



Redefining Drug Discovery Through Innovation

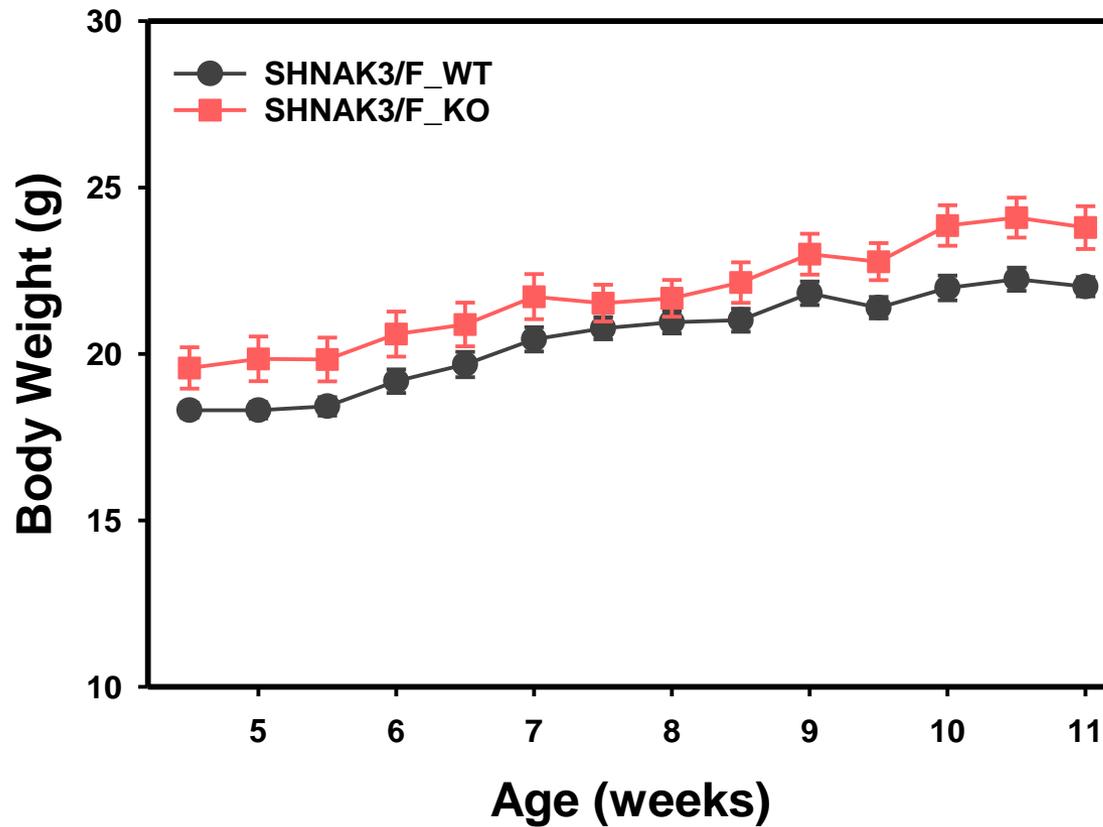
Shank 3 Mouse Model of Autism

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 α and Shank3 β isoforms and partial deletion of Shank3 γ
- 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



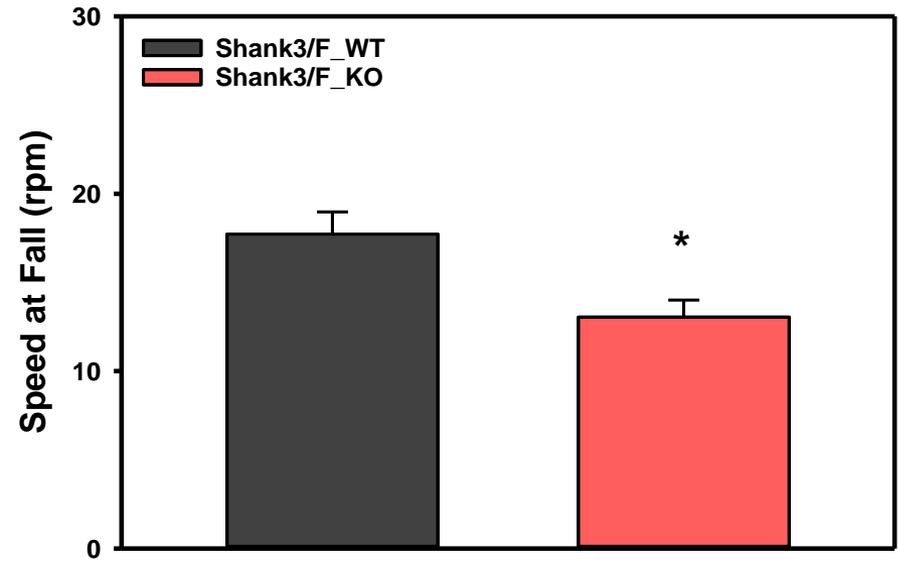
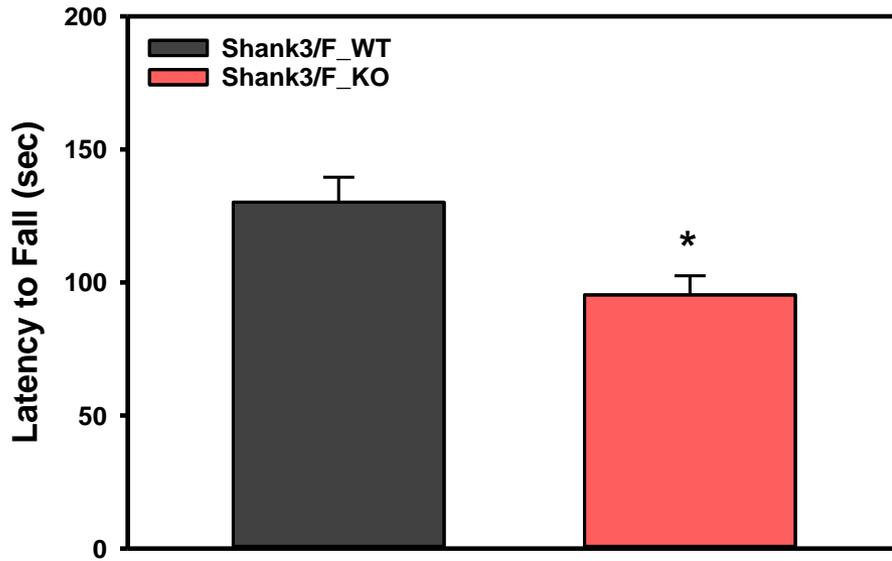


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Behavioral Assessments

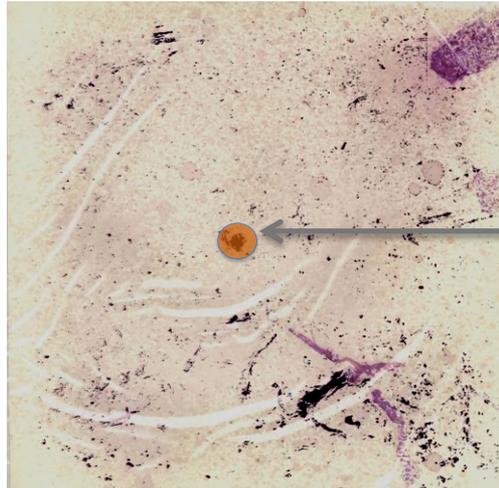


KO Mice Show Deficits in Rotarod Performance



Urine Open Field Test

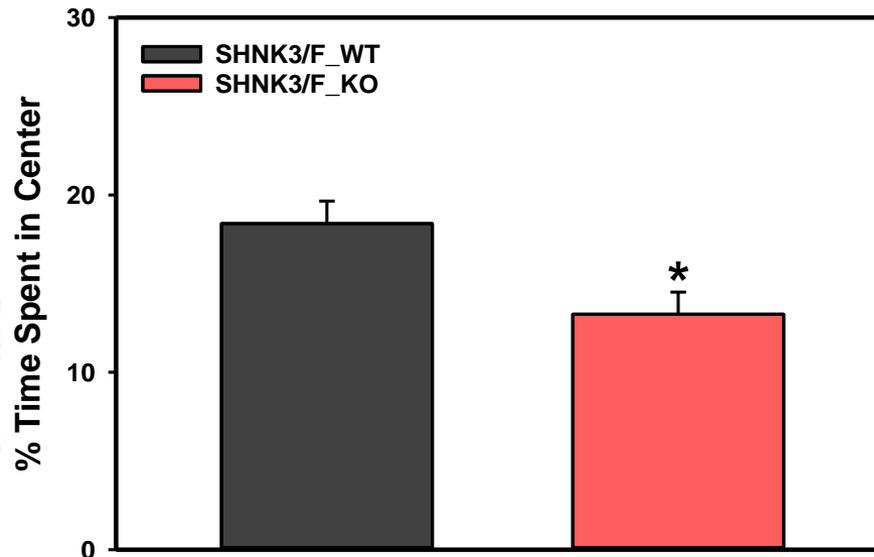
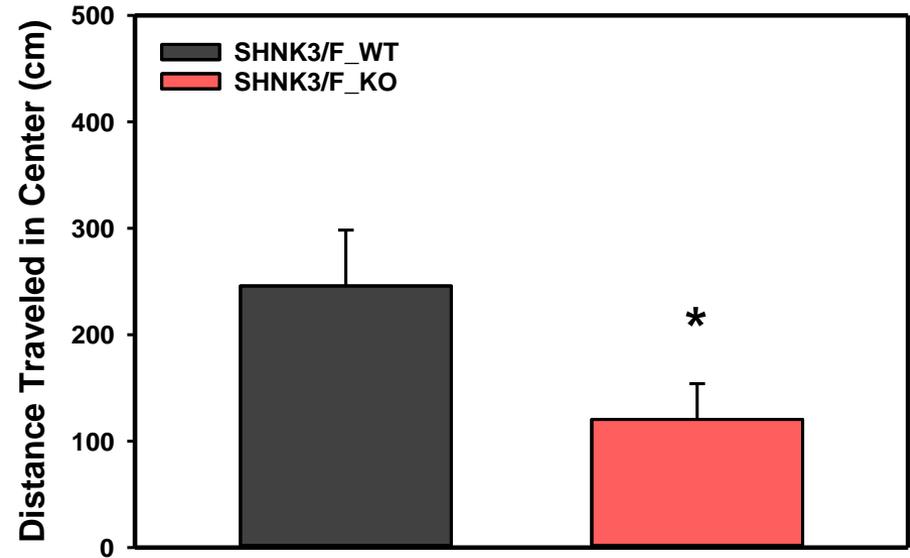
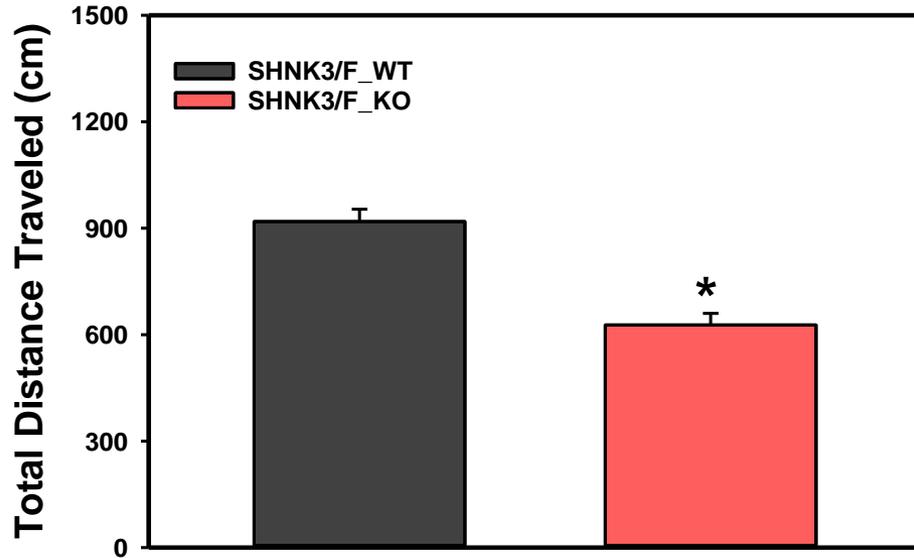
- Male mice are placed in an Open Field where they are presented with the urine of an estrus female
- Activity, proximity to the urine, ultrasonic vocalizations, and urine marking by the male are recorded to determine social and function
- Urine spots developed with Nindyrin Spary



Estrous female urine spot

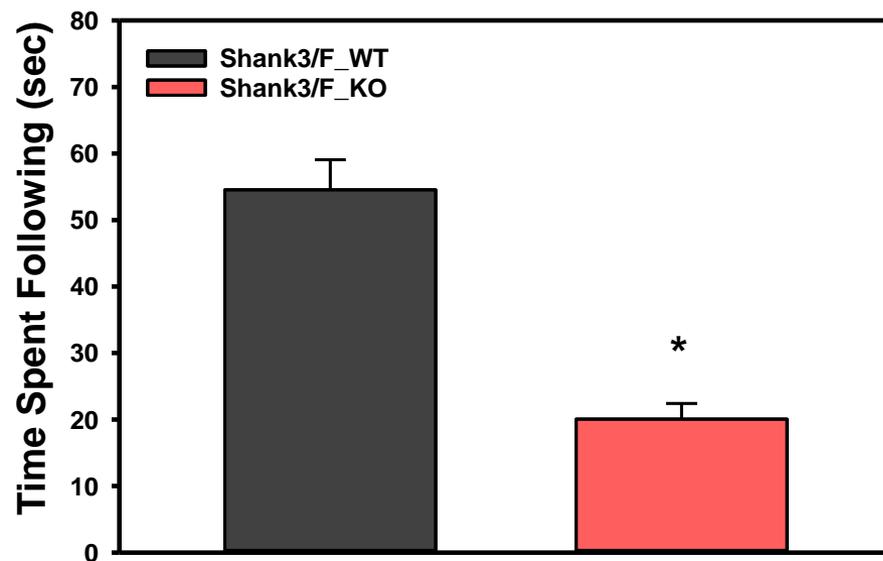
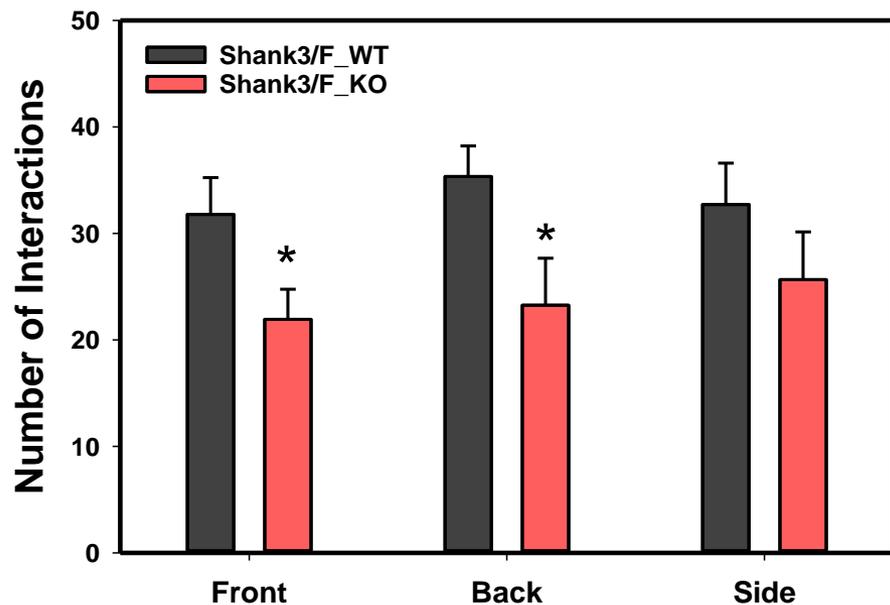


KO Mice Show Decreased Activity in the Open Field Following Exposure to Female Urine

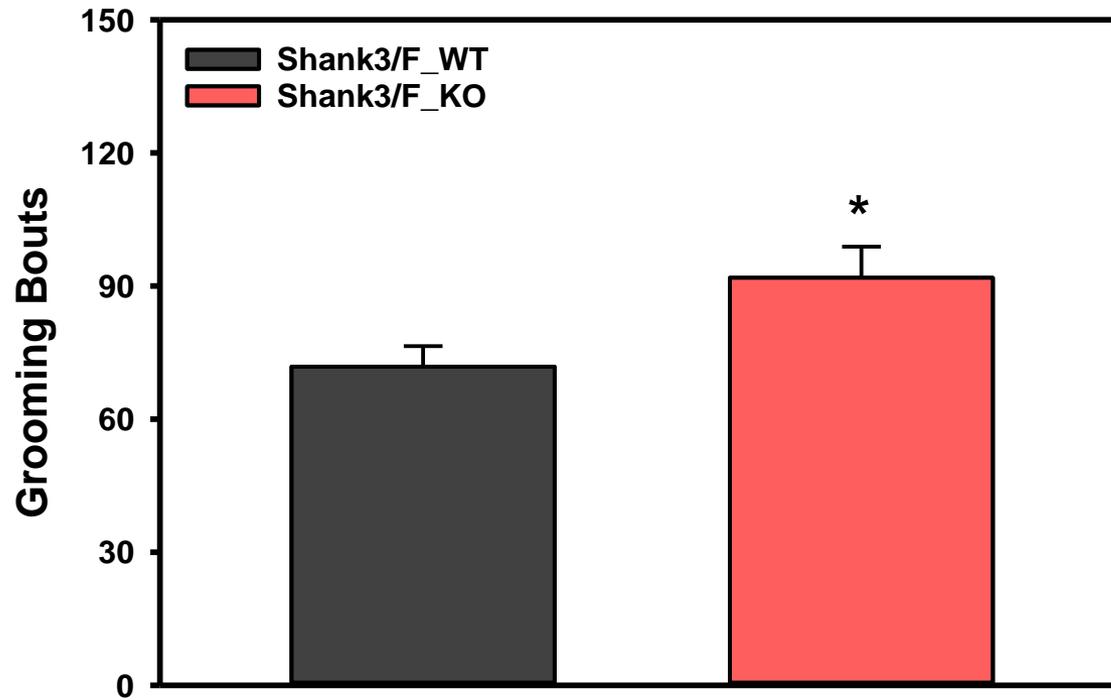


Reciprocal Social Interaction

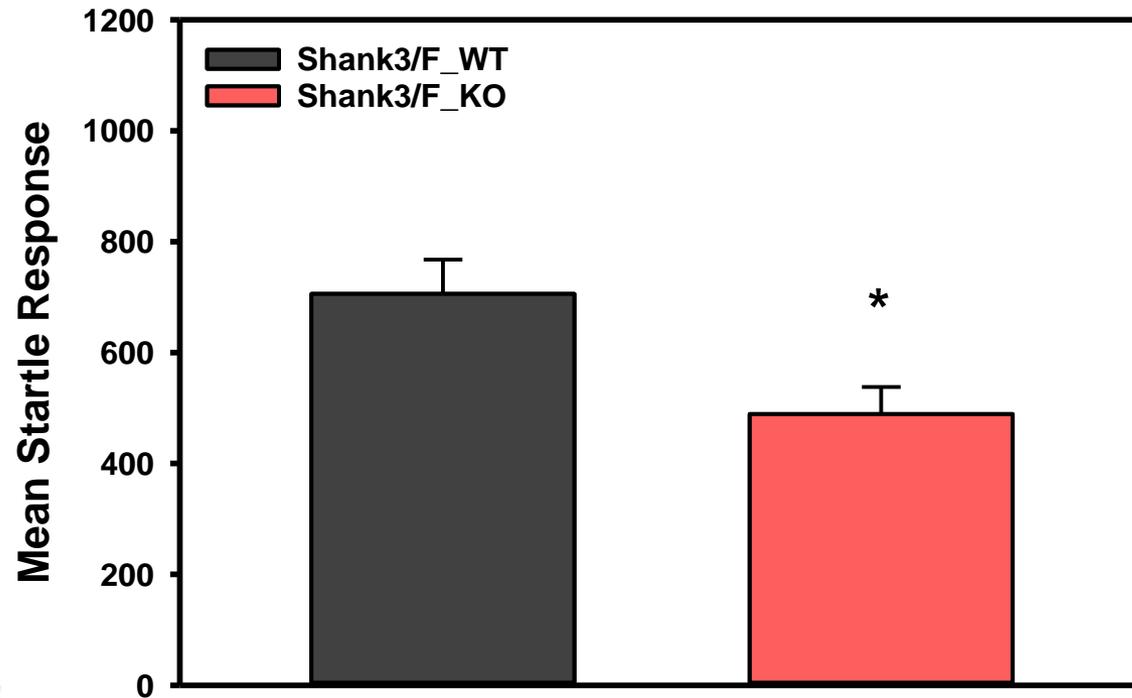
- Same-genotype, -sex, -age dyads are allowed to freely interact for 10 minutes
- Distance between mice, proximity, and interactions are measures of sociality



KO Mice Show Increased Grooming



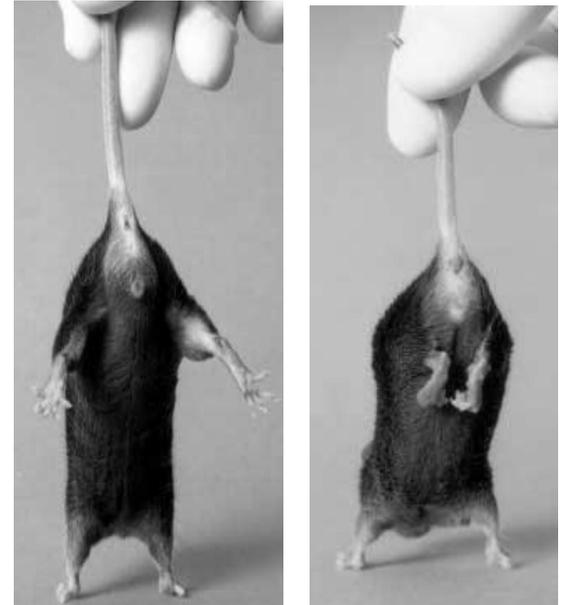
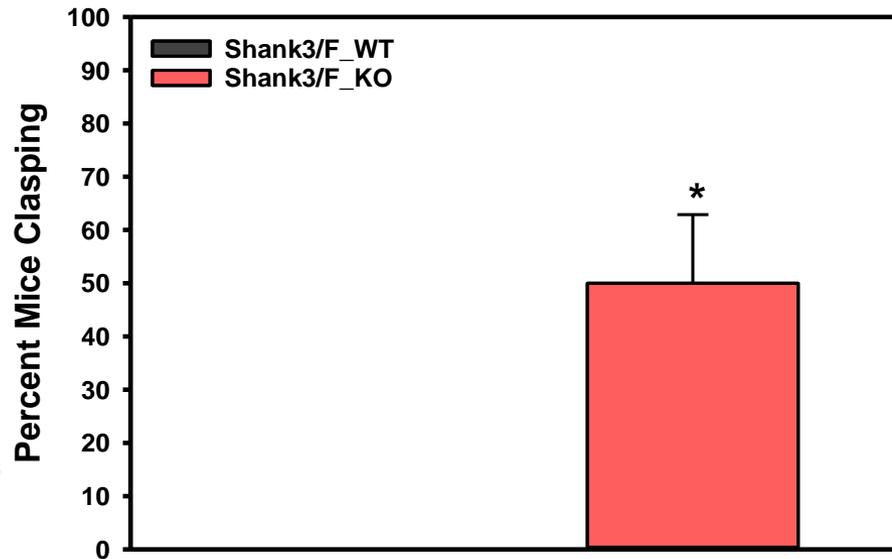
KO Mice Show Decreased Startle Response



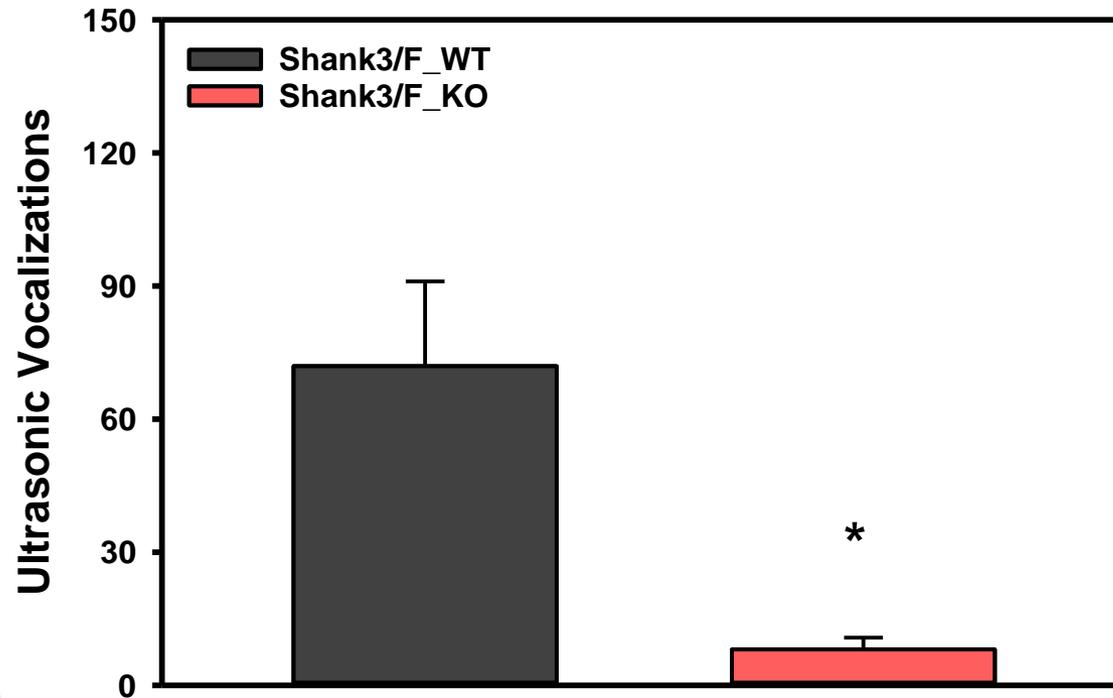
KO Mice Show Increased Hindlimb Clasp

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)



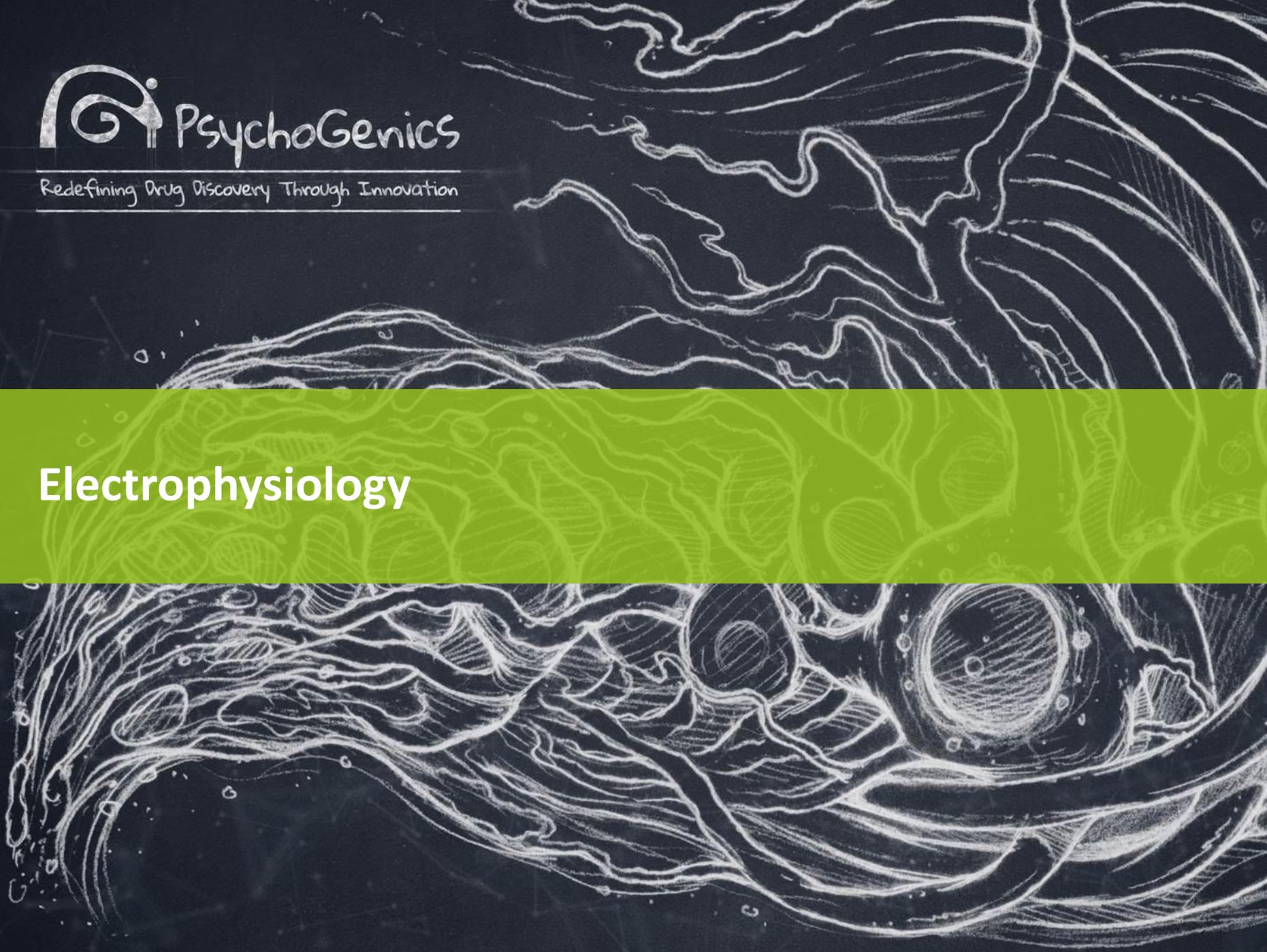
KO Mice Show Decreased Ultrasonic Vocalizations





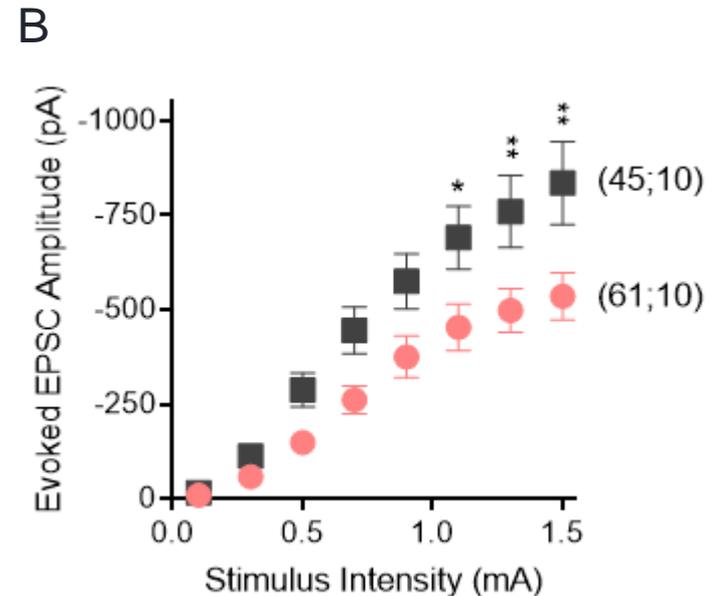
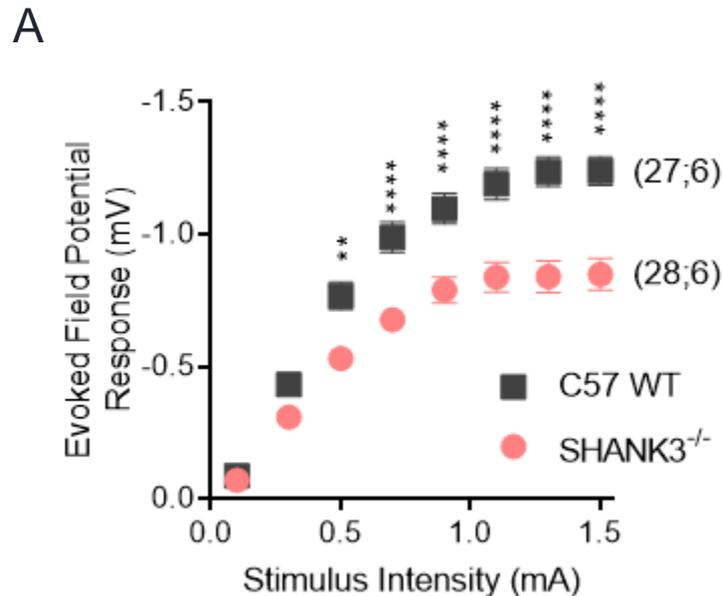
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Electrophysiology



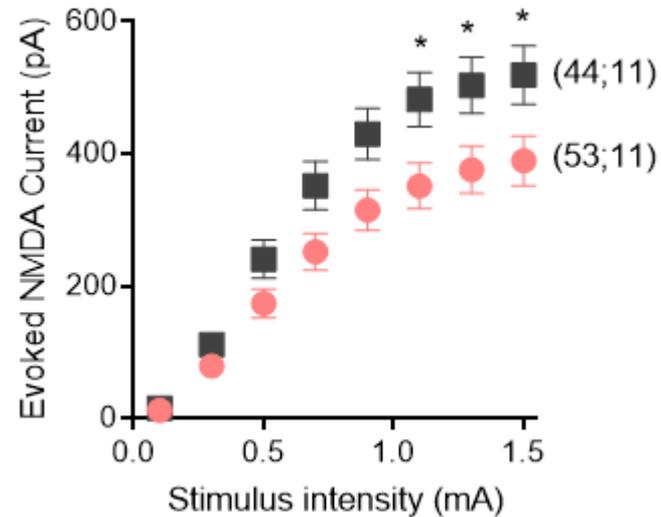
Impaired corticostriatal synaptic transmission in Shank3 KO

- 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.



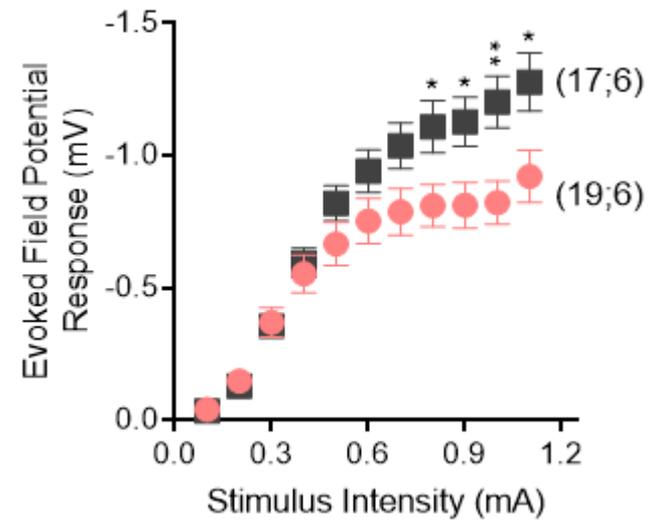
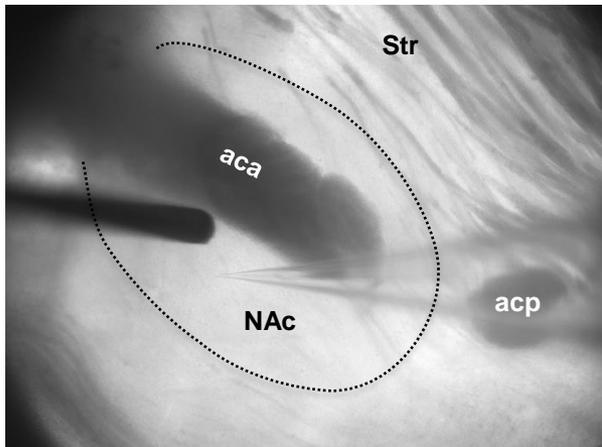
Impaired NMDA-mediated synaptic transmission in dorsal striatum in Shank3 KO

- 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).

