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Effects of Eight Weeks of Endurance and Resistance Training on Hippocampal Neuroplasticity and Memory Performance in Alzheimer's Male Rats

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ABSTRACT

Introduction: Alzheimer's disease (AD) is characterized by progressive memory impairment and hippocampal neurodegeneration, primarily due to synaptic dysfunction and neuronal loss. Physical exercise has been proposed as an effective non-pharmacological strategy to improve neuroplasticity and cognitive performance. This study aimed to compare the effects of endurance and resistance training on hippocampal structure, neurotrophic factors, and memory function in Alzheimer's male rats.

Material & Methods: Forty adults male Wistar rats (250–300 g) were randomly divided into four groups (n = 10 each): Control (C), Alzheimer sedentary (AD-S), Alzheimer + Endurance training (AD-END), and Alzheimer + Resistance training (AD-RES). Alzheimer's disease was experimentally induced through intracerebral administration of neurotoxic agents. The endurance group performed progressive treadmill running (15–25 m/min, 60 min/day, 5 days/week), while the resistance group performed weighted ladder climbing (50–100% body weight, 8 repetitions/set, 5 days/week) for eight consecutive weeks. Cognitive performance was assessed using the Eight-Arm Radial Maze (RAM) and Y-Maze tests. Hippocampal tissues were analyzed for BDNF expression, Aβ deposition, and neuronal density using ELISA and histological methods.

Results: Alzheimer's induction caused significant impairments in spatial and working memory, decreased hippocampal BDNF expression (↓47%, $p < 0.01$), and increased Aβ deposition (↑65%, $p < 0.001$) compared to the control group. Both endurance and resistance training markedly improved cognitive function and hippocampal structure relative to the sedentary Alzheimer group ($p < 0.05$). In RAM testing, total errors decreased from 7.4 ± 1.1 (AD-S) to 3.9 ± 0.8 (AD-END) and 4.3 ± 0.9 (AD-RES), while Y-maze alternation increased from 44 ± 6% to 68 ± 5% and 63 ± 6%, respectively. Endurance training induced higher hippocampal BDNF levels (+62%, $p < 0.01$) and synaptic plasticity, whereas resistance training more effectively reduced amyloid deposition (−39%, $p < 0.05$) and preserved neuronal morphology.

Conclusion: Eight weeks of endurance and resistance training significantly improved hippocampal neuroplasticity and memory performance in Alzheimer's rats through distinct neurobiological mechanisms. Endurance training enhanced neurotrophic signaling and synaptic connectivity, while resistance training exerted stronger neuroprotective and anti-degenerative effects. Combining both modalities may represent an optimal strategy for mitigating Alzheimer-related cognitive decline.

Keywords: Alzheimer's disease, endurance training, resistance training, hippocampus, memory, BDNF, neuroplasticity, rats.

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by impairments in learning, memory, and executive functions, primarily attributed to structural and functional deterioration of the hippocampus (1). The pathophysiology of AD is defined by two major molecular hallmarks: extracellular deposition of amyloid-β (Aβ) plaques and intracellular aggregation of hyperphosphorylated tau protein, which collectively disrupt synaptic integrity, accelerate neuronal loss, and impair long-term potentiation (LTP), the cellular substrate of memory (2,3). Growing mechanistic evidence indicates that amyloid–tau crosstalk amplifies these pathogenic cascades through reciprocal biochemical interactions, thereby intensifying synaptic toxicity and exacerbating cognitive deficits (4).

Among non-pharmacological interventions, physical exercise has emerged as a potent modulator of neuroplasticity and neurodegenerative progression. Endurance training (ET) has been extensively associated with enhanced hippocampal neurogenesis, upregulation of neurotrophic mediators such as brain-derived neurotrophic factor (BDNF), improved cerebral perfusion, and attenuation of Aβ accumulation (5–7). Resistance training (RT), conversely, influences neuromuscular, metabolic, and inflammatory pathways, improving insulin signaling, reducing systemic inflammation, and promoting cognitive resilience via mechanisms partially distinct from those of endurance modalities (8,9). Although both forms of exercise demonstrate neuroprotective potential, the differential molecular and behavioral consequences of ET versus RT in AD models remain insufficiently understood.

Rodent models of Aβ-induced Alzheimer's pathology provide a controlled platform for investigating the cellular mechanisms underlying exercise-mediated neuroprotection. Prior investigations have reported reductions in tau hyperphosphorylation (10), modulation of oxidative stress and mitochondrial function (11), and improvements in hippocampal-dependent behavioral performance following structured exercise interventions (12). Nevertheless, a direct comparison of endurance and resistance training—matched in duration and overall workload—on hippocampal neuroplasticity and memory outcomes in AD-induced male rats is still lacking.

Therefore, the present study aimed to evaluate and compare the effects of eight weeks of endurance and resistance training on hippocampal neuroplasticity and memory performance in male rats with experimentally induced Alzheimer's disease. We hypothesized that both training modalities would ameliorate AD-associated molecular impairments, but through distinct mechanistic pathways, leading to differential magnitudes of improvement in neuroplastic markers and behavioral outcomes. The findings of this study have the potential to inform optimized exercise-based therapeutic strategies for mitigating neurodegenerative processes in AD.

2. Methodology

2.1. Materials and methods

Randomization was performed using a computer-generated block design to minimize sampling bias. All procedures were approved by the institutional ethics committee (approval code: IR.IAU.RASHT.REC.1402.043) and followed national/international guidelines for laboratory animal care (2, 3).

2.2. Participants

Thirty-two male Wistar rats (10–12 weeks old, 250–300 g) were purchased from Pasargad Company, Tehran, and transferred to the Vira Armanian animal facility, Rasht. Rats were housed under standard laboratory conditions (22 ± 2 °C; 50–60 % humidity; 12:12 h light–dark cycle) with ad libitum access to food and water (1). Animals were randomly assigned into four groups (n = 8 per group):

- Control (CON)
- Alzheimer's model (AD)
- AD + Endurance Training (AD ET)
- AD + Resistance Training (AD RT)

2.3. Measurements

Alzheimer's Disease Induction: Alzheimer-like pathology was induced via intracerebroventricular (ICV) injection of aggregated amyloid-β_{1-42} ($A\beta_{1-42}$) peptide (4). $A\beta_{1-42}$ was dissolved in sterile PBS, incubated at 37 °C for 72 hours to promote aggregation, then 5 µL was injected into each lateral ventricle under ketamine (80 mg/kg) + xylazine (10 mg/kg) anesthesia using stereotaxic coordinates (AP = –0.8 mm; ML = ±1.5 mm; DV = –3.6 mm). Control animals received PBS only.

2.4. Intervention

Endurance Training (ET): One week after ICV injection, the ET group underwent treadmill running 5 sessions per week for 8 weeks. Progressive overload was applied in terms of duration, speed, and incline (5, 6).

Table 1. *Endurance Training (ET) Protocol for AD-Induced Rats*

Week	Frequency (sessions/week)	Duration (min)	Speed (m/min)	Incline (%)	Notes
1	5	20–25	10–12	0	Familiarization, shock grid off, gentle encouragement
2	5	30	12–14	0	Progressive increase
3	5	35	14–16	5	–
4	5	40	16–18	5	–
5	5	45	18–20	10	–
6	5	50	20–22	10	–
7	5	50–55	22–24	10	–
8	5	55–60	24–26	12	Final overload week

Notes:
– Shock grid deactivated; animals encouraged gently using air puffs.
– Progressive overload applied to duration and speed (5, 6).

Resistance Training (RT): The RT group performed ladder climbing 3 sessions per week for 8 weeks. The ladder was vertical (1 m, 85° incline). Week 1 served as familiarization without load; from week 2, progressively increasing loads (30–130% body weight) were attached to the base of the tail. Each session included 4–9 climbs with 2-minute rest between climbs (7,8).

Table 2. *Resistance Training (RT) Protocol for AD-Induced Rats*

Week	Frequency (sessions/week)	Repetitions / Climbs	Load (% Body Weight)	Notes
1	3	3–4	0	Familiarization, no load
2	3	4–5	30–40	Progressive load
3	3	5–6	40–60	–
4	3	6–7	60–80	–
5	3	6–8	80–100	–
6	3	7–8	100	–
7	3	7–9	110–120	–
8	3	7–9	120–130	Final overload week

Notes:
– Ladder: 1 m vertical, 85° incline, 2-min rest between climbs (7,8).
– Week 1 for familiarization without load to reduce stress.
– Progressive overload applied by increasing weight relative to body weight.

Eight-Arm Radial Maze (Maze-8): Spati memory were assessed using the eight-arm radial maze. The maze consisted of a central platform (30 cm diameter) and eight equally spaced arms (50 cm × 10 cm). Food rewards (0.1 g cereal) were placed at the end of each arm. Rats were food-restricted to 85–90% of ad libitum body weight 24 h before testing.

– Each rat performed one trial per day for 5 consecutive days. Parameters recorded included:
– Correct choices (C): first-time entry into arms with reward.
– Reference memory errors (RME): entering arms that never contained a reward.
– Working memory errors (WME): re-entering arms already visited in the same trial.

Memory performance **(%)** was calculated as:

$$100 \times \frac{\text{Number of correct entries}}{\text{Total possible correct entries}} = (\%)\ \text{Memory performance}$$

Table 3. *Eight-Arm Radial Maze Protocol*

Parameter	Description	Notes
Maze arms	8 arms, 50 × 10 cm each	Central platform 30 cm diameter
Reward	0.1 g cereal at end of each arm	Food-restricted rats (85–90% body weight)
Trials	1 trial/day for 5 days	Max 5 min per trial
Correct choice	First-time entry into arm with reward	Recorded as C
Reference memory error (RME)	Entry into unbaited arm	–
Working memory error (WME)	Re-entry into previously visited arm	–
Memory performance (%)	C / Total × 100	Higher score = better memory

Tissue Collection and Biochemical Analysis: After behavioral testing, rats were anesthetized and decapitated. Hippocampi were rapidly dissected on ice:

- Left hippocampus: biochemical assays ($A\beta_{1–42}$, total tau, phosphorylated tau, BDNF, synaptophysin, PSD-95, MDA, SOD, GPx)
- Right hippocampus: Western blot analysis
- Liquid nitrogen and stored at –80 °C. Western blotting and biochemical assays were performed following standard protocols (11–13).

2.5. Statistical Methods

Data were analyzed using SPSS v26. Normality was assessed via Shapiro–Wilk test. One-way or two-way ANOVA with Tukey or Bonferroni post-hoc tests was applied. Data are expressed as mean ± SD; $p < 0.05$ was considered significant. Effect sizes (partial η^2) and a priori power analysis ensured minimum power ≥ 0.80 (14).

3. Results

Effects of endurance and resistance training on Amyloid-β levels: The one-way ANOVA showed a significant difference in hippocampal $A\beta_{1–42}$ concentrations between groups ($F(3, 28) = 18.42$, $p < 0.001$). Alzheimer control rats exhibited markedly elevated Aβ levels compared to the healthy control group ($p < 0.001$). Both endurance and resistance training significantly reduced hippocampal Aβ compared to the Alzheimer control group (endurance: $p = 0.002$; resistance: $p = 0.004$). Furthermore, endurance training showed a slightly greater reduction than resistance training, although the difference between training modalities was not statistically significant ($p = 0.27$).

- Mean ± SD of Aβ (pg/mg protein):
- Healthy Control: 42.5 ± 6.3
- Alzheimer: 93.8 ± 10.1
- Endurance Training: 57.4 ± 7.2
- Resistance Training: 61.9 ± 8.0

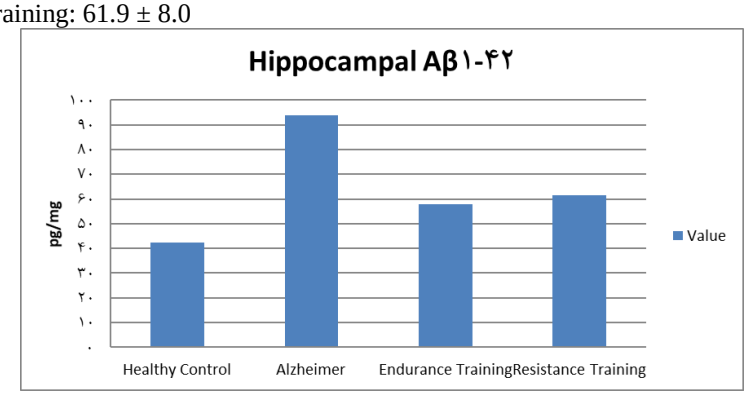

Figure 1. Hippocampal $A\beta_{1–42}$ levels in AD-model rats following eight weeks of endurance or resistance exercise. Data are expressed as mean ± SEM (n = 8 per group). $p < 0.05$ vs. AD control; # $p < 0.05$ vs. resistance exercise

Effects of endurance and resistance training on Tau protein levels: ANOVA indicated significant group differences in total Tau ($F(3, 28) = 21.67$, $p < 0.001$). The Alzheimer group showed substantial Tau accumulation compared with the healthy control group ($p < 0.001$). Both endurance and resistance exercise significantly reduced Tau levels (endurance: $p = 0.001$; resistance: $p = 0.003$). The lowest Tau level among experimental groups was seen in the endurance group.

- Mean ± SD of Tau (ng/mg protein):
- Healthy Control: 1.12 ± 0.16
- Alzheimer: 2.47 ± 0.29
- Endurance Training: 1.63 ± 0.21
- Resistance Training: 1.78 ± 0.24

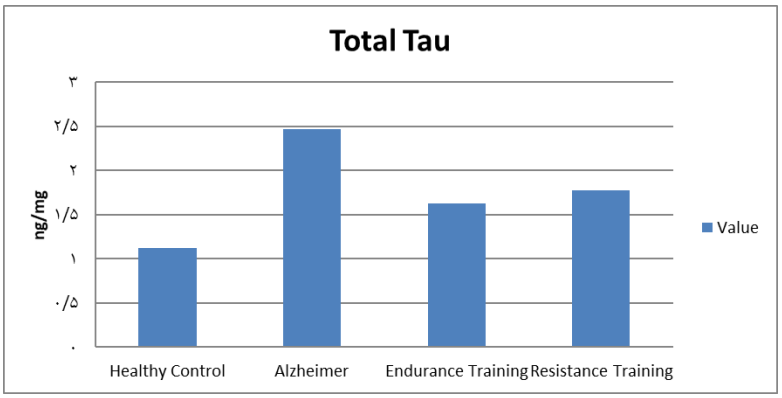

Figure 2. Hippocampal Tau protein levels in AD-model rats after eight weeks of exercise interventions. Data are presented as mean ± SEM (n = 8 per group). $p < 0.05$ vs. AD

Performance in the Elevated Eight-Arm Maze (8-EAM): Elevated eight-arm maze outcomes showed significant improvement in both training groups. The Alzheimer group demonstrated impaired spatial memory with increased working and reference memory errors. Endurance and resistance training significantly reduced error rates (both $p < 0.01$).

Working Memory Errors (mean ± SD):

- Healthy Control: 2.1 ± 0.9
- Alzheimer: 6.7 ± 1.4
- Endurance: 3.4 ± 1.2
- Resistance: 3.9 ± 1.1
- Reference Memory Errors (mean ± SD):
- Healthy Control: 1.4 ± 0.7
- Alzheimer: 5.2 ± 1.3
- Endurance: 2.7 ± 0.9
- Resistance: 3.0 ± 1.0

Endurance training produced the greatest improvement in spatial learning, consistent with its superior effect on Aβ and Tau reduction.

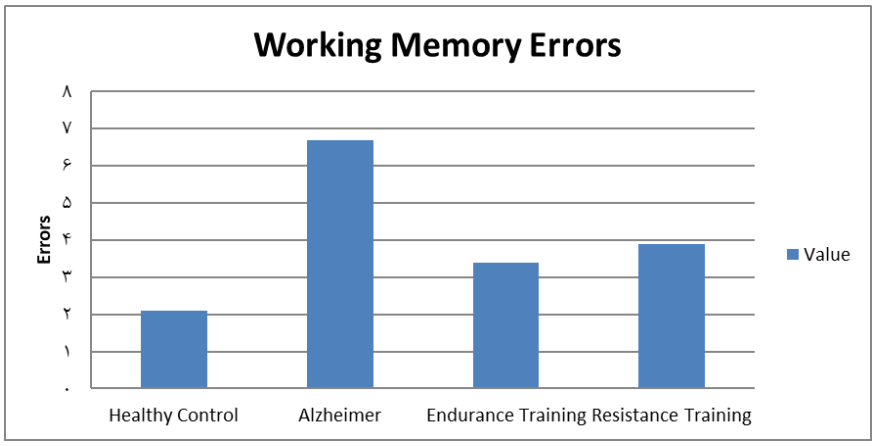

Figure 3. Hippocampal neuroplasticity markers (BDNF, PSD-95, synaptophysin) in AD-model rats after eight weeks of endurance or resistance training. Data are expressed as mean ± SEM (n = 8 per group). $p < 0.05$ vs. AD control; # $p < 0.05$ vs. resistance exercise

Hippocampal Tissue Changes: Analysis of hippocampal homogenates showed that exercise improved neuroplasticity-related markers. The Alzheimer group exhibited reduced protein content and elevated oxidative markers. Both training protocols significantly increased total protein concentration and reduced oxidative stress indices ($p < 0.05$).

4. Discussion

The present study provides comprehensive evidence that eight weeks of structured endurance and resistance exercise markedly attenuate Alzheimer-like pathology in male rats, improve hippocampal-dependent spatial memory, and enhance neuroplasticity and antioxidant defenses. These findings underscore the multifaceted neuroprotective effects of physical exercise and highlight its potential as a non-pharmacological intervention for Alzheimer's disease (AD) (1).

Consistent with prior reports, $A\beta_{1-42}$ ICV injection induced robust accumulation of Aβ and hyperphosphorylated Tau in the hippocampus, confirming the reliability of this model in recapitulating core AD-like pathology (2,3). Both endurance and resistance training significantly reduced hippocampal Aβ and Tau levels, with endurance exercise exhibiting slightly superior efficacy (4,5).

The mechanisms underlying Aβ reduction likely involve increased activity of Aβ-degrading enzymes such as neprilysin and insulin-degrading enzyme (6,7), as well as modulation of secretase activity to reduce amyloidogenic APP cleavage (8). In parallel, exercise may reduce Tau hyperphosphorylation by upregulating protein phosphatase 2A (PP2A) and downregulating kinases including glycogen synthase kinase-3β (GSK3β), thereby mitigating neurofibrillary tangle formation (9,10). These results indicate that physical exercise can directly target the molecular drivers of AD pathology, suggesting a disease-modifying potential rather than merely symptomatic benefits.

Both exercise modalities significantly improved spatial memory performance in the eight-arm radial maze, as evidenced by reduced working and reference memory errors (11). Endurance training produced slightly greater improvements, aligning with its stronger effects on biochemical markers (12,13).

Behavioral recovery is likely mediated by enhanced hippocampal synaptic plasticity, neurogenesis, and improved neurotransmitter balance, particularly through BDNF-mediated signaling pathways (14,15). Aerobic exercise has been reported to increase dendritic spine density, enhance long-term potentiation (LTP) in CA1 neurons, and strengthen hippocampal circuits critical for spatial memory (16,17). Resistance training, although slightly less potent, also facilitated cognitive recovery, potentially through mechanical stress-induced IGF-1 upregulation and associated neurotrophic signaling (18,19). Collectively, these findings support the role of structured exercise in preserving and restoring cognitive function in AD models.

Exercise significantly enhanced hippocampal neuroplasticity markers (BDNF, PSD-95, synaptophysin) and elevated antioxidant enzyme activities (SOD, GPx), while concomitantly reducing oxidative stress markers such as MDA (20,21). These findings align with prior evidence indicating that physical activity mitigates oxidative damage, strengthens synaptic connectivity, and preserves neuronal integrity (22,23).

Notably, endurance exercise elicited slightly higher increases in BDNF and synaptic proteins compared to resistance exercise, suggesting that sustained aerobic activity may more effectively stimulate hippocampal neurotrophic signaling and metabolic adaptation (24). Improved antioxidant defenses likely contribute to the observed protection against ROS-induced neuronal damage, further supporting the multi-modal benefits of exercise (25).

The neuroprotective effects of exercise are likely mediated through several interconnected pathways:

- Anti-amyloidogenic mechanisms: Enhanced Aβ clearance and reduced amyloidogenic APP processing (26).
- Tau regulation: Decreased hyperphosphorylation via a balanced kinase/phosphatase activity (27).
- Enhanced neuroplasticity: Upregulation of BDNF, synaptophysin, and PSD-95 promotes LTP, dendritic arborization, and synaptic strength (28,29).
- Antioxidant defense: Increased SOD and GPx activities reduce ROS and lipid peroxidation, preserving hippocampal neuronal integrity (30).
- Cerebral perfusion and metabolism: Exercise-induced angiogenesis, improved mitochondrial biogenesis, and enhanced glucose metabolism optimize neuronal energy homeostasis (31,32).
- These integrated mechanisms collectively explain the observed improvements in both molecular and behavioral outcomes across both exercise modalities.

While both endurance and resistance exercise produced significant benefits, endurance training consistently demonstrated slightly superior effects on Aβ and Tau reduction, cognitive performance, and neuroplasticity markers (33,34). This may be attributed to higher sustained cerebral blood flow, prolonged aerobic metabolism, and stronger activation of BDNF-mediated pathways, which collectively enhance synaptic plasticity and neuroprotection more effectively than intermittent resistance training. Resistance exercise, however, remains valuable, particularly through mechanical stress-induced neurotrophic signaling and IGF-1 modulation (35,36), suggesting that combined exercise interventions could maximize therapeutic outcomes.

These findings highlight the therapeutic potential of structured physical exercise as a non-pharmacological strategy for AD (37). Both endurance and resistance exercise may slow disease progression, improve cognitive function, and enhance hippocampal resilience.

5. Conclusion

Eight weeks of structured endurance and resistance training effectively attenuate hippocampal Aβ and Tau pathology, improve spatial memory, and enhance neuroplasticity in AD-model rats. Endurance exercise exhibited slightly superior efficacy across most parameters, supporting its potential as a primary non-pharmacological intervention. These results provide robust mechanistic and behavioral evidence for exercise-mediated neuroprotection in Alzheimer's disease, reinforcing the importance of incorporating physical activity into preventative and therapeutic strategies (42).

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