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Original Article

A Comparative Study on the Effects of Aerobic, Resistance, and Combined Exercise Training on Brain-Derived Neurotrophic Factor Gene Expression in an Animal Model of Parkinson's Disease

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Abstract

Introduction: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by dopaminergic neuron loss in the substantia nigra, leading to motor and non-motor symptoms. Brain-derived neurotrophic factor (BDNF) represents a potential molecular target in PD research. Thus, this study compared the effects of aerobic, resistance, and combined exercise (PD-COM) training on *BDNF* gene expression in the striatum and substantia nigra of a PD rat model.

Methods: Fifty male Wistar rats were equally divided into healthy control (HC), PD non-exercise, and PD with aerobic, resistance, or PD-COM groups. Parkinsonism was induced via unilateral 6-hydroxydopamine injection, and exercise interventions lasted 8 weeks (5 days/week). BDNF gene expression was quantified using quantitative polymerase chain reaction, and data were analyzed using one-way ANOVA and Tukey's test ($P<0.05$).

Results: Significant group differences were observed for BDNF expression in both the striatum and substantia nigra ($P<0.001$). BDNF expression significantly increased in both brain regions in the aerobic, resistance, and PD-COM groups compared with the PD non-exercise group (all $P\leq0.001$). Moreover, PD-COM produced the highest BDNF expression, reaching levels comparable to those observed in HCs. Finally, aerobic exercise resulted in higher substantia nigra BDNF expression than resistance exercise ($P=0.014$).

Conclusion: Combined aerobic and resistance exercise could highly increase BDNF messenger RNA expression in the striatum and substantia nigra compared with isolated exercise modalities, suggesting that combined training may provide a stronger stimulus for regulating BDNF-related molecular responses following dopaminergic injury.

Keywords: Parkinson's disease, Brain-derived neurotrophic factor, Aerobic exercise, Resistance exercise, Combined exercise

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by loss of dopaminergic neurons in the substantia nigra, causing motor and non-motor symptoms. PD affects 1–2% of people over 60, with prevalence projected to double by 2030 (1). In addition, the annual cost of PD exceeds $50 billion in the U.S. At the molecular level, brain-derived neurotrophic factor (BDNF) supports neuronal survival and is a promising target for slowing disease progression (2). Further, exercise upregulates BDNF expression and may improve patient outcomes (3). BDNF binds to tropomyosin receptor kinase B (TrkB), activating cyclic adenosine monophosphate response element-binding protein (CREB), mitogen-activated protein kinase, and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathways (4), thereby enhancing neuronal survival (5). Additionally, exercise increases BDNF via epigenetic mechanisms and activity-dependent processes (6). Aerobic, resistance, and combined exercise (PD-COM) may differently affect these pathways (7). However, effects on the nigrostriatal pathway remain poorly defined.

In rodents, aerobic exercise elevates BDNF and improves plasticity (8). Likewise, aerobic training increases striatal BDNF and preserves dopaminergic neurons in PD models (2). Nikokalam Nazif et al reported that treadmill training increased BDNF in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated mice (9). According to some human studies, high-intensity aerobic exercise raises serum BDNF in Parkinson's patients (3, 10), although effects may be transient (11). Resistance and PD-COM yield more variable effects; some findings in PD models are inconsistent (12). PD-COM in humans enhances BDNF more than aerobic alone (3,7,13), but animal studies are limited due to protocol differences and models such as 6-hydroxydopamine (6-OHDA) (14). Although previous studies have demonstrated that exercise can modulate BDNF-related responses in PD models, direct comparisons of aerobic, resistance, and combined exercise within the same experimental paradigm remain limited. Furthermore, the region-specific effects of different exercise modalities on BDNF expression in key components of the nigrostriatal

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pathway, including the striatum and substantia nigra, are not perfectly understood. Therefore, the present study aims to compare the effects of aerobic, resistance, and combined exercise training on BDNF messenger ribonucleic acid (mRNA) expression in the striatum and substantia nigra of a unilateral 6-OHDA-induced Parkinsonian rat model. It has been hypothesized that all exercise modalities would increase BDNF expression compared with sedentary Parkinsonian animals, with combined training producing a greater molecular response due to the integration of endurance-related and resistance-related stimuli.

Materials and Methods

Using an experimental design, this study investigated the effects of aerobic, resistance, and PD-COM on the gene expression of BDNF in a rat model of PD. The experiment was conducted at the Marvdasht Laboratory Research Center from February 2025 to May 2025. All procedures were approved by the Ethics Committee of Islamic Azad University of Najafabad and followed international guidelines for the care and use of laboratory animals. Adult male Wistar rats were employed in this study. Animals were obtained at eight weeks of age, weighing 290 ± 26.5 g, from the laboratory animal facility. Following acclimatization and confirmation of eligibility for inclusion, the animals were randomly allocated to five experimental groups (n = 10 per group), including healthy control (HC), Parkinsonian sedentary group (PD), Parkinsonian aerobic exercise group (PD-AE), Parkinsonian resistance exercise group (PD-RE), and Parkinsonian combined exercise group (PD-COM). Randomization was performed using a computer-generated random sequence to minimize allocation bias. It should be noted that the investigator responsible for group assignment was not involved in subsequent molecular analyses. Sample identification codes were used during tissue processing and molecular analyses. Moreover, investigators involved in RNA extraction, quantitative polymerase chain reaction (qPCR) procedures, and initial data processing were blinded to group allocation until completion of the analyses. Further, the sample size was determined a priori using G*Power software (version 3.1.9.7). The calculation was performed based on the one-way analysis of variance (ANOVA) model for comparison among five experimental groups, with an alpha level of 0.05 and a statistical power of 80%. Based on previous studies investigating exercise-induced alterations in BDNF expression in experimental PD models (9, 15), a large expected effect size (Cohen's f = 0.40) was assumed for this study. The analysis indicated that a total sample size of 50 animals (10 animals per group) was required to detect significant differences among the groups.

The rats were housed in standard cages (5 rats per cage) under controlled environmental conditions, including a 12:12 hour of light/dark cycle (lights on at 07:00), temperature of 22 ± 2°C, relative humidity of 50–60%, and ad libitum access to food and water. Before the intervention period, all animals underwent a one-week acclimatization period under these conditions. Parkinsonism was induced via unilateral injection of 6-OHDA into the right striatum, following previously described procedures (16). Next, rats were anesthetized with isoflurane (2–3% and 1–2% for induction and maintenance, respectively) and placed in a stereotaxic apparatus. Then, 4 µL of the 6-OHDA solution (2 µg/µL in physiological saline containing 0.2% ascorbic acid) was injected at a rate of 0.5 µL/min into the right striatum (coordinates: AP: + 0.5 mm, ML: −1.8 mm, DV: −3 mm relative to bregma). The needle was left in place for 3 minutes after injection in order to prevent backflow. The HC group received an equal volume of the vehicle solution instead of 6-OHDA. After surgery, the rats were housed individually for 48 hours, and their recovery was monitored. Seven days after 6-OHDA administration, lesion severity was assessed using an apomorphine-induced rotational test. Afterward, the animals received apomorphine (0.5 mg/kg, intraperitoneally), and contralateral rotations were recorded for 30 minutes. Animals displaying more than six rotations per minute were considered successfully lesioned and included in subsequent analyses.

Exercise interventions began seven days after surgery and were performed for 8 weeks, 5 days per week. In the aerobic training group, rats ran on a motorized treadmill designed for animals. The protocol began at 10 m/min for 30 minutes in the first week and progressively increased to 15 m/min for 60 minutes by the eighth week. In addition, each session included a 5-minute warm-up and a 5-minute cool-down at 8 m/min (17). In the resistance training group, rats climbed a 1-m vertical ladder at an 85° incline with 2-cm rung spacing. Weights were attached to their tails, starting at 5% of body weight in the first week and progressing to 15% by the eighth week. Further, each session included 3 sets of 10 repetitions, with 1-minute rest between repetitions and 2 minutes between sets (15). In the PD-COM group, the rats alternated between the two modes: 3 days per week of aerobic exercise (30 minutes at 12 m/min) and 2 days of resistance exercise (3 ladder climbs with 10% body weight), or vice versa, for a total of 5 training days per week (17).

After the 8-week training period, the rats were sacrificed 24 hours after the final exercise session using cervical dislocation. The substantia nigra and striatum were rapidly dissected from both hemispheres, snap-frozen in liquid nitrogen, and stored at −80°C for subsequent analysis. To assess *BDNF* gene expression, total RNA was first extracted from the tissues using the TRIzol reagent. Additionally, the quality and concentration of RNA were evaluated with a NanoDrop spectrophotometer (Table 1). Then, 1 µg of RNA was reverse-transcribed into complementary DNA using the high-capacity complementary DNA reverse transcription kit. The qPCR was performed using SYBR Green Master Mix on a StepOnePlus Real-Time PCR System (Applied Biosystems). Specific primers for BDNF (Forward: 5'-AGCTGAGCGTGTGTGACAGT-3'; Reverse: 5'-TCCATAGTAAGGGCCCGAAC-3') and reference genes *GAPDH* and *β-actin* were used. Likewise, relative gene expression was calculated using the 2^(-ΔΔCt) method, normalized to the geometric mean of the reference genes. Each sample was analyzed in technical triplicate, and

the mean cycle threshold (Ct) value of the replicates was employed for subsequent relative expression calculations. In addition, no-template controls were included to verify the absence of contamination.

Graphs were generated using GraphPad Prism software (GraphPad Software, San Diego, CA, USA). Data, presented as means ± standard deviations (SD), were analyzed using SPSS software (version 21, IBM Corporation, Armonk, NY, USA). The Shapiro–Wilk and Levene's tests were utilized to assess normality and homogeneity of variances, respectively. Differences among experimental groups (HC, PD, PD-AE, PD-RE, and PD-COM) were analyzed using ANOVA. When a significant overall group effect was detected, Tukey's post-hoc test was performed for pairwise comparisons. Eventually, effect sizes were quantified using partial eta squared (η^2), and statistical significance was set at $P < 0.05$.

Results

Successful induction of Parkinsonism was confirmed by apomorphine-induced rotational behavior. Based on the results, PD rats exhibited significantly higher rotations compared with HCs ($F(1,48) = 32.14$, $P < 0.001$), confirming the validity of the experimental model (Figure 1). This test was conducted seven days after 6-OHDA injection, and only animals with more than six rotations per minute were included in subsequent analyses.

Descriptive statistics for relative BDNF mRNA expression are presented in Table 2. The sedentary PD group exhibited the lowest expression in both regions, whereas PD-COM produced the highest values. Levene's test confirmed homogeneity of variance (Striatum: F=0.323, p=0.861; Substantia Nigra: F=0.433, p=0.784). One-way ANOVA revealed significant differences among groups for both striatum ($F(4,45)=24.29$, $p<0.001$, partial $\eta^2=0.683$) and substantia nigra $F(4,45)=55.16$, $p<0.001$, partial $\eta^2=0.831$) (Table 3)

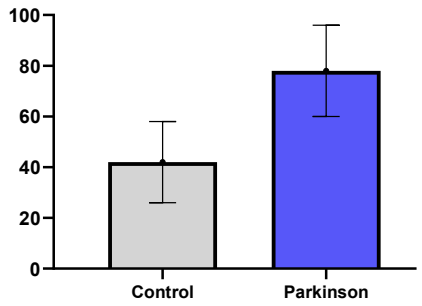

Figure 1. Apomorphine-Induced Rotational Scores in HC and PD Rats
Note. HC: Healthy control; PD: Parkinson's disease

Based on the results (Table 4), PD-COM significantly increased striatal BDNF compared with PD non-exercise (MD = 0.389, 95% CI: 0.263–0.515, $P < 0.001$), PD-AE (MD = 0.142, 95% CI: 0.016–0.268, $P = 0.020$), and PD-RE (MD = 0.198, 95% CI: 0.073–0.324, $P < 0.001$). Aerobic versus resistance exercise was not significantly different ($P = 1.000$).

Similarly, for substantia nigra BDNF (Table 5), PD-COM could substantially increase expression compared with PD (MD = 0.583, 95% CI: 0.460–0.706, $P < 0.001$), PD-AE (MD = 0.156, 95% CI: 0.033–0.279, $P = 0.007$), and PD-RE (MD = 0.300, 95% CI: 0.177–0.423, $P < 0.001$). Aerobic versus resistance exercise showed a smaller, significant difference (MD = 0.144, 95% CI: 0.021–0.267, $P = 0.014$).

Figure 2 illustrates mean ± SD BDNF expression for all groups, and asterisks indicate significant differences relative to PD.

Table 2. Relative BDNF mRNA Expression (Mean ± SD) Across Experimental Groups

Group	Striatum BDNF	Substantia Nigra BDNF
HC	1.009 ± 0.093	1.001 ± 0.122
PD	0.655 ± 0.088	0.512 ± 0.083
PD-AE	0.902 ± 0.086	0.939 ± 0.087
PD-RE	0.846 ± 0.109	0.795 ± 0.094
PD-COM	1.044 ± 0.116	1.095 ± 0.091

Note. n = 10 per group; mRNA: Messenger ribonucleic acid; SD: Standard deviation; ANOVA: Analysis of variance; BDNF: Brain-derived neurotrophic factor; HC: Healthy control; PD-AE: Parkinson + aerobic; PD-RE: Parkinson + resistance; PD-COM: Parkinson + combined Levene's test confirmed homogeneity of variance (striatum: $F = 0.323$, $P = 0.861$; Substantia nigra: $F = 0.433$, $P = 0.784$). One-way ANOVA revealed significant differences among groups for both striatum ($F(4,45) = 24.29$, $P < 0.001$, partial $\eta^2 = 0.683$) and substantia nigra ($F(4,45) = 55.16$, $P < 0.001$, partial $\eta^2 = 0.831$) (Table 2).

Table 1. RNA Concentration, Purity Indices, and Ct Values

Group	Brain Region	RNA Concentration (ng/µL)	A260/A280	A260/A230	Ct BDNF	Ct GAPDH	Ct β-Actin
HC	Striatum	175	2.00	2.15	22.8	18.5	20.0
HC	Substantia nigra	170	2.01	2.12	23.0	18.3	19.8
PD	Striatum	165	1.99	2.20	23.5	19.0	20.5
PD	Substantia nigra	160	2.00	2.18	23.8	18.8	20.3
PD-AE	Striatum	172	2.02	2.22	22.6	18.4	19.9
PD-AE	Substantia nigra	168	2.01	2.15	22.5	18.2	19.7
PD-RE	Striatum	170	1.98	2.10	23.2	18.7	20.2
PD-RE	Substantia nigra	165	2.00	2.14	23.4	18.6	20.1
PD-COM	Striatum	178	2.02	2.25	22.5	18.3	19.8
PD-COM	Substantia nigra	175	2.01	2.20	22.4	18.2	19.6

Note. HC: Healthy control; PD-AE: Parkinson + aerobic; PD-RE: Parkinson + resistance; PD-COM: Parkinson + combined; CI: Confidence interval; RNA: Ribonucleic acid; BDNF: Brain-derived neurotrophic factor; Ct: Cycle threshold; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase.

Table 3. One-Way ANOVA Results for BDNF Expression Across Groups

Dependent Variable	F (df)	*P* value	Partial η²
Striatum BDNF	24.29 (4.45)	<0.001	0.683
Substantia nigra BDNF	55.16 (4.45)	<0.001	0.831

Note. ANOVA: Analysis of variance; BDNF: Brain-derived neurotrophic factor.

Table 4. Tukey's HSD Pairwise Comparisons for Striatum BDNF

Comparison	Mean Difference	95% CI	*P* value
HC vs. PD	0.354	0.228–0.480	<0.001
PD-AE vs. PD	0.247	0.121–0.373	<0.001
PD-RE vs. PD	0.191	0.065–0.316	0.001
PD-COM vs. PD	0.389	0.263–0.515	<0.001
PD-COM vs. PD-AE	0.142	0.016–0.268	0.020
PD-COM vs. PD-RE	0.198	0.073–0.324	<0.001

Note. HSD: Honestly significant difference; CI: Confidence interval; HC: Healthy control; PD-AE: Parkinson + aerobic; PD-RE: Parkinson + resistance; PD-COM: Parkinson + combined.

Discussion

The present study provided a comparative evaluation of aerobic, resistance, and combined exercise training on BDNF mRNA expression in two critical regions of the nigrostriatal pathway, the striatum and substantia nigra, in a unilateral 6-OHDA-induced Parkinsonian rat model. It was revealed that all exercise modalities significantly increased BDNF expression compared with sedentary Parkinsonian animals, while combined aerobic and resistance training produced the greatest increase under the present experimental conditions. These findings suggest that exercise modality influences the magnitude of BDNF-related transcriptional responses following dopaminergic injury. Importantly, given that this study assessed only *BDNF* gene expression, the observed changes should be interpreted as molecular adaptations associated with exercise exposure rather than direct evidence of neuronal preservation, synaptic restoration, or functional recovery.

The reduced BDNF expression observed in Parkinsonian animals is consistent with previous evidence demonstrating the disruption of neurotrophic signaling following dopaminergic degeneration. BDNF is considered an important regulator of neuronal plasticity, synaptic remodeling, and adaptive responses within the central nervous system through the activation of signaling pathways such as TrkB-dependent mechanisms (4 and 5). According to previous experimental research, neurotoxic models of PD can alter neurotrophic factor expression; however, the extent of these alterations varies according to lesion model, severity of dopaminergic damage, and experimental timing (14). Therefore, the reduction of BDNF expression observed in the Parkinsonian non-exercise group may reflect impaired neurotrophic regulation following 6-OHDA-induced nigrostriatal disruption.

Aerobic training markedly increased BDNF expression in both examined brain regions, which is in line with the findings of previous experimental studies, showing that endurance-based exercise enhances neurotrophic responses

Table 5. Tukey's HSD Pairwise Comparisons for Substantia Nigra BDNF

Comparison	Mean Difference	95% CI	*P* value
HC vs. PD	0.489	0.366–0.612	<0.001
PD-AE vs. PD	0.427	0.304–0.550	<0.001
PD-RE vs. PD	0.283	0.160–0.405	<0.001
PD-COM vs. PD	0.583	0.460–0.706	<0.001
PD-COM vs. PD-AE	0.156	0.033–0.279	0.007
PD-COM vs. PD-RE	0.300	0.177–0.423	<0.001
PD-AE vs. PD-RE	0.144	0.021–0.267	0.014

Note. HSD: Honestly significant difference; HC: Healthy control; PD-AE: Parkinson + aerobic; PD-RE: Parkinson + resistance; PD-COM: Parkinson + combined; CI: Confidence interval.

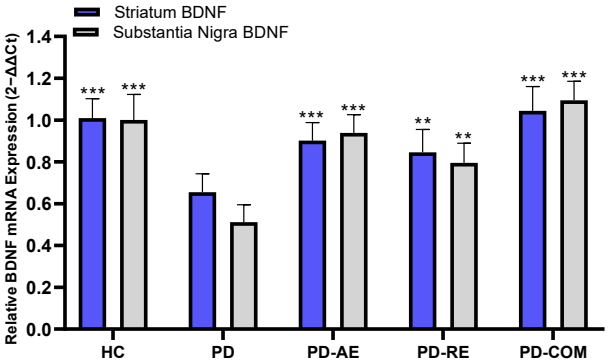

Figure 2. Relative BDNF mRNA Expression in **(A)** Striatum and **(B)** Substantia Nigra Across Experimental Groups

Note. BDNF: Brain-derived neurotrophic factor; mRNA: Messenger ribonucleic acid; SD: Standard deviation; ANOVA: Analysis of variance; Ct: Cycle threshold; PD: Parkinson's disease. Data are expressed as means ± SD (n = 10). Asterisks represent significant differences vs. the PD group ($^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$; one-way ANOVA, Tukey's post hoc). RNA quality and Ct values were consistent across groups (Table 5).

in Parkinsonian models. Nikokalam Nazif et al found that treadmill exercise increased *BDNF* gene expression in an 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinsonian mouse model, supporting the concept that aerobic activity can stimulate neurotrophic adaptations following dopaminergic injury (9). In addition, some studies reported that aerobic exercise-induced BDNF regulation may involve activity-dependent neuronal signaling, metabolic adaptations, and increased expression of plasticity-related pathways (6,8). Nevertheless, differences in experimental models, exercise intensity, duration, and biological outcomes assessed may explain variations among studies.

Likewise, resistance training could remarkably increase BDNF expression compared with sedentary Parkinsonian animals. Although resistance exercise has historically been investigated primarily in relation to muscular adaptations, emerging evidence indicates that mechanical loading may influence neurobiological responses through systemic metabolic alterations and exercise-induced signaling molecules. Previous studies have confirmed the heterogeneous effects of resistance training on BDNF-related outcomes, which may be attributed to differences in training protocols, loading progression, participant characteristics, and measurement techniques (18,19). In the current study, the progressive resistance protocol may

have provided an adequate stimulus for inducing BDNF transcriptional changes; however, the specific biological mechanisms underlying this response remain to be clarified.

A central finding of the present study was that combined exercise could considerably increase BDNF expression compared with isolated aerobic or resistance training. One possible explanation is that combined training integrates distinct physiological stimuli associated with both endurance and resistance exercise. Aerobic exercise may primarily enhance activity-dependent and metabolic pathways, whereas resistance exercise may contribute to additional mechanical and peripheral signals. The simultaneous activation of these complementary stimuli may create a broader regulatory environment for BDNF expression. However, this interpretation should be considered hypothesis-generating, as the present study did not directly measure downstream molecular pathways, including TrkB, CREB, PI3K/Akt signaling, or related neuroplasticity markers.

The findings are broadly consistent with those of previous research, suggesting that multimodal exercise may influence neurotrophic responses in PD. Recent clinical evidence indicates that combined exercise approaches may improve several functional outcomes and may be associated with changes in neurotrophic markers in individuals with PD (3,13). Similarly, experimental investigations have demonstrated that exercise can regulate neurotrophic and inflammatory pathways in Parkinsonian animal models (15). Nonetheless, direct comparison between the present findings and those of previous studies requires caution because existing literature substantially differs regarding animal models, exercise dose, disease stage, and outcome assessment. Therefore, the greater BDNF response observed after combined exercise in the current study should be interpreted as a modality-specific molecular response within this experimental framework rather than definitive evidence that combined exercise universally produces superior outcomes in PD.

Likewise, an important observation of the present study was that BDNF responses were detected in both the striatum and substantia nigra, although the magnitude of changes differed between regions. The substantia nigra represents the primary site of dopaminergic neuron vulnerability in PD, while the striatum serves as a major target region receiving dopaminergic projections. Accordingly, differences in regional responsiveness may reflect variations in baseline neurotrophic regulation, cellular vulnerability, or local adaptive capacity following neurotoxic injury. Nevertheless, the functional relevance of these region-specific molecular responses remains uncertain because neuronal survival, dopamine concentration, and histological alterations were not assessed in this study.

The interpretation of these findings should consider several limitations. First, the unilateral 6-OHDA model used in this study represents an acute neurotoxic lesion characterized by selective dopaminergic disruption and does not fully replicate the progressive and multifactorial nature of human PD. Hence, the observed changes in BDNF mRNA expression should not be interpreted as evidence of clinical efficacy or as direct support for specific rehabilitation protocols. Moreover, the relatively short intervention period and absence of longitudinal follow-up prevented conclusions regarding the durability of these molecular adaptations over the course of disease progression. Additionally, the present study evaluated BDNF at the transcriptional level only; therefore, increased mRNA expression cannot be assumed to reflect corresponding changes in protein abundance or biological activity. Furthermore, the absence of behavioral, histological, and neurochemical assessments limited conclusions regarding whether BDNF modulation was accompanied by functional improvements.

Finally, the intervention duration and single post-intervention assessment point prevented the determination of the persistence of exercise-induced molecular adaptations.

Conclusion

Combined aerobic and resistance exercise induced the higher increase in BDNF mRNA expression in the striatum and substantia nigra among the evaluated exercise modalities in a unilateral 6-OHDA-induced Parkinsonian rat model. In addition, aerobic and resistance training increased BDNF expression compared with sedentary Parkinsonian animals, indicating that different exercise modalities can modulate neurotrophic-related transcriptional responses following dopaminergic injury. Overall, these findings provide experimental evidence that combined exercise may represent a potent stimulus for regulating BDNF expression; however, they should not be interpreted as direct evidence of neuroprotection, neuronal recovery, or clinical effectiveness. Future studies incorporating behavioral assessments, protein-level analyses, dopaminergic markers, and longitudinal follow-ups are required to determine whether exercise-induced BDNF modulation is associated with functional benefits in PD.

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Artificial Intelligence Use Disclosure

It should be noted that artificial intelligence was used for language editing in the manuscript.

Authors' Contribution

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Formal Analysis: Elham Anari, Jamshid Banaei Borojeni, Elham Eftekhari Gheinani, Hamid Zahedi
Investigation: Elham Anari, Jamshid Banaei Borojeni, Elham Eftekhari Gheinani, Hamid Zahedi
Methodology: Jamshid Banaei Borojeni
Project Administration: Jamshid Banaei Borojeni
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Software: Jamshid Banaei Borojeni, Elham Eftekhari Gheinani
Supervision: Jamshid Banaei Borojeni
Validation: Jamshid Banaei Borojeni
Visualization: Elham Anari, Jamshid Banaei Borojeni, Elham Eftekhari Gheinani, Hamid Zahedi
Writing–Original Draft: Elham Anari, Elham Eftekhari Gheinani
Writing–Review & Editing: Elham Anari, Jamshid Banaei Borojeni, Elham Eftekhari Gheinani, Hamid Zahedi

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Data Availability Statement

The datasets generated during this study, including raw qPCR data, behavioral assessment records, and animal model parameters, are available upon reasonable request from the corresponding author. Data sharing also complies with institutional ethical guidelines for animal research confidentiality.

Ethical Approval

All experimental procedures involving animals were approved by the Ethics Committee of Islamic Azad University of Najafabad (approval No. IR.IAU.NAJAFABAD.REC.1404.093) and were conducted in full accordance with international guidelines for the care and use of laboratory animals (directive 2010/63/EU), the ARRIVE 2.0 guidelines for reporting animal research, and the institutional ethical standards of the Marvdasht Laboratory Research Center.

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References

1. GBD 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018;17(11):939-53. doi:10.1016/s1474-4422(18)30295-3
2. Lei S, Chen X, Chen P, Wang Z. Exercise prevention and treatment of Parkinson's disease mediated by brain-derived neurotrophic factor: role and mechanism. Chin J Tissue Eng Res 2025;29(25):5454-68. doi:10.12307/2025.503
3. Kaagman DG, van Wegen EE, Cignetti N, Rothermel E, Vanbellingen T, Hirsch MA. Effects and mechanisms of exercise on brain-derived neurotrophic factor (BDNF) levels and clinical outcomes in people with Parkinson's disease: a systematic review and meta-analysis. Brain Sci 2024;14(3):194. doi:10.3390/brainsci14030194
4. Bhardwaj R, Deshmukh R. Neurotrophic factors and Parkinson's disease. Clin Investig 2018;7(4):53-62.
5. Miller KM, Mercado NM, Sortwell CE. Synucleinopathy-associated pathogenesis in Parkinson's disease and the potential for brain-derived neurotrophic factor. NPJ Parkinsons Dis 2021;7(1):35. doi:10.1038/s41531-021-00179-6
6. Sleiman SF, Henry J, Al-Haddad R, El Hayek L, Abou Haidar E, Stringer T, et al. Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body β-hydroxybutyrate. Elife 2016;5. doi:10.7554/eLife.15092
7. Chen Y, Chen Y. The impact of combined aerobic and resistance exercise on the prognosis of early Parkinson's disease patients. Technol Health Care 2025;33(1):205-14. doi:10.3233/thc-240821
8. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci 2002;25(6):295-301. doi:10.1016/s0166-2236(02)02143-4
9. Nikokalam Nazif N, Khosravi M, Ahmadi R, Bananej M, Majd A. Effect of treadmill exercise on catalepsy and the expression of the BDNF gene in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine -induced Parkinson in male NMRI mice. Iran J Basic Med Sci 2020;23(4):483-93. doi:10.22038/ijbms.2020.37707.8960
10. Li JA, Loevaas MB, Guan C, Goh L, Allen NE, Mak MK, et al. Does exercise attenuate disease progression in people with Parkinson's disease? A systematic review with meta-analyses. Neurorehabil Neural Repair 2023;37(5):328-52. doi:10.1177/15459683231172752
11. Paterno A, Polsinelli G, Federico B. Changes of brain-derived neurotrophic factor (BDNF) levels after different exercise protocols: a systematic review of clinical studies in Parkinson's disease. Front Physiol 2024;15:1352305. doi:10.3389/fphys.2024.1352305
12. Rafie F, Rajizadeh MA, Shahbazi M, Pourranjbar M, Nekouei AH, Sheibani V, et al. Effects of voluntary, and forced exercises on neurotrophic factors and cognitive function in animal models of Parkinson's disease. Neuropeptides 2023;101:102357. doi:10.1016/j.npep.2023.102357
13. Rotondo R, Proietti S, Perluigi M, Padua E, Stocchi F, Fini M, et al. Physical activity and neurotrophic factors as potential drivers of neuroplasticity in Parkinson's disease: a systematic review and meta-analysis. Ageing Res Rev 2023;92:102089. doi:10.1016/j.arr.2023.102089
14. Blesa J, Przedborski S. Parkinson's disease: animal models and dopaminergic cell vulnerability. Front Neuroanat 2014;8:155. doi:10.3389/fnana.2014.00155
15. Abdi Sorve E, Tofigi A, Ghaderi Pakdel F, Ashrafi Osalou M. The effect of 3 different training patterns on the muscle strength of Parkinsonian rats induced by 6-hydroxydopamine. Stud Med Sci 2016;27(4):288-300.
16. Schwarting RK, Huston JP. The unilateral 6-hydroxydopamine lesion model in behavioral brain research. Analysis of functional deficits, recovery and treatments. Prog Neurobiol 1996;50(2-3):275-331. doi:10.1016/s0301-0082(96)00040-8
17. Tuon T, Souza PS, Santos MF, Pereira FT, Pedroso GS, Luciano TF, 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. doi:10.1155/2015/261809
18. Forti LN, Van Roie E, Njemini R, Coudyzer W, Beyer I, Delecluse C, et al. Dose-and gender-specific effects of resistance training on circulating levels of brain derived neurotrophic factor (BDNF) in community-dwelling older adults. Exp Gerontol 2015;70:144-9. doi:10.1016/j.exger.2015.08.004
19. Hortobágyi T, Vetrovsky T, Balbim GM, Sorte Silva NC, Manca A, Deriu F, et al. The impact of aerobic and resistance training intensity on markers of neuroplasticity in health and disease. Ageing Res Rev 2022;80:101698. doi:10.1016/j.arr.2022.101698