Studying the Single-cellular Substrates of Autism in a Mouse Model

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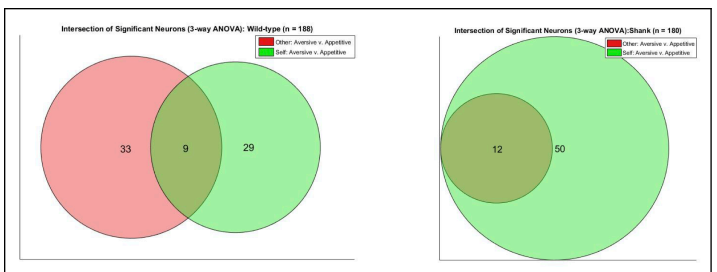
Introduction

Social dysfunction is among the most prominent features of autism spectrum disorder (ASD) as well as many other developmental and neuropsychiatric conditions. What precise neuronal mechanisms are disrupted in ASD, however, are unknown. The goal of this study is to provide a basic cellular-level understanding and treatment model for ASD.

Methods

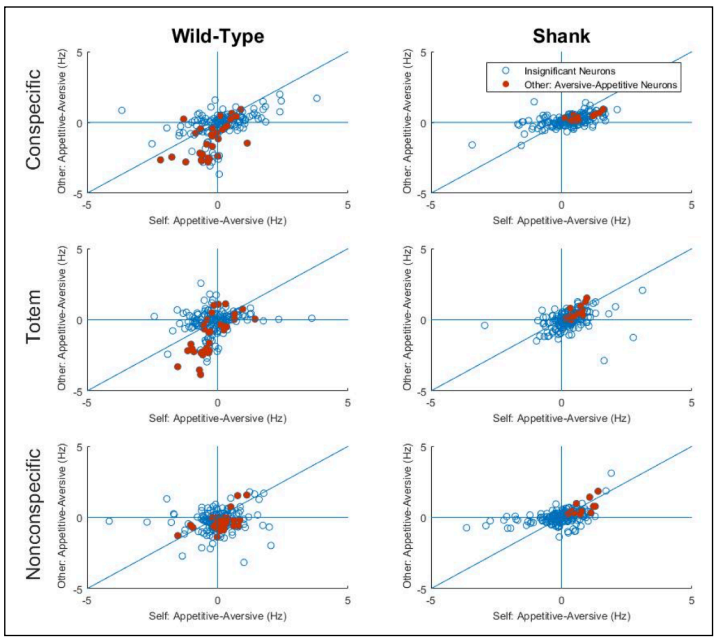
We developed an alternating appetitive/aversive paradigm in which socially-paired mice experienced both acute stress and food reward while we simultaneously recorded neuronal activity from medial prefrontal cortex. We compared WT to SHANK3 -/+ mice as a model of ASD, to explore the neuronal correlates socially relevant information and its dysfunction.



A venn diagram depicting neurons which encode for self- and other-valence. Notably, Shank mice display significantly more neurons which encode for self-valence (n = 50) than for other-valence (n = 12). Thus, while WT mice appear to have approximately two equally-sized, distinct populations for encoding their own experience and their partner's, Shank mice altogether lack neurons which specifically encode for their partner's.

Results

Individual medial prefrontal neurons in SHANK3 -/+ mice displayed markedly different response profiles compared to that of WT. Specifically, neurons in SHANK3 -/+ mice demonstrated little differential response when presented with another unfamiliar mouse or nonsocial totem undergoing the same condition. However, in trials where the recorded mouse and a familiar mouse both receive a negative (painful) stimulus, SHANK3 -/+ mice demonstrated a significantly attenuated firing rate in response to the conspecific mouse, while the WT mice did not show any such differences. This attenuation was not observed when the other mice received positive (rewarding) stimuli.



Conclusions

Our study reveals some of the basic neuronal coding mechanisms that are disrupted in ASD. In particular, they demonstrate that, at the cellular level, autistic mice lack the neuronal-equivalent of an "empathic" response compared to wild-type. This neuronal response may provide a foundational mechanism for egocentric behavioral often found in ASD and suggests a basic model for testing neurobiologically plausible treatments for individuals with autism.

References

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Learning Objectives

1) Wild-type and SHANK3 -/+mice demonstrate differential responses towards other mice based on whether the other mouse is conspecific or non-conspecific.

2) Under neutral conditions, both wild-type and SHANK3 -/+mice demonstrate an enhanced firing rate in response to a conspecific mouse receiving a painful stimulus.

3) Under painful conditions, SHANK3 -/+ mice exhibit an attenuated "empathetic" response, suggesting a neural mechanism in the medial prefrontal cortex that underlies egocentric characteristics that are a hallmark of autism