Study shows map of brain connectivity changes during development

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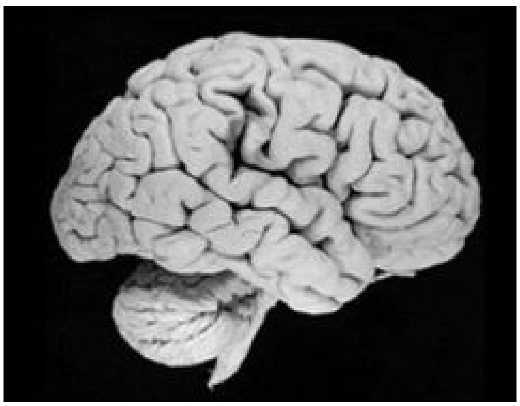

Modern human brain. Credit: Univ. of Wisconsin-Madison Brain Collection.

Connected highways of nerve cells carry information to and from different areas of the brain and the rest of the nervous system. Scientists are trying to draw a complete atlas of these connections -- sometimes referred to as the "connectome" -- to gain a better understanding of how the brain functions in health and disease.

New research conducted at The Scripps Research Institute shows that this road atlas undergoes constant revisions as the brain of a young animal develops, with new routes forming and others dropping away in a matter of hours. "We have shown that the connectome is dynamic during development, but we expect it will also change according to an individual's experience and in response to disease," says Scripps

Research Professor Hollis Cline, senior author of the study.

The study, published in the January 27, 2011 issue of *Neuron*, dispels some long-held notions of how connections between nerve cells are established, highlighting the interplay between formation and removal. The findings have implications for conditions in which these mechanisms may have gone awry, such as autism, schizophrenia, and perhaps Alzheimer's.

A Dynamic Map

Cline's group has been studying how experience—the different sights and sounds and other environmental cues picked up by neurons—change connections and activities in the brain through a process known as plasticity. "Based on our prior research we expected that the connectome would be dynamic," says Cline.

To start to document how the connectome changes and test current models of how the map is laid out, Cline and colleagues turned to the frog Xenopus laevis. They combined two new techniques to map in great detail all the connections that form during tadpole development in an area of the brain that receives and interprets signals from the eyes.

In the nervous system, information is handed from one nerve cell to another through two arms, called dendrites and axons, stretching out from opposite sides of each cell. The axon carries information away from a nerve cell, or neuron, and passes it to the dendrite of another; dendrites receive the information, which travels through the cell to the axon. The region where information is transferred from one neuron to another (and where axons and dendrites connect) is called the synapse.

The Cline group's approach relied on taking time-lapse images of growing axons and dendrites over several days. The researchers then zoomed in on synapses that formed using electron microscopy, a technique that magnifies objects up to 2 million times. This close-up view revealed some "surprising results about synapse formation and plasticity," says Cline.

Promiscuous Partners

Models of synapse formation typically show that as dendrites extend new branches, each branch forms an immature synapse with a target axon that is later either maintained or eliminated. But Cline's study shows instead the process is not as selective. Each growing dendrite samples not one but many possible partners before selecting one with which to maintain contact.

As new branches grow from dendrites, they form many immature synapses on axons. Then, as each new dendrite branch matures, most immature synapses are eliminated; the ones not eliminated mature into stable synapses. "We did not know that dendrites make so many connections that are then removed," says Cline. "It is always fun in science when you see that what was expected is not what actually happens."

Cline and colleagues also discovered that axon synapses don't form, as previously thought, on growing branches but rather at swellings, called boutons, located on stable axon branches.

Another surprise was that when growing dendrites go searching for potential partners, they reach out to axon boutons that had previously connected with other dendrites—"as if they were attracted to a restaurant that already has a line at the door, rather than trying a brand new one," says Cline.

Over time, these boutons decrease the number of connected partners to form mature connections with single dendrites.

Shining the Spotlight on Elimination

Up until now, researchers had focused their work primarily on determining how new connections form and on finding ways to enhance such formation. But Cline's findings that so many immature connections are removed during development puts greater emphasis on the process of elimination, she says.

Several studies have shown that brain activity helps new connections to form. Thus, Cline asked whether activity is also required for synapse elimination to occur. To answer this question, Cline and colleagues shut off activity in the visual system by keeping some of the tadpoles in darkness. These animals had many more immature synapses than animals that could see, indicating brain activity is needed for selecting which synapses should be eliminated.

The team now plans to look in more detail at the molecular signals involved in the elimination process, hoping to identify any genes that might be responsible. "It is possible that some genetic diseases are caused by the inefficient elimination of synapses," explains Cline. For example, individuals with a disease known as fragile X, a leading cause of mental retardation, are thought to have too many synapses, suggesting elimination did not occur properly.

More information: In addition to Cline, co-authors of the paper, "In Vivo Time-lapse Imaging and Serial Section Electron Microscopy Reveal Developmental Synaptic Rearrangements," include Jianli Li at Scripps Research and Alev Erisir at the University of Virginia in Charlottesville, VA.

Provided by The Scripps Research Institute