STRESS and mental HEALTH

Neuroscience News

Summer 2016

THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Stress is an inevitable part of life. In fact, stress in a child's life can be beneficial. Positive stressors like making new friends or starting the first day of school promote resilience. Tolerable stress, like the death of a loved one or a family disruption, can be properly managed with the right support.

Toxic stress, however, occurs when a child experiences hardship like abuse and neglect over long periods of time. This type of stress can leave lasting signatures that negatively affect long-term health and prosperity. Children exposed to toxic levels of stress are also linked to impairments in learning, behavior, and their physical and mental well-being. The appropriate understanding of the underlying biology is necessary in order to prevent, screen, and heal those who are overwhelmed with toxic stress. Creating science-based strategies that build strong foundations are crucial for educational success, economic productivity, and securing a healthy adult population.

In order to highlight the importance of this issue, the Picower Institute for Learning and Memory hosted its biannual spring Symposium on ***New Insights on Early Life Stress and Mental Health***. This event brought together a range of renowned experts to discuss how to address the far-reaching implications of early childhood adversity. We are especially grateful to Barbara Picower and the JPB Foundation, for making this event possible and for her longstanding support of those who remain committed to finding solutions that effectively address childhood development issues. In this newsletter we have included highlights of this work and major breakthroughs and accomplishments from our Institute this past spring.

Childhood adversity is a pressing issue and of meaningful importance to our Institute, the MIT community, and me. We encourage you to support the ongoing dialogue between scientists, practitioners, and policymakers to improve the health and lives of society's disadvantaged children everywhere.

LI-HUEI TSAI, DIRECTOR

Early Life Stress and the Pathways of Psychiatric Disorders

Adverse childhood experiences and toxic stress are linked to the development of mental disorders, such as anxiety, depression, and substance abuse. Some examples of toxic environments include living in poverty, abuse, neglect, witnessing drug use, domestic violence, and having parents with mental illness. More than 16 million children live in abject poverty in the United States and nearly two-in-three people in the U.S. have been exposed to traumatic childhood experiences.

Research has shown that the brain is impacted by negative childhood experiences and can result in social, emotional, and cognitive impairments that are also observed in anxiety and mood disorders, such as depression and bipolar disorder. In fact, having an anxiety disorder makes it nearly twice as likely to suffer from another mental illness, such as depression. Ultimately, early life toxic stress may result in premature death.

As such, the prevalence of toxic childhood experiences and its impact on mental health is an important public health issue that requires immediate attention to prevent unhealthy brain development, to buffer the looming strain of medical care, and to mitigate the loss of workforce productivity.

Current approaches to understanding mental health rely on symptom-based definitions and diagnoses. What makes mental illness difficult to treat, in part, is that such disorders give rise to similar symptoms. Therefore, a symptom-based approach may lack validity and impede our biological understanding of psychiatric disease. For example, a fever is a symptom of many ailments and a symptoms-based approach to address the fever does not always lead to the best treatment. Mental disorders are biological in nature and involve brain pathways that underlie cognition, emotion, and behavior.

IN THIS ISSUE

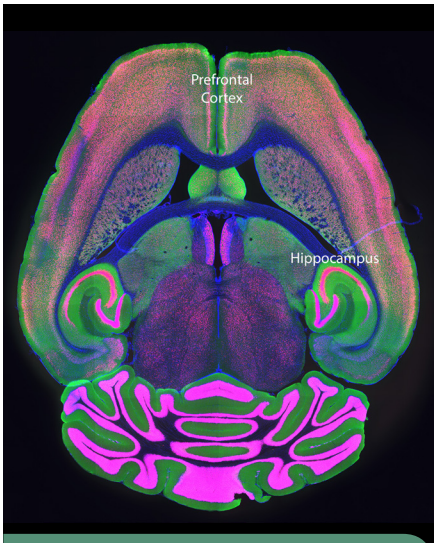
Understanding brain pathways, such as how memory systems change due to chronic stress and how environmental stressors can dysregulate brain pathways, can allow us to better define psychiatric diseases and help tailor early life interventions. When something stressful occurs, stress hormones such as cortisol and adrenaline are released from the brain into the blood stream. Normally, released stress hormones cause an additional release of hormones from the adrenal glands, located above the kidneys, which make their way back to the brain to stop the stress response. However, in the chronically stressed brain there is an overproduction and prolonged release of stress hormones that cannot be turned off, which in turn dysregulates gene activity, causes the hippocampus to shrink, the amygdala to grow, and disrupts the function of the prefrontal cortex, and nucleus accumbens -- among other physiological responses. Most individuals with depression and anxiety exhibit these very symptoms. Additionally, those with anxiety and mood disorders have functional deficits in both the prefrontal cortex and nucleus accumbens. For example, people with anxiety have difficulty regulating their emotional response, which is a function of the prefrontal cortex. Those with depression show decreased pleasure or interest in activities they once enjoyed, which is modulated by the nucleus accumbens. Stress hormones are an integral component to mental health and are the bridge between environmental stressors and changes in the brain's memory pathways.

To this end, several Picower Investigators focus on the learning and memory systems that are critical for regulating the stress response such as the hippocampus, amygdala, nucleus accumbens, and prefrontal cortex. For example, professor and director of the Picower Institute, **Li-Huei Tsai**, studies how altering genetic and epi-genetic activity can modify traumatic memories stored in the hippocampus, which is a brain region critical for autobiographical memory formation and for regulating the release of stress hormones in the brain. Professor **Kay Tye** studies social isolation and how the amygdala processes emotions and distinguishes negative experiences from positive ones. The amygdala is highly responsive to stress and helps us link cues in our environment to potential danger. Professor **Susumu Tonegawa's** lab has looked at how the nucleus accumbens, which is important for reward processing, combines memory information from the hippocampus and emotional information from the amygdala. Tonegawa's team has found that artificial activation of positive hippocampal memories triggers the hippocampus-amygdala-nucleus-accumbens pathway to help relieve depressive symptoms due to stress. Professor **Earl Miller** is a leading expert on the prefrontal cortex, which is a key region in regulating anxiety, stress, and is necessary for complex decision-making. Additionally, the prefrontal cortex is one of the first regions crippled by chronic and toxic stress. There is a clear relationship between the brain regions critical for learning and memory, their function in regulating stress, and how their dysfunction leads to mental illness.

Knowing how stress hormones lead to changes in specific areas of brain networks may help clinicians prescribe a better suited medication to treat a patient with mental illness. In knowing the interaction between stress hormones and brain activity, new therapies could be developed to better target brain dysfunction as a result of chronic or toxic stress. In addition, research on the brain networks crippled by stress will help provide clinicians with diagnostic tools to identify changes in brain anatomy and activity such as in helping children that have experienced adverse situations. A diagnosis based on neurobiology and symptoms will further enable caretakers to intervene and find the best treatments for children overwhelmed by chronic and toxic stress.

Ultimately, prevention of adverse childhood experiences is a better solution than treating mental illness later in life. Current tools to study the brain are advancing at an exceptional rate and are starting to challenge symptom-based diagnoses. Neuroscience research helps establish the foundation for biological-based diagnoses and allows us to link specific symptoms to specific disorders. As we enter into this new era of discovery, there is pervasive optimism in the field that we will soon be able to create treatments and interventions based on rigorous neuroscience that will halt and reverse the impact of adverse childhood experiences on mental health.

– Joshua Sariñana, PhD



The hippocampus and prefrontal cortex. Pink/red – nucleus of neurons, green – excitatory neurons, blue – white matter. Image Credit: Sachie Ogawa Kitamura.

The amygdala (lower right) projects axons to the nucleus accumbens (upper/middle left). Image Credit: Anna Beyeler & Craig Wildes.

Steven Flavell Joins the Picower Institute

At Oberlin College, Steve Flavell thought he'd play the guitar, sax and piano and study literature--anything but become a scientist. But what, he wondered, compelled some characters in literature to act so illogically and impulsively? By the time Flavell graduated, he had switched his major to neuroscience and went on to Harvard Medical School for his Ph.D. in neurobiology motivated by his question of why people act the way they do. More specifically, he studied how changes in the external world lead to changes within the brain at the synaptic and genetic level. Soon after his Ph.D. Flavell moved to Rockefeller University to work in the laboratory of Cori Bargmann. At Rockefeller, Flavell worked on a multi-dimensional project that threaded behavior, genetics, *in vivo* imaging, and optogenetics to study how the nervous system coordinates complex behaviors using C. elegans as his model. In C. elegans, he knew he had found a quantifiable way to study the idiosyncrasies of behavior.

C. elegans is a roundworm that is about the size of a pencil point. If you tap it on the nose, it backs up. It can learn to associate a neutral odor with hunger, and avoid the odor in the future. As it slithers over plates coated with bacteria, its meal of choice, it exhibits two distinct modes: roaming in search of food or dwelling, which involves less action and more eating. Its built-in behaviors resemble our sleep-wake cycles and uses some of the same neuromodulators, such as serotonin and dopamine.

The best thing about the creature, said Flavell, Assistant Professor at the Picower Institute for Learning and Memory, is that scientists have mapped every existing connection among the 302 cells in its nervous system, potentially allowing him to understand how this nervous system works in "really precise detail," he said.

Flavell wants to identify how broad-acting neuromodulators such as dopamine and serotonin regulate behaviors from the genetic to neuronal-circuit levels. The answer could shed light on why humans sometimes persist in states of depression or anxiety.

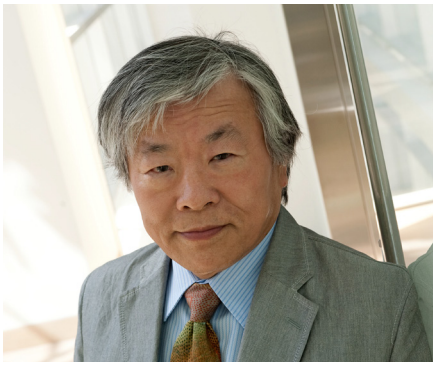
"If you understand the mechanism [by which these circuits function], you have a more precise understanding of how these states are organized in our brains."

Flavell believes that detailed mechanistic insights into neuromodulatory circuit function will one day allow researchers to pinpoint circuit deficits in the brains of patients suffering from depression and "target that circuit with a drug or other therapy to fix it," he said.

Using a genetic screen to identify molecular components that underlie the roundworm's two behavioral states, Flavell identified a neuropeptide signaling system mediated by pigment dispersing factor or PDF that resulted in enhanced dwelling when mutated. In contrast, he found that loss of a serotonin receptor caused increased roaming. "For reasons we don't fully understand, these serotonergic neurons become incredibly active right as the animal switches from roaming to dwelling," he said.

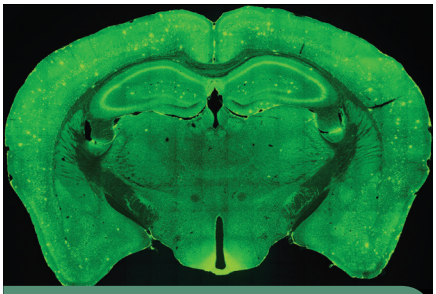
"If you get rid of one neuromodulator, the animals don't roam long enough. If you get rid of the other, they don't dwell long enough. If you get rid of both, the animals basically don't have any long-lasting behavioral states," he said.

Flavell hopes to take advantage of a state-of-the-art toolkit: behavioral analysis, genetics, neuronal imaging, and optogenetics. Because the worm's skin is transparent, he's building a microscope that could illuminate large populations of neurons in the animal's nervous system as it moves around. The long-term goal, he said, is to extend the investigation to mammalian models, but for now, C. elegans provides the perfect system.



Picower Institute Professor Susumu Tonegawa

Finding **Lost Memories** in **Alzheimer's** Mice



An Alzheimer's mouse brain. Image Credit: Dheeraj S. Roy

Memory loss is perhaps the most profound cognitive deficit observed in those with Alzheimer's disease. The hippocampus is a brain region crucial for autobiographical memories and exhibits degeneration in Alzheimer's disease. It is unknown whether hippocampal memory deficits observed in Alzheimer's patients is due to the inability to make new memories or the inability to access memories. **Picower Professor Susumu Tonegawa's** lab has shown that it is possible to retrieve memories in mice with Alzheimer's disease by artificially activating hippocampal neurons using optogenetics. With optogenetics neurons can be turned on or off by shining light on those cells. In additional sets of experiments the Tonegawa lab also showed that spines, small protrusions that receive input from other neurons, are less abundant in the Alzheimer's mice. However, when optogenetics was used to stimulate spine growth the Alzheimer's mice showed vastly improved memory performance. This research may help identify therapeutic approaches for memory improvement in those with Alzheimer's disease.

Published in **Nature**

Memory retrieval by activating engram cells in mouse models of early Alzheimer's disease. Dheeraj S. Roy et al., Nature. March 24, 2016.

Modifying Genes Impairs **Social Skills**

Picower Institute Professor Li-Huei Tsai

People with Rett Syndrome, a rare and debilitating neurodevelopmental disorder, exhibit many autism-like traits. Children with the disorder typically develop distinctive repetitive hand movements, such as wringing, as well as autistic traits. Research from **Picower Professor Li-Huei Tsai's** laboratory have identified a protein that plays an important role in the disorder. The syndrome is known to be caused by a mutation in the MeCP2 gene. Previous research has shown that one effect of this mutation is to prevent the gene from interacting with the protein complex NCoR/HDAC3. However, the precise function of the HDAC3 protein within the brain is still unclear. To investigate whether the protein plays a role in cognition, mice with the deleted HDAC3 were found to have social and intellectual impairment and loss of motor coordination, as well as repetitive actions similar to the distinctive hand wringing seen in patients with Rett Syndrome. The finding could open up a new avenue of research into Rett Syndrome, as well as a potential target for treating the disorder. It may also have implications for our understanding of autism spectrum disorder and learning disabilities.

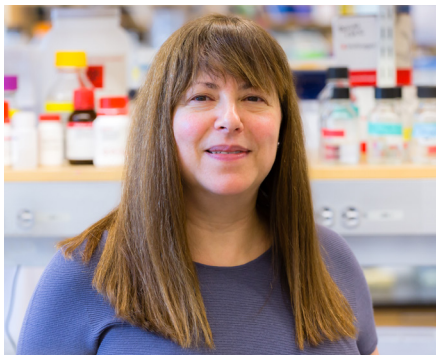
Published in **Nature Neuroscience**

Histone deacetylase 3 associates with MeCP2 to regulate FOXO and social behavior. Alexi Nott et al., Nature Neuroscience. July 18, 2016

An artist's rendition of the DNA double helix.

The Disappearing Reappearing Synapse

A new study from **Picower Professor Elly Nedivi's** Lab at MIT's Picower Institute for Learning and Memory sheds light on the innate plasticity of the adult brain at its most fundamental level--the synapse.



Picower Institute Professor Elly Nedivi

Neuron-to-neuron communication that allows the brain to coordinate activity and store new information takes place at synapses. Synapses can be added and eliminated in response to new information. If an outside stimulus doesn't enact a synaptic change, it doesn't register -- no learning or memory formation takes place. Synaptic remodeling is commonly thought to represent rearrangements in microcircuit connectivity. Villa et al. observed a new, reversible, type of synapse dynamics, unique to inhibitory synapses, which could provide flexible, input-specific gating of stable excitatory connections. Synaptic malfunctions are implicated in many neurological and neuropsychiatric disorders. A better understanding of how synapses are formed and dismantled in response to external stimuli can help address a wide range of such disorders, from drug addiction to mental illness.

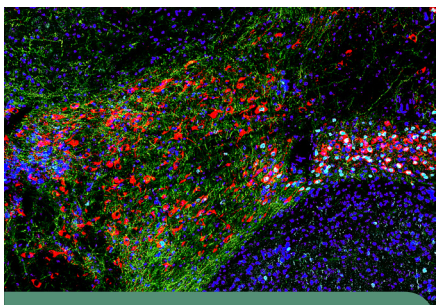
A cartoon depicting how an inhibitory connection being 'on' blocks information flow (red light), while its removal allows transmission (green light). Connections toggle between on and off.

Published in **Neuron**

Inhibitory Synapses Are Repeatedly Assembled and Removed at Persistent Sites In Vivo. Katherine L. Villa, Kalen P. Berry, et al., Neuron. February 17, 2016.

Dopamine to Activate Behavior

Picower Assistant Professor Kay Tye



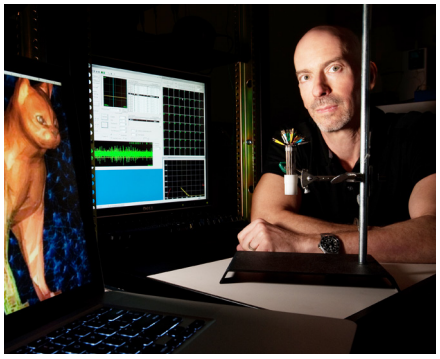
The ventral tegmental area, which makes the neuromodulator, dopamine (red). Also shown DNA (blue), neuron fibers (green) Image Credit: Caitlin Vander Weele

Dopamine is a neurotransmitter critical for motivation, learning, and seeking out reward. Yet, little is known about how such a rich repertoire of behaviors is mediated by dopamine. Recent work from the Laboratory of **Picower Assistant Professor Kay Tye** has provided greater insight into the role of dopamine and behavioral activation. Using optogenetics, a light sensitive protein that can turn on and off sets of neurons with light, researchers in her laboratory interrogated a brain circuit that regulates dopamine release. They found that by lifting the breaks off dopamine release positive reinforcement was enhanced. Professor Tye's research helps wed psychological function to brain circuits, which is crucial for understanding how brain dysfunction can lead to mental disorders such as compulsive reward seeking, such as gambling, binge eating, and addiction.

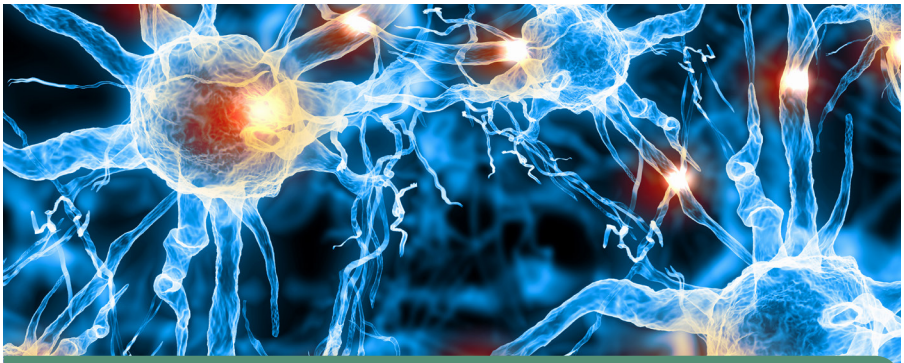
Published in **Neuron**

Inhibitory Input from the Lateral Hypothalamus to the Ventral Tegmental Area Disinhibits Dopamine Neurons and Promotes Behavioral Activation. Edward H. Neigh, Caitlin M. Vander Weele, et al., Neuron. June 15, 2016

Breaking Brain Waves to Support Working Memory



Picower Institute Professor Earl Miller



An artist's rendition of a group of neurons working in synchrony

Working memory is the ability to keep or manipulate information in mind like multiplying 18 by 37. Models of working memory require neurons to sustain activity for normal working memory. **Picower Professor Earl Miller** of the Picower Institute for Learning and Memory recently reported on how brain waves in the prefrontal cortex regulate working memory. Neurons can communicate as a chorus of activity that harmonizes over time. When many neurons harmonize at the same time they create brain waves of different lengths and sizes. One such wave is called beta, which is slower than the much faster gamma waves. Professor Miller's lab has shown that beta is interrupted by bursts of gamma waves to support working memory. His work challenges older models of working memory and gives greater insight into the function of the prefrontal cortex.

Published in **Neuron**

Gamma and Beta Bursts Underlie Working Memory. Michael, Lundqvist et al., Neuron. April 6, 2016.

Shedding Light on **Synaptic Plasticity**

Two populations of inhibitory neurons (blue) and (pink) that co-mingle in the visual cortex. Image Credit: Eitan Kaplan

The brain is shaped by experience and it is through synaptic plasticity that the environment modifies the connections of the brain. Brain development is particularly sensitive to experience during early life and affects how the brain will function as an adult. One way to study early life plasticity is to see how external stimuli, such as light, affects visual processing in the brain. **Picower Professor Mark Bear** studies synaptic plasticity, which is the ability for neurons to dynamically change their connections between one another, in the primary visual cortex. In a recent study his lab found that the inhibitory neurons enabled plasticity when rich visual stimulation was given to mice. The lack of visual input also resulted in synaptic plasticity but it did not require inhibitory neurons. This research sheds light on the mechanisms of synaptic plasticity and may help in understanding disorders such as autism and schizophrenia, which show altered forms of plasticity in inhibitory neurons.

Published in **eLife**

Contrasting roles for parvalbumin-expressing inhibitory neurons in two forms of adult visual cortical plasticity. Eitan S. Kplan, Sam F. Cooke., Robert W. Komorowski et al., eLife March 4, 2016.

Picower Institute Professor Mark Bear

NEW INSIGHTS ON

Early Life Stress & Mental Health

THE PICOWER INSTITUTE SPRING SYMPOSIUM

On May 12th the Picower Institute for Learning and Memory hosted its spring Symposium – New Insights on Early Life Stress and Mental Health – in Honor of Barbara Picower, President of the JPB Foundation.

Guest speakers presented perspectives ranging from clinical and educational practice to basic neuroscience research and focused on the issue of early childhood adversity and its impact on the brain and health.

Children who experience toxic stress without effective interventions are often the victims of disease later in life and therefore become everlasting burdens on society. Sociological studies have long indicated that children who experience neglect, abuse, and deprivation are at a much higher risk for disorders of depression, anxiety, and addiction as adults. Within the last two decades, scientists have been able to examine the biological repercussions of chronic childhood stress and have uncovered clues as to how these early life traumas cause lasting changes in DNA and the brain. Such alterations predispose vulnerable individuals to debilitative behavioral and psychiatric disorders, as well as significant physical diseases, in adolescence and adulthood.

The event brought together renowned experts to discuss how to address the far-reaching, physical, mental, and social implications of early childhood adversity. In his opening remarks, MIT President L. Rafael Reif said, "It is invigorating to see so many connections being made across disciplines, institutions, and generations, and to contemplate the likelihood of being on the verge of practical interventions and lasting solutions for early life stress."

A few highlights from the event included keynote speaker, Jack Shonkoff, the Julius B. Richmond FAMRI Professor of Child Health and Development at the Harvard T.H. Chan School of Public Health and the Harvard Graduate School of Education. Dr. Shonkoff is an expert in his field of the development and health of young children and families experiencing significant adversity. Dr. Shonkoff spoke about developing new knowledge and measurement capacity to assess the biological, bio-behavioral, and health consequences of excessive stress system activation. Dr. Nadine Burke Harris, founder and CEO of Center for Youth Wellness, seeks to recognize and effectively treat toxic stress in order to improve the health of children and adolescents exposed to traumatic childhood experiences. She and her staff use screening tools that surveys parents on how many adverse experiences their child has gone through. If a child has been exposed to four of them, their lifetime risk of heart disease and other illnesses increases. Geoffrey Canada, former President and Chief Executive Officer of the Harlem Children's Zone, spoke about breaking the cycle of generational poverty for the thousands of children and families his organization serves. Mr. Canada suggests that a sense of service and public education are critical in rebuilding community and furthering the lives of young people.

Picower Institute Professor Li-Huei Tsai and Barbara Picower, President of the JPB Foundation.

"IT IS CRUCIAL TO SUSTAIN A DEEP CONCERN FOR THE WELLBEING OF CHILDREN IN OVERWHELMING CIRCUMSTANCES IN ORDER TO PREVENT THEM FROM BECOMING VICTIMS TO DISEASE LATER IN LIFE."
- Barbara Picower

Thank you to Barbara Picower and the JPB Foundation for making this event possible and for their longstanding support of those who remain passionately dedicated to researching and implementing solutions that effectively address childhood development issues. The day was a tremendous success and stimulated new conversations and strategies for making the world a better place for children exposed to toxic stress.

Leveraging the Biology of Adversity
to Strengthen the Foundations of Healthy Development

Jack Shonkoff

Jack Shonkoff, Director of Harvard University's Center on the Developing Child, also chairs the National Scientific Council on the Developing Child, which aims to bring credible science to bear on public policy affecting children.

We humans are built to withstand some adversity, but we cannot thrive without help when negative impacts (abuse, neglect, poverty, violence, limited education, etc.) pile up and topple over our tolerable threshold. Good and bad early life experiences are biologically embedded in our bodies. Stable and supportive relationships and language-rich environments promote healthy brain development, well-regulated metabolic systems, strong cardiovascular systems, and a foundation for resilience. At the same time, there is no doubt that cumulative adversity causes physiological disruptions. Numerous studies have documented that those who experience excessive stress in childhood without the buffering support of adults are more likely to face chronic depression, heart disease, cancer, and addictions later in life.

"IDENTIFYING PROBLEMS DOESN'T MEAN WE KNOW WHAT TO DO ABOUT THEM," SAID SHONKOFF. HE URGED SYMPOSIUM ATTENDEES TO COLLABORATE IN ORDER TO PREVENT, REDUCE, AND MITIGATE THE CONSEQUENCES OF CHILDHOOD ADVERSITY.

He emphasized that state-of-the-art best practices, policies, and services should be the starting point rather than the finish line. He suggested that those in the field encourage the generation and testing of imaginative ideas. "We are making a difference, but we need to aim higher." Scientists should be enabled to fail and therefore innovate—to go beyond proving hypotheses and think about new ways to more accurately measure and evaluate the effectiveness of proposed approaches.

Awareness of variation combined with what scientists now know and are learning about critical periods for brain development suggest that interventions can be designed and more precisely targeted for specific subgroups of children. Shonkoff says scientists and others must ask why certain interventions work for some children and not others. And, which physiological disruptions are amenable to particular treatments? Creative imagination and rigorous science will foster the development of a diversified portfolio of intervention strategies to achieve breakthrough outcomes for the broad range of children facing adversity.

ACEs & Toxic Stress:
From Research to Practice to More Research

Nadine Burke Harris

Dr. Nadine Burke Harris is a pediatrician and founder of the Center for Youth Wellness (CYW) located in San Francisco, California. She created the CYW to leverage the science on the biological impact of early adversity on our children, families, and communities. Burke Harris was introduced to the scope and scale of toxic stress when she read the Adverse Childhood Experiences (ACE) study. The retrospective study examined ten categories of childhood adversity and found that approximately 67 percent had at least one ACE, and 12.6 percent reported four or more adverse childhood experiences. Those who scored four or more ACEs faced a dramatically increased risk for developing one of the ten leading causes of death in the U.S. and were twelve times more likely to attempt suicide.

Chronic activation of the stress response disrupts nearly every physiological system in the developing child. Harris believes this public health crisis mandates a national awareness campaign to address ACEs and toxic stress. Routine screening and early detection, ongoing investments in research, and the development of effective interventions will help interrupt the progression from early adversity to disease and early death.

The Brain and Body on Stress:
Epigenetics of Plasticity During the Life Course

Bruce McEwen

Bruce McEwen is the Alfred E. Mirsky Professor and is the Primary Investigator of the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology at Rockefeller University. His lab focuses on how stress affects the amygdala, prefrontal cortex, and hippocampus, which are critical for assigning value to emotional events, decision-making, attention, as well as learning and memory.

Stress increases the blood levels of cortisol and adrenaline, which can cause problems in the immune and metabolic systems when they are over stimulated and dysregulated. Early life experiences including toxic stress can impact the developing, adult, and aging brain's architecture and plasticity since the brain constantly changes over the course of a lifetime. When the regions of the brain responsible for regulating stress are altered by experience, both behavior and physiological responses are disrupted. The hippocampus, for example, which is important for memory and emotional regulation, shrinks with repeated stress while the amygdala becomes over active and enhances the likelihood of developing anxiety disorders. A chaotic home environment increases inflammation in adolescents and can disrupt the prefrontal cortex, the center of self-regulation that enables our ability to operate in the world. Given how much early life experiences influence gene expression patterns and the propensity for disease, how can we redirect the brain and body at different stages of life to alter negative outcomes? Improving the quality of life through consistent exercise, mindful stress reduction, and purposeful activity enables healthy outcomes.

Neural Correlates of Familial
and Socioeconomic Stress

John Gabrieli

John Gabrieli is a professor in the Department of Brain and Cognitive Sciences and the Director of the Imaging Center at MIT's McGovern Institute. Gabrieli is interested in exploring what a depressed brain looks like, and to what extent the different structure is a cause or consequence of the disease.

In studying brain activity in children at risk for depression, Gabrieli and colleagues found significantly higher response rates to negative versus positive facial images, whereas children born into families without depression are far more likely to respond to happy faces in pictures. This striking difference exposes the vulnerability many poor children face in terms of confronting depression later in life.

Gabrieli plans to track at-risk children who sustain enough resilience to avoid consequences like depression. He recently launched a study that will examine the brains of children who, despite living in poverty, perform very well on standardized tests.

DO THEIR BRAINS LOOK DIFFERENT, OR ARE THEY JUST FINDING ADAPTIVE WAYS TO SUCCEED IN THE WORLD?

There are many paths to success. The key is knowing which ones work best for diverse groups of children facing adversity. Gabrieli suggested that neuroimaging be added to the arsenal of tools scientists and practitioners use to develop early preventive interventions since brain measurements may be able to instantly indicate whether or not a particular therapy or treatment is positively changing brain structure and function.

Prevention, Poverty, & Pediatrics

Fan Tait

Pediatric neurologist Fan Tait serves as the Director of the American Academy of Pediatrics (AAP) Department of Child Health and Wellness.

Tait noted that families are one of the fastest-growing groups of homeless people in America.

IN ADDITION,

21 PERCENT OF THE POPULATION RECENTLY REPORTED FEELING UNCERTAIN THEY WOULD HAVE ACCESS TO ENOUGH FOOD TO SURVIVE.

As part of Bright Futures—guidelines for well-child care from birth to age twenty-one—the AAP is requesting that healthcare providers, with the help of the Academy and community resources, conduct extensive screening for fifteen to twenty measurement criteria. Tait is also leading the AAP effort to develop a National Center on Healthy, Resilient Children, focused on building stronger families and ending toxic stress. In the battle against childhood adversity, Tait says all of society's stakeholders, including practitioners, scientists, and community leaders, must partner and collaborate to influence early childhood policy and services, and determine which interventions will work best for specific groups of children.

The Survey of Wellbeing of Young Children *and its Use in Clinical Care*

Ellen Perrin & Chris Sheldrick

Ellen Perrin and Chris Sheldrick, pediatrics professors at the Tufts Medical Center, co-developed the Survey of Wellbeing of Young Children (SWYC), a screening instrument for ongoing monitoring of development in early childhood clinical care.

25 PERCENT OF CHILDREN SUFFER FROM DEVELOPMENTAL, EMOTIONAL, OR BEHAVIORAL DISABILITIES,

and that percentage is much higher among children living in poverty or with a chronic health condition. Pediatricians have the unique opportunity to become critical players in early intervention and prevention. But given limited time and resources, many pediatricians feel overwhelmed by guidelines and advice, including all the recommendations for screening protocols. Perrin and Sheldrick hope the SWYC will ease the burden of the challenges they face in daily practice.

Child First:
Research to Practice, Trauma to Healing

Darcy Lowell

Darcy Lowell, Associate Clinical Professor at Yale University School of Medicine, is the founder and CEO of Child First, a two-generation intervention serving the most vulnerable young children and families in order to prevent and heal the effects of trauma and adversity.

The Child First evidence-based model centers on facilitating a responsive, nurturing parent-child relationship, the absence of which diminishes a child's ability to regulate and manage stress. This leads to significant and prolonged disruption and damage of the brain and metabolic systems. Developing the secure and supportive caregiver relationship protects the brain and child. Children who are resilient and succeed despite adversity typically have this essential relationship with a parent or caregiver.

Child First care coordinators work with families to build care plans that reflect their specific needs and priorities. This process often enhances the self-esteem and executive functioning skills of young parents participating in consultations designed to improve outcomes for their families. Children experiencing toxic stress often are living in environments characterized by domestic violence, maternal depression, homelessness, and substance abuse. Understanding the full context of childhood adversity is a mandatory element of addressing threats to healthy development.

Children & Toxic Stress,
a Generation at Risk

Geoffrey Canada

The Picower Spring Symposium on Early Life Stress and Mental Health special speaker was Geoffrey Canada, a passionate advocate for education reform and past president of the Harlem Children's Zone.

Canada talked about the tough South Bronx neighborhood where he grew up. "All I saw was dark, scary, and sad," he recalled. Poverty depresses people for good reason. Well-intentioned parents may just not have the initiative or wherewithal to focus on properly caring for their children. When Canada arrived in Harlem in the seventies, guns were not a major problem. People were not getting shot, and kids were not killing kids.

That changed in the eighties. This kind of violence is an American problem, explained Canada. It may initially surface in the most vulnerable communities, but it is not because people of color live there, and it doesn't mean more affluent communities will not be affected. Despite the all-too-familiar response after a tragedy—"things like this don't happen here"—it turns out they do. Mass killings have terrorized white, middle-class suburban schools. Canada pointed to the heroin epidemic in white America as another example. These kids are in real trouble. This is a nationwide crisis that requires attention and investment, said Canada, to save and ensure the success of the next generation. Canada encouraged scientists to participate in public policy forums and focus on scalable solutions to address the adversity impacting today's youth.

JPB Foundation to Expand Innovation and Mentorship Programs

Barbara Picower, President of the JPB Foundation.

This year, Barbara Picower and the JPB Foundation have generously expanded two flagship research programs to include new Picower investigators, Drs. Emery Brown and Steve Flavell.

Dr. Brown is the Warren M. Zapol Professor of Anaesthesia at Harvard Medical School, the Edward Hood Taplin Professor of Medical Engineering and of Computational Neuroscience at M.I.T. and a practicing physician, seeing patients at Massachusetts General Hospital. He co-directs the Institute for Medical Engineering and Science (IMES) at MIT and is an elected member of the National Academy of Engineers. He is also a Fellow of the American Academy of Arts and Sciences and a member of the Institute of Medicine and the National Academy of Sciences. Dr. Brown's laboratory seeks to unravel how anesthesia works. Dr. Steve Flavell, a new junior faculty member at MIT, was a Helen Hay Whitney Fellow at Rockefeller University and examines how the brain sustains or switches between behavioral states at the molecular and circuit levels. His long-term goal is to understand how neural circuits generate sustained behavioral states, and how physiological and environmental information is integrated into these circuits.

The two programs, focused on innovation and mentorship, support high-risk, high-reward research that is often not typically funded through traditional sources and the development of junior faculty careers, respectively. Both programs have allowed for faculty to publish cutting-edge papers in some of the most respected scientific journals, give national and international lectures, leverage findings to bring in additional funding, and build on their already impressive records of success. Because of these exemplary programs, Picower investigators have also been recognized in mainstream press outlets like *PBS* and *The Economist*, and allowed them to bring new therapeutic strategies for brain illness to the biomedical industry. The power of philanthropy is exemplified by these successes.

Although our journey is an ambitious one, it would not be possible without Barbara Picower and the JPB Foundation's immense contributions. We are grateful for their guidance, overwhelmed by their generosity, and look forward to many more years of innovation and achievements.

Thank you to Robert & Bethany Millard

An Evening with MIT's Aging Brain Initiative dinner was hosted at the home of MIT's Corporation Chairman, Mr. Robert B. Millard '73 and his wife, Bethany. The event intended to spark discussion about a challenging global issue that affects us all. Highlights included new directions and the latest discoveries from MIT that may offer some non-invasive treatment strategies in the battle against Alzheimer's disease. The night was meant to inform, inspire, and further a cause determined in finding a cure for the dementias of aging.

We would like to extend a special thank you to Robert and Bethany Millard for their generosity and opening their home to us. They are champions of philanthropy and this opportunity allows for greater outreach and visibility for this important cause.

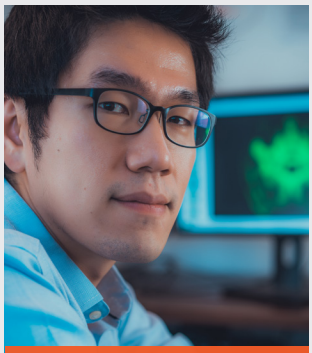
We are grateful to them for enabling this conversation on health and disease, which will surely lead to greater hope, understanding, and success of brain aging research.

- Li-Huei Tsai

Bethany and Robert B. Millard '73.

PICOWER Accomplishments

Kay Tye



Kwanghun Chung

Li-Huei Tsai

Myriam Heiman

KAY TYE received the ***2016 Presidential Early Career Award*** for Scientists and Engineers, the highest honor bestowed by the U.S. government on scientists and engineers that are in the early stages of their research careers. President Bill Clinton established the Presidential Early Career Awards in 1996 and awardees are selected for their commitment to community service through scientific leadership, public education, or community outreach.

KWANGHUN CHUNG has received the ***2016 McKnight Technological Innovations in Neuroscience Award***. The five-year, $875,000 grant gives emerging young scientists and engineers the freedom to pursue innovative ideas. Chung develops and applies novel technologies for integrative and comprehensive understanding of large-scale biological systems. Photo: Lillie Paquette/School of Engineering

LI-HUEI TSAI has been awarded the ***Javits Neuroscience Investigator Award***. The Javits Award is given to scientists for their superior competence and outstanding productivity. The Award provides long-term support to investigators with a history of exceptional talent, imagination, and preeminent scientific achievement.

MYRIAM HEIMAN has recently won several awards including the Fay/Frank Award from the Brain Research Foundation, the Jeptha H. and Emily V. Wade Award from MIT, and was named the Latham Career Development Chair at MIT. Heiman is an Assistant Professor at the Picower Institute for Learning and Memory and is a member the Broad Institute of MIT and Harvard.

Aging Brain Seminar Series

Upcoming Seminars

RUDOLPH TANZI

Vice-Chair, MGH Neurology (Research) & Director, Genetics and Aging Research Unit, MassGeneral Institute for Neurodegenerative Disease & Joseph P. and Rose F. Kennedy Professor of Neurology, Harvard Medical School

» November 30, 2016 at 4:00pm | MIT Building 46, Room 46-3189

BRADLEY HYMAN

Director, Massachusetts Alzheimer's Disease Research Center & John B. Penney Jr. Professor of Neurology, Harvard Medical School

» December 7, 2016 at 4:00pm | MIT Building 46, Room 46-3310

BRAD DICKERSON

Associate Professor of Neurology, Harvard Medical School Director of Clinical Applications, Morphometry Service Massachusetts General Hospital

» February 15, 2017 at 4:00pm | MIT Building 46, Room 46-3310

PATRICK PURDON

Associate Professor of Anaesthesia Massachusetts General Hospital

» March 15, 2017 at 4:00pm | MIT Building 46, Room 46-3310

Upcoming **Events**

For a list of ongoing scientific lectures, colloquia, and workshops, please go to: **picower.mit.edu**

Fall Symposium

Picower Institute Fall Symposium, October 25th, 2016

"NEUROBIOLOGY OF NEUROLOGICAL DISEASE" is the focus of The Picower Institute 2016 Fall Symposium scheduled for October 25, 2016. Many of the most debilitating neurological disorders remain without cure. This is true of all of the major neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and Amyotrophic Lateral Sclerosis. But recent insights from basic neurobiological studies, new investigative tools, cell type-specific studies, and human genetic data are all converging to stimulate new hypotheses and to provide a better understanding the molecular mechanisms of neurological disease. Renowned neurobiologists from around the world will gather at the Picower Institute's Fall 2016 Symposium to present their latest research findings and discuss vulnerability in and basic underlying mechanisms associated with neurological disease, as well as molecular pathways that could potentially be targeted for therapeutic treatments.

Keynote Speaker:

MICHAEL E. GREENBERG Ph.D. is the Chair of the Department of Neurobiology and Nathan Marsh Pusey Professor at Harvard Medical School.

Speakers:

SUSAN L. ACKERMAN, Ph.D. is a Howard Hughes Medical Institute (HMMI) investigator, one of the top distinctions in American biomedical research. The Ackerman Lab works to identify the genes, pathways and networks involved in the development of the central nervous system and the age-related death of neurons.

ROBERT H. BROWN, MD is the Chair and Professor at University of Massachusetts Medical School has focused on the identification of gene defects that elucidate the molecular pathogenesis of selected neuromuscular diseases including amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease), muscular dystrophy, adrenoleukodystrophy, hereditary neuropathy and hyperkalemic periodic paralysis.

MYRIAM HEIMAN, Ph.D.is the assistant professor of Neuroscience, at the Picower Institute for Learning and Memory aims to understand how neuronal identity is established and maintained, and how the molecular identity of a neuron determines its susceptibility to disease.

Richard Morimoto Ph.D. is the Bill and Gayle Cook Professor of Biology, Department of Molecular Biosciences, and Director of the Rice Institute for Biomedical Research at Northwestern University. His current research is to understand how organisms sense and respond to physiologic and environmental stress through the activation of genetic pathways that integrate stress responses with molecular and cellular responses that determine cell growth and cell death.

BETH STEVENS, Ph.D. is an assistant professor in the Department of Neurology at Harvard Medical School and the F. M. Kirby Neurobiology Center at Boston Children's Hospital. She has helped to identify the role of microglia in the pruning of synaptic cells during brain development and has also determined that the impaired microglial function and abnormal activation of this pruning pathway could be responsible for diseases like autism, schizophrenia, and Alzheimer's.

D. JAMES SURMEIER Ph.D. is the Nathan Smith Davis Professor and Chair of the Department of Physiology at the Feinberg School of Medicine at Northwestern University and Director of the Morris K. Udall Research Center of Research Excellence for Parkinson's Disease at Northwestern University. He is focused on the mechanisms underlying Parkinson's disease and schizophrenia. This pursuit employs a combination of electrophysiological, optical, genetic and behavioral approaches.

LI-HUEI TSAI, Ph.D. Professor in the Department of Brain and Cognitive Sciences, and Director of the Picower Institute for Learning and Memory at MIT her primary goal is to elucidate the mechanisms underlying neurological disorders affecting learning & memory. The major research areas include age disorders, autism, and Alzheimer's disease.

X. WILLIAM YANG, MD established his laboratory at UCLA in 2002, and has made significant contributions in the use of BAC transgenesis to model human neurodegenerative disorders including Huntington's disease (HD), Huntington's disease-like 2 (HDL2) and Parkinson's disease (PD), and the use of such models to dissect disease mechanisms and identify therapeutic targets. The Yang lab has also developed novel tools to study neuronal cell-type-specific gene expression, and to decipherin vivo protein interaction networks.

RICHARD YOULE, MD joined the Surgical Neurology Branch of NINDS in 1985 as a principal investigator where he has developed new treatment strategies for brain tumors. His lab is now exploring the molecular mechanisms of programmed cell death and engineering therapeutic proteins to regulate cell survival.

THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY

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Neuroscience News // Summer 2016

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.

SUPPORT THE PICOWER INSTITUTE

For more information on our research or how to make a gift to the Picower Institute for Learning and Memory, please contact: Asha Bhakar, PhD, abhakar@mit.edu, Tel: 617-258-0759.

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