# COSMOS INTHE CRANIUM

Neuroscience researchers explore our most magnificent and vast organ – from the mighty effects of tiny genes to the building blocks of thought.

STORY BY BEN BRUMFIELD ---- ILLUSTRATION BY MICHAEL MARSICANO

## THE BRAIN

**RESEARCH HORIZONS 31** 

## TUCKED AWAY INSIDE YOUR HEAD IS A LIVING GALAXY.

The human brain is believed to have more than 160 billion cells; more than half of them are neurons. And they often share thousands of connections with neighboring neurons to form somewhere between 100 trillion and a quadrillion circuits flashing day and night. That's many hundreds of times more circuits than there are twinkling stars in the Milky Way.

Innumerable barrages of electrochemical transmissions adjust your pulse and immune system, hold you upright, and allow you to do carpentry or calculus – all at the same time. Neural circuits let us eat, love, dream, or just be.

No room-filling supercomputer consuming millions of watts of power has come close to the composite abilities of our two heaping handfuls of gray and white matter. And our brain needs only 20 watts to operate, less than many lightbulbs.

At the Georgia Institute of Technology, a rare synergy of engineers and scientists, in cooperation with Emory University School of Medicine and other collaborators, is expanding data collection and analysis on the brain.

The research road ahead feels endless, many neuroscientists say, and comprehending how the brain generates the human psyche may be decades beyond the horizon. But neuroscience is in a forward lunge powered by sweeping national funding programs such as the BRAIN Initiative (Brain Research through Advancing Innovative Neurotechnologies), which is tapping into the brain to understand it and support well-being.

In this article, a sampling of Georgia Tech's many neurological researchers share fascinating insights about the brain and relate them to their work. We start microscopically with single molecules that have colossal effects on the brain, and end macroscopically with how the brain finds its way home, watches a movie, and how it never switches off.

## **MOLECULAR DESTINIES**

One misplaced molecule can steer a brain to ruin. A rare form of Alzheimer's disease called early onset familial Alzheimer's, for example, can be caused by one small mutation. But mutations happen all the time and are almost always harmless. So, in the lab, when a slip in a strand of DNA triggers a cascade of changes to a tiny animal's nervous system and overhauls its behavior, that piques researchers' interest. Patrick McGrath and Hang Lu at Georgia Tech develop experiments to identify these interesting mutations in micro-

neurological diseases.

to other beings."

*C. elegans* are like baggies of 302 neurons connected in a concise neural network that researchers can easily study. "In 1986, a team of researchers figured out how the neurons are all connected to each other," McGrath said. "And the sequence of the DNA has been known since 1998."

gene labeled npr-1.

C. elegans usually eat together in groups of 40 or 50, but after living in the lab for a few years, a strain suddenly turned up that ate alone. "It could have been caused by mutations on 100 genes," McGrath said, "but in fact, it was just a single genetic change." In *npr-1*.

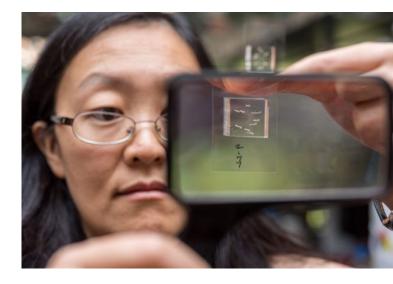
That affected the workings of a neuromodulator, a signaling molecule that touches large parts of the nervous system. The mutation triggered sweeping alterations in the sensing of oxygen, CO<sub>2</sub>, pheromones, and pain, which led to the isolative behavior. "This gene has a homolog in humans that is, in some way, modifying our brain activities," McGrath said. Exactly how is yet unclear.

The neural traits most interesting to science and medicine are much subtler ones, virtually undetectable when taken alone, but when added together by the

### NEUROLOGY TERMINOLOGY



Microscopic roundworms in the genus Caenorhabditis. Literally little bundles of nerves (each C. elegans contains 302 neurons and 56 glial cells), it is the first animal to have its connectome fully mapped. And since nerves first evolved, they haven't changed much, so what ails a roundworm's nerves can possibly ail ours too.



scopic C. elegans roundworms. They study changes in the structure of the nervous system or the animals' behavior and try to locate the genetic alterations behind them. Though they work with worms, McGrath, an assistant professor in the School of Biological Sciences, and Lu, a professor in the School of Chemical and Biomolecular Engineering, look for cues on how genetics can raise the risk of human

"The nerves in roundworms can be like our own, and important genes in C. elegans are quite similar to those in humans," Lu said. "That's the way evolution works. When something works well, like the basic structure of neurons, it gets passed on

With the connectome and genome so well laid out, the little worm has led the way in research relating the two. And some insights have shown potential to improve understanding of human neurology, like a marked mutation that turned up on a

To detect nearly invisible traits, School of Chemical and Biomolecular Engineer ing Professor Hang Lu has engineered microfluidic devices that hold C. elegans worms still, so a digital camera can photograph them

#### NEUROLOGY TERMINOLOGY

## Connectome

A map of neural connections in the brain, or the entire nervous system. In the case of C. elegans, the connectome has been completely constructed (below). Partial connectomes of a mouse's retina and visual cortex have been completed, and work is underway to construct a connectome for the human brain. Much like the genome, a structural map would be a powerful tool for neurological research



**RESEARCH HORIZONS 33** 



thousands, raise the risk of diseases like autism, depression, and schizophrenia.

To develop the capability to detect such nearly invisible traits, Lu has engineered microfluidic devices that hold *C. elegans* worms still, so a digital camera can photograph them, while an algorithm determines if neuron phenotypes (traits) have subtly malformed. Then software maps individual trait changes to individual gene mutations, so researchers can study possible links to disease.



Behavior is much of what the brain is for, so when studying how the brain evolved, it makes sense to give behavioral evolution abundant attention. That could lead to insights relevant to human disorders that diminish behavioral abilities, such as autism.

Oddly, autism's suspected genetic foundations have correlations with genes tied to the mating behavior of colorful fish called cichlids, which Georgia Tech evolutionary geneticist Todd Streelman studies.

"The genes that are activated in behaving fish brains have human homologs that are over-represented in a catalog of genes involved in autism spectrum disorder," said Streelman, a professor in Georgia Tech's School of Biological Sciences, which he also chairs.

Streelman pointed out that autism and cichlid mating rituals are not the same thing, but the rituals are social behavior, and also extremely repetitive. And autism, as well, typically involves social deficits and repetitive behavior.

To attract females ready to mate, some cichlid males build underwater sand castles; other species dig pits. In both cases, they spit mouthfuls of sand some 700 times in an hour.

When researchers crossed a castle-building species with a pit digger, the offspring constructed both pits and castles in sequence. "That suggested that you have two genetically determined neural networks," Streelman said. And they dictated complex behavior.

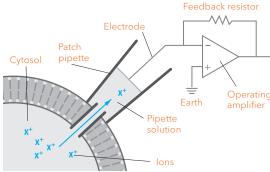
Streelman correlates genes with encoded behaviors - which some may call "instincts." He also checks the cichlid's brains for physical characteristics linked to the genes and behaviors.

Malawi cichlids are ideal genetic study subjects because they are evolutionary wonders. In just a million years, the branch of

#### NEUROLOGY TERMINOLOGY

## Patch clamp

The patch clamp technique allows for electrical measurements of a single neuron. A tiny glass pipette, its opening only one micron wide, is sealed to the outside of the cell membrane. As ions flow across the gradient through the channels, an electrode reads the current.





fish has popped out hundreds of species specialized for life in various ecological niches.

Cichlids have clearly identifiable varieties of phenotypes (traits), including varying behaviors, but their genomes fluctuate only slightly from species to species, making it easier than in most complex animals to pin down genes suspected of being behind specific traits. And RNA helps scientists locate them.

Genes not only orchestrate embryonic development but are also active in cells during life, including to influence behavior. They encode RNA in the process, which leaves a convenient marker.

"The technologies we have now enable you to figure out what parts of the brain have been activated during behavior, then sample RNA from those parts of the brain to find out what genes have been expressed," Streelman said.

#### 3 **GROUND NEURO**

Recording the flickers of one or a few neurons is important for understanding how the whole brain computes.

But for decades, scientists have been lucky if a hard day's work yielded even a single decent measurement from a neuron firing in a mouse's brain. Now, engineer Craig Forest has designed systems using robotics that can reliably take many measurements in a day.

"We're seeing a renaissance in tools to see how the brain works," said Forest, associate professor in Georgia Tech's George W. Woodruff School of Mechanical Engineering. "In the past decade, due to the BRAIN Initiative, there has been a paradigm shift in the tools."

Forest is a prime example of this shift, improving upon good technologies to exponentially burgeon the yield of data.

A Nobel Prize-winning hollow glass needle, called a patchclamp pipette, has long been considered the gold standard for electrical measurements of a single neuron. It has an opening at its tip just a micron across, and a skilled researcher with a few hours' time might be able to fiddle it onto a neuron in a living brain by hand. Mild suction clasps it onto the cell membrane, so it can pick up the neuron's electrical activity.

Forest and colleague Ed Boyden at the Massachusetts Institute of Technology thought there must be an algorithm that could do the job more precisely, so they built robots to operate

Genes tied to the mating behavior of cichlids, a type of fish, have correlations with autism's suspected genetic foundations.

patch-clamps, freeing scientists to do other things. But an annoying hitch remained.

After every attempted measurement, the scientist or the robot would have to discard the patch-clamp, because it was dirty, and get a fresh one. So, Forest and his team went to work on a robot that also self-cleaned the patch-clamp, making the needle reusable and multiplying the number of automated measurements per day.

Forest started his career fascinated by machines, until he discovered the most wondrous one, the brain, and dedicated his attention to it. "In one cubic millimeter of the cortex, there's 10,000 neurons. That's 10,000 microcircuits processing something. Humans have never made anything that complicated," he said.

That cubic millimeter is a functional unit called a cortical column.

Neuroscientist and biomedical engineer Bilal Haider deploys tools in awake brains to see how the rumblings inside an individual neuron relate to its neighbors' activities. He also uses computational analysis to predict the overall relation of a cortical column to a single neuron's firings.

Neurons are great at holding their fire — at *not* sending signals. Without this inhibition, our brains would crash in a frenzy of activity.

Most cortical neurons excite neighboring neurons to fire, but a fifth of them inhibit their neighbors instead. "They are very critically important for, first, not letting activity generate things like epilepsy, but also to set the clock of when messages are being passed," said Haider, an assistant professor at the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University.

In brain signaling, timing is quality; it's the difference between tapping out clear digital code to other neurons or just handing them noisy static. Inhibitory neurons create pauses between the taps.

In the cerebral cortex, which many refer to as gray matter, those taps constantly bombard neurons, but their reaction is usually stoic.



## HUMANS HAVE NEVER MADE ANYTHING THAT COMPLICATED."

School of Mechanical Engineering Associate Professor Craig Forest has developed automated patchclamping instruments to accelerate the recording of information from neurons. In this photo, an instrument is protected by a Faraday cage.

"The state is usually in balance, with the neuron sitting there happily between the excitatory and inhibitory forces," Haider said.

An orchestra of activity runs through a neuron even without it firing a single spike down to its synapses — or contact points with other neurons. Then a person does something that activates that part of the brain, and the neuron readily fires, and usually not alone: A mass of its neighbors fires together with it.

## 4 PARADOX LABYRINTH

The brain is a master of contradiction.

Though individual neurons are hesitant to fire, the brain's neural networks can still compute in milliseconds. Also, while the brain plays by many rules that are nearly the same across many species, from rodents to humans, viewed up close, those rules bend like eels.

Garrett Stanley, a mechanical engineer turned neuroscientist, studies the brains of rodents to understand neural networks, patterns that fire through the brain as it computes.

"We record from multiple parts of the brain simultaneously, which is signature work for our laboratory," said Stanley, a professor at the Wallace H. Coulter Department of Biomedical Engineering. Stanley's lab is able to measure many elements in neural pathways triggered by prodding a rat's whisker.

The tactile stimuli make their way as impulses traveling up



WHAT'S ON YOUR NERVES

 membrane
 0

 potential
 -20

 (mV)
 -40

 -60
 -00

 local field
 0

 (mV)
 -0

When Bilal Haider's team measured electric potential in a cortical column, they saw an orchestra of activity in the group of neurons (the local field potential) – excitatory and inhibitory forces were constantly at work, even though neurons actually sent signals (spikes in the membrane potential) only at comparatively rare intervals.

Funding for McGrath, Lu, Streelman, Forest and Haider was provided by the National Institute of Neurological Disorders and Stroke, the National Institute of General Medical Sciences, the National Institute of Biomedical Imaging and Bioengineering, and the National Institute on Aging, all part of the National Institutes of Health. Funding was also provided by the BRAIN Initiative, the Single Cell Grant program, and the National Science Foundation.

#### NEUROLOGY TERMINOLOGY

## Thalamus

The thalamus acts as a kind of "super-turnstile" for signals in the brain – it relays inputs coming from sensory systems to the cortex and also regulates states of sleep and wakefulness.

## Hippocampus

From the Greek for "sea monster" (a description of its shape), the hippocampus is responsible for spatial memory and navigation. It also plays an important role in the consolidation of memory.

> nerves to the brain, which then fires signals to multiple brain regions to compute information together and create perceptions. The neural pathways are pretty shifty.

> "Unlike a network of computers, our brain is always changing what it's doing and how it's doing it, based on what it's experiencing," said Chris Rozell, associate professor in Georgia Tech's School of Electrical and Computer Engineering, who collaborates with Stanley to produce new designs for experiments.

Neural pathways constantly reroute.

"Imagine a subway map where the rules are changing on the fly," Stanley said. "New lines suddenly appear, and old ones go





away, and fewer or more cars appear on the line spontaneously depending on passenger demands."

Those paths can engage a neuron that Stanley and Rozell are trying to study in a calm state, thus confounding observation, but they and former Georgia Tech researcher Steve Potter have devised a way of slightly distracting neural activity away from it. They have used genetically modified brain cells that they can make fire more by shining a light on them, a method called optogenetics.

And the team has added an innovation: a neural cruise control. "We use neural recordings as the speedometer to instantaneously raise or lower doses of light, which act as a gas pedal," Rozell said. That allows them to make neurons do a lot more of what they'd like them to do.

Rozell also makes computer science-based models that emulate the way the brain computes perceptions, though

## Cerebral cortex

The cerebral cortex is the outer layer of gray matter of the cerebrum, the large outer part of the brain. Neurons in this layer connect vertically to form cortical columns.

## Cerebellum

The cerebellum, along with the brainstem, is primarily concerned with motor control, contributing to our coordination, precision, and accurate timing of muscle movements.

brain-machine comparisons face a challenge. For example, machine networks have discrete parts for memory, graphics, processing, and also firm wiring.

"In a brain, those functions are all intertwined in flexible shared elements," Rozell said. Multiple back-and-forth pathways light up simultaneously, and Rozell wonders if the brain's computing may have something to do with those pathways coming into some sort of equilibrium.

The brain is so highly interconnected that every part of it seems like it's closely wired to every other part, opening up countless possible neural signaling pathways. But some very strong tendencies put reins on them.

"Not all of those paths are equally likely to be traveled," Stanley said. "Some connections are much better wired than others due to genetic determination, or learning behavior." Human behavior is partly genetically encoded and formed during development, like the capacity to speak, and partly learned, like mastering a language.

Some neural pathways are well paved, like signals for perception and motor movement traveling via the thalamus, a structure in the deep brain that acts as a neural super-turnstile. It is critical to coherent brain function, as it routes and modulates signals to and from the cortex, where some locations, like the visual cortex or the motor cortex, are assigned to specific functions.

## 5 SEAHORSE GPS

The hippocampus is aptly named. "Hippo" is ancient Greek for "horse," "kampos" for "sea monster." The deep brain region is curve-shaped like a sea horse, and it helps you get around from place to place by facilitating orientation.

It also slows down noticeably with age, and in Alzheimer's disease, the hippocampus succumbs early on, leaving sufferers disoriented. That disease helps put the hippocampus in researchers' focus.

Work on its encoding of location garnered scientists a Nobel Prize in 2014 for describing the brain's GPS. They also found that the hippocampus, which is important for memory as well, lays down some consistent neural code, contrasting with neural networks' often fluxing firing patterns.

"It was shown back in the 1970s that there are neuron groups in the hippocampus that fire in a particular location in space," said neuroscientist and biomedical engineer Annabelle Singer,





"There are very consistent areas of the human brain that are activated during navigation tasks," said Scott Moffat, associate professor in the School of Psychology. He uses an fMRI machine, above, to record the patterns of brain activity in humans who are navigating a virtual landscape, right.





who studies hippocampal function in mice at the Wallace H. Coulter Department of Biomedical Engineering. "If the mouse is running around this room, for example, when it gets to this one spot, there's a subset of cells that will fire." Other subsets fire when the mouse arrives at other spots.

The existence of such neural activity has also been corroborated in humans.

Let's label the cell groups that do this A, B, C and D. As you stroll to your local coffee shop (or as a mouse in a lab runs through a video maze toward a reward), neurons fire in sequence corresponding to recognized physical locations along the way. Sidewalk, fire A. Crosswalk, fire B. Supermarket entrance, fire C. Coffee shop counter, fire D.

Singer is researching how such cell groups collaborate to encode paths in the first place. And she has observed them firing in other instances. For example, when a mouse licks a delicious reward for running a maze, the pattern re-fires. "You get, really quickly, A-B-C-D. That's called reactivation, or replay."

What Singer does in mice, researcher Scott Moffat from the School of Psychology mirrors in his work with humans. He has human subjects navigate through video mazes inspired by video mazes rodents run, in part because, if mice and humans perform the same task, it makes comparing their brain activity easier.

But whereas Singer zeros in on finer neuron activities in a mouse's brain, Moffat uses functional magnetic resonance imaging (fMRI) to measure broader patterns in humans' brains. He focuses on diminishing navigational abilities in aging.

"There are very consistent areas of the human brain that are activated during navigation tasks," Moffat said. The hippocampus taps into nearby brain regions like the parahippocampus, which has an area for computing place recognition. It even lights up when people just look at pictures of places.



"Younger people activate these areas when doing spatial tasks," Moffat said. "When we run older people through these virtual navigation tasks, what we see pretty consistently is underactivation in the same areas."

In Alzheimer's patients, as these areas break down, sufferers begin to lose their way and can even go missing.

## I, ROBOT

Want to try an experiment that shows how your brain, without your even noticing, keeps you from tipping over?

Reach out your hand like you're going to pick up a glass, and then pull your hand back. Repeat that motion and observe

your torso. That back-and-forth sway is balance correction courtesy of your lower brain: the cerebellum and brainstem, which are adjusting multiple muscles to preserve your balance.

Now you have a small sampling of what mechanical engineer Lena Ting observes to study the nervous system's control of balance. She looks at the body in motion to gain insights about the brain.

"I can describe the mechanics, and if I have a good model of that, I should understand something about how the system is controlled, which gets me to what the brain and the nervous system are doing,"

said Ting, a professor in the Wallace H. Coulter Department of Biomedical Engineering. She started out studying biological motion control to apply it to robots, but now also concentrates on evaluating rehabilitation techniques for people suffering from neurodegenerative diseases like Parkinson's.

"We're looking at how muscles are controlled in functional units we call motor modules," she said. One motor module might be the combination of muscles that go to work when you extend your arm. Others would kick in when you hop on a bike.

Though motor modules work for the most part automatically, initially, they probably had to be learned, like when a child learns to stay balanced on a bike.

Also, our huge cognitive brain regions can override automatic balance to make us willfully walk upright when we otherwise couldn't, perhaps due to a neurological ailment. But that overriding has limitations, because the brain regions that do it aren't optimally wired for balance control.

"If you ride a bicycle, and you go through a narrow gap, if you think about it too much, you may wobble a lot," Ting said, "whereas, normally, you could probably pass through that space."

Elsewhere in the nervous system, your spinal cord is doing some things on its own, like triggering reflexes.

To watch these various functions interplay, in her lab at Emory University, Ting covers subjects in tracking markers and video records them while she purposely throws off their balance using a floorboard that shifts around abruptly. Cameras roll as the subjects strive to maintain posture - not an easy thing to do.

But watching them flail may help Ting assess the effectiveness of rehabilitation methods in treating neurological disabilities.



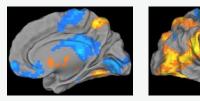
When cognitive neuroscientists say "cognition," they're not usually referring to how the brain ponders, but instead to how its networks learn facts, recall memories, or pay attention.

Though scientific understanding of "thought" and "psyche" may lie far down the research road, elements of "cognition" could be their building blocks, and the brick layer could be something called "cognitive control." Cognitive psychologist Eric Schumacher studies how cognitive control employs functions like attention, memory, and learning to make very simple decisions or complete a nominal task.

"When you're reading a book, you may want to understand the facts," said Schumacher, an associate professor in Georgia Tech's School of Psychology. "Your brain has to guide your eyes, encode the words, and link them up to knowledge you already have. There's a way your brain recruits systems to achieve that, which is what we mean by control."

Cognitive control constantly adjusts this coordination of senses, movements, knowledge, memory, and more. It's an array

#### GETTING SOME ACTION



Broad patterns of brain activity measured by functional Magnetic Resonance Imaging (fMRI).

of processes not yet completely understood, so to get a handle on some of them, Schumacher lets volunteers watch action movies and observes their brain activity in an fMRI.

"Things change as we go through the world, and movies, with their flow of actions, allow us to study that in a scanner," he said. For example, there's a marked contrast in the way the brain lights up during moments of high suspense and low suspense in the story line.

"With increasing suspense, you become more interested in the story, and regions of the brain's visual systems that process the center of the screen, where the movie is, become more active, selecting more information from the film, and regions that process the visual periphery become less active."

"That's neural evidence for the focusing of attention," Schumacher said.

Other brain regions – in the parietal and frontal lobes – are known for allocating that attention from one thing to the next. "There's more activity in those regions in moments of high suspense," Schumacher said.

And that cognitive control appears to link suspense with learning. "People are more likely to remember information presented at moments of high suspense than in moments of low suspense," Schumacher said.

Ting was provided by the National Institute for Neurological Disorders and Stroke and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, both part of the National Institutes of Health, and the National Science Foundation

Funding for Singer, Moffat, and



## "WHEN WE STARTED DOING THESE STUDIES, WE THOUGHT RESTING STATE ACTIVITY BASICALLY WOULD FLY UNDER THE RADAR.

# THERE'S MORE INFORMATION IN THIS MRI THAN WE'D EVER HOPED TO FIND."

#### 8 THE ZONE-OUT ZONE

Relax. Zone out. Welcome to the brain's default mode network, where it may feel like the mind is just wandering. But a lot is still going on in the brain, which never shuts off.

Don't believe it? Initially, Shella Keilholz didn't quite either. The physicist, who researches in neuroscience as associate professor in the Wallace H. Coulter Department of Biomedical Engineering, thought that any activity in a brain in default mode would be extremely faint.

"When we started doing these studies, we thought resting state activity basically would fly under the radar of our detection possibilities," she said. She's glad that was wrong. "There's more information in this resting state MRI than we'd ever hoped to find."

"All these areas like visual cortex and auditory cortex that are ready for input from the outside world, their activity goes down, and the activity in this default mode network and the areas attached to it go up," she said. The energy level, in sum, doesn't change. It just kind of spreads around the brain.

Even though a volunteer subject may be lying flat and still, areas in the brain responsible for hand movement appear to be softly talking to each other. The default mode network stays on during most of sleep. It's even on during a coma.

The brain transitions a lot between the default mode network and the task positive network, which becomes active when people do externally focused activities.

To research this, Keilholz has people gaze at a little blue dot and relax.

When the dot suddenly turns purple, the research subjects are supposed to punch a button, which requires the brain to quickly suppress the default mode network and jump into the task positive network.

Surprisingly, the more strongly a test subject went into default mode network, the more quickly they could bolt out of it and into the task positive network.

Keilholz has found an innovative way to address one of neuroscience's great challenges. In rodents, she is taking measurements on a neuronal level and is correlating them with broader measurements of the fMRI. This may someday allow scientists to know what is going on between small bunches of neurons just by looking at an MRI image. O

Ben Brumfield is a senior science writer with Georgia Tech's Institute Communications. He is a former CNN.com editor.

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