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Winter 2023
Dear Friends,

In my first year as Department Head, I focused on learning the different aspects of this remarkable and challenging job. Now in my second year, I have turned to thinking strategically about the department's future: how to maintain robustness in the diverse array of research programs distinguishing our department and how to keep us at the forefront of training world-leading researchers.

In this vein, my mind turns to our graduate students and the future of the BCS PhD program. The program remains one of the highest-rated in the world, and also highly selective: this year, our faculty are reviewing a record-high 800 applications to the program for an estimated 15 new student slots this fall. BCS is remarkably fortunate to attract interest from the best students in the world, and the faculty and I take very seriously our responsibility to offer them superb scientific training in a community and environment where they are welcomed and supported, and mentored on a path to success.

Our students invest their time and energy in our courses, labs, and community, and we invest our time and resources in them because they are the keys to the future of brain science. Their fresh eyes find new problems to tackle, new ways to crack old problems, and new intersections of theory, discovery, and technique that propel our science forward.

Our challenge today is making this exceptional experience available to as many students as we can, and to that end we have begun a process to articulate a vision for the department and goals to support it. One of the highest priorities is finding the financial resources to expand the number of students we can take into our graduate program. (Obligatory sales pitch: If you’re interested in supporting our efforts, please get in touch!)

Of the many ways I hope to make BCS a better place during my time as Department Head, strengthening our graduate program could be the most meaningful.

On a more personal note, as you may know, last fall I was away on medical leave; I’m thankful to report a strong recovery. Our Associate Department Heads, Laura Schulz and Josh McDermott, skillfully led the department in my absence. I am immensely grateful for their ongoing support, and, especially, for keeping everything running smoothly while I was away.

Michale Fee, PhD
Glen V. and Phyllis F. Dorflinger Professor of Neuroscience
Head, Department of Brain and Cognitive Sciences
New Faculty

Nidhi Seethapathi, who joined the faculty in January 2022, seeks new approaches to understanding movement and how it is controlled.

The computational models that Seethapathi builds in her lab aim to predict how humans will move under different conditions. If a person is placed in an unfamiliar environment and asked to navigate a course under time pressure, what path will they take? How will they move their limbs, and what forces will they exert? How will their movements change as they become more comfortable on the terrain? Seethapathi uses principles derived from a number of fields such as robotics, applied mathematics, and machine learning, to build models that answer these questions. Her group then tests these theories by placing real people in the same scenarios and observing their behavior.

Seethapathi’s hope is that her findings will inform the way doctors, therapists, and engineers help patients regain control over their movements after an injury or stroke, or learn to live with movement disorders like Parkinson’s disease.

To capture the complexity of human movement, Seethapathi and her team are devising new tools that will let them monitor people's movements outside the lab. They are also drawing on data from other fields, from architecture to physical therapy, and even from studies of other animals. “If I have general principles, they should be able to tell me how modifications in the body or in how the brain is connected to the body would lead to different movements,” she says. “I’m really excited about generalizing these principles across timescales and species.”

Jennifer Michalowski

Guangyu Robert Yang builds plastic models of brains — plastic as in capable of learning by altering the connection patterns among units. “In particular, I’m interested in building neural network models of brain functions, particularly cognition,” he says.

Yang joined the MIT faculty in the summer of 2021 as an assistant professor both in BCS and on the artificial intelligence and decision-making faculty of the Department of Electrical Engineering and Computer Science in the MIT Schwarzman College of Computing (SCC). Shared appointments like his are designed to maximize collaboration between the College and other MIT schools and departments.

Yang’s research connecting artificial neural networks to the actual functions of cognition is distinctive in its close interplay between computational and biological systems, and ambitious in its use of computational modeling to understand the optimization of neural systems which function to accomplish multiple tasks. As a postdoc with theoretical neuroscientist Larry Abbott at Columbia University, Yang applied principles of machine learning to study the evolution and organization of the olfactory system. The neural networks his models generated show important similarities to the biological circuitry, suggesting that the structure of the olfactory system evolved in order to optimally enable the specific tasks needed for odor recognition.

“MIT has always been one of my top choices,” says Yang. “I’m very excited about the people and the mindset here. I think there’s a strong urge shared by many faculty, students, and researchers here to build and use neural network models of brains. I’m also very excited about the interdisciplinary nature of my position. Besides the joint appointment between BCS and SCC, BCS on its own is already combining neuroscience and cognitive science.”

Tristan Davies

Guangyu Robert Yang. Photo: Gretchen Ertl
Understanding reality through algorithms

Neuroscience PhD student Fernanda De La Torre uses complex algorithms to investigate philosophical questions about perception and reality

Leah Campbell | School of Science

Although Fernanda De La Torre still has several years left in her graduate studies, she's already dreaming big when it comes to what the future has in store for her.

“I dream of opening up a school one day where I could bring this world of understanding of cognition and perception into places that would never have contact with this,” she says.

It's that kind of ambitious thinking that’s gotten De La Torre, a doctoral student in MIT’s Department of Brain and Cognitive Sciences, to this point. A recipient of the prestigious Paul and Daisy Soros Fellowship for New Americans, De La Torre has found at MIT a supportive, creative research environment that’s allowed her to delve into the cutting-edge science of artificial intelligence. But she's still driven by an innate curiosity about human imagination and a desire to bring that knowledge to the communities in which she grew up.

An unconventional path to neuroscience

De La Torre's first exposure to neuroscience wasn’t in the classroom, but in her daily life. As a child, she watched her younger sister struggle with epilepsy. At 12, she crossed into the United States from Mexico illegally to reunite with her mother, exposing her to a whole new language and culture. Once in the States, she had to grapple with her mother's shifting personality in the midst of an abusive relationship. “All of these different things I was seeing around me drove me to want to better understand how the mind works.”

But finding an outlet for that intellectual curiosity was challenging. As an undocumented immigrant, her access to financial aid was limited. Her high school was also underfunded and lacked elective options. Mentors along the way, though, encouraged the aspiring scientist, and through a program at her school, she was able to take community college courses to fulfill basic educational requirements.

It took an inspiring amount of dedication to her education, but De La Torre made it to Kansas State University for her undergraduate studies, where she majored in computer science and math. At Kansas State, she was able to get her first real taste of research. “I was just fascinated by the questions they were asking and this entire space I hadn't encountered,” says De La Torre of her experience working in a visual cognition lab and discovering the field of computational neuroscience.
Her research experience in cognition led her to a machine learning lab led by William Hsu, a computer science professor. There, De La Torre became enamored by the possibilities of using computation to model the human brain. Hsu's support also convinced her that a scientific career was a possibility. “He always made me feel like I was capable of tackling big questions,” she says fondly.

With the confidence imparted in her at Kansas State, De La Torre came to MIT in 2019 as a post-baccalaureate student in the lab of Tomaso Poggio, the Eugene McDermott Professor of Brain and Cognitive Sciences and an investigator at the McGovern Institute for Brain Research. The post-baccalaureate Research Scholars program is designed to provide additional research and academic training for outstanding recent college graduates who are from historically underrepresented minority groups or economically disadvantaged backgrounds.

With Poggio, De La Torre began working on deep-learning theory, an area of machine learning focused on how artificial neural networks modeled on the brain can learn to recognize patterns. “We don’t fully understand how these networks can go from knowing nothing and just being a bunch of numbers to outputting things that make sense,” says De La Torre.

De La Torre's primary advisor, though, is Associate Professor Josh McDermott, who leads the Laboratory for Computational Audition. With McDermott, De La Torre is attempting to understand how the brain integrates vision and sound. There are many unanswered questions about how our brains combine multiple signals into a coherent impression of the world. Many of the questions are raised by audiovisual illusions in which what we hear changes what we see. For example, if one sees a video of two discs passing each other, but the clip contains the sound of a collision, the brain will perceive that the discs are bouncing off, rather than passing through each other. Given an ambiguous image, that simple auditory cue is all it takes to create a different perception of reality.

“Telling us different things and, yet, we have to combine them somehow to make sense of the world,” says De La Torre.

De La Torre is using behavioral experiments to probe how the human brain makes sense of multisensory cues to construct a particular perception. Eventually she hopes to take the experiment into virtual reality.

Having the space to undertake intellectual explorations, and colleagues who encourage it, is one of De La Torre's favorite parts of MIT. “Beyond professors, there's also a lot of students whose way of thinking just amazes me,” she says. “I see a lot of goodness and excitement for science and a little bit of — it's not nerdiness, but a love for very niche things — and I just kind of love that.”

Fortunately, De La Torre says she was able to overcome those insecurities, both through a growing enthusiasm for the field and through the support of Poggio and her other colleagues in BCS. When the opportunity came to apply to the department’s PhD program, she jumped on it. “It was just knowing these kinds of mentors are here and that they cared about their students,” says De La Torre of her decision to stay on at MIT for graduate studies. “That was really meaningful.”

Expanding notions of reality and imagination

In her two years so far in the graduate program, De La Torre’s work has expanded the understanding of neural networks and their applications to the study of the human brain. Working with Guangyu Robert Yang, an assistant professor in the departments of Brain and Cognitive Sciences and Electrical Engineering and Computer Sciences and an associate investigator at the McGovern Institute, she’s engaged in what she describes as more philosophical questions about how one develops a sense of self as an independent being. She’s interested in how that self-consciousness develops and why it might be useful.

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“There’s something interesting happening where our brains are receiving two signals telling us different things and, yet, we have to combine them somehow to make sense of the world,” she says.

De La Torre is using behavioral experiments to probe how the human brain makes sense of multisensory cues to construct a particular perception. Eventually she hopes to take the experiment into virtual reality. 
BCS researchers discover that silent synapses are abundant in the adult brain

These immature connections may explain how the adult brain is able to form new memories and absorb new information

Anne Trafton | MIT News

MIT neuroscientists have discovered that the adult brain contains millions of “silent synapses” — immature connections between neurons that remain inactive until they’re recruited to help form new memories.

Until now, it was believed that silent synapses were present only during early development, when they help the brain learn the new information that it’s exposed to early in life. However, the MIT study revealed that in adult mice, about 30 percent of all synapses in the brain’s cortex are silent.

The existence of these silent synapses may help to explain how the adult brain is able to continually form new memories and learn new things without having to modify existing conventional synapses, the researchers say.

“These silent synapses are looking for new connections, and when important new information is presented, connections between the relevant neurons are strengthened. This lets the brain create new memories without overwriting the important memories stored in mature synapses, which are harder to change,” says Dimitra Vardalaki, an MIT graduate student and the lead author of the new study.

Mark Harnett, an associate professor in MIT’s Department of Brain and Cognitive Sciences and a member of the McGovern Institute for Brain Research, is the senior author of the paper, which appeared in Nature. Kwanghun Chung, a BCS and Picower Institute professor as well as an associate professor of chemical engineering at MIT, is also an author.

A surprising discovery

When scientists first discovered silent synapses decades ago, they were seen primarily in the brains of young mice and other animals. During early development, these synapses are believed to help the brain acquire the massive amounts of information that babies need to learn about their environment and how to interact with it. In mice, these synapses...
were believed to disappear by about 12 days of age (equivalent to the first months of human life).

However, some neuroscientists have proposed that silent synapses may persist into adulthood and help with the formation of new memories. Evidence for this has been seen in animal models of addiction, which is thought to be largely a disorder of aberrant learning.

Theoretical work in the field from Stefano Fusi and Larry Abbott of Columbia University has also proposed that neurons must display a wide range of different plasticity mechanisms to explain how brains can both efficiently learn new things and retain them in long-term memory. In this scenario, some synapses must be established or modified easily, to form the new memories, while others must remain much more stable, to preserve long-term memories.

In the new study, the MIT team did not set out specifically to look for silent synapses. Instead, they were following up on an intriguing finding from a previous study in Harnett’s lab. In that paper, the researchers showed that within a single neuron, dendrites — antenna-like extensions that protrude from neurons — can process synaptic input in different ways, depending on their location.

As part of that study, the researchers tried to measure neurotransmitter receptors in different dendritic branches, to see if that would help to account for the differences in their behavior. To do that, they used a technique called eMAP (epitope-preserving Magnified Analysis of the Proteome), developed by Chung.

Using this technique, researchers can physically expand a tissue sample and then label specific proteins in the sample, making it possible to obtain super-high-resolution images.

While they were doing that imaging, they made a surprising discovery. “The first thing we saw, which was super bizarre and we didn’t expect, was that there were filopodia everywhere,” Harnett says.

Filopodia, thin membrane protrusions that extend from dendrites, have been seen before, but neuroscientists didn’t know exactly what they do. That’s partly because filopodia are so tiny that they are difficult to see using traditional imaging techniques.

After making this observation, the MIT team set out to try to find filopodia in other parts of the adult brain, using the eMAP technique. To their surprise, they found filopodia in the mouse visual cortex and other parts of the brain, at a level 10 times higher than previously seen. They also found that filopodia had neurotransmitter receptors called NMDA receptors, but no AMPA receptors.

A typical active synapse has both of these types of receptors, which bind the neurotransmitter glutamate. NMDA receptors normally require cooperation with AMPA receptors to pass signals because NMDA receptors are blocked by magnesium ions at the normal resting potential of neurons. Thus, when AMPA receptors are not present, synapses that have only NMDA receptors cannot pass along an electric current and are referred to as “silent.”

**Unsilencing synapses**

To investigate whether these filopodia might be silent synapses, the researchers used a modified version of an experimental technique known as patch clamping. This allowed them to monitor the electrical activity generated at individual filopodia as they tried to stimulate them by mimicking the release of the neurotransmitter glutamate from a neighboring neuron.

Using this technique, the researchers found that glutamate would not generate any electrical signal in the filopodium receiving the input, unless the NMDA receptors were experimentally unblocked. This offers strong support for the theory the filopodia represent silent synapses within the brain, the researchers say.

The researchers also showed that they could “unsilence” these synapses by combining glutamate release with an electrical current coming from the body of the neuron. This combined stimulation leads to accumulation of AMPA receptors in the silent synapse, allowing it to form a strong connection with the nearby axon that is releasing glutamate.

The researchers found that converting silent synapses into active synapses was much easier than altering mature synapses.

“If you start with an already functional synapse, that plasticity protocol doesn’t work,” Harnett says. “The synapses in the adult brain have a much higher threshold, presumably because you want those memories to be pretty resilient. You don’t want them constantly being overwritten. Filopodia, on the other hand, can be captured to form new memories.”

**“Flexible and robust”**

The findings offer support for the theory proposed by Abbott and Fusi that the adult brain includes highly plastic synapses that can be recruited to form new memories, the researchers say.

“This paper is, as far as I know, the first real evidence that this is how it actually works in a mammalian brain,” Harnett says. “You need flexibility to acquire new information, but you also need stability to retain the important information.”

The researchers are now looking for evidence of these silent synapses in human brain tissue. They also hope to study whether the number or function of these synapses is affected by factors such as aging or neurodegenerative disease.
Alzheimer’s risk gene undermines insulation of brain’s “wiring”

In people carrying the APOE4 risk variant, a key brain cell type mismanages cholesterol needed to insulate neurons properly — another sign that APOE4 contributes to disease by disrupting lipids in the brain

David Orenstein | Picower Institute

It’s well-known that carrying one copy of the APOE4 gene variant increases one’s risk for Alzheimer’s disease threefold and two copies about tenfold, but the fundamental reasons why, and what can be done to help patients, remain largely unknown. A study published by an MIT-based team in *Nature* provides some new answers as part of a broader line of research that has demonstrated APOE4’s consequences, cell-type-by-cell-type, in the brain.

The new study combines evidence from postmortem human brains, lab-based human brain cell cultures, and Alzheimer’s model mice to show that when people have one or two copies of APOE4, rather than the more common and risk-neutral APOE3 version, cells called oligodendrocytes mismanage cholesterol, failing to transport the fat molecule to wrap the long vine-like axon “wiring” that neurons project to make brain circuit connections. Deficiency of this fatty insulation, called myelin, may be a significant contributor to the pathology and symptoms of Alzheimer’s disease because without proper myelination, communications among neurons are degraded.

Recent studies by the research group, led by MIT Professor Li-Huei Tsai, director of The Picower Institute for Learning and Memory and the Aging Brain Initiative at MIT, have found distinct ways that APOE4 disrupts how fat molecules, or lipids, are handled by key brain cell types including neurons, astrocytes, and microglia. In both the new and earlier studies, the team has identified compounds that appear in the lab to correct these different problems, yielding potential pharmaceutical-based treatment strategies.

The new study extends that work not only by discovering how APOE4 disrupts myelination, but also by providing the first systematic analysis across major brain cell types using single nucleus RNA sequencing (snRNAseq) to compare how gene expression differs in people with APOE4 compared to APOE3.

“Many methods to examine myelination

Some results reflected known Alzheimer’s pathology, but other patterns were novel. One in particular showed that APOE4-carrying oligodendrocytes exhibited greater expression of cholesterol synthesis genes and disruptions to cholesterol transport. The more APOE4 copies people had, the greater the effect. This was especially interesting given results from a prior analysis by Tsai’s and Kellis’s labs in 2019 that linked Alzheimer’s disease to reduced expression of myelination genes among oligodendrocytes.

Using a variety of techniques to look directly at the tissue, the team saw that in APOE4 brains, aberrant amounts of cholesterol accumulated within cell bodies, especially of oligodendrocytes, but was relatively lacking around neural axons.

The researchers identified compounds that appear to correct the problems they identified in the lab, yielding potential pharmaceutical treatments.

“Paper shows very clearly from the snRNAseq of postmortem human brains in a genotype-specific manner that APOE4 influences different brain cell types very distinctly,” says Tsai, a member of MIT’s Department of Brain and Cognitive Sciences faculty. “We see convergence of lipid metabolism being disrupted, but when you really look into further detail at the kind of lipid pathways being disturbed in different brain cell types, they are all different.

“I feel that lipid dysregulation could be this very fundamental biology underlying a lot of the pathology we observe,” she says.

The paper’s lead authors are Joel Blanchard, an assistant professor at Mt. Sinai’s Icahn School of Medicine who began the work as a postdoc in Tsai’s MIT lab; Djuna Von Maydell and Leyla Akay, who are graduate students in Tsai’s lab; and Jose Davila Velderrain, a research group leader at Human Technopole and former postdoc in the lab of co-corresponding author Manolis Kellis, a professor of computer science at MIT.

The researchers identified compounds that appear to correct the problems they identified in the lab, yielding potential pharmaceutical treatments.
have a role in cholesterol transport, and indeed transported less cholesterol out to their membranes. Later, when they were co-cultured with neurons, the APOE oligodendrocytes failed to myelinate the neurons as well as APO3 cells did, regardless of whether the neurons carried APOE4 or APOE3.

The team also observed that in postmortem brains there was less myelination in APOE4 carriers than APOE3 carriers. For instance, the sheaths around axons running through the corpus callosum (the structure that connects brain hemispheres) were notably thinner in APOE4 brains. The same was true in mice engineered to harbor human APOE4 versus those engineered to have APOE3.

**A productive intervention**

Eager to find a potential intervention, the team focused on drugs that affect cholesterol, including statins (which suppress synthesis) and cyclodextrin, which aids cholesterol transport. The statins didn’t help, but applying cyclodextrin to APOE4 oligodendrocyte cultured in a dish reduced accumulation of cholesterol within the cells and improved myelination in co-cultures with neurons. Moreover, it also had these effects in APOE4 mice.

Finally, the team treated some APOE4 mice with cyclodextrin, left others untreated, and subjected them all to two different memory tests. The cyclodextrin-treated mice performed both tests significantly better, suggesting an association between improved myelination and improved cognition.

Tsai said a clear picture is emerging in which intervening to correct specific lipid dysregulations by cell type could potentially help counteract APOE4’s contributions to Alzheimer’s pathology.

“It’s encouraging that we’ve seen a way to rescue oligodendrocyte function and myelination in lab and mouse models,” Tsai says. “But in addition to oligodendrocytes, we may also need to find clinically effective ways to take care of microglia, astrocytes, and vasculature to really combat the disease.”

In post-mortem brain tissue from APOE3 carriers black gold staining highlights clear streaks of myelin (top row). In people with one copy of APOE4 (bottom row) myelination is less evident. Image: Tsai Lab/The Picower Institute
These neurons have food on the brain

MIT scientists have discovered a population of neurons that light up whenever we see images of food

Anne Trafton | MIT News

A gooey slice of pizza. A pile of crispy French fries. Ice cream dripping down a cone on a hot summer day. When you look at any of these foods, a specialized part of your visual cortex lights up, according to a new study from MIT neuroscientists.

This newly discovered population of food-responsive neurons is located in the ventral visual stream, alongside populations that respond specifically to faces, bodies, places, and words. The unexpected finding may reflect the special significance of food in human culture, the researchers say.

“Food is central to human social interactions and cultural practices. It’s not just sustenance,” says Nancy Kanwisher, the Walter A. Rosenblith Professor of Cognitive Neuroscience and a member of MIT’s McGovern Institute for Brain Research and Center for Brains, Minds, and Machines. “Food is core to so many elements of our cultural identity, religious practice, and social interactions, and many other things that humans do.”

The findings, based on an analysis of a large public database of human brain responses to a set of 10,000 images, raise many additional questions about how and why this neural population develops. In future studies, the researchers hope to explore how people’s responses to certain foods might differ depending on their likes and dislikes, or their familiarity with certain types of food.

MIT postdoc Meenakshi Khosla is the lead author of the paper, along with MIT research scientist N. Apurva Ratan Murty. The study appeared in the journal Current Biology.

Visual categories

More than 20 years ago, while studying the ventral visual stream, the part of the brain that recognizes objects, Kanwisher discovered cortical regions that respond selectively to faces. Later, she and other scientists discovered other regions that respond selectively to places, bodies, or words. Most of those areas were discovered when researchers specifically set out to look for them. However, that hypothesis-driven approach can limit what you end up finding, Kanwisher says.

“There could be other things that we might not think to look for,” she says. “And even when we find something, how do we know that that’s actually part of the basic dominant structure of that pathway, and not something we found just because we were looking for it?”

To try to uncover the fundamental structure of the ventral visual stream, Kanwisher and Khosla decided to analyze a large, publicly available dataset of full-brain functional magnetic resonance imaging (fMRI) responses from eight human subjects as they viewed thousands of images.

“We wanted to see when we apply a data-driven, hypothesis-free strategy, what kinds of selectivities pop up, and whether those are consistent with what had been discovered before. A second goal was to see if we could discover novel selectivities that either haven’t been hypothesized before, or that have remained hidden due to the lower spatial resolution of fMRI data,” Khosla says.

To do that, the researchers applied a mathematical method that allows them to discover neural populations that can’t be identified from traditional fMRI data. An fMRI image is made up of many voxels — three-dimensional units that represent a cube of brain tissue. Each voxel contains hundreds of thousands of neurons, and if some of those neurons belong to smaller populations that respond to one type of visual input, their responses may be drowned out by other populations within the same voxel.

The new analytical method, which Kanwisher’s lab has previously used on fMRI data from the auditory cortex, can tease out responses of neural populations within each voxel of fMRI data.

“We were first quite puzzled by the results. Things like apples and corn and pasta all look so unlike each other, yet we found a single population that responds similarly to all these diverse items.”

– MIT postdoc Meenakshi Khosla
Using this approach, the researchers found four populations that corresponded to previously identified clusters that respond to faces, places, bodies, and words. “That tells us that this method works, and it tells us that the things that we found before are not just obscure properties of that pathway, but major, dominant properties,” Kanwisher says.

Intriguingly, a fifth population also emerged, and this one appeared to be selective for images of food. “We were first quite puzzled by this because food is not a visually homogenous category,” Khosla says. “Things like apples and corn and pasta all look so unlike each other, yet we found a single population that responds similarly to all these diverse food items.”

The food-specific population, which the researchers call the ventral food component (VFC), appears to be spread across two clusters of neurons, located on either side of the FFA. The fact that the food-specific populations are spread out between other category-specific populations may help explain why they have not been seen before, the researchers say.

“We think that food selectivity had been harder to characterize before because the populations that are selective for food are intermingled with other nearby populations that have distinct responses to other stimulus attributes. The low spatial resolution of fMRI prevents us from seeing this selectivity because the responses of different neural populations get mixed in a voxel,” Khosla says.

“The technique which the researchers used to identify category-sensitive cells or areas is impressive, and it recovered known category-sensitive systems, making the food category findings most impressive,” says Paul Rozin, a professor of psychology at the University of Pennsylvania, who was not involved in the study. “I can't imagine a way for the brain to reliably identify the diversity of foods based on sensory features. That makes this all the more fascinating, and likely to clue us in about something really new.”

The researchers also hope to study when and how this region becomes specialized during early childhood, and what other parts of the brain it communicates with. Another question is whether this food-selective population will be seen in other animals such as monkeys, who do not attach the cultural significance to food that humans do.
Cognitive scientists have long sought to understand what makes some sentences more difficult to comprehend than others. Any account of language comprehension, researchers believe, would benefit from understanding difficulties in comprehension.

In recent years researchers successfully developed two models explaining two significant types of difficulty in understanding and producing sentences. While these models successfully predict specific patterns of comprehension difficulties, their predictions are limited and don’t fully match results from behavioral experiments. Moreover, until recently researchers couldn’t integrate these two models into a coherent account.

A new study led by researchers from the MIT Department of Brain and Cognitive Sciences now provides such a unified account for difficulties in language comprehension. Building on recent advances in machine learning, the researchers developed a model that better predicts the ease, or lack thereof, with which individuals produce and comprehend sentences. They recently published their findings in the *Proceedings of the National Academy of Sciences (PNAS)*.

The senior authors of the paper are BCS professors Roger Levy and Edward (Ted) Gibson. The lead author is Levy and Gibson’s former visiting student, Michael Hahn, now a professor at Saarland University. The second author is Richard Futrell, another former student of Levy and Gibson who is now a professor at the University of California, Irvine.

“This is not only a scaled-up version of the existing accounts for comprehension difficulties,” says Gibson; “we offer a new underlying theoretical approach that allows for better predictions.”

The researchers built on the two existing models to create a unified theoretical account of comprehension difficulty. Each of these older models identifies a distinct culprit for frustrated comprehension: difficulty in expectation and difficulty in memory retrieval. We experience difficulty in expectation when a sentence doesn’t easily allow us to anticipate its upcoming words. We experience difficulty in memory retrieval when we have a hard time tracking a sentence featuring a complex structure of embedded clauses, such as: “The fact that the doctor who the lawyer distrusted annoyed the patient was surprising.”

In 2020, Richard Futrell first devised a theory unifying these two models. He argued that limits in memory don’t affect only retrieval in sentences with embedded clauses but plague all language comprehension; our memory limitations don’t allow us to perfectly represent sentence contexts during language comprehension more generally.

Thus, according to this unified model, memory constraints can create a new source of difficulty in anticipation. We can have difficulty anticipating an upcoming word in a sentence even if the word should be easily predictable from context — in case that the sentence context itself is difficult to hold in memory. Consider, for example, a sentence beginning with the words “Bob threw the trash [...];” we can easily anticipate the final word — “out”. But if the sentence context...
preceding the final word is more complex, difficulties in expectation arise: “Bob threw the old trash that had been sitting in the kitchen for several days [out].”

Researchers quantify comprehension difficulty by measuring the time it takes readers to respond to different comprehension tasks. The longer the response time, the more challenging the comprehension of a given sentence. Results from prior experiments showed that Futrell’s unified account predicted readers’ comprehension difficulties better than the two older models. But his model didn’t identify which parts of the sentence we tend to forget — and how exactly this failure in memory retrieval obfuscates comprehension.

Hahn’s new study fills in these gaps. As in Futrell’s original model, the researchers begin with the idea that our mind, due to memory limitations, doesn’t perfectly represent the sentences we encounter. But to this they add the theoretical principle of cognitive efficiency. They propose that the mind tends to deploy its limited memory resources in a way that optimizes its ability to accurately predict new word inputs in sentences.

This notion leads to several empirical predictions. According to one key prediction, readers compensate for their imperfect memory representations by relying on their knowledge of the statistical co-occurrences of words in order to implicitly reconstruct the sentences they read in their minds. Sentences that include rarer words and phrases are therefore harder to remember perfectly, making it harder to anticipate upcoming words. As a result, such sentences are generally more challenging to comprehend.

To evaluate whether this prediction matches our linguistic behavior, the researchers utilized GPT-2, an AI natural language tool based on neural network modeling. This machine learning tool, first made public in 2019, allowed the researchers to test the model on large-scale text data in a way that wasn’t possible before.

“This is a wonderful illustration of how modern tools of machine learning can help develop cognitive theory and our understanding of how the mind works,” says Gibson; “we couldn’t have conducted this research here even a few years ago.”

The researchers fed the machine learning model a set of sentences with complex embedded clauses such as, “The report that the doctor who the lawyer distrusted annoyed the patient was surprising.” The researchers then took these sentences and replaced their opening nouns — “report” in the example above — with other nouns, each with their own probability to occur with a following clause or not. Some nouns made the sentences to which they were slotted easier for the AI program to “comprehend.” For instance, the model was able to more accurately predict how these sentences end when they began with the common phrasing “The fact that” than when they began with the rarer phrasing “The report that.”

The researchers then set out to corroborate the AI-based results by conducting experiments with participants who read similar sentences. Their response times to the comprehension tasks were similar to that of the model’s predictions.

These results demonstrate that the new model outtrivels existing models in predicting how humans process language. Another advantage the model demonstrates is its ability to offer varying predictions from language to language.

“Prior models knew to explain why certain language structures, like sentences with embedded clauses, may be generally harder to work with within the constraints of memory, but our new model can explain why the same constraints behave differently in different languages,” says Levy.

According to Levy, further research on the model is needed to identify causes of inaccurate sentence representation other than embedded clauses.
Whether speaking Turkish or Norwegian, the brain’s language network looks the same

Over several decades, neuroscientists have created a well-defined map of the brain’s “language network,” or the regions that are specialized for processing language. Found primarily in the left hemisphere, this network includes regions within Broca’s area, as well as in other parts of the frontal and temporal lobes.

However, the vast majority of those mapping studies have been done in English speakers. MIT neuroscientists have now performed brain imaging studies of speakers of 45 different languages. The results show that the speakers’ language networks appear to be essentially the same as those of native English speakers.

The findings establish that the location and key properties of the language network appear to be universal. The work also lays the groundwork for future studies of linguistic elements that would be difficult or impossible to study in English speakers because English doesn’t have those features. Evelina Fedorenko, the Middleton Career Development Associate Professor of Neuroscience at BCS and a member of the McGovern Institute, is the senior author of the study, which appeared in *Nature Neuroscience*. Saima Malik-Moraleda, a PhD student in BCS and the Speech and Hearing Bioscience and Technology program at Harvard University, and Dima Ayyash, a former research assistant, are the lead authors of the paper.

Small studies of 40Hz sensory stimulation confirm safety, suggest Alzheimer’s benefits

A pair of early-stage clinical studies testing the safety and efficacy of 40Hz sensory stimulation to treat Alzheimer’s disease has found that the potential therapy was well tolerated, produced no serious adverse effects, and was associated with significant neurological and behavioral benefits among a small cohort of participants.

“Volunteers did not experience any safety issues and used our experimental light and sound devices in their homes consistently,” said Li-Huei Tsai, BCS and Picower professor who is the senior author of the paper published in *PLOS ONE*. “While we are also encouraged to see some significant positive effects on the brain and behavior, we are interpreting them cautiously given our study’s small sample size and brief duration. These results are not sufficient evidence of efficacy, but we believe they clearly support proceeding with more extensive study of 40Hz sensory stimulation as a potential non-invasive therapeutic for Alzheimer’s disease.”

In three studies spanning 2016-2019, Tsai’s lab discovered that exposing mice to light flickering or sound clicking at the gamma-band brain rhythm frequency of 40Hz — or employing the light and sound together — produced widespread beneficial effects. Treated mice modeling Alzheimer’s disease pathology experienced improvements in learning and memory; reduced brain atrophy, neuron, and synapse loss; and showed lower levels of the hallmark Alzheimer’s proteins amyloid beta and phosphorylated tau compared to untreated controls. The stimulation appears to produce these effects by increasing the power and synchrony of the 40Hz brain rhythm, which the lab has shown profoundly affects the activity of several types of brain cells, including the brain’s vasculature.

David Orenstein | Picower Institute
New CRISPR-based tool inserts large DNA sequences at desired sites in cells

Building on the CRISPR gene-editing system, MIT researchers have designed a new tool that can snip out faulty genes and replace them with new ones, in a safer and more efficient way. Using this system, the researchers showed that they could deliver genes as long as 36,000 DNA base pairs to several types of human cells, as well as to liver cells in mice. The new technique, known as PASTE, could hold promise for treating diseases caused by defective genes with a large number of mutations, such as cystic fibrosis.

“It’s a new genetic way of potentially targeting these really hard to treat diseases,” says Omar Abudayyeh, a McGovern Fellow at MIT’s McGovern Institute for Brain Research. “We wanted to work toward what gene therapy was supposed to do at its original inception, which is to replace genes, not just correct individual mutations.”

The new tool combines the precise targeting of CRISPR-Cas9, a set of molecules originally derived from bacterial defense systems, with enzymes called integrases, which viruses use to insert their own genetic material into a bacterial genome.

“Just like CRISPR, these integrases come from the ongoing battle between bacteria and the viruses that infect them,” says Jonathan Gootenberg, also a McGovern Fellow. “It speaks to how we can keep finding an abundance of interesting and useful new tools from these natural systems.”

Gootenberg and Abudayyeh are the senior authors of the new study, which appeared in *Nature Biotechnology*. The lead authors of the study are MIT technical associates Matthew Yarnall and Rohan Krajewski, former MIT graduate student Eleonora Ioannidi, and MIT graduate student Cian Schmitt-Ulms.

Anne Trafton | MIT News

Advanced imaging reveals mired migration of neurons in Rett syndrome lab models

Using an innovative microscopy method, scientists at BCS and the Picower Institute observed how newborn neurons struggle to reach their proper places in advanced human brain tissue models of Rett syndrome, producing new insight into how developmental deficits observed in the brains of patients with the devastating disorder may emerge.

Rett syndrome, which is characterized by symptoms including severe intellectual disability and impaired social behavior, is caused by mutations in the gene MECP2. To gain new insight into how the mutation affects the early stages of human brain development, researchers in the lab of Mriganka Sur, Newton Professor of Neuroscience in BCS, grew 3D cell cultures called cerebral organoids, or minibrains, using cells from people with MECP2 mutations and compared them to otherwise identical cultures without the mutations. Then the team led by postdoc Murat Yildirim examined the development of each type of minibrain using an advanced imaging technology called third harmonic generation (THG) three-photon microscopy. THG, which Yildirim has helped to pioneer in Sur’s lab working with MIT mechanical engineering Professor Peter So, allows for very high-resolution imaging deep into live, intact tissues without having to add any chemicals to label cells. Previous organoid imaging studies have required using technologies that cannot image all the way through the 3D tissue, or require killing the cultures.

The THG system allowed them to track the migration of newborn neurons from the rim around open spaces in the minibrains to the outer edge, which is analogous to the brain’s cortex. The nascent neurons in the minibrains modeling Rett syndrome moved slowly and in meandering paths compared to the faster motion in straighter lines exhibited by the cells without MECP2 mutation. Sur said the consequences of such migration deficits are consistent with what scientists hypothesize is going on in Rett syndrome fetuses. The study was published in *eLife*.

David Orenstein | Picower Institute
After a lifetime of blindness, newly-sighted can immediately identify human locomotion

When and how do we develop the ability to recognize human movement and distinguish it from other forms of movement? The ability to differentiate between the bodily movement of humans and other animals is reported to appear only approximately five months after birth. Many researchers therefore believe that babies learn to recognize human locomotion through repeated visual exposure.

A study by MIT and York University researchers suggests that a rethinking may be in order. The study is part of Project Prakash, founded by BCS professor Pawan Sinha, dedicated to treating early-onset blindness in children and young adults.

The study, published in *Neuropsychologia*, included two participants — 7 and 20 years old — almost entirely blind since birth. As part of the study, the participants watched videos displaying patterns of light representing the coordinated movements of walking humans, pigeons, and cats. They were then asked to describe what they saw.

Before the cataract removal, the blind subjects could see the lights only when looking up close, centimeters away from the monitor. Yet they could not ascribe any meaning to these patterns, which seemed to them merely random movements of lights. Immediately after surgery, in their very first minutes of exposure to unobstructed sight, the two patients identified the light patterns representing human locomotion.

“This result suggests that extensive visual exposure is not critical for the ability to identify human motion,” says Shlomit Ben-Ami, a Project Prakash researcher and a former MIT postdoc now at Tel Aviv University, who spearheaded the study. The researchers are exploring possible accounts for why the participants were able to identify human locomotion but not the movement of other animals. According to one hypothesis, learning to interpret the bodily movement of other humans may be based partly on familiarity with one’s own body movements and structure.

*Department of Brain and Cognitive Sciences*

**Holding information in mind may mean storing it among synapses**

In a study in *PLOS Computational Biology*, scientists at BCS and the Picower Institute compared measurements of brain cell activity in an animal performing a working memory task with the output of various computer models representing two theories of the underlying mechanism for holding information in mind. The results strongly favored the newer notion that a network of neurons stores the information by making short-lived changes in the pattern of their connections, or synapses, and contradicted the traditional alternative that memory is maintained by neurons remaining persistently active (like an idling engine).

While both models allowed for information to be held in mind, only the versions that allowed for synapses to transiently change connections (“short-term synaptic plasticity”) produced neural activity patterns that mimicked what was actually observed in real brains at work. The idea that brain cells maintain memories by being always “on” may be simpler, acknowledged senior author Earl K. Miller, but it doesn’t represent what nature is doing and can’t produce the sophisticated flexibility of thought that can arise from intermittent neural activity backed up by short-term synaptic plasticity.

“You need these kinds of mechanisms to give working memory activity the freedom it needs to be flexible,” said Miller, Picower Professor of Neuroscience in MIT’s Department of Brain and Cognitive Sciences. “If working memory was just sustained activity alone, it would be as simple as a light switch. But working memory is as complex and dynamic as our thoughts.”

Leo Kozachkov, who is the co-lead author alongside MIT graduate student John Tauber, said matching computer models to real-world data was crucial.

“Most people think that working memory ‘happens’ in neurons — persistent neural activity gives rise to persistent thoughts. However, this view has come under recent scrutiny because it does not really agree with the data,” said Kozachkov who was co-supervised by co-senior author Jean-Jacques Slotine, a professor in BCS and mechanical engineering. “We show that synaptic activity (instead of neural activity) can be a substrate for working memory. The important takeaway from our paper is: these ‘plastic’ neural network models are more brain-like, in a quantitative sense, and also have additional functional benefits in terms of robustness.”

*David Orenstein | Picower Institute*
Awards and Honors

**Faculty**

**Polina Anikeeva**
Pioneer Award, National Institutes of Health

**Mark Bear**
Elected member of the National Academy of Medicine

**Emery N. Brown**
Gruber Neuroscience Prize
Pierre M. Galletti Award

**Michale Fee**
Elected member of the American Academy of Arts & Sciences

**Guoping Feng**
Fellow, American Association for the Advancement of Science

**Ila Fiete**
Swartz Prize for Theoretical and Computational Neuroscience

**Edward (Ted) Gibson**
Ig Nobel Prize

**Nancy Kanwisher**
Award in the Neurosciences, National Academy of Sciences

**Roger Levy**
Opportunity Award Grant

**Rebecca Saxe**
Elected member of the American Academy of Arts & Sciences

**Nidhi Seethapathi**
Opportunity Award Grant

**Li-Huei Tsai**
Vallee Visiting Professorship

**Guangyu Robert Yang**
Searle Scholar

**Postdoctoral Fellows**

**Héctor de Jesús-Cortés**
School of Science Infinite Expansion Award

**Noga Zaslavsky**
Opportunity Award Grant

**Research Scientists**

**Jakob Voigts**
School of Science Infinite Expansion Award

**McGovern Fellows**

**Omar Abudayeh**
Termee Mentor Scholarship
Endpoints 20 (+1) Under 40 in Biopharma
Bloomberg New Economy Catalyst

**Jonathan Gootenberg**
Termee Scholar
Endpoints 20 (+1) Under 40 in Biopharma

**Graduate Students**

**Fernanda De La Torre**
Paul and Daisy Soros Fellowship for New Americans

**Eric Martinez**
Ig Nobel Prize

**Greta Tuckute**
Amazon Fellow

**Djuna von Maydell**
MIT Prize for Open Data

**Undergraduate Students**

**Michelle Hung**
Glushko Prize for Outstanding Undergraduate Research in Cognitive Science

**Alyssa Unell**
Glushko Prize for Outstanding Undergraduate Research in Cognitive Science

**BCS Departmental Awards**

**Faculty Awards**

**Ev Fedorenko**
BCS Postdoc Award to an Outstanding Postdoctoral Mentor

**Nancy Kanwisher**
BCS Award for Excellence in Undergraduate Advising

**Rebecca Saxe**
BCS Award for Excellence in Graduate Teaching

**Fan Wang**
BCS Award for Excellence in Undergraduate Teaching
BCS Award for Excellence in Graduate Mentoring

**Teaching Assistant Awards**

**Leyla Akay; Victoria Beja-Glasser; Gabi Drummond; Max Heinrich; Kristine Hocker; Di Kang; Maddie Leet; Raul Mojica-Alburs; Yizhi Wang; Nick Watters**
Angus MacDonald Award for Excellence in Undergraduate Teaching

**Mika Braginsky**
Walle Nauta Award for Continuing Dedication to Teaching by a Graduate Student

**Jarrod Hicks; Aida Piccato; Juan Santoyo; Charlie Shvartsman; Sadie Zacharek**
Walle Nauta Award for Excellence in Graduate Teaching

**Undergraduate Research Awards**

**Alex Abate; Caroline Bao; Cesar Duran; Crista Falk; Michelle Hung; Dana McCormack; Shreya Pandit; Simon Radhakrishnan; Somaia Saba; Keith Skaggs; Grace Song; Yizhi Wang**

**BCS DEIJ Impact Awards**

**Annie Cardinaux; Junyi Chu; Danielle Cosio; Lupe Cruz; Héctor de Jesús-Cortés; Francisco Garcia; Michael Happ; Anna Ivanova; Cecilia Pelligrini; Omar Rutledge; Cathy Wong**

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The Department of Brain and Cognitive Sciences held its ninth annual Champions of the Brain Fellows event on October 25, 2022. The virtual event celebrates BCS graduate students and those champions who make it possible for students to explore their scientific dreams and to drive the department’s exciting research.

MIT Dean of Science Nergis Mavalvala provided opening remarks for the celebration, detailing the importance of fellowship support to attracting the top students and faculty.

“Graduate students, whether you’re a physicist or a neuroscientist, are woven into the fabric of all the research that we do. They are partners in our thinking and are central to the research enterprise,” said Mavalvala.

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The annual Champions of the Brain Fellows event is supported by the Gerald J. and Marjorie J. Burnett Fellowship, a third year student in Elly Nedivi’s lab supported by the Gerald J. and Marjorie J. Burnett Fellowship, who presented her research on the role of inhibition in adult plasticity.

The concluding segment of the celebration included pre-recorded remarks from BCS Department Head Michale Fee, as well as remarks from Barrie R. Zesiger HM, MIT Corporation Life Member Emeritus and a founder of Champion of the Brain Fellows.

Zesiger discussed the impact of supporting neuroscience research through the next generation of scientists. She also encouraged continued involvement and support from the audience.

Fee emphasized the special, symbiotic relationship between graduate students and faculty. “Students see scientific problems with fresh eyes. They think about things differently. [W]ith their new perspective, students can bring deep, old questions back to life. And being able to see our own research through these fresh, creative, unjaded eyes helps keep me enthusiastic.”

Fee concluded: “By supporting our graduate students, you are helping to fire the engines of creativity in a promising young scientist, to enable them to do their best work in this extraordinary community of scholars. You are also supporting a legacy of faculty mentoring students, who then become mentors themselves — a generational cycle that is fundamental to advancing knowledge.”

The annual Champions of the Brain Fellows honors donors through an endowed, expendable, or corporate gift to support graduate students at the forefront of cutting-edge research in BCS.

To learn more about supporting BCS, visit bcs.mit.edu/give-bcs.
Footsteps Followed

The Emilio Bizzi Fellowship clears the way for adventurous graduate students to do their best work

Rachel Donahue | Office of The Corporation, and Tristan Davies | BCS

Institute Professor Emeritus Emilio Bizzi has spent his professional life tackling deceptively simple-looking problems. “For let’s say half of my career, I worked on one question: How do we move? How do we grab things and how do we use our hands? That is, the study of how the brain controls movements and coordinates them visually in order to produce a trajectory that avoids obstacles and gets to the target.” Among many crucial discoveries, Bizzi’s research formed the basis of a comprehensive theory to account for how the central nervous system solves the complex computational problem of executing limb movements. But he is quick to point out how much we have yet to understand, offering an elegant example of how adaptable this coordination can be: When Michelangelo painted the Sistine Chapel, “he painted parallel to the ceiling with muscles in a very different position and a different way of dynamically contracting than when he planned out the painting from a desk. This is an incredible feat; no robot can do this type of generalization.”

In more than 40 years on the MIT faculty, Bizzi also hasn’t shied away from taking on major challenges outside the lab. As director of the Whitaker College of Health Sciences, Technology, and Management from 1983 to 1987 he was a key player in the creation of BCS, working with department head Richard Held and Institute leadership to combine the Department of Psychology and the neuroscientific components of Whitaker. He then led the new department until 1997.

These leadership roles gave Bizzi a deep understanding of the need to secure funding to bring in exceptional students, and he recalls with sadness how the department has had to turn down potentially fantastic students, many international, because there were no funds to support them. The experience taught him that the scientific community thrives when it includes people from around the world adding their ideas and perspectives. This was a prime motivation behind the gift he made to establish the Emilio Bizzi Fellowship under the BCS Champions of the Brain Fellows program. As Bizzi was a founding member of the McGovern Institute for Brain Research, the fellowship is directed at supporting a student studying systems neuroscience in a McGovern lab.

Through this gift, Bizzi’s legacy will sustain future generations of students as they follow in his footsteps and tackle the hardest problems in neuroscience.

To learn more about the Champions of the Brain Fellows program or make a gift, contact Devan Monroe, Manager of Philanthropic Relations, at monroed@mit.edu or 617.324.6718.

Meet the First Bizzi Fellow

Raúl Mojica Soto-Albors first came to MIT when he was an undergraduate at the University of Puerto Rico at Mayagüez, where his professors selected him to attend the 2017 Quantitative Methods Workshop run by the Center for Brains, Minds and Machines (CBMM). The week-long annual workshop introduces a select group of students to the methods used in computational and cognitive neuroscience research. Raúl returned to Cambridge the following summer to work in Mark Harnett’s lab as part of the MIT Summer Research Program (MSRP); he returned a year later to continue the work as a visiting scholar.

Raúl joined the BCS doctoral program in 2019 and is now a fourth-year student in the Harnett lab, where he is studying how biophysics of neuronal dendrites influence learning and plasticity. “I’m very thankful to Professor Bizzi for funding my fellowship this year,” says Raúl, who was also the Gene Stark ’68, SM ’69, EE ’70, SCD ’72 fellow in 2019–20. “Knowing that alumni and faculty care about creating a supportive environment for students helps me to really focus on my research. I think it’s an important part of why BCS has a strong program that brings in such great students.”
The mission of the MIT Department of Brain and Cognitive Sciences is to reverse engineer the brain in order to understand the mind. To do that we delve deeply into the mechanisms of the brain at all levels — from molecules to synapses to neurons to circuits to algorithms to human behavior and cognition, we build links between those levels. To sustain and advance this mission, we offer undergraduate programs in Brain and Cognitive Sciences and Computation and Cognition in order to train the next generation of scientific leaders.

BCS News is published twice a year and is distributed without charge to alumni, donors, and other BCS community members.

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BCS is grateful for the generosity and support of our alumni and friends. To help support fellowships for tomorrow’s neuroscience leaders, visit giving.mit.edu/brain-cog and select the BCS Graduate Fellowships Fund #2735856 or use the following QR code:

To discuss opportunities to make an impact in BCS, contact:

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