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Rewiring the Autistic Brain

by Elizabeth Norton on 13 September 2012, 3:00 PM | 3 Comments

Signs of autism—such as impaired social skills and repetitive, ritualistic movements—usually begin to appear when a child is about 18 months old. Autism is thought to result from miswired connections in the developing brain, and many experts believe that therapies must begin during a "critical window," before the faulty circuits become fixed in place. But a new study online today in *Science* shows that at least one malfunctioning circuit can be repaired after that window closes, holding out hope that in some forms of autism, abnormal circuits in the brain can be corrected even after their development is complete.

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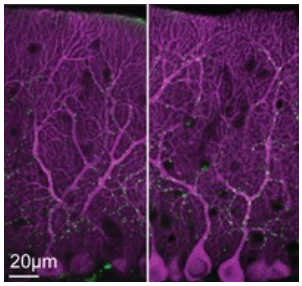

Faulty wiring. Shutting off the *Nlgn3* gene in mice (*right panel*) results in miswired synaptic connections, which may be fixable.

Credit: S. J. Baudouin et al., Science

According to developmental neurobiologist Peter Scheiffele of the University of Basel in Switzerland, autism doesn't result from a handful of "culprit" genes that point to a treatable flaw. Instead, patients appear to carry mutations in one out of dozens, even hundreds of risk genes. "This genetic complexity is a huge issue with respect to developing treatments [for autism]," Scheiffele says. To complicate the picture further, autism is not always an isolated disorder; it's often a common feature in syndromes that otherwise differ drastically. For example, in fragile X syndrome, a form of mental retardation, about 25% of patients are also autistic.

Scheiffele and colleagues were studying a gene called *neuroligin-3* (*Nlgn3*), involved in building the contact points, called synapses, between neurons. Many researchers believe that autism begins at the synapse, and mutations in *Nlgn3* have appeared in some forms of the disorder. Sheiffele's team was focusing on synapses in the cerebellum, a part of the brain that controls movement, but, according to recent research, may also be involved in social behavior. Abnormalities in this region may contribute to both the unusual movements and the social problems seen in autistic patients.

To get a better handle on the role of *Nlgn3*, the scientists studied mice whose *Nlgn3* genes were engineered with an on-off switch, called a promoter region, that is controlled by the antibiotic doxycycline. The animals were raised with the drug in their drinking water, which kept the switch in the off position. With the *Nlgn3* gene disabled in the mice, neurons in their cerebellum made the abnormal connections seen in the autistic brain.

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Specifically, and much to the researchers' surprise, the lack of *Nlgn3* led to the overactivation of a receptor abbreviated as mGluR1α. This receptor is a component of a pathway that is also disrupted in fragile X syndrome, though it results from mutations in an entirely different gene. In the mice, the overabundance of these receptors led the neurons to make synaptic connections in the wrong places.

To see if turning *Nlgn3* gene back on would correct these problems, the researchers withdrew the doxycycline. It worked: With *Nlgn3* functioning once more, levels of the extraneous receptor receded back to normal, and the misplaced synapses began to disappear.

"Our finding demonstrates that there is still flexibility after the 'critical window' of brain development," Scheiffele says. "It raises the question: To what extent can a miswired brain be corrected?" The next step, he says, is to see whether motor abnormalities, such as ladder-climbing difficulties, and social interactions can be corrected with similar treatment in the engineered mice. His team is also studying whether drugs that block the mGluR1α receptor can have the same effect as genetically controlling the *Nlgn3* gene, which isn't a treatment option for humans.

"This study holds out hope for children and even adults with developmental disorders. Maybe their conditions aren't set in stone and can be treated," says neuroscientist Kimberly Huber of the University of Texas Southwestern Medical Center in Dallas. Huber adds that drugs that block a similar receptor, mGluR5, are in clinical trials to treat fragile X syndrome.

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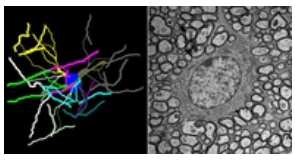

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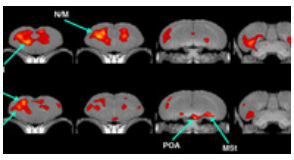

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Tom Davidson • 2 days ago

'Autistic' brains are certainly 'wired' differently. It is extremely encouraging that this research is showing ways that brain wiring can be altered even after the 'critical window' (whatever that may be) has closed and the connections are presumed to have been wired into place. Perhaps it is time we dropped the heuristically defined label 'autistic' and the idiosyncratic ex post facto judgments that lead to identifying alternatively programmed brains as 'miswired' or 'faulty,' and develop an operational definition based on empiricial observables and the brain's success or failure in performing certain functions.

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jd • a day ago

It has been said that if it weren't for aspergers (a form of autism) we'd all be sitting around in caves having great conversations. What if we "cured" Leonardo, jefferson, edison and so many other social outcasts?

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Pax • 11 hours ago • parent

Connecting historical figures to neurological disorders is rooted in speculation and therefore should not factor into this debate.

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