Summer 2023

bcs news

Reimagining Our Theories of Language

MIT brain+cognitive sciences

From the Department Head

Dear Friends,

As we approach the start of a new academic year, I would like to share with you what lies ahead for our department in the coming months. Over this spring and summer and into the fall, BCS has been working on a strategic planning process. The project's genesis is in the feedback our Visiting Committee provided in 2022. The committee noted that the breadth of research in our department can be both a strength and a challenge, suggesting that we have an opportunity to re-examine our mission and vision. What are the major scientific questions, issues, and emerging areas, and how should we position ourselves to address them? How might this guide decisions about faculty hiring or our academic programs? Working with an outside consultant, we have been gathering wide-ranging feedback on these questions, which we will synthesize into a strategic plan for BCS. I hope to update our community about the details of this plan as soon as possible.

This is a good opportunity to note that several of our staff members recently received MIT awards recognizing their outstanding contributions to our department (see the following page). Two of our staff, Kara Flyg and Farrah Belizaire, received MIT's Excellence Awards; Belizaire also received a School of Science Infinite Mile Award. I want to express my deep appreciation for the unwavering dedication of our staff. You all play an invaluable role in the success of the department.

Finally, I would like to highlight a symposium I had the pleasure of joining in June, celebrating former Department Head Mriganka Sur. The day long-event, titled "Cortical Plasticity and Dynamics," included talks by alumni of Mriganka's lab; many of his alumni also attended the symposium. Mriganka is not retiring yet — his lab is still very active! But this was a great time to look back and appreciate all he has accomplished.

I hope you enjoy the latest edition of *BCS News*, showcasing notable research led by BCS and Building 46 scientists. The cover feature surveys the work of three of our researchers — Ev Fedorenko, Ted Gibson, and Roger Levy — and their fascinating work on language and human cognition.

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

BCS Leadership

Laura Schultz, PhD
Professor of Cognitive Science
Associate Department Head for DEIJ

Josh McDermott, PhD
Associate Professor of Brain and Cognitive Sciences
Associate Department Head

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Cindy Li
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Laura Frawley
BCS Award for Excellence in Undergraduate Teaching

Ted Gibson
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Li-Huei Tsai
BCS Award for Excellence in Graduate Student Mentorship

Lawrence Udeigwe
BCS Award for Excellence in Graduate Teaching

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Jill Crittenden (Staff); Alex Ferguson (Grad); Ted Gibson (Faculty); Gregg Heller (Grad); Saima Malik Moraleda (Grad); Elise Malvicini (Staff); Josh McDermott (Faculty); Lace Riggs (Postdoc); Pramod RT (Postdoc)

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Faculty News

- Associate Professor Michael Halassa left the department in November 2022.
- Associate Professor Mark Harnett earned tenure in May 2023.

Reimagining Our Theories of Language

BCS is home to a unique intellectual triad focused on research in language and cognition: Ev Fedorenko, Ted Gibson, and Roger Levy. Using combinations of computational modeling, psycholinguistic experimentation, behavioral data, brain imaging, and large naturalistic language datasets, the three researchers believe they have an answer to a fundamental question: what is the purpose of language?

Maura R. O'Connor

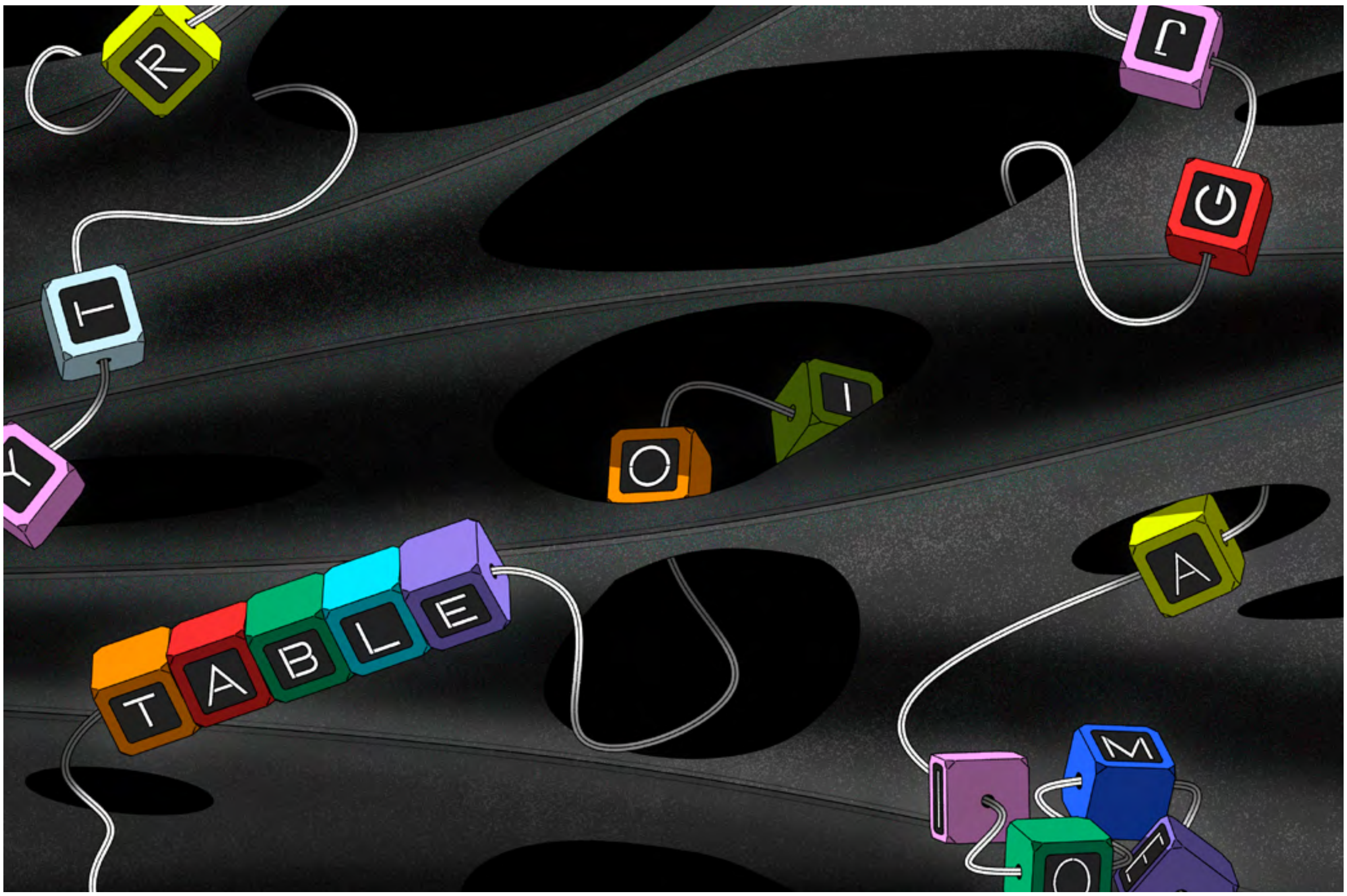
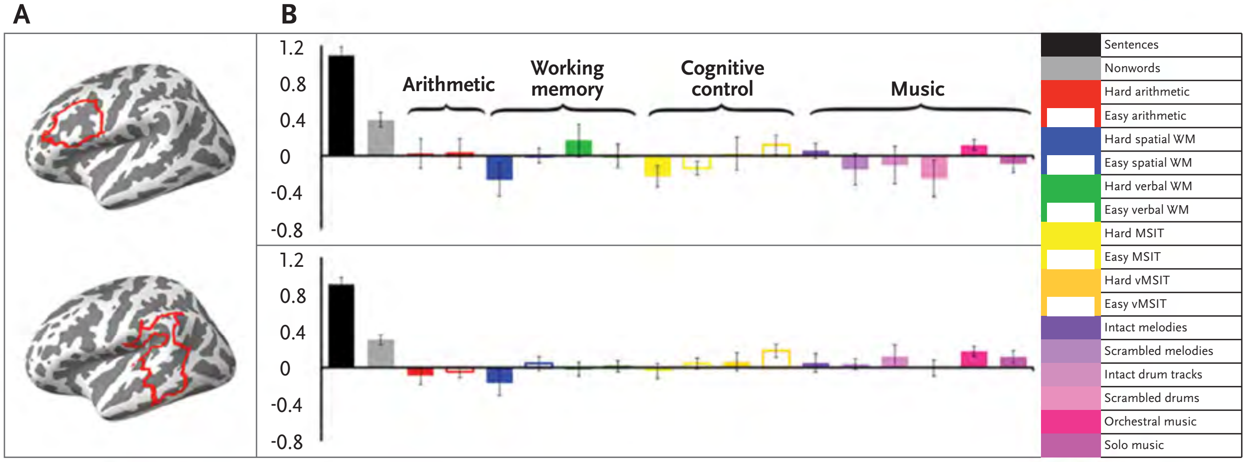


Image: Carolina Moscoso / Illustration Division

Over a decade ago, the neuroscientist Ev Fedorenko asked forty-eight English speakers to complete tasks like reading sentences, recalling information, solving math problems, and listening to music. As they did this, she scanned their brains using fMRI to see which circuits were activated. If, as linguists have proposed for decades, language is connected to thought in the human brain, then the language processing regions would be activated even during nonlinguistic tasks.

Fedorenko's experiment, published in 2011 in the *Proceedings of the National Academy of Sciences* (PNAS), showed that when it comes to arithmetic, musical processing, general working memory, and other nonlinguistic tasks, language regions of the human brain showed no response. Contrary to what many linguists have claimed, complex thought and language are separate things. One does not require the other. "We have this highly specialized place in the brain that doesn't respond to other activities," says Fedorenko, who is an Associate Professor at the Department of Brain and Cognitive Sciences (BCS) and the McGovern Institute. "It's not true that thought critically needs language."

The design of the experiment, using neuroscience to understand how language works, how it evolved, and its relation to other cognitive functions, is at the heart of Fedorenko's research. She is part of a unique intellectual triad at MIT's Department of Brain and Cognitive Science, including her colleagues Roger



Functional response profiles of two high-level language processing brain regions, taken from Ev Fedorenko's research. The data shows that healthy adults strongly engage the brain's language areas when they understand a sentence, but not when they perform other nonlinguistic tasks such as arithmetic, storing information in working memory, inhibiting prepotent responses, or listening to music.

Levy and Ted Gibson. (Gibson and Fedorenko have been married since 2007). Together they have engaged in a years-long collaboration and built a significant body of research focused on some of the biggest questions in linguistics and human cognition. While working in three independent labs – EvLab, TedLab, and the Computational Psycholinguistics Lab – the researchers are motivated by a shared fascination with the human mind and how language works in the brain. "We have a great deal of interaction and collaboration," says Levy. "It's a very broadly collaborative, intellectually rich and diverse landscape."

Using combinations of computational modeling, psycholinguistic experimentation, behavioral data, brain imaging, and large naturalistic language datasets, the researchers also share an answer to a fundamental question: what is the purpose of language? Of all the possible answers to why we have language, perhaps the simplest and most obvious is communication. "Believe it or not," says Ted Gibson, "that is not the standard answer."

Gibson first came to MIT in 1993 and joined the faculty of the Linguistics Department in 1997. Recalling the experience today, he describes it as frustrating. The field of linguistics at that time was dominated by the ideas of Noam Chomsky, one of the founders of MIT's Graduate Program in Linguistics, who has been called the father of modern linguistics. Chomsky's "nativist" theories of language posited that the purpose of language is the articulation of thought and that language capacity is built-in in advance of any learning. But Gibson, with his training in math and computer science, felt that researchers didn't satisfyingly test these ideas. He believed that finding the answer to many outstanding questions about language required quantitative research, a departure from standard linguistic methodology. "There's no reason to rely only on you and your friends, which is how linguistics has worked," Gibson says. "The data you can get can be much broader if you crowdsource lots of people using experimental methods." Chomsky's ascendancy in linguistics presented Gibson with what he saw as a challenge and an opportunity. "I felt like I had to figure it out in detail and see if there was truth in these claims," he says.

Three decades after he first joined MIT, Gibson believes that the collaborative research at the Department of Brain and Cognitive Sciences is persuasive and provocative, pointing to new ways of thinking about human culture and cognition. "Now we're at a stage where it is not just arguments against. We have a lot of positive stuff saying what language is," he explains. Levy adds: "I would say all three of us are of the view that communication plays a very import role in language learning and processing but also in the structure of language itself."

Levy points out that the three researchers completed PhDs in different subjects: Fedorenko in neuroscience, Gibson in computer science, Levy in linguistics. Yet for years before their paths finally converged at MIT, their shared interests in quantitative linguistic research led them to follow each other's work closely and be influenced by it. The first collaboration between the three

> For years before their paths finally converged at MIT, the researchers' shared interests in quantitative linguistic research led them to follow each other's work closely.

From left to right: Ev Fedorenko, Edward (Ted) Gibson, and Roger Levy. Photo: Gaelen Morse

was in 2005 and focused on language processing in Russian relative clauses. Around that time, Gibson recalls, Levy was presenting what he describes as "lovely work" that was instrumental in helping him to understand the links between language structure and communication. "Communicative pressures drive the structures," says Gibson. "Roger was crucial for that. He was the one helping me think about those things a long time ago."

Levy's lab is focused on the intersection of artificial intelligence, linguistics, and psychology, using natural language processing tools. "I try to use the tools that are afforded by mathematical and computer science approaches to language to formalize scientific hypotheses about language and the human mind and test those hypotheses," he says.

Levy points to ongoing research between him and Gibson focused on language comprehension as an example of the benefits of collaboration. "One of the big questions is: when language understanding fails, why does it fail?" Together, the researchers have applied the concept of a "noisy channel," first developed by the information theorist Claude Shannon in the 1950s, which says that information or messages are corrupted in transmission. "Language understanding unfolds over time, involving an ongoing integration of the past with the present," says Levy. "Memory itself is an imperfect channel conveying the past from our brain a moment ago to our brain now in order to support successful language understanding." Indeed, the richness of our linguistic environment, the experience of hundreds of millions of words by adulthood, may create a kind of statistical knowledge guiding our expectations, beliefs, predictions, and interpretations of linguistic meaning. "Statistical knowledge of language actually interacts with the constraints of our memory," says Levy. "Our experience shapes our memory for language itself."

All three researchers say they share the belief that by following the evidence, they will eventually discover an even bigger and more complete story about language. "That's how science goes," says Fedorenko. "Ted trained me, along with Nancy Kanwisher, and both Ted and Roger are very data-driven. If the data is not giving you the answer you thought, you don't just keep pushing your story. You think of new hypotheses. Almost everything I have done has been like that." At times, Fedorenko's research into parts of the brain's language system has surprised her and forced her to abandon her hypotheses. "In a certain project I came in with a prior idea that there would be some separation between parts that cared about combinatorics versus words meanings," she says, "but every little bit of the language system is sensitive to both. At some point, I was like, this is what the data is telling us, and we have to roll with it."

The researchers' work pointing to communication as the constitutive purpose of language, opens new possibilities for probing and studying non-human language. The standard claim is that human language has a drastically more extensive lexicon than animals, which have no grammar. "But many times, we don't even know what other species are communicating," says Gibson. "We say they can't communicate, but we don't know. We don't speak their language." Fedorenko hopes that more opportunities to make cross-species linguistic comparisons will open up. "Understanding where things are similar and where things diverge would be super useful," she says.

Meanwhile, the potential applications of language research are far-reaching. One of Levy's current research projects focuses on how people read and use machine learning algorithms informed by the psychology of eye movements to develop proficiency tests. By tracking the eye movements of people who speak English as a second language while they read texts in English, Levy can predict how good they are at English, an approach that could one day replace TOEFL. "It's an implicit measure of language rather than a much more game-able test," he says.

The researchers agree that some of the most exciting opportunities in the neuroscience of language lay with large language models that provide new opportunities for asking new questions and making new discoveries. "In the neuroscience of language, the kind of stories that we've been able to tell about how the brain does language were limited to verbal, descriptive hypotheses," says Fedorenko. Computationally implemented models are now amazingly good at language and show some degree of alignment to the brain, she adds. Now researchers can ask questions such as: what are the actual computations that cells are doing to get meaning from strings of words? "You can now use these models as tools to get insights into how humans might be processing language," she says. "And you can take the models apart in ways you can't take apart the brain."

A new approach to syntax

For almost a decade, Ted Gibson has taught a course at MIT called "Lab in Psycholinguistics." But when he gets to the course section focused on syntax, he never gives his students any reading. "There are tons of syntax textbooks," Gibson explains, "but I don't like any of them."

Syntax has long fascinated Gibson. How is meaning built from simple combinations of sounds that form words, which then form phrases and sentences? Most textbooks on the subject offer complicated explanations for this combinatorial power of language, including that of universal grammar – the idea that the process of language acquisition is innate and that there are rules of syntactic structure and categories shared by all languages. In contrast, Gibson's explanation of syntax builds on the ideas of Lucien Tesniere, whose 1959 book *Elements de syntax structural* proposed a theory of dependency grammar. "It basically says grammar is just connections between words," Gibson explains. While it is possible that some aspects of language structure are innate in the human brain, he believes the more likely explanation is that we learn syntax over time by linking the meaning of words to each other. "You just draw arrows [between words]. There are no other hidden structures there."

Over the years, Gibson's TedLab has uncovered evidence supporting dependency grammar, including research showing a cognitive cost when there is a greater distance between words whose meaning depends on one another. "Activations in the language network are even very sensitive to the dependence length," he says. "I've always worked on processing, and I didn't realize that I could push all the processing stuff back to grammar."

Gibson finally decided to write a paper on these findings, but its length grew and grew until he realized he had a book on his hands. The book, *Syntax: a Cognitive Approach*, will be published by MIT Press in fall 2023.

Maura R. O'Connor

Uncovering the Invisible Pressures Shaping Language

Sihan Chen, a PhD student in MIT's Department of Brain and Cognitive Sciences, studies the social and environmental factors that shape the development of languages

Department of Brain and Cognitive Sciences

Sihan Chen's fascination with languages began when he was a teenager in his high school choir in his hometown of Shenzhen, China. "We sang religious and folk songs in languages like Mandarin, English, Albanian, and Latin, and I would look up how to pronounce words in the different languages," he says.

These early experiences planted the seed for his current research interests in cognition and language as a third-year PhD student in MIT's Department of Brain and Cognitive Sciences (BCS). Under the guidance of Professor Edward (Ted) Gibson, Sihan studies how different languages have developed into what we see today, with a particular emphasis on environmental and social factors. "I was always interested in the invisible pressures that shape our languages over time," he says.

From engineering to languages

Despite Sihan's ongoing interest in language, he started on a different academic path. After completing the demanding entrance exams for Chinese universities, he made a last-minute decision to apply to US colleges. With just three months to prepare for the SAT and language test, he says his resume paled compared to his American peers' extensive extracurricular activities. He took the chance and landed at the University of Miami, where he pursued a major in mechanical engineering.

Alongside his engineering studies, Sihan dedicated several elective courses to his interest in linguistics. In one of these courses, he stumbled upon a thought-provoking paper, coincidentally written by a student from BCS, exploring how language influences our perception of color. "It fascinated me and made quite an impression," he recalls. Now, he is working on a paper challenging some of those findings.

Sihan says reading such papers in college helped him discover the perfect match between his intellectual interests and abilities, augmented by the skills he had acquired through his mechanical engineering training. Although the topics addressed in these papers were quite different from what he encountered in his major, the underlying thought process to solve the problems are similar. "You identify the process, break it down into different steps, and think about how you can model each mathematically and implement the model computationally." He decided to reach out to Ted Gibson, who further encouraged him to continue his work.

Approaching graduation, Sihan faced a tough decision between the more familiar path of biomedical engineering and pursuing his deepening passion for language and cognition. "I think it was clear this is where I wanted to go, but it was a tough decision." He decided to apply.

The communication thesis

Sihan's current work with Ted Gibson revolves around a central thesis of his lab: since we often use language to communicate, we have the incentive to use it efficiently. Sihan and his colleagues are looking into how different languages convey spatial information with spatial deictic demonstratives – words or phrases such as "here" and "from there" in English. "Efficiency here means communicating spatial information as accurately as possible, with a system involving as few demonstratives as possible," says Sihan. In communication, there is a trade-off between two factors: accuracy and simplicity, as one cannot fully achieve both at the same time. If one wants to pursue accuracy, the resulting spatial deictic system must be very complex. In contrast, if one intends to pursue simplicity, the resulting system won't be able to convey any information. Using tools in information theory and a database of 220 languages from various parts of the world, Sihan and his collaborators show that existing spatial deictic systems are very close to the optimal systems predicted by information theory. In addition, they also show that human languages prefer spatial demonstrative systems that have a consistent pattern.

Seeking how societal characteristics might shape language features, Sihan and his colleagues analyze data from diverse languages. They hypothesize two types of societies: exoteric societies, marked by mobility, large population size, and a significant number of second language speakers, and esoteric societies, characterized by being more close-knit, having less migration, and fewer second language speakers. Exoteric languages,

> Sihan's work with Ted Gibson revolves around a central thesis: we have the incentive to use language efficiently.

Sihan Chen. Photo: Justin Knight

such as English, are widely-spoken and have more complex syntax but simplified morphology. Conversely, esoteric societies tend to have languages with more complex morphology, such as more noun cases. English, for example, rarely has cases, except in pronouns where it distinguishes between nominative and accusative cases with pronouns like ‘I’ and ‘me’ and uses the genitive case with ‘my,’ indicating a relationship, and that’s about it. But other, more esoteric languages have up to 15 cases, including cases for objects, direction, and location. We think that this difference in noun cases arises from word learning processes, where second language learners focus on rules, while native speakers memorize these specific variations.”

Trying to see what influences the way humans speak, Sihan’s research also extends to acoustics. A waveform is a visual representation of a sound you might be familiar with from your audio player. Waveforms depict the amplitude of a wave over time, comprising delicate and minuscule oscillations that amalgamate into a broader pattern known as the modulation envelope. “We want to determine the frequency of this broader oscillation, which can also be described as the rhythm of speech,” Sihan explains. Previous research revealed that in eight languages, this rhythm of speech typically exhibits a frequency peaking at 4 hertz — a rhythm that researchers believe is related to the coordination between speech production and comprehension. “We expanded this research to 94 languages, and we are now analyzing 4 million recordings to determine further the prevalence of this phenomenon across different regions of the globe,” says Sihan.

Reflecting on his research and studies in the last three years, Sihan says MIT’s Department of Brain and Cognitive Sciences is a highly supportive environment, fostering collaboration among individuals from diverse backgrounds. “There is always someone available to offer assistance and guidance,” he says. “it’s so cool to see people from different backgrounds with their own expertise coming together collaboratively to uncover fascinating secrets of the human mind.”

Bacterial injection system delivers proteins in mice and human cells

With further development, the programmable system could be used in a range of applications including gene and cancer therapies

Allessandra DiCorato

Researchers at the McGovern Institute for Brain Research, MIT's Department of Brain and Cognitive Sciences (BCS), and the Broad Institute of MIT and Harvard have harnessed a natural bacterial system to develop a new protein delivery approach that works in human cells and animals. The technology, recently described in *Nature*, can be programmed to deliver a variety of proteins, including ones for gene editing, to different cell types. The system could potentially be a safe and efficient way to deliver gene therapies and cancer therapies.

Led by MIT Associate Professor Feng Zhang, who is a McGovern Institute and BCS investigator and Broad Institute core member, the team took advantage of a tiny syringe-like injection structure, produced by a bacterium, that naturally binds to insect cells and injects a protein payload into them. The researchers used the artificial intelligence tool AlphaFold to engineer these syringe structures to deliver a range of useful proteins to both human cells and cells in live mice.

"This is a really beautiful example of how protein engineering can alter the biological activity of a natural system," says Joseph Kreitz, the study's first author, a graduate student in biological engineering at MIT, and a member of Zhang's lab. "I think it substantiates protein engineering as a useful tool in bioengineering and the development of new therapeutic systems."

"Delivery of therapeutic molecules is a major bottleneck for medicine, and we will need a deep bench of options to get these powerful new therapies into the right cells in the body," adds Zhang. "By learning from how nature transports proteins, we

Purified Photorhabdus virulence cassettes (PVCs), imaged using transmission electron microscopy. Image: Joseph Kreitz/Broad Institute, McGovern Institute

Feng Zhang

The researchers used the AI tool AlphaFold to engineer the natural syringe structures to deliver useful proteins to human cells and cells in mice.

were able to develop a new platform that can help address this gap."

Zhang is senior author on the study and is also the James and Patricia Poitras Professor of Neuroscience at MIT and an investigator at the Howard Hughes Medical Institute.

Injection via contraction

Symbiotic bacteria use the roughly 100-nanometer-long syringe-like machines to inject proteins into host cells to help adjust the biology of their surroundings and enhance their survival. These machines, called extracellular contractile injection systems (eCISs), consist of a rigid tube inside a sheath that contracts, driving a spike on the end of the tube through the cell membrane. This forces protein cargo inside the tube to enter the cell.

On the outside of one end of the eCIS are tail fibers that recognize specific receptors on the cell surface and latch on. Previous research has shown that eCISs can naturally target insect and mouse cells, but Kreitz thought it might be possible to modify them to deliver proteins to human cells by re-engineering the tail fibers to bind to different receptors.

Using AlphaFold, which predicts a protein's structure from its amino acid sequence, the researchers redesigned tail fibers of an eCIS produced by Photorhabdus bacteria to bind to human cells. By re-engineering another part of the complex, the scientists tricked the syringe into delivering a protein of their choosing, in some cases with remarkably high efficiency.

The team made eCISs that targeted cancer cells expressing the EGF receptor and showed that they killed almost 100 percent of the cells, but did not affect cells without the receptor. Though efficiency depends in part on the receptor the system is designed to target, Kreitz says that the findings demonstrate the promise of the system with thoughtful engineering.

The researchers also used an eCIS to deliver proteins to the brain in live mice — where it didn't provoke a detectable immune response, suggesting that eCISs could one day be used to safely deliver gene therapies to humans.

Packaging proteins

Kreitz says the eCIS system is versatile, and the team has already used it to deliver a range of cargoes including base editor proteins (which can make single-letter changes to DNA), proteins that are toxic to cancer cells, and Cas9, a large DNA-cutting enzyme used in many gene editing systems.

In the future, Kreitz says researchers could engineer other components of the eCIS system to tune other properties, or to deliver other cargoes such as DNA or RNA. He also wants to better understand the function of these systems in nature.

"We and others have shown that this type of system is incredibly diverse across the biosphere, but they are not very well characterized," Kreitz said. "And we believe this type of system plays really important roles in biology that are yet to be explored."

This work was supported, in part, by the National Institutes of Health, Howard Hughes Medical Institute, Poitras Center for Psychiatric Disorders Research at MIT, Hock E. Tan and K. Lisa Yang Center for Autism Research at MIT, K. Lisa Yang and Hock E. Tan Molecular Therapeutics Center at MIT, K. Lisa Yang Brain-Body Center at MIT, Broad Institute Programmable Therapeutics Gift Donors, The Pershing Square Foundation, William Ackman, Neri Oxman, J. and P. Poitras, Kenneth C. Griffin, BT Charitable Foundation, the Asness Family Foundation, the Phillips family, D. Cheng, and R. Metcalfe.

40 Hz vibrations reduce Alzheimer's pathology, symptoms in mouse models

Tactile stimulation improved motor performance, reduced phosphorylated tau, preserved neurons and synapses and reduced DNA damage, a new study shows

David Orenstein | Picower Institute

Evidence that non-invasive sensory stimulation of 40 Hz gamma frequency brain rhythms can reduce Alzheimer's disease pathology and symptoms, already shown with light and sound by multiple research groups in mice and humans, now extends to tactile stimulation. A new study by MIT scientists shows that Alzheimer's model mice exposed to 40 Hz vibration an hour a day for several weeks showed improved brain health and motor function compared to untreated controls.

The MIT group is not the first to show that gamma frequency tactile stimulation can affect brain activity and improve motor function, but they are the first to show that the stimulation can also reduce levels of the hallmark Alzheimer's protein phosphorylated tau, keep neurons from dying or losing their synapse circuit connections, and reduce neural DNA damage.

"This work demonstrates a third sensory modality that we can use to increase gamma power in the brain," said Li-Huei Tsai, corresponding author of the study, director of The Picower Institute for Learning and Memory and the Aging Brain Initiative at MIT, and Picower

Li-Huei Tsai

Professor in the Department of Brain and Cognitive Sciences (BCS). "We are very excited to see that 40 Hz tactile stimulation benefits motor abilities, which has not been shown with the other modalities. It would be interesting to see if tactile stimulation can benefit human subjects with impairment in motor function."

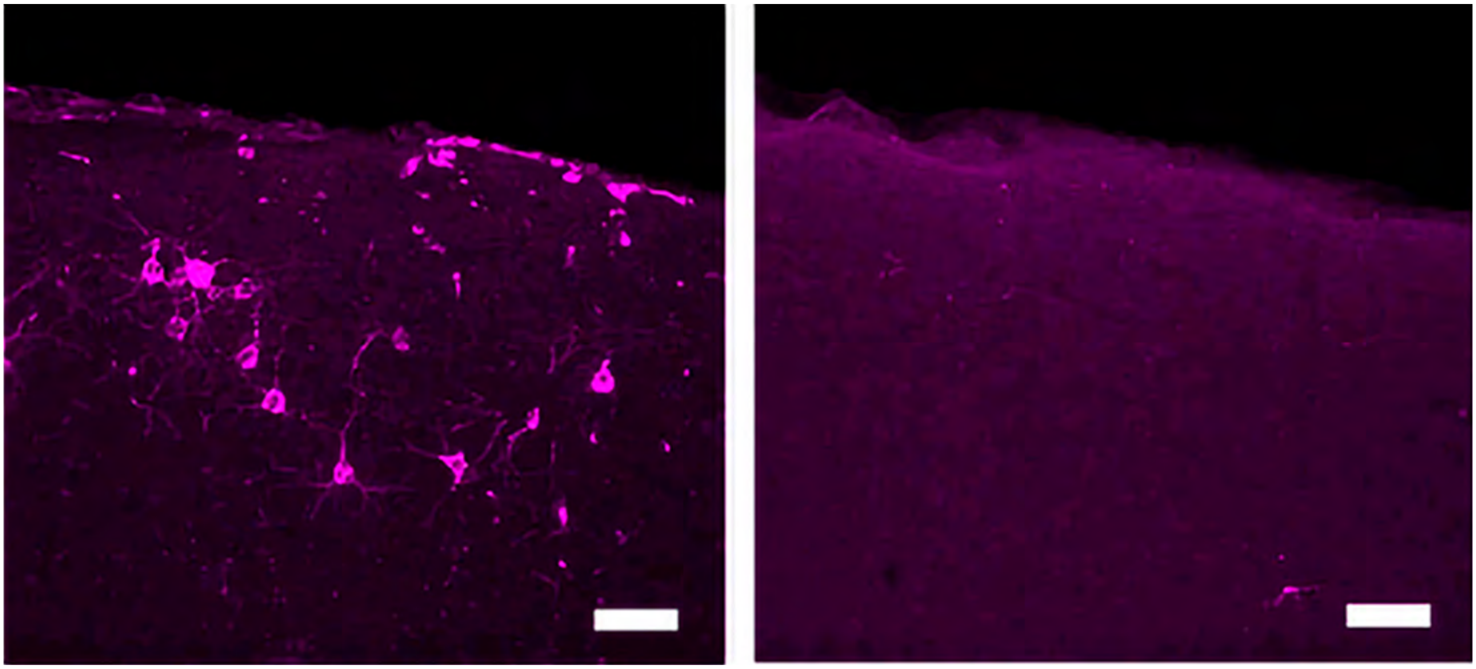
Ho-Jun Suk, Nicole Buie, Guojie Xu and Arit Banerjee are lead authors of the study in *Frontiers in Aging Neuroscience* and Ed Boyden, Y. Eva Tan Professor of Neurotechnology at MIT, is a co-senior author of the paper. Boyden, an affiliate member of The Picwoer Institute, is also appointed in BCS as well as the Departments of Bioengineering and Media Arts and Sciences, the McGovern Institute for Brain Research, and the K. Lisa Yang Cener for Bionics.

> "This work demonstrates a third sensory modality that we can use to increase gamma power in the brain."
>
> - Li-Huei Tsai

Feeling the vibe

In a series of papers starting in 2016, a collaboration led by Tsai's lab has demonstrated that light flickering and/or sound clicking at 40 Hz (a technology called GENUS for Gamma Entrainment Using Sensory stimuli), reduces levels of amyloid-beta and tau proteins, prevents neuron death and preserves synapses and even sustains learning and memory in a variety of Alzheimer's disease mouse models. Most recently in pilot clinical studies the team showed that 40 Hz light and sound stimulation was safe, successfully increased brain activity and connectivity and appeared to produce significant clinical benefits in a small cohort of human volunteers with early-stage Alzheimer's disease. Other groups have replicated and corroborated health benefits of 40 Hz sensory stimulation and an MIT spin-off company, Cognito Therapeutics, has launched stage III clinical trials of light and sound stimulation as an Alzheimer's treatment.

The new study tested whether whole-body 40 Hz tactile stimulation produced meaningful benefits in two commonly used mouse models of Alzheimer's neurodegeneration, the Tau P301S mouse, which recapitulates the disease's tau pathology, and the CK-p25 mouse, which recapitulates the synapse loss and DNA damage seen in human disease. The team focused its analyses in two areas of the brain: the primary somatosensory cortex (SSp), where tactile sensations are processed, and the primary motor cortex (MOp), where the brain produces movement commands for the body.



An enlarged detail from a figure in the paper highlights reductions in phosphorylated tau (magenta) in primary somatosensory cortical neurons in Tau P301S model mice treated with 40 Hz tactile stimulation (right). An image from an untreated control is on the left. Image: Tsai Lab/The Picower Institute

To produce the vibration stimulation, the researchers placed mouse cages over speakers playing 40 Hz sound, which vibrated the cages. Non-stimulated control mice were in cages interspersed in the same room so that all the mice heard the same 40 Hz sound. The differences measured between the stimulated and control mice were therefore made by the addition of tactile stimulation.

First the researchers confirmed that 40 Hz vibration made a difference in neural activity in the brains of healthy (i.e. non-Alzheimer's) mice. As measured by expression of c-fos protein, activity increased two-fold in the SSp and more than 3-fold in the MOp, a statistically significant increase in the latter case. Once the researchers knew that 40 Hz tactile stimulation could increase neural activity, they assessed the impact on disease in the two mouse models. To ensure both sexes were represented, the team used male P301S mice and female CK-p25 mice.

P301S mice stimulated for three weeks showed significant preservation of neurons compared to unstimulated controls in both brain regions. Stimulated mice also showed significant reductions in tau in the SSp by two measures, and exhibited similar trends in the MOp. CK-p25 mice received six weeks of vibration stimulation. These mice showed higher levels of synaptic protein markers in both brain regions compared to unvibrated control mice. They also showed reduced levels of DNA damage.

Finally, the team assessed the motor abilities of mice exposed to the vibration vs. not exposed. They found that both mouse models were able to stay on a rotating rod significantly longer. P301S mice also hung on to a wire mesh for significantly longer than control mice while CK-p25 mice showed a positive, though non-significant trend.

"The current study, along with our previous studies using visual or auditory GENUS demonstrates the possibility of using non-invasive sensory stimulation as a novel therapeutic strategy for ameliorating pathology and improving behavioral performance in neurodegenerative diseases," the authors concluded.

Support for the study came from The JPB Foundation, The Picower Institute for Learning and Memory, Eduardo Eurnekian, The DeGroof-VM Foundation, Halis Family Foundation, Melissa and Doug Ko Hahn, Lester Gimpelson, Eleanor Schwartz Charitable Foundation, The Dolby Family, Kathleen and Miguel Octavio, Jay and Carroll Miller, Anne Gao and Alex Hu and Charles Hieken.

Spatial computing enables flexible working memory

Brain applies rhythms to physical patches of the cortex to selectively control just the right neurons at the right times to do the right things

David Orenstein | Picower Institute

Routine tasks that require working memory, like baking, involve remembering both some general rules (e.g. read the oven temperature and time from the recipe and then set them on the oven) and some specific content for each instance (e.g. 350 degrees for 45 minutes for a loaf of rye, but 325 degrees for 8 minutes for cookies). A new study provides a novel explanation for how the brain distinctly manages the general and specific components of such cognitive demands.

The research led by scientists at MIT's Picower Institute for Learning and Memory and the Karolinska Institute and KTH Royal Institute of Technology in Stockholm, Sweden, shows that the brain creates distinct spaces in the cortex for each general rule and controls those patches with brain rhythms, a concept the authors call "Spatial Computing." This system, evident in the study's experiments in animals, explains how the brain can easily sustain a consistent understanding of a process even when the specific contents keep changing (like the time and temperature for bread vs. cookies). It also answers a few questions neuroscientists have wrestled with about the physiological operations that underlie working memory.

Earl Miller

"Your brain can instantly generalize. If I teach you to follow some rules, like remembering C, A, and B and putting them into alphabetical order, and then I switch the contents to F, D and E you wouldn't miss a beat," said Earl K. Miller, Picower Professor in the Picower Institute and co-senior author of the study in *Nature Communications*. "Your brain can do this because it represents the rules and the contents at different physical scales. One can just be plugged into the other."

Working memory workings

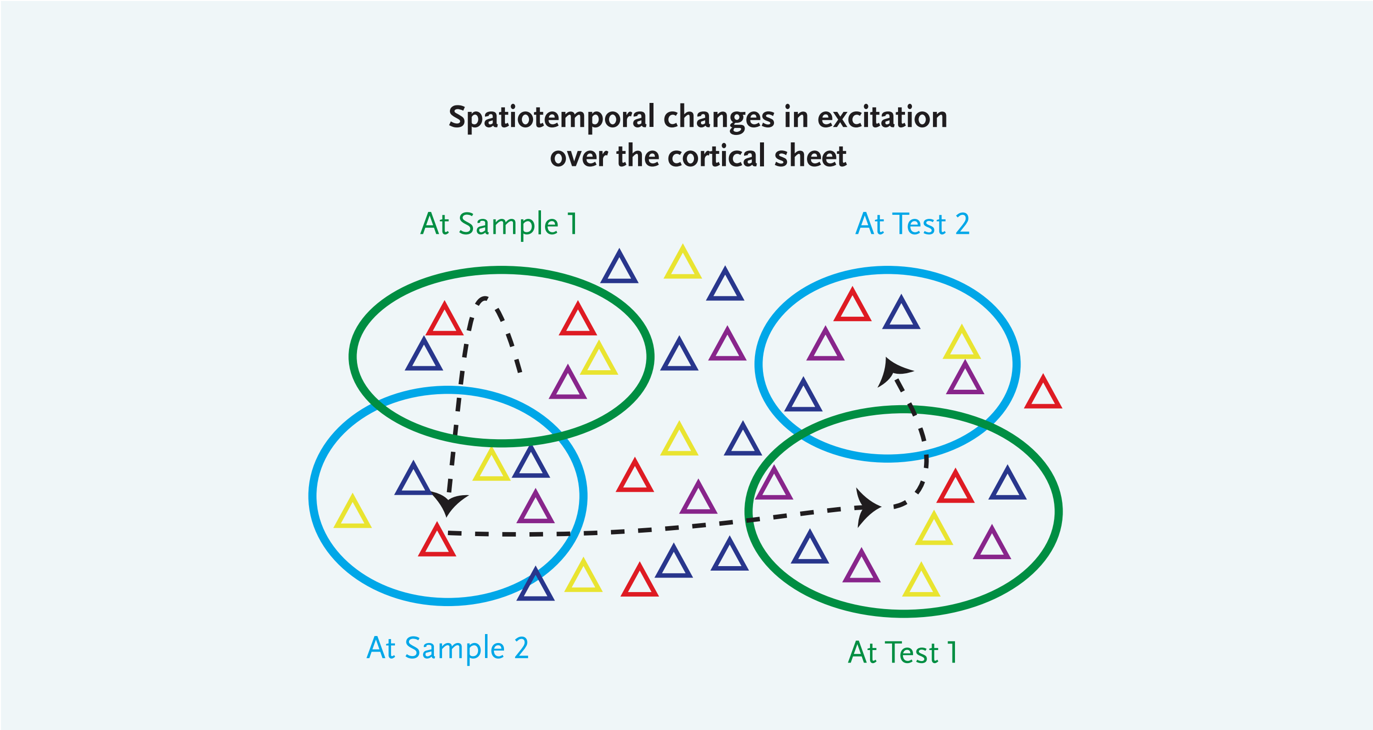
Years of research by Miller's lab, much of it led by lead author Mikael Lundqvist who is now at Karolinska, have shown that working memory tasks are governed by an interplay of brain rhythms at distinct frequencies. Slower beta waves carry information about task rules and selectively yield to faster gamma waves when it's time to execute operations such as storing information from the senses or reading it out when recall is needed. But these waves operate on networks of millions of neurons, only a smattering of which are actually storing the individual items of information relevant at any particular time. Moreover, neurons that carry information about specific items are found all over the place. Some become electrically excited, or "spike," in response to different task rules than others, and they often tend to spike at least somewhat even when their information isn't relevant.

So how can these rather imprecise rhythms selectively control just the right neurons at the right times to do the right things? Why are neurons whose spiking relates to specific items scattered and redundant? What makes one neuron that's particular to "350 degrees" perk up when that information has to be stored but another neuron with that information perk up when it needs to be recalled?

The researchers realized that all these questions could be resolved by the Spatial Computing theory. Individual neurons representing information items can be scattered widely around the cortex, but the rule that's applied to them is based on the patch of the network they are in. Those patches are determined by the pattern of beta and gamma waves.

"By analyzing a lot of single neurons throughout the years, we had always wondered why so many of them appeared to behave similarly," Lundqvist said. "Regardless of if they preferred the same external stimulus or not, many neurons shared similar patterns of activity during working memory. And these patterns switched from task to task. It also appeared that neurons that were closer together within prefrontal cortex more often shared the same pattern. It started us thinking that memory representations might actually dynamically flow around in prefrontal cortex to implement task rules."

So say your friend calls you at the gym, asking you to retrieve a watch they accidentally left in their locker. This requires turning the padlock dials to the numbers in the combination (e.g. 24, 17, 32). Spatial Computing says that when you hear the combination your brain creates distinct patches for each step (first, second, third). Within each patch the neurons representing the combination number of that particular step become especially excited by gamma waves applied at the time the rule is relevant (i.e. 24 in the "first" patch, 17 in the "second" patch and 32 in the "third" patch). In this way individual neurons encoding specific items of information can be selectively associated with general rules by the brain waves controlling the patches they inhabit. In any given patch, all the neurons may be



The Spatial Computing concept: Triangles represent neurons. Colors represent specific information they encode. The ovals represent patches in which brain waves represent task rules. For instance, Sample 1 could be the first instruction to remember. In a specific instance of a task, the neurons representing content presented at sample 1 (say, the yellow triangle) would spike the most in the Sample 1 patch.

excited somewhat by the gamma waves, but the ones representing the item that fits the rule will spike the most.

"This way memory representations could be dynamically reshaped to fit current task demands independent of how individual neurons are connected or which stimulus they prefer," said co-senior author Pawel Herman of KTH. "It may explain our impressive generalization capabilities in novel situations."

This is not to say that any patch is forever fixed. The patches can come and go for however long they are needed wherever the brain happens to form them for the task at hand. There is no permanent "remember oven temperature" patch in the brain.

"This gives the brain flexibility," Miller said. "Cognition is all about flexibility."

Experimental evidence

The researchers weren't just theorizing. To test Spatial Computing in real physical brains, they made four experimental predictions about what they should observe as animals played working memory games such as remembering a set of images in an order.

The first prediction was that there should be distinct neural signals about the rules and individual item information. Indeed, the team measured that bursts of waves carried rule information. Individual neural spikes, meanwhile, carried a mix of individual items and task rules, consistent with them representing individual items and having specific rules imposed on them.

The second prediction was that rules information should be spatially organized and the third prediction was that these rule-enforcing spatial patterns should be consistent so long as the game rules remained the same, regardless of whether the individual items changed. Sure enough, the researchers found that there were different locations of gamma bursts for different rules and that these stayed stable even when the individual items varied during each game.

The final prediction was that the activity of the brain waves should cause neural spiking activity to represent the right information at the right times. This was reflected in the experimental observations, as well. The researchers saw different brain wave patterns for when the brain had to store images in memory and when it had to recall the "right" one. Generally, beta waves were more reduced and neurons spiked more and in a wider area during recall than during storage.

The paper doesn't answer every question about working memory. It's not clear yet, how neurons encoding specific information in one patch might be associated with their brethren in another patch or how the brain controls the patches. More research can answer those further questions about the implications of the new theory of Spatial Computing.

In addition to Miller, Lundqvist, and Herman the paper's other authors are Scott Brincat, Jonas Rose, Melissa Warden and Timothy Buschman.

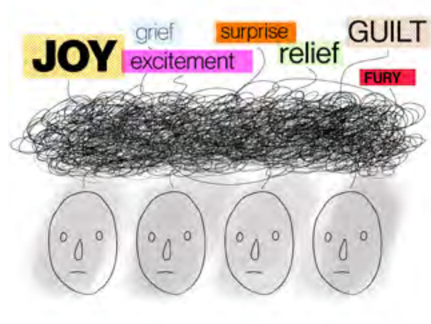
Study funders include The Picower Institute and The JPB Foundation, The European Research Council, the Swedish Research Council, the Brain and Behavior Research Foundation, the National Institutes of Health, and the Office of Naval Research.

Computational model mimics humans' ability to predict emotions

Using insights into how people intuit others' emotions, researchers have designed a model that approximates this aspect of human social intelligence

Anne Trafton | MIT News

MIT neuroscientists designed a computational model that can predict other people's emotions — including joy, gratitude, confusion, regret, and embarrassment — approximating human observers' social intelligence. The model was designed to predict the emotions of people involved in a situation based on the prisoner's dilemma, a classic game theory scenario in which two people must decide whether to cooperate with their partner or betray them.



To build the model, the researchers incorporated several factors that have been hypothesized to influence people's emotional reactions, including that person's desires, their expectations in a particular situation, and whether anyone was watching their actions.

"These are very common, basic intuitions, and what we said is, we can take that very basic grammar and make a model that will learn to predict emotions from those features," says Rebecca Saxe, the John W. Jarve Professor of Brain and Cognitive Sciences, a member of MIT's McGovern Institute for Brain Research, and the senior author of the study.

Sean Dae Houlihan PhD '22, a postdoc at the Neukom Institute for Computational Science at Dartmouth College, is the lead author of the paper, which appeared in *Philosophical Transactions A*. Other authors include Max Kleiman-Weiner PhD '18, a postdoc at MIT and Harvard University; Luke Hewitt PhD '22, a visiting scholar at Stanford University; and Joshua Tenenbaum, a professor of computational cognitive science at MIT and a member of the Center for Brains, Minds, and Machines and MIT's Computer Science and Artificial Intelligence Laboratory (CSAIL).

To try to model how human observers predict emotional responses to events before they occur, the researchers used scenarios taken from a British game show called "Golden Balls." On the show, contestants are paired up with a pot of $100,000 at stake. After negotiating with their partner, each contestant decides, secretly, whether to split the pool or try to steal it. If both decide to split, they each receive $50,000. If one splits and one steals, the stealer gets the entire pot. If both try to steal, no one gets anything.

Depending on the outcome, contestants may experience a range of emotions — joy and relief if both contestants split, surprise and fury if one's opponent steals the pot, and perhaps guilt mingled with excitement if one successfully steals.

To create a computational model that can predict these emotions, the researchers designed three separate modules. The first module is trained to infer a person's preferences and beliefs based on their action, through a process called inverse planning. "This is an idea that says if you see just a little bit of somebody's behavior, you can probabilistically infer things about what they wanted and expected in that situation," Saxe says.

Using this approach, the first module can predict contestants' motivations based on their actions in the game. For example, if someone decides to split in an attempt to share the pot, it can be inferred that they also expected the other person to split. If someone decides to steal, they may have expected the other person to steal, and didn't want to be cheated. Or, they may have expected the other person to split and decided to try to take advantage of them.

The model can also integrate knowledge about specific players, such as the contestant's occupation, to help it infer the players' most likely motivation.

The second module compares the outcome of the game with what each player wanted and expected to happen. Then, a third module predicts what emotions the contestants may be feeling, based on the outcome and what was known about their expectations. This third module was trained to predict emotions based on predictions from human observers about how contestants would feel after a particular outcome. The authors emphasize that this is a model of human social intelligence, designed to mimic how observers causally reason about each other's emotions, not a model of how people actually feel.

Once the three modules were up and running, the researchers used them on a new dataset from the game show to determine how the models' emotion predictions compared with the predictions made by human observers. This model performed much better at that task than any previous model of emotion prediction.

The model's success stems from its incorporation of key factors that the human brain also uses when predicting how someone else will react to a given situation, Saxe says. Those include computations of how a person will evaluate and emotionally react to a situation, based on their desires and expectations, which relate to not only material gain but also how they are viewed by others.

Research In Brief

Studies of unusual brains reveal critical insights into brain organization, function

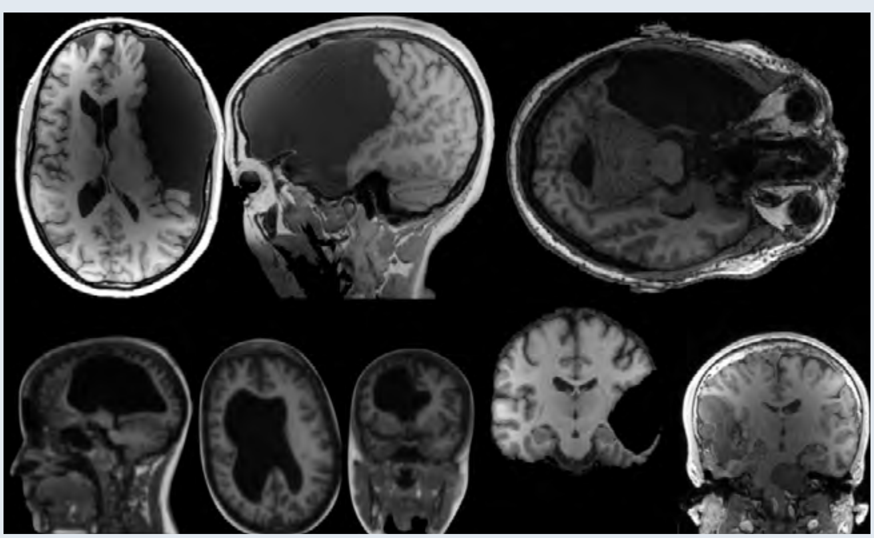
E.G. (a pseudonym) is an accomplished woman in her early 60s. She also has, likely since birth, been missing her left temporal lobe, a part of the brain known to be critical for language. In 2016, E.G. contacted McGovern Institute for Brain Research Investigator Evelina Fedorenko to see if her team might be interested in including her in their research.

Previous studies have shown that language processing relies on an interconnected network of frontal and temporal regions in the left hemisphere of the brain. E.G.'s unique brain presented an opportunity for Fedorenko's team to explore how language develops in the absence of the temporal part of these core language regions.

Their results appeared recently in the journal *Neuropsychologia*. They found, for the first time, that temporal language regions appear to be critical for the emergence of frontal language regions in the same hemisphere — meaning, without a left temporal lobe, E.G.'s intact frontal lobe did not develop a capacity for language.

They also reveal much more: E.G.'s language system resides happily in her right hemisphere. "Our findings provide both visual and statistical proof of the brain's remarkable plasticity, its ability to reorganize, in the face of extensive early damage," says Greta Tuckute, a graduate student in the Fedorenko lab and first author of the paper. "It is incredible that a person can use a single hemisphere — and the right hemisphere at that, which in most people is not the dominant hemisphere where language is processed — and be perfectly fine," says Tuckute.

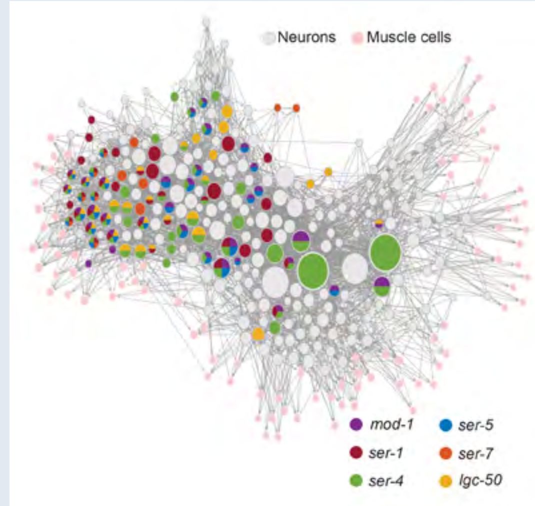
Thea Singer



A collection of anatomical MRIs from the Interesting Brains project.
Image: Hope Keanl/Fedorenko lab

From molecular to whole-brain scale in a simple animal, study reveals serotonin's effects

In a new study, researchers at BCS and The Picower Institute for Learning and Memory at MIT presented a comprehensive accounting of how serotonin affects a simple animal model's behavior from the scale of individual molecules all the way to the animal's whole brain.



A wiring diagram of the C. elegans worm shows neurons and muscle cells (dots) that express receptors for serotonin. Each color denotes a specific receptor. Some neurons express more than one.

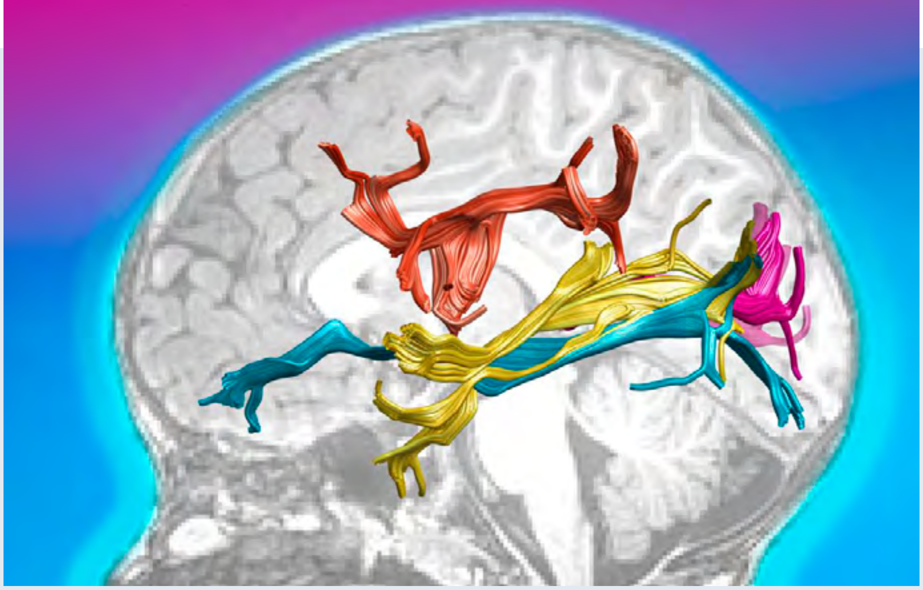
"There have been major challenges in rationally developing psychiatric drugs that target the serotonergic system," said Steve Flavell, associate professor in The Picower Institute and MIT's Department of Brain and Cognitive Sciences, and senior author of the study in *Cell*. "The system is wildly complex. There are many different types of serotonergic neurons with widespread projections throughout the brain and serotonin acts through many different receptors, which are often activated in concert to change the way that neural circuits work."

These same complexities that scientists face in people are all afoot in the nematode worm *C. elegans*, but to a more manageably limited degree. Flavell's team has developed imaging technologies that enable them to track and map neural activity across the worm's brain simultaneously. The lab was therefore able to produce a novel study revealing how the far-reaching molecular activity of serotonin changes brain-wide activity and behavior.

"These results provide a global view of how serotonin acts on a diverse set of receptors distributed across a connectome to modulate brain-wide activity and behavior," the research team wrote in *Cell*.

The study's co-lead authors are Picower Institute postdoc Ugur Dag, MIT Brain and Cognitive Sciences graduate student Di Kang, and former research technician Ijeoma Nwabudike.

David Orenstein | Picower Institute



MIT neuroscientists discovered anatomical changes that occur in the white matter pathways linking visual-processing areas of the brain in children who have congenital cataracts surgically removed. This image shows the late-visual pathways in the brain.

Scientists discover anatomical changes in the brains of the newly sighted

For many decades, neuroscientists believed there was a “critical period” in which the brain could learn to make sense of visual input, and that this window closed around the age of 6 or 7.

Recent work from MIT Professor Pawan Sinha has shown that the picture is more nuanced than that. In many studies of children in India who had surgery to remove congenital cataracts beyond the age of 7, he has found that older children can learn visual tasks such as recognizing faces, distinguishing objects from a background, and discerning motion.

In a new study, Sinha and his colleagues now discovered anatomical changes that occur in the brains of these patients after their sight is restored. These changes, seen in the structure and organization of the brain’s white matter, appear to underlie some of the visual improvements that the researchers also observed in these patients. The findings further support the idea that the window of brain plasticity, for at least some visual tasks, extends much further than previously thought.

Bas Rokers, an associate professor and director of the Neuroimaging Center at New York University Abu Dhabi, is the senior author of the study, which appeared in the *Proceedings of the National Academy of Sciences*. The paper’s lead authors are Caterina Pedersini, a postdoc at New York University Abu Dhabi; Nathaniel Miller, who is studying medicine at the University of Minnesota Medical School; and Tapan Gandhi, a former postdoc in the Sinha Lab who is now an associate professor at the Indian Institute of Technology. Sharon Gilad-Gutnick, an MIT research scientist, and Vidur Mahajan, director of the Center for Advanced Research on Imaging, Neuroscience, and Genomics, are also authors of the paper.

Anne Trafton | MIT News

Self-assembling proteins can store cellular “memories”

As cells perform their everyday functions, they turn on a variety of genes and cellular pathways. MIT engineers have now coaxed cells to inscribe the history of these events in a long protein chain that can be imaged using a light microscope.

Cells programmed to produce these chains continuously add building blocks that encode particular cellular events. Later, the ordered protein chains can be labeled with fluorescent molecules and read under a microscope, allowing researchers to reconstruct the timing of the events.

This technique could help shed light on the steps that underlie processes such as memory formation, response to drug treatment, and gene expression.

“There are a lot of changes that happen at organ or body scale, over hours to weeks, which cannot be tracked over time,” says Edward Boyden, the Y. Eva Tan Professor in Neurotechnology, a professor of biological engineering and brain and cognitive sciences at MIT, a Howard Hughes Medical Institute investigator, and a member of MIT’s McGovern Institute for Brain Research.

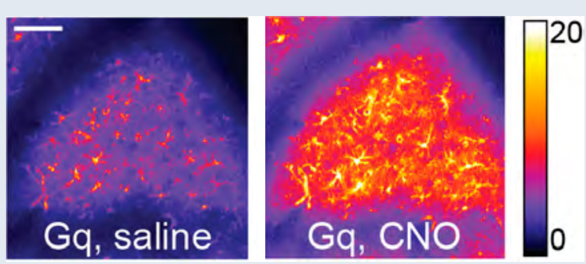
If the technique could be extended to work over longer time periods, it could also be used to study processes such as aging and disease progression, the researchers say.

Boyden is the senior author of the study, which appears today in *Nature Biotechnology*. Changyang Linghu, a former J. Douglas Tan Postdoctoral Fellow at the McGovern Institute, who is now an assistant professor at the University of Michigan, is the lead author of the paper.

Anne Trafton | MIT News

Astrocyte cells critical for learning skilled movements

From steering a car to swinging a tennis racket, we learn to execute all kinds of skilled movements during our lives. You might think this learning is only implemented by neurons, but a new study by researchers at The Picower Institute for



Researchers intervened in the brains of mice to affect the contribution of astrocytes to motor learning. Imaging based on calcium levels in astrocytes demonstrates the effect of one such intervention (activating Gq signaling with a chemical called CNO). Cells lit up bright orange upon CNO application (right panel). Credits: Image: Jennifer Shih/Sur Lab

Learning and Memory at MIT shows the essential role of another brain cell type: astrocytes.

Just as teams of elite athletes train alongside staffs of coaches, ensembles of neurons in the brain's motor cortex depend on nearby astrocytes to help them learn to encode when and how to move, and the optimal timing and trajectory of a motion, the study shows. Describing a series of experiments in mice, the new paper in the *Journal of Neuroscience* reveals two specific ways that astrocytes directly impact motor learning, maintaining an optimal molecular balance in which the neuronal ensembles can properly refine movement performance.

"This finding is part of a body of work from our lab and other labs that elevate the importance of astrocytes to neuronal encoding and hence to behavior," says senior author Mriganka Sur, the Newton Professor of Neuroscience in The Picower Institute and MIT's Department of Brain and Cognitive Sciences. "This shows that while the population coding of behaviors is a neuronal function, we need to include astrocytes as partners with them."

Picower Institute postdoc Jennifer Shih and former Sur Lab postdocs Chloe Delepine and Keji Li are the paper's co-lead authors.

David Orenstein | Picower Institute

TA Spotlight:

Thomas Hikaru Clark

Dept. of Brain and Cognitive Sciences

Thomas Hikaru Clark was a high school teacher with no plans for academia when he learned about the research being done at MIT's Department of Brain and Cognitive Sciences. "During my undergrad, I was interested in computer science and linguistics, but never really found a satisfying way to combine those research interests," he says. "But then a classmate from college connected me with the exciting, interdisciplinary language research happening at BCS, re-sparking my desire to pursue research."

Clark, now a second-year PhD student in BCS, didn't leave his passion for teaching behind, as evidenced by his recent TA Spotlight Award. The award is a chance for BCS graduate students to nominate peers who have gone above and beyond in their dedication and commitment to TA-ing.

Clark recently TA-ed for Course 9.66 (Computational Cognitive Science) with professor Josh Tenenbaum. "My favorite thing about TA-ing is working with students during office hours and recitations," he says. "Taking complex ideas and breaking them down into smaller components, along with providing examples and multiple levels of explanations, feels very rewarding. It was great to see the progress among students who consistently came to office hours over the course of the semester."

A particularly memorable moment from the class was the first glimpse of experimental data students collected for their final projects. "Examining this data and generating visualizations allowed the students to take ideas from the class and actually investigate how they stack up with reality," he says.

Clark's research combines experimental and corpus data with AI language models to understand information-theoretic pressures on language production and processing. "I'm particularly interested in how people solve the complex problem of communication despite constraints, such as in non-neurotypical populations," he says. Clark is co-advised by Roger Levy and Ted Gibson.

TA-ing has contributed to his research, Clark says. "Being a TA for 9.66 reinforced my knowledge of core computational cognitive science concepts, exposing me to the latest papers and meeting new people, such as the other TAs and the students in the class. I have enjoyed staying in touch with some of the students I mentored, including at least one student who is working on expanding his project into a publishable work," he says. "Being able to help out with this is giving me a broader repertoire of cognitive science skills."

What would be Clark's advice for BCS students? "Don't worry too much about extrinsic incentives like grades, and simply pursue the things that you find exciting, interesting, and thought-provoking. Find the people and resources who will help you learn more about these topics and ask lots of questions. Finally, make sure to prioritize your mental health and well-being."

"TA Spotlights" is an occasional series featuring BCS's most outstanding teaching assistants, their work, and their journey as educators.

brain+cognitive sciences

Massachusetts Institute of Technology
77 Massachusetts Ave
Cambridge, MA 02139

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bcs news

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.

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