Chronicle / *Lab Book*

Hangry? Here's Why

Scientists unravel why feeling hungry can also mean feeling angry.

LET'S BE HONEST; dieting is rough. Hunger can deflate a dieter's spirit and render friends and co-workers unbearable.

Still, hunger is evolutionarily beneficial, as it signals when our bodies need food. Eating activates reward systems in the brain, but scientists have puzzled for decades over why our mood turns bleak when hunger hits.

Scott Sternson, a group leader at Janelia Research Campus, decided to tackle that question in mice. His team started by looking at the brain's agouti-related peptide (AGRP) neurons, which, when activated in mice optogenetically, elicit voracious eating.

The researchers presented well-fed mice with two flavored gels; the mice showed no preference for one over the other, and neither had nutritional value. Whenever the mice nibbled at one of the gels, scientists activated their AGRP neurons. Surprisingly, the mice began avoiding that gel.

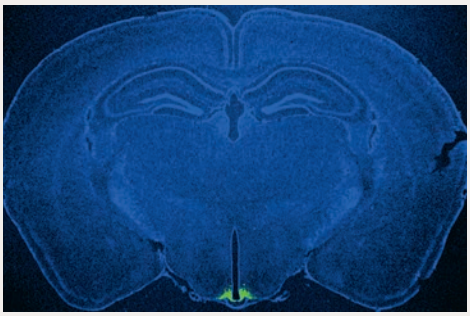
To further test the link, Sternson's team activated the AGRP neurons every time the mice went to a certain part of their cage. Sure enough, the mice began avoiding that area.

When the scientists peered into the rodents' brains, they observed that AGRP neurons are indeed active when the animals are hungry. But the neurons showed low activity during eating. In fact, they're inhibited as soon as food is sensed.

Thus, it appears that AGRP neurons encourage us to pursue food to avoid a state of physiological need for nutrients. Based on his team's findings, published April 27, 2015, in *Nature*, Sternson thinks the unpleasant feeling associated with AGRP activation prompts the drive to find food. This is important evolutionarily, as animals often face risks in seeking food. If hunger is unpleasant, animals are more likely to take that risk, ensuring their survival.

While that works for animals, it's tough on dieters. "When people try a weight-loss diet and find it to be unpleasant … it's pretty likely that the elevated activity of the AGRP neurons has something to do with it," Sternson says.

With that in mind, scientists are looking at how they might interfere with AGRP neuron activity. If the neurons behave similarly in humans, help in dropping those extra pounds may not be far off. *–Anzar Abbas*



The brain's hunger-sensitive AGRP neurons (green) are responsible for the unpleasant feeling that drives us to snack.

IN BRIEF

TEASING OUT NEURONAL FUNCTION

The brain holds a host of different kinds of neurons, each with its own job. Though you might think neuronal cells are highly organized, they are in fact intertwined in a colossal tangle. For scientists who want to study particular neuron types individually, teasing them apart is a major challenge.

Now, a team of researchers – led by HHMI Investigators Jeremy Nathans and Joseph Ecker, and Janelia Group Leader Sean Eddy – has devised a way to study individual cell types without getting mired in the tangle. Rather than trying to separate cells of a certain type from their neighbors, they've developed a way to isolate their nuclei. From there, they can study the cells' DNA, which provides information about the cells' activity and history.

"We weren't sure what to expect. This was an exploratory, discovery-level project," says Ecker of the study, published June 17, 2015, in *Neuron*.

But already, the method has revealed astonishing differences in cell types previously thought to be similar in function. "That means there's a lot of additional information here," says Ecker. Using the new technology, scientists will not only be able to delve even deeper into the secrets of the brain, but they might also gain greater understanding of other systems in the body as well.

RADICAL VACCINE HAMPERS HERPES

The herpes simplex virus infects millions of people worldwide, yet the pathogen has for decades thwarted attempts to develop a vaccine.

Most efforts by scientists to create a herpes vaccine have focused on glycoprotein D (gD), a protein that triggers the production of protective antibodies. However, attempts to exploit gD in a vaccine have been futile.

"It was necessary to shake the field up and go another route," says virologist and infectious disease physician Betsy Herold. So she and HHMI Investigator William Jacobs, both at the Albert Einstein College of Medicine, joined forces to take a radically different approach.

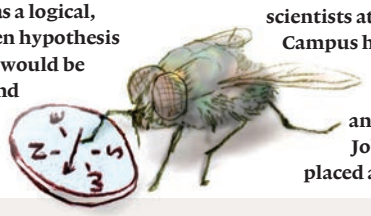
Instead of using gD, the researchers used a mutant strain of the virus lacking gD. "Once we had this mutant in our hands," says Herold, "it was a logical, scientifically driven hypothesis to say, 'This strain would be 100-percent safe and might elicit a very different immune response than the gD subunit vaccines that have been tried.'"

The study, published March 10, 2015, in *eLife*, tested the hypothesis in mice. The new vaccine completely protected the mice from the most common herpes infections, without any adverse effects.

If the vaccine works in humans as well as it does in mice, it could have a profound impact on the global prevalence of herpes.

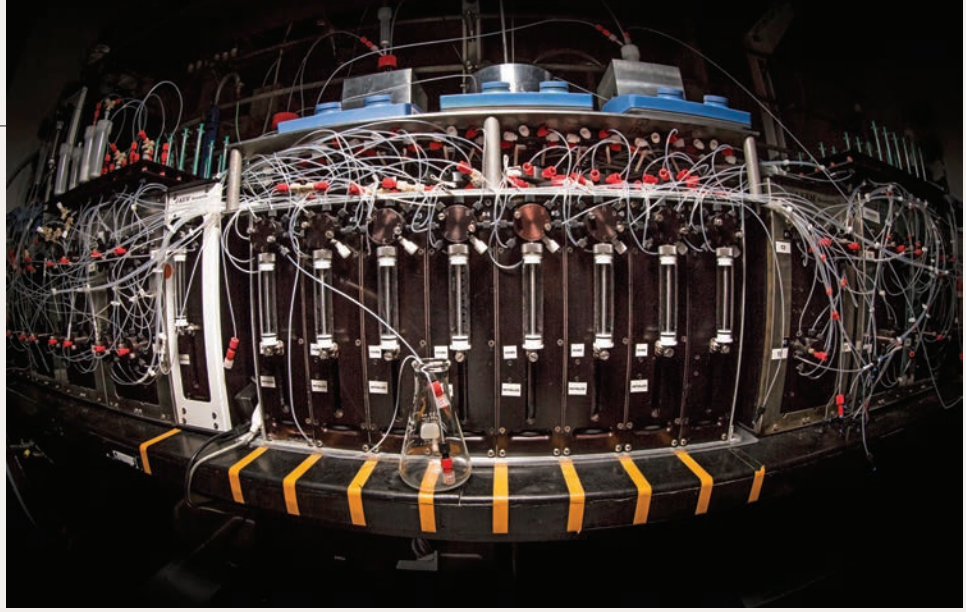
A COMPASS FOR FLIES

If you've ever made your way through a dark room, you've relied on neurons to help maintain your balance and bearings without vision. A fly's brain is much less complex than a human's, yet flies, too, can keep a sense of direction in the dark, scientists at Janelia Research Campus have found.



Group Leader Vivek Jayaraman and postdoc Johannes Seelig placed a tethered fly

Photo: Christopher Magnus, Illustration: Leif Parsons



Taking cues from nature, this molecule-making machine couples chemical building blocks to create small molecules.

Made-to-order Molecules

A new invention acts as a molecular 3-D printer.

WHEN CHEMIST FRIEDRICH WÖHLER accidently made synthetic urea about 200 years ago, he stumbled upon a feat that has occupied scientists ever since: the synthesis of small molecules.

Today, we use small molecules everywhere. You can find them in most medicines, foods, scientific research – even coffee sweeteners and light bulbs. Yet when it comes to the vast possibilities arising from small molecule production, we've barely scratched the surface.

"The bottleneck is synthesis," says Martin Burke, an HHMI early career scientist at the University of Illinois at Urbana-Champaign. To date, making small molecules has required a customized approach achievable only by highly trained specialists.

But now, Burke and his team have developed an invention that extends that ability from a select few to anyone with a computer. "We've created a machine that can do on-demand small molecule synthesis – kind of like a 3-D printer for small molecules."

Burke says the machine, described in *Science* on March 13, 2015, was inspired by living organisms. "Nature makes most small molecule natural products through very simple building-block chemistry. ... So in a sense, nature is already telling us the answer."

The machine takes basic chemical modules and stitches them together to create small molecules. When mixed and matched in different combinations, these building blocks can generate a plethora of new small molecules – made automatically and using relatively little effort.

"History speaks strongly to the major impact that can be achieved when you take a powerful technology like molecule making and put it into the hands of everyone," says Burke, whose long-term vision is to have a website where anyone in the world – a chemist, biologist, engineer, or high school student – can order small molecules to be made and shipped directly to themselves. For now, the machine is already enabling a new biotech company to enhance its drug development efforts; it has the broader potential to expand possibilities in many fields of scientific research. *– Anzar Abbas*

in a virtual reality arena to observe the insect's neurons as it walks. The study, published May 14, 2015, in *Nature*, focused on a part of the fly brain called the ellipsoid body, a donut-shaped structure suspected to be involved in directional movement.

The researchers saw a strong relationship between the fly's orientation relative to its visual surroundings and the neurons activated in the ellipsoid body. When the fly changed direction, even in total darkness, neuronal activity shifted from one part of the ellipsoid body to another, much like the needle of a compass.

"We think we have a window into the fly's internal model of its world," says Vivek, who believes ellipsoid body neurons may share characteristics with human head direction cells. "We're starting to see increasing evidence that the fly may have a lot to tell us about how our own brains work, even when it comes to more complex aspects of cognition."

RARE MUTATION MAKES FLU FATAL

While catching the flu might be an inconsequential annoyance for many of us, the flu virus can prove life threatening in some people. Research led by HHMI Investigator Jean-Laurent Casanova at Rockefeller University tackled the question of why some patients respond differently to the virus than others.

The study, published April 24, 2015, in *Science*, describes a two-year-old girl who had been treated for a severe case of the flu at the Necker Hospital for Sick Children in France. The researchers sequenced her exome to hunt down the reason for her immune system's weakened response to the virus.

What they found was a rare mutation in her *IRF7* gene, known to be responsible for the production of antiviral molecules called interferons. Without the functional protein, a patient would have an inadequate response to the flu virus.

"Now we have proof that life-threatening flu, an infectious disease, can also be a genetic disease," says Casanova, whose past work has identified other mutations that make patients more vulnerable to a variety of infectious diseases.

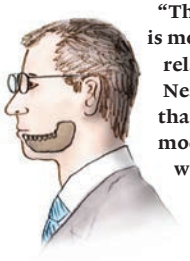
Understanding *IRF7*'s role in fighting the flu virus may allow doctors to consider other treatment options, such as administering interferons, when faced with severe unexplained flu.

JAWBONE REVEALS NEANDERTHAL ORIGINS

Scientists have successfully retrieved and examined DNA from a 40,000-year-old bone.

And not just any old bone. This human jawbone, found in 2002 in a Romanian cave called Peștera cu Oase, dates back to a critical period of Europe's history when modern humans were replacing Neanderthals. Scientists have always wondered how this transition happened. Now, the bone's DNA indicates that it belonged to a modern human whose recent ancestors included Neanderthals.

On average, humans today living outside Sub-Saharan Africa owe about 2 percent of their genes to Neanderthal ancestors. The study, published August 13, 2015, in *Nature*, shows that 6 to 9 percent of the Oase bone's DNA came from Neanderthals.



"The sample is more closely related to Neanderthals than any other modern human we've ever looked at before," says David

Photo: L. Brian Stauffer, Illustration: Leif Parsons

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A Test Tells the Tale

One drop of blood reveals a history of viral infection.

STEPHEN ELLEDGE AND his research team at Brigham and Women's Hospital in Boston have developed a technique that will allow doctors to learn about a patient's entire viral infection history from just a single drop of his or her blood.

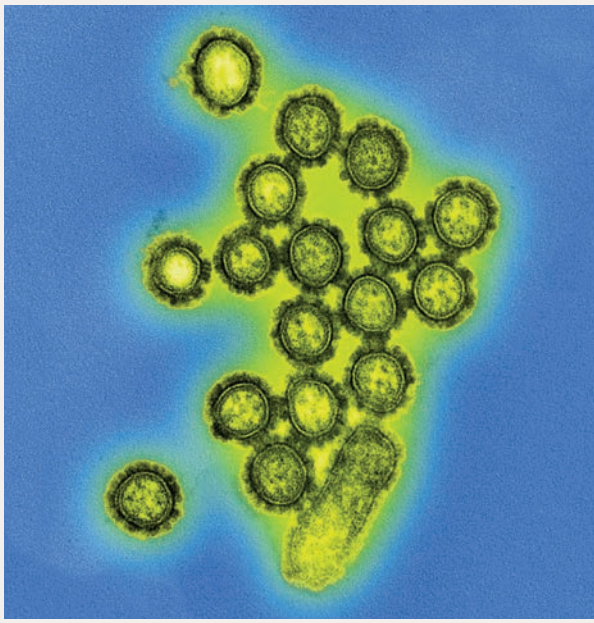
The technique, called VirScan, is a giant leap forward from current tests designed to hunt for individual viruses. VirScan, which costs only $25, searches for all 206 species of viruses known to infect humans. Evaluated in more than 500 people on four continents, the test is proving beneficial in both health care and medical research.

With a more thorough patient clinical history, a doctor can make better treatment decisions. "You could go to the doctor once a year and get all your viruses checked," says Elledge, an HHMI investigator. "It's cheap to do it, it's routine, and your doctor might pick up on new infections … before they do a lot of damage."

Knowing patient viral infection histories can also help scientists studying diseases understand associations previously unknown to them. "We have an ability to now ask, 'Okay, what about autoimmune diseases like type 1 diabetes,'" says Elledge. "Is there an association between that disease and a particular type of viral infection?"

VirScan works by exploiting the fact that we have memories of past viral infections floating in our blood – immune particles that will attack a given virus if it decides to return. The test introduces a host of virus-mimicking molecules into a patient's blood sample to see which ones elicit a response. If a particular virus molecule is attacked, it is likely the person was exposed to that virus in the past. The team published details of the test on June 5, 2015, in *Science*.

Elledge thinks VirScan might see its greatest potential in developing countries, where doctors could use the test to track the extent of new viral epidemics in entire populations. *–Anzar Abbas*



Using a single drop of blood, a new test can detect antibodies against more than 200 species of virus, including this influenza virus.

Photo: National Institute of Allergy and Infectious Diseases, Illustration: Leif Parsons

IN BRIEF

Reich, an HHMI investigator at Harvard Medical School, who co-led the study with Svante Pääbo at the Max Planck Institute in Germany.

The data suggest that the Oase individual had a Neanderthal ancestor as recently as four to six generations back. "It's an incredibly unexpected thing," Reich says. "In the last few years, we've documented interbreeding between Neanderthals and modern humans. But we never thought we'd be so lucky to find someone so close to the event."

LESSONS FROM PARROTS

If you've wondered how parrots can imitate humans so well, you're in good company – many scientists have marveled at the behavior. Among them is HHMI Investigator Erich Jarvis of Duke University, who studies how certain birds mimic humans.

Scientists have known that the brains of certain vocal-learning bird species have specialized neurons involved in learning to produce sounds, but they did not know why parrots are better at imitating compared to other rare vocal-learning bird groups. In a study published June 24, 2015, in *PLOS ONE*, Jarvis and his postdoc Mukta Chakraborty found that parrots have a "shell system" of vocal-learning neurons not found in other species. This shell surrounds a "core system" found in songbirds and hummingbirds.

By comparing nine different parrot species, the team learned that the larger this shell was in a particular species' brain, the better those birds were at imitating spoken language. This suggested the shell might play a role in the skill.

Jarvis hypothesizes that the shell emerged from a duplication of the core language region millions of years ago, developing a more complex function as it evolved. "Maybe in the human brain we have multiple duplications of an ancient pathway that's controlling our complex speech abilities."

COMPLEX SENSORY CIRCUITS

We rarely use just one sense at a time. Even when we eat, our experience is affected by a food's look, feel, and smell, as well as its taste. Other creatures' brains appear to be wired similarly.

Fruit fly larvae seem to integrate cues from multiple senses, too. For example, a larva is more likely to roll over to defend itself from a predator if it's sensing a noxious stimulus – stinging, for example – and physical cues at the same time, according to findings from scientists at Janelia Research Campus.

Janelia Group Leaders Marta Zlatic and Albert Cardona led a team that mapped the neurons involved in this behavior. In a study published April 20, 2015, in *Nature*, the researchers mechanically stimulated fruit fly larvae while activating their nociceptor, or injury-sensing, neurons to understand the circuits involved from the point of stimulation to when the larva rolls over.

Surprisingly, they found that the circuits for nociceptive and mechanical stimulation were integrated on multiple levels, resulting in a very sophisticated structure. "Initially, I would have thought this circuit would be simpler, but the complex network could really allow the animal to do a complex computation and react to very particular combinations of cues," says Zlatic.

The team has made its electron micrograph information freely available, with the hope that it will help in mapping the insect's entire nervous system.