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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Neuroscience News

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THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Dear Friends,

You've likely heard the old saying: "How do you get to Carnegie Hall? Practice, practice, practice." Well, it turns out what put me on stage at the Boston Symphony Orchestra in April was practicing neuroscience (I haven't picked up a violin in years).

At the BSO I joined a panel discussion among colleagues including MIT music professor Tod Machover. The subject of our discussion was research suggesting that stimulating the brain via the senses (including with rhythmic sound) can affect our health. For instance, my lab has found that exposing mice or people to light that flickers and sound that clicks at 40 Hz may increase the power and synchrony of that "gamma" rhythm among networks of neurons in the brain. We've seen signs that it induces a healthier response to Alzheimer's disease pathology.

This research has surprised many neuroscientists, including me. For a long time the field dismissed neural rhythms, or "brain waves," as mere byproducts of brain function with no causal importance. But our research indicates that stimulating rhythms can affect the underlying activity of neurons and other cell types. For instance on page 3 we describe how 40 Hz sensory stimulation may help clear Alzheimer's-associated proteins from the brain. There are new indications that other disorders could also be treated, including "chemo brain" (p.4) and Down syndrome (p. 7).

Earl Miller and Emery Brown pay close attention to brain waves, too. Our cover story (p.9) describes their research showing the central role that brain waves have in endowing us with consciousness and cognition. This spring Miller has published a trio of review papers (p. 5 and 6) arguing that understanding brain waves could help us understand how the brain organizes thought.

An interesting new theme in both Earl's and my investigations is the idea that brain waves not only emerge from underlying cellular activity, they also may influence it.

There is still a lot of work to do to understand how the brain works on its multiple scales, from genes and molecules to networks of millions of cells. So to quote another rhythmic reference, "The beat goes on."

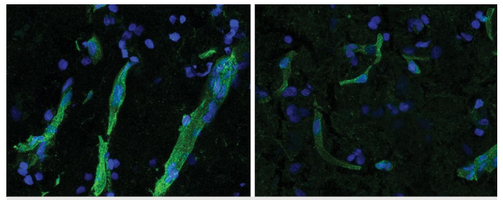
LI-HUEI TSAI, DIRECTOR

The Picower Institute for Learning and Memory

ALS, FTLD show strong molecular overlaps

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 donors with inherited vs. sporadic forms of the diseases showed similarly altered gene expression changes, even though these were previously thought to have different causes. That suggests that similar molecular processes could be going awry downstream of the diseases' origins.



Motor cortex tissue from a donor with ALS (right) shows reduced amounts of HLA-E (green) in blood vessels compared to a control (left). Researchers found reduced expression of HLA-E in both ALS and FTLD.

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 Myriam 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 that they express, and in how these genes changed in expression in each disease.

"These similarities were quite striking, suggesting that therapeutics 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 ultimately 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 the 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 primary cilia, tiny antenna-like structures on a cell's surface that sense chemical changes in the cell's surrounding environment. Cilia 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 not previously associated with either disease, also shared many of the same characteristics and showed similar disruptions.

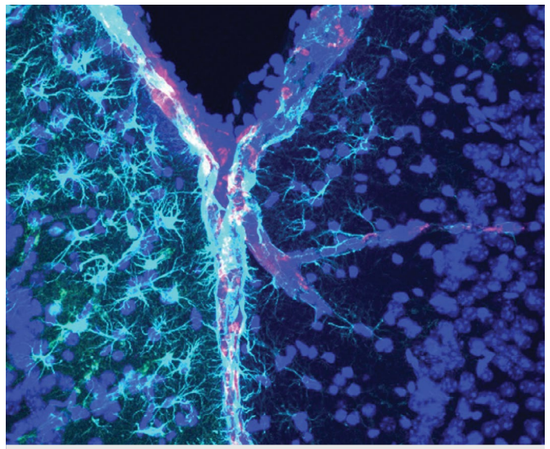
Looking beyond neurons, the study characterized gene expression differences in many other brain cell types. Notably, researchers saw several signs of trouble in the brain's circulatory system. The blood-brain barrier (BBB), a filtering system that tightly regulates which molecules can go into or come 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.

How sensory gamma rhythm stimulation clears amyloid

In a study in *Nature*, researchers at The Picower Institute revealed a key mechanism that may contribute to the apparent benefits of sensory stimulation of gamma frequency brain rhythms: clearance of amyloid proteins, a hallmark of Alzheimer's disease pathology, via the brain's glymphatic system, a recently discovered "plumbing" network parallel to the brain's blood vessels.

"Ever since we published our first results in 2016, people have asked me how does it work? Why 40 Hz? Why not some other frequency?" said study senior author Li-Huei Tsai, Picower Professor of Neuroscience. "These are indeed very important questions we have worked very hard in the lab to address."

The new paper describes a series of experiments, led by Mitch Murdock when he was a doctoral student, showing that when sensory gamma stimulation increases 40 Hz power and synchrony in the brains of mice, that prompts a particular type of neuron to release peptides. The study results further suggest that those short protein signals then drive specific processes that promote increased amyloid clearance via the glymphatic system.



An image from the research highlighting astrocytes (cyan), other cells (blue), and brain vasculature, along which glymphatic clearance occurs.

"We do not yet have a linear map of the exact sequence of events that occurs," said Murdock, who was jointly supervised by Tsai and co-author and collaborator Ed Boyden, Y. Eva Tan Professor of Neurotechnology. "But the findings in our experiments support this clearance pathway through the major glymphatic routes."

Because prior research has shown that the glymphatic system is a key conduit for brain waste clearance and may be regulated by brain rhythms, the team hypothesized that it might help explain the lab's prior observations that gamma sensory stimulation reduces amyloid levels in Alzheimer's model mice.

Working with "5XFAD" mice, which genetically model Alzheimer's, Murdock and co-authors replicated the lab's prior results that 40 Hz sensory stimulation increases 40 Hz neuronal activity and reduces amyloid. Then they set out to measure whether there was any correlated change in the fluids that flow through the glymphatic system to carry away wastes. Indeed, they measured increases in cerebrospinal fluid in the brain tissue of mice treated with sensory gamma stimulation compared to untreated controls. They also measured an increase in the rate of interstitial fluid leaving the brain. Moreover, in the gamma-treated mice they measured increased diameter of the lymphatic vessels that drain away the fluids and measured increased accumulation of amyloid in cervical lymph nodes, which is the drainage site for that flow.

To investigate how this increased fluid flow might be happening, the team focused on the aquaporin 4 (AQP4) water channel of astrocyte cells, which enables the cells to facilitate glymphatic fluid exchange. When they blocked APQ4 function with a chemical, that prevented sensory gamma stimulation from reducing amyloid levels and prevented it from improving mouse learning and memory. And when, as an added test they used a genetic technique for disrupting AQP4, that also interfered with gamma-driven amyloid clearance.

In addition to the fluid exchange promoted by APQ4 activity in astrocytes, another mechanism by which gamma waves promote glymphatic flow is by increasing the pulsation of neighboring blood vessels. Several measurements showed stronger arterial pulsatility in mice subjected to sensory gamma stimulation compared to untreated controls.

Using single-cell RNA sequencing to track changes in cell gene expression, the scientists saw that gamma sensory stimulation promoted changes consistent with increased astrocyte AQP4 activity.

The data also revealed that upon gamma sensory stimulation a subset of neurons, called "interneurons," experienced a notable uptick in the production of several peptides. One peptide in particular, VIP, is associated with Alzheimer's-fighting benefits and helps to regulate vascular cells, blood flow and glymphatic clearance.

The team ran further tests revealing increased VIP in the brains of gamma-treated mice. A sensor of peptide release showed that sensory gamma stimulation resulted in an increase in peptide release from VIP-expressing interneurons.

But did this gamma-stimulated peptide release mediate the glymphatic clearance of amyloid? To find out, the team ran another experiment: they chemically shut down the VIP neurons. When they did so, and then exposed mice to sensory gamma stimulation, they found that there was no longer an increase in arterial pulsatility and there was no more gamma-stimulated amyloid clearance.

Tsai and Murdock said that while this paper focuses on what is likely an important mechanism—glymphatic clearance of amyloid—by which sensory gamma stimulation helps the brain, it's probably not the only underlying mechanism that matters. The clearance effects shown in this study occurred rather rapidly but in lab experiments and clinical studies weeks or months of chronic sensory gamma stimulation have been needed to have sustained effects on cognition.

With each new study, however, scientists learn more about how sensory stimulation of brain rhythms may help treat neurological disorders.

A noninvasive treatment for **"chemo brain"**

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 with 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 have 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 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.

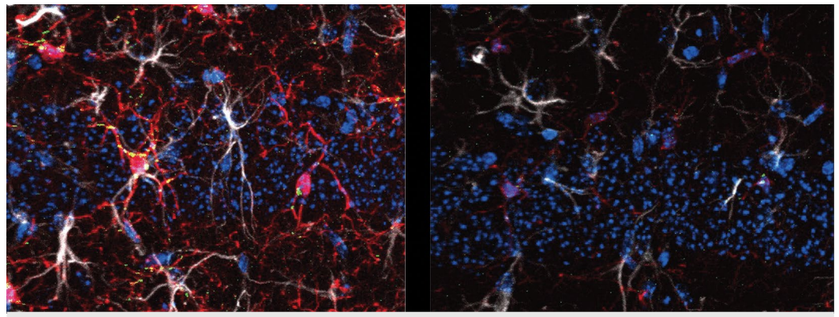
In the new study, the researchers set out to see whether this treatment could also counteract the cognitive effects of chemotherapy treatment. Research has shown that these drugs can induce inflammation in the brain, as well as other detrimental effects such as loss of white matter — the networks of 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.

"We also found that this treatment improved learning and memory, and enhanced executive function in the animals."

"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.



Red staining denotes microglia cells bearing the inflammatory marker Iba1+. In mice exposed to cisplatin but left untreated with 40Hz stimulation (left), a lot of red staining is evident. In cisplatin-exposed mice who received 40Hz treatment (right) the red staining (and inflammation) is reduced.

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 therapy 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.

Bursts of beta rhythms implement **cognitive** control

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.

Drawing on experimental data, mathematical modeling and theory, the scientists make the case that bursts of beta rhythms control cognition in the brain by regulating where and when higher gamma frequency waves can coordinate neurons to incorporate new information from the senses or formulate plans of action. Beta bursts, they argue, quickly establish flexible but controlled patterns of neural activity for implementing intentional thought.

"Cognition depends on organizing goal-directed thought, so if you want to understand cognition, you have to understand that organization," said Picower Professor Earl K. Miller, a study author. "Beta is the range of frequencies that can control neurons at the right spatial scale to produce organized thought."

Miller and colleagues wrote that studying bursts of beta rhythms to understand how they emerge and what they represent would not only help explain cognition, but also aid in diagnosing and treating cognitive disorders.

"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 bursting in inhibitory control processes … and their importance in ADHD, schizophrenia and Alzheimer's disease," they wrote in the journal *Trends in Cognitive Sciences*.

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 brain "waves" or "rhythms."

The stakes of studying the brain at that scale, wrote Picower Professor Earl K. Miller and research scientists Scott Brincat and Jefferson Roy in *Current Opinion in Behavioral Science*, might not only include understanding healthy higher-level cognition but also how those functions become disrupted in diseases such as Parkinson's, schizophrenia and epilepsy.

The bridge between the scale of individual neurons and the broader-scale coordination of many cells is founded on electric fields, the researchers write. Via a phenomenon called "ephaptic coupling," the electrical field generated by the activity of a neuron can influence the voltage of neighboring neurons, creating an alignment among them. In this way, electric fields both reflect neural activity but also influence it.

Miller's lab has published numerous studies showing that lower-frequency rhythms in the so-called "beta" band originate in deeper layers of the brain's cortex and appear to regulate the power of faster-frequency "gamma" rhythms in more superficial layers. By recording neural activity in the brains of animals engaged in working memory games the lab has shown that beta rhythms carry "top down" signals to control when and where gamma rhythms can encode sensory information, such as the images that the animals need to remember in the game.

Some of the lab's latest evidence suggests that beta rhythms apply this control of cognitive processes to physical patches of the cortex, essentially acting like stencils that pattern where and when gamma can encode sensory information into memory, or retrieve it. Miller calls this theory "Spatial Computing."

Another advantage consistent with cognitive control being based on an interplay of large-scale coordinated rhythmic activity is "Subspace coding." Brain rhythms organize the otherwise massive number of possible outcomes that could result from, say, 1,000 neurons engaging in independent spiking activity. Instead of all the many combinatorial possibilities, many fewer "subspaces" of activity actually arise, because neurons are coordinated, rather than independent.

How the brain can be flexible and focused

Every day our brains strive to optimize a trade-off: With lots of things happening around us even as we also harbor many internal drives and memories, somehow our thoughts must be flexible yet focused enough to guide everything we have to do. In a new paper in *Neuron*, a team of neuroscientists describes how the brain achieves the cognitive capacity to incorporate all the information that's relevant without becoming overwhelmed by what's not.

The authors, including Earl K. Miller, Picower Professor in The Picower Institute, argue that the flexibility arises from a key property observed in many neurons: "mixed selectivity." Neuroscientists used to think each cell had just one dedicated function, but newer evidence shows that many neurons can participate in a variety of computational ensembles, each working in parallel. When a rabbit considers nibbling on your lettuce, a single neuron might be involved in not only the assessment of how hungry it feels but also whether it can hear a hawk or smell a coyote nearby and how far away the lettuce is.

While mixed selectivity has the backing of copious evidence—it has been observed across the cortex and in other brain areas such as the hippocampus and amygdala—there are still open questions. For instance, how are neurons recruited to tasks and how do neurons that are so "open-minded" remain tuned only to what really matters to the mission?

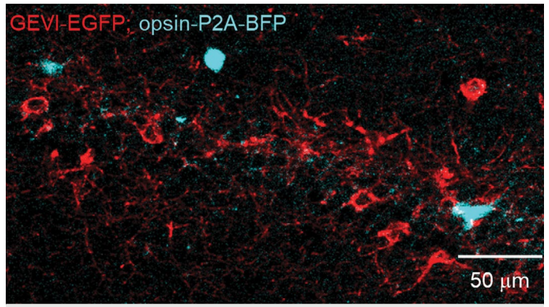
In the new study, the authors propose that two mechanisms work together to recruit neurons into computational ensembles that help them focus even as they integrate multiple inputs.

One mechanism is oscillations, or "brain waves," which are produced in the brain when many neurons all maintain their electrical activity at the same rhythm. This coordinated activity enables information sharing, essentially tuning them together like a bunch of cars all playing the same radio station (maybe the broadcast is about a circling hawk). Another mechanism is neuromodulators. These are chemicals that upon reaching receptors within cells can influence their activity. A burst of acetylcholine, for instance, might attune neurons with the right receptors to certain activity or information (like feeling hungry).

Study shows a key neural mechanism of **remembering** locations

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 that sense of location.

When place cells become activated at their target location, they emit an endocannabinoid chemical signal to suppress the incoming circuit connections, called "synapses," of a specific type of inhibitory neuron. If the scientists disrupted the endocannabinoid signaling during this process, place cells would lose their ability to refine their tuning to the location, making their sense of place less accurate.



To study an interaction between cells key to refining memories of locations, scientists engineered inhibitory neurons (cyan) to make them controllable with light, and altered pyramidal neurons (red), to express a genetically encoded voltage indicator that reports their electrical activity.

Showing that this process, called "depolarization-induced suppression of inhibition" (DSI), is key to refining memory of locations required multiple cutting-edge methods, said co-lead author Linlin Fan, assistant professor in The Picower Institute. The emerging tools allowed the team, based at Stanford University at the time, to literally see and control the electrical activity of the circuit and to visualize the endocannabinoid signals.

The new fundamental insight into the action of endocannabinoids in the brain, modeled in the mice, could help improve understanding in humans both of epilepsy and also the potential effects of marijuana use on learning and memory, the researchers said.

The researchers had mice run on a treadmill as key landmarks periodically passed them by. Meanwhile they labeled and observed two specific kinds of cells in the hippocampus region of the brain, which forms memories of places. One kind of cells were pyramid-shaped place cells, which become trained by circuit activity to represent a specific landmark. The other kind of cells were connected inhibitory cells, distinguished for expressing the protein CCK and for having receptors for endocannabinoids. Over several experiments the researchers were able to see how the cell types interacted.

Fan said the study results raise new questions about how cannabis use could affect this endocannabinoid-dependent learning and memory process.

"The active ingredient in cannabis can 'hijack' this endocannabinoid pathway," Fan said.

She plans to probe the mechanism further.

Tsai presents stimulation study at Mass. Down Syndrome Congress

With early lab and clinical studies indicating that non-invasive sensory stimulation of a gamma frequency brain rhythm may improve cognition in Alzheimer's disease, researchers in the Alana Down Syndrome Center and The Picower Institute are beginning to also test it with volunteers from the Down syndrome community.

At a presentation March 23 in Worcester, Mass., at the Massachusetts Down Syndrome Congress 40th Anniversary Conference, Alana Center and Picower Institute Director Li-Huei Tsai said her research team is recruiting volunteers to try out the potential therapy, which involves flickering light and clicking sound at 40Hz, a gamma band frequency of the brain associated with processing sensory information and also memory and cognition.

Li-Huei Tsai speaks at the 40th Anniversary Conference of the Massachusetts Down Syndrome Congress.

Decades ago the life expectancy of people 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.

Tsai's team at the Alana Center recently began to test whether 40Hz sensory stimulation could help with Down syndrome. As in the Alzheimer's experiments, Tsai's team started with mice. The data so far is preliminary—it has not yet been peer-reviewed and published—but Down syndrome model mice treated with 40Hz stimulation appear to show improved cognition.

The team has also begun a clinical study of people 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.

Understanding the "fever effect" in **autism**

When some people with autism spectrum disorders experience an infection 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 eventually develop therapies that mimic the "fever effect" to similarly improve symptoms.

"Although it isn't actually triggered by the fever, per se, the 'fever effect' is real, and it provides us with an opportunity to develop therapies to mitigate symptoms of autism spectrum disorders," said Gloria Choi, associate professor in The Picower Institute. Choi will collaborate via the grants, which will provide $2.1 million over three years, with Jun Huh, associate professor of immunology at Harvard Medical School.

The Marcus Foundation has been involved in autism work for more than 30 years, helping to develop the field and addressing everything from awareness to treatment to new diagnostic devices.

"I have long been interested in novel approaches to treating and lessening autism symptoms, and Drs. Choi and Huh have honed in on a bold theory," said Bernie Marcus, founder and chairman of The Marcus Foundation. "It is my hope that this Marcus Foundation Medical Research Award helps their theory come to fruition and ultimately helps improve the lives of children with autism and their families."

For a decade, Huh and Choi have been investigating the connection between infection and autism. A 2020 paper showed that mice that developed autism symptoms as a result of a maternal infection while *in utero* would exhibit improvements in their sociability when they contracted infections later in life. The scientists discovered that this effect depended not on elevated body temperature, but on over-expression of IL-17a, an immune system signaling molecule. When the scientists administered IL-17a directly to the brains of mice with autism-like symptoms whose mothers had not been infected during pregnancy, the treatment still produced improvements in symptoms.

This work suggested that mimicking the "fever effect" could produce similar therapeutic effects for multiple autism-spectrum disorders, with different underlying causes. But the research also left wide-open questions. How exactly does IL-17a lead to symptom relief and behavior change in the mice? Does the fever effect work in the same way in people?

In the new research, Choi and Huh hope to examine the fever effect in detail, including by establishing and analyzing a biobank of samples from volunteers with autism.

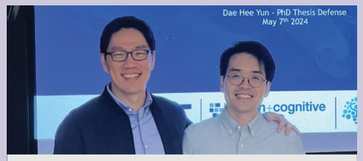
Five new PhDs minted in Picower labs

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"

Sara Kornfeld Simpson

- **Dr. Sara Kornfeld Simpson**, Bear Lab, "Physiology and Plasticity of Primary Visual Cortex in Wild-Type and Fragile X Syndrome Model Mice"
- **Dr. Yuxuan Tian**, Chung Lab, "Multiplexed, scalable, and functionality compatible platforms for 3D spatially resolved proteomic profiling"



Kwanghun Chung and Dae Hee Yun

- **Dr. Dae Hee Yun**, Chung Lab, "Illuminating the Brain: Advances in High-Resolution, Multi-Scale Proteomic Labeling and Imaging"
- **Dr. Katya Tsimring**, Sur 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 alter 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"

In the halls of MIT, a distinctive thread of compassion weaves through the fabric of education. As students adjust to a postpandemic normal, many professors have played a pivotal role by helping them navigate the realities of hybrid learning and a rapidly changing postgraduation landscape.

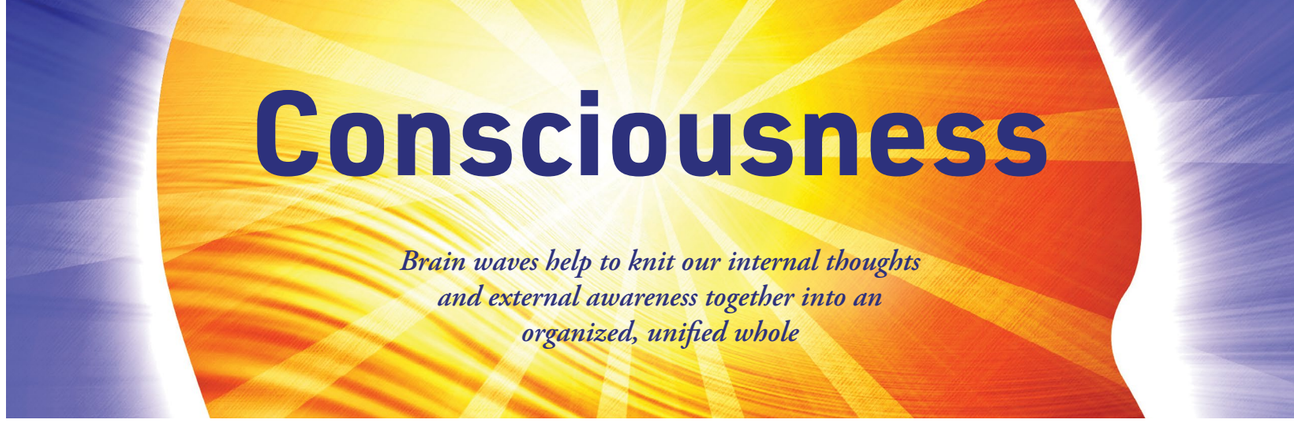
The Committed to Caring (C2C) program at MIT is a student-driven initiative that celebrates faculty members who have served as exceptional mentors to graduate students. Twenty-three MIT professors including Picower Investigators Myriam Heiman and Emery N. Brown have been selected as recipients of the 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, Brown and Miller 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.

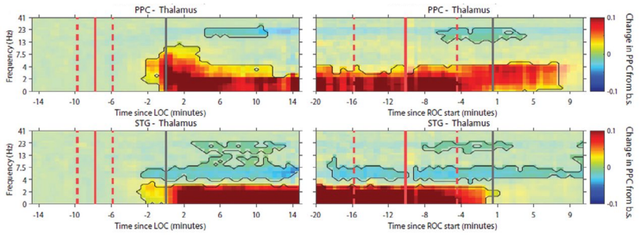
These waves can vary in their power, frequency, location and degree of alignment (or "phase"). Miller and Brown have shown that these properties differ markedly and systematically when we are conscious vs. when we are not. When brain wave patterns aren't conducive to information exchange via synchronized, aligned, higher-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 sights, 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 23 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 dexmedetomidine produce states of unconsciousness that differ from that of sleep 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 class, 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 steadiness 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 thalamus and various cortical regions.

Last year Brown's lab published a clever method for assessing unconsciousness while volunteers received dexmedetomidine. Speaking with volunteers can prolong wakefulness and accelerate reawakening. 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 reawakened—no dialogue

(Continued on next page)

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 notes, 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.

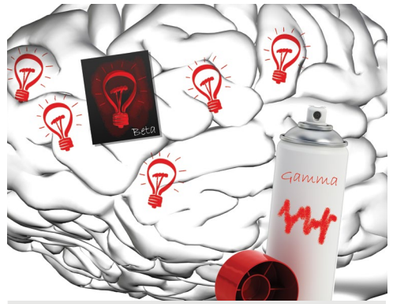
"I can make you unconscious by making your brain hyperactive in some sense, or I can make you unconscious by slowing it down," Brown said at the time. "The more general concept is there's a dynamic—we can't define it precisely—which is associated with you being conscious and as soon as you move away from that dynamic by being too fast or too slow, or too discoordinated 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 their propagation from region to region. While awake and then under anesthesia, animals received sound and touch stimulation. As researchers have shown for decades, a region in the animals' brains that processes raw sensory input still processed the incoming stimulus, even while under anesthesia. But Brown and Miller also measured neural spiking, waves and synchrony in three other regions of the cortex. During wakefulness, by all measures, all four cortical regions shared a neural response to the stimulus. Under anesthesia, such activity was absent outside the sensory region.

Waves of conscious cognition

If anesthetics knock brain waves out of a pattern that enables consciousness and cognition, what does that pattern look like and how does it integrate experience? Miller has been working on that for years. In 2007 his lab published a study showing that when a new sensory stimulus focused an animal's attention, synchrony between cortical regions was evident in fast "gamma" frequency brain waves. When they focused attention based on task rules, synchrony was evident in relatively slower "beta" waves.

Further studies by the Miller lab have shown that this dynamic—beta waves carry information about rules and intentions; gamma waves encode sensory information—also applies in tasks of working memory and making predictions. The research has also shown that beta seems to regulate gamma to control cognition. When beta waves are prominent, gamma power is suppressed. For instance, when an animal playing a memory game needs to remember a newly presented image, beta gives way so gamma can encode the image. But when the image needs to be remembered in advance of the memory test, beta takes over and prevents gamma from encoding distractions.



The Spatial Computing theory posits that beta rhythms act like stencils, dictating where gamma rhythms can encode information in the cortex, for instance from the senses.

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 primacy 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 lock, according to Spatial Computing, your brain's beta waves will assign the 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 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? Answering any of those questions will require future "waves" of research and insight.

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