DOWN SYNDROME LINKED TO FAULTY BRAIN COMMUNICATION

Fragile X, Down Syndromes Linked To Faulty Brain Communication – Article Date: 16 Apr 2007

The two most prevalent forms of genetic mental retardation, Fragile X and Down syndromes, may share a common cause, according to researchers at Stanford University School of Medicine. The problem, a crippled communication network in the brain, may also be associated with autism.

Although the genetics of the disorders are very different, the end result for the brain seems to be the same, said Daniel Madison, PhD, associate professor of molecular and cellular physiology. "It's as if you had every light in your house wired to just one or two switches, rather than having many switches that can be flipped on or off in complex combinations to control the lighting in one room," he said.

Madison is the senior author of a paper on Fragile X syndrome in mice, which will be published in the April 11 issue of the Journal of Neuroscience. He published a related study on mice with Down syndrome symptoms in the Feb. 15 issue of the Journal of Physiology.

Madison is a member of Stanford's Down Syndrome Research Center, started in 2003 by researchers at the School of Medicine and Lucile Packard Children's Hospital to accelerate the application of research to effective treatments for the condition.

In the latest study, Madison and postdoctoral scholar Jesse Hanson, PhD, studied Fragile X syndrome, which is a leading cause of mental retardation in this country. Affected people tend to have learning disabilities, distinct physical characteristics such as enlarged ears and a long face, and such behavioral problems as attention deficit disorder, speech disturbances and unusual responses to various sights or sounds. Although it's not known why, about one-third of people with Fragile X also develop autism - a much higher percentage than in the general population. This makes Fragile X, which can be studied in mice, the only genetic model for autism.

As the syndrome's name suggests, the responsible gene, called Fmr1, is located on the X chromosome. Because boys have only one X chromosome while girls have two, boys are usually more severely affected when Fmr1 is mutated. Girls are not immune to the condition, however. A phenomenon called X-inactivation, which randomly silences one member of every X chromosome pair, creates a mosaic of affected and unaffected nerve cells in the brain.

In some conditions linked to the X chromosome, such as hemophilia, the normal cells can cover for their useless peers. Not so for an elite corps of brain neurons. Here, where cooperation and communication are key, a few deadbeats in the mix can be disastrous.

The researchers' discovery of the muddled communication networks in the brain hinged on two advances. One was their creation of an Fmr1 mosaic mouse with brain characteristics similar to those of people with Fragile X. The other was the use of specialized microscopes and tiny needles to eavesdrop directly on individual conversations between two cells. Before this study, investigators relied on a strain of mice in which every cell carried a mutated Fmr1 gene, and they inferred how cells municated by results from experiments on groups of cells.

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The new approach allowed Madison's team to see that cells with a mutated Fmr1 gene have a very selective flaw: they are less likely than normal cells to reach out and form connections, or synapses, with their neighbors. Although normal cells in the mosaic brain can reroute around these potential dead ends, the resulting neural network has fewer cells and is less complex. "If, for example, 10 percent of normal nerve cells are now responsible for half your neural network, the information-carrying capacity of your brain goes down," he said.

Madison said the findings from this study point researchers in a new direction. "Until now the emphasis in the field has been on the receiving, or post-synaptic, side of the synapse," he said. "But these results unequivocally show that the pre-synaptic cells are the important ones in this defect."

The result paralleled the researchers' earlier finding in the brains of the mice with Down syndrome symptoms: more connections are made by fewer cells. "We believe that these reduced-complexity networks are the basis for the mental retardation that occurs with both syndromes," Madison said.

If so, the problem is rooted in early development. Synapse formation appears at first to be completely disordered, with connections between neurons making random paths like hairline cracks racing across a breaking sheet of ice. But as the person or animal begins to learn and remember, the more well-trodden paths, or cracks, connect in purposeful, yet unique ways.

"No two nerve cells will always be connected in the same way in different people," said Madison. "But populations of cells will develop similar connections as the developing brain practices using its own network. If we can compensate for the synaptic deficiency of the mutant cells, we may begin to start to think about ways to increase the mental capacity of patients with Down syndrome or Fragile X."

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Stanford University Medical Center integrates research, medical education and patient care at its three institutions - Stanford University School of Medicine, Stanford Hospital & Clinics and Lucile Packard Children's Hospital at Stanford. For more information, please visit the Web site of the medical center's Office of Communication & Public Affairs at http://mednews.stanford.edu/.

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