



Physical Exercise Promotes Coordinated Muscle and Motor Cortex Plasticity Through Modulation of Disease-Related Pathology in 3xTg-AD Mice



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1. INTRODUCTION

Alzheimer's disease (AD) is the most prevalent neurodegenerative condition worldwide, characterized by progressive cognitive decline. Its hallmark histopathological features include neurofibrillary tangles formed by tau protein aggregates and neuritic plaques composed of amyloid-beta ($A\beta$) deposits. Beyond cognitive impairments, increasing evidence suggests that AD also affects motor function, leading to balance disturbances, muscle atrophy, and coordination difficulties. In light of this complexity, physical exercise has emerged as a promising non-pharmacological intervention, being a planned, repetitive, and regulated activity. However, its specific effects on motor deficits remain to be fully elucidated.

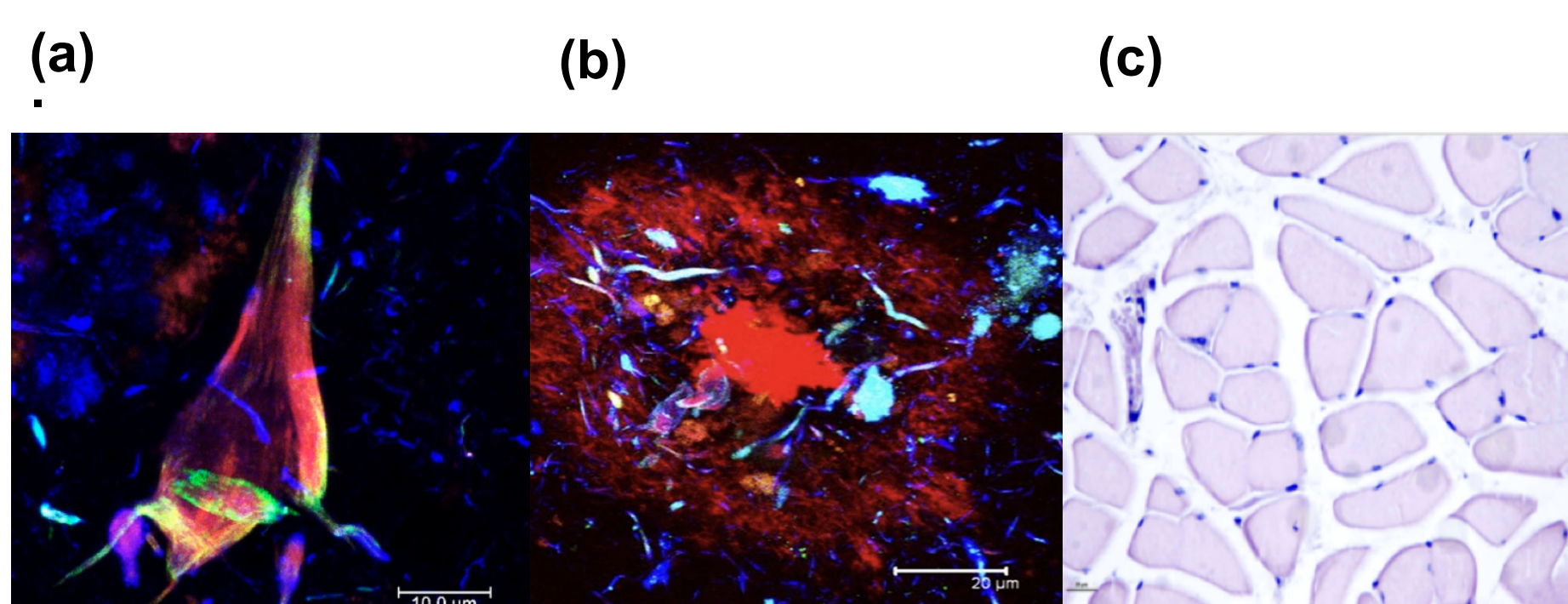


Figure 1. Neuropathological markers and ACC in AD. (a) Neurofibrillary tangles (b) Neuritic plaques (c) Muscle atrophy

2. OBJETIVE

This study aims to analyze the effects of physical exercise on motor impairments and neuropathological signs in the 3xTg-AD model of Alzheimer's disease.

3. METHODOLOGY

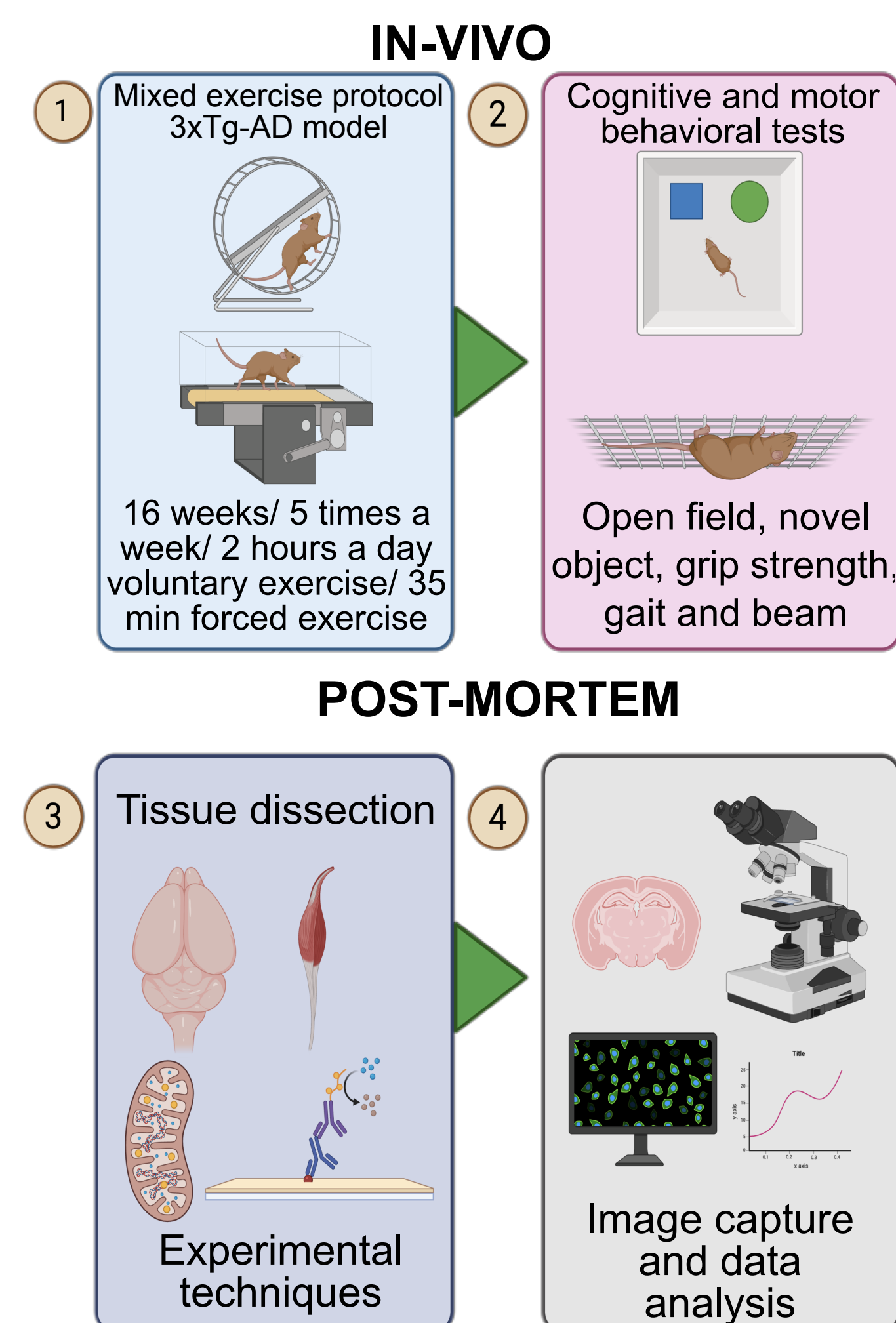


Figure 2. Methodology. A total of 64 twelve-month-old male mice (3xTg-AD and Non-Tg) were divided into four groups (n=16). A 16-week mixed exercise protocol was applied. Locomotor and cognitive performance were evaluated through behavioral tests. Muscle mass and mitochondrial activity in muscle and brain were assessed via bioimpedance, histology, and high-resolution respirometry.

4.1 Exercise Mitigates Motor Alterations Without Affecting Memory Performance in the 3xTg-AD Model

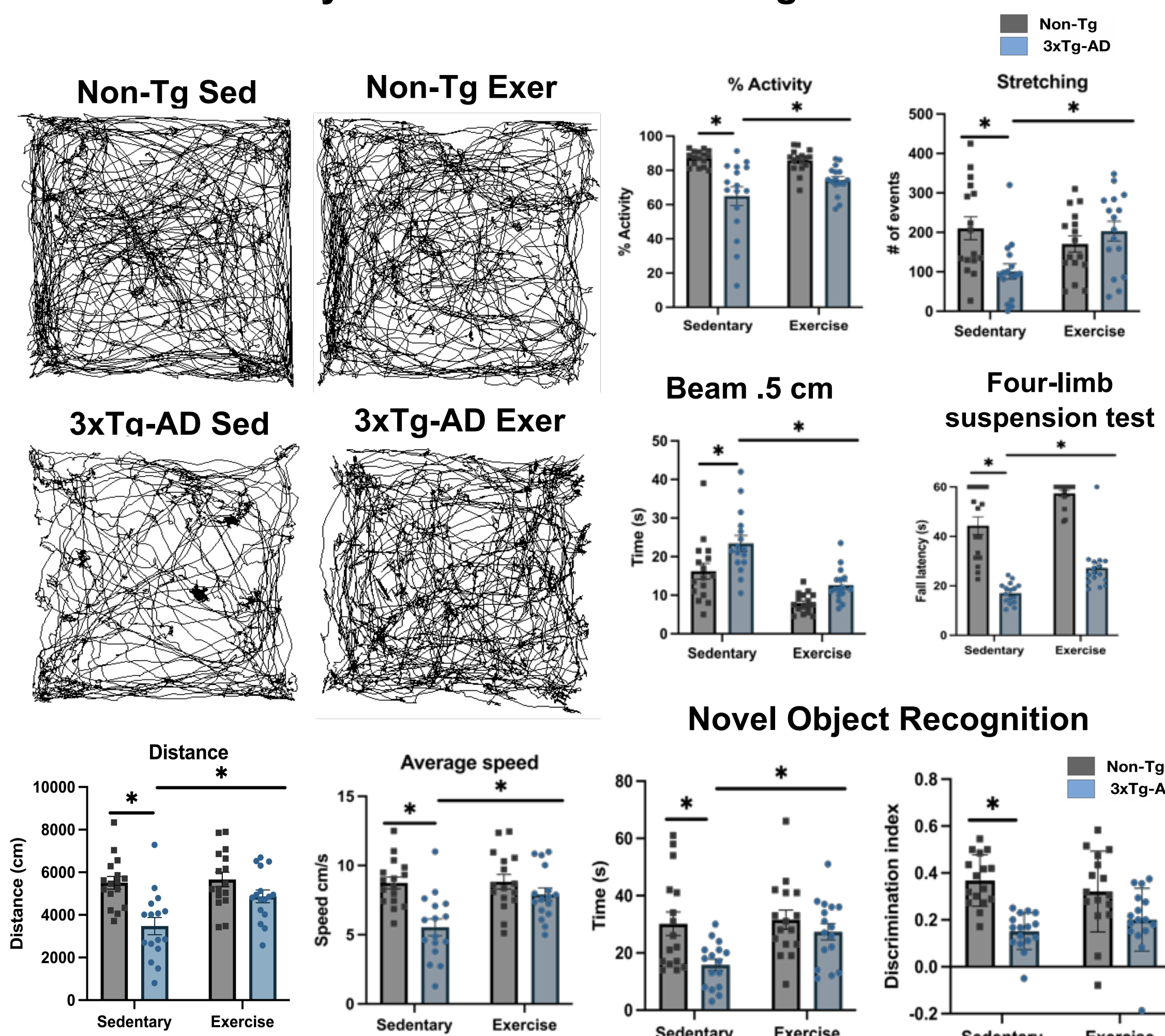


Figure 3. Exercise effects on motor and memory performance in the 3xTg-AD model. (a) Representative open field trajectories. (b-h) Behavioral assessments of motor function. (i-j) Recognition memory assessment. Data are presented as mean $\pm$ SEM (n = 16). Statistical analyses were performed using two-way ANOVA followed by Tukey's post hoc test. *p < 0.05.

4.4 Physical Exercise Selectively Modulates Amyloid Pathology

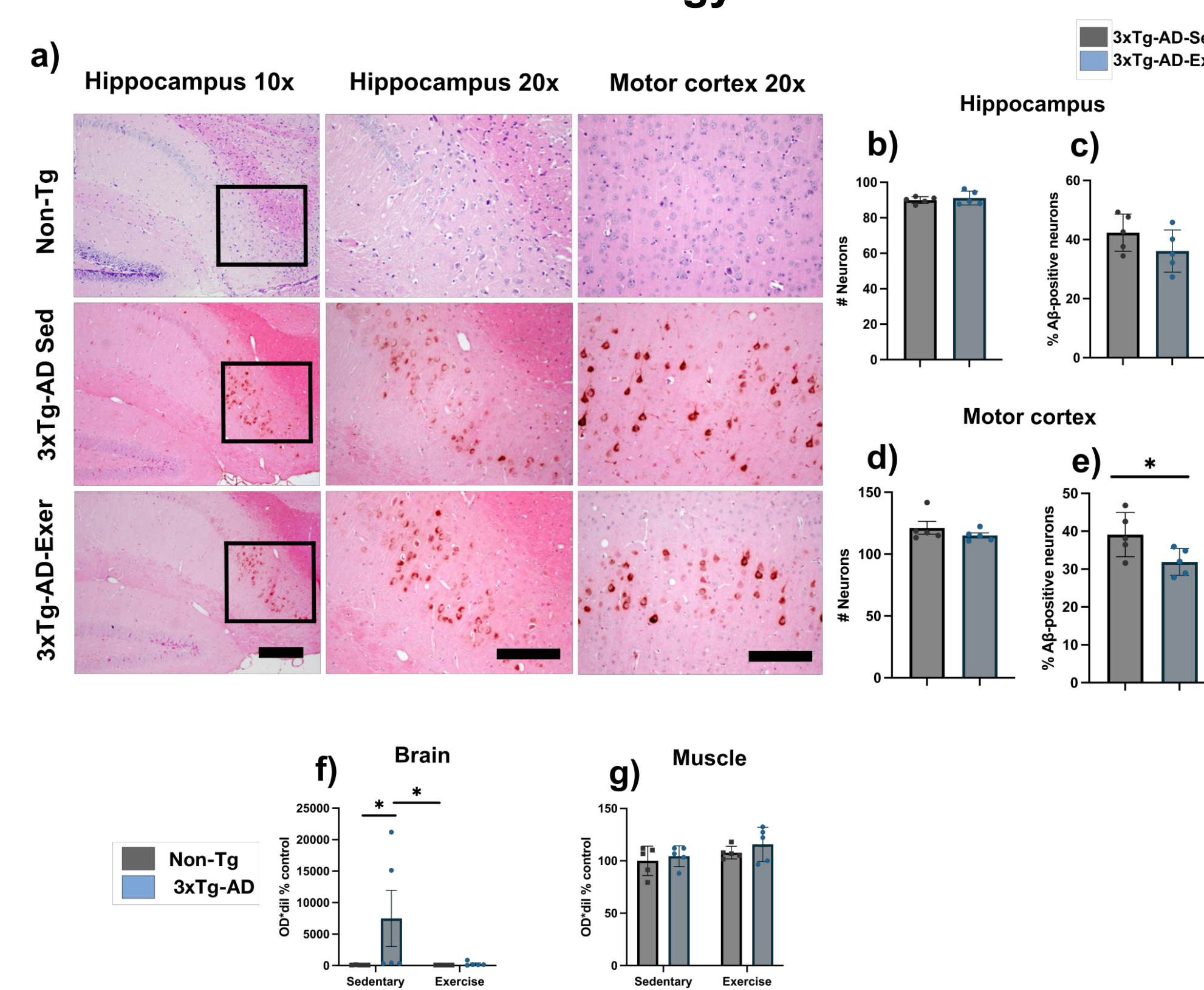


Figure 6. Effects of exercise on amyloid pathology. (a) Representative histological images of the hippocampus and motor cortex. (b-e) Histopathological assessments. (f-g) Biochemical assessments of amyloid burden. Data are presented as mean $\pm$ SEM (n = 5 per group). Statistical analyses were performed using Student's t-test. *p < 0.05.

5. CONCLUSIONS

The mixed physical exercise intervention improves motor performance and promotes coordinated structural and bioenergetic adaptations in the motor cortex and skeletal muscle in advanced stages of AD. These findings highlight physical exercise as a promising non-pharmacological strategy to preserve functionality and mitigate physical decline.

4. RESULTS

4.2 Exercise Induces Limited Changes in Gait Performance in the 3xTg-AD Model

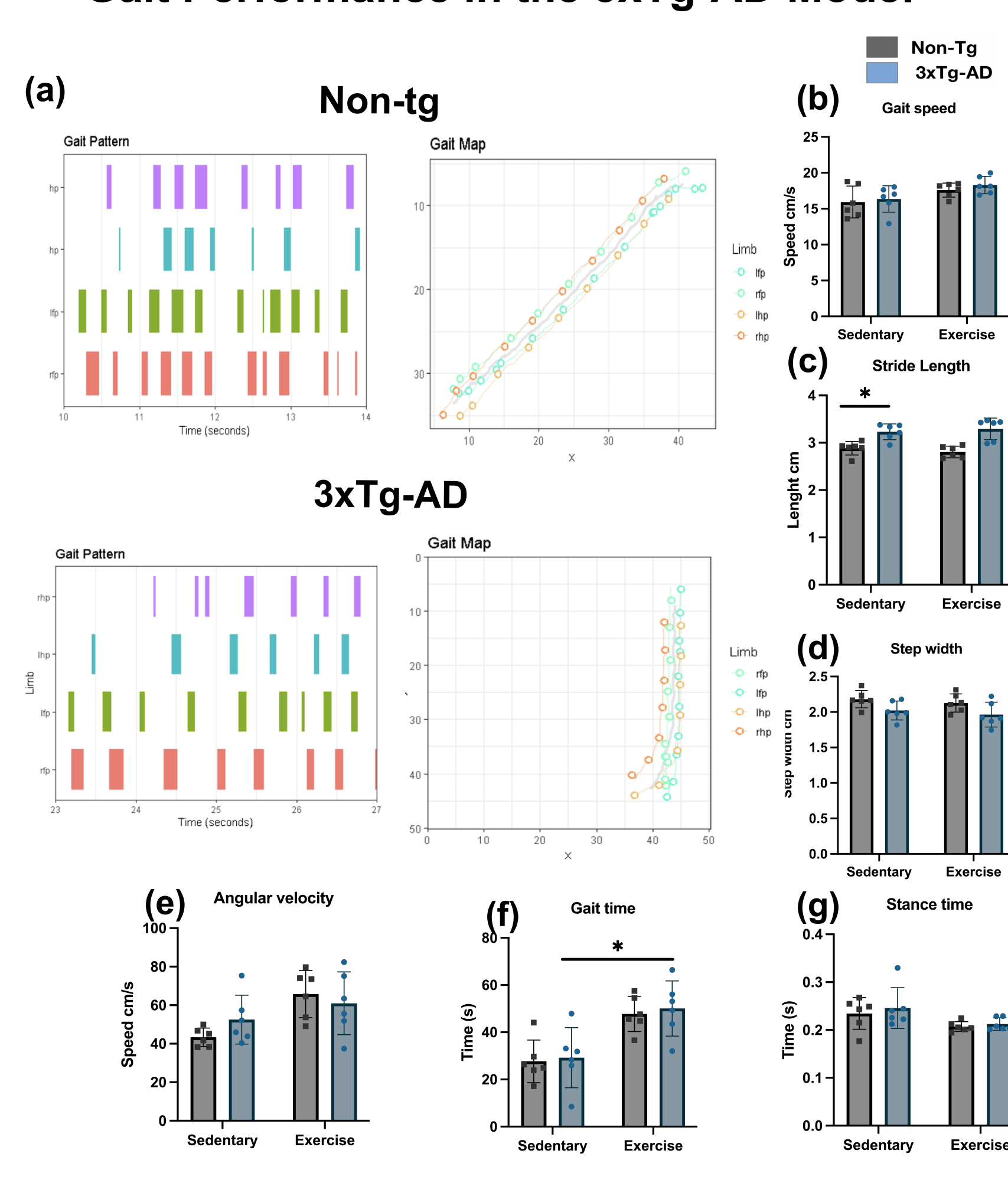


Figure 4. Exercise effects on gait performance in the 3xTg-AD model. (a) Representative gait patterns and gait maps. (b-g) Gait assessments. Data are presented as mean $\pm$ SEM (n = 6). Statistical analyses were performed using two-way ANOVA followed by Tukey's post hoc test. *p < 0.05.

4.3 Exercise Restores Body Composition and Muscle Morphology

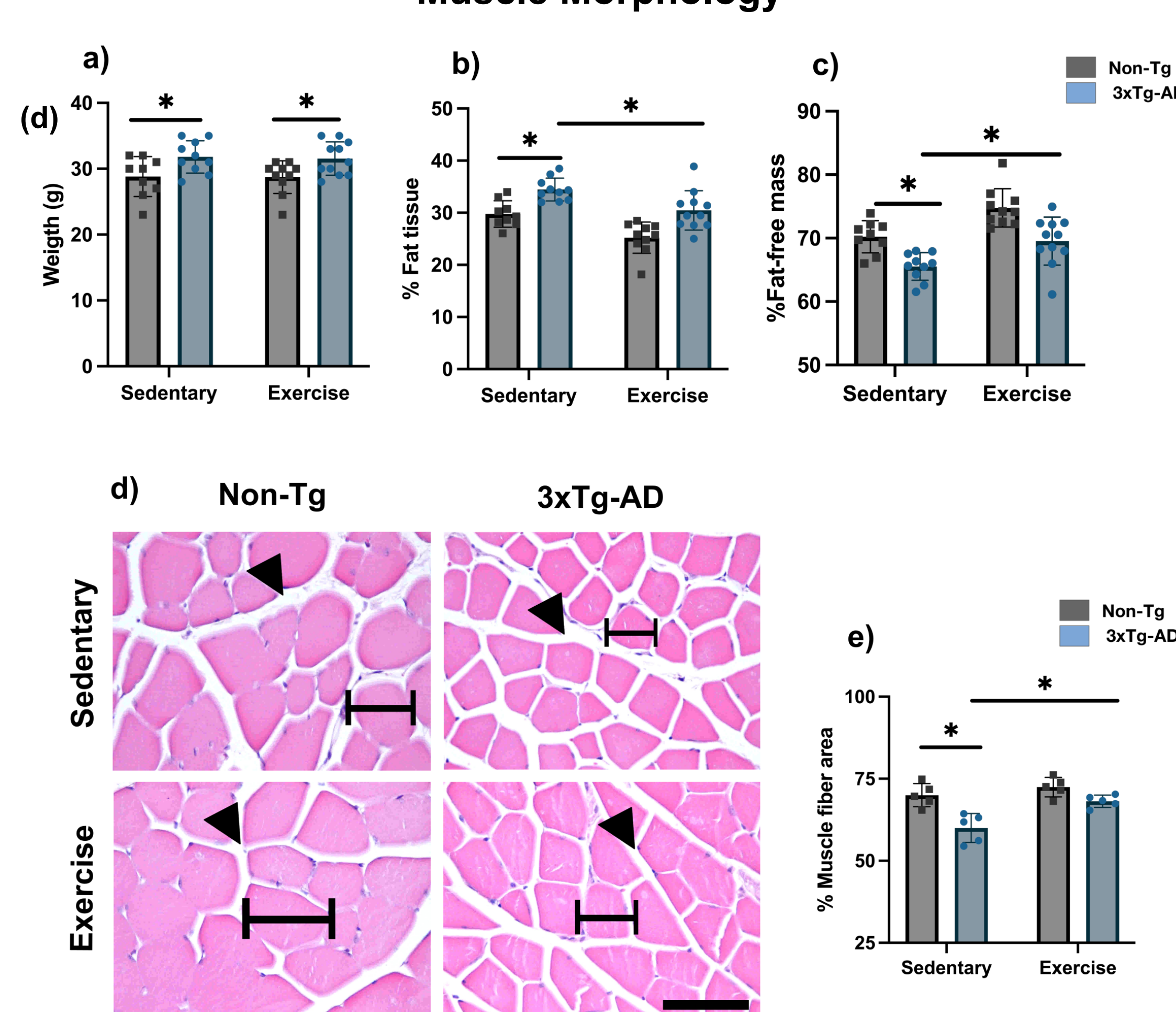


Figure 5. Exercise effects on body composition and muscle morphology in the 3xTg-AD model. (a-c) Body composition assessments. (d) Representative H&E images of skeletal muscle. (e) Muscle morphology assessment. Data are presented as mean $\pm$ SEM (n = 6-16). Statistical analyses were performed using two-way ANOVA followed by Tukey's post hoc test. *p < 0.05.

4.5 Exercise Induced Changes in Mitochondrial Complexes in Muscle and Brain

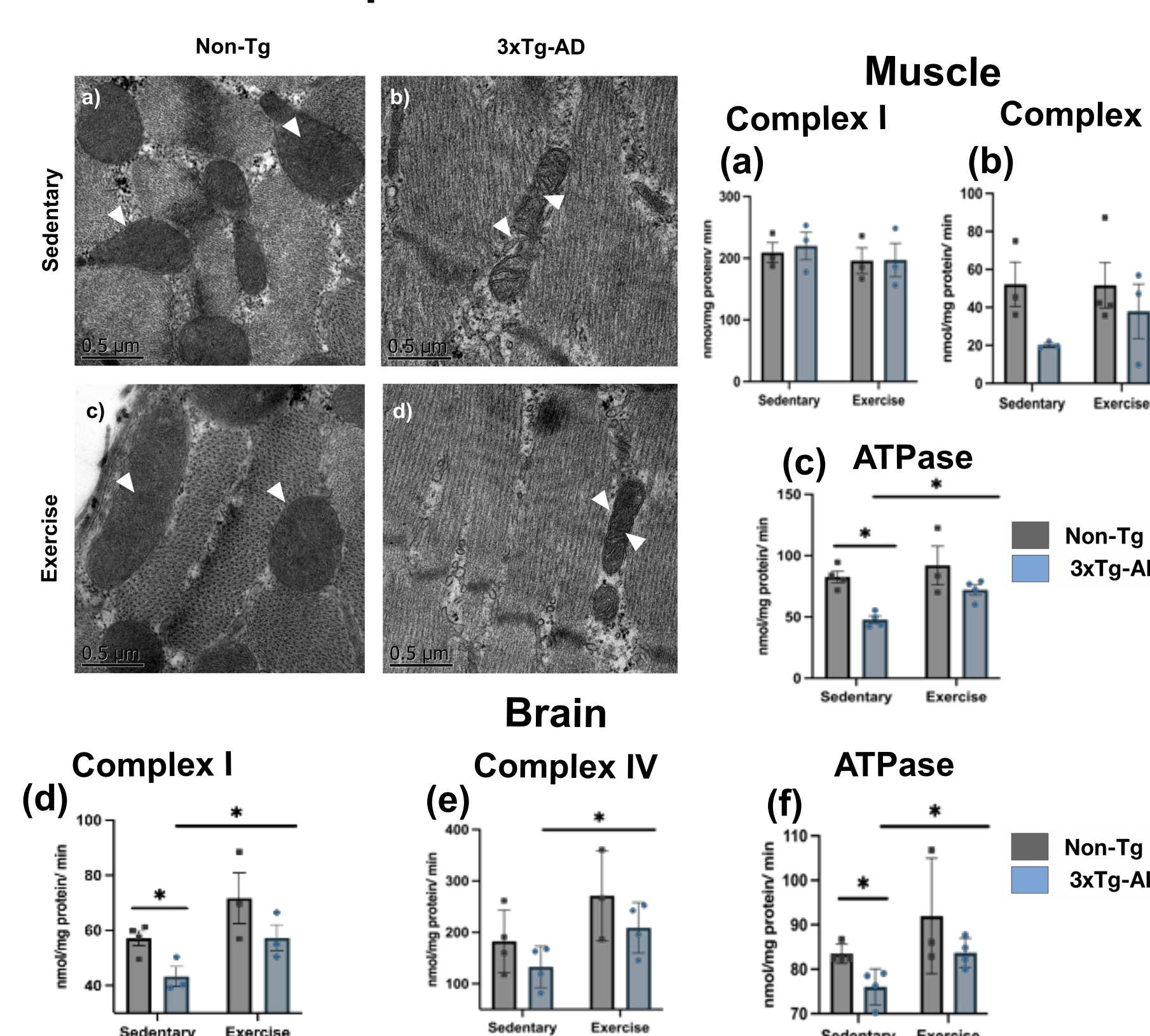


Figure 7. Effects of exercise on mitochondrial complexes and ATPase activity. (a) Representative transmission electron microscopy images of skeletal muscle mitochondria. (b-f) Bioenergetic assessments in muscle and brain tissues. Data are presented as mean $\pm$ SEM (n = 3-4 per group). Statistical analyses were performed using two-way ANOVA followed by Tukey's post hoc test. *p < 0.05.

4.6 Exercise Promotes Structural Plasticity of Motor Neurons

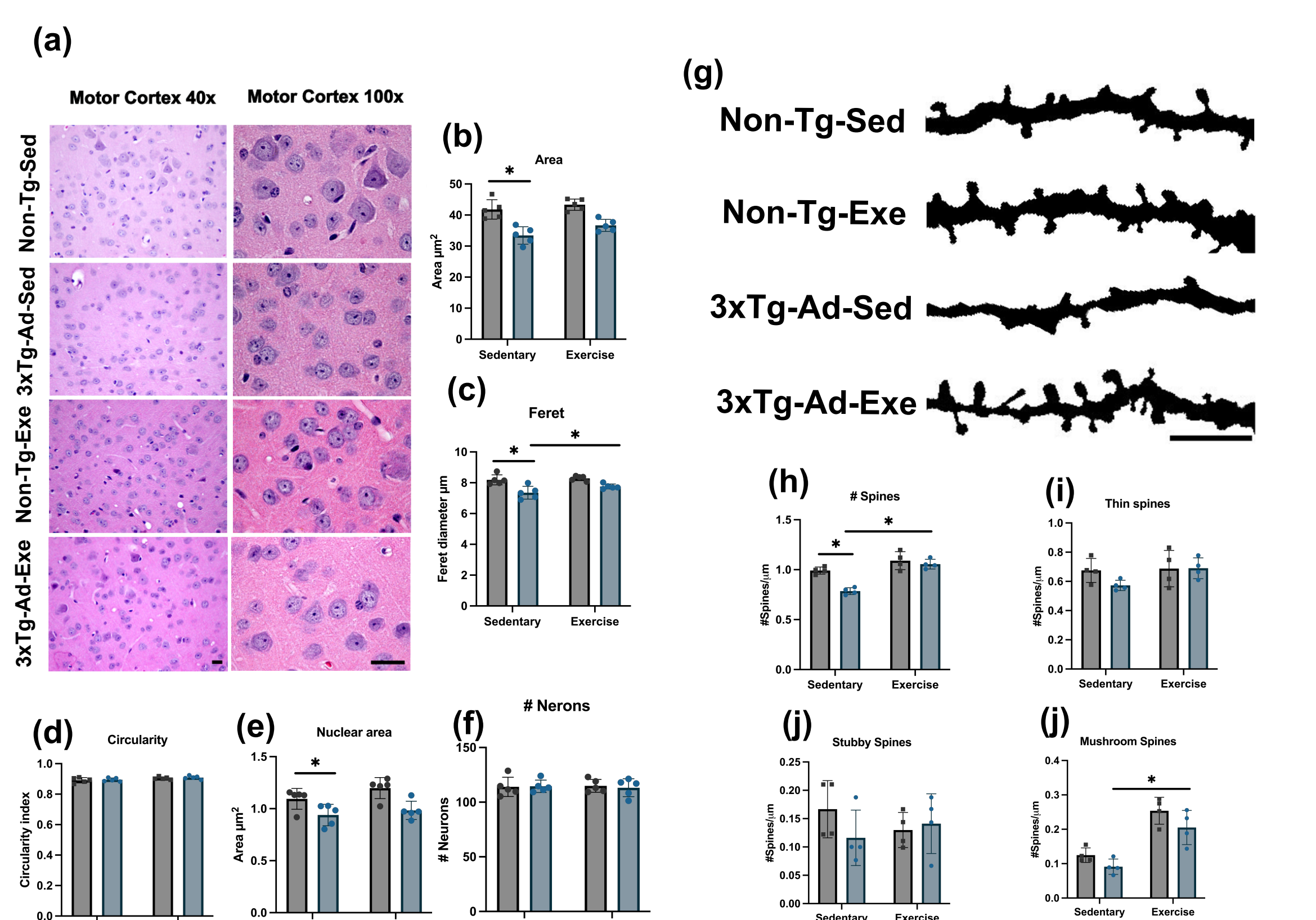


Figure 8. Exercise effects on neuronal structure and synaptic plasticity in the 3xTg-AD model. (a) Representative hematoxylin and eosin (H&E) images of the motor cortex. (b-f) Morphological assessments of motor neurons. (g) Representative Golgi-Cox images of dendritic spines. (h-i) Assessments of dendritic spine density and morphology. Data are presented as mean $\pm$ SEM (n = 4-6 per group). Statistical analyses were performed using two-way ANOVA followed by Tukey's post hoc test. *p < 0.05.

6. BIBLIOGRAPHY

- Andrade-Guerrero, Jesús et al. "Alzheimer's Disease: Understanding Motor Impairments." Brain sciences vol. 14,11 1054. 24 Oct. 2024. doi:10.3390/brainsci14111054
- Andrade-Guerrero, Jesús et al. "Alzheimer's Disease: An Updated Overview of Its Genetics." International journal of molecular sciences vol. 24,4 3754. 13 Feb. 2023. doi:10.3390/ijms24043754
- Andrade-Guerrero, Jesús et al. "Advancing Alzheimer's Therapeutics: Exploring the Impact of Physical Exercise in Animal Models and Patients." Cells vol. 12,21 2531. 27 Oct. 2023. doi:10.3390/cells12212531
- Belfiore, Ramona et al. "Temporal and regional progression of Alzheimer's disease-like pathology in 3xTg-AD mice." Aging cell vol. 18,1 (2019): e12873. doi:10.1111/

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