Consciousness

Emerging evidence shows how brain waves help to knit our internal thoughts and external awareness together into an organized, unified whole.

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On the surface, the movement disorder amyotrophic lateral sclerosis (ALS) and the cognitive disorder frontotemporal lobar degeneration (FTLD), which underlies frontotemporal dementia, manifest in very different ways. They also primarily affect different regions of the brain.

However, doctors and scientists have noted several similarities over the years. An MIT study in *Cell* reveals that the diseases have remarkable overlaps at the cellular and molecular levels, revealing potential targets that could yield therapies applicable to both disorders. The study also showed that brain circuits with inherited vs. sporadic forms of the diseases showed similarly altered gene expression changes, even though these were previously thought to derive from different causes.

That suggests similar molecular processes could be driving very downstream of the diseases’ origins.

The paper tracked RNA expression patterns in 620,000 cells spanning 44 different cell types across motor cortex and prefrontal cortex from postmortem brain samples of 73 donors diagnosed with ALS, FTLD, or who were neurologically unaffected. The study’s senior authors are Myrtis Heiman, associate professor in The Picower Institute, MIT computer science professor Manolis Kellis, and Veronique Belzil, director of the ALS Research Center at Vanderbilt University. Sebastian Pineda, a graduate student jointly supervised by Heiman and Kellis, led the study.

The results revealed that in both diseases the most vulnerable neurons were almost identical, both in the genes they express, and in how these genes changed in expression in each disease. “These similarities were quite striking, suggesting that therapies for ALS may also apply to FTLD and vice versa,” Heiman said. “Our study can help guide therapeutic programs that would likely be effective for both diseases.”

In ALS, known to cause progressive paralysis and early death, the most endangered cells in the brain are upper motor neurons (UMN) in layer 5 of the motor cortex. Meanwhile, in behavioral variant frontotemporal dementia, the most common type of FTLD, characterized by changes to personality and behavior) the most vulnerable neurons are spindle neurons, or von Economo cells, found in layer 5 of more frontal brain regions. While these cells look different under the microscope, and make distinct connections in brain circuits, their gene expression in health and disease proved to be strikingly similar.

The researchers found many of the genes involved in the two diseases implicated primarily in clila, tiny antenna-like structures on a cell’s surface that sense chemical changes in the cell’s surrounding environment. Clila are necessary for guiding the growth of axons, or long nerve fibers that neurons extend to connect with other neurons. Cells that are more dependent on this process, typically those with the longest projections, were found to be more vulnerable in each disease.

The analysis also found another type of neuron, which highly expresses the gene SCN4B and which was seen to produce several of the same sets of proteins, a hallmark of Alzheimer’s disease pathology, via the brain’s glymphatic system. The blood-brain barrier (BBB), a filtering system tightly associated with either disease, also shared many of the same characteristics and showed similar disruptions. Looking beyond neurons, the study characterized gene expression differences in many other brain cell types. Notably, researchers saw several signs of trouble in the brain’s circulatory system. The blood-brain barrier, which regulates which molecules can go in or come out of the brain through blood vessels, is believed to be compromised in both disorders.

For instance, they found a reduction of HLA-E, a molecule thought to inhibit BBB degradation by the immune system.
Patients undergoing chemotherapy often experience cognitive effects such as memory impairment and difficulty concentrating—a condition known as “chemo brain.” MIT researchers have now shown that a noninvasive treatment that stimulates gamma frequency brain waves may hold promise for treating chemo brain. In a study of mice, they found that daily exposure to light and sound at a frequency of 40 Hz protected brain cells from chemotherapy-induced damage. The treatment also helped to prevent memory loss and impairment of other cognitive functions.

“The treatment can reduce DNA damage, reduce inflammation, and increase the number of oligodendrocytes, which are the cells that produce myelin surrounding the axons,” said Professor Li-Huei Tsai, director of the Picower Institute. “We also found that this treatment improved learning and memory, and enhanced executive function in the animals.”

Tsai is the senior author of the new study in Science Translational Medicine. The paper’s lead author is TaeHyun Kim, an MIT postdoc.

Studies in Alzheimer’s model mice has found that exposure to light flickering at 40 Hz or sounds with a pitch of 40 Hz can stimulate gamma waves in the brain, which has many protective effects, including clearing amyloid beta proteins. Using light and sound together provides even more significant protection. Phase II clinical trials in people with early-stage Alzheimer’s disease have found the treatment is safe and offers some neurological and behavioral benefits.

In the new study, the researchers set out to see whether this treatment could also counteract the cognitive effects of chemotherapy treatment. Research has shown that chemotherapy can induce inflammation in the brain, as well as other detrimental effects such as loss of white matter—the networks of nerve fibers that help different parts of the brain communicate with each other. Chemotherapy drugs also promote loss of myelin, the protective fatty coating that allows neurons to propagate electrical signals. Many of these effects are also seen in the brains of people with Alzheimer’s.

“Chemo brain caught our attention because it is extremely common, and there is quite a lot of research on what the brain is like following chemotherapy treatment,” Tsai says. “From our previous work, we know that this gamma sensory stimulation has anti-inflammatory effects, so we decided to use the chemo brain model to test whether sensory gamma stimulation can be beneficial.”

As an experimental model, the researchers used mice that were given cisplatin, a chemotherapy drug often used to treat testicular, ovarian, and other cancers. The mice were given cisplatin for five days, then taken off of it for five days, then on again for five days. One group received chemotherapy only, while another group was also given 40 Hz light and sound therapy every day.

After three weeks, mice that received cisplatin but not gamma therapy showed many of the expected effects of chemotherapy: brain volume shrinkage, DNA damage, demyelination, and inflammation. These mice also had reduced populations of oligodendrocytes, the brain cells responsible for producing myelin.

However, mice that received gamma therapy along with cisplatin treatment showed significant reductions in all of those symptoms. The gamma therapy also had beneficial effects on behavior: Mice that received the treatment performed much better on tests designed to measure memory and executive function.

Using single-cell RNA sequencing, the researchers analyzed the gene expression changes that occurred in mice that received the gamma treatment. They found that in those mice, inflammation-linked genes and genes that trigger cell death were suppressed, especially in oligodendrocytes. In mice that received gamma treatment along with cisplatin, some of the beneficial effects could still be seen up to four months later. However, the gamma treatment was much less effective if it was started three months after the chemotherapy ended.

The researchers also showed that the gamma treatment improved the signs of chemo brain in mice that received a different chemotherapy drug, methotrexate, which is used to treat breast, lung, and other types of cancer. Because of its widespread effects, Tsai’s lab is also testing gamma treatment in mouse models of other neurological diseases, including Parkinson’s disease and multiple sclerosis.

“My lab’s major focus now, in terms of clinical application, is Alzheimer’s; but hopefully we can test this approach for a few other indications too,” Tsai says.

In the brain, individual cells electrochemically transmit signals in circuits, but at the large scale required to produce cognition, millions of cells act in concert, driven by rhythmic signals at varying frequencies. Studying one frequency range in particular, beta rhythms between about 14–30 Hz, holds the key to understanding how the brain controls cognitive processes— or loses control in some disorders—neuroscientists argue in a new review article.

“Understanding cognition—and its dysfunction—requires learning its rhythms. Given the relevance of beta oscillations in cognition, we foresee a major change in the practice for biomarker identification, especially given the prominence of beta rhythms in inhibitory control processes... and their importance in ADHD, schizophrenia and Alzheimer’s disease,” they wrote in the journal Trends in Cognitive Science.

Experimental studies covering several species including humans, a variety of brain regions, and numerous cognitive tasks have revealed key characteristics of beta waves in the cortex, the authors write. Beta rhythms occur in quick but powerful bursts; they inhibit the power of higher frequency gamma rhythms; and though they originate in deeper brain regions, they travel within specific locations of cortex. Considering these properties together, the authors write that they are all consistent with precise and flexible regulation, in space and time, of the gamma rhythm activity that experiments show carry signals of sensory information and motor plans.

**Understanding cognition—and its dysfunction—requires learning its rhythms.**

Cognition is an emergent property in the brain. It cannot be understood by looking only at individual cells. It’s apparent only by observing how millions of cells act in coordination, argues a trio of MIT neuroscientists. In a new article, they lay out a framework for understanding how thought arises from the coordination of neural activity driven by oscillating electric fields—also known as a brain “wave” or “rhythms.” The study of the brain at that scale, they write, provides a unique opportunity to study brain function.

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When place cells become activated at their target location, they emit an activity that reports their electrical activity.

Knowing where you are is so important, the brain has special cells that dedicate themselves to the purpose. In a new study in Science, a team of neuroscientists has, for the first time, demonstrated in live behaving animals a long-hypothesized mechanism that such “place cells” employ to refine their tuning to the location, making their sense of place less accurate.

The researchers had mice run on a treadmill as key landmarks periodically passed them by. Meanwhile they labeled and observed two specific kinds of mice with autism-like symptoms whose mothers had not been infected with a virus that sparks a fever, their autism-related symptoms seem to improve. With a pair of grants from The Marcus Foundation, scientists at MIT and Harvard hope to explain how this happens in an effort to develop therapies to improve symptoms. Such a therapy, which involves flickering light and a gamma band frequency of the brain associated with learning and memory, the researchers said. The team has also begun a clinical study of human patients with Down syndrome. Testing so far is finding that light or light and sound combined increases the strength of the 40Hz gamma rhythm in the brain, as it does in Alzheimer’s patients and mouse models. With more volunteers, the team hopes to determine if the stimulation produces cognitive or functional benefits, Tsai said. The team is especially looking to include people in their 20s and 30s before the onset of Alzheimer’s disease symptoms.

When with Down syndrome was very low but today, many speakers at the MDSC conference noted, it extends past 60 years. But after the age of 40 the prevalence of Alzheimer’s disease among people with Down syndrome becomes very high. Many researchers believe a major reason is that the amyloid precursor protein gene, a risk factor for Alzheimer’s, resides on chromosome 21, which is the chromosome that has an extra copy in Down syndrome. Several studies in mice have indicated that 40Hz sensory stimulation may help clear the accumulation of amyloid proteins from the brain. Meanwhile, early stage studies with human volunteers have found evidence of improvements in cognition.

How the brain can be flexible and focused

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Understanding the "fever effect" in autism

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Five new PhDs minted in Picower labs

Congratulations to five MIT graduate students who have each recently earned doctoral degrees for research in Picower Institute labs. Their studies ranged from new technologies for imaging brain structure and function, to understanding the dynamic roles of neural circuit connections in brain health and disease, to whether Alzheimer’s can be better understood by examining brain waves during sleep.

- **Dr. Alex He**, Brown Lab, "State-space Modeling of Neural Oscillations: Toward Assessing Alzheimer’s Disease Neuropathology with Sleep EEG”
- **Dr. Sara Kornfeld Simpson**, Bear Lab, "Illuminating the Brain: Advances in and Synaptic Basis of Mouse Binocular Labeling and Imaging”
- **Dr. Yuxuan Tian**, Chung Lab, "Multiplexed, scalable, and functionality compatible platforms for 3D spatially resolved proteomic profiling”
- **Dr. Dae Hee Yun**, Chung Lab, "Illuminating the Brain: Advances in High-Resolution, Multi-Scale Proteomic Labeling and Imaging”
- **Dr. Katy Tolmien**, Sae Lab, "Cellular and Synaptic Basis of Mouse Binocular Cortical Circuit Development”

Steve Flavell earns tenure

On May 6 Brain and Cognitive Sciences Interim Department Head Josh McDermott announced to the faculty that Picower Institute Investigator Steve Flavell had been awarded tenure at MIT effective July 1. McDermott praised Flavell’s "terrific scientific achievements and exceptional mentorship." Flavell’s lab seeks to discover neural mechanisms that allow brain circuits to generate long-lasting behavioral states and studies how physiological and sensory cues affect the outputs of the neural circuits that control those states. Working in the model organism, the C. elegans worm, the lab has recently published studies relating neural activity across the brain to behaviors, and mapping effects of serotonin release neuron by neuron brainwide.

Faculty honored as “Committed to Caring”

The Committed to Caring (C2C) program at MIT is a student-driven initiative that celebrates faculty members who have served as exceptional mentors to graduate students. Twenty-three MIT professors including Picower Investigators Myriam Heiman and Emery N. Brown have been selected as recipients of the C2C award for 2023-25, marking the most extensive cohort of honorees to date. These individuals join the ranks of 75 previous C2C honorees.

The actions of these MIT faculty members over the past two years underscore their profound commitment to the well-being, growth, and success of their students. These educators go above and beyond their roles, demonstrating an unwavering dedication to mentorship, inclusion, and a holistic approach to student development. They aim to create a nurturing environment where students not only thrive academically, but also flourish personally.

BCS department recognizes Picower Institute members

Kudos to three Picower Institute members who earned Brain and Cognitive Sciences Department awards this spring.

- **Associate Professor Steve Flavell**, who received an award for Excellence in Graduate Mentorship
- **Research Scientist David Stoppel**, who was honored with the Angus MacDonald Award for Excellence in Undergraduate Teaching
- **Laboratory Administrator Rhonda Valenti of the Brown Lab**, who was recognized as a “Go-to Person”

Evidently you are conscious and, better yet, you are indulging one of its useful privileges: cognition. But how does your brain achieve your current experience of integrating sensory information—the words and images on this page—with the internal knowledge, motivations and reasoning you are using to understand them?

Picower Professor Earl K. Miller and Edward Hood Taplin Professor Emery N. Brown think about that question (and related ones) a lot, both independently and in close collaboration. But they do so for opposite reasons. As a cognitive neuroscientist, Miller’s job is to discern how the brain endows us with intellectual abilities such as attention, working memory and reasoning. As an anesthesiologist, Brown’s job is to reliably induce, maintain and then conclude a safe and appropriate level of unconsciousness for his patients.

"I’m interested in unconsciousness because I’m interested in consciousness and I think Emery would say the opposite," Miller quipped. By comparing and contrasting brain activity in both states, Miller and Brown are building an understanding of how unconsciousness and consciousness each become manifest. The crux of their findings is that consciousness and cognition require the transmission of information via brain waves, which arise from the rhythmic electrical activity of coordinated groups of neurons. Think of brain waves as biological Wi-Fi signals. They integrate brain regions that have different information processing responsibilities into functional networks.

These waves can vary in their power, frequency, location and degree of alignment (or “phase”). Miller and Brown have shown that these properties differ markedly and systematically when we are conscious vs. when we are not.

When brain wave patterns aren’t conducive to information exchange via synchronized, aligned, high-frequency signals, the experience of consciousness in which external sensation and internal thought feel integrated, falls apart, Miller said.

“Consciousness is a unified experience of the rights, sounds, feelings, knowledge, etc. in any given moment. Many major theories of consciousness involve knitting together networks across the brain so they can create that unified experience,” said Miller, who on April 4 remotely delivered a keynote address to the 30th Annual Science of Consciousness Conference at the University of Arizona. “And for the same reason these brain wave dynamics can organize thoughts, they can also knit together the unified experience of consciousness. We found that loss of consciousness is associated with the dramatic alterations of these dynamics through the different effects of different anesthetic drugs.”

Unconscious lessons

Brown has long studied how anesthetic drugs like propofol, ketamine, or desmethylmedicaine produce states of unconsciousness that differ from that of deep by profoundly (but only temporarily) impairing sensory and cognitive processing. He and colleagues have traced how the drugs’ molecular effects on neurons in specific brain regions alter normal oscillatory activity in key brain circuits.

Brown’s work has shown that each drug produces a distinct brain wave signature in patients that systematically varies with factors such as drug dose, patient age and patient state of health. Monitoring these signatures with scalp-mounted electroencephalogram (EEG) electrodes in the operating room in real-time, a practice that he employs and advocates, reduces the guesswork of inferring how unconscious the patient is. Why rely solely on physical signs such as a lack of movement and stillness of heart rate and blood pressure when you can also directly measure brain state? With a brain-based indicator of unconsciousness, anesthesiologists can refine anesthetic dosing, preventing the administration of too little or, more commonly, too much.

Data from research by the Brown and Miller labs shows strong increases in synchrony only in very slow brain wave frequencies (deep red color) between the thalamic and various cortical regions.

Last year Brown’s lab published a clever method for assessing unconsciousness while volunteers received desmethylmedicaine. Speaking with volunteers can prolong wakefulness and accelerate waking from the “breathe-squeeze” test required volunteers to squeeze a ball every time they breathed. Once they couldn’t they were judged unconscious and once they resumed, they were deemed waked up—no dialogue
required. Meanwhile, the researchers correlated the apparent loss and resumption of consciousness with the brain state changes apparent in the EEG.

In collaboration with Miller, who works with research animals, Brown has further validated the EEG signatures of some anesthetics by simultaneously measuring the electrical discharges (or “spikes”) of hundreds of individual neurons. Brain waves (or “rhythms”) arise when spikes of large groups of neurons are synchronous, so these measures confirmed directly from brain cells what the waves measured from outside the head seemed to indicate.

“It gives me a way of interpreting the EEG in a way that is much more neurophysiologically based,” Brown said. “When I see a dramatic alteration of spiking activity associated with whatever rhythm I’m looking at, it lends support to the idea that altering rhythms is associated with impairing the ability of the brain regions to communicate with each other.”

In 2021 Brown and Miller’s labs showed that under propofol, neurons that spiked as many as 10 times a second during wakefulness spiked once a second or less. The brain therefore could only produce waves of very low frequency across the cortex. Wave coordination and power at higher frequencies associated with consciousness were greatly reduced. The study also showed reduced coordination between the cortex and a deeper region called the thalamus. Consciousness is not solely produced by the cortex, Brown noted, but that is where most cognitive functions take place.

Brown and Miller have also used spiking data from animals and EEG data from humans to establish ketamine’s brain wave signature. Unlike with propofol, ketamine-mediated unconsciousness included periods of high-frequency waves alternating every 4 to 10 seconds with low frequency waves. This pattern is also quite different from consciousness.

“I can make you unconscious by making your brain hyperactive in some sense, or I can make you unconscious by slowing it down,” Brown said at the time. “The more general concept is there’s a dynamic—we can’t define it precisely—which is associated with you being conscious and as soon as you move away from that dynamic by being too fast or too slow, or too disordinated or too hypercoordinated, you can become unconscious.”

Last November Brown and Miller showed that unconsciousness under propofol is characterized not just by a broad change in brain wave patterns but by a disruption in the propagation from region to region. While awake and then under anesthesia, animals received sound and sensory stimuli that both were received normally while awake and then were blocked by the anesthetic drugs. That difference—when the image needs to be remembered in advance of the memory test, beta takes over and prevents gamma from encoding distractions—suggests that beta is associated with consciousness.

Miller’s research, including a paper earlier this year, has shown that beta waves arise most strongly across the cortex in its deeper layers while gamma waves have primary in more superficial layers. Studies in his lab have also shown that these waves physically travel through specific areas of cortex (and that anesthetics radically alter those travels).

All this evidence—that beta controls gamma in spatially precise ways—led Miller to formulate a new theory of cognitive control: Spatial Computing. To selectively control just the right neurons at the right times to do the right things, the brain uses beta waves like a stencil, patterning when and where gamma waves are “allowed” to encode new information. In this way, the brain can recruit groups of neurons to represent new information within the context of a task’s rules. When you hear the combination of a task, according to Spatial Computing, your brain’s beta waves will assign that task rules (turn left, turn right, turn left again) to specific patches of your cortex and then neurons in each patch will encode the relevant number of the combination (e.g. 32, 14, 19). Spatial Computing answers some questions about how thoughts and sensory experiences are integrated quickly and flexibly enough to produce useful cognition, Miller said. Brain waves are based on electric fields, so they can arise and spread very fast. By assigning both task rules and sensory encoding responsibilities to neurons in a patch, Spatial Computing explains how the cells can come to represent multiple aspects of a task (a property called “mixed selectivity”). Moreover, the involvement of different wave frequencies enables task rules and sensory encoding to vary independently. If the combination changes, the brain doesn’t have to relearn the rules. The beta waves encoding the rules can stay the same even as the gamma waves encoding the new numbers vary.

Along with the answers it provides, Spatial Computing raises big questions, too. Miller acknowledges: How does the brain generate the waves that implement these dynamics? Does the brain formulate a map to manage its thoughts? Is that map therefore a map of your consciousness in some way? Answers to any of those questions will require future “waves” of research and insight.

**Upcoming EVENTS**

**The Kogie Vallee Distinguished Lecture**

**September 24, 2024: Lectures**

Hosted by The Picower Institute for Learning and Memory, MIT

**September 25, 2024: Workshops**

The Kogie Vallee Distinguished Lecturer’s give a public lecture about their own science and meet more informally and in workshops with fellow scientists at the host institution to talk about women in science and career building.
OUR VISION
The Picower Institute is a community of scientists dedicated to understanding the mechanisms that drive learning and memory and related functions such as cognition, emotion, perception, and consciousness. Institute researchers explore the brain at multiple scales, from genes and molecules, to cells and synapses, to circuits and systems, producing novel insights into how disruptions in these mechanisms can lead to developmental, psychiatric, or neurodegenerative disease.

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TOP ROW: Mark F. Bear, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences; Emery Brown, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, Department of Brain and Cognitive Sciences, Institute of Medical Engineering and Science core faculty; Gloria Choi, Mark Hyman Jr. Career Development Associate Professor, Department of Brain and Cognitive Sciences; Kwanghun Chung, Associate Professor, Departments of Chemical Engineering and Brain and Cognitive Sciences, Institute of Medical Engineering and Science core faculty; Linlin Fan, Assistant Professor, Department of Brain and Cognitive Sciences; Steven Flavell, Associate Professor, Department of Brain and Cognitive Sciences, Myriam Heiman, Associate Professor of Neuroscience, Department of Brain and Cognitive Sciences; Troy Littleton, Menicon Professor of Biology and Neuroscience, Departments of Biology and Brain and Cognitive Sciences.

BOTTOM ROW: Earl Miller, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences; Elly Nedivi, William R. (1964) & Linda R. Young Professor of Neuroscience, Departments of Brain and Cognitive Sciences and Biology; Sara Prescott, Assistant Professor of Biology; Mriganka Sur, Paul E. Newton Professor of Neuroscience, Director of The Simons Center for the Social Brain, Department of Brain and Cognitive Sciences; Susumu Tonegawa, Picower Professor of Biology and Neuroscience, Departments of Brain and Cognitive Sciences and Biology, Investigator, Howard Hughes Medical Institute, Investigator and Director of the RIKEN-MIT Center for Neural Circuit Genetics; Li-Huei Tsai, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director, The Picower Institute for Learning and Memory; Brady Weissbourd, Assistant Professor of Biology; Matthew Wilson, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Director, The Picower Institute for Learning and Memory.