

UNTIL RECENTLY, SCIENTISTS BELIEVED THAT INHERITED DEVELOPMENTAL BRAIN DISORDERS, SUCH AS FRAGILE X SYNDROME, RETT SYNDROME, TUBEROUS SCLEROSIS, AND AUTISM, WERE CAUSED BY PERMANENT BRAIN ABNORMALITIES. NEW RESEARCH NOW SUGGESTS, HOWEVER, THAT THESE DEVASTATING DISORDERS MAY RESULT FROM DISRUPTIONS AT THE TRILLIONS OF TINY JUNCTURES, OR SYNAPSES, BETWEEN BRAIN CELLS — DISRUPTIONS THAT MAY ONE DAY PROVE REVERSIBLE.

SYNAPSE COMMUNICATION AND DEVELOPMENTAL BRAIN DISORDERS

At the junction between two neurons, or nerve cells, is a miniscule gap, about 20 nanometers (billionths of a meter) wide — a point of virtual contact. This physical gap functions as the site of communication from one neuron to another through chemical signals. Given a non-stop flurry of messages, synapses are crucial for brain function, including cognition (thinking). Without well-formed and well-running synapses, learning, memorizing, planning, and reasoning become slower or even impossible.

With advances in genetics and molecular biology, neuroscientists have recently begun to investigate synapses in the hopes of unraveling the mysteries of a number of inherited developmental brain disorders, such as fragile X syndrome, Rett syndrome, tuberous sclerosis, and autism. So far, the results have been promising. The research suggests that in some cases damage from these disorders may potentially be reversed by treatments that alter synaptic function.

This exciting research is leading to:

- A greater understanding of the neurobiological causes of inherited mental retardation.
- Treatments that may one day reverse the cognitive impairments and other symptoms of genetic brain disorders.

The role of synapses in inherited developmental brain disorders emerged from research on **fragile X syndrome**, the most common form of inherited mental retardation that also causes autism symptoms in 15–30 percent of cases. Fragile X syndrome results from an X chromosome gene mutation that stifles the production of a particular protein (the fragile X mental retardation protein, or FMRP). Without FMRP, neurons develop abnormally long and spindly dendritic spines, the little branchlike projections that receive inputs from synapses by other neurons. Thin spines

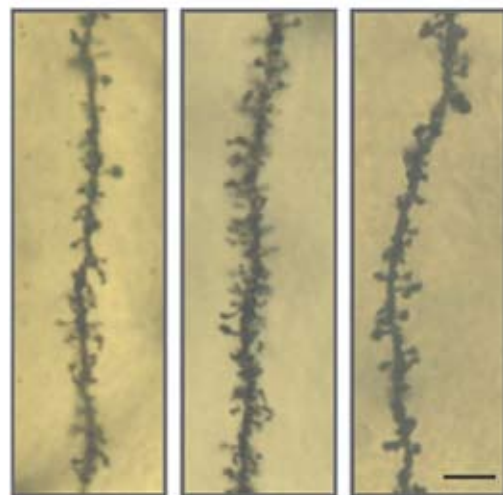


IMAGE COURTESY OF MARK BEAR, HOWARD HUGHES MEDICAL INSTITUTE, MASSACHUSETTS INSTITUTE OF TECHNOLOGY

▲ IN FRAGILE X MENTAL RETARDATION, THE LACK OF THE PROTEIN FMRP CAUSES AN OVERPRODUCTION OF DENDRITIC SPINES. FMRP NORMALLY ACTS AS A “BRAKE” ON SYNAPSE GENERATION, BALANCING THE “ACCELERATOR” EFFECTS OF MGLUR5. THE THREE PANELS SHOW DENDRITES FROM A NORMAL OR “WILD-TYPE” MOUSE (LEFT); FROM THE FRAGILE X MOUSE MODEL, WHICH LACKS FMRP (MIDDLE); AND FROM THE FRAGILE X MOUSE MODEL AFTER MGLUR5 HAS BEEN REDUCED (RIGHT). THE INCREASED DENSITY OF SPINES IN THE FRAGILE X MOUSE MODEL IS RESCUED TO NORMAL LEVELS BY REDUCING MGLUR5.

are associated with weak connections — and communication — between neurons.

Scientists have recently identified a second major player in this spine-shaping process. Many of these synapses have special receptors for the chemical messenger glutamate. These receptors, known as metabotropic glutamate receptors, or mGluR5 (“M-Glue-Are-5”), are engaged in a delicate push-pull balancing act with FMRP. Without FMRP, their signals run unchecked, over-activating the synapses — and interfering with the development of normal spines.

Researchers are now trying to determine if blocking these receptors might be an effective therapy for fragile X syndrome. Studies involving mice bred with the disorder have produced

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encouraging results. Reducing mGluR5 signals in the mice resulted in more normal dendritic spines, improved memory, a restoration of normal body growth, and reduced seizures — symptoms also experienced by people with fragile X syndrome. Human research studies involving receptor blockers may begin soon.

Yet another protein, MeCP2 (methyl-CpG binding protein 2) has been found to play a critical role in fine-tuning the number of synapses formed in the developing brain. Too much MeCP2 leads to excess synapses, while too little causes a shortage. The latter situation occurs in the childhood brain disorder **Rett syndrome**. In both cases, the result is mental retardation and may include autism symptoms, among others. Researchers are now looking for ways to design effective therapies that might balance the expression of MeCP2 in the brain.

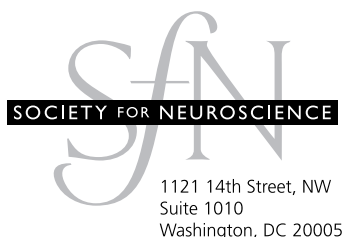
Synapse malfunction is also thought to be involved with **tuberous sclerosis**, a brain disorder associated with mutations in two genes, TSC1 and TSC2. Half of the estimated 50,000 Americans with tuberous sclerosis have autism and epilepsy. Many also have severe mental retardation. Even individuals with mild cases are likely to experience learning disabilities and short-term memory problems.

The mutated genes in tuberous sclerosis lead to excessive activity of a protein that helps regulate synaptic signals — the affected genes normally

provide instructions that prevent cells from growing and dividing too fast or in an uncontrolled way. In recent studies, scientists investigated whether treatments of rapamycin (a drug used to prevent tissue rejection after organ transplants) could inhibit this overactivation in mice bred with tuberous sclerosis. The treatment not only prevented the mice from experiencing seizures, it also restored their ability to store memories and learn. Human research studies are underway.

Autism may also originate with abnormalities in synaptic proteins that span the gap across the synapse. One area of focus is the neuroligin family of proteins and their interacting partners, which are encoded by genes mutated in some people with autism. The mutations trigger either an over- or underexpression of these proteins, which disrupts the sending and receiving of messages at synapses. This may explain the problems with social interaction, behavior, and learning experienced by the more than 1 million Americans with autism.

Much more research is needed to fully understand the role of synapses in autism and other genetic conditions that affect learning and other cognitive skills. But scientists are optimistic that the study of these points of virtual contact between neurons may one day lead to monumental advancements in the treatment of these devastating brain disorders.



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