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Mitochondrial Metabolism Dictates Neurons' Growth Rate

Altering the rate of respiration in mitochondria changes how fast neurons grow, making mouse neurons grow more like human ones and vice versa, a study finds.

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ABOVE:
A human cortical neuron
RYOHEI IWATA

Human brains grow extraordinarily slowly—a trait many neuroscientists speculate is related to our distinctive intellect. But how and why a human neuron takes years to grow when a mouse neuron grows for mere weeks has remained unclear. Now, scientists have uncovered one piece of the puzzle: Neuron growth is mediated by its mitochondria's metabolism, according to a January 26 study in *Science*. The finding could not only help answer fundamental questions about brain development, the study authors say it could widen treatment options for developmental disorders.

“This is the most exciting study I’ve read in a while,” says Suzana Herculano-Houzel, a biologist and neuroscientist at Vanderbilt University who wasn’t involved in the research. “It opens a path for finding answers to, what is to me, one of the biggest questions we have: What makes different brains different?”

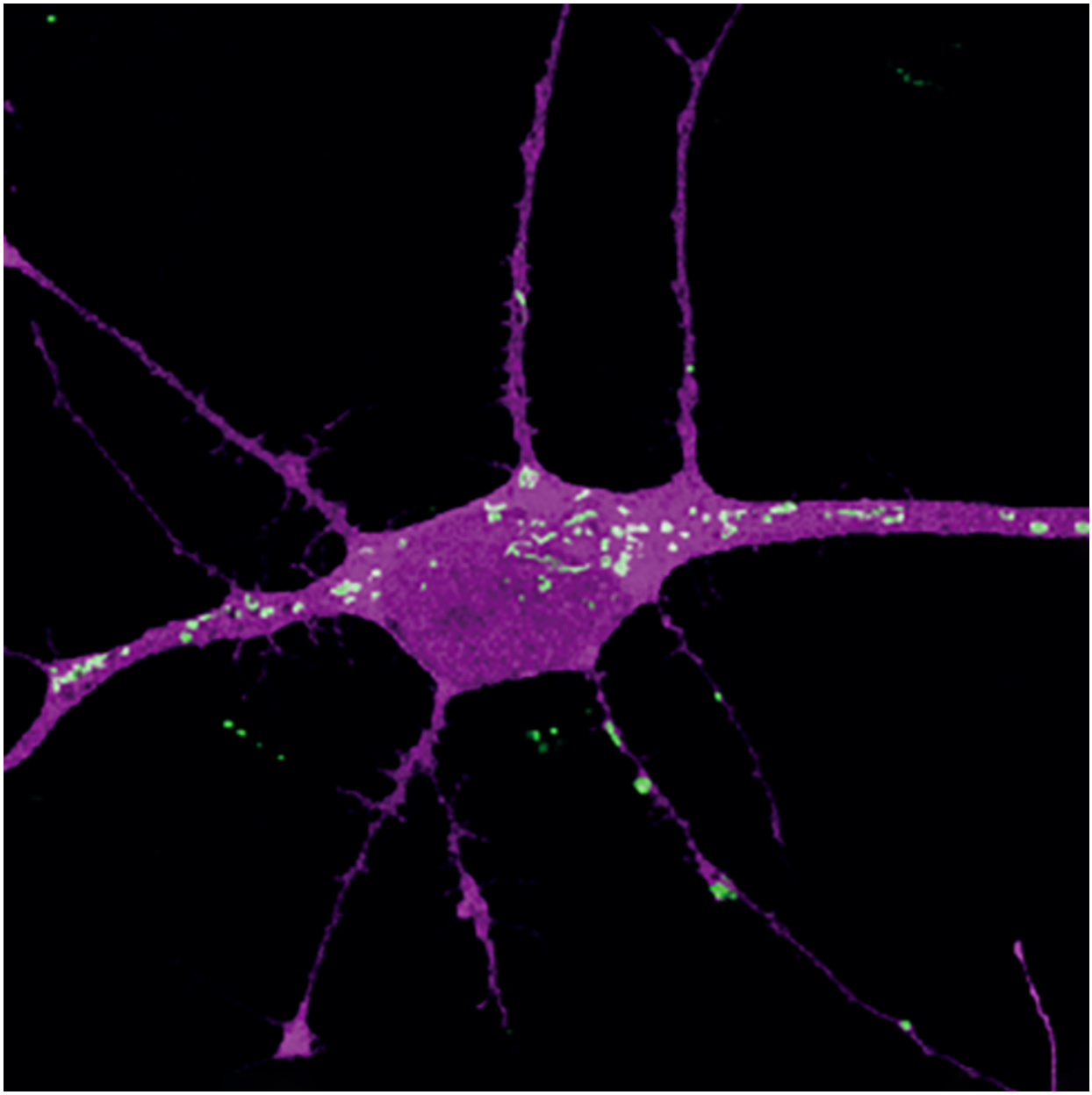
For senior study author and developmental biologist Pierre Vanderhaeghen, the underlying cause of human neurons’ prolonged growth had long lay tantalizingly out of reach. Nearly a decade ago, he and colleagues at the Free University of Brussels in Belgium put human cortical neurons inside mouse brains, expecting them to grow faster. But to their surprise, the human neurons still grew slowly when transplanted. This suggested to Vanderhaeghen, who also works at the Flanders Institute for Biotechnology and the Catholic University of Leuven, that the cause of a neuron’s glacial growth was intrinsic to the neuron itself and not the consequence of signals from the surrounding brain, he explains.

Moreover, he and his colleagues at the time noted that every single aspect of the neuron, from its dendrites to its synapses to its axon, grows in synchrony, indicating that the growth is regulated by a ubiquitous, basal component of the cell. Other research had posited that mitochondria may somehow play important roles in the development of cells. So he and his team set out to investigate whether mitochondria are involved in regulating neuron growth.

First, though, they needed to ensure they could accurately pinpoint the age of any given neuron. Knowing a neuron’s age is vital for gauging its growth over time, but getting an exact birthdate for each neuron had been next to impossible, Vanderhaeghen explains, as neurons don’t develop at the same rate as one another, even when their original stem cells are created at the same time. However, stem cells can only become neurons after promoter *NeuroD1* is activated. So Vanderhaeghen and colleagues came up with a genetic tool that uses an engineered recombinase enzyme called CreER that identifies when *NeuroD1* is turned on and immediately tags the neuron—essentially flagging its “birth.” With the ability to date the neurons, Vanderhaeghen and his team could start testing the effect mitochondria have on neuron growth rates.

Initially, Vanderhaeghen says, the team examined mitochondrial morphology and genetics. But on a whim, they also decided to look at the organelles’ respiration rates—basically, how much oxygen they consume, which is also a measure of how much cellular fuel they produce. They used oxygraphy to monitor the oxygen intake of mouse neurons for the first 20 days after their birth—and were stunned to find that after two weeks, the oxygen consumption rate of neurons had grown to nearly ten times that of human neurons.

From there, Vanderhaeghen says everything fell into place. The team knew they could manipulate



A human neuron with mitochondria stained in white

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mitochondrial respiration pharmacologically, so they sped up metabolism in human cortical neurons in vitro. Vanderhaeghen recalls a moment in the lab looking at the neurons; at only a few weeks old, the accelerated cortical neurons were considerably more mature than a normal human neuron. “To us, this was a big eureka moment,” he says. “There we thought, ‘this is it.’”

The scientists tested the same principle in vivo, speeding up the mitochondrial metabolism of human neurons and implanting them into mice, as well as slowing down the mitochondrial metabolism of mouse neurons both in culture and inside the mice’s brains. The results from both in and out of the brain aligned: Human neurons with increased metabolic rates grew faster than normal, and mouse neurons with decreased mitochondrial metabolic rates displayed slower growth.

Many scientists theorize that the human brain’s slow growth is part of what allows for our unique mental capacities. Knowing that a metabolism regulator can slow or speed up that growth will allow

for further studies into what makes us human, Vanderhaeghen posits. He adds that targeting mitochondrial metabolism could one day be considered in the treatment of some developmental disorders, which can arise from brain development that is either too fast or too slow. However, he emphasizes that this study is only the beginning. “I would be very naive to think that mitochondria are the [only] solution” to resolving issues related to developmental timing, he says. “Mitochondria are just one mechanism, and there are probably going to be many others.”

Nonetheless, Herculano-Houzel is excited to see where this research will go. “That is the definition of good science: You answer one question, and that brings up ten new questions you didn’t know you had,” she says. “What happens if you play with energy transfer in a developing brain? Do you directly affect the size of the brain? Do you affect how many neurons are generated? These are all fundamental questions, and they can all be asked now.”