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FOR HEALTH pg. 8

Neuroscience News

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THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY

Study Lifts the Veil on 'Valence'

THE AMYGDALA IS A TINY HUB OF EMOTIONS where in 2016 a team led by Kay Tye found specific populations of neurons that assign good or bad feelings, or "valence," to experience. Learning to associate pleasure with a tasty food, or aversion to a foul-tasting one, is a primal function key to survival.

In a new study in *Cell Reports*, Tye's team returned to the amygdala for a deep dive into its inner workings. Focusing on a particular section called the basolateral amygdala, the team showed how valence-processing circuitry is organized and how key neurons in those circuits interact with others. What they reveal is a region with distinct but diverse and dynamic neighborhoods where valence is sorted out both by connecting with other brain regions, and also by sparking cross-talk within the basolateral amygdala itself.

"Perturbations of emotional valence processing are at the core of many mental health disorders," said Tye, associate professor of neuroscience in the Picower Institute and the Department of Brain and Cognitive Sciences. "Anxiety and addiction, for example, may be an imbalance or a misassignment of positive or negative valence with different stimuli."

Anna Beyeler, a former postdoctoral associate in Tye's lab now a faculty member at the University of Bordeaux, France, led the study, which identified neurons in mice used to encode positive and negative valence about tasting sweet sucrose and bitter quinine. The team mapped the arrangement of the neurons, traced their projections to different brain regions and measured their influence in exciting or inhibiting neighboring neurons. In all, they mapped more than 1,600 cells.

■ In **Cell Reports:**

Organization of Valence-Encoding and Projection-Defined Neurons in the Basolateral Amygdala, Jan. 23, 2018, https:// goo.gl/m1Zp5Y
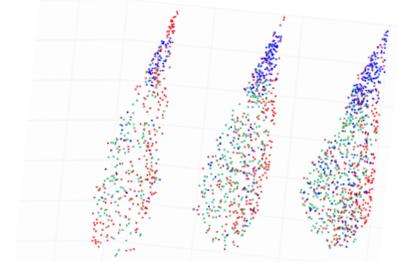
Views of the basolateral amygdala map the intermingled "neighborhoods" of neurons that project to different other regions.

New Algorithm to Analyze EEGs

WHEN TRACKING BRAIN ACTIVITY VIA ELECtroencephalograms (EEGs) in the operating room, seismic vibrations, or biodiversity over a million years, measuring the frequency of an occurrence over a period of time can yield critical insights. But researchers have been limited to looking at pieces of the data at a time to assemble the big picture, instead of looking at the big picture all at once.

In a new study in the *Proceedings of the National Academy of Sciences*, MIT researchers have unveiled a new algorithm, "state-space multitaper time-frequency analysis" (SS-MT). SS-MT provides a framework to analyze time series data in real-time, enabling researchers to work in a more informed way with large sets of data that are nonstationary, i.e. their characteristics evolve over time. It allows researchers to quantify the shifting properties of data and make formal statistical comparisons between arbitrary segments of it.

"The algorithm functions similarly to the way a GPS calculates your route when driving. If you stray away from your predicted route, the GPS triggers the recalculation to incorporate the new information," said senior author Emery Brown, a member of the Picower Institute, the Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, and associate director of the Institute for Medical Engineering and Science.

To test the algorithm, Brown and postdoc Seong-Eun Kim analyzed EEG recordings measuring brain activity from patients receiving general anesthesia for surgery. The SS-MT algorithm provided a highly denoised spectrogram characterizing the changes in power across frequencies over time. They also used the SS-MT's inference paradigm to compare different levels of unconsciousness in terms of the differences in the spectral properties of these behavioral states.

■ In **PNAS:**

State-space multitaper time-frequency analysis, Dec. 18, 2017, https://goo.gl/WD9opW
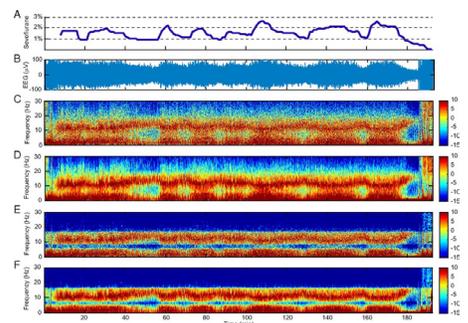
The SS-MT algorithm reduces noise and increases resolution of raw EEG data (row B) to produce better spectrograms (rows E & F) than traditional methods (rows C & D).

Specifically Remembering New Places

IF YOU ENTER A PLACE YOU KNOW WELL, YOUR brain recognizes that most of the information is already stored in long-term memory. But if the setting is unfamiliar, your brain creates a new memory of it almost immediately.

MIT neuroscientists have now discovered how this occurs. A small region of the brainstem, known as the locus coeruleus (LC), is activated in response to novel sensory stimuli, and this activity triggers a flood of dopamine into a hippocampus region called the CA3 to store a memory of the new location.

"We have the remarkable ability to memorize some specific features of an experience in an entirely new environment, and such ability is crucial for our adaptation to the constantly changing world," said Susumu Tonegawa, senior author of the study, Picower Professor of Biology and Neuroscience, and director of the RIKEN-MIT Center for Neural Circuit Genetics at the Picower Institute.

Akiko Wagatsuma, a former MIT research scientist, is the lead author of the study, which appeared in the *Proceedings of the National Academy of Sciences*.

To uncover the role of LC-CA3 communication, the researchers genetically engineered mice so that they could selectively block the neuronal connections between those regions.

To test the mice's ability to form new memories, the researchers placed them in a space that they had never seen before. The next day, they placed them in the same space. Mice whose LC-CA3 connections were not disrupted spent much less time exploring the space on the second day, because the environment was already familiar to them. However, when the researchers interfered with the LC-CA3 connection during the first exposure to the space, the mice explored the area on the second day just as much as they had on the first.

The authors found that this mechanism was not required for other types of memory, such as memories of fearful events, but appeared to be specific to memory of new environments.

■ In **PNAS:**

Locus coeruleus input to hippocampal CA3 drives single-trial learning of a novel context, Jan, 9, 2018, https://goo.gl/z2LRR4
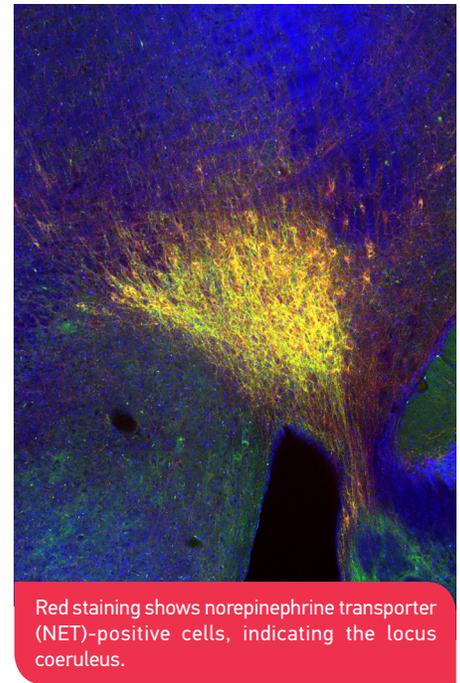
Red staining shows norepinephrine transporter (NET)-positive cells, indicating the locus coeruleus.

Toward a New Theory of Memory Formation

NEUROSCIENTISTS HAVE LONG BELIEVED THAT memories of events are stored when synaptic connections between them are strengthened via protein synthesis, but that is not necessarily so according to a new paper in the *Proceedings of the National Academy of Sciences* by the research group of Picower Professor Susumu Tonegawa.

In a 2015 paper, Tonegawa and his colleagues showed for the first time that memories could be stored even when synthesis of the cellular proteins is blocked. Tonegawa proposes that the pattern of connections that form among engram cells during the first few minutes after an event occurs are sufficient to store a memory.

In the new paper, experimental evidence shows that even though memories held by "silent engrams," in which protein synthesis has been blocked, cannot be naturally recalled, the memories persist for at least a week and can be "awakened" days later by treating cells with a protein that stimulates synapse formation. Protein synthesis may therefore be necessary for memory retrieval, but not storage.

"One of our main conclusions in this study is that a specific memory is stored in a specific pattern of connectivity between engram cell ensembles that lie along an anatomical pathway. This conclusion is provocative because the dogma has been that a memory is instead stored by synaptic strength," said Tonegawa, director of the RIKEN-MIT Center for Neural Circuit Genetics at the Picower Institute, and the study's senior author.

"What we are saying is that even without new cellular protein synthesis, once a new connection is made, or a pre-existing connection is strengthened during encoding, that new pattern of connections is maintained," Tonegawa said. "Even if you cannot induce natural memory recall, the memory information is still there."

Dheeraj Roy, a recent MIT PhD recipient, is the lead author of the paper.

■ In **PNAS:**

Silent memory engrams as the basis for retrograde amnesia, Nov. 14, 2017, https://goo.gl/WuPRLC
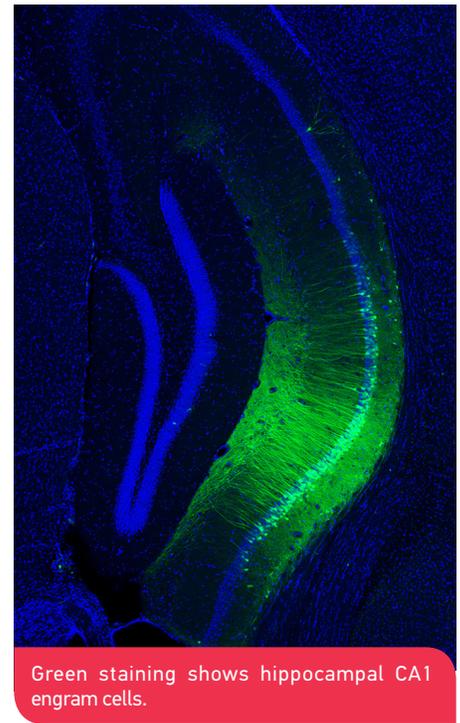
Green staining shows hippocampal CA1 engram cells.

Study: Drug Might Help with Autism

HUMAN CHROMOSOME 16P11.2 DELETION syndrome, characterized by intellectual disability, impaired language, communication and socialization skills, and autism spectrum disorder (ASD), is caused by the absence of about 27 genes on chromosome 16.

Research from the laboratories of Picower Professor Mark Bear and Jacqueline Crawley at the University of California, Davis, has identified a potential therapeutic. They found that R-Baclofen reverses cognitive deficits and improves social interactions in two lines of 16p11.2 deletion mice.

The findings, published in the journal *Neuropsychopharmacology*, suggest the drug has the potential to treat humans with 16p11.2 deletion syndrome and ASD.

Growing knowledge about genetic mutations in people with autism is enabling researchers to evaluate hypothesis-driven drug interventions for their ability to reverse the biological and behavioral consequence of specific mutations that cause autism. One of the genes in the 16p11.2 deletion region regulates the inhibitory neurotransmitter GABA. Researchers tested the hypothesis that increasing GABA neurotransmission using R-baclofen, which binds to GABA-B receptors, could reverse ASD-analogous behavioral symptoms in a mouse model of 16p11.2 deletion syndrome.

In the study, co-led by former Bear Lab doctoral student Laura Stoppel, researchers report the results of studies using two independently derived lines of mutant mice, each missing a chromosomal region analogous to human 16p11.2. Normal and mutant mice at both labs were tested after receiving R-baclofen in their drinking water on three tasks: novel object recognition, object location memory, and contextual recognition learning and memory. R-baclofen-treated mutant mice scored better after treatment on each cognitive task than the untreated mutant mice. R-baclofen also increased scores on a standard assay of mouse social behaviors — male-female reciprocal social interactions — in the 16p11.2 mutant mice.

■ In **Neuropsychopharmacology:**

R-Baclofen Reverses Cognitive Deficits and Improves Social Interactions in Two Lines of 16p11.2 Deletion Mice, Oct. 6, 2017, https://goo.gl/wW1uD2

Research Tracks Microglia Role in Alzheimer's

MICROGLIA CELLS, WHICH CLEAR AWAY dead cells from the brain and help to maintain healthy neuronal wiring, were recently found to be entangled with toxic amyloid beta plaques in tissue from Alzheimer's disease (AD) patients. Researchers had previously believed that microglia help to protect the brain from neurodegeneration by digesting the amyloid plaques, but it now appears the immune system may play a role in its progression.

"There are still a lot of very basic things that we don't know about microglia, such as whether cells in the healthy and diseased brain are all the same, or whether there are different groups, and how they become more inflammatory in the diseased state," said Picower Professor Li-Huei Tsai, director of the Picower Institute.

To better understand microglia, Tsai's team used single-cell RNA sequencing to study individual microglia cells in mice where the gene for a protein called p25 was overstimulated in the brain, prompting symptoms very similar to those of AD in humans. Their research, published in the journal *Cell Reports*, represents the first time individual microglia have been studied in this way. They used the technique to study what happens to microglia cells at various points in the progression of neurodegeneration.

"This allowed us to follow how microglia respond to the progression of the disease, and the worsening conditions in the mouse brain," said lead author and postdoctoral associate Hansruedi Mathys.

Surprisingly, they found that just one week after p25 induction, the microglia had already begun to respond to the threat by proliferating more than cells in the control mice.

They then looked at the response from the microglia at two and six weeks after p25 induction, and found that the cells had stopped proliferating, and had instead begun to mount a pronounced immune response.

They also discovered distinct groups of microglia, which were found only in the later stages of neurodegeneration. They found that the different types of microglia have very different distribution patterns.

The researchers now hope to investigate whether the genes that are expressed by the microglia might offer a potential new target for drug discovery.

■ In **Cell Reports:**

Temporal Tracking of Microglia Activation in Neurodegeneration at Single-Cell Resolution, Oct. 10, 2017, https://goo.gl/epmdV2
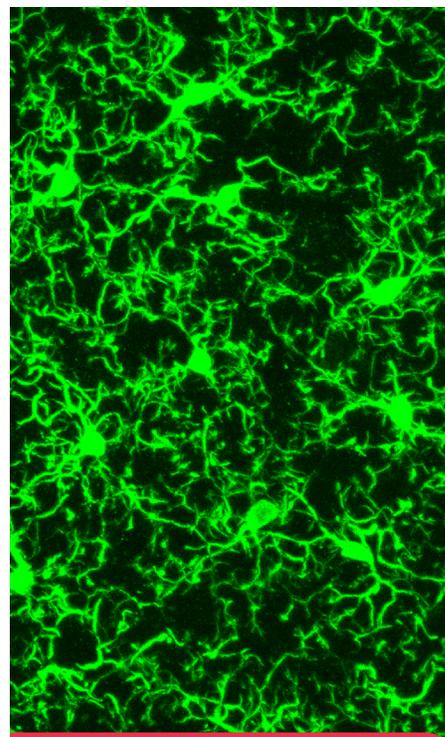
Microglia, the immune cells of the brain, transition into an inflammatory state in mouse models of Alzheimer's disease.

Brain Waves Reflect Different Types of Learning

THE BRAIN ENGAGES IN TWO TYPES OF learning — explicit and implicit. In a new study, for the first time, researchers were able to distinguish each type by the brainwave pattern it produces.

These neural signatures could guide studies of the neurobiology of how we both learn motor skills and work through complex cognitive tasks, said Earl Miller, Picower Professor of Neuroscience at the Picower Institute and the Department of Brain and Cognitive Sciences, and senior author of the study in *Neuron*.

"Our ultimate goal is to help people with learning and memory deficits," Miller said. "We might find a way to stimulate the brain or optimize training techniques to mitigate those deficits."

Explicit learning "is learning that you have conscious awareness of, when you think about what you're learning and you can articulate what you've learned, like learning the steps of game," Miller explained. "Implicit learning is the opposite. You might call it motor skill learning or muscle memory, the kind of learning that you don't have conscious access

to, like learning to ride a bike."

During explicit learning tasks, monkeys showed an increase in alpha2-beta brain waves (oscillating at 10-30 Hertz) following a correct choice, and an increase delta-theta waves (3-7 Hertz) after an incorrect choice. The alpha2-beta waves increased with learning during explicit tasks, then decreased as learning progressed.

The increase in alpha-2-beta brain waves during explicit learning "could reflect the building of a model of the task," Miller explained. "And then after the animal learns the task, the alpha-beta rhythms then drop off, because the model is already built."

By contrast, delta-theta rhythms only increased with correct answers during an implicit learning task, and they decreased during learning.

The neural signatures could help identify changes in learning strategies that occur in diseases such as Alzheimer's, with an eye to diagnosing these diseases earlier or enhancing certain types of learning to help patients cope

with the disorder, said Roman F. Loonis, a graduate student and first author.

The Neural Circuitry of 'Ripple Bursts'

BRAIN WAVES ARE A PRODUCT OF HARMO-nized neuronal activity and are important for memory formation. However, precisely where brain waves are generated and how the information that they carry interacts are not well known. Research from the lab of Susumu Tonegawa, Picower Professor of Biology and Neuroscience, and director of the RIKEN-MIT Center for Neural Circuit Genetics at the Picower Institute, has identified the neural circuits in mice that underlie the formation of specific brain waves known as ripple bursts.

In a study published in *Neuron,* Tonegawa's lab investigated how ripple bursts in the hippocampus, a brain region critical for spatial learning and memory, are produced. During periods of rest, ripples co-occur with activation of hippocampal neurons called place cells. Place cells are specialized neurons linked to specific locations along a track that fire in sequence when rodents take breaks from running the course and when the animal is asleep. Previous research has shown that the length of this mental replay

of the track can be extended when ripples are chained together, a phenomenon called ripple bursts. Identifying the neural circuits that elicit ripple bursts and extended replay had remained elusive.

Led by first author and research associate Jun Yamamoto, the team showed that the length of this mental replay and ripple bursts depends on input from the medial entorhinal cortex. However, ripple bursts and extended replay are only affected when the animal is awake, not when it is asleep. When another region of the hippocampus, called CA3, was inhibited, ripples and replay were suppressed both in the awake and sleep states.

These findings show how spatial information carried by brain waves interact, and where the waves are generated. The study may provide greater insight into neurodegenerative diseases that result in spatial memory deficits, such as Alzheimer's disease.

Faculty Profile:
Kwanghun Chung

KWANGHUN CHUNG HAS ALWAYS BEEN interested in the complexity of the brain and how it works.

But it was while developing techniques to image the nervous system of a very simple organism, the tiny roundworm *C. elegans*, that he first became interested in applying his skills to study the larger and much more complex human brain.

After completing his undergraduate studies at Seoul National University in South Korea in 2005, Chung embarked on his doctoral studies at the Georgia Institute of Technology, where he developed automated systems for high-throughput imaging and molecular phenotyping of organisms.

"During my PhD I studied *C. elegans*, which has a very simple nervous system with only 302 neurons, and yet studying it was still a very daunting challenge," said Chung, a member of the Picower Institute and the Samuel A. Goldblith Career Development Assistant Professor of Chemical Engineering at MIT. "So I thought, if studying the *C. elegans*' nervous system is difficult, how challenging would it be to study the human brain, which has 80 billion neurons?"

To develop new enabling technologies to allow human and mammalian brains to be studied in much more detail, Chung moved to Stanford University in 2010, where he joined the laboratory of Karl Deisseroth, professor of bioengineering and of psychiatry and behavioral sciences.

While at Stanford, Chung developed a technique known as CLARITY, published in *Nature* in 2013, which enables system-wide structural and molecular analysis of even large biological tissue samples.

"The technique makes tissue transparent, while preserving the structures and molecules," Chung said. "That enables 3D imaging and phenotyping of the brain and other large-scale samples."

That year Chung came to MIT, where his group now develops technologies to expand his holistic imaging and phenotyping approach.

One such technology is SWITCH, which controls the chemical reactions needed for tissue preservation and labelling. Published in *Cell* in 2015, this technology allows researchers to preserve tissues including human brains, label a set of particular proteins and image
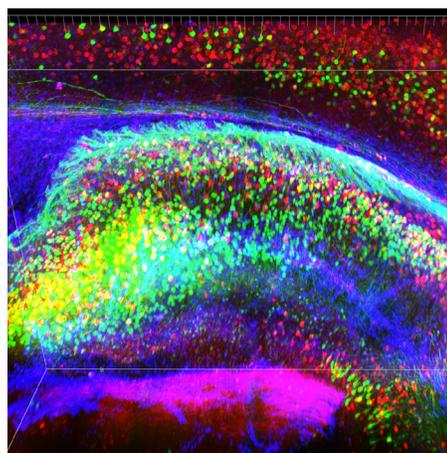
CLARITY makes thick biological tissue optically transparent to reveal labeled cells in 3D, such as these in the hippocampus.
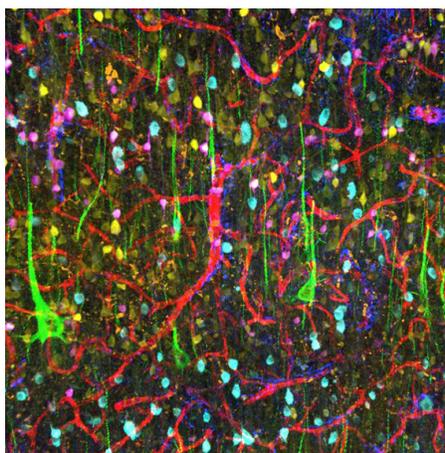
SWITCH allows scientists to perform many labeling rounds on the same tissue and is scalable to large volumes
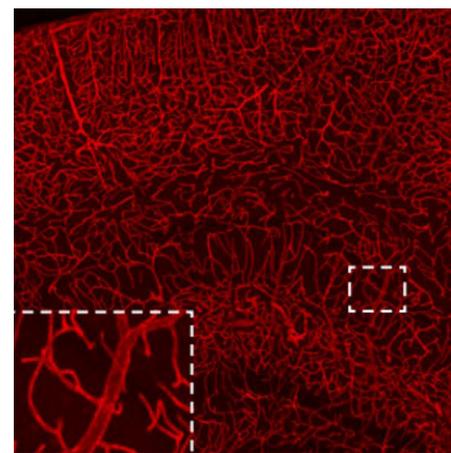
MAP allows for imaging tissue at multiple scales by making it reversibly expandable while preserving its proteins, nanoscopic details and connectivity.

them, before washing away the molecular tags and starting the process all over again for another set of proteins.

"The SWITCH technique enables highly multiplexed imaging and phenotyping, where you can image many different cells, molecules, or structures within a single tissue, whereas with traditional approaches you would have had to pick which molecule, cell type or structure you wanted to characterise," Chung said.

In 2015 Chung's team also developed a technique known as stochastic electrotransport, published in the *Proceedings of the National Academy of Sciences*, which speeds up the movement of molecules through a tissue sample without damaging the surrounding structure.

"Without this technique it can take weeks or even months to label a tissue sample the size of a mouse brain with antibodies, but if you use this technique you can do it in one or two days," Chung said.

Finally, Chung and his team developed a technique known as magnified analysis of proteome (MAP), which expands a tissue sample while preserving its sub-cellular architecture. In this way, the brain can be adjusted in size, allowing researchers to view it at four times higher resolution, for example. The paper describing the technology appeared in *Nature Biotechnology* in 2016.

Ultimately, Chung hopes his technologies will help the neuroscience and biomedical research community to accelerate the pace of discovery, and speed up the development of new therapies.

PICOWER PEOPLE

Kay Tye has earned two recent honors. In December, she received a promotion to Associate Professor with Tenure in the Picower Institute and the Department of Brain and Cognitive Sciences. Not long before, she won a National Institutes of Health Director's Pioneer Award, a special grant that the NIH says supports "exceptionally creative scientists pursuing new research directions." Tye will study the neural correlates of socialization, including social rank and social isolation, by methods including wirelessly recording in the brains of large groups of socially interacting mice.

On Feb. 16, **Emery Brown**, Edward Hood Taplin Professor of Computational Neuroscience and Health Sciences & Technology, spoke at the world's largest scientific conference, the Annual Meeting of the American Association for the Advancement of Science. Through neuroscience research and statistical modeling he developed a theoretical and analytical understanding of EEG measurements in patients under general anesthesia, he said. Now, by monitoring EEG in real time in the operating room, anesthesiologists like him can provide better care.

With a new NIH BRAIN Initiative grant, Assistant Professor **Steven Flavell** is studying the neural mechanisms that allow animals to sustain long-lasting behavioral states (e.g., sleep and wake, emotional, and cognitive states). Flavell aims to identify the circuit-wide neural dynamics that define distinct behavioral states in the simple model organism C. elegans. The group will examine how specific neuromodulators, such as serotonin, coordinate the activity of their target neurons to organize whole-circuit activity patterns over long stretches of time.

The Picower Institute has welcomed a new affiliate member: **Michael Halassa**, assistant professor in the department of Brain and Cognitive Sciences. A neuroscientist and psychiatrist, Halassa aims to understand the basic circuit mechanisms of how information is routed in the brain and how disruptions in these circuits can lead to neurological and psychiatric disorders. "Michael Halassa's work illuminates how the brain filters various sensory information through the thalamus to influence the function of the prefrontal cortex," said Institute Director and Picower Professor Li-Huei Tsai. "His work is of great interest to the Picower community and complementary of many of the Picower Institute researchers. We are pleased to have him join our community." From 2009-2014, Halassa was a postdoctoral fellow in the lab of Matthew Wilson, Sherman Fairchild Professor in Neurobiology.

In January, the School of Science honored Picower postdoctoral associates Kendrick Jones, Cody Siciliano and Ashley Watson with Infinite Kilometer awards. "Recipients of the award are exceptional contributors to their research programs," the school notes. "In many cases, they are also deeply committed to their local or global MIT community, and are frequently involved in mentoring and advising their junior colleagues, participating in the school's educational programs, making contributions to the MIT Postdoctoral Association, or contributing to some other facet of the MIT community."

Innovative Insights, Methods Raise Clinical Potential of Instilling Brain Waves

FOR A LONG TIME, MANY NEUROSCIENTISTS believed that everything they needed to know could be observed in the anatomy of neurons, synapses, circuits and regions, says Picower Professor of Neuroscience Earl Miller. Brain rhythms, or oscillations, were seen as incidental.

"People knew about brain waves but they were thought of like the humming of a car engine – they reflect the engine running, but they don't have anything to do with how the engine runs," Miller said.

But Miller did not accept that anatomy was everything. Circuits don't change quickly enough to produce the fluidity of behavior and cognition. He formulated a hypothesis that also employs a car metaphor: Circuit anatomy provides the infrastructure of roads, but rhythms guide which ones are actually driven during a particular behavior. A rhythm provides this direction and coordination because only the ensembles of neurons that join in the oscillation gain the ability to communicate and cooperate with each other, as if on a conference call.

Sure enough, evidence has been mounting – including three new papers from Miller's lab – that brain rhythms have a causal role in brain function. This growing consensus suggests that manipulating them could help patients. Several Picower Institute research findings over the last 15 months, including in lab of Picower Professor and Institute Director Li-Huei Tsai, have made this prospect especially enticing. They directly point to new ways that non-invasively instilling brain rhythms might benefit patients with Parkinson's disease, Alzheimer's disease and cognitive and attentional deficits.

As experiments testing this potential are getting underway, the Institute will also highlight rhythms at a symposium April 4 in which experts including Miller will discuss "Brain Rhythms in Health and Disease" (see page 11). The symposium will explore the newest thinking about how studying and altering brain rhythms could address neurological and psychiatric disease, often in cases where drugs have not.

Fighting Neurodegeneration

When patients have Parkinson's disease, for example, and are not responding well to medications, they can undergo surgery to receive an implanted "deep-brain" stimulator (DBS) in the subthalamic nucleus. The device produces a steadily oscillating electrical field to "pace" what would otherwise be erratic and excessive oscillations. This restoration of rhythm can curb symptoms such as tremor.

But Dr. Diane Chan, a clinician at Massachusetts General Hospital and Brigham and Women's Hospital and a researcher in Tsai's lab, notes that because surgery and implants carry risks such as infection or stroke, the treatment is restricted to patients with urgent need. That's why she is excited to test a new non-invasive (i.e. no implants) method of delivering oscillatory stimulation deep in the brain developed by Tsai and Ed Boyden, associate professor in the Departments of Biological Engineering and Brain and Cognitive Sciences, the MIT Media Lab and McGovern Institute, and co-director of the MIT Center for Neurobiological Engineering. In June 2017 in *Cell* they showed they could deliver oscillating electrical fields into tightly focused volumes deep within the brains of mice, for instance to the hippocampus.

The system works by generating high frequency fields –too high to stimulate neurons – from head-mounted electrodes. Importantly, the supplied frequencies differ by exactly the amount to be instilled. Where the waves interfere in the brain, what remains is this difference frequency. In the paper, for example, they generated fields of 2 kHz and 2.01 kHz, yielding a difference frequency of 10 Hz where the waves interfered. In experiments in the paper, they showed that they could reposition where that spot was simply by varying the field strengths.

The team reported several other crucial demonstrations. One was that when they focused on the hippocampus, overlying regions like the cortex remained unaffected. This overcomes a drawback of transcranial magnetic stimulation, a clinically approved brain stimulation technology. Another was that they could use the 10 Hz frequency to affect behavior: By moving the

signal around the motor cortex, they compelled mice to move different body parts. Finally, they found no adverse safety effects.

Now they'll ask whether the technology, called temporal interference (TI), could benefit patients with neurological conditions. Chan, Tsai and Boyden are planning experiments in which TI will treat mouse models of Parkinson's disease. Essentially they hope to provide DBS non-invasively. Myriam Heiman, Latham Family CD Assistant Professor in the Picower Institute, who studies neurodegenerative diseases, is collaborating.

Success in mice and eventually in people could create new treatment possibilities. Chan said more Parkinson's patients might be able to receive TI than can receive implanted treatment. Boyden added that with a system like TI where the location, frequency and strength of an instilled rhythm can easily be varied, clinicians could tailor treatment more precisely for each patient.

Producing innovations for societal impact, derived from basic research, is a key goal of the Aging Brain Initiative, Tsai said.

Producing innovations for societal impact, derived from basic research, is a key goal of the Aging Brain Initiative, Tsai said.

"One of the main missions is to quickly translate experimental results to patients," Tsai said. "We are very fortunate here to have people from all

Gamma
31-120 Hz

Beta
13-30 Hz

Alpha
8-12 Hz

Theta
4-7 Hz

Delta
.5-3 Hz
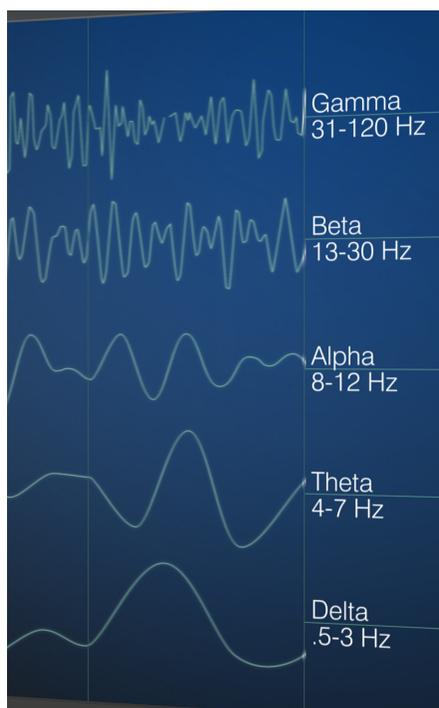
the different disciplines working together so we can come up with these less traditional types of treatment approaches."

TI might also have an impact on Alzheimer's disease, Tsai adds. In December 2016, in a powerful demonstration of the potential of non-invasively manipulating brain rhythms, she, Boyden and Emery Brown, Edward Hood Taplin Professor of Computational Neuroscience and Health Sciences & Technology, discovered that having mice gaze at lights that flicker at 40 Hz – the frequency of a gamma rhythm in the brain – helped Alzheimer's model mice to reduce the buildup of harmful amyloid beta proteins. The experiments reported in *Nature* showed that entraining the gamma rhythm in the visual cortex coordinated beneficial activity, for instance increasing the activity of microglia, specialized brain cells that clear away harmful protein plaques. Gamma light flicker therapy has since begun human trials.

Tsai's lab is interested to learn whether TI can help extend or enhance that effect by delivering gamma frequencies directly to other regions. Tsai's hope is that gamma therapy can provide an effective Alzheimer's treatment, especially as drug trials continue to disappoint.

Waves and Cognition

Miller studies the role of rhythms in cognition and working memory, where we exert rapid, volitional control over the information we

process. Early in 2018 he showered the field with evidence from experiments in animals that a coordinated byplay of beta and gamma rhythms in the pre-frontal cortex (PFC) enables such functions.

In *Nature Communications*, his team showed that gamma rhythms appear to modulate read-out from working memory, for instance when the stored sensory information is needed for cognition. Beta rhythms, meanwhile, control when gamma is active and appear necessary for gating access to, and clearing out, working memory for storing new information. In the *Proceedings of the National Academy of Sciences*, Miller's lab showed that the rhythms emerge during working memory tasks in distinct layers of the (PFC): Gamma operates among neurons in superficial cortical layers while beta operates among neurons in the deep layers. This fits with known anatomy, he said: Deep layers carry "feedback" from higher-level to lower-level cortex so they are where a beta control signal would be expected. The superficial layers carry "feedforward" sensory information from the outside world and contain sensory-related gamma rhythms.

In *Neuron,* Miller's group examined the role of rhythms amid the task of sorting images into relatively literal or abstract categories. Monkeys employed different rhythms in different areas of the cortex: The literal thinking involved entraining gamma in the ventral PFC, while more abstract thinking came about with bursts of beta rhythms in the dorsal PFC.

Miller, too, is considering how non-invasive brainwave manipulation could help patients with psychiatric conditions, such as in autism or schizophrenia, where working memory or reasoning may be aberrant. Another idea might be to intervene to enhance alpha and beta rhythms to modulate attention, Miller said.

"Let's say you have a brain that is having trouble focusing attention and top-down control," he said. "That depends, according to our new model, on alpha and beta rhythms. If you could strengthen those, in theory, you could improve people's ability to stay on task."

The ability to evaluate such questions depends on the insights and technologies that Picower Institute scientists have developed. How might it enhance health to look beyond the brain's anatomy to its rhythmic activity? Stay tuned to these frequencies.

Upcoming EVENTS

05.09.18 *Early Life Stress & Mental Health*

The Picower Institute's biennial spring symposium, "Early Life Stress & Mental Health" is a daylong event that will feature talks and panel discussions among neuroscientists, psychologists, physicians, policy experts and parents as they examine how experience and biology combine to affect the development of young minds.

Keynote speaker Geoffrey Canada, MS, is renowned worldwide for pioneering work helping children and families in Harlem, and as a thought leader and passionate advocate for education reform. From 1990 to 2014, Canada served as the President and CEO for the Harlem Children's Zone. He continues to serve as president of the HCZ and Promise Academy Boards.

Mark Bear, PhD, is a Picower Professor of Neuroscience in the Picower Institute at MIT. He studies how experience and deprivation modify synaptic connections in the brain. Current foci of the lab include mechanisms and regulation of naturally occurring synaptic plasticity in the visual cortex, and pathophysiology of genetically defined developmental brain disorders.

Marc Berman, PhD, is an assistant professor of psychology at the University of Chicago. He seeks to understand the relationship between individual psychological and neural processing and environmental factors. His lab utilizes brain imaging, behavioral experimentation, computational neuroscience and statistical models.

Renee Boynton-Jarrett, MD, ScD, is an associate professor of pediatrics at Boston University School of Medicine and the founding director of the Vital Village Community Engagement Network. Her work focuses early-life adversities as life-course social determinants of health. She has a specific concentration on psychosocial stress and neuroendocrine and reproductive health outcomes.

Nadine Burke Harris, MD, MPH, is a pediatrician and leader in transforming the response to early childhood adversity and the resulting toxic stress that dramatically impacts health and longevity. She is the founder and CEO of the San Francisco-based Center for Youth Wellness, an organization that seeks to create a multidisciplinary clinical model that effectively treats toxic stress in children.

Paul Farmer, MD, PhD, is chief strategist and co-founder of Partners In Health, Kolokotrones University Professor and chair of the Department of Global Health and Social Medicine at Harvard Medical School, and chief of the Division of Global Health Equity at Brigham and Women's Hospital. Farmer and colleagues have pioneered novel, community-based treatment strategies that demonstrate the delivery of high-quality health care in resource-poor settings.

Frank Farrow, MS, is president of the Center for the Study of Social Policy. Farrow has focused CSSP on work that has a clear tie to improved results for children, families and communities; a commitment to equity and to CSSP's evolution as an anti-racist organization; and to strategies that integrate service system reform, community change and policy analysis.
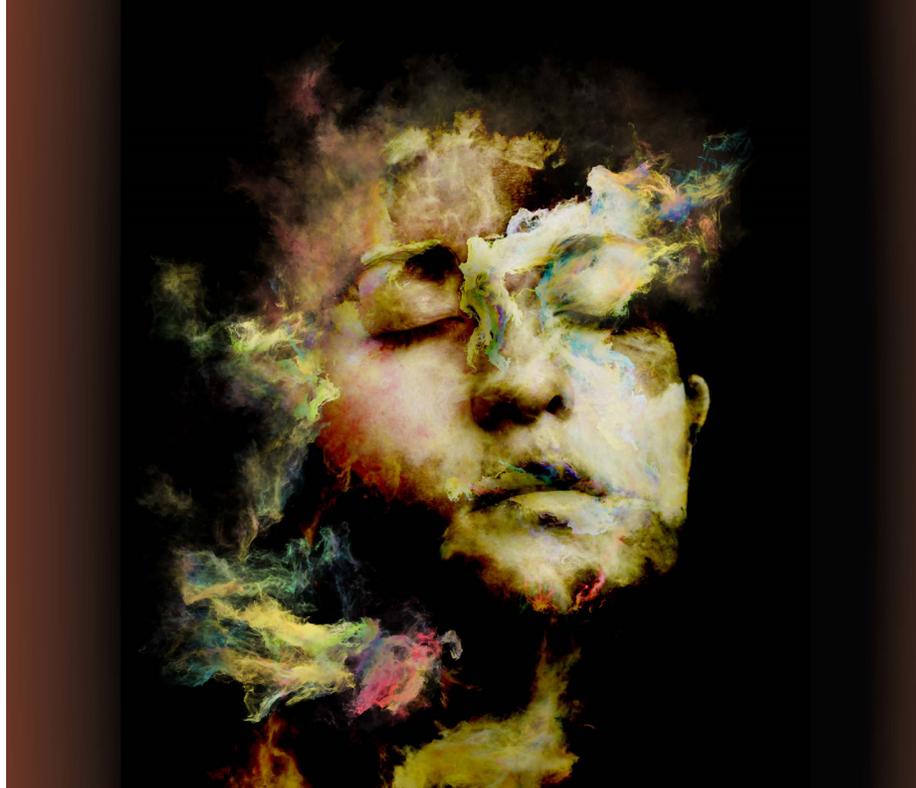
Ravi Raju, MD, PhD, is a visiting fellow in the lab of Picower Professor and Institute Director Li-Huei Tsai and a clinical fellow at Boston Children's Hospital. He is interested in the epigenetic effects of early life adversity and their link to social determinants of health and disease.

Jonathan Rose, MS, is president and founder of Jonathan Rose Companies LLC, a multi-disciplinary real estate development, planning, and investment firm. His business, public policy and not-for-profit work all focus on creating more environmentally, socially and economically resilient cities.

Frank Schilbach, PhD, is an assistant professor of economics at MIT. His research examines correlates of poverty, including substance abuse, physical pain, sleep deprivation, and depression. He seeks to understand their impacts on cognitive function, decision-making, and worker productivity.

Laura Schulz, PhD, is a professor of cognitive science in the Department of Brain and Cognitive Sciences at MIT. Her research looks at how children infer concepts and causal relations to engage in prediction, explanation, and intervention; factors that support curiosity and exploration; and how these abilities inform and interact with social cognition.

Jack Shonkoff, MD, is a pediatrician and the Julius B. Richmond FAMRI Professor of Child Health and Development at Harvard University. He is also a professor of pediatrics at Harvard Medical School and Boston Children's Hospital and director of the Center on the Developing Child at Harvard.

Picower Institute - May 9, 2018, 9AM - 5PM

EARLY LIFE STRESS & MENTAL HEALTH

Picower Institute - April 4, 2018, 9AM - 5PM

BRAIN RHYTHMS
in
HEALTH & DISEASE
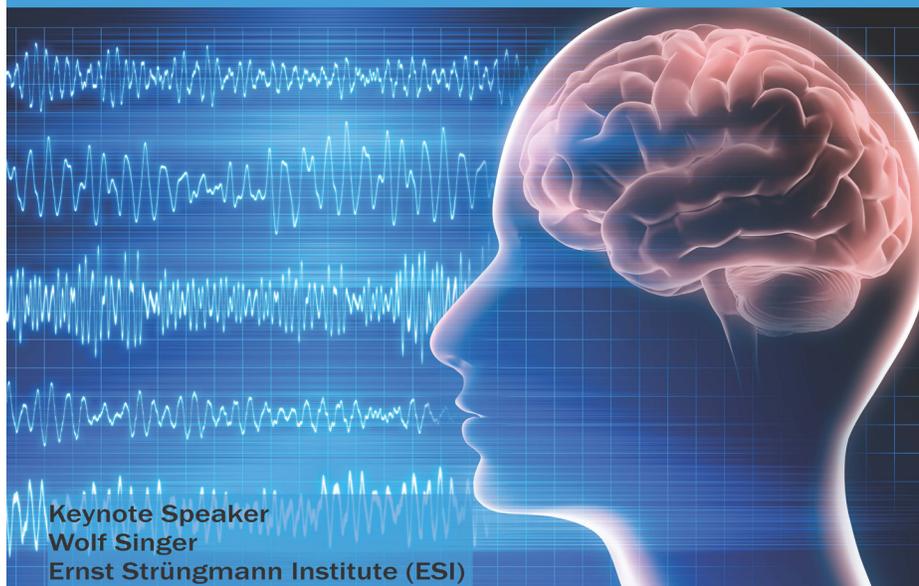
Keynote Speaker
Wolf Singer
Ernst Strüngmann Institute (ESI)

Marie Carlen
Karolinska Institute
Solna, Sweden

Laura Colgin
UT Austin
Austin, USA

Pascal Fries
ESI
Frankfurt, Germany

Peter Jonas
IST Austria
Klosterneuburg, Austria

Nancy Kopell
Boston University
Boston, USA

Earl Miller
Picower Institute, MIT
Cambridge, USA

Christopher Moore
Brown University
Providence, USA

Jorge Palop
UCSF
San Francisco, USA

Annabelle Singer
Georgia Tech
Atlanta, USA

Vikaas Sohal
UCSF
San Francisco, USA

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04.04.18 *Brain Rhythms in Health & Disease*

At this daylong symposium, 11 experts in cellular, circuit, systems, and behavioral neuroscience will come together to present their emerging understanding of the mechanistic role of neuronal oscillations in brain dynamics, cognition, behavior, and in disease. They'll discuss the latest advances and important challenges in the scientific study of rhythms and synchronized neural activity.

Keynote speaker Wolf Singer, MD, is a professor, senior research group leader and founding director of the Ernst Strüngmann Institute for Neuroscience in Cooperation with Max Planck Society in Frankfurt, Germany. His research focuses on the analysis of neuronal processes in the mammalian cerebral cortex that underlie higher cognitive functions and their deterioration in disease.

Marie Carlén, PhD, is an associate professor and group leader in the Department of Neuroscience at the Karolinska Institutet in Stockholm, Sweden. She studies normal network functions in cognition and mechanisms underlying psychiatric disorders to identify cellular and molecular targets for therapies for mental disorders.

Laura Colgin, PhD, is an associate professor in the Department of Neuroscience at the University of Texas at Austin. The main goals of her studies are to understand the functional significance of the different types of rhythms within the entorhinal-hippocampal network and to uncover their underlying mechanisms.

Pascal Fries, MD, PhD, is a professor and director at the Ernst Strüngmann Institute. He studies neuronal synchronization's mechanisms, its consequences and its cognitive functions.

Peter Jonas, MD, is a professor at the Institute of Science and Technology Austria in Klosterneuburg. The main goal of his research is to understand how specific properties of synapses shape higher network functions in the brain. Multiple lines of research focus on neurons in the hippocampus.

Nancy Kopell, PhD, is the William Fairfield Warren Distinguished Professor at Boston University, and co-director of the Center for Computational Neuroscience and Neural Technology at Boston University. An applied mathematician, she investigates questions including how the brain produces its dynamics and how brain rhythms take part in cognition.

Earl Miller, PhD, is a Picower Professor of Neuroscience at the Picower Institute for Learning and Memory and the Department of Brain and Cognitive Sciences at MIT. Interests in the Miller laboratory center around the neural mechanisms of attention, learning, and memory needed for voluntary, goal-directed behavior, particularly in the prefrontal cortex.

Christopher Moore, PhD, is a professor of neuroscience at Brown University. He studies neocortical dynamics, seeking to understand the meaning of these dynamics for perception, and the mechanisms that generate them. Methods include computation, behavior, optogenetics, electrophysiology and imaging.

Jorge Palop, PhD, is an assistant professor in the Department of Neurology at the University of California at San Francisco School of Medicine and assistant investigator at the Gladstone Institute of Neurological Disease. He seeks to elucidate and prevent the neural processes that underlie cognitive disturbances in neurological conditions, especially Alzheimer's disease.

Annabelle Singer, PhD, is an assistant professor in the Department of Biomedical Engineering at Georgia Tech and Emory University. Her research takes a multi-dimensional approach to deciphering neural activity, examining how neural activity both predicts behavior and is received and interpreted via synaptic inputs by downstream cells.

Vikaas Sohal, MD, PhD, is an associate professor in the University of California at San Francisco School of Medicine's psychiatry department. He studies prefrontal cortex circuits to understand how neurons, their inputs, and their interconnections give rise to patterns of circuit activity, and how these contribute to normal cognition and pathological behaviors in disorders such as schizophrenia and autism.

MIT Colloquium on Brain & Cognition

03.22.18 **Hokto Kazama, PhD**
RIKEN Brain Science Institute

04.19.18 **Kang Shen, PhD**
Stanford University, HHMI

Neuroscience News // Spring 2018

OUR VISION

The Picower Institute is a community of scientists focused on a common question: How is the brain modified by experience?

To answer this question we use multiple levels of analysis, ranging from molecular to behavioral, and exploit the tools of modern molecular biology and genetics to dissect the contributions of specific molecules, synapses, cells and circuits to behavior.

We work to understand the pathophysiological mechanisms underlying complex disorders of the brain that affect emotion and cognition.

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TOP ROW: Mark F. Bear, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Investigator, Howard Hughes Medical Institute (HHMI); **Emery Brown**, Edward Hood Taplin Professor of Computational Neuroscience and Health Sciences & Technology, The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology; **Kwanghun Chung**, Assistant Professor, Departments of Chemical Engineering and Brain and Cognitive Sciences, Institute of Medical Engineering and Science core faculty; **Steven Flavell**, Assistant Professor of Neuroscience, The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology; **Myriam Heiman**, Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences, Broad Institute core member; **Troy Littleton**, Picower Professor of Biology and Neuroscience, Departments of Biology and Brain and Cognitive Sciences; **Earl Miller**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences.

BOTTOM ROW: Elly Nedivi, Professor, Departments of Brain and Cognitive Sciences and Biology; **Mriganka Sur**, Paul E. Newton Professor of Neuroscience, Director of The Simons Center for the Social Brain; **Susumu Tonegawa**, Picower Professor of Biology and Neuroscience, Departments of Brain and Cognitive Sciences and Biology, Investigator, Howard Hughes Medical Institute, Investigator and Director of the RIKEN-MIT Center for Neural Circuit Genetics; **Li-Huei Tsai**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director, The Picower Institute for Learning and Memory; **Kay Tye**, Associate Professor of Neuroscience, Department of Brain and Cognitive Sciences; **Matthew Wilson**, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Director, The Picower Institute for Learning and Memory; **Weifeng Xu**, Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences.