crucial role as a line of defense against ER stress, chronically elevated URP leads to cell death rather than cell rescue. For example, the accumulation of α-syn aggregate causes ER stress to release Ca^{2+} and thus contributes to intracellular Ca^{2+} dysregulation, which leads to neuronal cell death in the dopaminergic neurons.[204,205] Given this observation, recent studies have investigated whether endurance exercise-induced protection against PD is associated with mitigating ER stress-induced Ca^{2+} dysregulation. Studies have found that 8 weeks of progressive high-intensity treadmill exercises (15–22 m/min) ameliorates PD-induced Ca^{2+} overload by reinforcing Ca^{2+} reuptake into the sarcoplasmic reticulum via enhancing sarco/endoplasmic reticulum Ca^{2+}-ATPase II (SERCA II) by enhancing Ca^{2+}-calmodulin dependent kinase IIα (CaMKIIα) activities.[195,206] Additionally, Liu et al. have confirmed that increased CaMKIIα levels in response to 8 weeks of progressive high-intensity treadmill exercise (up to a speed of 22 m/min for 40 min/day) are associated with restoration of dopaminergic neurons in the striatum and amelioration of motor deficits in 6-OHDA-induced PD rats.[207] In addition, although nothing is

known about the direct relationship between exercise and UPR in animal models of PD, given a previous study showing that voluntary wheel-running exercise upregulates UPR proteins without causing apoptosis,[208] it can be presumed that exercise-mediated UPR modulation may be a potential protective contributor to PD. Nonetheless, further studies are warranted to confirm a potential UPR-related hypostasis.

10.5. Autophagy and mitophagy

Autophagy is a critical lysosome-dependent catabolic process by which damaged proteins, lipids, and DNA are safely discarded to help sustain normal cellular function.[209] Thus, disrupted autophagy has been implicated in PD,[210–212] while improved autophagy alleviates PD-induced motor (gait, pole, and rotarod tests) and cognitive (nest building) impairment.[213,214] Autophagy is assessed by measuring the overall flow of autophagic processes. Generally, the increased levels of microtubule-associated protein 1A/1B-light chain 3 (LC3-II), which is a prime marker of matured autophagosomes, along with reduced levels of p62, which is degraded with autophagosomes, are considered normal autophagy flux. Also other changes in autophagy-related proteins including BECLIIN, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), autophagy-related 5 and 7 (ATG5 and ATG7), lysosome-associated membrane protein 2 (LAMP2), a transcription factor EB (TFEB), and lysosomal protease CATHEPSIN L are referenced when assessing autophagy.[215] A recent study has shown that another lysosomal protease, CATHEPSIN D, has been reported to be critically attributed to dopaminergic neuron protection by removing α-syn via autophagy.[216]

While the pharmacological intervention approach to targeting autophagy modulations remains to be revealed, endurance exercise has emerged as a potent autophagy inducer in various organs,[217,218] including brains.[167,219] Indeed, recent studies have demonstrated a critical role of exercise-induced autophagy in neuroprotection against PD, as moderate-intensity treadmill exercise (12 m/min for 60 min/day, 5 days/week for 6–8 weeks)-induced autophagy was correlated with improved motor dysfunction and revival from neuronal death in the striatum and SNc of MPTP-induced PD mice,[76,169,220,221] supporting the growing concept that exercise-induced autophagy can be a crucial protective mechanism against PD.

Besides autophagy, mitophagy, a specific autophagic process for selectively eliminating dysfunctional and senescent mitochondria, is pivotal in maintaining neurons in the brain, as impaired mitophagy is involved in PD pathologies.[210,222] These studies shed novel insight into mitophagy as a potential leverage as a therapeutic strategy for PD. Mitophagy is particularly regulated by the PTEN-induced putative kinase 1 (PINK1)-Parkin pathway to maintain mitochondrial quality control. This process involves mitochondrial dynamics regulations, including fission for damaged mitochondria removal[223,224] and removal and fusion for improving oxidative phosphorylation and integrity.[225–227]

In healthy mitochondria, PINK1 imported into the inner mitochondrial membrane is cleaved and degraded by mitochondrial processing peptidase (MPP) and presenilin-associated rhomboid-like protein (PARL).[51,56] Conversely, in damaged mitochondria losing their membrane potential, mitochondrial fission proteins such as mitochondrial fission factor (MFF), Dynamin-Related Protein 1 (DRP1), and fission 1 (Fis1) converge on the mitochondrial outer membrane to signal for mitophagy.[228–231] The resultant depolarized and fragmented mitochondria use the adenine nucleotide translocator (ANT) complex to anchor PINK1 on the outer membrane, not the inner membrane, to hinder its degradation by MPP and PARL.[51] Then, the PINK1 undergoes autophosphorylation, recruits E3 ligase PARKIN to the outer mitochondrial membrane, and phosphorylates it to initiate mitophagy.[232] The phosphorylated PARKIN then implements polyubiquitination on target molecules in mitochondria, including a voltage-dependent anion channel (VDAC) and a dynamin-related GTPase protein MFN1 and 2 to facilitate fission by interfering with the fusion state.[233] Subsequently, p62 proteins bind to these polyubiquitinated proteins of targeted mitochondria via its ubiquitin-binding domain.[234] Consequently, the p62-mitochondria complex is tethered to LC3-II of autophagosomes via the p62's LC3-interacting region (LIR) of LC3-II, enclosed to autophagosomes, and degraded for mitophagy.[235,236] In addition to p62, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) has been reported to function as a mitophagy mediator. For example, although considered a pro-apoptotic protein causing loss of mitochondrial membrane potential via opening mitochondrial permeability transition pore (mPTP) and initiating apoptosis,[237,238] BNIP3 engages in mitophagy without disrupting mPTP and cell death.[228,239,240]

Numerous review articles claim plausible theories and opinions about the potential protective mechanism of exercise-induced mitophagy. Nevertheless, original research supporting the theories remains scarce. Currently, two studies are available, but even the two investigations claimed exercise-induced mitophagy without providing direct evidence of mitophagy. For example, in a rat model of a 6-OHDA-induced PD study, using 4 weeks of high-intensity treadmill exercise (15 m/min for 30 min/day, 5 days/week), the authors have reported that exercise-induced mitochondrial dynamics restoration, such as an increase in mitochondrial fusion proteins optic atrophy 1 (OPA1) and MFN2 and a fission protein DRP1 in conjunction with a mitophagy marker PARKIN is associated with protection against PD.[241] However, this did not assess mitochondrial content in the isolated autophagosomes or lysosomal fraction containing mitochondria to measure mitophagy, as suggested in other studies.[242,243] Also, a mouse model of an MPTP-induced PD study has reported that improved mitophagy by 8 weeks of moderate-intensity treadmill exercise (12 m/min for 60 min, 5 days/week) is associated with neuroprotection against PD. In this study, the authors viewed increased autophagy flux (reduced p62 and LC3-II/LC3-I ratio and increased lysosomal associated membrane protein 2 and Cathepsin L) and reduced mitophagy markers (PINK1 and PARKIN) as improved mitophagy without direct evidence as addressed above.[220]

Consequently, there is no clear evidence of whether exercise modulates mitophagy, and thus, the emerging hypothesis that exercise-induced mitophagy is crucial to neuroprotection against PD remains esoteric. Potential reasons for such a paucity of information could be related to technical difficulties in measuring mitophagy. For instance, besides previously mentioned isolation techniques for autophagosome and lysosome fractions, the timing of mitophagy measurement (a snapshot capture of mitochondria in the autophagosomes vs. autolysosomes) may lead to different outcomes. To circumvent this limitation, pharmacological inhibition of mitophagy induction by 3-methylamine or Ly294002 will allow researchers to examine the therapeutic potential of exercise-induced mitophagy in neuroprotection against PD. If exercise-induced mitophagy blockage renders no protection or partial protection, mitophagy's protective role in exercise can be substantiated. One additional approach to solving such technical difficulties in assessing exercise-induced mitophagy may be the mt-Keima[244] or mito-QC[245] transgenic mouse models. These models devise pH-sensitive fluorescence in mitochondria. For example, mitochondria in the cytosol, where pH is normal, remain in green fluorescence, but when mitochondria are translocated to the lysosome due to mitophagy, the green fluorescence in mitochondria turns red due to low pH in the lysosome. Thus, assessing fluorescence color changes using fluorescence microscopy will allow the assessment of mitochondria transportation to the lysosome (i.e., green to red), representing mitophagy.

11. Conclusion

Parkinson's disease (PD) is a neurodegenerative disease impairing motor functions (e.g., bradykinesia, resting tremor, rigidity, and postural instability) and emotional limbic activity (e.g., depression and

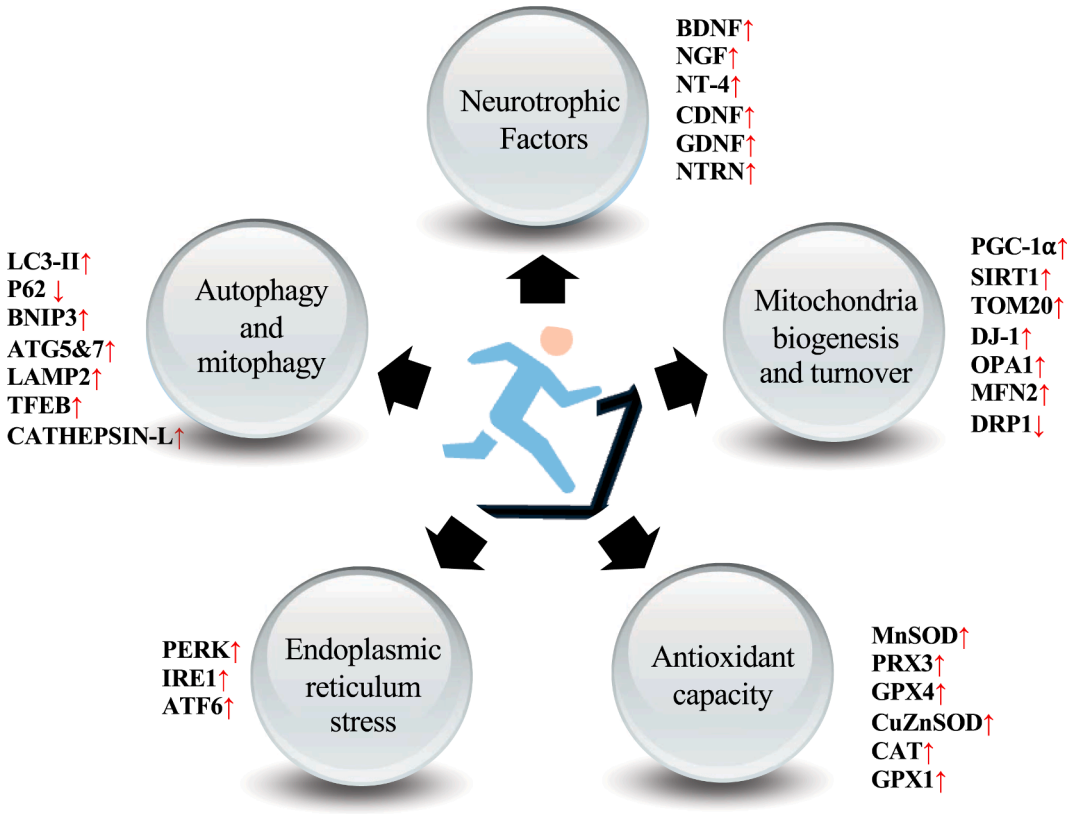

Fig. 5. A schematic outline of molecular mechanisms of exercise-induced neuroprotection against PD. Exercise-induced alterations in the following five criteria: 1) neurotrophic factors, 2) mitochondrial modifications via biogenesis and turnover, 3) antioxidant capacity, 4) endoplasmic reticulum stress, and 5) autophagy and mitophagy have been implicated in recovering a healthy cellular environment. These five factors are necessary to work mutually to ensure the proper amelioration of neuronal function by facilitating neurogenesis, mitochondrial biogenesis, and antioxidant availability, as well as enhancing the removal of cellular toxic elements via autophagy and mitophagy. Abbreviation: LC3-II: Microtubule-associated protein 1A/1B-light chain 3-II, BNIP3: BCL2 and adenovirus E1B 19-kDa-interacting protein 3, ATG5&7: Autophagy related 5&7, LAMP2: Lysosomal-associated membrane protein 2, TFEB: Transcription factor EB, BDNF: Brain-derived neurotrophic factor, NGF: Nerve growth factor, NT-4: Neurotrophin-4, CDNF: Cerebral Dopamine Neurotrophic Factor, GDNF: Glial cell line-derived neurotrophic factor, NTRN: Neurturin, PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, SIRT1: Sirtuin 1, TOM20: Translocase of outer mitochondrial membrane 20, OPA1: Optic atrophy 1, MFN2: Mitofusin 2, DRP1: Dynamin-related protein 1, MnSOD: Manganese superoxide dismutase, PRX3: Peroxiredoxin 3: GPX4: Glutathione peroxidase 4, CuZnSOD: Copper Zinc superoxide dismutase, CAT: Catalase, GPX1: Glutathione peroxidase 1, PERK: PKR-like ER Kinase, IRE1: Inositol-Requiring Enzyme 1, ATF6: Activating Transcription Factor 6.

anxiety). Genetic mutations and environmental toxic factors, or both have been suggested to contribute to the pathogenesis of PD. Currently, there is no cure for PD, but regular exercise training has gained growing recognition as a potent therapeutic strategy. Interestingly, most clinical studies have suggested that the degrees of exercise benefits (emotional relief vs. functional/neurophysiological restoration) in PD patients are in an exercise-intensity manner. For example, low to moderate-intensity endurance exercise is effective in enriching anxiety, depression, and tremors, while high-intensity endurance exercise ameliorates motor function and delays the adverse progression of PD. Intriguingly, only high-intensity exercise exhibits neurogenesis, evidenced by fMRI and PET scans, indicating that moderate to high-intensity exercise seems necessary to retrieve functional neuro-synaptic communication by improving neuroplasticity.

Preclinical studies using rodent models of PD have provided insight into molecular mechanisms responsible for exercise-induced protection against PD. For example, 1) upregulation of exercise-induced neurotrophic factors (e.g., BDNF, CDNF, and GDNF) facilitates neurogenesis, 2) improvement in mitochondrial biogenesis, antioxidative capacity, and ER stress attenuates PD-induced neurodegeneration, and 3) autophagy modulations by exercise training (e.g., activation and termination processes for optimal autophagy flux) facilitate the elimination of dysfunctional mitochondria to sustain a healthy cell environment.

In summary, as shown in Fig. 5, clinical and pre-clinical studies collectively support the notion that various exercise modes effectively alleviate PD's psychological and motor symptoms and their adverse progression. More importantly, clinical studies maintain that high-intensity aerobic exercise would be a more potent therapeutic strategy for improving motor impairment because it elevates nigrostriatal plasticity and neurogenesis, while low-intensity is rather effective in appeasing psychological symptoms. Currently, the molecular mechanisms and the extent to which different intensities of exercise (low vs. moderate vs. high intensity) distinctively influence neuroprotection remain unclear due to the scarcity of preclinical studies examining the effects of exercise intensities on PD. Thus, future preclinical studies with standardized evaluation criteria (e.g., % changes in dopaminergic death and regeneration and motor function scores) are warranted to molecularly and mechanistically support the ponderance of exercise intensity.

CRediT authorship contribution statement

Youngil Lee: Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Conceptualization. **Beomsoo Ju:** Writing – review & editing, Visualization, Data curation, Conceptualization. **Yohan Cheon:** Writing – review & editing, Visualization, Data curation. **Namita Mishra:** Writing – review & editing, Writing – original draft, Conceptualization. **Emma Fletcher:** Writing – review & editing. **Panagiotis Koutakis:** Writing – review & editing. **Gulnaz T.**

Javan: Writing – review & editing. **Young C. Jang:** Writing – review & editing.

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Declaration of competing interest

The authors declare they have no financial interests/personal relationships that could have appeared to influence the work reported in this paper.

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