NEWS

Mouse models for autism debut

BY **MEREDITH WADMAN**

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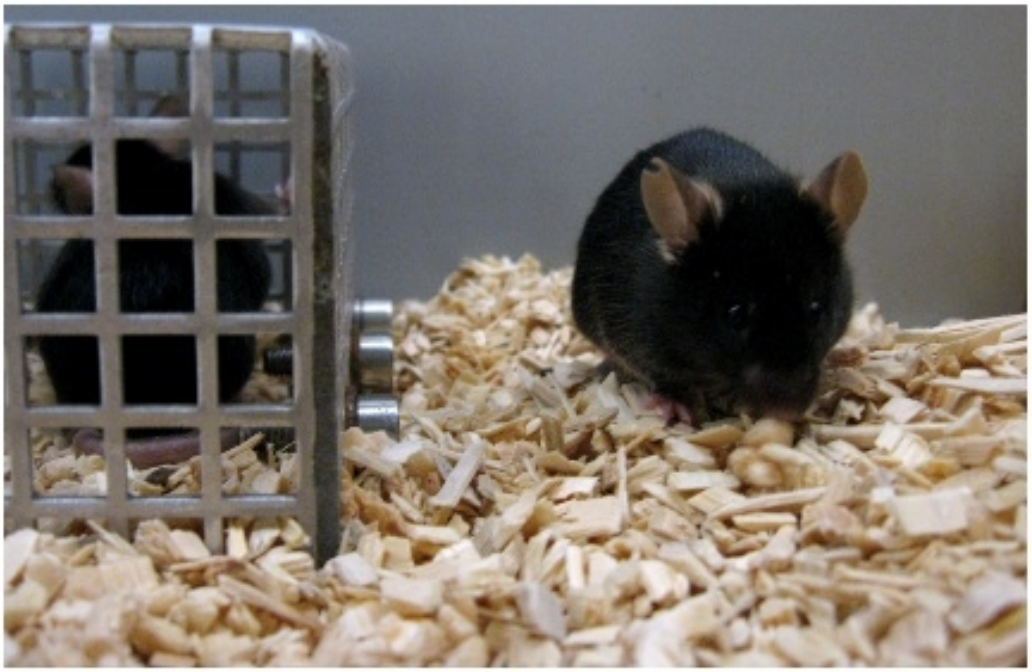
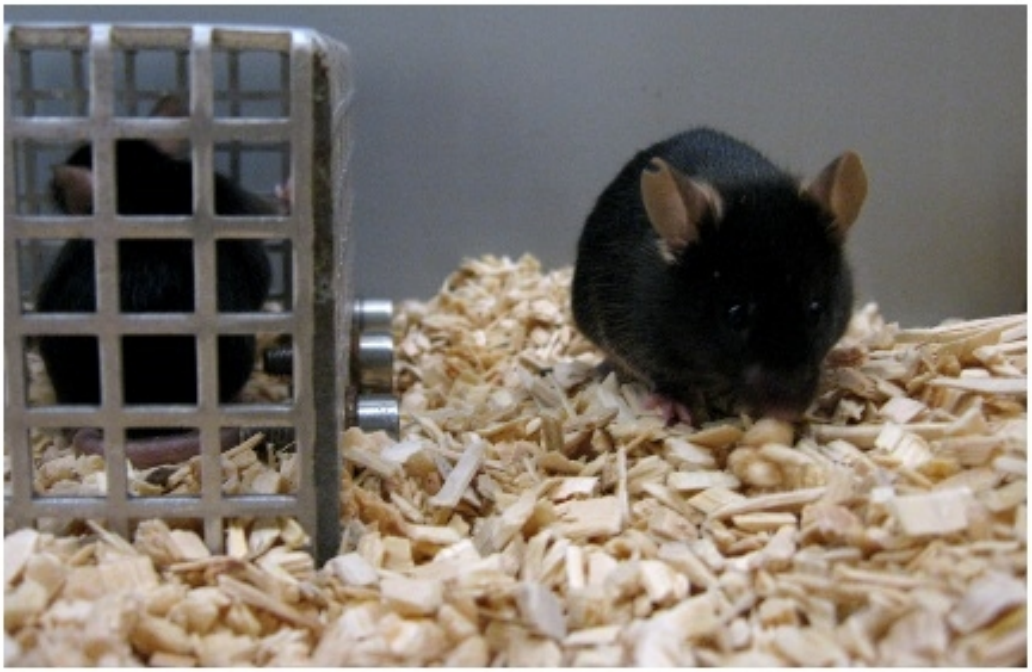




T. Südhof and N. Brose

Two research groups have achieved an elusive goal: producing mouse models that show distinct social and behavioral abnormalities reminiscent of autism.

In early February, European researchers reported that they had created a mouse model for autism by inserting a genetic mutation known to cause autism in people[1].

Last September, a team at the University of Texas Southwestern Medical Center in Dallas described a different mouse model that carries another mutation linked to autism[2].

Before September, scientists working on autism had few choices for animal models that mimicked the social and behavioral problems associated with the disease, without other symptoms that complicate the picture.

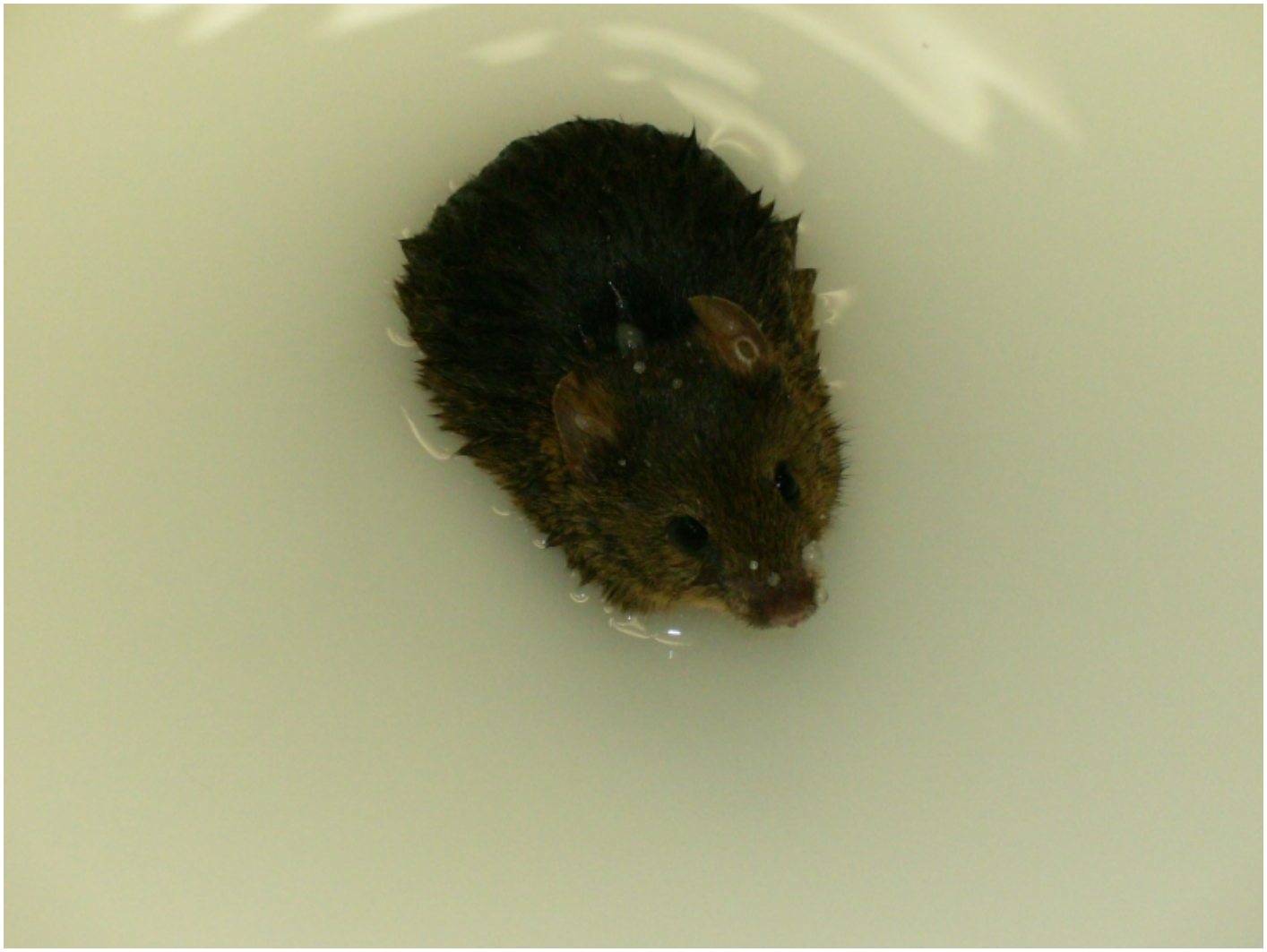
For example, some mice are excellent models for related diseases, such as fragile X syndrome or Rett syndrome. Like people with these disorders, these mice show some symptoms of autism, but also have other serious problems, including profound mental retardation.

Other, inbred mice have multiple behavioral abnormalities, some of which can be labeled as symptoms of autism - but they are hardly perfect models for stand-alone autism. Mice genetically engineered to lack the hormone oxytocin[3] also show autism-like behavior ? but the trouble is, a lack of oxytocin hasn't been implicated in autism.

The two new models are the first to capture many of the symptoms seen specifically in classic autism spectrum disorders.

"We now have great animal models that have isolated socio-behavioral impairment, which allow extensive studies of the mechanism that underlies such impairment, and what we can do to improve that," says **Huda Zoghbi**, a geneticist at Baylor College of Medicine in Houston, Texas, who was not involved with either study.

Important differences:



Two new mouse models capture many of the symptoms seen in autism spectrum disorders.

Tom Südhof and Nils Brose

Model behavior: Two new mouse models capture many of the symptoms seen in autism spectrum

disorders.

Mice and humans are different enough that a mutation that affects social behavior in humans would not necessarily be expected to have the same effect in mice, notes **Daniel Geschwind**, director of the **Center for Autism Research and Treatment** at the University of California, Los Angeles.

"Before these papers, most would have been skeptical that you would see very analogous and almost specific behavioral deficits in mice as you see in patients with the same mutation," Geschwind says. "But the fact that the behavioral deficits are so similar and so specific in these mice makes one very optimistic that they may be exceptional models."

Thomas Südhof and his group at the University of Texas Southwestern Medical Center introduced into mice a single-letter mutation in the gene encoding a protein called neuroligin-3, a member of a family of proteins known to be important in helping neurons communicate across synapses. The mutation had been identified in 2003 in two Swedish brothers, one with autism and one with the related Asperger's syndrome[4].

The mutant mice are just as coordinated and mobile as, and no more anxious than, their unaffected litter mates. But they show impaired social behavior, spending less time than their normal litter mates interacting with a novel, caged mouse.

Similarly, when the mutant mice are given the choice between examining an empty cage and a cage with a novel mouse in it, they show far less preference for the caged mouse than do their wild-type litter mates.

In an interesting twist, the mutant mice have better spatial learning and memory abilities than their wild-type counterparts. They also showed an increase in both the frequency and strength of the inhibitory ? or dampening ? messages sent across synapses.

Autism is thought to be associated with an imbalance of excitatory and inhibitory signaling across brain synapses, though the exact mechanisms involved are unknown[5].

The finding presents an immediate possibility that Südhof is testing: "Can we behaviorally improve this mouse by simply attenuating inhibitory synaptic function?" he asks. "A lot of anti-anxiety drugs do that."

In the more recent paper, a team led by **Nils Brose** of the Max Planck Institute in Gottingen, Germany altered the gene encoding another protein in the same family, neuroligin-4, so that it is produced only in a stunted, non-functioning form.

The mutation was first discovered in a large French family in which it was present in both males with and without autism, all of whom were mentally retarded[6].

The resulting mutant mice don't have any measurable abnormalities in a laundry list of functions that include hearing, vision, smell, memory, anxiety, motor coordination and their overall curiosity toward inanimate objects. But the mice have highly selective social and communication deficits.

Antisocial animals:

For instance, when the mice are placed in an open area, the mutant mice spend 45 percent less time interacting with each other than do wild-type mice. Compared with unaffected mice, the mutant mice also take longer to attack an intruder mouse in their own territory, and many don't attack at all.

In an important finding given the language problems seen in autism, Brose's group also used ultrasound to measure vocalizations by the mice. They found that, compared with unaffected controls, mutant male mice exposed to females in heat take more than three times longer to start calling ? a normal mating behavior ? and emit 48 percent fewer calls.

Brose's group has also found deficits in signaling at synapses mediated by the neurotransmitter glutamate in the post-mortem brainstems of the mutant mice. Based on those unpublished data, Brose suggests that glutamate-boosting drugs might improve or reverse the mice's symptoms.

"The good news in this context is that synaptic transmission can be modulated with pharmacological tools," says Brose. "This is already being done in depression and in schizophrenia."

Brose is also exploring gene therapy to introduce a normal copy of the gene in the mutant mice and see whether their behavior normalizes.

These models are an enormous improvement over what was previously available, but they are imperfect.

For instance, neither model displays the repetitive moments that are characteristic in people with autism. What's more, the two mutations occur only in a tiny fraction, probably less than one percent, of people with autism.

"People shouldn't get hung up on 'I have the perfect autism model,'" says Zoghbi. "Both the papers are interesting, but we are in the learning stage."

References:

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