Sociological studies have long indicated that children born to poverty are likely to remain in poverty as adults, and 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 begun 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 that predispose vulnerable individuals to debilitating behavioral and psychiatric disorders, as well as significant physical diseases, in adolescence and adulthood.

On May 13, we were thrilled to sponsor the annual Picower Institute for Learning and Memory Spring Symposium, bringing together scientists, physicians, and other experts to share their latest insights, exchange ideas, and contribute to an enhanced collective understanding of early life stress and how to effectively intervene to attenuate deleterious impact on lifetime mental and physical health. We are most grateful to Barbara Picower, president of the JPB Foundation, for making this event possible and for her longstanding support of those who remain passionately dedicated to researching and implementing solutions that effectively address childhood development issues.

We invite you to read snapshots of the event speakers’ presentations in this newsletter and to view them on the Events page of our website at picower.mit.edu. We are proud to help facilitate and encourage an ongoing dialog between scientists, practitioners, and policy makers to improve the health and lives of society’s disadvantaged children and their caregivers, thereby counteracting the inevitable adversity we face together as citizens of the global community.

Li-Huei Tsai, Ph.D.
Director

FROM THE DIRECTOR

LI-HUEI TSAI
Leveraging Community-Based Intervention Research to Advance Knowledge about Recovery from Early Life Stress

PHIL FISHER

The work of Phil Fisher, psychology professor and research scientist at the University of Oregon, focuses on the more than half a million children in U.S. foster care systems, an excellent context for studying the effects of and predicting the ability to recover from early life adversity. Maltreated children in this environment lag behind other low-income kids in the same communities on nearly all cognitive, behavioral, and physical health indicators.

Fisher talked about the critical role parents and caregivers play, as mediators, in terms of affecting outcomes, and the extent to which their input and influence can be improved through intervention and thereby reduce or reverse the effects of early life adversity. Fisher, one of several Symposium speakers affiliated with Harvard University’s Center on the Developing Child, described how his research team validated a conceptual causal framework via randomized clinical trials that targeted malleable caregiving processes. Part of the effort involved evaluating how interventions can impact transitory and prolonged outcomes, in terms of both underlying neural systems and downstream behavior.

Internationally adopted children and those in foster care do not exhibit the typical peak in stress-hormone (cortisol) levels shortly after awakening. Instead, the diurnal pattern in the HPA axis is blunted, starting low in the morning and remaining the same or decreasing throughout the day. This suggests that neglectful caregiving maps directly to alterations in underlying neural systems. In another study, images of the prefrontal cortex region in the developing brains of foster care children indicate insensitivity to corrective feedback on a computer task—additional evidence of the effect of stress on plasticity. Specific kinds of maltreatment appear to have a pervasive impact on neurobiological systems and downstream behavior. The good news is that supportive therapeutic programs for caregivers can lead to better regulated cortisol levels and improved executive functioning in children.

While significant progress has been documented, Fisher highlighted a couple of caveats. Only 30 percent of the foster care children studied revealed the patterns summarized above; that’s three times the rate in the comparable low-income population, but it is still a relatively small sample. Fisher also says innovative, more precise two-generational models are required to accurately associate interventions, systems, and outcomes; advance scientific knowledge; and impact society in terms of harnessing community programs to reverse the impacts of childhood adversity.

Causal Relationships between Stress, Dopamine, & Behaviors Relevant to Mental Health

KAY TYE

Kay Tye, junior faculty member at the Picower Institute and professor of neuroscience in MIT’s Brain and Cognitive Sciences Department, emphasized the value of using animal models to gain insights about human psychiatric diseases and inform the development of more effective therapies with fewer side effects. She focused her presentation on depression, the leading cause of medical disability in the United States, affecting up to 17 percent of the population and costing the nation an estimated $53 billion annually. Characterized by reduced motivation, anhedonia, and diminished social interaction, currently available antidepressant medications are only moderately effective in treating the symptoms of depression.
A healthy brain effectively balances behaviors that seek potentially positive rewards with those that avoid potentially negative consequences. In psychiatric diseases like depression, there is a disproportionate motivation toward one side of the equation, and therefore an imbalance. Tye’s research team studies the causal relationship between dopamine—associated with motivation—and depression-related behaviors using optogenetic tools to dissect neural circuits in transgenic mice.

The Picower scientists recently discovered that when mice are presented with an inescapable stressor, like hanging from their tails, and dopamine is inhibited, the animals immediately spend less time struggling to escape. When dopamine is activated, the reverse is true. When mice are subjected to unpredictable chronic mild stress, similar to what disadvantaged children at the heart of the Symposium experience, they mimic symptoms of depression when dopamine is inhibited, but these behaviors are reversed when dopamine is activated. Looking at social interaction, Tye’s team found that increased dopamine levels promoted social interaction in non-stressful conditions, but less interaction was documented among adult mice that had been exposed to stress.

Reverse translation research allows precise manipulation and control of neural circuits in mice, enabling scientists to better understand human disease-relevant behaviors, identify stages of life in which organisms are most sensitive to stress, and develop new, more effective therapies to treat mental illness.

Understanding Developmental & Intergenerational Trauma Effects Occurring through Epigenetic Processes

Kerry Ressler, psychiatry and behavioral sciences professor at Emory University, studies the molecular mechanisms, behavioral processes, and impacts of childhood and adult trauma that underlie fear and anxiety illnesses, including Posttraumatic Stress Disorder (PTSD). One of the central issues Ressler highlighted in his presentation was individual variability when it comes to risk versus resilience in those with a history of neglect or trauma, given that only about 30 percent develop a significant fear-related disorder. Two-thirds of children in foster care and high-risk inner-city populations recover from early life adversity and grow into emotionally healthy adults.

Ressler noted that those with fear and anxiety disorders consistently reveal hyperactivity in the amygdala, the region of the brain responsible for emotional learning, including fear response. He pointed to the amygdala’s hardwired neural circuitry as the “lowest hanging fruit in psychiatry” when it comes to providing scientists with a clear understanding of what causes the symptoms involved in a panic attack. So the more intriguing question is how the hippocampus and prefrontal cortex modulate the amygdala in such a way that causes one person to experience an overwhelming, pathological fear response while another is able to express a more controlled, resilient reaction. Also, how people remember a traumatic event contributes to its long-term impact. If there was a pharmaceutical protocol that could be delivered within hours of a trauma, similar to treatments for heart attack and stroke, perhaps harmful memories could be extinguished, thereby enhancing the recovery process.
In exploring the concept of intergenerational transmission, Ressler’s team conducted epigenetic experiments on the olfactory systems of transgenic mice. They discovered that mice trained to be afraid stay afraid unless stress-hormone receptors are blocked or animals are retrained. However, researchers also found that offspring inherit the trained fears of their fathers unless the fear is extinguished prior to mating, so the components of transmission appear to be dynamic.

Scientists have also found that maltreated children who possess a particular version of a gene are at greater risk for psychiatric disorders. And the chemistry of DNA changes when parts of genes are “turned off” (differential methylation) in those who experience childhood adversity, disrupting amygdala regulatory functioning downstream in the presence of stress. Ressler’s work indicates that environmental components like child abuse combined with biological risk factors lead to the brain’s emotional learning systems being primed for faulty stress response to adult trauma, thereby increasing the likelihood of developing a fear-related condition like PTSD.

**The Role of Sleep in Stress, Development, and Cognition**

--- MATT WILSON ---

Matt Wilson, professor of neuroscience at MIT and the Picower Institute, specializes in the mechanisms of memory formation. The focus of his Symposium presentation was how cognitive processing related to memory might be altered during sleep to mitigate the behavioral consequences of traumatic stress.

Wilson’s work involves exploring the hippocampal systems critical to learning and memory. He showed the electrical activity in a rat brain as the animal explores its environment. When the rat is moving, it rapidly processes new sensory information, whereas when stationary, it appears to be thinking about something else, registering hippocampal activity associated with remote events. Decoding the neural activity associated with three fundamental states—active engagement/locomotion, quiet wakefulness (inattentiveness), and sleep allows examination of patterns of thought that correspond to experience associated with reward during these different states. Wilson is testing the idea that various dopamine neurons respond differently to expectation versus delivery of rewards, and the modulation of dopamine signaling is contingent not only on activation of the hippocampus but on the content of thought.

As other speakers also noted, there’s a significant amount of learning and memory processing (consolidation) that occurs after an experience. We constantly reactivate, reevaluate, and in some cases extinguish memories of past events, making modifications that are critical to survival. It appears that powerful memory associations are formed during the “active” state, reinforced during the “quiet wakeful” state, and then rebalanced during the “sleep” state. Wilson and his colleagues are investigating what may be promising opportunities for intervention during these sleep-state readjustments, looking at ways the content of memories might be manipulated while we’re asleep. In closing, he promised to show interested Symposium attendees how to change their dreams that very night!

**Toxic Stress—Changing the Paradigm of Clinical Medicine**

--- NADINE BURKE HARRIS ---

Pediatrician Nadine Burke Harris founded the Center for Youth Wellness (CYW) and the Bayview Child Health Center, located in one of San Francisco’s most impoverished and violent communities. The ambitious goals of Harris and the CYW include: preventing, screening, and healing
the impacts of childhood adversity; raising public awareness regarding the implications of toxic stress; and changing conventional standards of healthcare, education, and pediatric medicine nationwide. Early adversity is a major contributor to 75 percent of the chronic diseases that drive the nation’s $2 trillion annual healthcare expenditure.

Harris has earned international attention for her innovative approach to addressing adverse childhood experiences as a significant risk factor for adult disease. Her work demonstrates the need to reassess the relationship between poverty, child development, and health, and how the practical applications of Kaiser’s Adverse Childhood Experiences (ACE) study can improve health outcomes. The ACE study surveyed more than 17,000 adults in the San Diego area in the nineties.

ACE scores consist of one point for each category of adverse childhood experience. Harris and others have found that patients with a score of four or higher are twice as likely as those with no trauma history to be diagnosed with cancer or heart disease, seven times as likely to be alcoholics, and twelve times as likely to attempt suicide. The life expectancy of people with ACE scores of six or higher is reduced by twenty years. Those with ACE scores of seven or higher who do not smoke, drink to excess, or carry significant extra weight have a 360 percent higher risk of developing the heart disease that is the nation’s number one killer. On the flip side, among Bayview Health Center children who had an ACE score of 0, only 3 percent demonstrated learning or behavioral problems in school.

Compassionately interrogating children and adults about their traumatic experiences is no more invasive or less important than a prostate exam, says Harris. Adversity correlates not only with emotional difficulties but also significant medical consequences. Treating trauma like other medical issues is at the core of Harris’s methodology and practice, which are rooted in science. Harris addresses many of the challenges commonly regarded as “social” issues on a molecular, neurochemical level, and that translates into more effective care for her patients.

It is no longer just about the connections between childhood disadvantage and diminished educational outcomes. The science provides evidence that intervening early can improve learning, behavioral, and mental and physical health outcomes. The effects of early stress can be reversed through various psychological and stress-reduction therapies, and by nurturing responsive behavior in caregivers. Harris and others vigilantly advocate a broader, multidisciplinary approach aimed at addressing the mental and physical outcomes facilitated by disparities in childhood experience. For starters, every child, regardless of race or socioeconomic status, should have a primary care doctor (preferably one like Nadine Burke Harris).

Developmental Origins of Chronic Physical Aggression: From Social Learning to Epigenetics

Richard Tremblay

Richard Tremblay, professor of pediatrics and psychology at the University of Montreal and professor of early childhood development at University College Dublin, talked about chronic physical aggression (CPA), mainly a male problem, beginning with an explanation of what criminologists worldwide call the “age crime curve.” In studies examining the trajectories of physical aggression in boys and young men over time, the data suggest that in most males, aggressive behavior gradually increases in childhood, peaks in adolescence, and decreases with age. The reason violent male youths typically don’t face an arrest until they are young adults is likely a byproduct
of societal toleration; their behavior typically yields more negative impact, and therefore punishment, as they grow older, bigger, and stronger. But at this point, intervention may be too late since CPA starts in early childhood.

Contrary to earlier hypotheses, recent studies indicate that aggressive behaviors most likely are not learned by observation, given that youth violence in the United States has decreased substantially in the last decade despite the infiltration of increasingly violent video games. Following studies that looked at boys from kindergarten to age fifteen, Tremblay and his team wanted to investigate earlier causal mechanisms of CPA to help determine optimal timing for intervention and prevention. As evidenced from young boys fighting over toys—even in the presence of a lot of them and despite learning not to behave aggressively—Tremblay’s team found that normal physical aggression first appears in boys between the ages of twelve and eighteen months, increases for a couple of years, starts to decrease around four years old, and surges in adolescence.

Looking at chronic aggression from an epigenetics perspective, adult males with a history of CPA reveal differential DNA methylation profiles, specifically in terms of in vitro serotonin synthesis. So while CPA is predominantly a male problem, Tremblay’s research proposes intergenerational intervention that includes at-risk girls, the future mothers of potentially violent men. The data indicate that the prenatal and early postnatal environments, as well as maternal physical and mental health, can affect genetic expression that influences brain development and downstream behavior. While scientists agree that more clinical trials are required to properly evaluate the impacts of intervention, it appears that enriching the maternal environment very early on, to encourage everything from proper nutrition during pregnancy to supportive parenting in early childhood, can help minimize the factors responsible for cyclical reproduction of chronically aggressive children who become violent adults.

Effects of Early Life Stress on Fear Regulation in Developing Humans and Mice

B.J. Casey, director of the Sackler Institute for Developmental Psychobiology at Weill Cornell Medical College, focuses on adolescence and biologically targeted treatments for psychiatric illnesses that often manifest during this sensitive transitory period of development. Misdiagnosed and undertreated anxiety and stress disorders, affecting as many as 30 percent of teenagers, can lead to chronic mental and physical illness, and sometimes death.

Radical rewiring of the fear response takes place during adolescence, precipitated by significant changes in prefrontal cortex and hippocampal circuit projections to inhibitory cells in the amygdala that modulate the fight-or-flight reaction. It is normal to initially take note of potentially significant environmental threat cues, but when repeated exposure to these signals delivers no threat, the healthy brain evaluates relevancy, recognizes lack of danger, and appropriately regulates response. In adolescents with high anxiety, there’s weakened connectivity between the regional neural circuits associated with fear response latency, leading to heightened emotional reactivity and diminished regulatory ability.

While measuring cued fear in both mice and humans, Casey and her team discovered and replicated the finding that while children, adolescents, and adults similarly acquire fear, adolescents demonstrate more difficulty learning to extinguish
fear. Young adults seem to vigilantly maintain their reactions to potential threat cues, and it has nothing to do with context. If you place an adolescent mouse in the same cage in which it was shocked the day before, it is fearless.

In order to better understand how early life stress may impact fear response, Casey and others have studied adopted children who spent time in orphanages before moving to the United States. The previously institutionalized children who showed elevated activity in the amygdala in response to potential threat cues also demonstrated a more averted gaze to threatening stimuli, as well as less eye contact with adoptive parents when reunited after playing computer games.

There is a critical window of time in adolescence when stressors can permanently alter brain circuitry, preventing the healthy development of regulatory systems that resolve emotional stress.

Human Brain Transcriptome Dynamics of Neurodevelopmental Disorders

Daniel Weinberger

The work of Daniel Weinberger, professor at the Johns Hopkins School of Medicine and director and CEO of the Lieber Institute for Brain Development at the Johns Hopkins Medical Center, focuses on abnormal brain development as a risk factor for neuropsychiatric disorders, particularly schizophrenia.

The Lieber Institute examines subtle genetic variations that may translate into molecular mechanisms that underlie psychiatric illness. In looking at some specific genes of interest in the prefrontal cortex, Weinberger and his team discovered novel genotypes with unique physiological properties associated with risk for schizophrenia. The scientists also found that about half of these previously unknown genetic structures linked to neurodevelopmental disorders are more abundantly expressed during fetal life, more so in the case of severe disability syndromes. Interestingly, genes associated with neurodegenerative disease show less expression fetal than in adult life.

Studies of one of the first genes ever associated with schizophrenia, neuregulin, support these findings. Scientists had been unable to show any relationship between functional risk variants and known forms of neuregulin, but strong molecular associations were later revealed with a particular isoform of the gene found only in the brain. And this version of the gene was four times more abundant in the fetal versus adult brain. Weinberger and his colleagues continue to explore whether the genes that demonstrate a strong fetal effect are more relevant to the emergence of psychiatric illness.

Adopting a broader view, Lieber Institute scientists use their BrainCloud (http://braincloud.jhmi.edu)—an application for exploring the transcriptome dynamics of three hundred normal human brains across the lifespan, from fourteen weeks to age ninety—to look at the architecture, expression patterns, and variations of gene sets associated with neurodevelopmental disorders.

Restoring Brain Functions: Recovery from Genetic and Environmental Adversity

Mark Bear

Mark Bear, professor of neuroscience at the Picower Institute, opened his presentation with pessimistic and optimistic scenarios regarding the prospects for treatment and prevention of brain-related disease. By the time a diagnosis is delivered, have we
missed the critical period for intervention and lost any hope of modifying the implications of disease? Or is there always some benefit to be gained from intervention—ideally correcting the trajectory of derailed brain development to recover normal function, or at least reducing the rate of decline? Bear says we can exploit our knowledge of neurobiology to overcome deleterious effects of early adversity and repair genetic brain development disorders.

He talked first about Fragile X, a rare single-gene intellectual disability disorder known as the leading inheritable cause of autism. In studying this condition in mice, scientists discovered how a form of synaptic plasticity, altered by the absence of a particular protein, can be triggered by activating a specific glutamate receptor, and that excessive activation is associated with many of the symptoms of Fragile X syndrome. Bear likened the protein to brakes on a car and the receptor to the accelerator; without brakes, the neurological consequences of Fragile X are exaggerated. In experiments in which glutamate receptor expression was reduced by half, eight characteristics of Fragile X were reversed. These findings, validated by numerous investigators using multiple species and approaches, have encouraged ongoing drug trials to test the therapeutic efficacy of receptor inhibitors. However, human clinical trials involve a lot of educated guesses about variables like patient selection, dosage, and treatment duration.

In Bear’s second example, he talked about early-life onset of amblyopia, severely limited vision in one eye leading to diminished visual acuity. Over time, the brain stops responding to stimulation of the deprived eye, compensating with increased responsiveness in the healthy eye. So scientists have explored the possibility of restoring vision to the disconnected eye by patching the strong eye and forcing the weak eye to work. Some responsiveness is restored, but it is often at the expense of losing strength in the previously dominant eye. However, in experiments that placed animals in the dark for ten days before returning them to light, normal binocular function was fully restored, documenting an ability to rejuvenate synaptic plasticity in the visual cortex and thereby promote recovery. In conclusion, treatments for single-gene disorders, some of which were thought to be intractable, can be successful well after presentation of symptoms.

**Convergence: Translating What We Discover into What They Do**

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Pat Levitt, program director at the Institute for the Developing Mind at the Children’s Hospital of Los Angeles, serves as scientific director of the National Scientific Council on the Developing Child, which shares research findings with government policy makers to help inform decisions regarding program investment. The council’s work—translating scientific discoveries into meaningful clinical outcomes—was the focus of Levitt’s Symposium remarks.

The ways in which complex findings related to child development and neuroscience are communicated to and interpreted by target audiences make a difference. It is not a matter of dumbing down the details, says Levitt. Practitioners and others are hungry for complex scientific information, but it has to be shared in terms they understand so they can act on it. It might be helpful to explain, for instance, that the brain is built over time, influenced by a combination of genes and experience. Basic skills are learned first because simple circuits are formed first. And when talking about early childhood adversity, the serve and return metaphor can help people understand how critical nurturing relationships are in terms of child and brain development, which in turn form the foundation of prosperous communities.

*Continued on next page ➤*
When scientists talk about how changes in neural connections impact social, emotional, and physical systems, the biology becomes real to those who are not biologists. For example, toxic stress in childhood resulting from neglect or abuse without caring, supportive adults acting as buffers results in constant activation of the stress response and overload of developing systems. Why does this matter? Because prolonged elevation of stress hormones in children can stunt the growth of neural connections required for learning, with lifetime consequences. The takeaway is that we need to make sure vulnerable children have access to stable, nurturing relationships.

Levitt encourages his fellow scientist to help policy makers and others understand basic principles of neuroscience that show how delayed remediation is not an economical choice. Trying to change poorly formed mature brain circuitry is far more costly than improving prenatal environments. We know many things about brain development—including that it starts very early—but much more research is needed. Scientists must continue to enhance their ability to effectively communicate with those making critical decisions about investments in local, regional, national, and global intervention programs.

Driving Science-Based Innovation to Achieve Breakthrough Outcomes for Children Experiencing Toxic Stress

Harvard Professor Jack Shonkoff, director of the university’s Center on the Developing Child, where he collaborates with several Symposium speakers, chairs the National Scientific Council on the Developing Child—leading scholars in neuroscience, psychology, pediatrics, and economics who bring credible science to bear on public policy affecting children.

Shonkoff addressed the core issue of how to mobilize the rapidly growing science frontier at the center of the Symposium to drive groundbreaking policies and practices that result in breakthrough outcomes for children facing adversity. Investing in comprehensive community-based intervention programs is not enough. He reiterated the need to capture scientific complexity in approachable language that effectively informs decision makers. Like Apple’s masterminds of elegant simplicity, multidisciplinary childhood development experts have to dig deeply into the details to extract the essence and translate insights into innovative policy and practice strategies.

In order to achieve breakthrough outcomes, Shonkoff says we need deeper understanding of: the causal brain mechanisms through which adverse childhood experiences facilitate lifelong learning, behavior, and health problems; how impacts of adversity vary with age; and individual differences, both in terms of vulnerability versus resilience and why particular interventions work for some kids but not others.

Shonkoff says the fifty-year-old conceptual framework centered on school readiness that still guides today’s early childhood policies does not serve the significant portion of the population affected by adversity. Childhood health disparities among the nation’s social classes have not budged in decades and will not improve until the focus of the conversation changes, and we devise a balanced approach that both protects and enriches the body’s developing organs and systems. Skill building and coaching for adult caregivers who can buffer children against the impacts of adversity are critical elements of the equation.

Childhood development practitioners and policy makers want guidance from the science community. Working together, they can brainstorm new approaches to ongoing health challenges presented by early life stress and adversity.
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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); Kwanghun Chung, Assistant Professor, Departments of Chemical Engineering and Brain and Cognitive Sciences. 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.

MIDDLE ROW: Earl Miller, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences; 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.

BOTTOM ROW: Li-Huei Tsai, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director, The Picower Institute for Learning and Memory. Kay Tye, Assistant 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.