

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and synaptic dysfunction, which strongly correlates with disease severity. Disruption of synaptic signaling, including imbalances in inhibitory neurotransmission, contributes to impaired neural circuit function and cognitive deficits. MicroRNAs (miRNAs) are key regulators of gene expression in the central nervous system and play important roles in synaptic function, neuronal survival, and plasticity. Dysregulation of miRNAs has been increasingly linked to AD pathology. Previous work from our laboratory identified microRNA-502-3p (miR-502-3p) as elevated in AD post-mortem brains and AD mouse models and demonstrated its role in reducing GABAergic signaling and synaptic protein expression¹⁻⁵. Despite these findings, the functional impact of miR-502-3p on cognitive behavior remains unclear. In this study, we evaluated the effects of altered miR-502-3p expression on learning and memory using transgenic mouse models. Behavioral performance was assessed across multiple assays to determine the role of miR-502-3p in cognitive dysfunction associated with AD.

Purpose

To investigate the role of miR-502-3p in cognition behavior using transgenic and knock-out mouse models.

Materials and methods

Animal models: Female wild-type (WT), miR-502-3p overexpression transgenic (Tg), and miR-502-3p knockout (KO) mice were used in this study. All animals were maintained on a C57BL/6 genetic background and were six months of age at the time of behavioral testing. WT mice (n=10), served as controls, while miR-502-3p Tg (n=10) and miR-502-3p KO (n=10) mice were generated in collaboration with Cyagen Biosciences (Santa Clara, CA, USA). All experimental procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Texas Tech University Health Science Center (TTUHSC) El Paso (Protocol # 26001).

Open-field Test: The open-field test was used to assess locomotor activity, arousability, exploratory, and anxiety-like behaviors in mice; conducted using standard rodent protocols (Seibenhener & Wooten, 2015).

Novel Object Recognition (NOR) Test: Used to evaluate recognition memory based on preference for novel objects; performed according to established procedures in rodents (Antunes and Biala, 2012).

Y-Maze Test: Used to assess spatial working memory through spontaneous alternation behavior; conducted using established mouse protocols (Kraeuter et al., 2019).

Rota-rod Test: Used to evaluate motor coordination, balance, and motor performance; conducted according to established rodent protocols (Deacon, 2013).

Statistical Analysis: Behavior was recorded and analyzed using AnyMaze Software 7.4. NORT, Y-Maze, Open-field, and MWM tests were conducted using Stoelting Co. apparatus instruments. Rota-rod test was conducted using a PanLab Rota Rod apparatus. One-way ANOVA was used to measure statistical significance for all experiments.

Study timeline

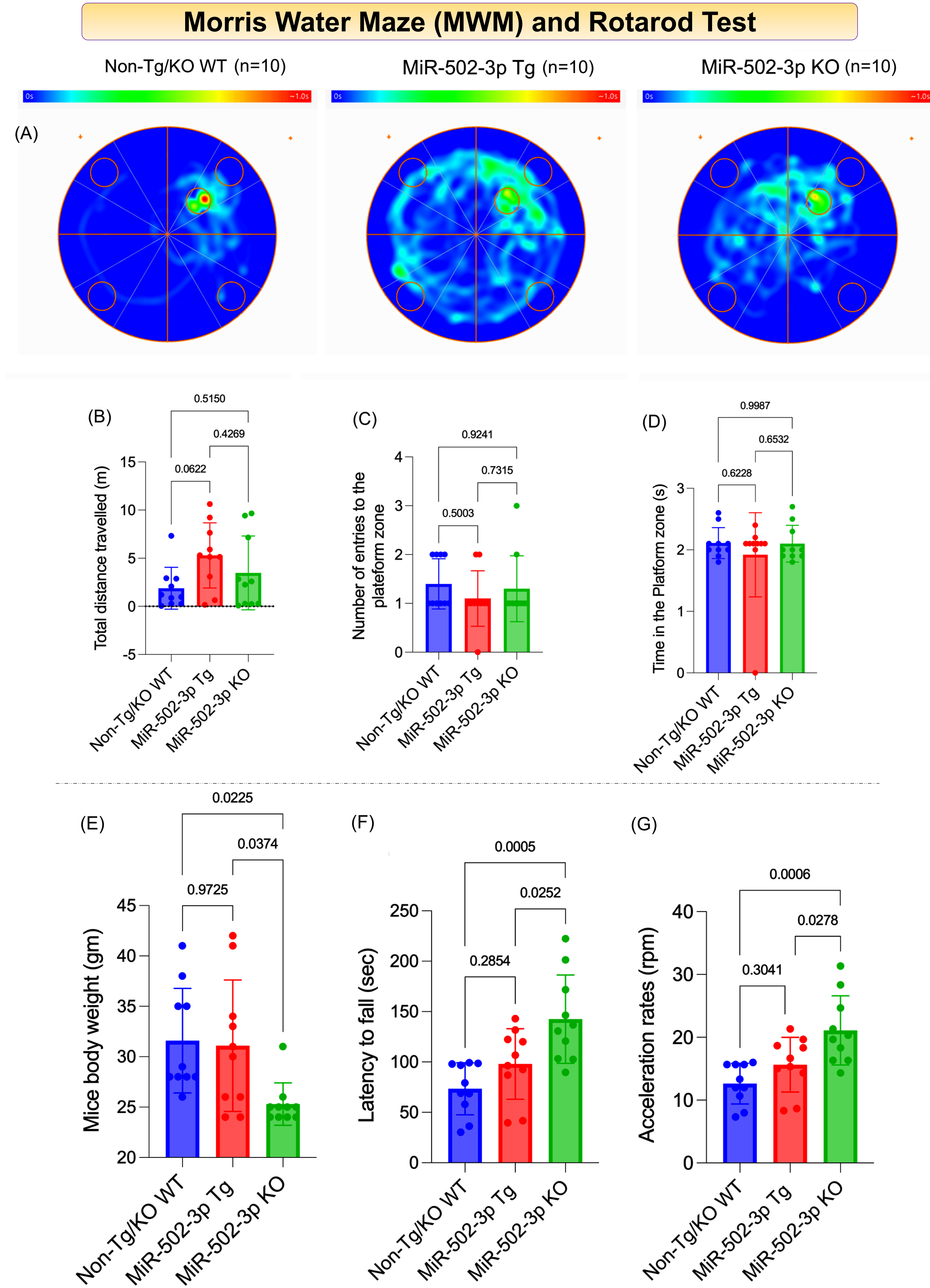
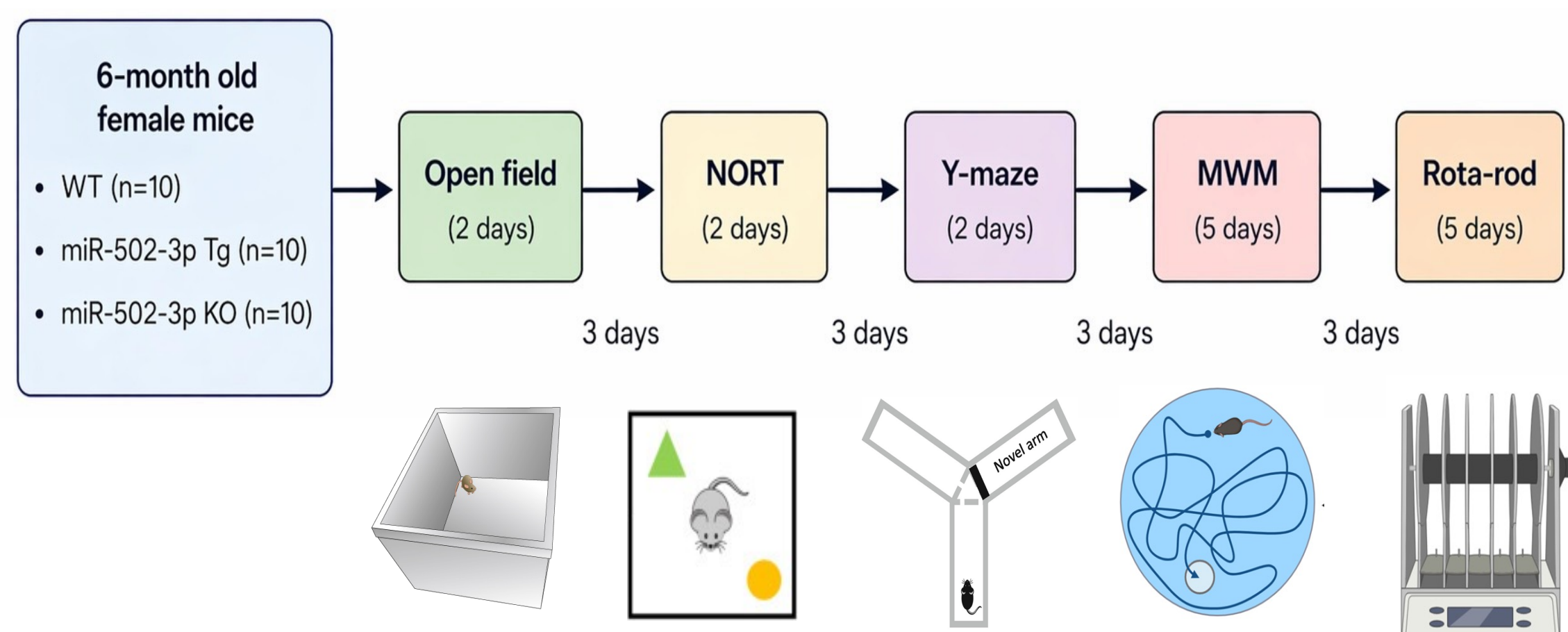


Fig. 1: Representative heat maps (A) and Morris Water Maze (MWM) performance measures, including total distance traveled, platform-zone entries, and time spent in the platform zone (B-D). Body weight, latency to fall, and acceleration rate at fall (E-G) were assessed in the rotarod test for WT, miR-502-3p Tg, and KO mice. Data are presented as mean $\pm$ SEM (n = 10/group).

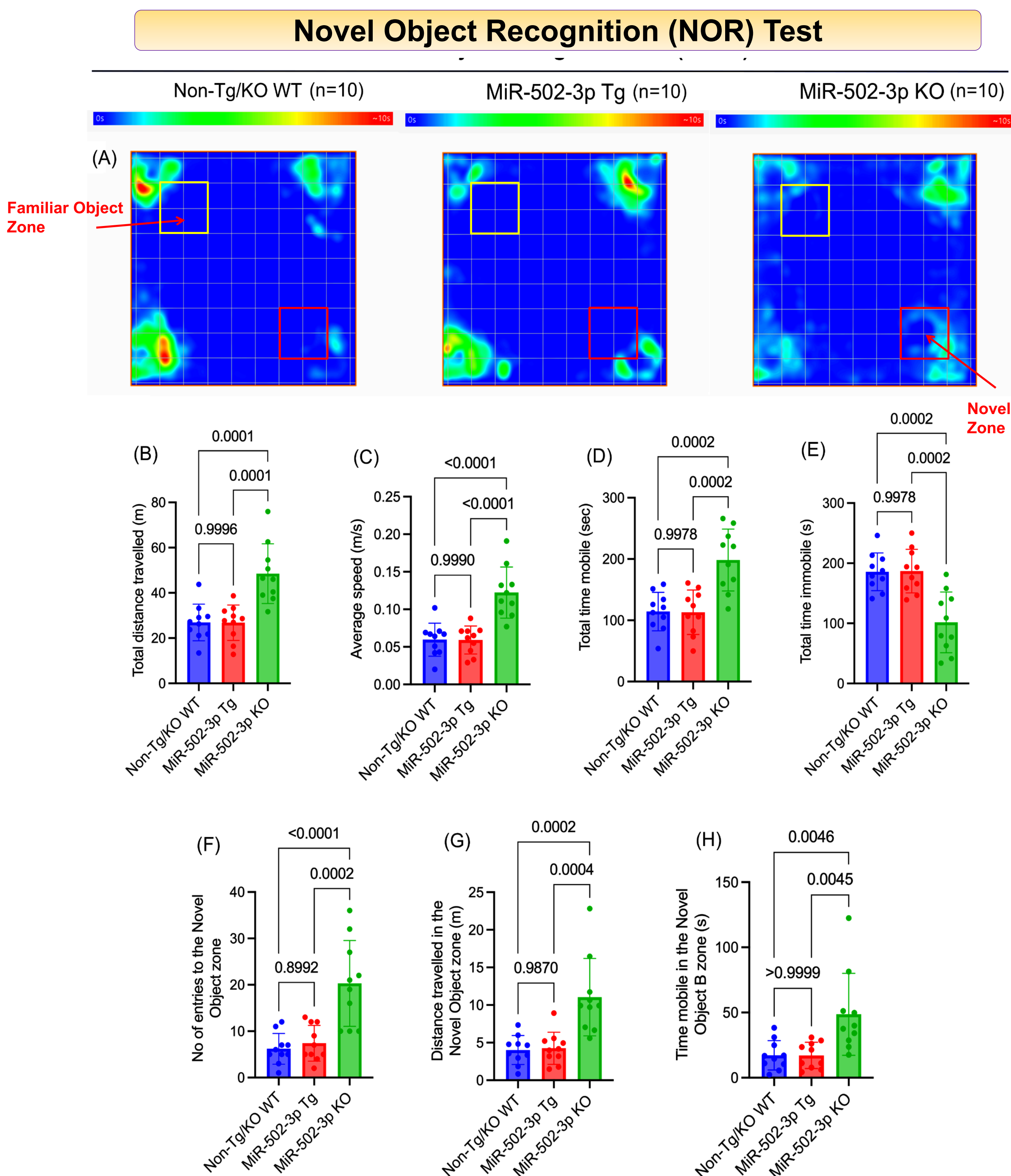


Fig. 2: Representative heat maps (A), locomotor activity parameters (B-E), and novel object exploration measures (F-H) in WT, miR-502-3p Tg, and KO mice. Data are mean $\pm$ SEM (n = 10/group).

Results

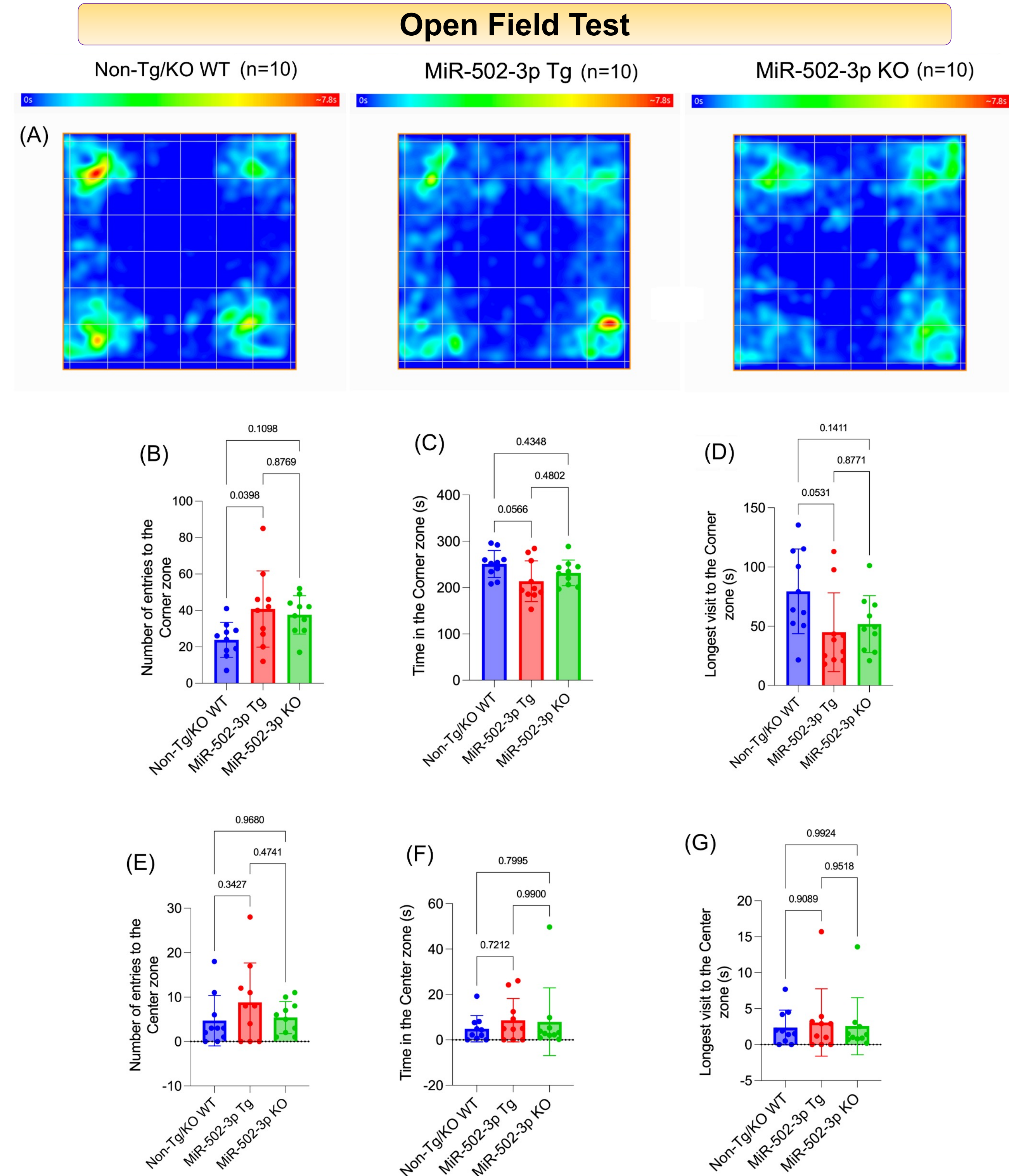


Fig. 3: Representative heat maps (A), corner-zone activity parameters (B-D), and center-zone activity parameters (E-G) in WT, miR-502-3p Tg, and KO mice. Data are mean $\pm$ SEM (n = 10/group).

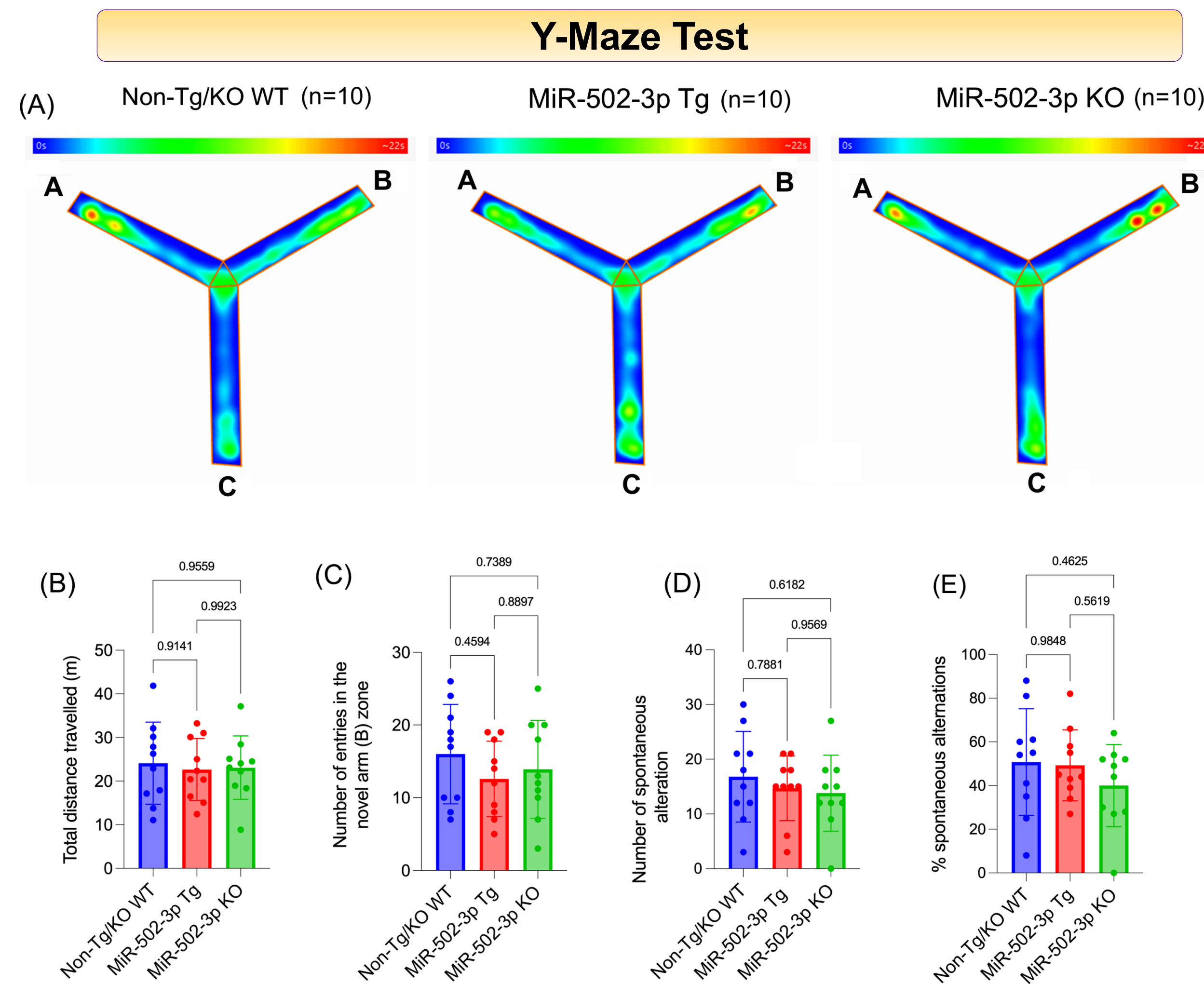


Fig. 4: Representative heat maps (A) and Y-maze performance measures including total distance traveled, novel arm entries, spontaneous alternations, and percentage of spontaneous alternations (B-E) in WT, miR-502-3p Tg, and KO mice. Data are mean $\pm$ SEM (n = 10/group).

Summary & Conclusions

- miR-502-3p KO mice exhibited enhanced exploratory activity and novel object recognition, and showed improved motor performance by remaining longer on the rotarod at higher acceleration rates compared with WT and miR-502-3p Tg mice.

Acknowledgements

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