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Research shows mice brains are 'very wired up' at birth, suggests experience selects which connections to keep

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Ask the average person the street how the brain develops, and they'll likely tell you that the brain's wiring is built as newborns first begin to experience the world. With more experience, those connections are strengthened, and new branches are built as they learn and grow.

A new study conducted in a Harvard lab, however, suggests that just the opposite is true.

As reported on June 7 in the journal *Neuron*, a team of researchers led by Jeff Lichtman, the Jeremy R. Knowles Professor of Molecular and Cellular Biology, has found that just days before birth mice undergo an explosion of neuromuscular branching. At birth, the research showed, some muscle fibers are contacted by as many as 10 nerve cells. Within days, however, all but one of those connections had been pruned away.

"By the time mammals – and humans would certainly be included – are first coming into the world, when they can do almost nothing, the brain is probably very wired up," Lichtman said. "Through experience, the brain works to select, out of this mass of possible circuits, a very small subset…and everything else that could have been there is gone.

"I don't think anyone suspected that this was taking place – I certainly didn't," he continued. "In some simple muscles, every nerve cell branches out and contacts every muscle fiber. That is, the wiring diagram is as diffuse as possible. But by the end, only two weeks later, every muscle fiber is the lifelong partner of a single nerve cell, and 90 percent of the wires have disappeared."

Though researchers, including Lichtman, had shown as early as the 1970's that mice undergo an early developmental period in which target cells including muscle fibers and some neurons are contacted by multiple nerve cells before being reduced to a single connection, those early studies and his current work were hampered by the same problem – technological challenges make it difficult to identify individual nerve cells in earlier and earlier stages of life.

And though the use of mice that have been genetically-engineered to express fluorescent protein molecules in nerve cells has made it easier for researchers to identify nerve cells, it remains challenging to study early stages of development because the fluorescent labeling in the finest nerve cell wires often becomes so weak as to be invisible.

"We typically begin studying these mice at about a week after birth, but as we began to look at earlier and earlier stages, the fluorescent color was coming up ever more weakly," Lichtman said. "If you went from post-natal day seven to post-natal day four, there were very few labeled cells. And if you went to post-natal day zero, there were none."

Eventually, he said, J.D. Wylie, one of the lead authors, took a new idea – using antibodies to label nerve cells – and a bit of luck for the research to pay off.

"We were just very lucky that one of the first animals we looked at, we saw a labeled axon," Lichtman said. "Once we saw it, I knew it was just a matter of time until we got another, but it wasn't until J.D. did 50 more than we found it, so to get the 20 or so examples we have, thousands of mice had to be looked at. Had we not seen that first one, I think we might have given up on this. It took a lot of effort and work, but it showed something that we've never seen before, which is a remarkable amount of connectivity."

Simply identify the axons, however, was only the first step.

To fully understand how widely diffuse the branching becomes early on, researchers had to count how many different nerve cells were contacting muscle fibers. To accomplish that feat, Juan Carlos Tapia, the other lead author used a new technique the lab had developed for serial electron microscopy that allowed him to capture images of as many as 10 axons connecting to a single muscle fiber.

After reaching its peak at birth, researchers found the branching was quickly pruned back, until just a single nerve axon remains connected to each muscle fiber. Though there isn't a definitive answer to what is driving that pruning process, Lichtman said there is strong suggestive evidence that points to experience.

"We think that experience must be the engine that allows some branches to survive and the vast majority to disappear," he said. "If this were a stereotypical developmental program, you might imagine that it might trim off whole parts of the arbor, but when you look at where the ten percent of surviving branches are located, you see the arbor extends over the same area, it simply has fewer branches. It has chosen, at the terminal level, which branches to keep and which not to."

In future studies, Lichtman plans to study how those decisions are made, work that could potentially lead to insight into a number of disorders, including autism.

"That is one theory people have talked about, whether autism could be a disorder where connections that should have been trimmed back weren't, and as a result stimuli are much more intense than they should be," he said. "There are stories about children with autism spectrum disorders who cannot run in their bare feet on grass, because it's just too painful."

Ultimately, Lichtman said, the paper spotlights the unique developmental strategy undertaken by all mammals, including humans.

"This is a strategy to generate a nervous system that is tuned to the world it finds itself in," Lichtman said. "Interestingly, this is not the predominant strategy of nervous systems on the planet. Most animals – insects for example – come into the world knowing, based on their genetic heritage, exactly how to behave.

"It seems like a paradox – why would the best brains seem to be the most backward, and take the longest to figure out how to do things?" he asked. "Rather than allowing our genes to tyrannize our behavior, we more than any other animal are under the tyranny of the environment we find ourselves in. If you start with a nervous system that allows for any wiring diagram, you need only choose the right option for a particular environment. That's why humans today are behaving differently than our grandparents, and our grandparents are different from people 1,000 years ago, or 10,000 years ago. Whereas a fruit fly today and a fruit fly 1,000 years ago are probably behaving the same way"

Provided by Harvard University

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