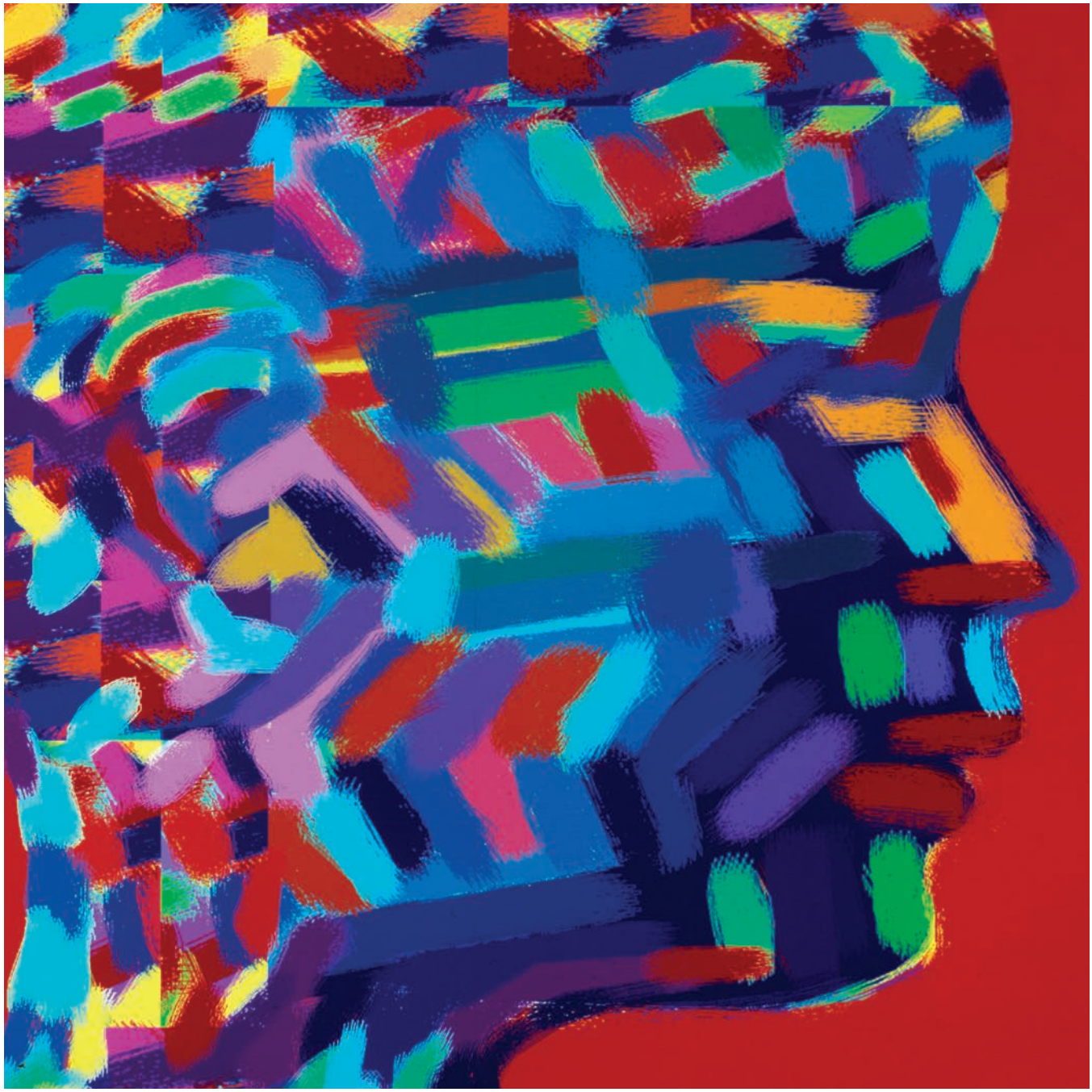
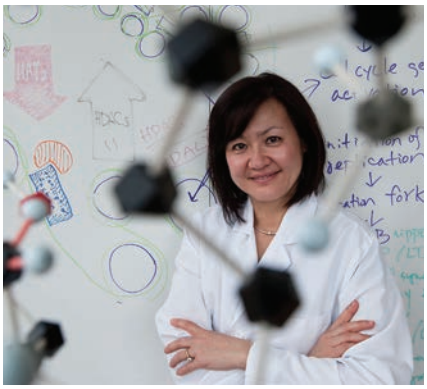


Neuroscience News

Special Edition, Spring 2012

THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY



Li-Huei Tsai

Director, Picower Institute for Learning and Memory

Photo / Len Rubenstein

FROM THE DIRECTOR
LI-HUEI TSAI

At the Picower Institute for Learning and Memory, we study how chronic stress is a major risk factor for life-long depression and anxiety disorders, substance abuse, poor academic performance, and Alzheimer's disease. As we celebrate our 10th anniversary, we are excited that our research can contribute to solving one of society's most painful problems, the life-long, deleterious consequences of chronic stress on young children.

Even seasoned researchers are shocked by the prevalence of children living in environments of physical or emotional abuse or neglect, maternal depression, marital discord, alcohol and drug abuse, random violence, and other adversities. In addition to its affects on mental and cognitive health, we now know that childhood chronic stress is a strong risk factor for physical diseases, too. The flip side of these dire consequences is that intervening to ameliorate childhood stress, or "immunize" children against it, can bring life-long benefits.

Barbara Picower, President of the JPB Foundation, has a long-standing involvement in issues affecting children and society. We are grateful that she is interested in bringing awareness of these childhood issues to the research community and to identify new opportunities to solve these critical social problems. To help that happen, we organized an unusual symposium that brought together basic scientists, physicians, epidemiologists, and other experts involved in understanding the impact of early life stress on mental and physical health. We invite you to read about their presentations inside this newsletter, and to view it on the Events page of our website. We hope this discussion serves as just the beginning of a helpful dialog about how our scientific research can improve the lives of young children to benefit them as individuals and also the society in which we all live together.

COVER:
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Buffering the Life-Long Consequences of Childhood Stress

Though we may not appreciate it at the nerve-wracking moment when we must deliver a televised speech or strike out the last batter in the 9th inning, occasional stress has a beneficial function in our lives. It highlights things that are important in our environment, hones our attention, and directs our resources, explained Picower Institute for Learning and Memory (PILM) investigator Matt Wilson as he introduced the full-day, PILM-sponsored symposium, New Insights on Early Life Stress and Mental Health, on April 18, 2012. But stress becomes negative, even toxic, when it happens relentlessly. Chronic stress mutes the productive, evolutionarily adaptive effect of stress and exaggerates the impact of traumatic events.

Young children are the most vulnerable to chronic stress, and the effects on their mental and physical health, general wellbeing, and cognitive abilities are dramatic and life long. This vulnerability stems from the intersecting roles of a child's environment with the genetic and developmental factors that shape the body's mental and physical responses to experiences during the formative years. But because researchers are discovering the mechanisms underlying those interactions, we have targets for intervention that can "immunize" children against the toxicity of stressful adversities. The challenge of targeting those interventions was the multi-faceted focus of the 11 symposium speakers. Here is a snap shop of their presentations, ranging from chromatin to policy.

Rewiring the Trajectory for Vulnerable Children: A Foundation Perspective

Jane Isaacs-Lowe, PhD (Robert Wood Johnson Foundation)

Isaacs-Lowe discussed the translation of "the science of neurons into solutions where children live, work, and play." Childhood exposure to violence, abuse, neglect, family or housing instability, gang violence, and other adversities correlates not only with later mental health problems, but also high-risk behaviors and physical diseases including cancer, diabetes, and heart disease. In fact, the Federal Reserve sees early childhood development as an economic development issue because it so strains the health and social service system and the justice system. They also see evidence-based early interventions that reduce these negative effects (but need more widespread adoption) as providing major returns on investment.

The Brain on Stress: Adaptive Plasticity in Response to the Social Environment

Bruce McEwen, PhD (Rockefeller University)

McEwen described how stress hormones, including glucocorticoids, mediate a non-linear network connecting learning and memory, metabolism, inflammation, and cardiovascular function. In investigations of the impact of stress on the brain, researchers find that glucocorticoids structurally remodel key areas of the brain by epigenetic changes that alter gene expression. (See box on epigenetics.) In occasional stress, low levels of glucocortocoids protect neurons by repressing the expression of certain genes, but in chronic stress, they have damaging effects. One mechanism for this damage, McEwen found, is the effect on neural dendrites that connect neurons to one another. In chronic stress, dendrites disappear in the hippocampus, where memories form, and they appear in the amygdala, a brain region involved in fear and anxiety. But these negative effects are reversible with antidepressants, physical exercise (which increases volume in the hippocampus), cognitive behavioral therapy (which decreases amygdala volume), and social support and integration.

About Epigenetics

Epigenetics refers to processes that change how the genome functions without changing the actual sequence of DNA. It involves molecules that remodel the chromatin that is tightly wound around the DNA. Acetyl groups open up chromatin, exposing underlying genes to transcription factors that will express, or activate, the genes. Methyl groups close the chromatin, repressing gene expression. Experiences and the environment can add or remove these groups to various regions of the genome, so even identical twins with the same genome develop differently.

Preventing Early Adversity and Improving The Life Chances of Socially Disadvantaged Children and Families

John Eckenrode, PhD (Cornell University)

Most childhood development programs focus on school age children, but targeting children from birth to age three provides more benefits, Eckenrode said. A successful example is the long-running Nurse-Family Partnership program that focuses on low-income pregnant women, primarily unmarried teens. A nurse begins visiting the mother prior to the birth and helps set goals for both the mother and child because research shows that mothers largely mediate a child's outcome. The children experienced almost 80 percent less child abuse and neglect compared to control groups. As young adults, they had fewer arrests and sexual partners, lower rates of smoking, alcohol use, and delinquency, among other benefits. Efforts are underway to scale up the program and replicate it internationally, but it is hard to engage policy makers' attention for a program with impacts 20 or more years down the road.

Effects of Maternal Care on Gene Regulation and Behavior

Michael Meaney, PhD (McGill University)

Meaney introduced an evolutionary biology perspective when discussing epigenetics as a mechanistic explanation for the observed transgenerational effect of maternal depression and emotional neglect on children and even grandchildren. He studied rats and looked at how often the mothers lick their pups (a form of grooming and maternal nurturing). Pups of low-licking mothers (whether a biological or foster parent)

developed behavioral symptoms of chronic stress that correlated with their epigenetic changes. They lost the methyl groups that repress the expression of glucocorticoid receptors, and the resulting increase in these receptors made the pups more sensitive to stress. He found a similar epigenetic change in the brains of suicides who had suffered childhood abuse, but not in those with no history of abuse. In rats, stroking the pups of low-licking mothers rescued their epigenetic state and behavior. That suggests that treating depressed mothers so they become more emotionally connected to their children could make children less vulnerable to chronic stress and more resilient when faced with life's adversities.

The Lifelong Impact of Adverse Childhood Experiences on Health and Society. Neurobiology & Epidemiology Converge

Robert Anda, MD, MS (CDC)

The CDC's Adverse Childhood Experiences (ACE) Study Concept looks at ten categories: emotional, physical and sexual abuse; emotional and physical neglect; violence against the mother, household substance abuse, mental illness, or incarceration; and parental separation or divorce. ACEs tend to cluster in families. For example, where there is violence against the mother, there is a 95% chance that the child experiences another ACE, and a 50% chance of having five ACEs. In an escalating "dose response" to ACEs, the more adversity in a child's life, the more vulnerable the child. A child with seven ACEs has a 100% chance of having developmental delay, for example. When correlating the number of ACEs to other diverse outcomes—childhood depression, school grade failure, being a victim of domestic violence or sexual assault, attempted suicide, teen pregnancy, incarceration, liver disease or heart disease, and early death—all the graphs show negative outcome escalating as ACEs accumulate. "We've never seen the power of an exposure having so many outcomes on public health," said Anda. But because the impact of childhood adverse experiences is so non-random, there is an opportunity to prevent this "intergenerational transmission of the biology of stress" and the "biological prison pipeline." Anda compared this "national public health crisis" to the seven-headed Hydra in Greek mythology. Just as Hercules required a collaborator to defeat the Hydra, so researchers and policy makers must work together to slay this monster.

Translating Developmental Science into Healthy Lives

Andrew Garner, MD, FAAP (American Academy of Pediatrics)

Garner provided a 30,000-foot perspective on how pediatricians can assist in translating the science of chronic stress into children's lives. The early childhood "ecology" encompasses health, learning, and behavior, and this ecology becomes biology that drives development across generations in what he called the Eco-Bio-Develo (EBD) Framework. Pediatricians must realize that psychological and social stress is every bit as biologic as lead and other chemical toxins in a child's environment, and their primary intervention must be to make childhood adversity less toxic by providing social buffers. Positive parenting, social-emotional learning (which includes play), and maternal support are primary interventions that have demonstrated a large, long-term impact on factors like self-esteem, academic achievement, self-control, and executive function. Many pediatricians are now keyed into looking at depression in children, but few are attuned to the importance of maternal support in turning off the physical stress response in children. Garner said the American Academy of Pediatrics' is now incorporating these concepts into its objectives.

"Activating Dopamine Neurons Acutely Rescues a Stress-Induced Depression Phenotype"

Kay Tye, PhD (Picower Institute)

Two symptoms of depression are loss of motivation, which involves a brain region called the ventral tegmental area (VTA), and loss of pleasure, involving the "reward circuit" in nucleus acumbens (NA). The brain chemical dopamine is important in both of these functions, but until recently researchers did not have the techniques to probe the causal connection of dopamine to emotional processing and motivated behaviors. Tye now uses optogenetics, a method of using light to activate or inhibit selective types of neurons, to decode the neural circuits in the VTA and NA in chronically stressed rodents. She described her new work demonstrating that inhibiting dopamine neurons in these regions mimics depression-like behaviors, while stimulating dopamine restores motivated, pleasure-seeking behaviors. She also analyzed the subpopulations of neurons that modulate these behaviors to define the precise circuitry involved. Tye explained that although the human cortex differs from rodents', we share basic stress-related and emotional states that are mediated by subcortical regions like the VTA and NA. Studying these basic circuits provides insights into more complex circuits, and from a clinical perspective, understanding how they are conserved across species will help translate these findings into humans

The DNA Methylation Landscape of Early Life Adversity.

Moshe Szyf, PhD (McGill University)

Szyf recalled when researchers used to "clean" DNA samples of epigenetic markers, such as removing the methyl groups now known to be key adaptive responses of the genome in early life experiences and to explain many of the differences among individuals. He studies DNA methylation as a signal of early life stressors and childhood adversity. He has found that different tissues have somewhat different responses, fitting the hypothesis of the body-wide effect of stress leading to various mental and physical symptoms. He found a similar pattern of stress-induced demythelation in the offspring of low-grooming rats, mentioned by Michael Meaney, and human victims of child abuse. Also, different adversities, such as poverty and low status, leave different

methylation signatures in the genome. In a dynamic feedback system, a child's chemical, social, and "biosphere" environment works through the epigenome to alter the phenotype (emotional or physiological state and behaviors), and that phenotype defines the next encounter with the environment—and alters individual responses to drugs known to act through epigenetic modifications.

The Convergence of Epigenetics and Stress in Cognitive Impairment and Repair

Li-Huei Tsai, PhD (Picower Institute)

Tsai studies the effect of chronic stress on learning and memory, and also investigates major depression as a risk factor for Alzheimer's disease, which is mediated by neurotoxic insults. She recently showed a convergence of chronic stress and neurotoxic insults in inducing similar signaling events affecting epigenetic gene expression and cognitive impairment in mice. She focused on a brain region critical for the formation of new memories, the dentate gyrus of the hippocampus, where she looked at histone deacytelase 2 (HDAC-2), an epigenetic mark that keeps chromatin tightly wound and represses gene expression. She found that HDAC-2 is very sensitive to chronic stress and neurotoxic insults, and it responds to these negative environmental signals by silencing a large number of genes necessary for memory formation, leading to impaired cognitive function. But treating the cognitively impaired mice with HDAC-2 inhibition rescued their capacity to learn and remember. Tsai traced the source of the signaling for this epigenetic change to the basal and lateral amygdala (BLA), a brain region that processes anxiety and fear. She proposes that chronic repetitive stress works through the BLA circuit to send signals to the hippocampus that lead to HDAC-2 suppression of genes important for memory formation. Since this is an epigenetic effect, she hopes it can be reversed through chemical therapeutics or other measure to ameliorate the impaired mental function.

Leveraging the Biology of Adversity to Shape the Future of Early Childhood Policy

Jack P. Shonkoff, MD (Harvard University)

How do we use the science of chronic stress to usher in a 21st century approach to early childhood policy? Since the 1960s, this policy has focused on school readiness, educational approaches, and access to medical homes, rather than on strategies to reduce barriers to learning and promoting health, Shonkoff said. The scientific exploration of the causal mechanisms, at the level of gene/environment interactions, explain disparities in life outcomes that must now lead to new protective interventions. The prefrontal cortex, for example, is important for executive function, planning, impulse control, attention, and other functions associated with academic performance, healthy life-style choices, and general success in life. Growing up in a chaotic environment impairs the development of these skills. Although prefrontal skills can be acquired through practice, coaching, and training, we do not teach these skills to at-risk children. We must mobilize science to create new models for early childhood policies that build protective capacities in children growing up in adversity and reduce the disparities in life outcomes.

Closing Remarks: Go Forth and Collaborate

Steven Hyman, MD (Broad Institute and formerly director of the National Institute of Mental Health), closed this "amazing day" with some take-home caveats and to-dos. Science does not tell policy makers what to do, and it is not helpful to leap from basic mechanisms to policy. We need to treat for resilience to childhood adversities. Animal models can generate hypotheses about chronically stressed phenotypes, but they cannot directly stand for human biology or predict the efficacy of mediation. When we identify specific stressors, we need to ask what is the active ingredient that sends kids on a bad trajectory, and which interventions are actually feasible. We must instill an experimental culture into policy and education, and recognize the complexity of the issues. And we should stop stumbling on hurdles we can already clear. For example, we know the benefit of treating maternal depression on a child's outcome, but ob/gyns are not attuned to it. We know that exercise protects cognitive abilities, but we are cutting physical education in schools. To effect change, scientists should go back to the lab, but also go out, advocate, and collaborate.

Congratulations to Professor Matt Wilson for being one of the newly elected members to The American Academy of Arts and Sciences.

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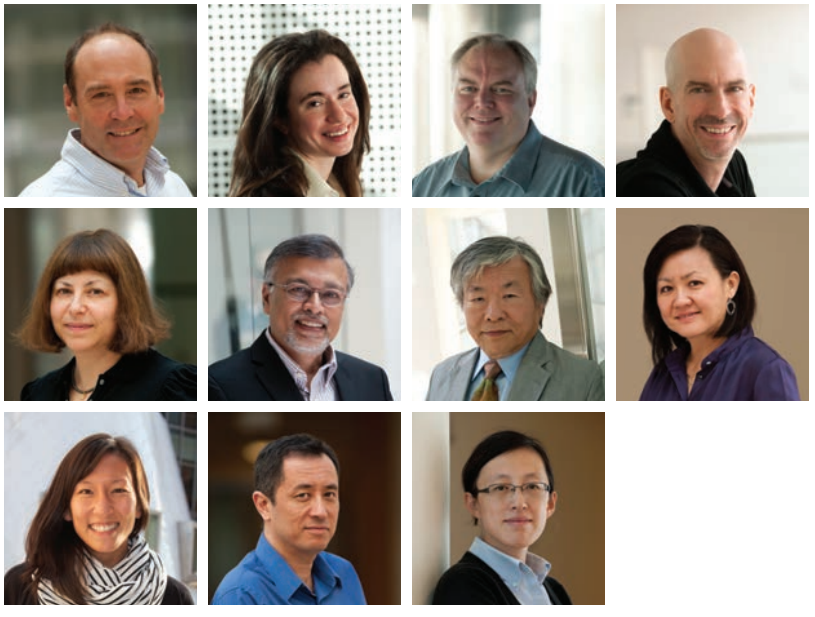

TOP ROW: Mark F. Bear, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Investigator, Howard Hughes Medical Institute (HHMI); Myriam Heiman, Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences, Broad Institute core member; Troy Littleton, Picower 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.
MIDDLE 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, Alumni Investigator, Howard Hughes Medical Institute, Alumni 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, Investigator, Howard Hughes Medical Institute.
BOTTOM ROW: 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.

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