NEWS

Three autism mouse models marked by defects in same circuit

BY **NICHOLETTE ZELIADT**

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Problems with social interactions stem from faulty wiring of a deep-brain circuit, according to unpublished results from three different mouse models of autism, presented Tuesday at the **2015 Society for Neuroscience annual meeting** in Chicago.

Inhibiting this circuit improves social interactions in one of the models, and stimulating it worsens them. The findings point to a potential target for treating social deficits in autism.

“We wanted to understand how different genetic changes associated with autism converge,” says **Audrey Brumback**, a postdoctoral fellow in **Vikaas Sohal**’s lab at the University of California, San Francisco, who presented the findings. “One level of convergence is at the level of neuronal circuit physiology.”

One of the models Brumback and her colleagues studied lacks the autism-linked gene **CNTNAP2**. The second is missing the **FMR1** gene, which is mutated in the autism-related disorder **fragile X syndrome**. The third group of animals were exposed prenatally to the **epilepsy** drug valproic acid (VPA), which **increases autism risk**.

The researchers focused their attention on neurons in a deep layer of the prefrontal cortex, a brain region implicated in social cognition. They looked specifically at two subtypes of neurons that send signals to two distant brain regions: the thalamus, which relays sensory and motor information, and the **corpus callosum**, a dense nerve bundle that connects the two hemispheres of the brain.

Circuit similarity:

All three autism models show similar electrical properties in both types of neurons. The cells that signal to the thalamus fire less frequently than those in controls, and have lower electrical excitability. Neurons that signal to the corpus callosum are unaffected.

The researchers then looked at whether the activity of this circuit plays a role in the abnormal social behaviors of these animals. For these experiments, they have used only the VPA-exposed animals so far. That's because, of the three groups, the animals in this one spend the least time interacting with unfamiliar mice.

[The neurons that send signals to the thalamus typically become active as a mouse investigates an unfamiliar cagemate, the researchers found. These neurons are active for a shorter period of time in VPA-exposed mice than in controls.]

Brumback and her colleagues used a method called **optogenetics** to genetically engineer neurons in the VPA-exposed mice to turn on or off in response to light. Inhibiting the neurons connecting to the thalamus enhances social exploration, whereas boosting the activity of this circuit worsens their social behavior, the researchers found. Inhibiting all of the neurons has no effect on social interactions.

The findings fit with brain imaging studies of people with autism that show **alterations in the connections** between the prefrontal cortex and the thalamus. [They do not fit with the finding that VPA mice, which are less social than controls, have less activity in the circuit at baseline, however.]

[They are also somewhat counterintuitive.] "When I started these experiments, I anticipated that exciting the hypoexcitable neurons would improve the social phenotype," Brumback says. Instead, she observed the opposite effect.

"The next step I need to do is to understand what these cells are doing — what their baseline patterns and frequencies of activity are, and how that changes during social interaction," she says. "Another outstanding question is whether this is specific for [this circuit], or if this is generalizable to other areas."

*For more reports from the 2015 Society for Neuroscience annual meeting, please **click here**.*

REFERENCES:

1. Brumback A.C. *et al. Mol. Psych.* Epub ahead of print (2017) **PubMed**