



# Sex-dependent impacts of environmental enrichment on Angelman Syndrome mice

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## Abstract

Angelman Syndrome (AS) is a rare neurodevelopmental disorder caused by mutations or deletions of the maternal allele of UBE3A. AS in humans is marked by intellectual disability, epilepsy, ataxia, autism, and a happy/excitable demeanor; in mice, these symptoms are displayed as deficits in various behavioral assays including the open field test, marble burying, rotarod, novel-object recognition, and forced swim. We hypothesized that long-term post-weaning environmental enrichment (EE)—which provided mice with increased cage space, toys, treats, and running wheels—would at least partially rescue performance on these tasks. We tested both males and females to determine if there are differences in treatment outcomes on behavioral tasks. We found that EE for male AS mice reduced the motor coordination deficits usually seen in rotarod performance and restored species-specific marble burying behavior. We also examined alterations of behavior in the open field test and in the forced swim task. EE also ameliorated the weight phenotype in AS mice. Interestingly, female AS mice did not respond to environmental enrichment in the same way as the male mice. Future experiments may examine cellular and molecular changes in the brain as a result of post-weaning EE.

## Background

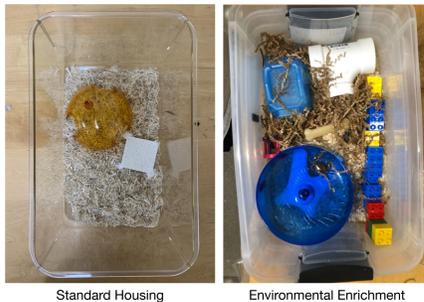
**Environmental enrichment (EE)**—which provides mice with cognitive enrichment—has shown therapeutic potential for many brain disorders.

**Angelman Syndrome (AS)** is a rare neurodevelopmental disorder marked by:

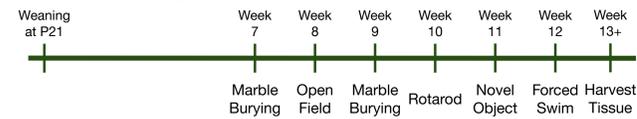
- Intellectual disability
- Epilepsy
- Ataxia
- Autism-like symptoms
- Happy demeanor

**Mice**

- UBE3A<sup>tm-/-</sup> (AS) mice
- UBE3A<sup>tm-/-</sup> littermate controls
- C57B6/J background

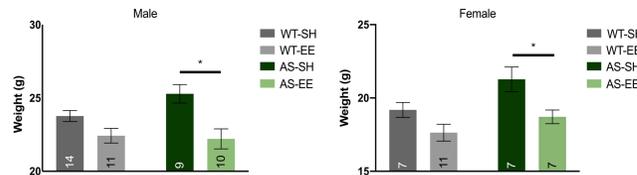


### Behavioral Testing Timeline



## Weights

AS mice have shown a significant increase in weight compared to WT mice, in both males and females (Sonzogni et al. 2018).



The increased weight phenotype is fully rescued in both male and female AS mice subjected to EE (\*, p<0.05).

## References

Huang, H.-S. et al. (2013) *Behav. Brain Res.* 243:79-90.  
 Born, H.A. et al. (2017) *Scientific Reports* 7:8451.  
 Koyavski, L. et al. (2018) *Molecular Neurobiology* 56:5998-6016.  
 Sonzogni, M. et al. (2018) *Molecular Autism* 9:47.  
 Woo, C. C., & Leon, M. (2013). *Behavioral Neuroscience* 127(4):487-97.

## Acknowledgements

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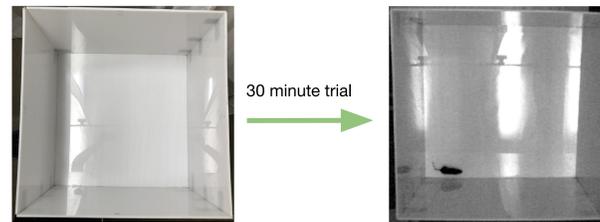


## We hypothesize that...

**Environmental enrichment will at least partially rescue prevalent AS behavioral phenotypes.**

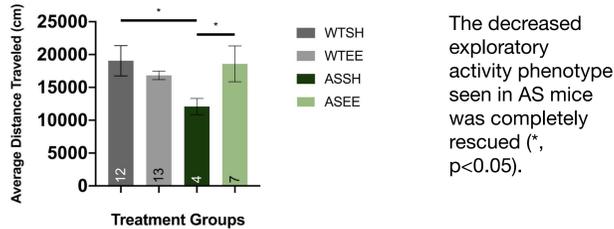
**Exploratory activity was fully rescued for male AS mice with 8 weeks of environmental enrichment.**

Open field tests exploratory activity, anxiety, and mouse specific behaviors.



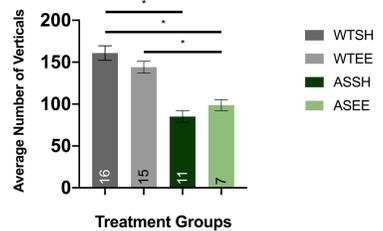
AS mice display hypoactivity and fewer rearing episodes in the open field assay (Born et al. 2017).

### Male Distance Traveled 30 min



The decreased exploratory activity phenotype seen in AS mice was completely rescued (\*, p<0.05).

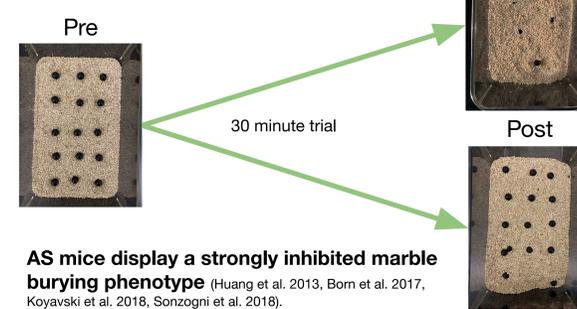
### Male Verticals



The decreased vertical rearing phenotype was not rescued within AS male mice (\*, p<0.05).

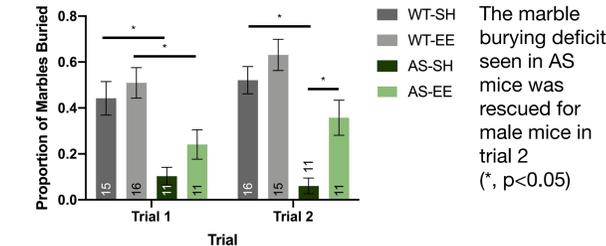
**Marble burying behavior was rescued for male AS mice with 9 weeks of environmental enrichment.**

Marble burying tests anxiety, motor behavior, and repetitive behavior.



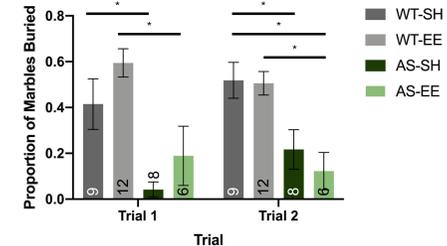
AS mice display a strongly inhibited marble burying phenotype (Huang et al. 2013, Born et al. 2017, Koyavski et al. 2018, Sonzogni et al. 2018).

### Male Marble Burying



The marble burying deficit seen in AS mice was rescued for male mice in trial 2 (\*, p<0.05)

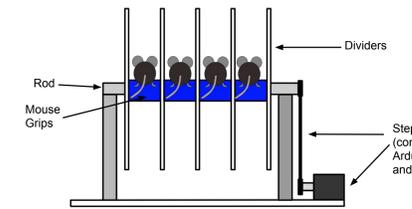
### Female Marble Burying



The marble burying deficit seen in AS mice was not rescued for female mice in either trial (\*, p<0.05).

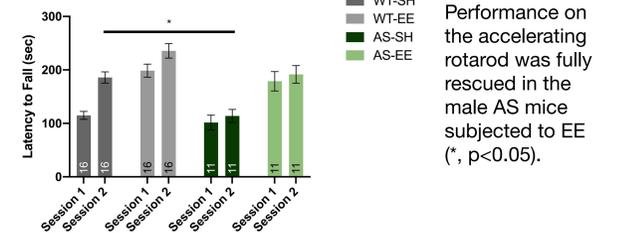
**Rotarod performance was rescued in male AS mice with 10 weeks of environmental enrichment.**

Rotarod tests for motor coordination and learning.



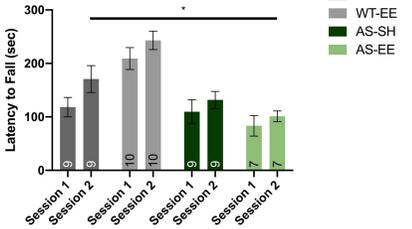
The rod accelerates from 4-40 RPM over 5 minutes to measure how long the mice stay on the rod and how they progress over multiple trials. AS mice have negative motor coordination and learning phenotypes, and thus do poorly on this task (Sonzogni et al. 2018).

### Males



Performance on the accelerating rotarod was fully rescued in the male AS mice subjected to EE (\*, p<0.05).

### Females



Performance on the accelerating rotarod was not rescued in the female AS mice subjected to EE (\*, p<0.05).

## Conclusions

**Environmental enrichment (EE)** showed a number of effects on male AS mice behavior:

- Restoration of species-specific marble burying behavior
- Reduction of motor coordination deficits usually seen in rotarod performance
- Recovery of exploratory activity levels in the open field test

Female AS mice did not respond to EE in the same ways.

## Human Implications of Research

**Current Implications:**

- EE is a viable and accessible treatment option for AS patients (Woo & Leon, 2013).

**Future Implications:**

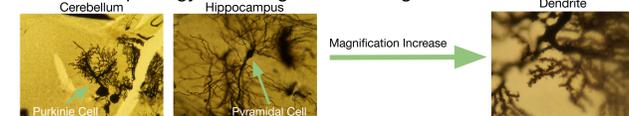
- Immunoblot analysis of post-weaning EE brains could reveal a pharmaceutical drug treatment for AS.

## Future Directions

In the future we may investigate:

- The effects of EE on novel-object recognition and forced swim, behaviors that are also commonly disrupted in AS mice.
- The effects of EE on hippocampal synaptic plasticity/long-term potentiation (LTP) in AS mice.
- Cellular and molecular changes in the brain as a result of post-weaning EE.

- Neuron morphology with Golgi-Cox staining



- Immunoblot analysis to examine EE-dependent changes in molecules associated with plasticity and seizure susceptibility

- The effects of a longer period of EE on behavior for female AS mice.