Doing the right thing: can neuroscience research make it easier?

Yale undergraduate believes that healthy messages can be made more persuasive

Despite the health risks, about 1.1 billion people smoke tobacco worldwide, and cigarette manufacturers spend more than $8 billion annually on product promotion. But what if advertising aimed at rooting out smoking was as effective as ads that encourage it?

For Emily Yudofsky, the idea of using powerful marketing techniques to influence behavior for the better was more than just a dream. A Yale College junior majoring in psychology, Yudofsky established her own “neuromarketing” company, Applied Resonance Research, in 2007, with the goal of using imaging technologies to enhance the effectiveness of public-service advertising.

With funding from the Yale Interdisciplinary Research Consortium on Stress, Self-Control and Addiction (IRCSSA), Yudofsky is now using the medical school’s functional MRI (fMRI) facility to study how product branding influences the brain. While in high school in Houston, Yudofsky attended neuroimaging conferences. Having developed a strong interest in the field, she secured a summer position with a team of neuroscientists and behavioral scientists at Baylor College of Medicine’s Human Neuroimaging Laboratory. A study taking place in the lab at that time, the results of which were published in the journal Neuron in 2004, reported that subjects’ preference for a popular soft drink increased when drunk from cups bearing the drink’s logo, and that brain regions involved in decision-making and memory were more stimulated when sips of Diet Coke were drunk from cups bearing the drink’s logo.

For Emily Yudofsky, the idea of using healthy messages to influence behavior was made possible by applying the tools of neuromarketing.

$5 million grant funds dyslexia study

Probing the ‘lexinome’ in hopes of a genetic test for reading disorders

Jeffrey R. Gruen, M.D., a School of Medicine scientist whose discovery of a gene involved in dyslexia was named one of the top 10 scientific breakthroughs of 2005 by the journal Science, has received a $5.2 million grant from the New York-based Manton Foundation to further his research on the genetics of dyslexia.

The Manton Foundation was established in 1991 by Sir Edwin Manton and his wife, Lady Manton, the former Florence V. Brewer. Born in England in 1909, Edwin Manton, known to friends and colleagues as “Jimmy,” was successively director, executive vice president and senior advisor at American International Group. For his role as a major benefactor of Tate Gallery in London, Manton was knighted in 1994 by Queen Elizabeth II of England. The foundation supports education, the arts, conservation, health care and medical research.

Gruen, associate professor of pediatrics, investigative medicine and genetics, will use the grant monies to launch a new study that will compare the complete genomes of 1,000 dyslexic children with those of 1,000 fluent readers to obtain a fine-grained view of genes that are known to play a role in reading disabilities, and possibly to identify new genes that confer a risk of developing dyslexia. The ultimate goal of Gruen’s work is to devise a practical genetic test for dyslexia, making it possible for parents and teachers of children with dyslexia to begin educational interventions early in life, the time when researchers have shown those interventions to have the most significant and lasting impact on reading ability. In addition, the new study will enroll children of non-European ancestry, who have been underrepresented in research on the genetics of dyslexia, Gruen says.

“I have a folder full of e-mails from desperate parents who’ve read ‘Dyslexia,’ ” Gruen says. “With support from The Manton Foundation, Jeffrey Gruen has embarked on a new exploration of the genetics of dyslexia.”

Philanthropists aid a young scientist’s innovative research

Alison P. Galvani, Ph.D., assistant professor of epidemiology at the Yale School of Public Health, who at age 29 was one of the youngest-ever recipients of a Guggenheim Fellowship, combines psychological, economic and medical insights to generate mathematical models of infectious diseases. Galvani’s research on the epidemiology of infectious diseases has enjoyed the generous support of the late Miriam Burnett and that of her son Charles Burnett III, who have contributed more than $650,000 to support Galvani’s work. “The gifts from Miriam and Charles Burnett have been wonderful in facilitating my research,” says Galvani.

While growing up in San Francisco, Galvani was always keenly interested in math and science, and Galvani, page 4
Intestinal fortitude

Yale physician-scientist advances the genetics of inflammatory bowel disease

In 1932, JAMA: The Journal of the American Medical Association published "Regional Ileitis: A Pathologic and Clinical Entity," which described 14 patients who had been treated at New York's Mount Sinai Hospital for fever, abdominal pain, diarrhea and emaciation. Despite its rather understated title, the article was soon recognized as a classic, and its first author, Burrill B. Crohn, M.D., has been immortalized by that honor peculiar to medicine, his name forever conjoined to an illness.

Today, Crohn's disease and ulcerative colitis fall under the broader clinical umbrella of inflammatory bowel disease, or IBD. According to Judy H. Cho, M.D., associate professor of medicine and one of the world's leading experts on the genetics of IBD, both diseases are chronic autoimmune conditions with similar symptoms, primarily distinguished by the regions of the gastrointestinal tract on which they wreak their havoc.

When Cho entered medical school at The Ohio State University in her hometown of Columbus, she planned to become a surgeon. But "when I saw the neurosurgeons standing in the OR for twelve hours," she says with a laugh, "I decided it wasn't for me." Instead, after her residency at Northwestern University, Cho completed a fellowship in gastroenterology in 1992 at the University of Chicago. She got great satisfaction caring for IBD patients, she says, because the disorder’s chronic nature allowed her to build close relationships that approached those enjoyed by a primary care physician. Some cases of IBD can be successfully managed with immunosuppressant drugs, but up to two-thirds of patients require hospitalization or surgical treatment at some point in their lives.

But 60 years after Crohn’s JAMA paper, the causes of IBD remained a scientific mystery. "In about 1993," says Cho, "I was sitting in a lab flipping through Science and saw a paper from Bert Vogelstein's lab [at Johns Hopkins] which ultimately led to the identification of a whole new class of genes that, when mutated, cause a hereditary form of colon cancer.

"Because IBD is also a familial disease, Cho recalls, "it clicked in my mind at that moment that genetic research was a perfect melding of clinical relevance and basic science." Soon after, Cho collected her first DNA samples from her patients. In 2001, before moving to Yale, Cho and colleagues at the University of Michigan were the first to establish a genetic vulnerability, in a gene known as NOD2, for Crohn's disease.

Now, in addition to directing Yale's Inflammatory Bowel Disease Program, an interdisciplinary group of gastroenterologists, radiologists, surgeons and pathologists, Cho chairs the steering committee of the IBD Genetics Consortium, a group of seven academic centers devoted to unraveling causes of the disease. This January, Cho and other members of the consortium linked regions on two chromosomes with ulcerative colitis.

But the successes in IBD genetics thus far are "low-hanging fruit," Cho says, adding that further progress will require careful classification of IBD patients, whose symptoms and clinical course can vary wildly from case to case.

"The major role to do genetics is to develop new therapeutic targets and to refine our understanding of the disease," she says. "We're not lacking for potential targets, but we're lacking an understanding of how the immune mediators associated with IBD combine to cause disease. Part of this means figuring out how to follow patients better over long periods of time, which our present research system doesn't do very well.

With an eye to the future, Cho acts as a mentor to young physician-scientists through the Yale Center for Clinical Investigation. "Human translational work is much more complex than classic basic science," she says, largely because the lives of human patients don't unfold in the tightly controlled confines of the lab. So Cho sets her sights with a wide range. "It will be very challenging to develop a novel therapy," she says, "but the intermediate goal is to somehow classify people a little bit better.

Lifelines

Judy Cho

Newest research building is recognized for environmental features

The research building at 10 Amistad Street in New Haven has been awarded the LEED Gold certification by the U.S. Green Building Council’s Leadership in Energy and Environmental Design. Completed in 2008, the building houses the School of Medicine’s program in Vascular Biology and Therapeutics, the Yale Stem Cell Center and the Human and Translational Immunology program.

"Right from the outset the team was charged with incorporating green attributes in alignment with Yale’s sustainability strategy, which includes striving for outstanding environmental performance in the design, renovation and construction of its facilities," says Virginia Chapman, the medical school’s director of construction and renovation.

The 120,000-square-foot building has many green attributes, ranging from its accessible structural features and the materials used in its construction, to its waste management and energy conservation systems.

Many of the materials used in the building’s construction were produced locally and selected for their high recycled content, and recycling of debris reduced the amount of construction waste by 70 percent. A lab waste recycling program has also been incorporated. Water collected on the roof of the research building at 10 Amistad St. is used in ultra-low-flow lavatories and dual-flush toilets.

Skin cancer expert is appointed new Smith Professor

David J. Lefell, M.D., deputy dean for clinical affairs, chief executive officer of Yale Medical Group and professor of dermatology and surgery, has been named the David Paige Smith Professor of Dermatology.

Lefell specializes in the diagnosis and treatment of melanoma and other skin cancers. He is an expert in Mohs surgery, a technique in which skin cancers are removed layer by layer and studied immediately under a microscope using a frozen section method. The Mohs technique allows removal of the entire tumor, providing the highest cure rate and minimizing scarring. The Cutaneous Oncology Unit that Lefell founded in 1988 treats more than 1,500 patients per year.

His research focuses on non-melanoma skin cancer, wound healing and cancer epidemiology. Lefell and colleagues discovered the skin cancer gene PTCH in 1996, and he has conducted collaborative research clarifying the role of ultraviolet radiation in skin cancer and skin aging. Other research includes the role of the p53 gene in skin cancer and the development of innovative diagnostic devices.

As deputy dean of the School of Medicine, Lefell has been responsible for the growth and development of the school’s clinical practice.

David Paige Smith, who joined Yale’s medical faculty in 1873, was a grandson of Nathan Smith, a premier physician in post–Revolutionary War New England. Nathan Smith was a central figure in the establishment of the Medical Institution of Yale College, as the School of Medicine was known at the time.

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Medicine@Yale

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Versatile molecule protects against IBD

Immune system signaling molecules known as cytokines are believed to play a major inflammatory role in autoimmune diseases, in which the body’s immune defenses somehow turn on its own cells.

Things aren’t so simple in the case of the cytokine interleukin-22 (IL-22, below), postulated as a protective agent whose overproduction could switch the inflammation of skin cells seen in psoriasis but appears to protect cells in inflamed livers. Scientists from the laboratory of Richard A. Flavell, Ph.D., Sterling Professor of Immunobiology, and Regeneron Pharmaceuticals have found that IL-22 also plays a protective role in inflammatory bowel disease (IBD; see related story, p. 2). As reported in the December issue of Science, mice that were deficient in interleukin-22 had more severe forms of colitis and higher mortality.

Postdoctoral associate and first author Lauren A. Zenewicz, Ph.D., says the discovery could lead to IBD treatments without the side effects of current immunosuppressive therapies, which induce increased susceptibility to infections.

Aspirin for the heart, now for the liver?

The popular pain and fever reliever acetaminophen, better known as Tylenol but sold under many other trade names, is usually thought of as an aspirin alternative. But a new Yale study has found two ways to block a central application, says Mehal. “Many people think of aspirin on a daily basis to prevent cardiovascular disease, whereas the evidence for the use of aspirin to prevent livers.

Change was rapid in the early 1970s. It was a time, Spencer says, when “people were breaking away from the concept that you recorded from the scalp with EEG and got kind of a general localization” of seizure activity. As a medical student at Washington University in St. Louis, Spencer had learned to monitor the brain more directly with electrode arrays placed on the dura, a thin, leathery covering of the brain just beneath the skull. On his arrival at Yale as a neurosurgery resident in 1971, Mattson’s EEG/tech- nique was the main tool for monitoring seizure activity, but Spencer saw the replacement of scalp electrodes with intracranial electrodes, both arrays and depth electrodes inserted into the cortex.

Spencer and Yale colleagues soon discerned that most seizures in the brain’s temporal lobe—the most common site of origin for “partial” seizures, those that begin in a localized place—originate in the hippocampus, a structure deep in the brain that plays a key role in managing memory. By more precisely localizing the sources of seizures, Yale neurosurgeons became able to perform surgeries that interrupted seizures but preserved critical functions—especially language and vision—by removing only deeper portions of the brain’s temporal lobe. Examining the tissue removed during these operations in the mid-1980s, Nihal C. de Lanerolle, d.phil., now professor of neurosurgery and neurobiology, discerned that hippocampal damage from a majority of epilepsy patients had fewer brain cells than those from unaffected people. When Anne Williamson, Ph.D., associate professor of neurosurgery, performed electrophysiological measurements with slices of the removed tissue, she observed electrical changes that correlated with the chemical abnormal-ities de Lanerolle had observed.

Epilepsy, page 6
Neuromarketing from page 1

the drink in an fMRI scanner were accompanied by a visual presentation of the drink’s brand.

The study “showed that brand- ing alone can change the way people make decisions,” Yudofsky says. This work inspired her to ponder the pos- sibility of studying neural responses to marketing with an eye toward lessen- ing the impact of public health prob- lems such as smoking and obesity.

Research motivated Yudofsky was invited by the Yale Entrepreneurial In- stitute (YEI) to be one of 12 participants in the YEi’s inaugural summer fellow- ship program.

Yudofsky found willing mentors at the medical school in Hilary Blumberg, M.D., associate professor of psychiatry and diagnostic radiology, and Rajita Sinha, Ph.D., professor of psychiatry and UCSF director. Sinha helped Yudofsky to secure grant money to conduct fMRI research at the medi- cal school’s Arlan’s Center for Medi- cal Research and Education with the guidance of Marvin M. Chun, Ph.D., professor of psychology and Yudofsky’s advisor. In particular, she is studying brain activity associated with public-service ads aimed at preventing obesity. While brain function is measured in the fMRI scanner, “subjects are asked to make a decision between two differ- ent objects or food items, and they’re told to think about the consequences of their choices,” Yudofsky explains. “Then they’re shown obesity-preven- tion ads and another advertisement, and again asked to make decisions between two different items—some of the choices are healthful and some are unhealthful.”

By applying imaging technolo- gies to similar psychological tasks, Yudofsky, the subject of a recent New York Times profile, hopes “to assess validly in the brain the effectiveness of public service advertisements and other modes of communication on influenc- ing healthful choices, decisions, and behaviors.” Her ultimate goal, she says, is “to improve public health and dimin- ish human suffering.”

Galvani from page 1

she encountered a book during high school that would change the course of her life. After reading The Blind Watch- maker, the bestselling account of modern evolutionary biology by Uni- versity of Oxford biologist Richard Dawkins, D.Phil., Galvani wrote a letter to Dawkins pointing out what she considered to be a minor incon- sistency in his genetic mechanism of speciation. “He agreed and encour- aged me to come to Oxford Univer- sity” Galvani recalls.

After completing her undergradu- ate degree in biology at Oxford, con- centrating on evolution and ecology, Galvani stayed on to earn her doctor- ate under the supervision of Lord Robert May, Ph.D., in the university’s very strong program in epidemiology, she says, “because I see epidemiology as the ecology of infectious disease, which I find fascinating.”

In her current work at the Yale School of Public Health, she incorpo- rates game theory and the psychology of decision-making to create simulations that take crucial human factors—the likelihood of compli- ance with manda- tory vaccination, the perception of risk, the role of social networks and more—into account, allowing her to easily compare the outcomes of various public health scenarios, a tool that government offi- cials are finding increasingly valuable in designing public policy.

Funding received from Miriam and Charles Burnett has enabled Gal- vani to expand the scope of her stud- ies and increase the range of collabo- rations nationally and internationally.

“Our research encompasses a wide variety of topics, including the inter- vention of influenza, tuberculosis, dengue fever and human papilloma virus,” says Galvani. “I have observed increasing interest by policymakers in this tool.”

Out & about

December 11, 2008: Benefactors of the Yale Eye Center (YEC) joined faculty from the Department of Ophthalmology and Visual Science for a PLAQUE UNVEILING IN THE YEC’S NEW LOCATION at Temple Medical Center in New Haven. 1. Homer McK. Rees and Coverly R. Rees. Last year, Homer Rees, member of the Yale College Class of 1951, established the Homer McK. Rees Research and Lectureship Fund. 2. Yale Eye Center Advisory Board member Peter Thorne and Jimmy K. Lee, M.D., assistant professor of ophthalmology and visual science. A recent gift from Thorne established the Peter Thorne Research and Lectureship Fund. 3. From left: James C. Tsal, M.D., M.B.A., chair and Robert R. Young Professor of Ophthalmology and Visual Science; M. Bruce Shields, M.D., chair emeritus and Marvin L. Sears Pro- fessor of Ophthalmology and Visual Science; Rocky Cingari, chair of the Yale Eye Center Advisory Board and member of the Lions Club of Darien, Conn.; and Michael Del Re, presi- dent of the Connecticut Lion’s Eye Research Foundation (CLERF). After 90 years of partnership to prevent blindness, the cumulative total of CLERF grants to Yale tops $3 million, and the founda- tion has pledged to donate an additional $1 million to support research on macular degeneration and glaucoma, as well as pediatric eye care.

Advances
Health and science news from Yale

Can we really ‘catch’ healthy behaviors?

Research suggesting that certain behaviors affecting health are “contagious”—spread from person to person who quit smoking are likely to influence friends to do the same, or that happiness spreads from one person to another—has generated a great deal of media buzz. But the statistical techniques used to establish these so-called network effects are imperilable. In the December 4 issue of the British Medical Journal, the team reports “surprisingly high” network effects for these conditions that disappeared with statistical refinements.

“Our results suggest caution in attributing similarities of health outcomes between friends to a ‘contagious’ process,” Fletcher explains.

A needless barrier to good patient care

According to the 2000 U.S. Census, more than 22 million Americans have limited proficiency in English, a 53 percent increase from 1990. Language barriers in health care have limited proficiency in English, a 53 percent increase from 1990. Language barriers in health care have led to problems where none exist,” says Jason M. Fletcher, Ph.D., M.S., assistant professor of public health.

Fletcher and a colleague studied headaches, acne and height conditions for which network effects are implausible. In the December 4 issue of the British Medical Journal, the team reports “surprisingly high” network effects for these conditions that disappeared with statistical refinements.

“Our results suggest caution in attributing similarities of health outcomes between friends to a ‘contagious’ process,” Fletcher explains.

Not just weight loss: the new stomach surgery

Diabetes, apnea spur a reassessment of bariatric surgery’s role

Bariatric surgery, a long popular operation for patients who want to lose weight, has gained some weight of its own in recent years. One called “stomach stapling” and viewed simply as a technique to help the obese shed pounds, the surgery has recently been shown to cure or greatly improve such obesity-related conditions as type 2 diabetes and obstructive sleep apnea—often long before any significant weight is lost.

“There’s been a huge change in the way we think about this surgery,” says Robert Bell, M.D., assistant professor of surgery and director of the Yale Bariatric Surgery Program. “We used to think that if you helped a person lose weight, these weight-related problems would slowly get better as a function of the weight loss.” What actually happens, according to Bell, is that metabolic changes brought on by the surgery cause immediate improvements in the weight-related disorders. Surprisingly, and for reasons that are not fully understood, these metabolic changes apparently don’t occur if the patient loses weight naturally.

These findings prompted the American Society of Bariatric Surgery in June 2007 to change its name to the American Society of Metabolic and Bariatric Surgery, signifying “a shift in emphasis,” Bell says. “It’s not so much about weight loss; it’s really more about getting patients healthier.”

A study published in Jama, the Journal of the American Medical Association, in January 2008 found that 73 percent of patients resolved their type 2 diabetes after gastric banding surgery. Another JAMA study published in October 2004 found that after bariatric surgery, diabetes was eradicated in 76.8 percent of patients and eradicated or improved in 86 percent of patients.

“Unbeknownst to everybody doing this surgery was that there’s a lot more going on than just that the patient ended up more easily,” Bell said. “There’s a variety of hormonal changes that occur that really were not described until this decade. It is these hormonal changes that confer the added medical benefits.”

The first surgical procedure to aid in weight loss was introduced in 1950s, and was purely malabsorptive, surgically reducing, thereby restricting how much of food the stomach can hold. Feeling fuller faster

The implications of these findings are significant, says Bell, who predicts there will be a move toward earlier interventions, with surgeons operating on patients who are overweight but not yet obese, a transition that will most likely require the compilation of long-term efficacy data to convince insurance companies to change their coverage policies.

“Right now you have to be a certain size and have a body mass index (BMI) of 40 or more to be covered,” Bell said. A BMI of between 19 and 24 is considered normal; 25 to 30 is overweight, 30 to 35 is obese and 35 to 40 is morbidly obese. In November, the Centers for Medicare & Medicaid Services, a division of the Department of Health and Human Services, announced that bariatric surgery would not be covered by Medicare or Medicaid for beneficiaries with a BMI below 35.

Bell also anticipates the procedure being performed on younger patients. Bell, who performs about 100 gastric bypass surgeries a year, has done four on 17-year-olds. (Most insurers require the patient to be at least 18.) “It makes sense to help these patients when they’re younger,” he says, “because the years of obesity haven’t added up, causing destruction to bones and joints that limit their exercise, which is key to the long-term success of this surgery.”

Bell knows it will take time for patients, physicians and insurers to view gastric bypass surgery as more than just a weight-loss operation, but in his own practice, that’s exactly what’s happening. “Although we still talk about obesity and weight loss,” Bell says, “we really focus on the fact that it’s a cure for diabetes, hypertension, sleep apnea and high cholesterol.” Medications, the usual course of treatment for these ailments, just manage the symptoms, Bell says. “Surgery eradicates the disease. It’s gone.”

Yale Netcast
“Is Bariatric Surgery for You?”

Surgeon Robert Bell (right) consults with a patient about bariatric surgery options. Once recommended strictly for weight loss, bariatric procedures have recently been found to have other benefits, including rapid and complete remission of type 2 diabetes, obstructive sleep apnea and other obesity-related disorders in a majority of patients, sometimes “before they leave the hospital,” says Bell.

Surgery limits the amount of food the stomach can hold by reducing its capacity to a few ounces. Three procedures, all of which are offered by Yale surgeons, are covered by insurance carriers in the United States.

• In gastric bypass, the stomach is surgically shrunk from the size of a football to that of a golf ball. The smaller stomach pouch is then attached to the middle of the small intestine, bypassing the duodenum, the section of the small intestine that absorbs the most calories.

• Similar to gastric bypass, biliopancreatic diversion with duodenal switch involves the surgical construction of a sleeve-shaped stomach which is attached to the final section of the small intestine, bypassing the duodenum.

• In laparoscopic adjustable gastric banding, a silicone band filled with saline is wrapped around the upper part of the stomach to create a small pouch and cause restriction. The size of the restrictions can be adjusted after surgery by adding or removing saline from the band.

None of these procedures is a substitute for exercise or healthy eating, cautions bariatric surgeon Robert Bell. “It’s not like you have the surgery and—voilà—you lose all kinds of weight. You have to put a lot of effort into it. It’s an adjunct, a tool to help you lose the weight.”

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Covering all the bases: the Yale Epilepsy Program

A team with deep expertise in the understanding and treatment of seizures

Hal Blumenfeld, m.d., ph.d.
Associate professor of neurosurgery, neurobiology and neurosurgery
“I’m interested in understanding epilepsy in order to try to improve patient quality of life.”

Richard A. Bronen, m.d.
Professor of diagnostic radiology and neurosurgery
“My research interests include imaging of epilepsy, cortical dysplasias, temporal lobe anatomy, and aneurysms.”

R. Todd Constable, Ph.D.
Professor of diagnostic radiology, neurosurgery and biomedical engineering
“My interests focus not only on the development of MRI techniques to provide high quality pictures of anatomy but on the development of such techniques for providing information on function.”

Nihal C. de Lanerolle, Ph.D., Ph.m., D.C.
Associate professor of neurosurgery and neurobiology “The focus of our research is the anatomical and molecular characterization of seizure foci, in particular the hippocampal seizure focus in patients with temporal lobe epilepsy.”

Robert B. Ducky, m.d.
Associate professor of diagnostic radiology “High for markers of seizure susceptibility in the electrical activity of the brain recorded during intracranial monitoring or with clinically implanted neuromonitoring devices used to treat epilepsy.”

James S. Duncan, Ph.D.
Professor of diagnostic radiology and biomedical engineering “My efforts within the neuroscience program have been to perform research that will help us to better integrate the multimodal information necessary for both diagnosis and to perform image-guided epilepsy surgery.”

Tore Elié, M.D.
Associate research scientist in neurosurgery and laboratory medicine “Using chemical profiling by mass spectrometry, my laboratory’s research focuses on the discovery of novel diagnostics and therapeutics of epilepsy.”

Hoby P. Hetherington, Ph.D.
Professor of neurosurgery and functional and diagnostic radiology “The overall goal of our work is to develop and utilize magnetic resonance imaging techniques to characterize the metabolic and biomarker changes associated with epilepsy.”

Jung H. Kim, m.d.
Professor emeritus and senior research scientist in pathology “In addition to neuropathological evaluation of surgically resected brain tissue, we quantitatively evaluate the morphological changes using digital images with clinical parameters and electrophysiological, biochemical and imaging findings.”

Susan Levits, Ph.D.
Clinical professor of pediatrics and neurology “Our clinical interests include pediatric epilepsy and clinical neurophysiology. Our research interests involve the roles and prediction of intractability and morbidity on children.”

Richard H. Mattson, M.D.
Professor emeritus and senior research scientist in neurology “I continue to look for novel antiepileptic drugs that bring possibilities for control and perhaps a cure to patients who have epilepsy.”

Jullie W. Pan, Ph.m., Ph.d.
Associate professor of neurosurgery, diagnostic radiology and neurology “The data we gather using imaging techniques is used to identify the brain regions, giving rise to seizures to aid in surgical planning and to develop new therapeutic approaches to treating epilepsy.”

Xenophon Papademetris, Ph.D.
Assistant professor of diagnostic radiology and biomedical engineering “Medical image analysis can be broadly defined as the extraction of quantitative information from medical images. One aspect of this work that relates to epilepsy is the registration of images from different modalities into a common coordinate space.”

Ognen A. Petroff, M.D.
Associate professor of neurology “We use a variety of tools to better understand the mechanisms of cerebral metabolism that promote epileptic seizures, and to develop therapies, which lead to a more normal state of cerebral function.”

Marcia N. Spann, M.A.
Associate research scientist in neurology “My current research aims to better understand and decipher the neurochemical communication, involved in childhood absence epilepsy, in particular those involved in attention and learning.”

Denis S. Spencer, Ph.D.
Chair and Harvey and Katie Cushing Professor of Neurosurgery “Epilepsy research at Yale has a unique emphasis on the continuum of human investigation, from clinical research, which is established in the methods of imaging, electrophysiology, neurochemistry, genetics and epidemiology in order to clearly define the human pathophysiology; to basic laboratory investigation of surgically resected human tissue substrates and the use of tissue fibroblasts in developing animal models for new therapies.”

Susan S. Spencer, M.D.
Director, Yale Epilepsy Program Professor of neurology and neurosurgery “There is increasing evidence that many forms of epilepsy are generated in networks of aberrantly functioning, connected regions of the brain, rather than in single abnormal areas.”

Francine M. Teata, M.D.
Clinical professor of pediatrics and neurology “We have been involved, along with Dr. Anne Berg, in a longitudinal study that continues to provide unique information about the outcomes of epilepsy in children over the course of more than a decade after initial diagnosis.”

Kenneth P. Vives, M.D.
Associate professor of neurosurgery “We are participating in a clinical trial of an implantable device designed to detect focal seizure activity and treat this activity through the use of electrical stimulation.”

Anne Williamson, Ph.D.
Assistant professor of neurosurgery “My interests include the neurotransmitter representation of language, electrical cortical stimulation mapping, transcranial magnetic stimulation, fMRI of language and memory, and deep brain stimulation.”

F. Scott Winstelny, Ph.D.
Assistant professor of neurosurgery “My research focuses on the neurotransmission regulation of the vestibular nucleus and alterations in brain activity produced by depression.”

Kun Wu, M.D., Ph.D.
Associate research scientist in neurosurgery “I co-lead functional imaging, electrophysiological data with structural MRI or CT images, into the neurovascular system that allows the neurosurgeon to guide therapeutic intervention without harming normal brain function.”

Hitze P. Zaveri, Ph.D.
Associate research scientist in neurology “My goal is to understand how seizures are generated and predict seizures with advanced computational methods and abort them once they have been detected.”
Grants and contracts awarded to Yale School of Medicine
May/June 2009

Federal

Srap Aksoy, NIH, Tissue–Trypanosome Interaction, 2 years, $45,421 • Jeffrey Brender, NIH, Molecular Models of Immune-Mediated Vascul- itis, 5 years, $2,068,645 • Alfred Both- well, NIH, p53—Mediated Inhibition of Vasc- uitis, 2 years, $155,428 • Sajal Banerjee, NIH, Parathyroid Hormone-Related Peptide, 4 years, $2,035,479 • William Cafferty, NIH, Molecular Genetics of Cerebral Reversal Reac- tion after Spinal Cord Injury, 2 years, $179,820 Tara Chaplin, NIH, Gender, Emotional Annual, and Risk for Adolescent Substance Abuse, 5 years, $77,714 • Lynn Cooley, NIH, Oxytocin Development in Drosophila, 4 years, $2,963,907 • Jonathan Cornwell, NIH, Transpo- son Mutagenesis Screen for Human Cancer Gene Discovery, 3 years, $147,570 • Endri Fikrig, NIH, Borrelia burgdorferi Interactions with Budes spirochaetes, 5 years, $2,100,304 • Jorg Galin, NIH, Virulence Factors of Salmonella typhimurium, 3 years, $2,068,646; NIH, Host Cell Sig- naling Pathways Induced by Salmonella, 5 years, $2,995,445 • Carlos Gilio, NIH, Treatment of Obesity and Binge Eating: Stepped Care Versus Standard Behavioral Weight Loss, 5 years, $3,027,963 • Shoal Hissain, NIH, Calcinurin in Pathologic Amyotrophic Lateral, 2 years, $1,855,400 • Manisha Juthani-Mcnell, NIH, UTI in Nursing Home Residents: Research Training Intervention, and Clinical Investigations, 5 years, $798,255 • Anthony Koelske, NIH, Regulation of Dendritic Shape and Spine Dynamics and Dysphoria Stability, 3 years, $1,160,972 • Geoffrey Lander, NIH, T- Wave Abnormalities and Emotion in Daily Life, 5 years, $1,747,607 Patti Lee, NIH, Home Oxygenation in Lang Endothelial Deposition Outcomes, 5 years, $2,068,242 Chiang-Shan Li, NIH, Cortical Control and Cognitive Dependence, 5 years, $1,591,444 Riad Al Khatib, NIH, Genetics and Evolution of Human Disease, 5 years, $1,522,800 • Jinyu Lai, NIH, Decipher the Genetic Basis of Tumor Metastasis from in Vitro to In Vivo, 3 years, $621,018 • Laura Manuelidis, NIH, New Animal and Culture Models to Rapidly Evaluate Infectivity of the rights, 2 years, $455,063 • Andrew Miranker, NIH, Conformations and Dynam- ics of Amyloid-Induced Membrane Disruption, 2 years, $416,950 • Eilif Paulistl, NIH, DTV Neuroanatomy and Analysis of Motor Recruitment and Metabolism, 5 years, $629,100 Christoph Pitterger, NIH, CREB and the Molecu- lar Underpinnings of Habit Learning, 5 years, $994,230 John Rose, NIH, Immune Regulation in SV40- induc- ed Macropuses in Mice, 3 years, $1,969,912 • Ruth Shula, NIH, Role of Oxytocin in Morphine Dependence and Withdrawal, 2 years, $96,472 • Jody Stinch, NIH, Efficiency and Equity in Health and Healthcare? 2nd Biennial ASPE Conference, 1 year, $520,000 • Bruce Staley-Gottschalk, NIH, Nicotine Vaccine and Nicotine Occupancy of Brain Nictine Receptors, 2 years, $353,523 Ning Sun, NIH, Statistical Methods to Study Dynamic TranscerebralRegulatoryNetworks,2years,$455,020 Jan Tew, NIH, Stress and Defense (U.S.), Stimulant Therapy and Memory Strength: Impli- cations for the Emergence and Treatment of PTSD, 18 months, $213,410 • Chris- tian Tsichlak, NIH, RNA Capping in Trypanosomes, 3 years, $2,068,541 Non-Federal

Amy Aronstam, Nat’l Alliance for Research on Schizo- phrenia and Depression, The Role of DHC in Primate Premotor Cortical Networks, 1 year, $99,900 • Elizabeth Bradley, South Essex Partnership with Foundation Trust, Leadership Workshop, 1 year, $120,000 • Leo Cooney, Association of Directors of Geriatric Academic Programs, Chief Medical Director Training in the Care of Older Adults, 2 years, $114,000 Mark Gerstein, European Bioinformatics Institute, EBI Data Analysis Center, 4 years, $837,968 • Elena Grigorenko, Columbia University–Teachers College, Maternal Drug Use, Psychopathology and Child Adaptation, 1 year, $123,628 • Robert Heimer, U.S. Civilian Research and Defense Foundation, Russian Research and Methodological Center for VTIV, 2 years, $79,078 • Kevin Herold, Juvenile Diabetes Research Founda- tion Int’l, The Role of the Pancreas in Beta Cell Regeneration, 2 years, $451,111; The Children’s Hospital of Philadelphia, Progenitors of Beta Cell Mass Expansion in Arterial Autonomous Diabetes, 1 year, $370,660 • Roger Jos, Amer- ican Psychiatric Institute for Research and Edu- cation, Characterization of Abnormal Neural Connectivity in Autism Spectrum Disorders using Combinatory Magnetic Resonance Imaging Techniques, 1 year, $86,992 • Patricia Keenan, The Pennsylvania State University, Regional Quality Strategy Evaluation Aligning Forces for Quality II, 18 months, $75,763 • Trace Kershaw, Duke University, Project Partnership, 6 months, $49,747 • Paul Lombrozo, FRA Research Foundation, The Role of step in Fragile X Syndrome, 1 year, $84,400 • Stephanie Massaro, Anagen, Inc., Regulation of Mega- rapyric Differentiation in Human Embryonic Stem Cells, 1 year, $40,000 • Linda Mayes, Columbia University–Teachers College, Family Research Consortium V: Transdisciplinary Con- sortium on Mental Health, 3 years, $228,177 • University of California- Irvine, Parent/Healthcare Provider Behaviors and Child’s Anxiety, 1 year, $63,527 • Paiko Rakai, March of Dimes, Origin, Morphogenetic Characteristic and Fate of Canoeform Type 1 Receptor (CR1) Containing Intermembrane in Developing Mammalian Cerebrum, 3 years, $298,662 • Albert Simmons, Medical University of South Carolina, Col- lagenase Inhibition in Heart Failure, 2 years, $198,394 • Hugh Taylor, Wyeth Pharmacologi- cals Inc., Mechanism of Tissue-Specific Estrogen Complex (TREC) Action in the Endometrium, 1 year, $224,000 Dyslexia from page 1

about our work and hope that I can provide some sage advice to help the third grader who comes home cry- ically detesting English. Most of the students in my school student whose standardized test scores make college seem out of reach, says Gruen. “These families could have been helped through the creation of a simple, inexpensive dyslexia screening test that could apply to the general American population, including groups who have been excluded from dyslexia research up to now. We have the knowledge and the capability to develop such a test.”

According to Gruen, there is good reason to believe that these four genes tell much of the genetic story of reading disorders, which affect between 7 and 20 percent of the population.

“Studies have shown that the number of loci—areas in chromosomes where there is an effect—is very limited,” Gruen says. “So we’re not talking about 10. I think it’s likely that these four genes, or even two of the four, will be found to have large effects.”

Accordingly, with a grant from the National Institute of Neurological Disorders and Stroke, Gruen has launched a study of these four genes using DNA taken from 10,000 English children whose developmental behavioral profile has been tracked from birth through high school. By documenting the range of mutations in the four “dyslexia genes” in these children and correlating these variants with reading ability and aca- demic accomplishment, Gruen says, we can begin to assign the relative risk each gene and variant contribute to the development of dyslexia, a neces- sary component for any future genetic test to be of value.

In another effort to establish how gene variants change the way in which the brain codes and interprets writ- ten language, Gruen has begun a series of “imaging-genetics” studies. Using functional magnetic resonance imaging (fMRI) to record activation in specific reading centers of the brain in awake, alert subjects, his group is linking individual differences in brain activity during specific reading tasks to particular genetic variations.

Unlike the study of the English children, which specifically targets four genes, the project undertaken by the new Manton Foundation grant will be a genome-wide association study, or GWAS (“go-waz”), exploring the entire genomes of the 2,000 study subjects at a fine level of detail. In addition to finding new vari- ants in the four previously discovered genes, some of which may not yet have been uncovered in European-Ameri- can populations, Gruen says that the wide net cast by the GWAS method may unveil entirely new genes that confer a risk of developing reading disabilities.

The new grant will also fund fMRI research on a subgroup of 200 subjects, which Gruen says will be the largest imaging-genetics study of dyslexia to date. While juggling these multiple scientific endeavors, Gruen keeps his eye on the prize of an eventual genetic test for dyslexia. “Unfortunately a lot of kids, possibly as many as a third, are missed—either misdiagnosed or not diagnosed at all. Now you’ve got a kid who hits fourth or fifth grade and they’re struggling; their self-esteem begins to diminish, and it almost becomes a self-fulfilling prophecy,” Gruen says. “If you can identify these kids early, by third grade, and get them into an intervention program, you can frequently get them reading up to grade-level, and that effect is long-last- ing. That’s a wonderful thing.”

Gruen says that the School of Medicine, which combines scientific prowess with an interdisciplinary, collegial spirit, has been an ideal incubator for his ideas. “It’s all here,” he says. “It’s a unique confluence of strength in genetics, dyslexia, imag- ining and neurobiology. I don’t think, there’s another place where I could have been where this work would have come together like it has.”

Medicine@Yale March/April 2009 7 With support from the National Institutes of Health and the Connecticut Stem Cell Research Program, Diane S. Krause, M.D., Ph.D., professor of laboratory medicine and pathology and associate director of the Yale Stem Cell Program, is studying bone-marrow cells that differentiate into cartilage, bone, muscle, lung and liver tissues. Here, lung tissue from a male mouse is stained for the Y chromosome (yellow dots). CD163+ blood cells (red), and the tyrosinase-related protein 2 (green) and cytokeratin-positive cells (green) (courtesy of Diane Krause).
Innovative teacher, RNA expert is new Ford Professor

Michael J. Caplan, M.D., Ph.D., professor of cellular and molecular physiology and of cell biology, has been named the C.N.H. Long Professor of Physiology.

Caplan is renowned for his research on the sorting and trafficking of ion transport proteins in epithelial cells, “polarized” cells in which the positioning of various transport proteins in different regions of the membrane is crucial to their proper function. His laboratory team focuses on identifying the proteins that interact with ion transporters to determine their localization and trafficking properties. His research group also studies two genes that are mutated in polycystic kidney disease and the unique trafficking processes that govern the distributions of polycystin-1 and -2, the proteins encoded by these genes.

Currently the inaugural chair of the Department of Cellular and Molecular Physiology, Caplan has been honored with numerous awards for his scientific contributions, including the School of Medicine’s Charles W. Bohm Falk Lecture Prize, the Young Investigator Award Lectureship of the American Physiological Society, the Young Investigator Award from the American Society of Nephrology, a fellowship from the David and Lucille Packard Foundation, and a Science Foundation National Young Investigator Award, among others.

An associate editor of the journal Physiologist, Caplan is also on the editorial boards of many other scientific journals, including the American Journal of Physiology: Renal Physiolog, the Journal of the American Society of Nephrology, and The Journal of General Physiology. He serves on the scientific advisory boards of the American Society for Cell Biology, the American Society for Biochemistry and Molecular Biology, and the National Institutes of Health study sections.

New Duberg Professor explores the brain’s intricate networks

David A. McCormick, Ph.D., an expert on the cellular networks of the brain’s cerebral cortex and thalamus, has been named Dorys McConnell Duberg Professor of Neuroscience. Recently, McCormick and colleagues discovered that synaptic communication within the cortex operates in both an analog and digital mode, and his lab is currently investigating how axons and synapses may operate in this regime. He is also studying rapid forms of plasticity of the visual cortex, the mechanisms by which the cortex generates changes in vision that allow for the perceptual “filling-in” of regions of visual space and help the visual system adapt to prolonged light stimulation. McCormick also conducts studies of the thalamus, a brain region involved in information flow to and from the thalamus, and in deep and consciousness.

A graduate of Purdue University, McCormick received his Ph.D. in neuroscience from Stanford University. He was a postdoctoral fellow at Stanford before joining the faculty in 1987 as an assistant professor in the Department of Neurobiology. He was named a full professor in 1994 and served as director of graduate studies in neurobiology from 1994 to 1999. McCormick has earned numerous honors for his research, including the John R. Whittier Award from the Committee to Combat Huntington’s Disease, the Donald B. Lindsey Award for Outstanding Research in Behavioral Neuroscience, the Jane and Peter Pattison Award, a Sloan Foundation Award, the Esther and Joseph Klingenfeld Fund Senior Investigator Award, a McKnight Foundation Investigator Award, the Yngve Zetterman Prize from the Swedish Physiological Society and a Jacob Javits Investigator Award from the National Institutes of Health.

McCormick is the associate editor of the journal Cerebral Cortex, among others, and a reviewing editor for Thalamic and Related Systems. He serves on the editorial board of Visual Neuroscience. He is a member of the Society for Neuroscience, the American Physiological Society and the International Brain Research Organization.

In addition, McCormick is an avid cyclist who rides with and serves as faculty sponsor to the Yale cycling team, winners of the Ivy League championship for the last three seasons. Dorys McConnell Duberg was the daughter of David Hall McConnell, founder of the Avon Corporation. After her death, her husband, H. John Duberg, established the Norman Dorys McConnell Duberg Charitable Trust—which has endowed several other professorships and fellowships, particularly at Johns Hopkins University—in her memory in 1981. H.J. John Duberg died in 1990.

Protein sorting, kidney disease are interests of Long Professor

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Protein basic to life is research focus of new Higgins Professor

Mark Hochstrasser, Ph.D., the newly named Eugene Higgins Professor of Molecular Biophysics and Biochemistry, is engaged in research at the crossroads of biochemistry and genetics aimed at understanding how specific proteins are rapidly degraded within cells while most others are not.

Using baker’s yeast as a model system, Hochstrasser and his laboratory team focus on ubiquitin, a fundamental regulatory protein found, as its name implies, throughout all cells and cell-like organelles. Among many other functions, ubiquitin tags proteins for destruction. Defects in the ubiquitin pathway have been linked to cancer, developmental abnormalities, Parkinson’s disease, Alzheimer’s disease and certain forms of mental retardation.

In related research, Hochstrasser is analyzing the function and dynamics of protein modification by other, ubiquitin-independent proteins. In particular, he is studying, called sumo, attaches to many other proteins and is crucial for progression of the cell cycle.

Hochstrasser holds two patents related to this work, which has been published in numerous scientific and medical journals, including Nature, the Journal of Cell Biology, Cell, the Proceedings of the National Academy of Sciences, Genetics and Nature Cell Biology.