Autism's Cause May Reside in Abnormalities at the Synapse
Author(s): Ken Garber
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Environment counts. Despite the highly genetic nature of autism, which researchers are now deciphering, specialized school programs help.

NEUROSCIENCE

Autism's Cause May Reside in Abnormalities at the Synapse

New genetic evidence is leading researchers to home in on the cleft separating neurons as the site where the disorder may originate

No one knows what causes autism, which in its broad definition affects about 1 in every 150 children. The impaired social interaction, communication deficits, and restricted and repetitive behaviors seen in people with the condition have confounded scientists since it was first identified in 1943. Because only a minority of autistic persons have severe intellectual disability, and some show exceptional cognitive talents, relatively subtle changes in the brain are probably responsible. Now a flurry of new discoveries is pointing to one possible site of autism's origin: the synapse.

Synapses are junctions across which neurons communicate. They are essential for sensory perception, movement coordination, learning, and memory—virtually all brain function. "The synapse is like the soul of the brain," says Huda Zoghbi, a pediatric neurologist at the Baylor College of Medicine in Houston, Texas. "It's at the root of everything."

Zoghbi was the first to propose, in 2003, that altered synapses might be responsible for autism. But direct evidence was thin. Now "there seems to be a confluence of data flowing," says Stephen Scherer, a geneticist at the Hospital for Sick Children in Toronto, Ontario.

Until the mid-1980s, experts considered autism a strictly environmental disorder, with most of the blame falling on faulty parenting. Now we know that "autistic spectrum disorder," the term specialists prefer, is overwhelmingly genetic. Based mostly on studies of fraternal and identical twins, University of Illinois at Chicago autism researcher Edwin Cook concludes that genetic factors contribute about 90% to autism, with environmental factors contributing no more than 10%. Autism is "the most heritable of neurodevelopmental disorders that are complex in origin," says Scherer. (Biology is not destiny, of course, because the environment affects the form any genetic disorder takes, and autistic children often improve if placed in the right learning setting.)

Abnormalities of chromosomes, many of them visible under the microscope, are thought to account for 10 to 20% of autism cases. The effect of multiple genes acting in combination probably accounts for most of the rest. Two groups recently reported that many autism patients have novel deletions and duplications in their genomes (*Science*, 20 April 2007, p. 445), probably arising when chromosomes cross over during meiosis. Researchers are honing in on the individual genes responsible.

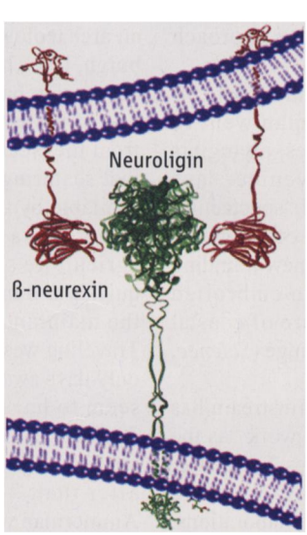
Because autism is a spectrum of disorders, different gene combinations will play a role in different individuals. What's generating excitement now is the discovery of mutations in single genes that, in rare instances, seem able to cause autism. These genes may be pointing directly at a general mechanism for the disorder, at the synapse.

The first autism genes?

Zoghbi's provocative 2003 synapse hypothesis rested partly on work that year by a group led by Thomas Bourgeron at the Pasteur Institute in Paris, France, that found mutations in proteins called neuroligins in two pairs of Swedish brothers with autism spectrum disorder. Neuroligins are proteins expressed on the surface of the postsynaptic neuron that bind to proteins on the presynaptic neuron called neurexins, spanning the synapse and forming a physical tether. Together, neuroligins and neurexins are thought to play key roles in the formation and functioning of synapses.

Some researchers contested the Pasteur Institute findings, however, because no other reports of these mutations in other individuals with autism followed; some even questioned whether the Swedish brothers actually had autism. "If it wasn't [autism], it was pretty damn close," says Scherer.

These rare neuroligin mutations and other suggestive evidence linking some neuroligin-binding proteins to autism led Bourgeron to postulate a "neuroligin autism pathway" in which abnormalities in any of these dozen or more proteins could predispose their possessors to the disorder. Bourgeron buttressed his case this January, when his group identified mutations in one of these proteins, Shank3, in three autistic individuals. In such rare cases, mutations in this single gene seem to be sufficient to cause autism. Other groups, according to Scherer, are also reporting Shank3 mutations in autistic patients. "It's being replicated for sure," he says. In the one published study so far, Shank3 mutations appear to



Critical connection. Neurexins and neuroligins coming together in the synapse. Alterations in these proteins could change how neurons communicate and lead to autism.

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account for about 1% of autism cases.

Then, in March 2007, the Autism Genome Project Consortium, a group of over 50 institutions in North America and Europe, reported results of a 5-year study on the genetics of autism in 1600 families. In addition to several new chromosomal regions implicated in the disorder, the researchers found the neurexin-1 gene associated with autism. Since neurexins bind to neuroligins at the synapse, this finding boosted the neuroligin autism pathway idea, although the study's authors did not look for specific neurexin mutations. (Several groups are now sequencing the gene.) Shank3 abnormalities also turned up in some Autism Genome Project families, reports Scherer, the study's coprincipal investigator, again implicating the neuroligin pathway.

Bourgeron now feels vindicated. "People in the field are really accepting that this is a pathway which is associated with autism," he says. "When we published the neuroligin [report in 2003], nobody believed it."

Mutations in single synaptic genes, including neuroligins, neurexins, and Shank3, will probably explain only a small number of autism cases—5% at most, Scherer estimates. In the most convincing case so far, Shank3, "a single gene could cause this complex disease type," says Scherer. "That's tremendously important," Scherer explains, because it could provide clues to cellular defects underlying all autism. In Alzheimer's disease, for example, mutations in the ß-amyloid precursor protein (APP) account for a tiny fraction (less than 0.1%) of all cases yet were crucial in revealing the likely disease mechanism: the abnormal deposit of amyloid plaques in the brain. "This field, autism, is probably about 7 years behind the Alzheimer's story," says Scherer.

Orchestrating the synapse

Now the race is on to figure out how neuroligins and their binding proteins are contributing to autism. "What exactly do these proteins do at synapses?" asks Thomas Südhof, a neuroscientist at the University of Texas Southwestern in Dallas. "That's ... crucial for understanding autism."

Südhof's lab discovered neurexins in 1992 and neuroligins in 1995. They have been studied intensely ever since, because they seemed to hold the key to how synapses form, and thus to brain development. At first their pairing was thought to physically tether the synapse, but it later became clear that they also promote the recruitment of neurotransmitter receptors and various structural molecules to the synapse—in fact, orchestrating a complete synapse. Neuroligins and neurexins "are unbelievably important proteins," says Südhof. "They're life or death."

Clues to their possible role in autism are now appearing. One theory is that an abnormal neuroligin pathway upsets the balance of excitatory and inhibitory synapses in neurons, thereby affecting learning and memory, and thus language and social communication. Broadly speaking, synapses can be either excitatory, when the neurotransmitter glutamate is released, or inhibitory, with release of the neurotransmitter gamma-aminobutyric acid (GABA). The ratio of excitatory and inhibitory synapses on a neuron determines whether it will fire in any given situation. In the 21 June issue of *Neuron*, Südhof reported that in experiments in cells, overexpressing neuroligin-1 leads to excitatory transmission at synapses, whereas neuroligin-2 overexpression leads to inhibition. Südhof speculates that an alteration in either neuroligin could change the excitatory-inhibitory balance, subtly changing the number of neurons that are firing during brain development. Such disruptions could eventually produce the lasting symptoms of autism, he explains, because synapses change with use, becoming more or less sensitive to stimuli depending on experience. This "synaptic plasticity" is the basis of learning and memory.

That's just one possibility. The synapse is extraordinarily complex, both chemically and structurally, and a lot could go wrong there as the brain develops. Studies in animals to understand the different components of the synapse and to determine mutation effects are just beginning.

Many research groups are now focusing on finding links between synapse genes and autism. Cook argues for a broader approach, including whole genome scans for other genes that might have less individual effect but may account for more autism cases. (Some such studies are in progress.) "To say one or the other approach ... is the right way to go is, I think, at this point naïve," Cook says.

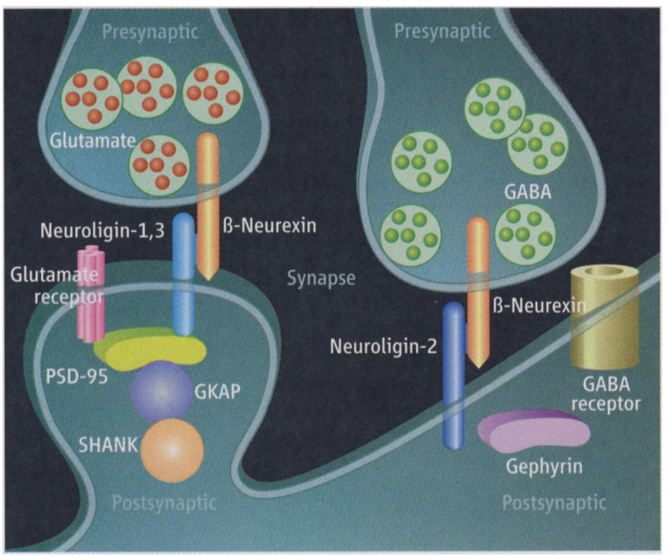
Few genes or many?

The hope is that most cases of autism are caused by just a few strongly acting genes, rather than many weak genes in concert. Simpler genetics would accelerate understanding of the disorder, as well as facilitate early diagnosis and genetic counseling, and provide more discrete targets for therapy. Bourgeron notes that a single abnormal gene—or even a single gene copy, as with Shank3—can, in rare instances, cause autism. But even Bourgeron doubts that altered synapses by themselves are enough to cause most cases. "Autism is not a single entity," he stresses.

He speculates that a combination of abnormal synapses and altered neural networks—the complex circuitry involving the billions of neurons that permits language and social interaction—could combine to cause most cases of autism. Factors that could alter neural networks include a global, as opposed to neuron-level, shift in the excitatory-inhibitory balance, increased neuron numbers (many autistic children have large heads), or high levels of the neurotransmitter serotonin, seen in about a quarter of autistic patients.

Besides synapse abnormalities, many causes of autism have been postulated, from altered neuron migration during early development to chronic inflammation in the brain. Imaging and post-mortem studies suggest that "underconnectivity" between brain regions is at the heart of the disorder (*Science*, 24 June 2005, p. 1856). Underconnectivity and altered synapses are not mutually exclusive. "If you have regionally different synapse dysfunction, you're going to have differences in connectivity between different brain regions," says Südhof. "That's exactly what you would predict."

In the end, it may all come down to the synapse. **–KEN GARBER**



Autism's origin? Neuroligins and neurexins, proteins crucial for aligning and activating synapses, have now been implicated in autism, along with the Shank3 scaffolding protein. An altered balance between excitatory synapses (*left*) and inhibitory (*right*) could affect learning and memory during development.

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