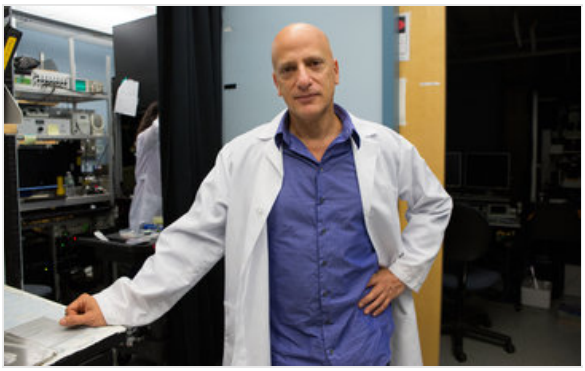
Study Finds That Brains With Autism Fail to Trim Synapses as They Develop

Photo



David Sulzer, a neurobiologist at Columbia, led a study that may help explain symptoms of autism like oversensitivity to noise, as well as why many people with autism also have epilepsy. Credit Ruth Fremson/The New York Times

As a baby's brain develops, there is an explosion of synapses, the connections that allow neurons to send and receive signals. But during childhood and adolescence, the brain needs to start pruning those synapses, limiting their number so different brain areas can develop specific functions and are not overloaded with stimuli.

Now a new study suggests that in children with autism, something in the process goes awry, leaving an oversupply of synapses in at least some parts of the brain.

The finding provides clues to how autism develops from childhood on, and may help explain some symptoms like oversensitivity to noise or social experiences, as well as why many people with autism also have epileptic seizures.

It could also help scientists in the search for treatments, if they can develop safe therapies to fix the system the brain uses to clear extra synapses.

The study, published Thursday in the journal Neuron, involved tissue from the brains of children and adolescents who had died from ages 2 to 20. About half had autism; the others did not.

Photo

The researchers, from Columbia University Medical Center, looked closely at an area of the brain's temporal lobe involved in social behavior and communication. Analyzing tissue from 20 of the brains, they counted spines — the tiny neuron protrusions that receive signals via synapses — and found more

Researchers found more spines in children with autism. Spines branch out from one neuron and receive signals from other neurons through connections called synapses, so more spines indicate more synapses. Credit Guomei Tang, PhD and Mark S. Sonders, PhD/Columbia University Medical Center

spines in children with autism.

The scientists found that at younger ages, the number of spines did not differ tremendously between the two groups of children, but adolescents with autism had significantly more than those without autism. Typical 19-year-olds had 41 percent fewer synapses than toddlers, but those in their late teenage years with autism had only 16 percent fewer than young children with autism.

One child with autism who was 3 when he died had more synapses than any of the typical children of any age, said David Sulzer, a neurobiologist and senior investigator of the study.

Experts said the fact that young children in both groups had roughly the same number of synapses suggested a clearing problem in autism rather than an overproduction problem.

“More is not better when it comes to synapses, for sure, and pruning is absolutely essential,” said Lisa Boulanger, a molecular biologist at Princeton who was not involved in the research. “If it was overgrowth, you’d expect them to be different from the start, but because the synapse difference comes on so late, it’s probably pruning.”

Dr. Sulzer’s team also found biomarkers and proteins in the brains with autism that reflected malfunctions in the system of clearing out old and degraded cells, a process called autophagy.

“They showed that these markers of autophagy decrease” in autism-afflicted brains, said Eric Klann, a professor of neural science at New York University. “Without autophagy, this pruning can’t take place.”

The findings are the latest in an area of autism research that is drawing increasing interest. For years, scientists have debated whether autism is a problem of brains with too little connectivity or too much, or some combination.

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Ralph-Axel Müller, a neuroscientist at San Diego State University, said there was growing evidence of overconnectivity, including from brain imaging studies he has conducted.

“Impairments that we see in autism seem to be partly due to different parts of the brain talking too much to each other,” he said. “You need to lose connections in order to develop a fine-tuned system of brain networks, because if all parts of the brain talk to all parts of the brain, all you get is noise.”

More synapses also create opportunity for epileptic seizures because there are more electrical signals being transmitted in the brain, Dr. Klann said. More than a third of people with autism have epilepsy.

In addition to analyzing the human brains, the Columbia team studied mice they programmed to develop tuberous sclerosis complex, a rare genetic disease that is often accompanied by autism. The mice developed some social behaviors that resemble autism in humans.

In the mice, a key protein called mTOR was hyperactive, which impaired the brain’s ability to clear out unnecessary synapses. By giving the mice the drug rapamycin, the scientists were able to reduce mTOR’s activity, fix the process of pruning synapses, and eliminate the abnormal social behaviors.

“They could treat with rapamycin and restore behavior and restore the pruning,” said Kimberly Huber, a neuroscientist at University of Texas Southwestern. “It’s a very exciting paper. It suggests these deficits in pruning may be contributing to these autism behaviors.”

When they tried the experiment in mice with broken pruning ability that could not be repaired by the drug, the behavior did not improve. That, Dr. Sulzer said, added more evidence that pruning problems were linked to symptoms of autism.

Dr. Sulzer also said that while the mice had a specific and rare disorder, many of the hundreds of genes that have been associated with autism risk in one way or another were linked to the mTOR protein at some stage.

Experts and the authors cautioned that it was much too early to know if a drug like rapamycin, an immunosuppressant with potentially serious side effects, could be used successfully in people with autism. The condition can only be approximated in mice, so the study results may not translate to humans. And the mice studied had a rare genetic disease that accounted for a fraction of autism disorders.

“We don’t know if it’s this particular flavor of autism,” Dr. Boulanger said. “This drug has really horrible side effects, and you don’t want to give it to everybody.”

But even though the drug may not be a treatment for people, the research gives hope that another therapy might be found to correct the pruning problem in childhood or adolescence, after autism symptoms emerge.

“The pruning problem seems to happen later in development than one might think,” Dr. Klann said. “It suggests that if you could intervene in that process that it could be beneficial for social behavior.”