NEWS

Sound processing skewed in mouse model of Rett syndrome

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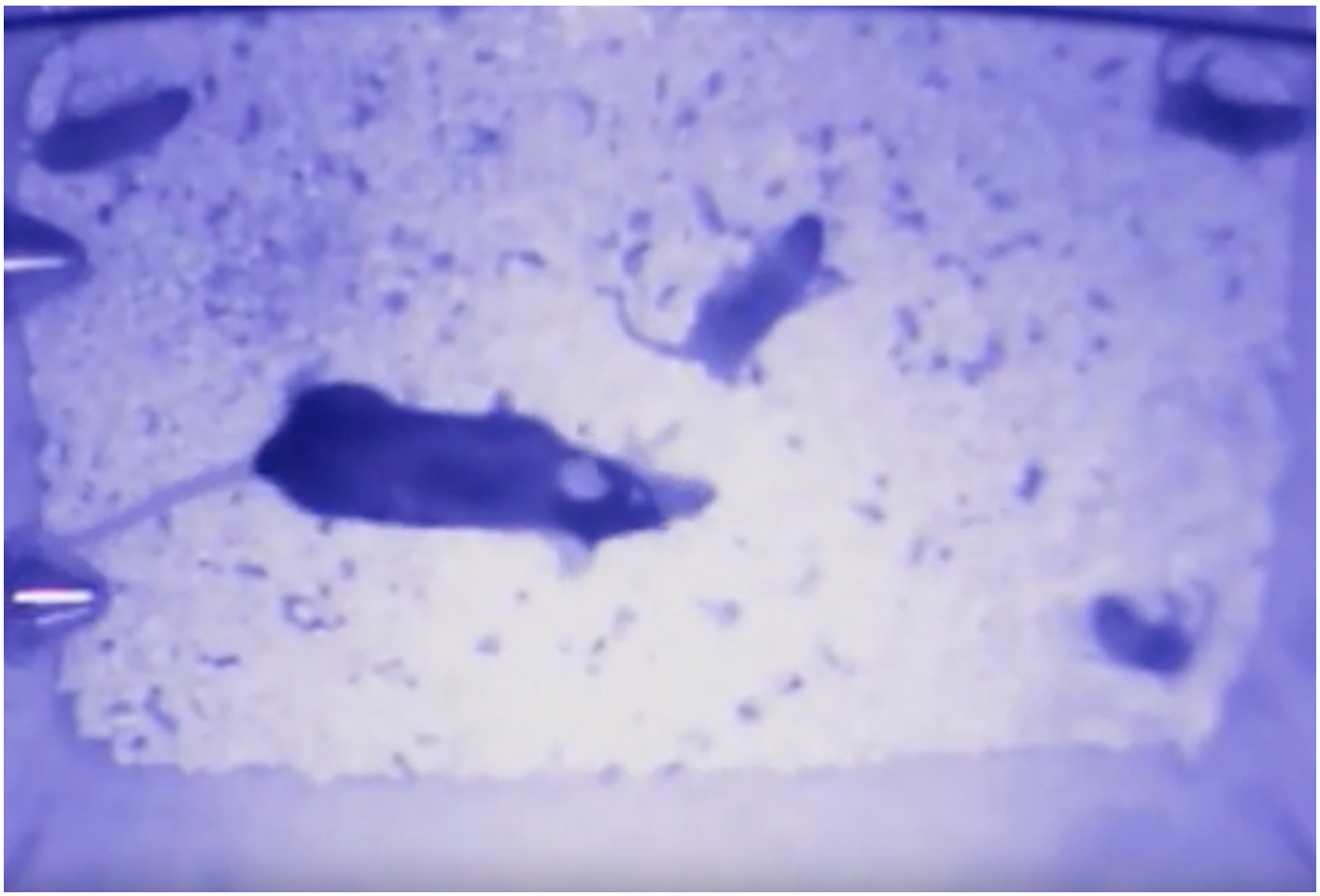

Researchers have traced an unusual maternal behavior in female mice modeling Rett syndrome to a neural circuit that processes sound. They have also found a drug that reverses this behavior.

The unpublished results, presented Wednesday at the **2015 Wiring the Brain meeting** in Cold Spring Harbor, New York, point to a possible pathway that links the genetic deficit in Rett syndrome to specific behavioral abnormalities.

“We want to understand what’s happening at the molecular level, how that manifests at the circuit level, and then connect that to behavior,” says lead investigator **Stephen Shea**, assistant professor at Cold Spring Harbor Laboratory in New York.

Most cases of Rett syndrome stem from mutations in **MeCP2**, a gene located on the X chromosome. These mutations are usually fatal in boys. But because girls have two X chromosomes, some of their cells express a working copy of the gene.

This mosaic expression pattern may help to explain why some girls are more severely affected than others. It also makes it difficult to model the disorder in female mice.

“It’s really difficult to study Rett in females because of this random X chromosome inactivation — every animal is different from another,” says **Keerthi Krishnan**, a postdoctoral fellow **Josh Huang**’s lab at Cold Spring Harbor Laboratory who presented the work.

But Krishnan noticed that female mice missing a copy of MeCP2 have one thing in common: As mothers, they have trouble retrieving pups that wander from the safety of their nest.

Pup gathering requires the mother to hear and respond to the distress calls of her pups. This led the researchers to home in on a neural circuit involved in processing sound.

Surrogate struggles:

To avoid the potentially confounding effects of pregnancy hormones and the possibility that pups missing a copy of MeCP2 make abnormal distress calls, the researchers studied normal pups and surrogate female mice with no prior maternal experience. These stand-ins perform poorly at pup gathering at first, but typically learn the skill quickly from a veteran mother.

However, surrogates missing a copy of MeCP2 struggle to learn the behavior, even after living with a mother and her pups for five days.

Surrogates with damage to the auditory cortex — a brain region that processes sounds, including pup vocalizations — performed just as poorly as the Rett mice. What’s more, mice missing MeCP2 in only the auditory cortex also showed this poor performance.

“It’s MeCP2 specifically in the auditory cortex that’s important for this behavior,” Krishnan says. “Now we’re narrowing down the circuit.”

[After living with a mother and her pups, female surrogates produce inhibitory signals in the brain in response to pup vocalizations. Surrogates deficient in MeCP2 show this same response, but unlike in controls, it is accompanied by an increase in the levels of parvalbumin, a marker of inhibitory neurons.] They also have unusually high numbers of structures called perineuronal nets, which surround neurons and impede their ability to communicate with each other. [Both changes likely produce an increase in inhibitory signaling.]

“They can hear, because we know the cells in the auditory cortex respond to the pups,” Krishnan says of the mice. But their brains appear to process the sounds differently, she says.

When the researchers counter these brain changes — either by genetically dampening the inhibitory signals or by injecting a drug called chondroitinase ABC that prevents the formation of perineuronal nets — the surrogates successfully learn to gather the pups. [Deleting MeCP2 from only parvalbumin neurons in mice impairs their ability to learn this behavior.]

The findings suggest that the lack of MeCP2 hinders a process called experience-dependent plasticity — the ability of neuronal connections to change in response to various experiences. This problem may also exacerbate behavioral symptoms in people with Rett syndrome, Shea says.

Shea doesn’t envision using chondroitinase ABC therapeutically in humans, but he says the findings reveal a potential therapeutic target worthy of further investigation. “It suggests that MeCP2 might act during specific temporal windows that could be targets for intervention,” he says.

For more reports from the 2015 Wiring the Brain meeting, please **click here**.

REFERENCES:

1. Krishnan K. *et al. Nat. Commun.* **8**, 14077 (2017) **PubMed**