HUMAN HEALTH
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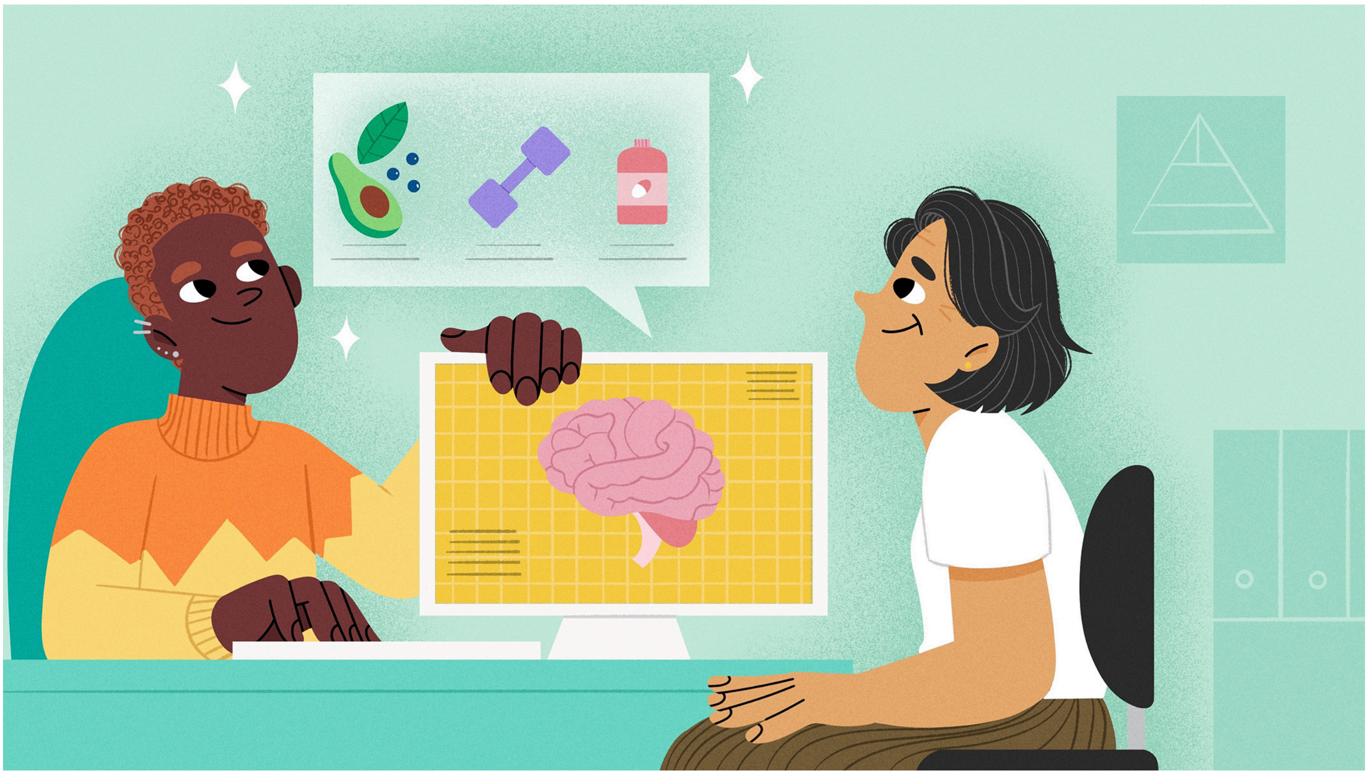

CAN WE KEEP THE BRAIN ENERGIZED AS IT AGES?

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AGE: 14

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AGE: 15

As people age, their brains can become less efficient and more likely to have problems with thinking, learning, and remembering. By understanding what happens in the brain to cause these changes, researchers could find ways to keep older people's brains healthy for longer. The brain needs a lot of energy to function, so understanding its energy production and use are important scientific goals. Questions about the brain are often difficult to study, because the brain has many types of cells interacting in complex ways. To tackle this challenge, our group created a detailed computer model, which is like a virtual brain. We discovered that aging makes the brain's metabolism less flexible and more fragile, meaning brain cells have a harder time responding to challenges and recovering from damage. This model could help researchers explore how factors like diet, exercise, or medicines might keep our brains healthier for

longer, potentially reducing age-related brain issues like dementia and improving quality of life as we get older.

AGING AFFECTS OUR BODIES...AND BRAINS!

As people get older, their bodies go through a number of obvious changes—they get more wrinkles, their hair turns gray (or falls out!), and sometimes they move more slowly. People's brains also change as they age, but these changes are not as easy to see. For some people, aging-related brain changes are normal and do not cause any major issues. But for others, the brain can age in an unhealthy way, leading to conditions like dementia. Dementia is a disorder that makes it hard for people to remember things, understand new information, and do everyday tasks. Globally, the number of people living with dementia is expected to increase from ∼57 million in 2019 to 153 million in 2050 [1].

ENERGY METABOLISM

The process by which the brain converts nutrients like glucose and oxygen into energy, allowing brain cells to perform their functions effectively and stay healthy.

METABOLITES

Small molecules produced or used during metabolism, which help keep the brain's cells functioning properly by participating in energy production and other essential chemical processes.

Scientists still do not know exactly what happens in the brain as it ages, nor do they understand what causes the difference between healthy vs. unhealthy brain aging. The brain is a difficult organ to study—it contains many types of cells and molecules working together in complex ways. One idea is that the brain's **energy metabolism** plays a big part in how well it ages [2, 3]. Just like a car needs fuel to keep going, our brains need energy to work well. Brain energy metabolism is how the brain makes and uses energy to keep all its functions running smoothly. Metabolism involves thousands of tiny chemicals called **metabolites** that work together in a complicated network to keep brain cells active and healthy. Could changes in metabolite levels explain the changes that are seen in the brain as it ages?

A COMPUTER MODEL TO STUDY THE AGING BRAIN

Since studying the human brain directly can be tricky, our research group decided to build a computer model of brain energy metabolism. A computer model is like a virtual experiment that uses math equations to represent real-life processes—whether it is how a car engine works, how weather systems move, or, in our case, how the brain's cells and molecules interact. Our computer model allows us to simulate what happens inside the brain as it ages, giving us a way to explore complex processes that would be hard to study directly.

GLUCOSE

A type of sugar that acts as the main source of energy for the brain and body. It is essential for brain cells to perform tasks like thinking, learning, and moving.

We built three main brain elements into our computer model: neurons, astrocytes, and blood vessels. Neurons are brain cells that communicate with other cells using electrical signals, to help a person think, move, and feel. Astrocytes are helper cells that support neurons and keep them healthy. Blood vessels bring nutrients, like oxygen and **glucose** (a type of sugar), to the brain so it has the fuel it needs to keep going.

To understand how changing levels of metabolites and other important molecules affect the brain during aging, we collected and combined a lot of data about brain proteins, nutrients, and brain functions from scientific papers published by other researchers. By plugging these data into our computer model, we could ask questions and test ideas that would be impossible to test on living people—like how aging might affect metabolite levels, neuron electrical activity, or the metabolic network that keeps the brain strong and adaptable. We can also study which treatments could help the brain stay strong as we age.

We wanted other researchers to be able to use our model as an example, to help them build their own computer models of other conditions and diseases. So, we made the computer program (written in the Julia programming language) publicly available. For more information, you can check out the Blue Brain Project.

BRAIN ENERGY SUPPLY AND ENERGY USE DECREASE WITH AGING

As the brain ages, its energy metabolism begins to change [3]. Our model showed that aging affects the levels of several molecules in brain cells. Some molecules appear to increase in aging, while others seem to decrease or stay basically the same (Figure 1).

One of the most important metabolites in the brain is **adenosine triphosphate (ATP)**—a molecule that serves as the main energy source for all cells in the body. Our computer model showed that more ATP is available in young brains than in aging brains. As ATP production starts to slow down, it may be more difficult for brain cells to keep up with the demands of thinking, moving, and learning.

ADENOSINE TRIPHOSPHATE (ATP)

A molecule that stores and provides energy for cells to perform their functions. It acts as the main energy source for all cells in the body, including brain cells.

Next, we used our model to ask whether aging-related changes in metabolism can change the way neurons work. We found that neurons send weaker signals in the aging brain. Neurons need energy to send their electrical signals, so the model tells us that the aging brain has both a lower *supply* of energy (in the form of ATP) and a lower *need* for energy (because of weaker signaling). Reduced signaling ability means that neurons may struggle to keep up with daily tasks.

THE AGING BRAIN "BREAKS" MORE EASILY

In addition to producing and using less energy, our computer model showed that the aging brain also becomes more fragile and less able to repair itself. Think of the brain's metabolic network as the system of streets in your town, and imagine that you need to bring some medicine to a sick friend. In a young brain, there are lots of open routes and well-maintained roads, making it easy for essential molecules, like

Figure 1

The brain's metabolism begins to shift as it gets older. When older vs. younger neurons are activated, molecules show three types of patterns: **(A)** Some, like ATP, are higher in young brains and decrease in old brains. **(B)** Others, like potassium, stay basically the same as the brain ages. **(C)** Still others, like sodium, are higher in older brains than in younger brains.

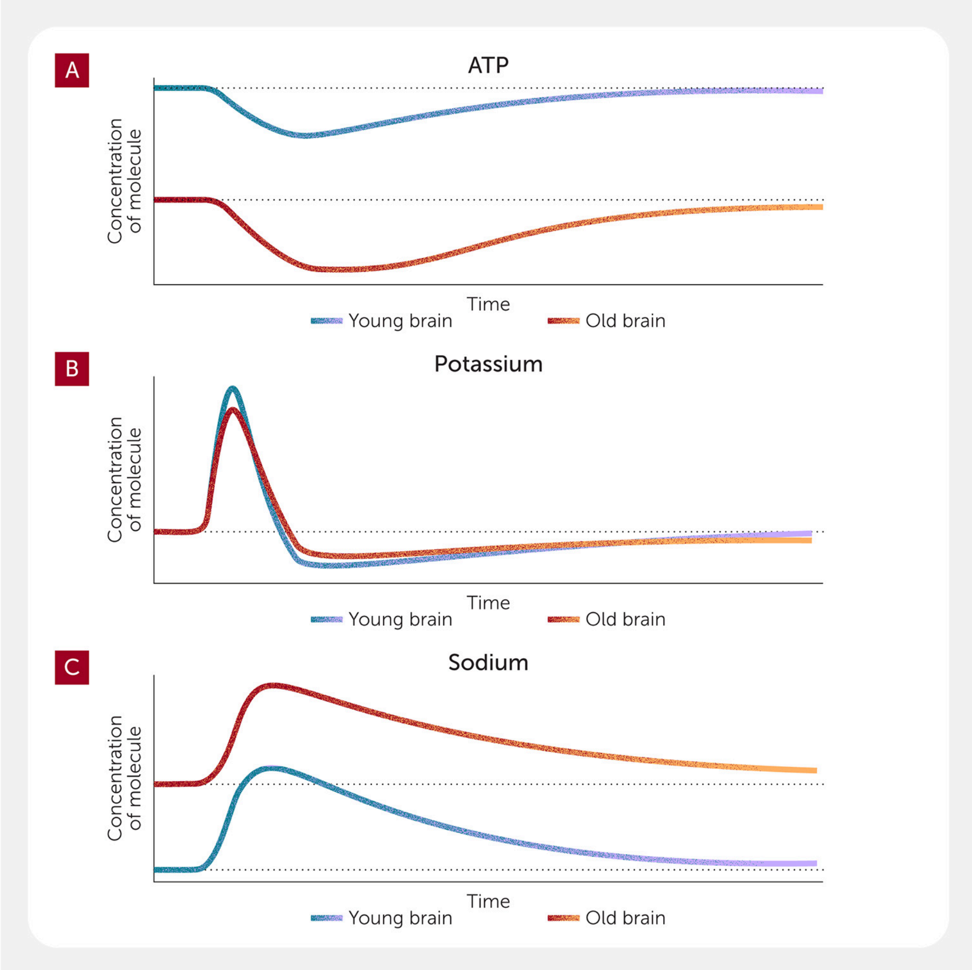

Figure 1

energy-carrying ATP, to reach all parts of the brain. This is like having many ways to get to your friend's house—you could take Main Street, cut through the park, or take the highway. Even if one route is closed, there are still plenty of other ways to get there quickly (Figure 2A).

But as the brain ages, it is like more and more roads are blocked off, and some bridges are out. Now, there might only be one or two paths left, or maybe you cannot make it to your friend's house at all. The same thing happens in an aging brain—when it experiences stress (like a minor injury or everyday wear-and-tear) there are fewer ways to get important metabolites where they are needed to help the brain recover (Figure 2B). This makes the brain more fragile and less adaptable, meaning it is less able to handle challenges or repair itself over time.

However, the model showed some interesting differences between neurons and astrocytes when it comes to adaptability. As the brain ages, metabolism in neurons becomes less adaptable. This means neurons struggle more to respond to changes or handle stress

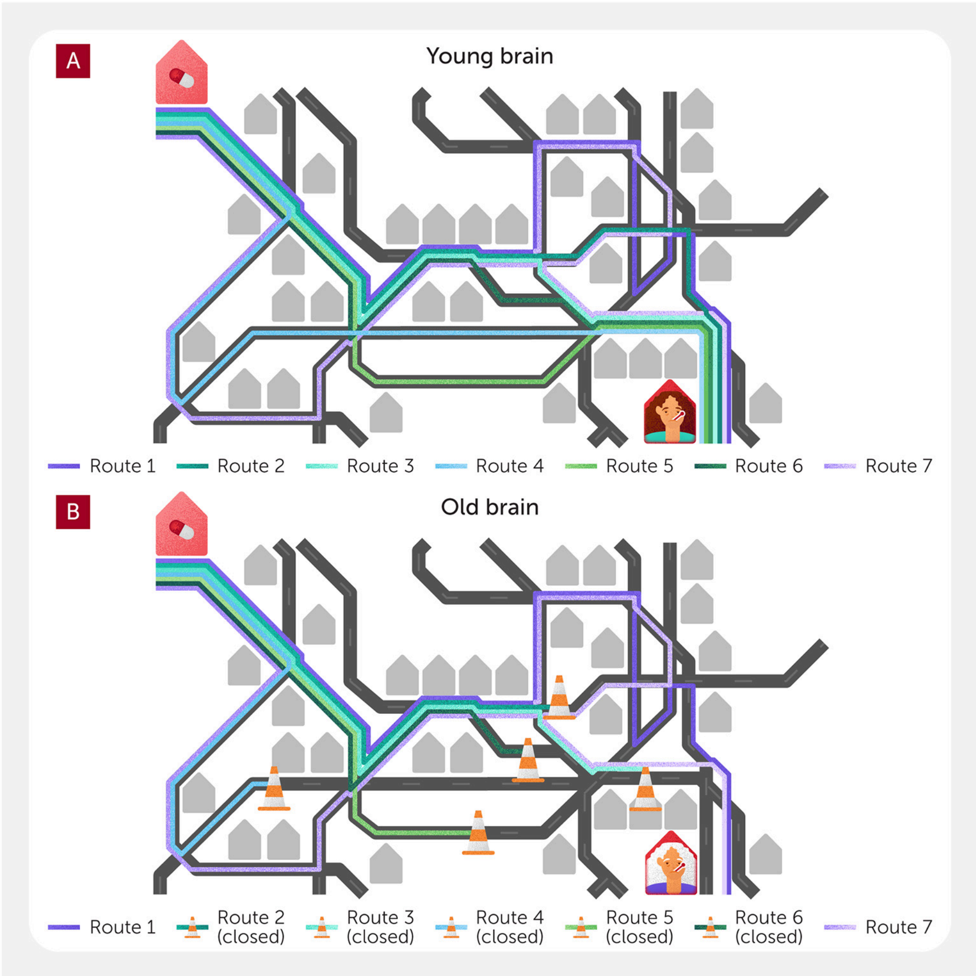

Figure 2

Figure 2

Think of the brain's metabolic network as the roads in your town, and imagine you wanted to deliver some medicine to a sick friend. **(A)** A young brain is like a town with many well-maintained routes to your friend's house. If one road is closed, plenty of other options are available. Likewise, in the young brain, metabolites can easily travel to the brain areas where they are needed. **(B)** An old brain is like a town with many damaged or blocked roads, limiting your options for getting across town. When metabolites cannot move through the brain easily, it becomes more fragile and less adaptable.

because the processes that produce energy are not as flexible as they used to be. On the other hand, astrocytes seem to have *more* adaptable metabolites as they age. What does this mean for the brain? One possibility is that astrocytes are doing more to keep themselves strong, becoming a bit "selfish" to stay healthy as they age [4]. Another way to think about it is that astrocytes are making a "self-sacrifice"—stepping up to help support the neurons, which are struggling with aging. Either way, these changes can make it harder for the brain to stay strong and bounce back from stress, increasing the risk of issues like dementia over time.

Can we help the aging brain become stronger and more adaptable? Are there ways to support neurons and astrocytes so they can keep working well as we grow older?

LIFESTYLE HABITS MAY HELP REPAIR THE AGING BRAIN

Our computer model offers clues about strategies to keep the brain's metabolism strong, even as people grow older. The model supports previous research showing that certain well-known healthy lifestyle habits—like a balanced diet, regular exercise, and specific vitamins or supplements—could help brain cells bounce back from stress and continue functioning well (Figure 3).

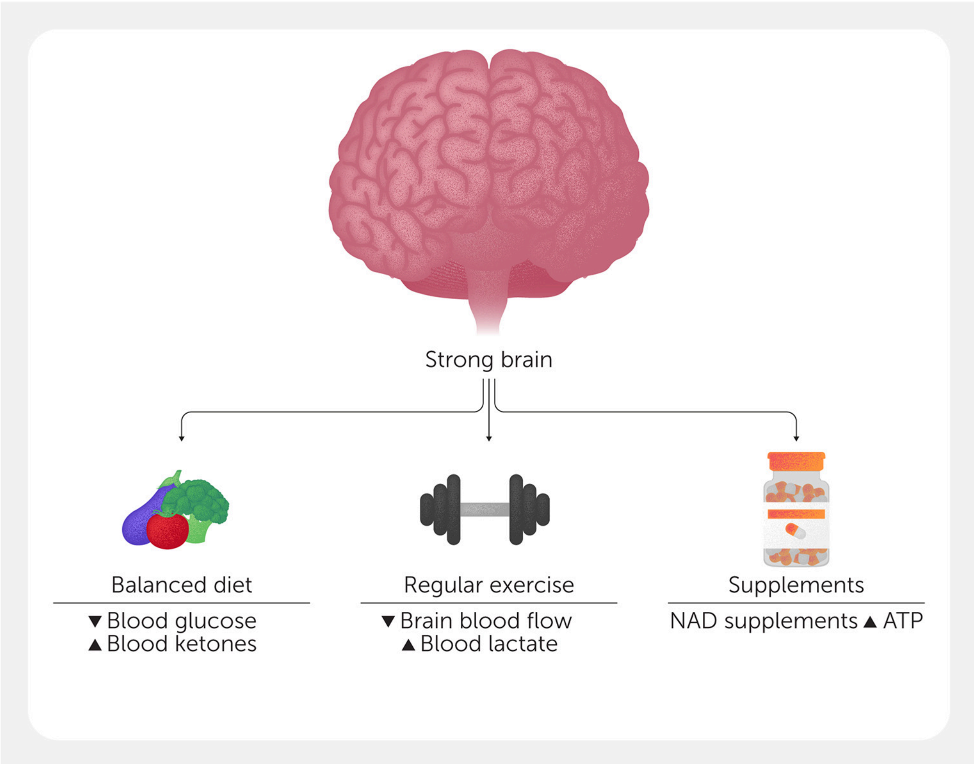

Figure 3

Figure 3

Our computer model supports research showing that healthy lifestyle habits, like a balanced diet, regular exercise, and taking certain supplements, play a role in keeping the brain's metabolism strong as people grow older. Thus, these habits can aid the brain's recovery from stress and normal wear-and-tear, which helps older brains to remain alert and flexible.

In terms of diet, the model suggests that eating in a way that lowers blood glucose and raises blood **ketones** (which are substances made when you burn fat for energy) may help the brain. These changes can make it easier for cells to get the energy they need, especially under stress. Exercise has a similar effect: it increases blood flow to the brain, which delivers nutrients that support energy production and help repair cells. Physical activity also raises the level of **lactate** in the blood, a substance the brain can use along with ATP for extra fuel during demanding tasks [5].

Many people already take vitamins and other dietary supplements to keep their brains and bodies healthy. **NAD supplements** are one type of supplement that may play an important role. NAD is a molecule that helps the brain's mitochondria—the cell's powerhouses—produce ATP. In the presence of higher NAD levels, our model shows that cells produce more ATP and respond better to challenges, which could help older brains stay alert and flexible.

KETONES

Molecules produced by the liver when the body burns fat for energy, often during low carbohydrate intake or fasting. The brain can use ketones as an alternative energy source.

LACTATE

A molecule produced when the body breaks down glucose for energy, especially during exercise. The brain can use lactate as an additional energy source to support its functions.

NAD SUPPLEMENTS

Supplements that increase the levels of NAD, a molecule that helps cells, including brain cells, produce energy and respond better to stress and damage.

SUPPORTING NEURON FUNCTION AND FUTURE DIRECTIONS

In our computer model, a combination of a healthy diet, regular exercise, and NAD supplements raised ATP levels in neurons and astrocytes, bringing them closer to the levels seen in a younger brain. However, the model showed that these lifestyle changes alone were not enough to make aged neurons signal like young neurons. In other words, the neurons could produce more energy, but they still were not signaling as strongly or precisely as those in a younger brain. To address this, we tweaked the model conditions to increase the activity of a molecule that neurons need to send electrical signals, called the **sodium-potassium pump**. Increasing the activity of this molecule to youthful levels made neurons' signals stronger and more like those in a young brain. Interestingly, insulin, a substance well-known for controlling blood glucose, can also boost the sodium-potassium pump's activity, supporting the model's findings on the benefits of diet and exercise. So, our model suggests that the sodium-potassium pump could be a potential target for therapies aimed at restoring youthful brain function.

SODIUM-POTASSIUM PUMP

A protein in cell membranes that moves sodium out and potassium into cells, using energy. It helps maintain electrical signals in brain cells for proper communication and function.

While these results are promising, they come from a computer model—so scientists need to conduct further experiments to confirm whether these strategies work in real life. Still, our findings provide exciting insights into how diet, exercise, and targeted supplements could help protect the brain as it ages. By better understanding the aging brain's unique challenges, scientists can develop new ways to support brain health, potentially helping people stay sharp, active, and independent as they grow older—and hopefully reducing the risk of age-related conditions like dementia.

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YOUNG REVIEWERS

AYXA, AGE: 14

I am a drawing and painting enthusiast, I enjoy making digital and traditional art. I am not much of reader, however I like mysteries and comedies. Watching animations and series is something similar to a hobby for me. I love watching stuff that have psychological and dark themes, on the other hand comedies capture my heart too. Traveling and exploring new countries is how I spend my time during holidays.

FRANEK, AGE: 15

Hello, my name is Franek, I am 15 years old. I have been interested in mathematics and science from an early age. I practice martial arts successfully. In my free time I like reading books.

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Polina Shichkova worked on brain energy metabolism and brain aging as a neuroscience Ph.D. student at the Blue Brain Project at EPFL. After defending her thesis, she joined the company Biognosys as a scientist, where she continues to explore the biology of various complex disorders. During her bachelor's and master's studies, she worked on several projects in bioinformatics and computational drug discovery. In her free time, she enjoys hiking, arts, and dance.
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Daniel Keller is the group leader of Molecular Systems at the Blue Brain Project. As a neuroscientist, his research examines how brain cells are distributed according to their molecular identities, as well as the biochemical pathways in those cells. In particular, his group examines how the brain regulates the supply of energy and nutrients. In his free time, he enjoys running and traveling.

HENRY MARKRAM

Markram is a neuroscientist with a passion for understanding how the brain works. He began his career in South Africa and later studied and worked in Israel, the United States, and Europe. He has made groundbreaking discoveries about how brain cells communicate, how memories form, and how the brain changes over time. His best-known work, spike timing dependent plasticity, helps explain how neurons strengthen their connections. At the Swiss Federal Institute of Technology (EPFL), he launched the Blue Brain Project, using supercomputers to create virtual models of the brain. These models help scientists explore how brains process information, how disorders like autism affect the brain, and how we might develop new treatments. Henry's research continues to uncover the intricate designs of the brain, paving the way for future breakthroughs in neuroscience.