

Reevaluation of Age-Related Behavioral Phenotypes in the SAMP8 Mouse Model of Senescence

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Introduction

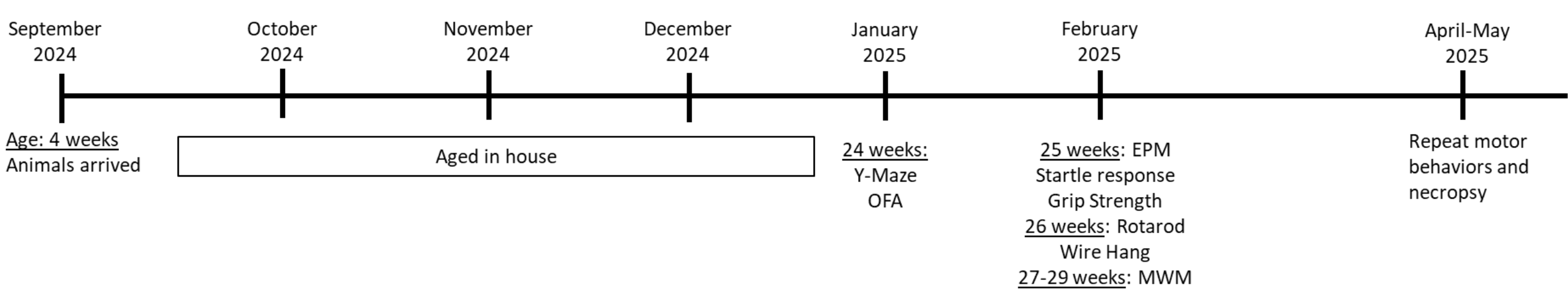
The study of age-related changes in learning, memory, cognition, muscle physiology, and other senescence-related biological factors is an important task in the face of an aging population and rising healthcare costs. Understanding the biological mechanisms underlying deficits in these processes can lead to better diagnostic tests and interventional treatments to improve quality of life and extend lifespan. Translational animal models are an important tool for studying senescence; however, aging animals to an advanced age for study can be costly and may require years of waiting before data are obtained. The senescence-accelerated mouse (SAM) lines were selectively bred from AKR mice that exhibited phenotypes of early-onset aging¹. The SAM-prone mouse line 8 (SAMP8) has been especially useful in the study of aging-related cognitive decline and sarcopenia^{2,3}. The SAMP8 mouse line has been maintained for nearly 40 years, raising concerns about possible genetic drift and a gradual loss of phenotypes associated with the line. This study was conducted to assess whether SAMP8 mice continue to exhibit canonical phenotypes associated with this model.

Methods

- Animals: 48 mice from Inotiv's breeding colony were acquired for study: 12M/12F SAM-resistant (SAMR1/Ta) and 12M/12F SAMP8/TaHsd mice. Animals were aged to 24-weeks-old before behavioral assessments took place.

Group	n	Sex	Genotype
1	12	Male	SAMR1
2	12	Female	SAMR1
3	12	Male	SAMP8
4	12	Female	SAMP8

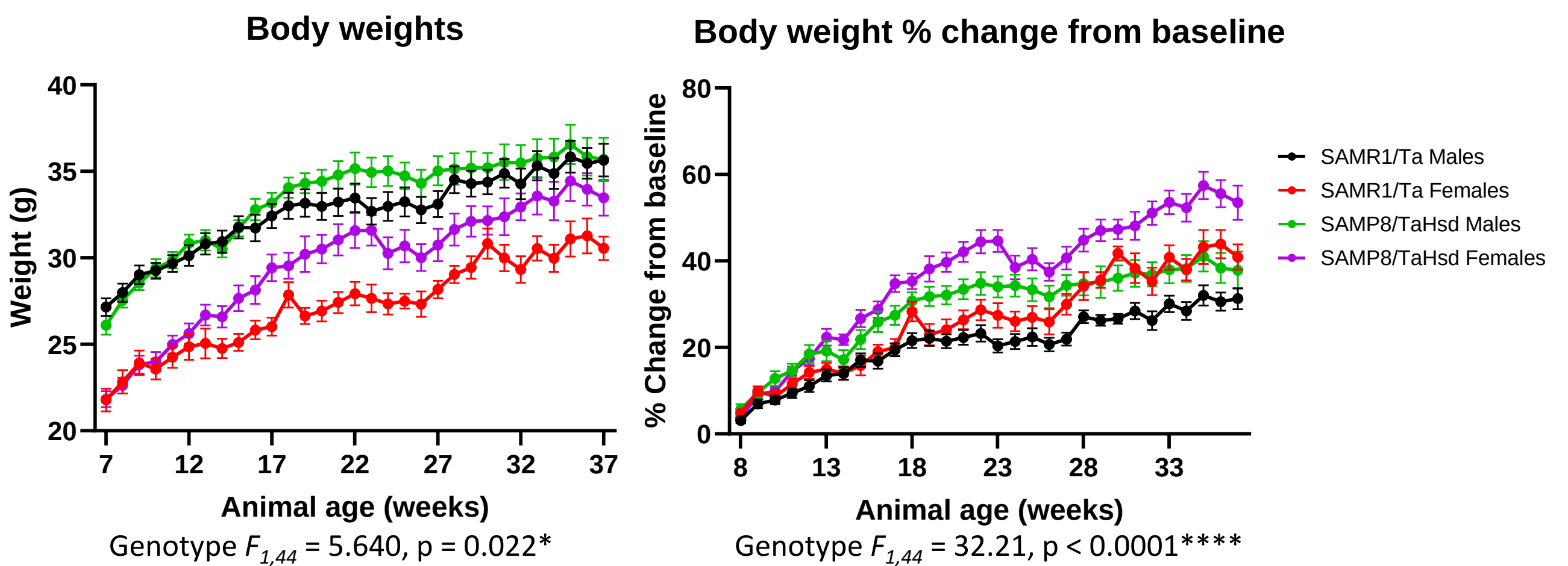
- Study timeline:



- Behaviors assessed:

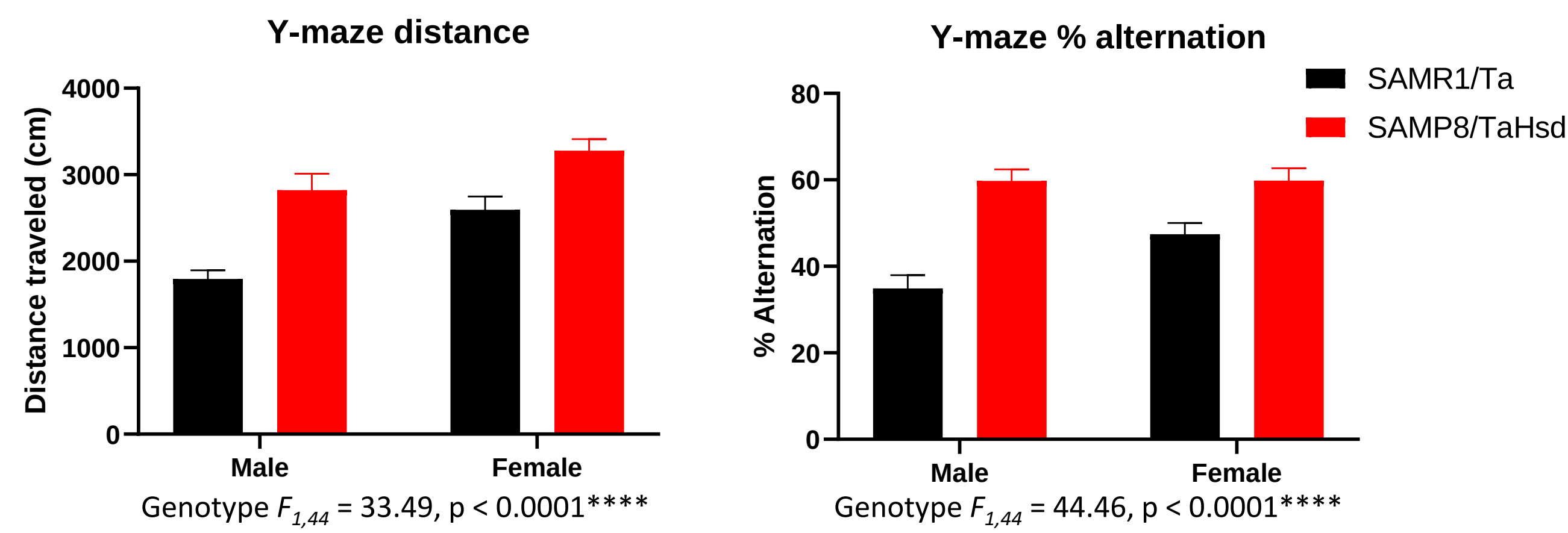
- >**Y-maze**: At 24-weeks-old. 10-minute test of spontaneous alternation %, tracked using Noldus EthoVision software.
- >**Open field analysis (OFA)**: At 24-weeks-old. 10-minute test to track locomotion and time spent in center of apparatus, tracked using Noldus EthoVision software.
- >**Startle response**: At 25-weeks-old and at 37-weeks-old. Tested the presence of a reaction to a 120 db noise.
- >**Elevated plus maze (EPM)**: At 25-weeks-old. 10-minute test on EPM apparatus, measuring time spent in the open arms. Tracked using Noldus EthoVision software.
- >**Grip strength testing**: At 25-weeks-old and at 37-weeks-old. Tested the force necessary for an animal to lose its grip on a wire mesh grid attached to a force meter. Tested using both the forelimbs and all four limbs.
- >**Accelerating rotarod**: At 26-weeks-old and 36-weeks-old. Maximum test length of 6 minutes with RPMs increasing over time. The latency to fall was measured, along with RPMs at time of fall and total distance traveled.
- >**Wire hang**: At 26-weeks-old and at 36-weeks-old. Mice were allowed to grab a wire grid with all four limbs and inverted over a cushion for a maximum of 2.5 minutes. The latency to fall was recorded.
- >**Morris water maze (MWM)**: Tested in cohorts at 27- to 29-weeks-old. 6 days of training followed by a short-term memory probe 2 hours after the final training session and a long-term memory probe 24 hours after the final training session. Tracked using Noldus EthoVision software.

Body weight over time



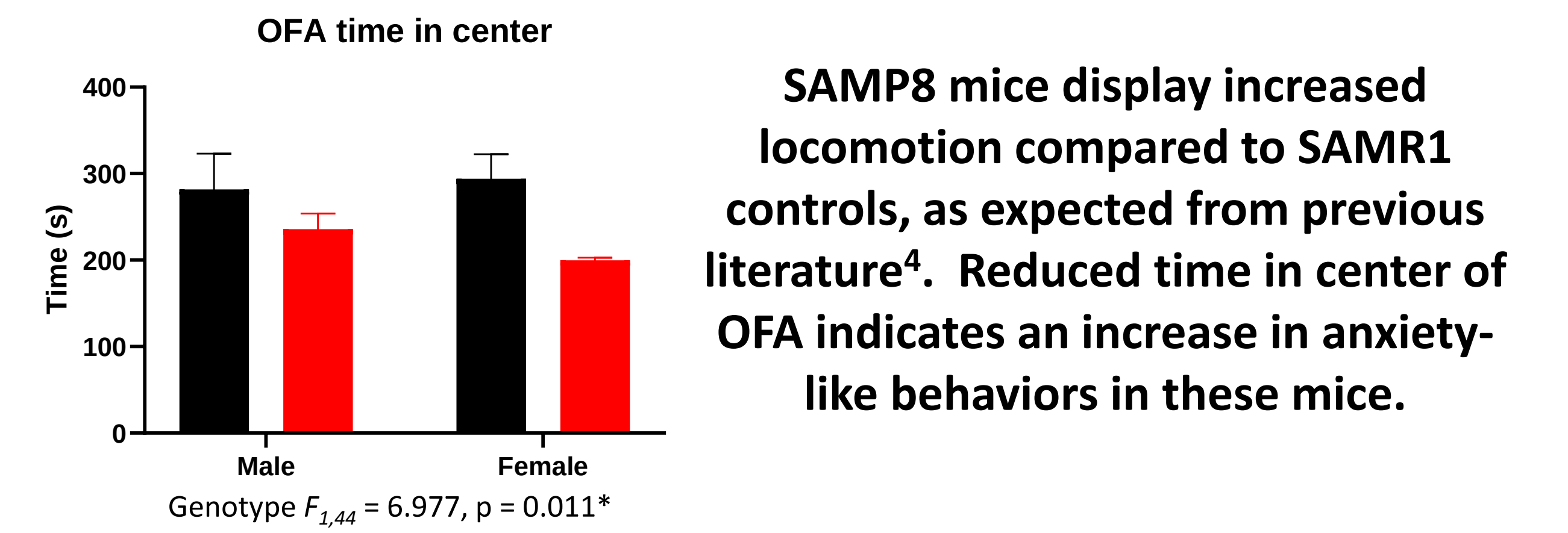
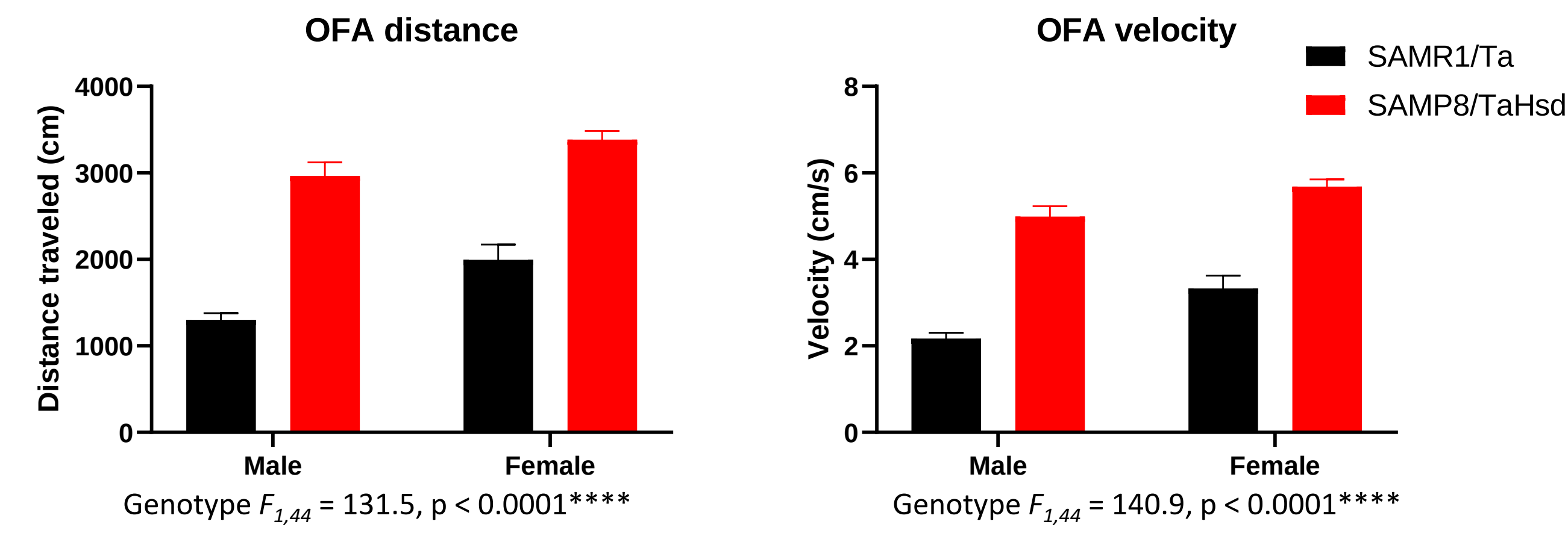
SAMP8 mice gain more weight over time compared to SAMR1 controls. This is the opposite of the expected result: previous research⁴ has shown reduced weight gain in SAMP8 mice.

Y-maze: Working memory

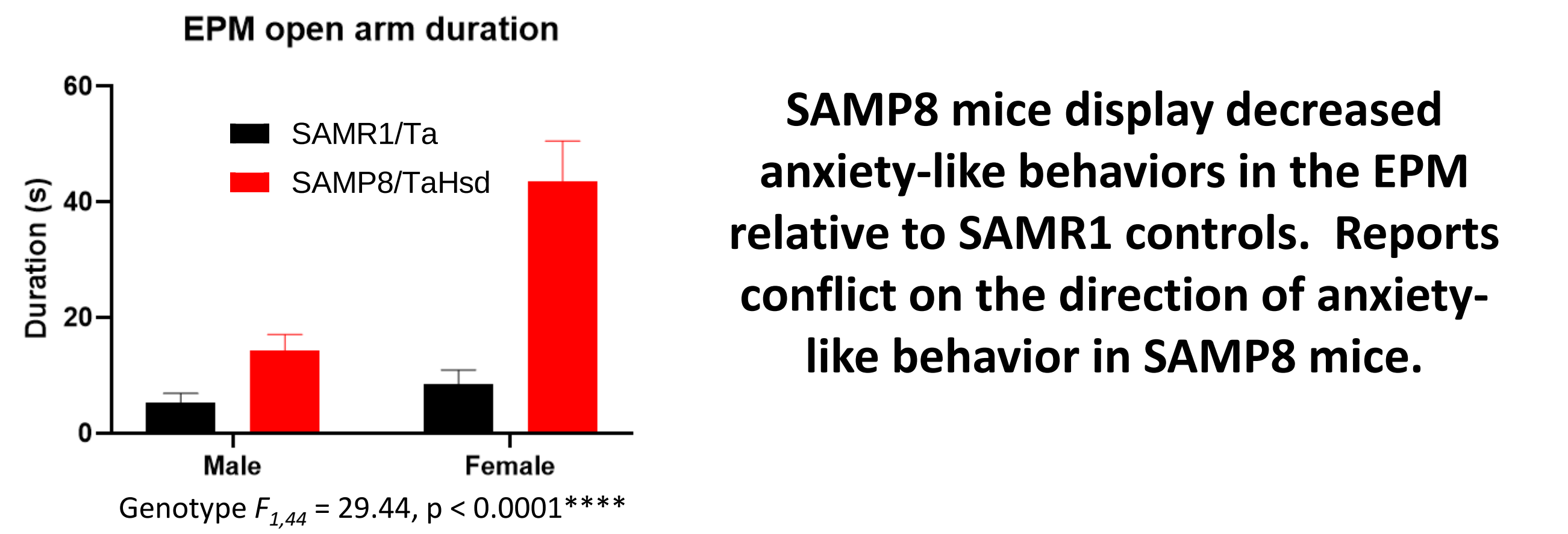


SAMP8 mice display increased locomotion compared to SAMR1 controls, as expected. Working memory performance is increased in SAMP8 mice compared to SAMR1 controls, which is the opposite of expected results⁵.

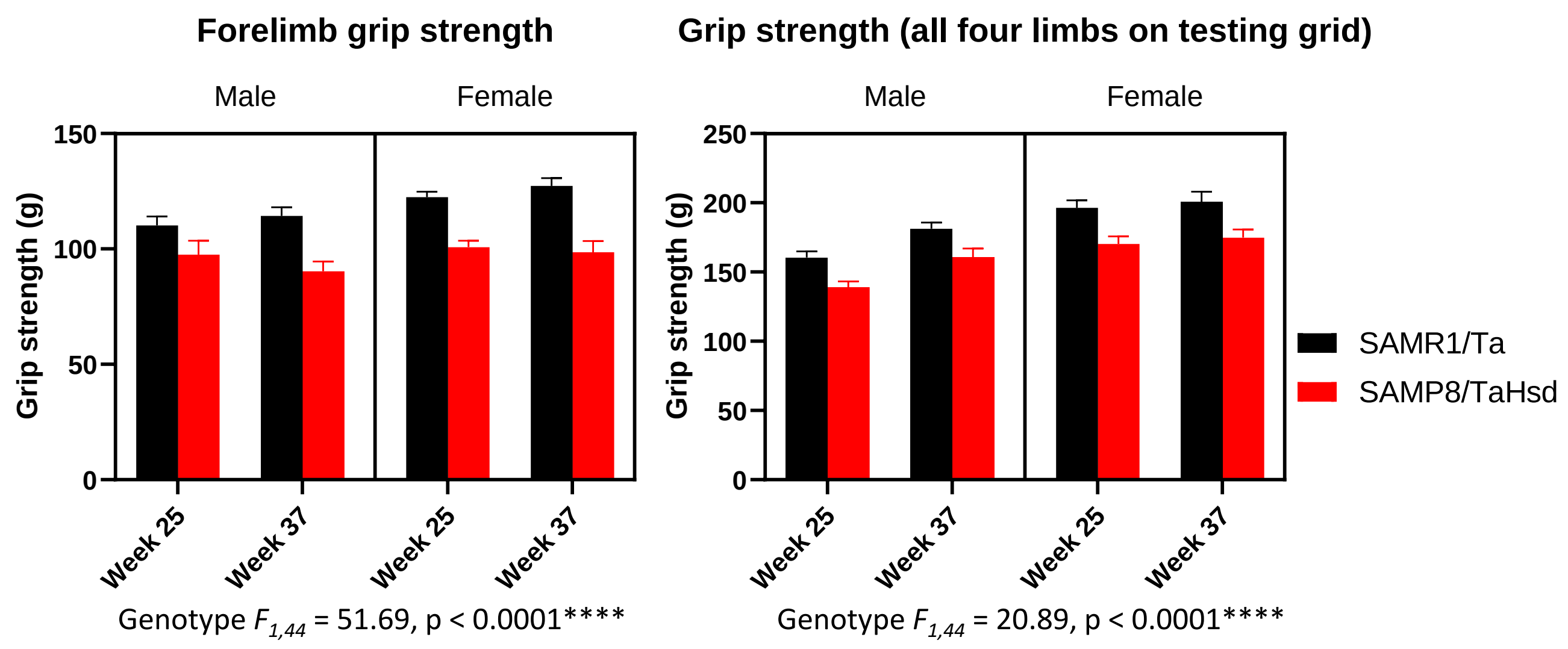
Open field analysis (OFA): Locomotion and anxiety



Elevated plus maze (EPM): Anxiety

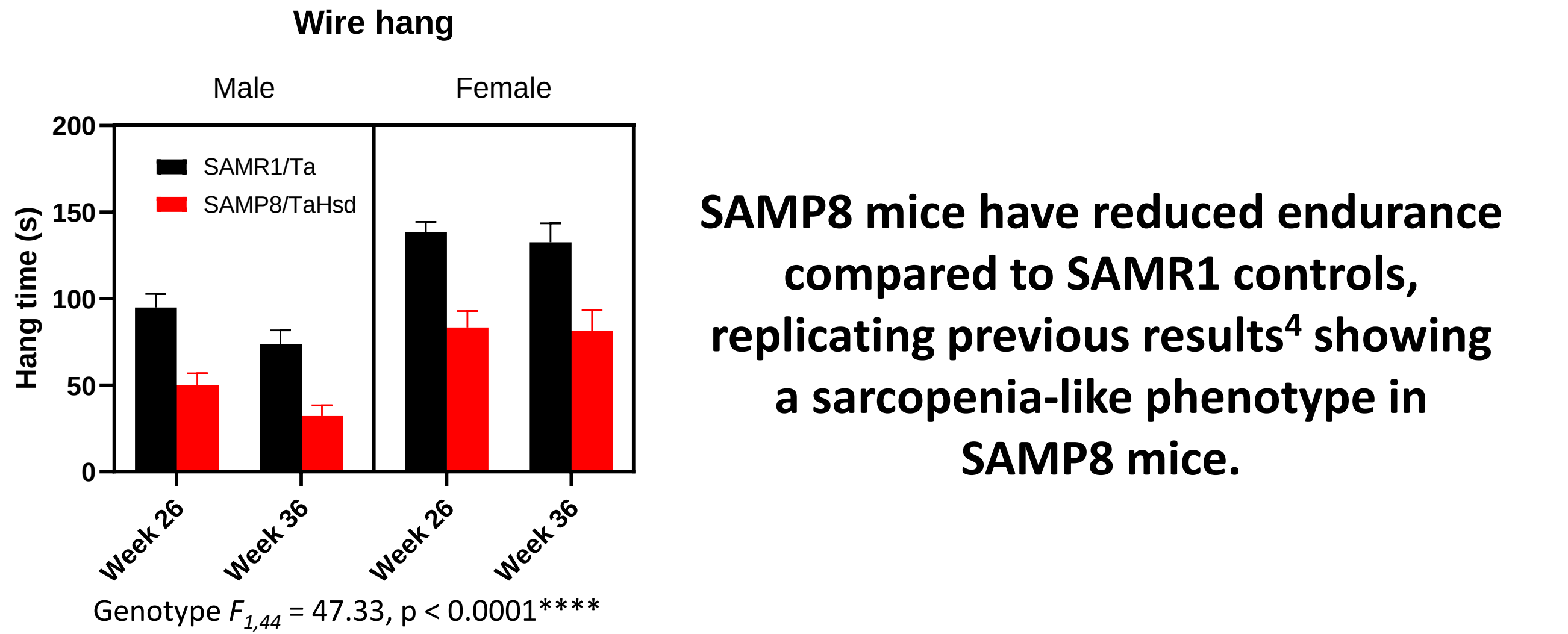


Grip strength

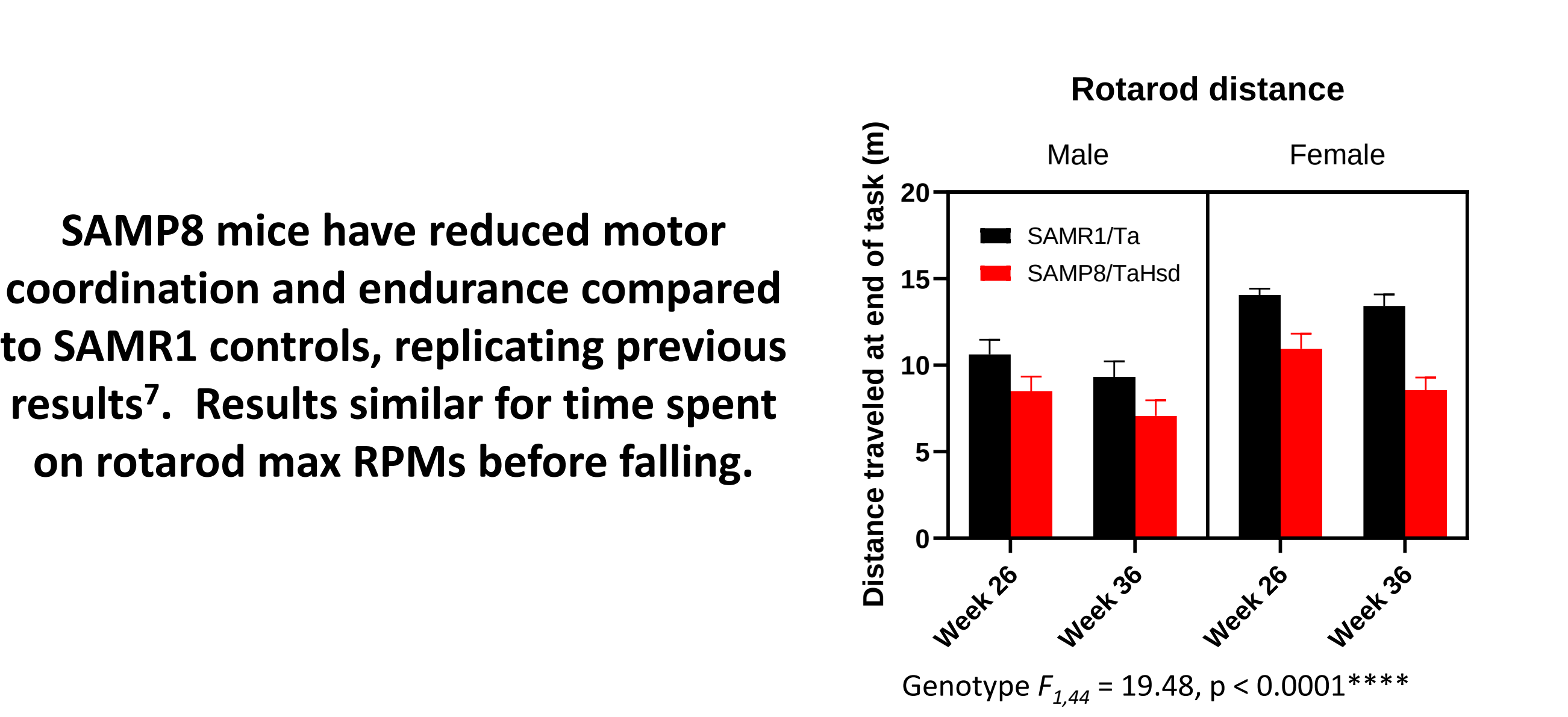


SAMP8 mice exhibit deficits in muscle strength at both time points tested, replicating the results of previous research⁶.

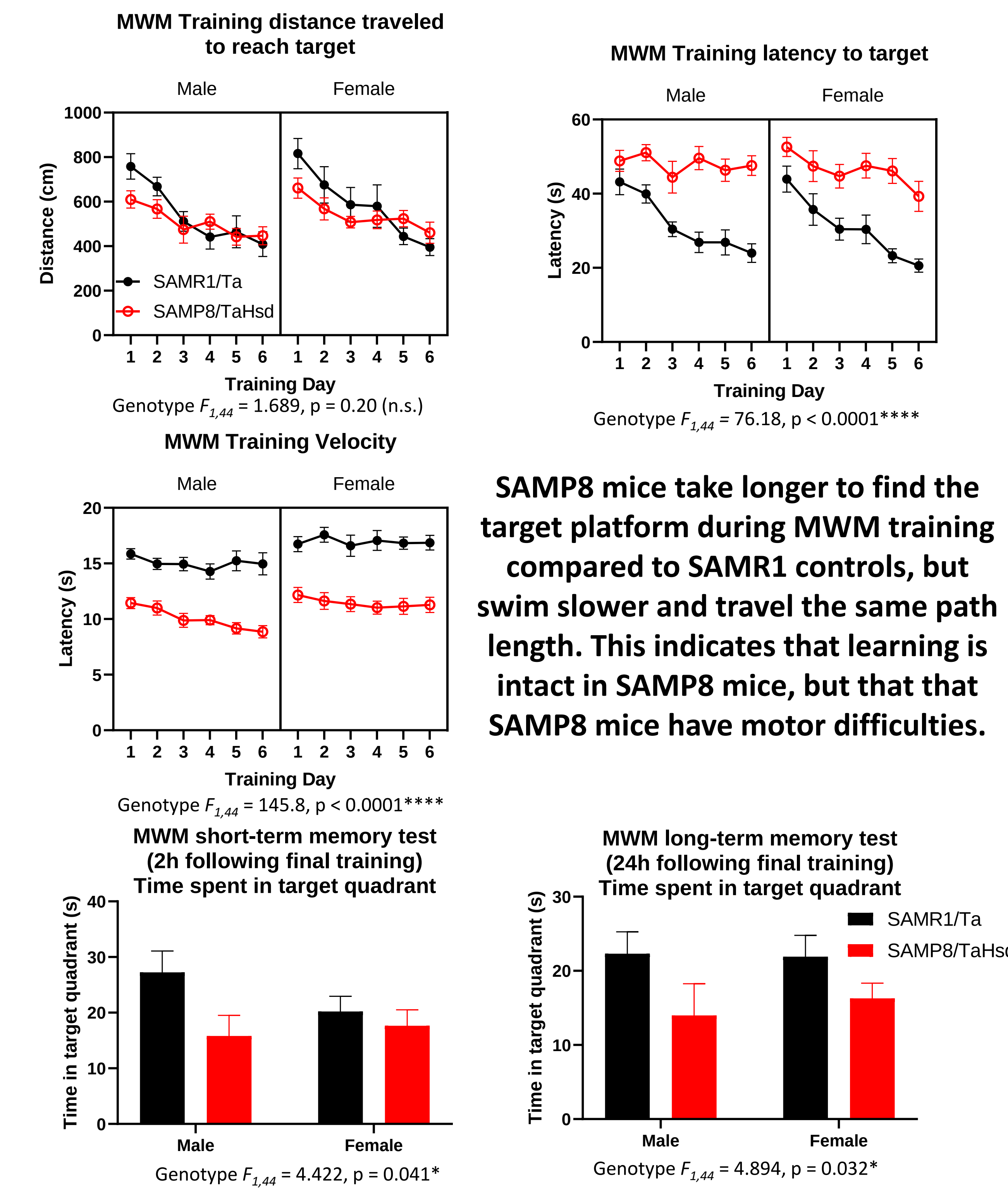
Wire hang



Accelerating rotarod



Morris water maze (MWM): Spatial learning and memory



SAMP8 mice take longer to find the target platform during MWM training compared to SAMR1 controls, but swim slower and travel the same path length. This indicates that learning is intact in SAMP8 mice, but that that SAMP8 mice have motor difficulties.

SAMP8 spend less time in the target quadrant during both short- and long-term memory probes with the platform removed than SAMR1 mice, indicating that memory deficits are present in SAMP8 mice as previously reported⁸.

Startle response

Animal Age	Positive startle responses/ Total # of animals tested			
	Group 1: SAMR1/Ta Males	Group 2: SAMR1/Ta Females	Group 3: SAMP8/TaHsd Males	Group 4: SAMP8/TaHsd Females
Age 25 weeks	12/12	12/12	11/12	12/12
Age 37 weeks	11/12	12/12	10/11	10/12

No significant differences between SAMP8 and SAMR1 mice during auditory startle testing, contrary to expected results.

Summary

SAMP 8 mice continue to display many classically described phenotypes characteristic of the line: increased locomotor activity, altered anxiety, deficits in muscle strength and motor coordination, and deficits in cognition. Other phenotypes were different than previous accounts, as in this study SAMP8 mice did not display hearing loss, had increased working memory, and gained more weight than SAMR1 control mice.

References

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