



Redefining Drug Discovery Through Innovation

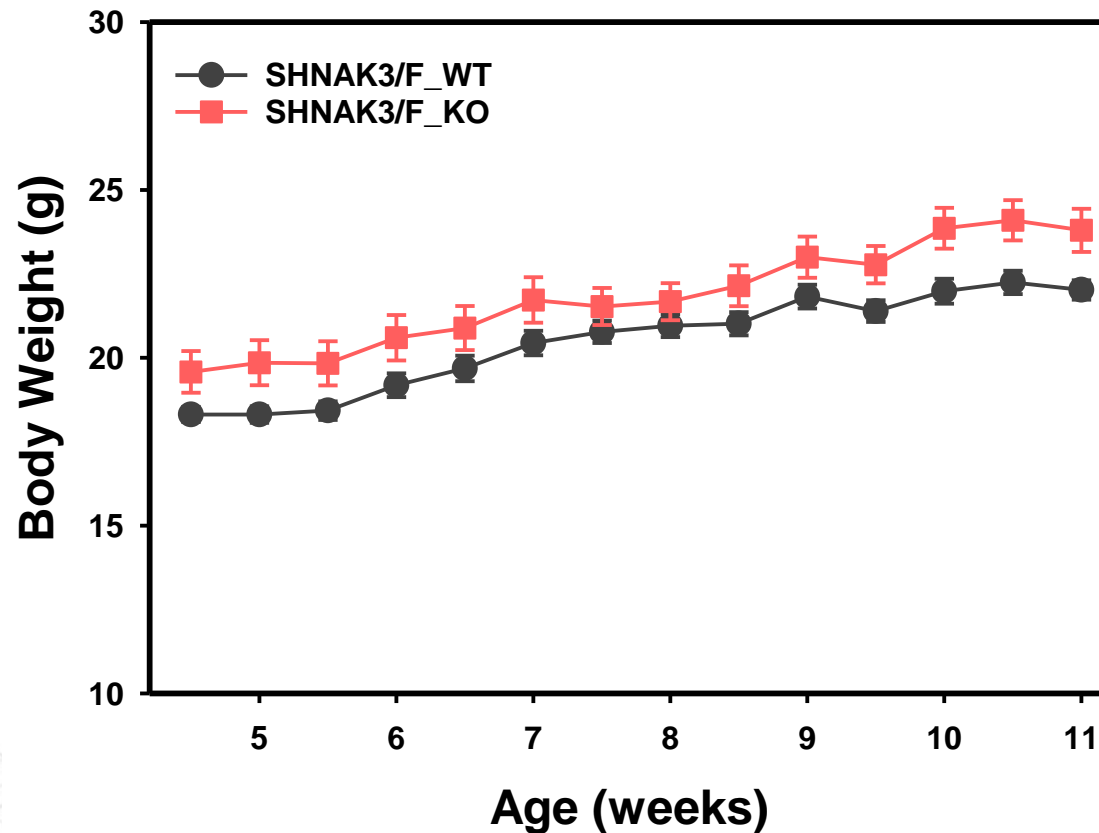
## **Shank 3 Mouse Model of Autism**

# Background

- About 2% of people with autism carry harmful mutations in SHANK3, a protein that helps organize the connections between neurons
- Developed by Guoping Feng, Shank3 –Feng mice harbor a deletion of exons 13-16 of the PDZ domains leading to the deletion of the Shank3 $\alpha$  and Shank3 $\beta$  isoforms and partial deletion of Shank3 $\gamma$
- These mice exhibit some social, communicative, repetitive, and sensory processing abnormalities associated with autism spectrum disorder.
  - Displays some social deficits
  - Shows a decrease in activity and locomotion compared to littermate controls, including reduced rearing
  - Shows gait differences compared to littermate controls
  - Displays some anxiety-like behaviors
  - Shows reduced startle responses and increased prepulse inhibition of startle



# No Significant differences in Body Weight Between WT and KO Mice



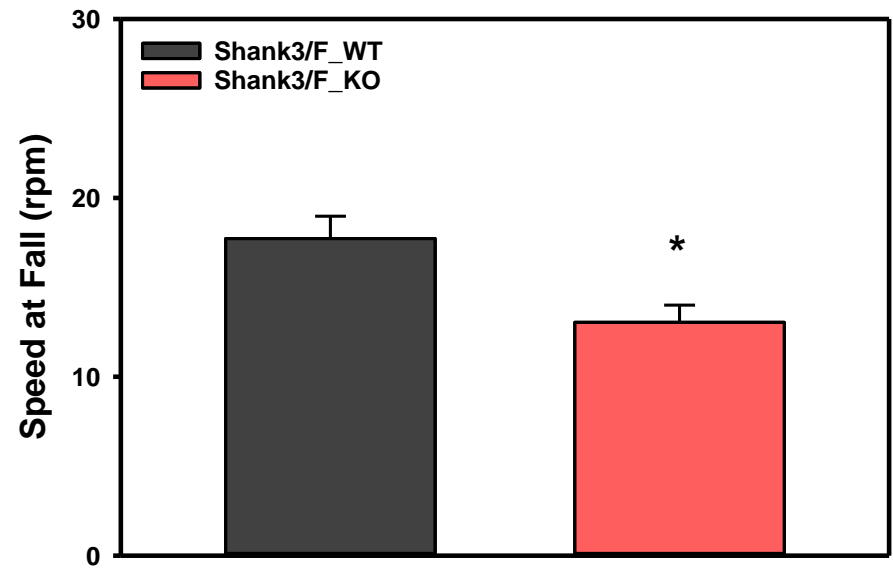
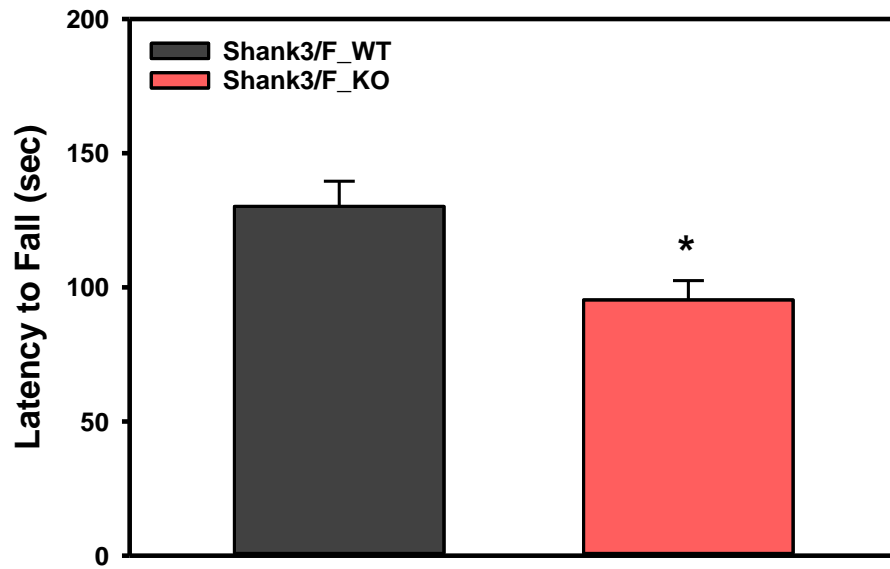




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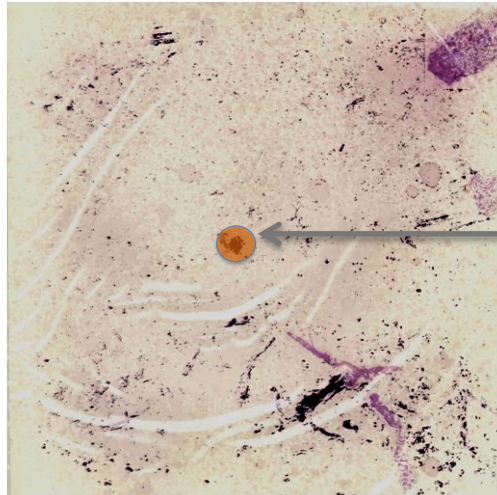
## Behavioral Assessments

# KO Mice Show Deficits in Rotarod Performance



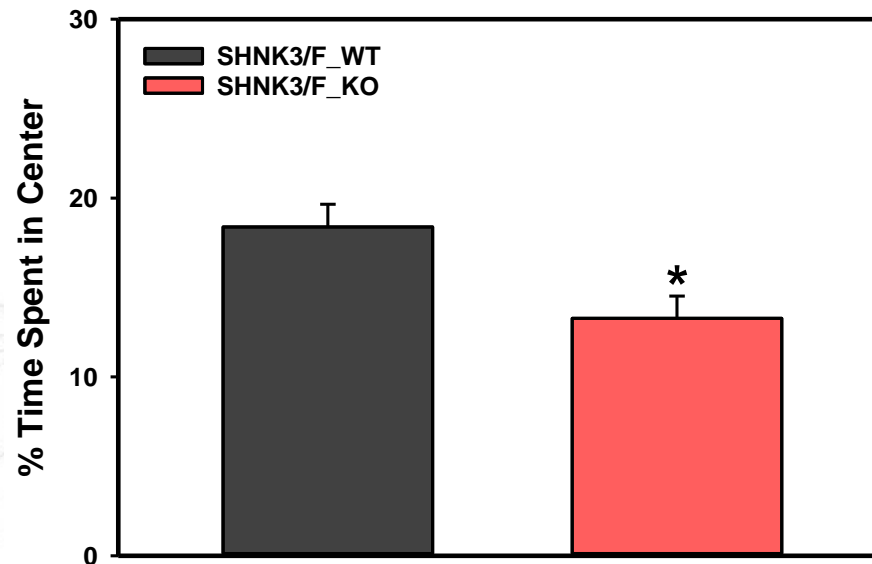
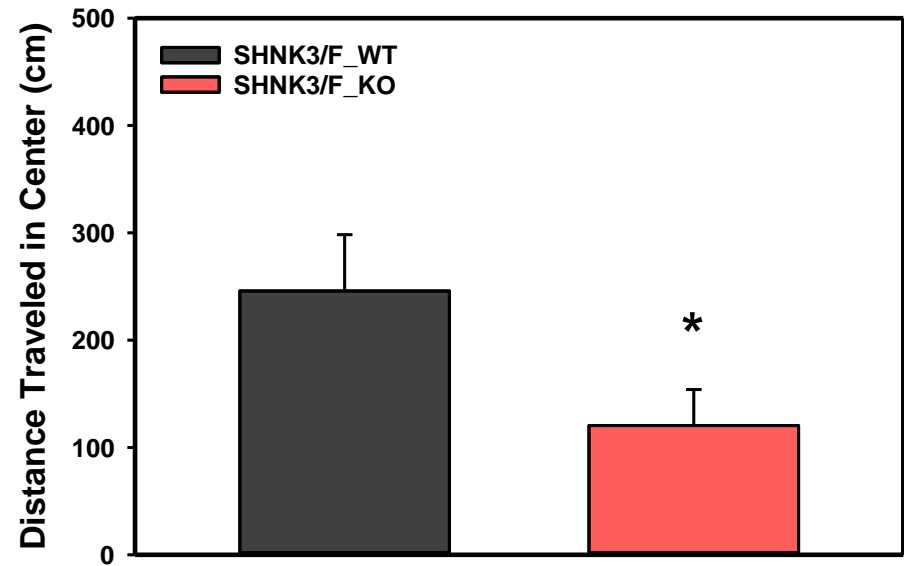
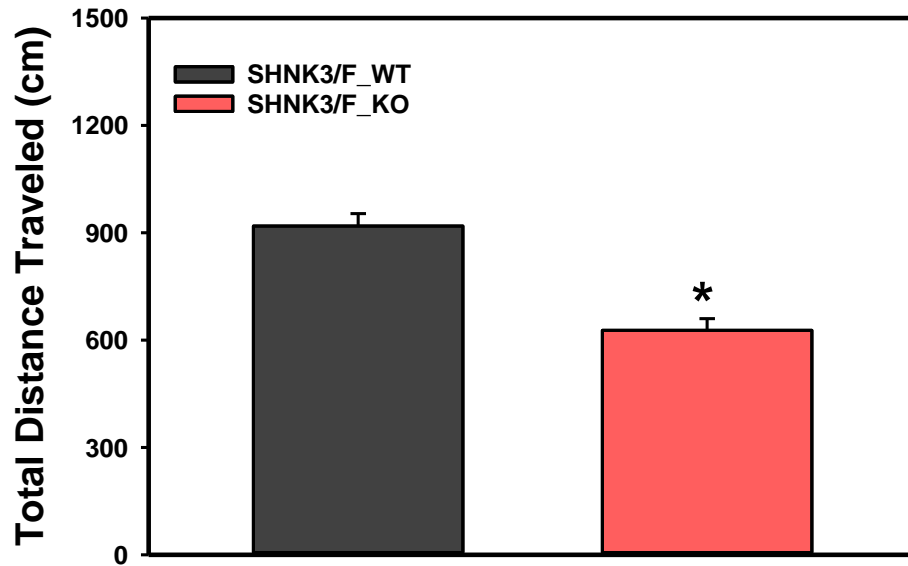
# Urine Open Field Test

- Male mice are placed in an Open Field where they are presented with the urine of an estrus female
- Activity, proximity to the urine, ultrasonic vocalizations, and urine marking by the male are recorded to determine social and function
- Urine spots developed with Nindyrin Spary



Estrous female urine spot

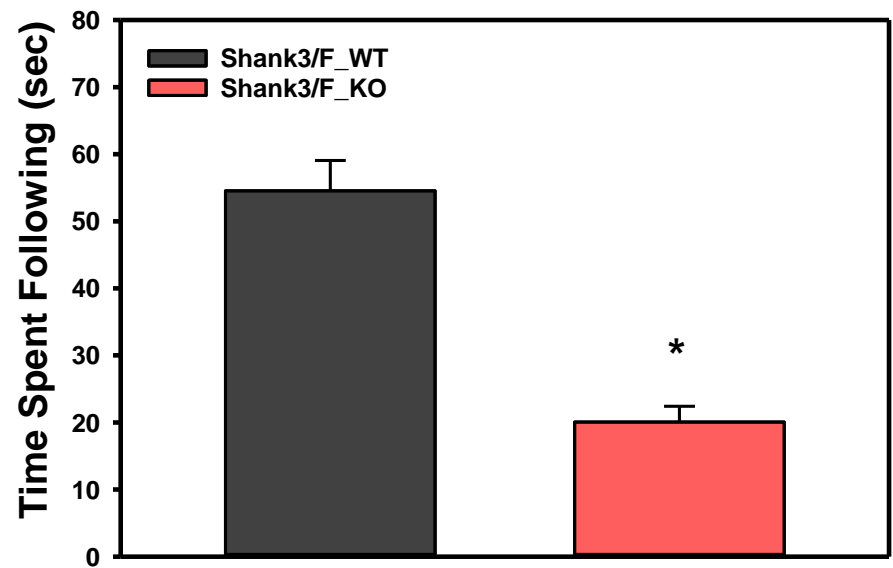
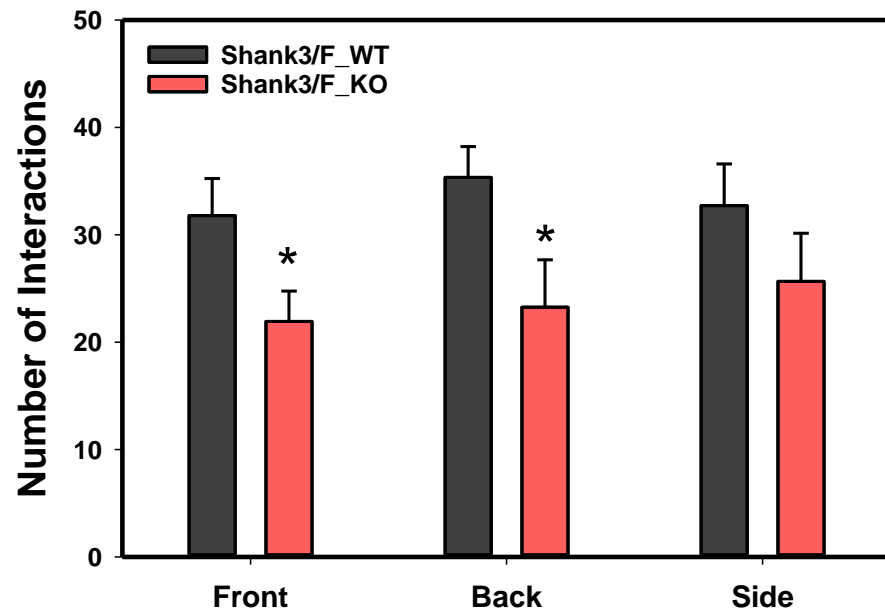
# KO Mice Show Decreased Activity in the Open Field Following Exposure to Female Urine





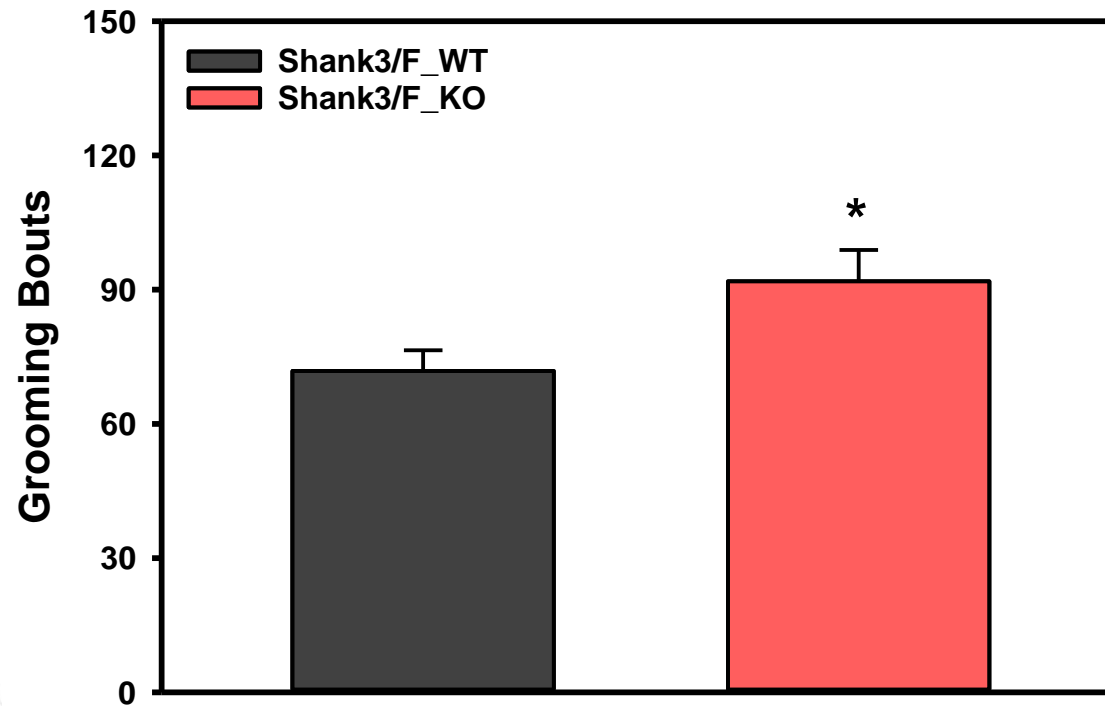
# Reciprocal Social Interaction

- Same-genotype, -sex, -age dyads are allowed to freely interact for 10 minutes
- Distance between mice, proximity, and interactions are measures of sociality

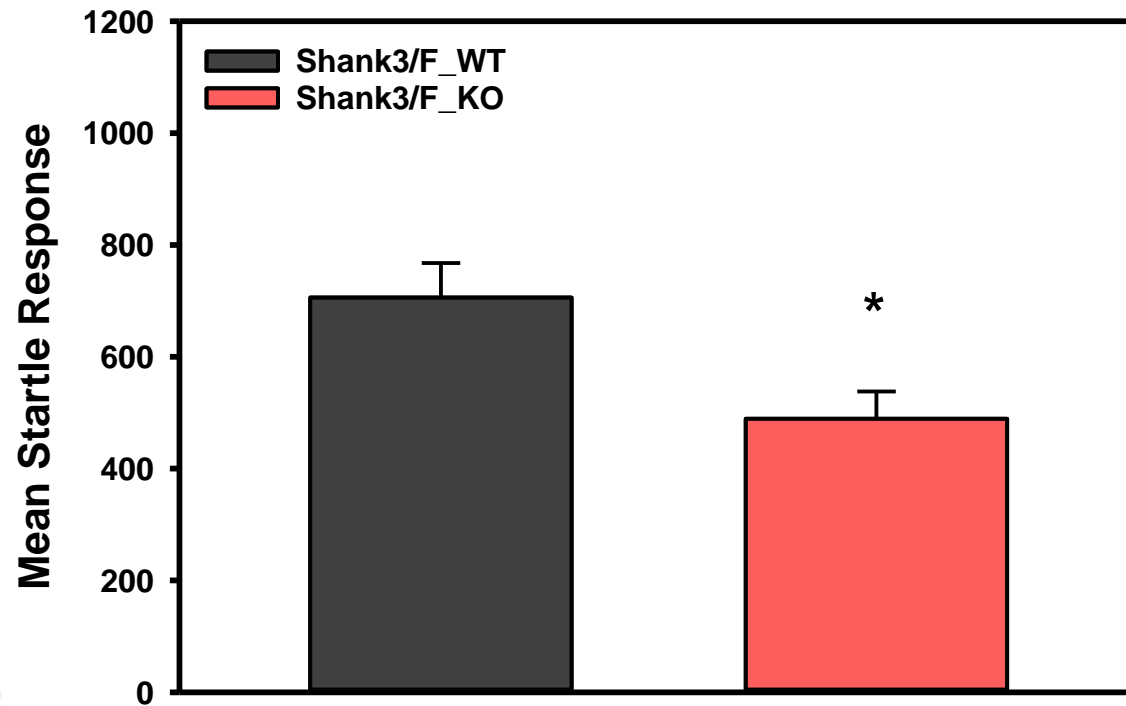




# KO Mice Show Increased Grooming



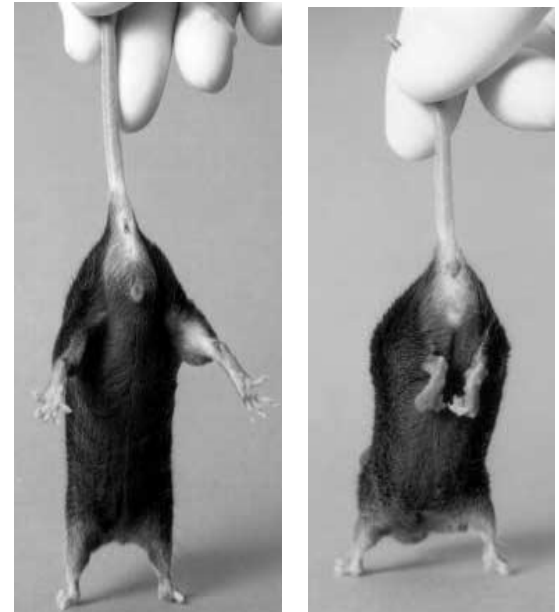
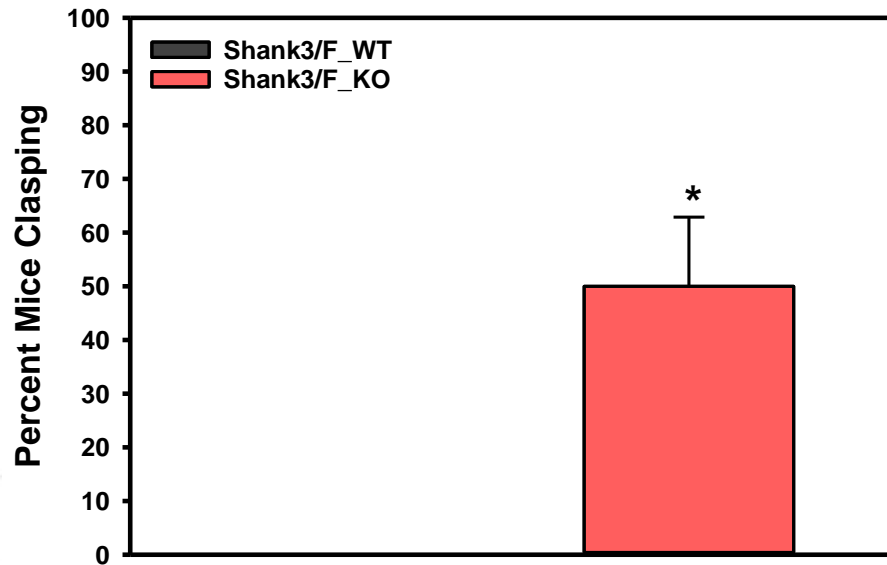
# KO Mice Show Decreased Startle Response



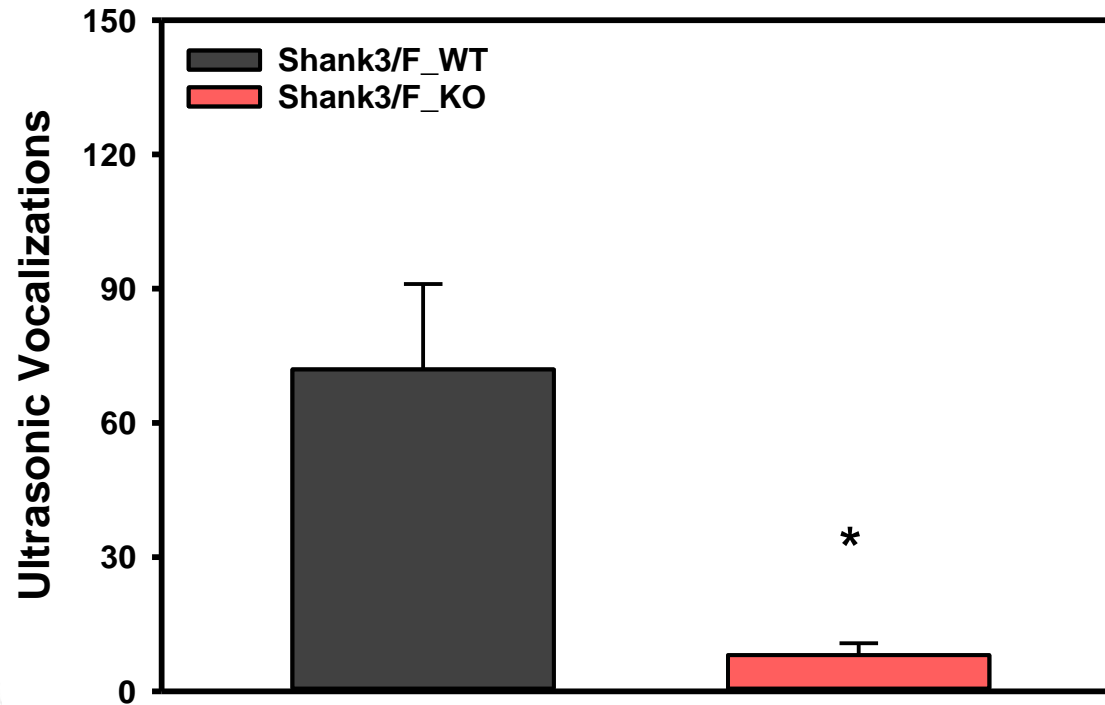
# KO Mice Show Increased Hindlimb Clasping

Mice are lifted gently by the tail with front limbs just above the surface

Clasping of hind legs is noted (normal is a spread in the hind legs)



# KO Mice Show Decreased Ultrasonic Vocalizations





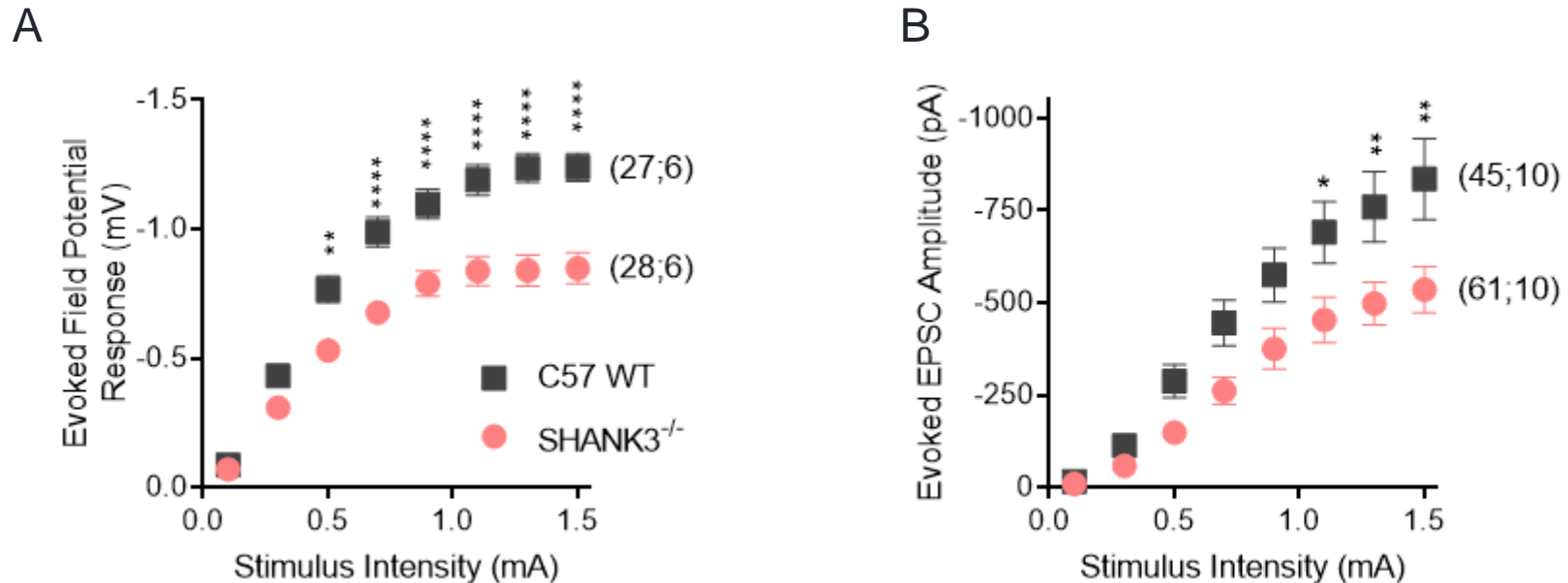


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# Electrophysiology

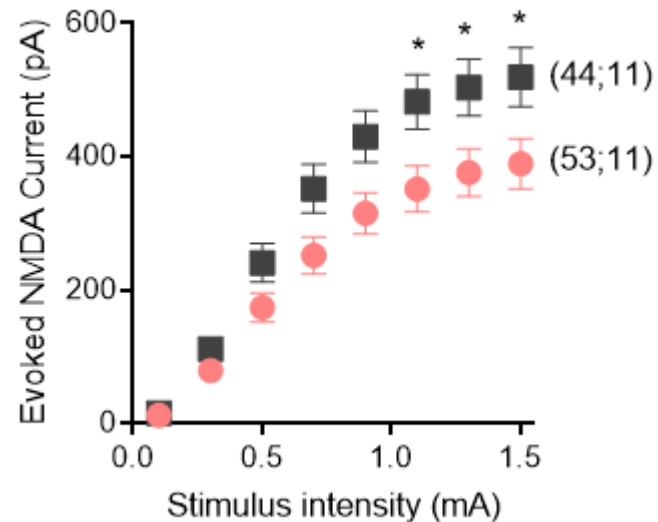
# Impaired corticostriatal synaptic transmission in Shank3 KO

- Extracellular field potential responses **(A)** and whole-cell currents in medium spiny neurons **(B)** were evoked in dorsal striatum by stimulating corpus callosum.
- Brain slices were prepared from male mice aged 10 weeks for extracellular field potential recordings **(A)** and 14 weeks for whole-cell patch clamp recordings **(B)**.
- Numbers in parenthesis show number of slices (cells); animals used.



# Impaired NMDA-mediated synaptic transmission in dorsal striatum in Shank3 KO

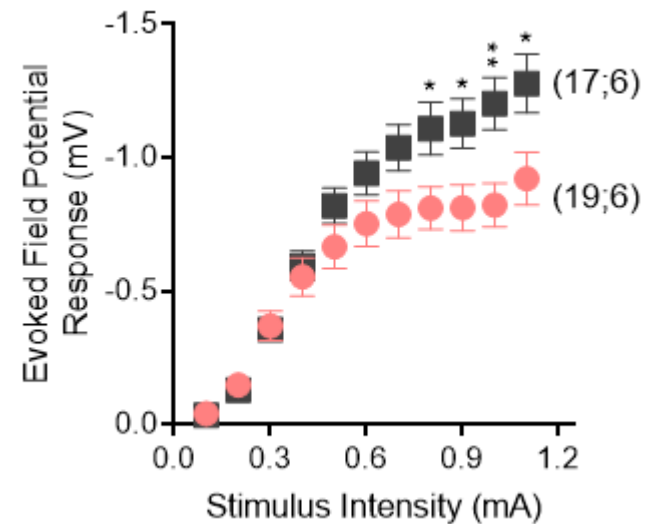
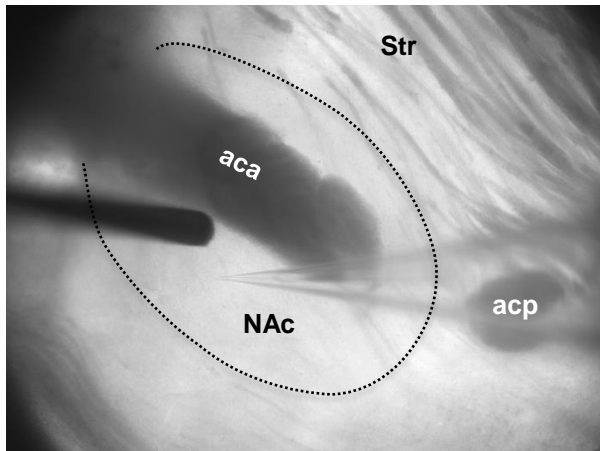
- Whole-cell NMDA-mediated currents in medium spiny neurons were evoked in dorsal striatum by stimulating corpus callosum in 14 weeks old male mice.
- Numbers in parenthesis show number of cells; animals used.





# Impaired synaptic transmission in nucleus accumbens in Shank3 KO

- Extracellular field potential responses were evoked in nucleus accumbens (NAc) by stimulating terminals within the nucleus in 10 weeks old male mice.







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## Molecular markers

# Decreased expression of synaptic proteins in striatum and BDNF in cortex in Shank3 KO

- Expression of synaptic proteins in striatum and BDNF in cortex was assessed by qPCR in 16 weeks old male Shank3 KO mice (n=10).

