

Exercise Effects on Cognition and Anxiety in eNOS-deficient Mice are Negated by the Inhibition of $\alpha 5\beta 1$ integrin

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1. INTRODUCTION

Exercise attenuates neurocognitive decline in VCI.

- Vascular cognitive impairment (VCI) is a form of cognitive impairment that arises due to vascular disruptions
- VCI is associated with a decrease in cerebral blood flow (CBF), eNOS (endothelial nitric oxide) function, and NO (nitric oxide) production^{1,2}
- VCI is characterised by executive dysfunction, brain atrophy, and white matter lesions³

However, the molecular pathway of how exercise results in neurological benefits has yet to be fully identified.

- Exercise attenuates decreases in eNOS⁴ and CBF⁵
- $\alpha 5\beta 1$ integrin is a receptor on endothelial cells in the blood brain barrier, upregulated during vascular injury⁶
- ATN-161 is small peptide inhibitor of $\alpha 5\beta 1$ integrin

2. HYPOTHESIS

We hypothesize that exercise-induced neurological benefits act through eNOS and $\alpha 5\beta 1$ integrin related pathway.

5. CONCLUSION

Our results demonstrate that the neurological benefits of exercise do not solely depend on the presence of eNOS, but also on the presence of a functioning $\alpha 5\beta 1$ receptor. This study showed that mice that received the exercise only treatment regime displayed behaviors that were altered by ATN-161.

In the open filed test, exercise only mice displayed less anxiety, which was reversed by the combination of ATN-161 and exercise. Exercise only mice were able to locate the platform within the shortest distance in the shortest amount of days. This timing was also reversed with the introduction of ATN-161. Therefore, a functional $\alpha 5\beta 1$ receptor is necessary to see the cognitive benefits of exercise.

ACKNOWLEDGMENTS

PRESENTOR



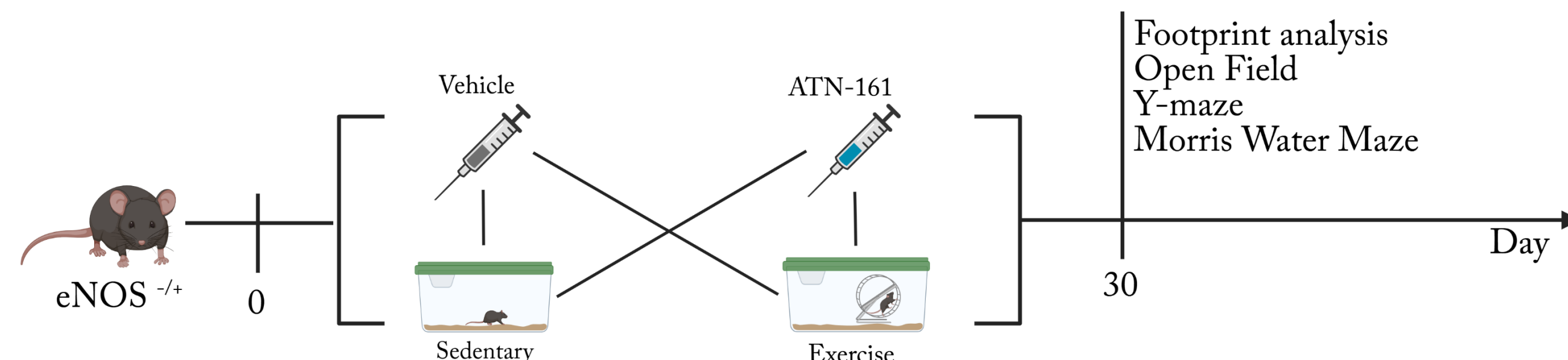
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3. METHODS

To test this hypothesis, we used ATN-161 to inhibit $\alpha 5\beta 1$ integrin in eNOS-deficient mice to determine its effects on exercise benefits.

- 45, 17-month-old eNOS^{+/-} mice were divided into four groups: sedentary, ATN-161 only, Exercise only, and Exercise and ATN-161
- Exercise was done through free access to a running wheel for a period of 30 days
- 1 mg/kg of ATN-161 or vehicle through intraperitoneal injection once every other day during the 30-day exercise period
- At 18-mo, behavior tests were performed: footprint analysis, Y-maze, open field, and morris Water Maze



4. RESULTS

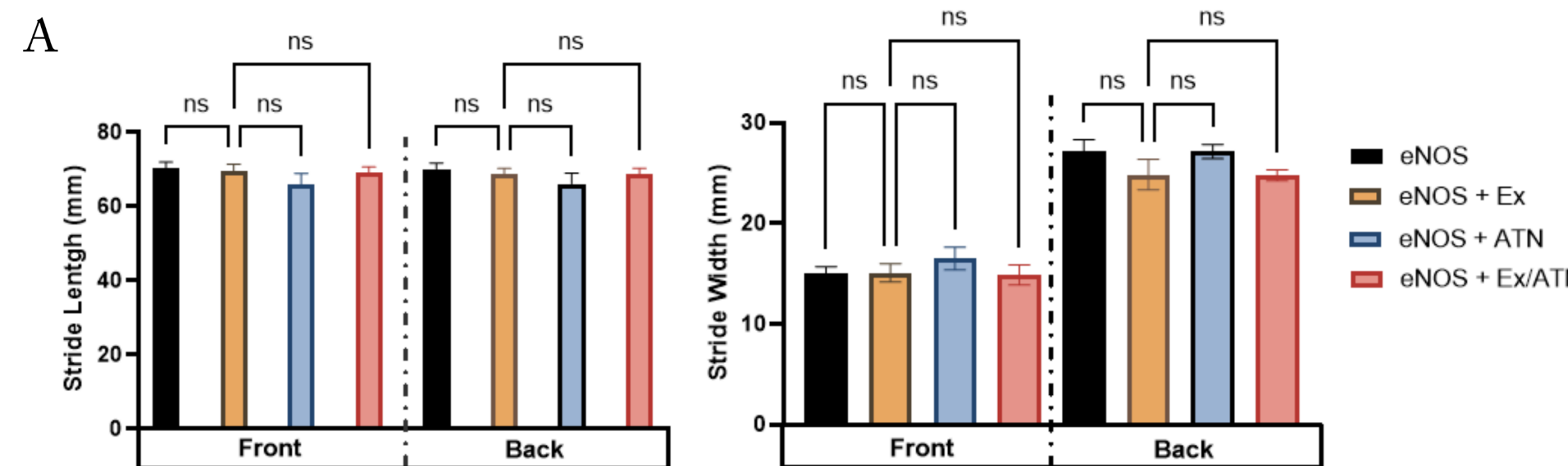


Figure 2: ATN-161 did not alter gait of mice. Foot print analysis of eNOS mice stride length (A) and stride width (B) of front and back paws. Ex; exercise only group. ATN; ATN-161 only group. Ex/ATN; exercise and ATN-161 group. ns; non-significant.

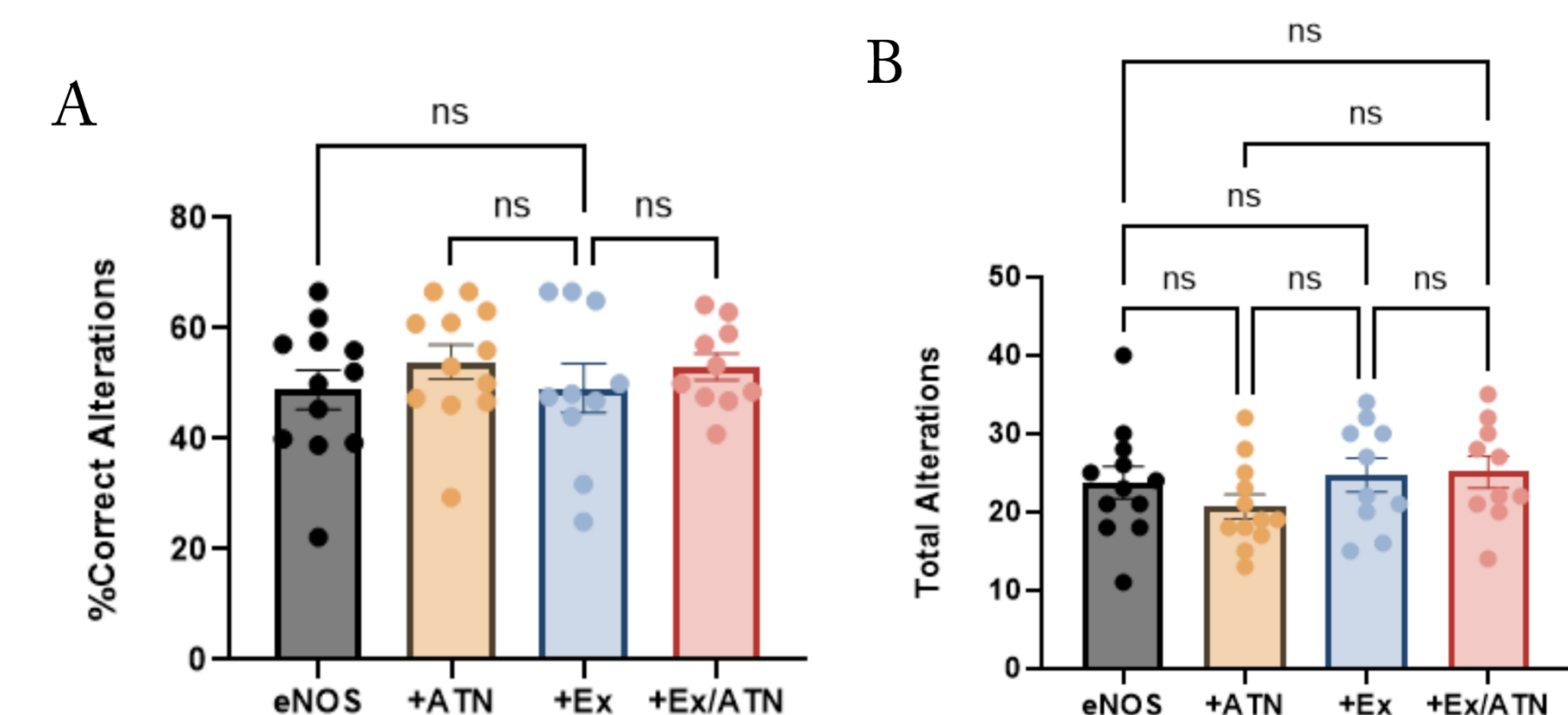


Figure 3: ATN-161 did not result in short term memory deficits. Y-maze test performance %correct alterations (A) and total alterations (B) of eNOS mice. Ex; exercise only group. ATN; ATN-161 only group. Ex/ATN; exercise and ATN-161 group.

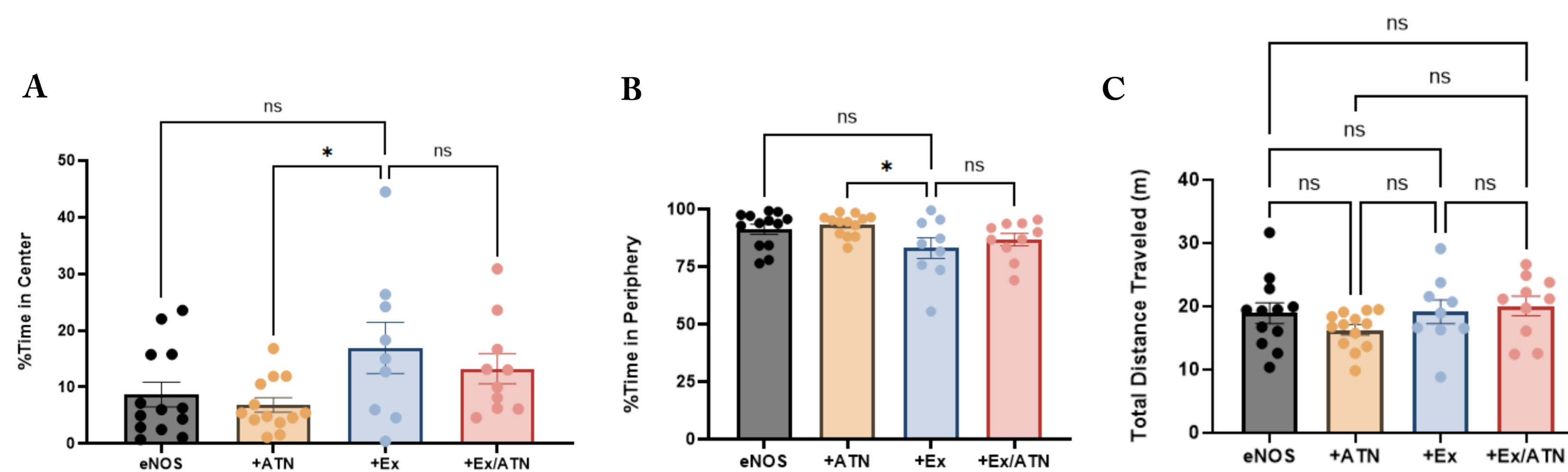


Figure 5: ATN-161 delayed exercised-induced cognitive benefits. The activity wheel showed no significant difference in distance ran between the two exercise groups (A): Exercise and Exercise with ATN-161. However, because there was a significant difference in average swim speed between the groups that exercised and those that did not in the Morris Water Maze test (B), distance to the platform was analyzed. In the Morris Water Maze test, Exercise only mice displayed a trending difference in distance to the platform (C). * <0.5 . Ex; exercise only group. ATN; ATN-161 only group. Ex/ATN; exercise and ATN-161 group. All Sed; all mice that experienced sedentary movement. All Ex; all mice that experienced exercise.

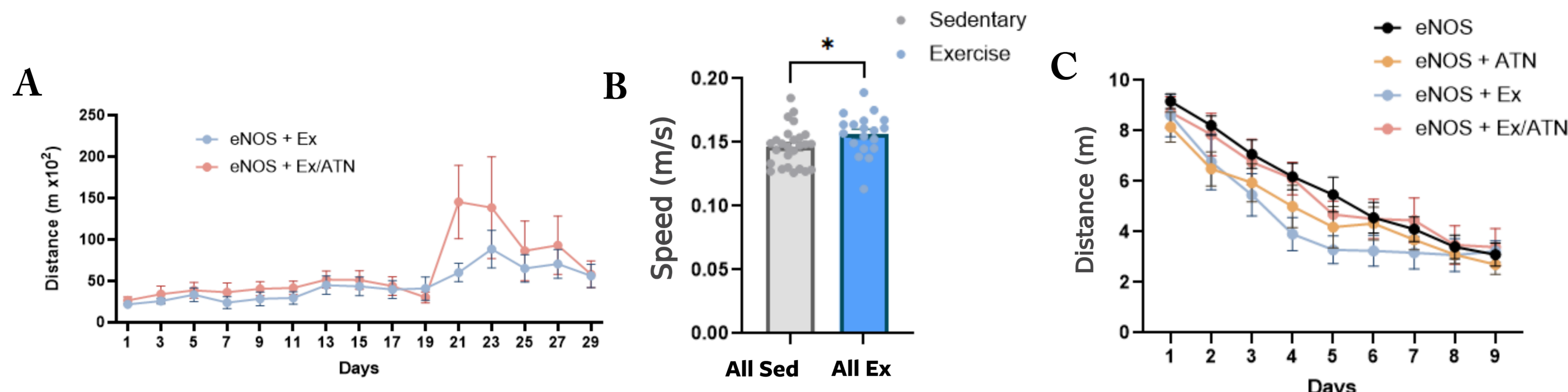


Figure 4: ATN-161 reversed anxiety loss resulting from Exercise. In the open field test, mice in the exercised only group spent significantly more time in the center (A) and less time in the periphery (B) of the open field apparatus. Significance in both time spent in the center and in the periphery was lost when exercise was combined with ATN-161. There was no significant difference in total distance traveled (C) between any group. * <0.5 . Ex; exercise only group. ATN; ATN-161 only group. Ex/ATN; exercise and ATN-161 group.