

The Sleeping Brain

Neural activity during sleep has a signature structure that the brain uses to make important improvements in our thinking and wellness

Pg. 9

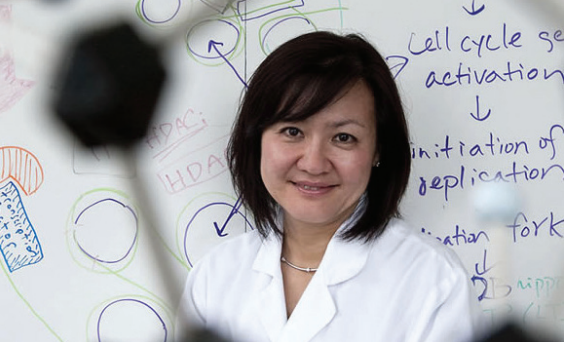
Neuroscience News



FALL 2023



THE PICOWER
INSTITUTE
FOR LEARNING AND MEMORY



DIRECTOR'S MESSAGE

Dear Friends,

People can get through life knowing very little about how the brain works (in fact, most do), but what gets everyone at The Picower Institute excited about work each day is that when we actually investigate the brain's many mechanisms, we can make discoveries that are at once both wondrous and useful.

Take sleep, for example. It comes naturally to us all. We don't have to know anything about it to do it or to reap its benefits. But when we investigate how it works, we gain a new depth of appreciation for just how marvelous and important it is.

Our cover story (page 9) conveys a glimpse into what Matt Wilson, Laura Lewis and Emery Brown are learning about how the brain enhances our cognition and maintains brain health by taking advantage of the very different way neural activity is structured during sleep compared to during wakefulness. Sleep is about so much more than just restoring our energy. The more we open our eyes to the brainwide transformation that occurs during sleep, the more we realize how vital it is to sustaining our wellness every day and across our lifespan.

Why else have we been investing ourselves in investigating the brain recently? Take a look at the diverse discoveries that follow in our news pages. Steve Flavell shows us how the entire brain of an animal represents and produces its behaviors. Troy Littleton provides new insight into how neurons can develop into hundreds of different forms and functions despite all starting from the same DNA. Earl Miller breaks new ground in describing how electric fields implement brain function.

While those discoveries reveal fascinating aspects of the brain's fundamental workings, others on the pages ahead demonstrate specific ways to address urgent health concerns: Emery's lab describes a new way to prevent surgical patients from going into too deep an anesthetic state and my lab shows two new approaches with therapeutic potential for Alzheimer's disease.

These are just the latest examples of what excites us about studying the brain. And because you're reading through this edition, we know you're eager to learn more about the brain, too.

LI-HUEI TSAI, DIRECTOR

The Picower Institute for Learning and Memory

Relating brain activity and behavior in a simple animal

To understand the full relationship between brain activity and behavior, scientists have to map this relationship for all of the neurons across a whole brain—a so far insurmountable challenge. But after inventing new technologies and methods for the purpose, a team of scientists in The Picower Institute has produced a rigorous mapping of how the cells in the tractably tiny brain of a humble *C. elegans* worm encode almost all of its essential behaviors, such as movement and feeding.

In *Cell*, the team presents new brain-wide recordings and a mathematical model that accurately predicts the versatile ways that neurons represent the worm's behaviors. Applying that model specifically to each cell, the team produced an atlas of how most cells, and the circuits they take part in, encode the animal's actions. The atlas therefore reveals the underlying "logic" of how the worm's brain produces a sophisticated and flexible repertoire of behaviors, even as its environmental circumstances change.

"This study provides a global map of how the animal's nervous system is organized to control behavior," said senior author Steven Flavell, Lister Brothers Associate Professor. "It shows how the many defined nodes that make up the animal's nervous system encode precise behavioral features, and how this depends on factors like the animal's recent experience and current state."

To make the needed measurements, Flavell's lab invented a new microscope and software system that automatically tracks almost all behaviors of the worm (movement, feeding, sleeping, egg-laying, etc.) and the activity of every neuron in its head (cells are engineered to flash when calcium ions build up). The team used the system to record simultaneous behavior and neural data from more than 60 worms as they roved about their dishes, doing whatever they wanted.

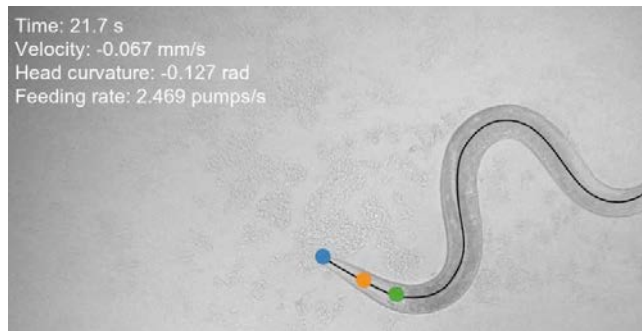
Data analysis revealed three novel observations about neural activity in

the worm: Neurons track behavior not only of the present moment but also the recent past; they tune their encoding of behaviors, such as motion, based on a surprising variety of factors; and many neurons simultaneously encode multiple behaviors.

By carefully analyzing patterns of how neural activity correlated with behaviors the scientists developed the *C. elegans* Probabilistic Neural Encoding Model. The model, encapsulated in a single equation, accounts for how each neuron represents various factors to accurately predict whether and how the neural activity reflects behavior. Nearly 60 percent of the neurons in the worm's head indeed accounted for at least one behavior.

To turn the model into a mapping, or atlas, the team then applied the model's capability to each of the worm's specific neurons, which have all been previously mapped out. Doing that required labeling each neuron with a unique color so that its activity could be associated with its identity. The team did this in dozens of freely-moving animals, which provided them with information of how almost all of the defined neurons in the worm's head related to the animal's behavior.

Another major outcome of the team's work was the finding that while most neurons always obeyed the predictions of the model, a smaller set of neurons in the worm's brain—about 30 percent of those that encode behavior—was able to flexibly remap their behavior encoding, essentially taking on new jobs. They even watched this remapping occur when they temporarily changed a worm's state by heating an area around its head—a harmless annoyance for the worm.



A microscope image is annotated to track details of worm behavior. Blue, orange, and green dots track the head while the black line marks its posture.

Molecule reduces inflammation in Alzheimer's models

Though drug developers have achieved some progress in treating Alzheimer's disease (AD) with medicines that reduce amyloid-beta protein, other problems of the disease including inflammation continue unchecked. In a new study, Picower Institute scientists describe a candidate drug that in human cell cultures and Alzheimer's mouse models reduced inflammation and improved memory.

The target of the new "A11" molecule is a genetic transcription factor called PU.1, which amid AD becomes an overzealous director of inflammatory gene expression in the brain's microglia immune cells. A11 suppresses this problematic activity by recruiting other proteins that repress the inflammatory genes PU.1 works to express. But because A11 concentrates mostly in the brain and does not reduce PU.1 levels, it does not appear to disrupt PU.1's other job, which is to ensure the production of a wide variety of blood cells.

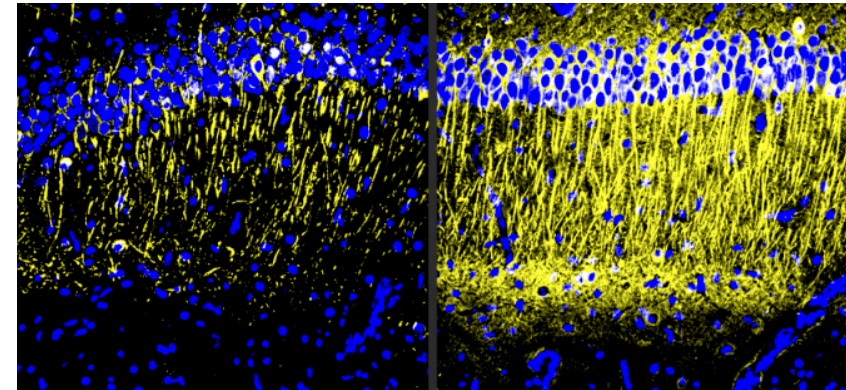
"Inflammation is a major component of AD pathology that has been especially hard to treat," said study senior author Li-Huei Tsai, Picower Professor and director of MIT's Aging Brain Initiative. "This preclinical study demonstrates that A11 reduces inflammation in human microglia-like cells as well as in multiple mouse models of Alzheimer's disease and significantly improves cognition in the mice. We believe A11 therefore merits further development and testing."

Elizabeta Gjoneska of the National Institutes of Health is a co-corresponding author with Tsai. As a postdoc, Gjoneska co-led a 2015 collaboration that implicated PU.1 as a regulator of errant microglia inflammation in a mouse model of AD. Ever since, Tsai has been seeking a safe way to curb unhealthy PU.1 activity.

Genetically knocking down PU.1 in the body is not a viable therapeutic strategy given its importance in normal healthy function. The team therefore screened more than 58,000 small molecules from libraries of FDA-approved drugs and novel chemicals to see if any could safely and significantly reduce key inflammation and AD-related genes regulated by PU.1 in cell cultures. After several rounds of increasingly stringent screening, they narrowed the field down to six chemicals. A11 was by far the most potent among them.

They tested the effects of A11 doses on the function of human microglia-like cells cultured from patient stem cells. When they exposed the microglia-like cells to immune molecules that typically trigger inflammation, cells dosed with A11 exhibited reduced expression and secretion of inflammatory cytokines and less of the cell body shape changes associated with microglia inflammatory responses. The cells also showed less

accumulation of lipid molecules, another sign of inflammatory activation. Looking at gene expression, the scientists observed that A11-treated cells exposed to inflammatory triggers behaved much like unperturbed



The brains of Alzheimer's model mice treated with A11 (right) showed more tubulin (yellow), a marker of neuronal health, than untreated controls (left).

microglia, suggesting that A11 helps prevent microglia from overreacting to inflammatory cues.

Two more lab tests aimed at understanding how A11 exerts its effects revealed that it doesn't change PU.1 levels. Instead it counteracts PU.1 activity by recruiting several proteins that repress expression of PU.1's targets. Essentially amid AD, A11 tamps down what PU.1 amps up.

"A11 represents a first-in-class molecule that converts

PU.1 from a transcriptional activator to a transcriptional repressor, resulting in a controlled state of microglial inflammation," the authors wrote.

Next the team focused on whether it worked as a medicine in mouse models of Alzheimer's disease.

Pharmacological tests indicated that A11 is readily cleared from tissues and is capable of reaching brain cells. Moreover, in healthy mice the chemical successfully crossed the blood-brain barrier and remained in brain cells much longer than anywhere else.

Finally the team tested the effects of the drugs on Alzheimer's disease pathology and symptoms in three mouse strains that each model different aspects of Alzheimer's disease: CK-p25 mice (severe neurodegeneration), Tau P301S transgenic mice (tauopathy), and 5XFAD mice (amyloid pathology).

Male and female CK-p25 mice dosed with A11 showed less inflammatory response among microglia and astrocyte cells and lost fewer neurons than untreated controls. TauP301S Tg mice responded similarly, also exhibiting a significant reduction of phosphorylated tau protein in the hippocampus region of the brain, which is an essential area for memory. In 5XFAD mice, amyloid was significantly reduced.

The team subjected the Tau P301S Tg and CK-p25 mice to mazes designed to test their short-term working memory and longer-term learning. In both models and on both tests, A11-treated mice performed significantly better than untreated controls. For example, in the "Morris Water Maze," where mice have to learn the location of a submerged platform that allows them to rest, treated CK-p25 mice learned much faster than untreated ones.

Much more testing needs to be done before A11 could become an approved medicine, Tsai said, but she noted that it could complement the new treatments that target amyloid.

Tracking **brain waves** could reduce post-op complications

A new study in which MIT researchers analyzed the EEG patterns of patients under anesthesia has revealed brain wave signatures that could help anesthesiologists determine when patients are transitioning into an especially deep state of unconsciousness called “burst suppression.” This could enable them to prevent patients from falling into that state, reducing the risk of postoperative brain dysfunction.

“Now that we have pointed out these patterns, they’re very easy to see,” said senior author Emery N. Brown, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience.

Brain waves, which are generated by synchronized neuronal activity, oscillate at different frequencies. Commonly used anesthesia drugs such as propofol have a significant effect on these oscillations. During anesthesia induced by propofol or other anesthetics that increase the effectiveness of GABAergic inhibitory receptors, the brain enters a state of unconsciousness known as slow-delta-alpha (SDA). This state is characterized by slow (0.1-1 hertz), delta (1-4 hertz) and alpha (8-14 hertz) oscillations.

Higher doses lead to burst suppression. When patients enter this state, they are more likely to experience postoperative confusion, delirium, and memory loss. These effects, which can last for hours, days, weeks, or months, are more common in elderly patients.

In the study published in the *Proceedings of the National Academy of Sciences* the MIT team set out to analyze transitions between SDA and burst suppression in 10 healthy volunteers and 30 patients who were undergoing surgery.



Under general anesthesia, alpha waves started to wax and wane. As the dose increased, waxing was shortened and waning was prolonged, until the patient reached burst suppression. When the amount of drug was reduced, the amplitude of the alpha waves began to increase again. The researchers also found a distinctive pattern in the slow and delta waves. As the amount of drug was increased, the frequency of these waves became slower and slower.

The researchers hypothesize that propofol exerts these effects through its influence on neuron metabolism.

The findings could offer anesthesiologists more refined control over a patient’s state of unconsciousness during surgery, Brown said. He now hopes to develop an algorithm that could generate a warning that a patient is approaching burst suppression, which could be displayed on a monitor in the operating room.

40 Hz vibrations combat Alzheimer’s pathology, symptoms in mice

Evidence that sensory stimulation of 40 Hz gamma frequency brain rhythms can reduce Alzheimer’s disease (AD) pathology and symptoms, already shown with light and sound by multiple research groups in mice and humans, now extends to tactile stimulation. AD model mice exposed to 40 Hz vibration an hour a day for several weeks showed improved brain health and motor function.

“This work demonstrates a third sensory modality that we can use to increase gamma power in the brain,” said Picower Professor Li-Huei Tsai, corresponding author of the study and director of the Aging Brain Initiative at MIT. “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.”

Tsai’s lab has led several collaborative studies demonstrating that light flickering and/or sound clicking at 40 Hz reduces levels of amyloid-beta and tau proteins, prevents neuron death and preserves synapses and even sustains learning and memory in a variety of AD mouse models. Most recently in early stage 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 AD.

The new study in *Frontiers in Aging Neuroscience* tested whether whole-body 40 Hz tactile stimulation produced meaningful benefits in two commonly used mouse models of Alzheimer’s neurodegeneration. 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.

One type of AD model mice stimulated for three weeks showed significant preservation of neurons compared to unstimulated controls in two key brain regions. Stimulated mice also showed significant reductions in tau. The other model mice received six weeks of vibration stimulation. These mice showed higher levels of synaptic protein markers in two brain regions compared to unvibrated control mice. They also showed reduced levels of DNA damage.

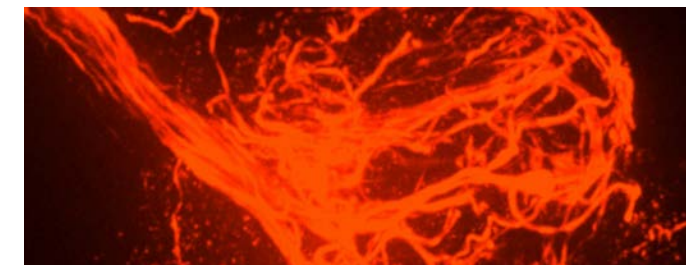
Finally the team assessed the motor abilities of mice exposed to the vibration vs. not exposed. They found significant improvements in treated mice compared to controls.

Without **key protein**, neuronal axons and synaptic connections fall apart

Perhaps the most obvious feature of a neuron is the long branch called an axon that ventures far from the cell body to connect with other neurons or muscles. If that long, thin projection ever seems like it could be vulnerable, a new MIT study shows that its structural integrity may indeed require the support of a surrounding protein called Perlecan. Without that protein in *Drosophila* fruit flies, researchers at The Picower Institute found, axonal segments can break apart during development and the connections, or synapses, that they form end up dying away.

Perlecan helps make the extracellular matrix, the proteins and other molecules that surround cells, stable and flexible so that cells can develop and function in an environment that is supportive without being rigid.

“What we found was that the extracellular matrix around nerves was being altered and essentially causing the nerves to break completely.



In neurons lacking the protein perlecan, neural axon structure unravels, forming a tangled ball

Study connects **neural gene expression** differences to functional distinctions

Figuring out how hundreds of different kinds of brain cells develop from their unique expression of thousands of genes promises to not only advance understanding of how the brain works in health, but also what goes wrong in disease. A new MIT study that precisely probes this “molecular logic” in two neuron types of the *Drosophila* fruit fly, shows that even similar cells push and pull many levers to develop distinct functions.

In *Neuron* a Picower Institute team of neurobiologists shows that the neuronal subtypes differed from each other in how they expressed more than 800 genes, or ~5% of the total genes encoded in the fly genome. By manipulating genes whose expression differed most prominently, the scientists were then able to show how they produced several of the functional differences between the cells.

“There is a global effort in neuroscience to identify all the different types of neurons to define their unique properties and their gene expression profiles,” said study senior author Troy Littleton, Menicon Professor of Neuroscience. “That information can be used as a toolkit for studying how newly found disease genes map on to those particular neurons to indicate which ones might be most affected in specific brain disorders.”

To assess gene expression, lead author Suresh Jetti employed a technique called “isoform patchseq” in which he identified the exact same tonic and phasic neurons in hundreds of flies and extracted RNA from their individual nuclei and cell bodies. The technique, while very hard work,

Broken nerves eventually led to the synapses retracting,” said Menicon Professor Troy Littleton, senior author of the study in *eLife*.

Humans need at least some Perlecan to survive after birth. Mutations that reduce, but don’t eliminate, Perlecan can cause Schwartz-Jampel syndrome, in which patients experience neuromuscular problems and skeletal abnormalities. The new study may help explain how neurons are affected in the condition, Littleton said, and also deepen scientists’ understanding of how the extracellular matrix supports axon and neural circuit development.

When the research team knocked out the gene called “trol” that encodes Perlecan in flies, they saw that neurons appeared to “retract” many synapses during a late stage of larval development. Proteins on the muscle side of the synaptic connection remained, but the neuron side of the connection withered away.

They found that the Perlecan was mostly found in a structure called the neural lamella, which surrounds axon bundles and acts a bit like the rubbery cladding around a TV cable to keep the structure intact. That suggested that a lack of Perlecan causes trouble along axons due to its absence in the extracellular matrix surrounding nerve bundles.

Looking segment by segment along axons, they found that where axons were breaking down, synapse loss would soon follow, suggesting that axon breakage was the cause of the synapse retraction.

provided the team with an unusually rich vein of transcriptomic information from precisely the cells of interest, Littleton said.

In all, the expression of 822 genes was significantly different between the two neuron types. About 35 of the genes were known to help guide the growth of the axon branches that neurons extend to forge their connections with muscle – a set of differences pertinent to why tonic neurons innervate only one muscle while phasic ones innervate many. Other differentially expressed genes related to the structure and function of synapses, while more than 20 others suggested differences in the neuromodulatory chemicals each neuron was sensitive to as inputs.



Professor Troy Littleton works with study lead author Suresh Jetti in the lab. Image by Whit Wales

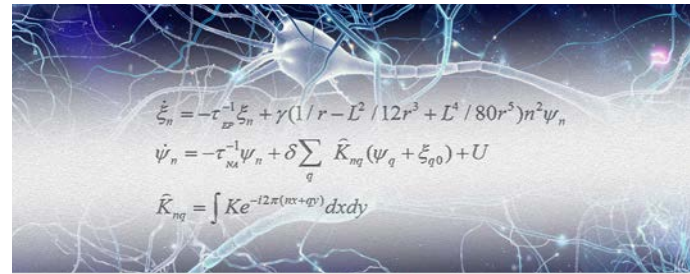
Electric fields bring brain networks together

New evidence suggests that at least some of the coordination among networks of neurons comes from electric fields.

As animals played working memory games, the information about what they were remembering was coordinated across two key brain regions by the electric field that emerged from the underlying electrical activity of all participating neurons, a study in *Cerebral Cortex* shows. The field, in turn, appeared to drive the neural activity, or the fluctuations of voltage apparent across the cells' membranes.

If the neurons are musicians in an orchestra, the brain regions are their sections, and the memory is the music they produce, the study's authors said, then the electric field is the conductor.

The physical mechanism by which this prevailing electric field influences



Scientists used mathematical modeling to calculate the electric fields that represent information among neurons.

the membrane voltage of constituent neurons is called “ephaptic coupling.” Membrane voltages are fundamental to brain circuit activity. When they cross a threshold, neurons “spike,” sending an electrical transmission that signals other neurons across connections called synapses. But any amount of electrical activity could contribute to a prevailing electric field which also influences the spiking, said Picower Professor and study senior author Earl K. Miller.

“Many cortical neurons spend a lot of time wavering on verge of spiking” Miller said. “Changes in their surrounding electric field can push them one way or another.”

The study looked at two regions in the brain relevant to the working memory game the animals were playing. As the animals played, the scientists recorded the local field potentials (LFPs, a measure of local electrical activity) produced by scores of neurons in each region. The scientists fed this recorded LFP data into mathematical models they developed to predict individual neural activity and the overall electric fields.

The models allowed them to then calculate whether changes in the fields predicted changes in the membrane voltages. The researchers then checked causality between the two brain regions and found that electric fields, but not neural activity, reliably represented the transfer of information between the regions FEF and SEF. Finally, they used another mathematical technique to determine that the two regions were, in fact, processing the same memory.

Brain's electrical encoding of information might 'tune' sub-cellular structures

A new paper by researchers at MIT, City —University of London, and Johns Hopkins University posits that the electrical fields within brain networks may influence the physical configuration of neurons' sub-cellular components to optimize network stability and efficiency, a hypothesis the authors call “Cytoelectric Coupling.”

“The information the brain is processing has a role in fine-tuning the network down to the molecular level,” said Picower Professor Earl K. Miller, who co-authored the paper in *Progress in Neurobiology*.

A major focus of Miller's lab is studying how higher-level cognitive functions such as working memory can rapidly, flexibly and yet reliably emerge from the activity of millions of individual neurons. Neurons are capable of dynamically forming circuits by creating and removing connections, called synapses, as well as strengthening or weakening those junctions. But that merely forms a “roadmap” around which information could flow, Miller said. The specific neural circuits that collectively represent one thought or another, Miller has found, are coordinated by rhythmic activity, more colloquially known as “brain waves.”

In the new study, the authors combine this model of rhythmic electrical activity coordinating neural networks with other lines of evidence that electrical fields can influence neurons at the molecular level.

Researchers, for example, have studied ephaptic coupling, in which neurons influence each other's electrical properties via the proximity of their membranes, rather than solely relying on electrochemical exchanges across synapses. This electrical cross-talk can affect neural functions

including when and whether they spike to relay electrical signals to other neurons in a circuit.

Miller and co-authors also cite research showing other electrical influences on cells and their components including how neural development is guided by fields and that microtubules can be aligned by them.

If the brain carries information in electric fields and those electric fields are capable of configuring neurons and other elements in the brain that form a network, then the brain is likely to use this capability. The brain can use fields to ensure the network does what it is supposed to do, the authors suggest.



Picower Professor Earl K. Miller

New award funds study of a remarkable example of neural regeneration

The *Clytia hemisphaerica* jellyfish is not only a hypnotically graceful swimmer, but also an amazing neuron manufacturing machine with a remarkable ability to expand and regenerate its nervous system. With a new fellowship award from the Esther A. & Joseph Klingenstein Fund and the Simons Foundation, MIT Assistant Professor Brady Weissbourd will study how the tiny, transparent animals use this ability to build, organize, and rebuild a stable, functional, and robust nervous system throughout their lives.

“As we look more broadly across the animal kingdom it is amazing to see how similar the basic biology is of animals that look completely different – even jellyfish have neurons similar to our own that generate their behavior,” said Weissbourd, a faculty member in MIT's Department of Biology and The Picower Institute, whose work to engineer genetic access to *C. hemisphaerica* in 2021 established it as a new neuroscience model organism. “At the same time, it could be just as important to examine what is different across species, particularly when it comes to some of the incredible capabilities that have evolved.”

The competitively awarded fellowship, which provides \$300,000 over three years, will enable Weissbourd's lab to tackle several questions raised by the jellyfish's prodigious production of neurons. Where does the constant stream of newborn neurons come from and what guides them to their eventual places in the jellyfish's mesh-like neural network? How



Assistant Professor Brady Weissbourd presents some of his research

does the jellyfish organize these ever-changing neural populations—for instance into functional circuits—to enable its various behaviors?

Another question hails from the surprising results of an experiment in which Weissbourd ablated the entire class of the neurons that the jellyfish uses to fold up its umbrella-shaped

body—about 10 percent of 10,000 or so neurons that it has. He found that within a week enough new neurons had taken their place that the folding behavior was restored. Weissbourd's studies will also seek to determine how the animal can so readily bounce back from the destruction of a whole major neural network and the behavior it produces.

“We were studying the neural control of a particular behavior and stumbled across this shocking observation that the subnetwork that controls this behavior is constantly changing size and can completely regenerate,” Weissbourd said. “We want to understand the mechanisms that allow this network to be so robust, including the ability to rebuild itself from scratch. I'm very grateful to the Klingenstein Fund and the Simons Foundation for supporting this work.”



Members of The Picower Institute for Learning and Memory, the Department of Brain and Cognitive Sciences and the McGovern Institute for Brain Research headed to Cape Cod in early June for a joint retreat that blended scientific presentations, career training and time to enjoy a beach resort together. We thank Wendy Fisher and her siblings, who in 2008 established an endowment at The Picower Institute honoring their parents and creating the annual Dana and Betty Fisher Retreat.

Picower postdoc earns Burroughs Wellcome Fund award

Picower Institute postdoctoral fellow Rebecca Pinals is among nine winners of the Burroughs Wellcome Fund's 2023 Career Awards at the Scientific Interface.

The awards recognize “exceptional researchers whose work exemplifies the collaborative spirit necessary for breakthrough discoveries,” for instance because they are working at the intersection of multiple disciplines, according to BWF's announcement. Pinals and the other winners will each receive a five-year, \$500,000 grant supporting their research.

In the lab of Picower Professor Li-Huei Tsai, Pinals is creating a nanosensor-integrated human “brain-on-a-chip” culture of multiple cell types to enable novel studies of neurodegeneration. Combining tiny sensors into more realistic brain-like tissue that models Alzheimer's could improve understanding of how the disease gains its terrible hold on the brain.

“I believe this research will be transformative in providing insight into the earliest stages of neurodegenerative disease dynamics, toward

identifying key nodes in disease progression at which we can effectively intervene and, ultimately, prevent this devastating disease,” Pinals said. “More broadly, I aim to co-develop nano-tools that operate at high spatiotemporal resolution, together with tractable neuro-models that more accurately recapitulate features of the human brain, to open new avenues of research in neurobiology.”

Pinals said she is grateful for the support the award will provide, and the support she's had along the way, as she looks to set up her own lab in the future.

“I am foremost grateful, and completely ecstatic to receive this recognition!” Pinals said. “This funding will help me through a critical transition from my postdoctoral position into my independent career as faculty. I am incredibly grateful to all of my mentors, colleagues, friends, and family who helped me get to this point.”

New Picower PhDs

Five graduate students in Picower Institute labs earned PhDs in mid-to-late spring for advancing knowledge in areas of neuroscience as diverse as consciousness, Down syndrome and technology to map the human brain.

Dr. Indie Garwood, Brown Lab, “Probing the depths of unconsciousness with multifunctional neurotechnology”

Dr. Webster Guan, Chung Lab, “Scalable Subcellular Resolution Mapping of the Human Brain”

Dr. Brennan Jackson, Tsai Lab, “The Impact of Gamma Stimulation on Neurological Phenotypes of Alzheimer’s Dementia and Down Syndrome”

Dr. Mitch Murdock, Tsai Lab, “Clearance Systems at Brain Borders”

Dr. Joyce Wang, Bear Lab, “Investigating the role of thalamic activity in visual cortical plasticity”

SUNY Downstate honors Emery N. Brown

Edward Hood Taplin Professor Emery N. Brown donned a cap and gown May 11 to take part in graduation ceremonies at The State University of New York Downstate Health Sciences University in Brooklyn, NY. SUNY Downstate bestowed an honorary Doctor of Science degree on Brown, citing “his expertise in developing signal-processing methods for neuroscience data analysis and applying these to the field of anesthesiology.”

Farrah Belizaire earns two awards for DEIJ efforts

Congratulations to Farrah Belizaire, Diversity, Equity, Inclusion, and Justice program officer in the Department of Brain and Cognitive Sciences, The Picower Institute for Learning and Memory, and the McGovern Institute for Brain Research. Belizaire’s work earned her two MIT recognitions this spring: an MIT School of Science Infinite Mile Award and an MIT Excellence Award.



Bear Lab graduate student Joyce Wang defends her thesis



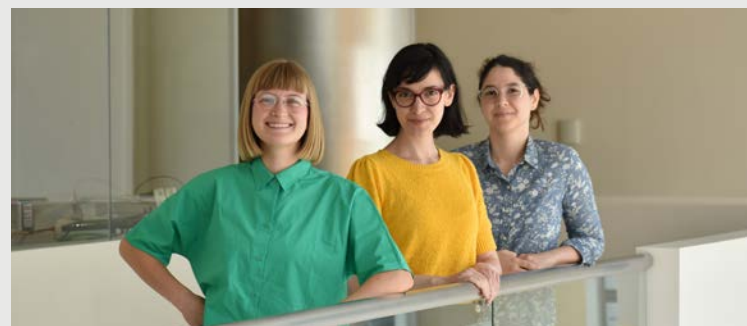
Edward Hood Taplin Professor Emery N. Brown (middle) receives a doctoral degree at SUNY Downstate.

Summer springboard

Taylor Baum, Josefina Correa Menéndez and Karla Alejandra Montejó have each become stand out graduate students in the lab of Edward Hood Taplin Professor Emery N. Brown via different paths, but a common thread is that as undergraduates they all participated in the MIT Summer Research Program in Biology and Neuroscience. Scan the code to read their stories and to learn how when students find MSRP-BIO, it helps them find their future in research.



Read about their stories



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Neural activity during sleep has a signature structure that the brain uses to make profound improvements in our thinking and wellness

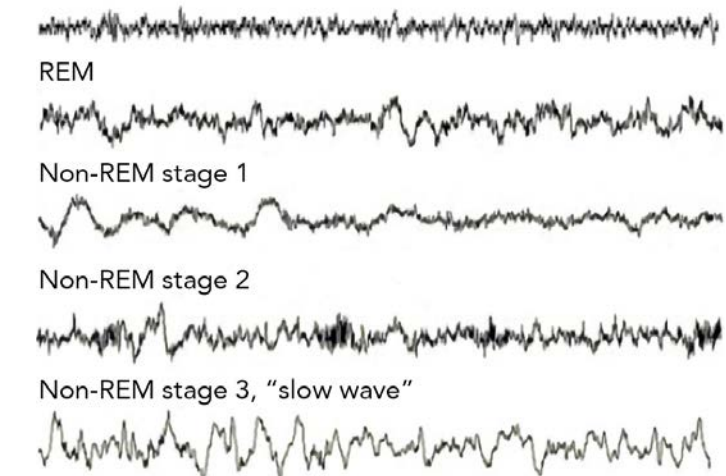
As a longtime scholar of the brain’s arousal states, neuroscientist and anesthesiologist Emery N. Brown is deeply aware of the science behind sleep’s importance for health and wellness, but he still starts the discussion in colloquial terms: “You realize how important it is when you can’t get it,” quipped Brown, Edward Hood Taplin Professor of Computational Neuroscience and Medical Engineering in The Picower Institute and the Institute for Medical Engineering at MIT.

Indeed, we all know the feeling when we’ve slept poorly: We’re groggy, foggy and cranky. But what Brown and other scientists can tell you based on studying the slumbering brain is that sleep does much more than just help us feel refreshed and ready in the morning.

“Sleep is linked to preserving brain health and brain function in fundamental ways,” said Laura Lewis, Athinoula A. Martinos Associate Professor and a Picower Institute affiliate faculty member who studies the neuroscience of sleep. “It’s involved in actively enhancing complex cognition, maintaining our ability to rally our attentional resources, and then also at a ‘housekeeping’ level, it maintains the physiological health of the brain.”

The structure of sleep

Sleep emerges from biochemical changes among circuit nodes or “nuclei” deep in the brain. Brown summarized one such mechanism for



Neural activity, reflected in brain wave patterns, changes during sleep phases. Image courtesy Emery N. Brown

colleagues in a review article in *The New England Journal of Medicine* in 2010. During wakefulness a major arousal center of the brain, the locus coeruleus, pumps out a chemical called norepinephrine, which suppresses the activity of another region called the preoptic area (POA) of the hypothalamus. But once we’ve been awake too long, a different chemical called adenosine builds up. When that binds to cells in the POA, it inhibits arousal circuits and promotes sleep.

Over the years, Lewis and other scientists have learned that sleep’s onset and cycles involve a “constellation” of circuit nuclei and brain chemicals. In a review in *Science* in 2021, she wrote that the broad-based transformation of neural circuit activity during sleep likely represents the interaction of these many components to transform neural activity brainwide.

These sweeping changes in circuit activity give sleep a signature structure, which we go through every 90 minutes. You might see reports of “deep,” “core” and “REM” sleep from your smartwatch. Scientists, however, define sleep’s phases based on the neural circuit activity evident in the oscillating patterns (or brain waves) measured in the lab with electroencephalograms (EEGs). Brain waves are produced by large networks of neurons all firing in synchronicity. This correlation indicates shared activity.

By these measures, sleep has four stages: one REM (“rapid eye movement”) phase and three non-REM phases. In non-REM sleep, waves become high in amplitude and slow in frequency. In REM sleep, which is brought about by increases of the brain chemical acetylcholine in the brain’s outer surface, or cortex, the brain exhibits relatively high-frequency, low-amplitude rhythms (but still slower and higher amplitude than during wakefulness). During different Non-REM phases, and in different regions of the brain, the big slow waves of sleep often envelop briefer patterns of activity including “sharp wave ripples,” “spindles,” and “K-complexes” that indicate specific bouts of neural activity.

This is an important point, says Sherman Fairchild Professor Matthew Wilson. The brain is not idle during sleep. Instead, it’s taking advantage of changed activity patterns to perform needed functions.

“Sleep oscillations are way of organizing activity during sleep,” Wilson said. “The brain is just as active during sleep as it is during wakefulness. It’s just a different kind of activity.”

Sleep improves memory and maintenance

Wilson investigates how the brain makes use of memory to function intelligently in the world. He studies sleep because that’s when the

brain performs much of the needed work. As a postdoc in the early 1990s he noticed that rats who had been running mazes would while asleep replay the same patterns of activity in a brain region called the hippocampus, which forms memories of our experiences in the environment around us. The finding provided support for observations that memory improves with sleep.

Years of Wilson's research have revealed how the mammalian brain processes its representations of experience during distinct phases of sleep. During non-REM sleep, within each new slow wave, small chunks of experience are replayed at high speed. In REM sleep, by contrast, Wilson's team has shown that memories are replayed in real-time and sensations like motion are rekindled. In REM, animals appear to relive the memory and feeling of experience (i.e. they dream). Together these findings suggest that the brain uses the structure of sleep to build useful models of the world based on how it can manipulate representations of experience, Wilson said. Segments of experience can be represented and considered in different ways during non-REM sleep and reassembled and rehearsed (as dreams) during REM sleep.

In a recent paper, Wilson's lab reported new evidence from mice that while some "place cell" neurons in the hippocampus quickly encode a basic map of an experienced space, the brain employs sleep to recruit more neurons to fill in that map with detail about the routes connecting those dots and cues encountered along the way.

Several of Wilson's studies have shown that the hippocampus communicates with the cortex during sleep as it replays representations of experience. The lab's most recent paper shows that during the peaks or "up states" of slow waves, the prefrontal cortex (the locus of reasoning

and executive function) triggers short bursts of high-frequency activity in the hippocampus called sharp-wave ripples. That hippocampal activation then appears to precede the onset of the "down" state in the retrosplenial cortex, (which considers spatial contexts). The lab is currently working on decoding the contents of the crosstalk, Wilson said, but its participants and structure suggest the mice may be processing their experiences of the day to better understand what to do in similar situations.

As sleep's structure enables the brain to process representations of experience, Lewis has shown that it also enables more basic brain maintenance. Studies show that poor sleep can increase people's risk for Alzheimer's disease later in life. After an influential study at the University of Rochester in 2013 showed that the brain clears away proteins that are hallmarks of Alzheimer's during sleep, Lewis became interested in studying how this occurs.

Lewis earned her PhD in Brown's MIT lab in 2014 and after a postdoc at Harvard started her own research group at Boston University and Massachusetts General Hospital (she moved her BU lab to MIT and

Better sleep and health

affiliated with The Picower Institute earlier this year). In 2019 she published a study in *Science* that explained how sleep enables waste clearance via the cerebrospinal fluid (CSF) that pervades the brain in a circulatory system parallel to its blood vessels. Combining non-invasive measures of brain waves, blood flow, and CSF flow in sleeping human volunteers, Lewis found that during slow wave sleep the rise and fall of neural activity causes a correlated increase and decrease in blood volume. When blood flows out, CSF is drawn in. When blood flushes in, CSF is pushed out. CSF is the bath that envelops the brain, and the flow of CSF transports waste out of the brain.

At MIT, Lewis continues to study several aspects of sleep and health. In one arm of research she's studying how the brain wakes up with astonishing quickness considering how comprehensively altered brain activity is during sleep. In a new arm, she's studying how sleep loss undermines our capacity for attention, in health and in neurological and psychiatric disorders.

Appointed in MIT's Department of Electrical Engineering and Computer Science, Lewis is also working to advance the fundamental capabilities of technologies such as magnetic resonance imaging (MRI) so that it can image the brain with sharper resolution and quicker timing. Improving what MRI can reveal about brain activity is critical because it's the best technology for observing sleep's brainwide activity non-invasively in human subjects.

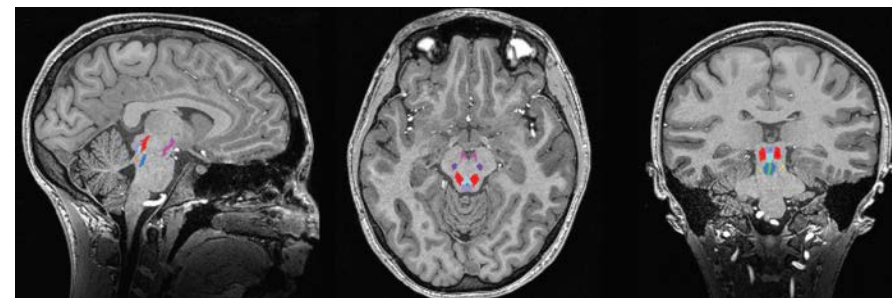
After all, better understanding the dynamics of human sleep can lead to important opportunities to improve sleep and therefore health. Getting better sleep, Wilson notes, is not merely a matter of getting more sleep. Because of how the brain exploits the structure of sleep, sleep quality requires it to be uninterrupted so that the brain can cycle through all the phases. For many people, that can be easier said than done and so they turn to off-the-shelf sleep aids, but many of those medicines are actually not producing natural sleep states, said Brown. Instead, they are acting like sedatives, or weak anesthetics, which unnaturally induce relaxation in hope that you will then achieve natural sleep.

That's why Brown is planning to launch new studies of the one anesthetic that actually triggers the same natural mechanism as real sleep. Dexmedetomidine acts much like adenosine to promote an arousal state that matches natural non-REM sleep in EEG. A big question is whether "dex"-induced sleep then progresses naturally through the cycle of the other phases. If it does, it would be a better sleep aid than what's on the market. The study is one of several Brown is advancing through his efforts to establish the Brain Arousal State Control Innovation Center at MIT and MGH.

Lewis, meanwhile, is interested in learning how the uniquely structured brain state of sleep could offer a new window for therapeutic interventions more generally. Therapies are typically administered when people are awake, she notes.

"The whole brain and body are operating in a very different way during sleep," she said. "There's an intriguing opportunity to think about how could we possibly modulate that or enhance that to confer benefit."

The brain naturally uses the structure of sleep to advance our cognition and improve our health. Maybe we can do that, too.



Colored spots mark nuclei involved in sleep and arousal state regulation. Image courtesy Laura Lewis.

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