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BRAIN RESEARCH INSTITUTE UCLA

Neuroscience News

Brain Awareness Week at BRI

"Alas, poor Yorrick...."
A student from Culver City Middle School contemplates a brain in a jar during the annual Brain Awareness Week hosted by the Brain Research Institute and organized by UCLA neuroscience students. Photo courtesy of Culver City Middle School. *Story, page 2*

In this issue:

Plus! Learning and Memory Special Section:

Message from Chris Evans, Director of the UCLA Brain Research Institute

While the Brain Research Institute (BRI) was formally founded 51 years ago, its roots go back even further. The founding members – Drs. John French, Horace Magoun, Donald Lindsley and Charles Sawyer – established monthly, then weekly meetings. Often held over dinner, these meetings were a place where scientists from UCLA working in the neurosciences could discuss their work. Neurologists, zoologists, marine biologists, and psychologists would talk, argue, learn, and collaborate.

The BRI today is far larger, but in this aspect, it is unchanged. The BRI is at its best when it is a place where great minds can meet and together create something new and unexpected.

The early dinner meetings gave way to journal clubs in which scientists with common interests could keep abreast of their fields. Over the years, journal clubs have formalized themselves into the BRI Affinity Groups. There are more than 20 at present, and they reflect the range of neuroscience research at UCLA. They encompass fields as diverse as addiction and neural repair or focus on specific model systems used in common by our members, such as the Zebra Fish Affinity Group.

Their activities vary according to their needs. Some meet on an ad hoc basis, others have weekly gatherings, and others organize regional symposia and invite speakers.

In the coming years, a number of the BRI Affinity Groups will be taking the next step as they become Integrative Neuroscience Centers (INCs). The centers will provide a more distinct identity for the different areas of excellence established by UCLA neuroscientists and will help build research communities around particular topics.

The first affinity group to make the leap will be the Integrative Center for Learning and Memory (ICLM), which will launch next year with an international symposium at UCLA. This special issue of *Neuroscience News* is commemorating the ICLM's creation with articles on the new Center and its research, as well as profiles on its current co-leader, Dr. Alcino Silva, and this year's Magoun Lecturer, Dr. Kelsey Martin. These distinguished researchers are deeply passionate about what they do, and the BRI is honored to count them as members and contribute to their research and investigations.

Brain Awareness Week Keeps Growing

This year's Brain Awareness Week (BAW) had more than 300 middle and high school students from the Los Angeles area visit UCLA neuroscience labs, speak to scientists, and learn about the brain. The annual event draws on the expertise of more than 60 student-volunteers and several BRI members and is designed to inform younger pupils on the wonders of the brain, while exposing them to neuroscience and neuroscientists.

Aida Attar and Sarah Madsen, both Ph.D. scholars in the Interdepartmental Graduate Program for Neuroscience (NSIDP) were the chief coordinators of this year's BAW.

"We try to reach a lot of Title I schools, as well as schools missed by Project Brainstorm outreach efforts," said Attar. Project Brainstorm sends UCLA neuroscience students to local schools to teach K-12 pupils about the brain but cannot schedule activities at all schools that show interest each year.

Attar said that during BAW, the students visiting are treated to a full day's schedule of activities. Starting in the Gonda (Goldschmied) Neuroscience and Genetics Research Center's first floor conference room, students make their way through six activity stations where they learn about a specific area of the brain's function.

"The best part was touching the brain – that was something I never thought I would be able to do. It was squishy and kind of gross – like chewing gum," said Navin Khenkaew, an eighth-grader from Le Conte Middle School in Hollywood. His classmate, Emily Hernandez, was also impressed by the brain and said the most impressive fact she learned was that if you get hit in the area of the back of the head, you can go blind.

Bonnie Anderson, a science teacher from Le Conte Middle School, was impressed by the BAW activities. "It's a great way to get students excited for high school. Any time you can give them hands-on activities that relate to their lives, they will learn a lot and engage with the lesson more."

Later in the day, students visited different neuroscience labs at UCLA to learn how research is conducted and to participate in hands-on exercises such as microscopy and pipetting. They were also treated to a career panel Q & A session with neuroscience students, academics, and private-sector scientists.

"At this age, they're making a lot of choices in their life. This experience will help guide them," said Raymond Owusu, an algebra teacher from Le Conte Middle School.

According to Attar, it isn't just the visiting students who benefit from participating in BAW. Her stable of volunteers was energized as well, signing up for extra shifts at the stations and in the labs.

"A lot of what we do in the lab doesn't pay off for months or years; it's delayed gratification. With the kids, you get the feedback right away. You see the immediate reward."

BRI Welcomes Carol A. Kruse, M.D., Ph.D.

Cancer Specialist to Collaborate with BRI Members at UCLA

Dr. Carol A. Kruse's arrival this year at UCLA from the Sanford Burnham Medical Research Institute in La Jolla, was a bit of a homecoming for the cancer researcher. She earned her Ph.D. from UCLA and continued her research career in Denver before moving to San Diego. Her lab focuses primarily on developing immune-cell therapies and gene therapies to treat brain cancers. She collaborates with neurosurgeon and fellow BRI member, Dr. Linda Liau (profiled Fall 2010). Preclinical findings from her lab are being translated into a Phase I dose-escalation trial, in which donated white blood cells from healthy individuals are "trained" to attack brain tumors.

Enrolled patients are given injections of cells called alloreactive cytotoxic T lymphocytes (CTLs) directly into the resected beds of the brain tumor. Dr. Kruse and her team make the immunotherapeutic CTL and perform the correlative laboratory- and immune- response experiments following treatment, while Dr. Liau treats the patients.

"Patients come in for infusions every other month, and we use different donor cells every time, so the tumor cells aren't able to develop resistance," explains Dr. Kruse.

Dr. Kruse decided to come to UCLA because she and Dr. Liau have been awarded a National Institutes of Health (NIH) grant to pursue this therapy. She explained that investigations in the 1990s had shown some success on patients for whom no other medical therapy was effective. One of six patients survived 40 months after starting treatment, and two others are still thriving today.

Kruse uses glioma cell cultures as a model system, in addition to mouse and rat or human xenograft brain tumor models. In one project they are evaluating CTL generation when dendritic cells at various activation states are induced using nanoparticles to deliver pathogen-associated molecular pattern molecules. Another study is focused on combining innovative cellular and gene therapy approaches. Kruse's lab is engineering alloreactive CTL to deliver replication competent retroviruses within the brain to reach the infiltrating tumor cells. The retroviral vectors code for "suicide genes" causing the transduced tumor cells to die when the pro-drug is administered. The translation of the combined treatments may be available in a few years, providing badly needed treatment options for brain tumor patients.

In addition to being able to work more closely with Dr. Liau, Dr. Kruse said that the BRI and UCLA provide an excellent collaborative environment.

"It's an opportunity to work with researchers and clinicians who are in similar fields." Dr. Kruse also collaborates with Dr. Robert Prins and Dr. Noriyuki Kasahara at UCLA.

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BRAIN RESEARCH INSTITUTE UCLA

Local Student Wins National Brain Bee

Brain Research Institute, USC Zilkha Neurogenetic Institute, and L.A. City College Sponsor Qualifying Event

The neuroscience communities of UCLA, USC, and Los Angeles City College congratulate Thanh-Liem Huynh-Tran, winner of the 2011 National Brain Bee held in Maryland. Besting 41 competitors from across the country, the eleventh-grader from the Cate School in Carpinteria, California, won a scholarship, an internship with a working neuroscientist, and the opportunity to compete as the U.S. representative in the International Brain Bee in Florence, Italy, in July.

Huynh-Tran qualified by winning the Los Angeles Brain Bee in January, beating 28 competitors. The annual event is co-sponsored by the BRI and the Zilkha Neurogenetic Institute and is coordinated by and held at Los Angeles City College.

Huynh-Tran's main reason for entering the competition was for the eight-week internship with a scientist at the NIH, but he is nervous about his upcoming trip to Italy. "America's had a winning streak for a while, winning almost 10 competitions," he told Santa Barbara's *Independent*. (Photo courtesy Le-Thanh Tran)

"I would like to congratulate Thanh-Liem for his accomplishment. We're very happy for him but not surprised; it was clear, seeing him in action here, that he had the capability to go much further in this competition," said Dr. Chris Evans, BRI Director. The BRI also sponsored the travel expenses for Huynh-Tran and one of his parents to Maryland.

The Los Angeles Brain Bee is a neuroscience competition for high-school students designed to test their knowledge, wit, and comprehension of brain facts and principles. The Brain Bee also features entertaining lectures and art displays. Amy Sweetman, a Professor of Psychology at Los Angeles City College, is its founder and organizer in Los Angeles. The event helps her teach neuroscience concepts but goes far beyond that level.

"I feel that understanding how the brain works not only helps us to understand ourselves, but also promotes empathy and tolerance for others, as we become aware of the reasons for differences in perception, the underlying causes of mental illness, and developmental cognitive changes that occur throughout the lifespan," she wrote in an email.

"I think Thanh-Liem's win will definitely help bring credibility to the Los Angeles Brain Bee. He will be representing the United States in Florence, Italy... We are extremely proud of his accomplishment and are very glad that we could help to spur on his studies in the field of neuroscience," she continued.

Among the judges were last year's winner, Christopher Hvroj; BRI Director, Dr. Chris Evans; BRI Associate Director for Outreach, Dr. Joe Watson; and USC's Dr. Jason Chan.. Dr. Chan's participation with BRI members was a natural extension of the many research collaborations between the two Institutes, according to Dr. Pat Levitt, Director of the Zilkha Neurogenetic Institute at USC.

"The joint sponsorship of the Los Angeles Brain Bee also reflects our common goal of promoting the burgeoning scientific interests of our best and brightest young students. Teaming up to support our Los Angeles teens, and for Thanh-Liem to win the national title, is a wonderful validation of this joint venture," said Dr. Levitt.

Together, the Brain Bee and its sponsors encourage interest in the brain and promote careers in biomedical research. The Los Angeles event is one of more than 70 Brain Bees that are held throughout the United States and one of only four held in the West.

To win the national event, Huynh-Tran had to demonstrate knowledge of brain sciences that included microscopy exercises, interpretation of an MRI, neuroanatomy quizzes, as well as written and oral examinations. The competitions were held March 18-19 and were interspersed with lectures from neuroscientists and visits to the University of Maryland's School of Medicine.

Le-Thanh Tran, Huynh-Tran's father, credited his son's accomplishment in part to the support he received from last year's local Brain Bee winner, Christopher Hrvoj, who took the time to prepare him for the rigors of the national competition.

"Chris pointed us to resources we didn't know about and gave us his old flashcards," said Tran. "This has been a true highlight for our family, one which we'll never forget."

BRI Presents Prizes at Los Angeles County Science Fair

In addition to sponsoring the Brain Bee, the BRI also awarded a prize at the annual Los Angeles County Science Fair, held from April 14-16, 2011, at the Pasadena Convention Center. This prize honors outstanding projects with neuroscience implications.

The 2011 award went to Alexa Aranjo, a junior from Chadwick School in Palos Verdes, for her project, "The Neurobiological Effect of Ginko Biloba on the Mouse Hippocampus." Aranjo also won the third-place medal in the animal physiology category. Honorable mention went to Soli Rachwal, Golden Rock School, for her investigation titled "Can Pill Bugs Learn." Both students received a certificate and a small cash prize in recognition of their efforts.

More than 1,000 youngsters participated in the Fair, now in its 61st year, making it one of the oldest science contests in the United States. It aims to encourage the application of creativity and critical thought to scientific problems. Submitted projects run the gamut of the sciences, from psychology to paleontology to engineering.

The judging process is quite rigorous. Entrants using human and vertebrate subjects must submit their research plans for approval months in advance and keep a daily log of their experiments. Contestants are expected to explain their work before a panel of judges.

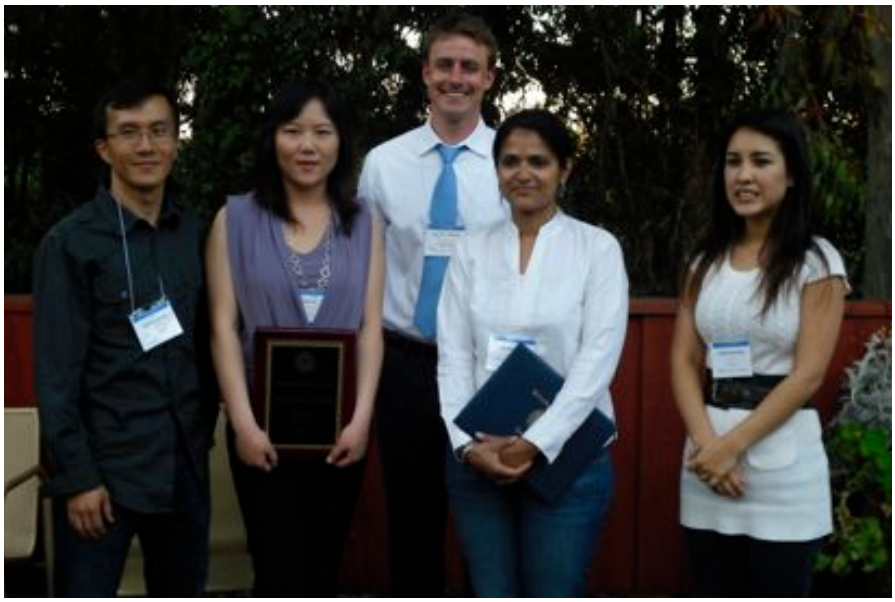
Want to match wits with Huynh-Tran? Here are a few of the questions he had to answer on his journey to Italy.

1) What enzyme extracted from a root can be used to study activity and connections within the nervous system?

2) Mutations in the gene for what receptor causes naturally occurring narcolepsy in two dog species?

Answers: 1) horseradish peroxidase 2) type 2 orexin receptor

UCLA Postdoctoral Awards



On May 12, 2011, a sizable contingent of BRI-affiliated postdoctoral scholars, students, and professors enjoyed food and music in the Faculty Center. There were nine BRI finalists for the Chancellor's Award for Postdoctoral Research this year.

Above: Award nominees (from left) Yossan-Var Tan, (mentor, Dr. James Waschek), Xue Hua (mentor, Dr. Paul Thompson), Zachary Taylor (mentor, Dr. Warren Grundfest), Tina Mukherjee (mentor, Dr. Uptal Bannerjee), and Nanthia Suthana (mentor, Dr. Itzhak Fried). Not pictured are nominees Adrian Cheng (mentor, Dr. Carlos-Portera Cailliau), Sandra Rieger (mentor, Dr. Alvaro Sagasti), Katharina Schlacher (mentor Dr. Hong Wu), and Geng Wang (mentor, Dr. Carla Koehler).

Right: Dr. Hua (with mentor Dr. Paul Thompson) was one of five UCLA fellows university-wide to receive the Chancellor's Award. She delivered a touching thank you speech that spoke of her gratitude for her lab colleagues and Thompson's mentorship.

Neuroscience Quotables

"People... thought a concussion was a psychological phenomenon... if you could play through the pain of an injured shoulder, you should play through the pain of getting your bell rung."

~ Dr. David Hovda, on concussions in sports in the *Toronto Star*

"When the protesters come to my house, they chant: 'We will never give up.' But neither will I."

~ BRI Associate Director for Research, Dr. David Jentsch, who has been a target of violence from animal rights activists, in *The Chronicle of Higher Education*

Congratulations

Nancy Wayne, Ph.D., to Become Associate Vice Chancellor for Research

BRI member, Dr. Nancy L. Wayne, Professor of Physiology in the David Geffen School of Medicine at UCLA, has been appointed Associate Vice Chancellor for Research. Her appointment, which will become effective July 1, 2011, was announced by Vice Chancellor for Research, Dr. James S. Economou.

Dr. Wayne will focus primarily on laboratory safety and will be responsible for communications with faculty to enhance the effectiveness of such programs and policies effecting researchers in more than 3,000 labs on campus. She also will work closely with Environment, Health & Safety and other groups on campus in improving compliance with state- and federally mandated safety regulations.

A reproductive neuroendocrinologist who joined UCLA in 1992, Dr. Wayne is an active member of the BRI's Laboratory of Neuroendocrinology. Her research is focused on understanding cellular and molecular mechanisms by which neuroendocrine cells respond to internal and external signals and how these neurophysiological responses influence reproductive behaviors.

Tom Otis, Ph.D., Awarded Grant for Brain Microscope Facility

With broad support from the neuroscience community including the BRI, Dr. Thomas Otis, Professor and Vice Chair of Neurobiology in the David Geffen School of Medicine at UCLA, has received a $600,000 grant from the National Center for Research Resources to build a new microscope system for studying brain cells and brain circuitry. Boosted by UCLA's contribution of $90,000 to buy the technology, the grant will create a state-of-the-art facility shared by faculty in neurobiology, physiology, biological chemistry, and the Jane and Terry Semel Institute for Neuroscience and Human Behavior at UCLA..

The microscope's advanced optical technology will enable parallel manipulation and measurement of neurons' activity within specialized circuits in the brain. The system will also permit the sophisticated tracking and precise manipulation of optically tagged signaling proteins in cell-biology experiments.

Shuo Lin, Ph.D., and Yi Sun, Ph.D., Awarded Stem Cell Grants

BRI Members Drs. Shuo Lin and Yi Sun were among six UCLA faculty to receive a total of $8 million in grants from the California Institute of Regenerative Medicine (CIRM) to investigate basic mechanisms underlying stem-cell biology and differentiation. Drs. Lin and Sun are also members of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA.

Dr. Lin's grant will fund efforts to develop a protocol for the differentiation of human embryonic stem cells into vascular-endothelial cells for the study and treatment of cardiovascular disease. Dr. Sun's project seeks to develop a new way to monitor the connectivity and function of transplanted neurons in vivo.

SPECIAL FEATURE: LEARNING AND MEMORY

Professors Alcino Silva, Ph.D., David Glanzman, Ph.D., and Michael Fanselow, Ph.D., are the directors of the new Integrative Center for Learning and Memory.

New Learning and Memory Center Long Time in Making

In some ways, the launch of the Integrative Center for Learning and Memory (ICLM) is to the cognition research community at UCLA as a hat is to the invisible man: making visible something amazing that was right there all along. The first of the BRI-affiliated Integrative Neuroscience Centers, the ICLM is capping off years of development in the BRI's learning and memory community, giving it an individual identity and cohesion that will guide future development.

"It essentially reflects the maturing of our learning and memory community, because we have been quite successful in terms of the national and international projection of this community," explains Dr. Alcino Silva.

"We are an official unit at the University now, giving us a certain status. It allows us to be a target for fundraising, it gives us a presence on the Web that is distinct, and it gives us a presence in the university's administrative structure."

Dr. Silva, along with Drs. David Glanzman and Michael Fanselow, has been guiding the development of the ICLM. Fanselow says that the administrative identity is a welcome change for the learning and memory community.

"The UCLA campus has one of the best, and largest, collections of researchers studying learning and memory in the world. But we are scattered among several different departments and units," explains Dr. Fanselow. "Many people outside of UCLA don't realize that we are here. Having the Center gives a single 'face' to the field and to the public, emphasizing the rich depth we have assembled to understand learning and memory."

Dr. Glanzman explains that the ICLM had a long gestation; it was first imagined in 1998 when the Gonda (Goldschmied) Neuroscience and Genetics Research Center first opened. It originally took shape with what was then called the Learning and Memory Project (LMP).

"When we formed the LMP—which was simply a loosely organized group of UCLA neuroscientists and psychologists whose research focused on the biology of learning and memory—Alcino, Michael, and I actually envisioned that there one day would be a formal center for learning and memory at UCLA. But at that time, we had no resources whatsoever (except for our enthusiasm and energy)," recalled Glanzman.

The LMP started with a journal club that still meets every Friday at 9:30 a.m. The academic networks built through it eventually led to the creation of a graduate course: The Biology of Learning and Memory. The largest single event the group organizes is the Southern California Learning and Memory Symposium. In its tenth year, it is valuable for students in the course and students and researchers at multiple Southern California universities and institutes, where all can network and learn together.

All of these activities will continue with the new ICLM, but it will now have dedicated funding of its own, rather than relying on support from disparate departments. Better still, the ICLM will have its own identity and will aid in recruiting students and attracting outside funding.

Dr. Glanzman said that while the learning and memory community is a notable strength within the University's neuroscience community, it is not the only one. The ICLM is reflective of the growth of neuroscience in the last few years, growth that will find some expression in the formation of the other planned Integrative Neuroscience Centers..

"Learning and memory represent one area of excellence in neuroscience at UCLA, but it's certainly not the only one. Other areas include imaging and neural circuits. The new Center will be a model for how to grow those areas at UCLA," he said.

SPECIAL FEATURE ON LEARNING AND MEMORY

Memories Are Made of These

Kelsey Martin, M.D., Ph.D., is the 2011 Horace Magoun Lecturer

The road that took Dr. Kelsey Martin from studying English literature at Harvard to delivering the 2011 Magoun Lecture at UCLA was more convoluted than most paths followed by her peers. According to Dr. Martin, whose studies on how memories are formed have broken new ground in the field, it all makes sense.

"What I liked about reading literature was the characters—why people are the way they are, why they react and behave the way they do. So essentially, what we study in my lab is the underpinnings of how our experiences change our brain circuitry to determine how we react to situations in the way that we do," she said.

There is still quite some distance from the character of Jay in *The Great Gatsby* to the character of RNA trafficking in the synapses in sea slugs, but Dr. Martin made the transition smoothly. Soon after her graduation from Harvard, she joined the Peace Corps in what is now the Democratic Republic of Congo, working on a project for maternal health. Child mortality was high, especially in October when measles would ravage the community. Dr. Martin's team established a vaccination program.

"That year, there were no measles, and it was almost like a conversion experience. I came back and decided to go to medical school," she said.

While working toward her pre-med requirements. Dr. Martin got a job studying HIV transmission in children, in the early years when the virus was not well-understood. Her interest in virology led to an M.D./Ph.D. project at Yale, studying how the influenza virus infects epithelial cells.

By the time she finished, she was determined that a research career was for her. "It's the stage where most people go on to do their residency, but it was really clear to me that I wanted to conduct research in the lab."

Dr. Martin took her interest in cell-trafficking mechanisms to Columbia University in the laboratory of Dr. Eric Kandel, a 2001 Nobel Prize winner who studies the molecular biology of learning and memory. The jump from viruses to memory was not as great as it appears, said Dr. Martin, as the question she was examining—how the viral material gets into the cell—was largely one of cell trafficking (i.e., how viral proteins and RNA are transported to the right destination within the host cell). In Dr. Kandel's lab, she examined the related question of how signals in neurons get to the nucleus. The implications of how those tiny proteins are shuffled and directed throughout our brains decided her career.

"What I work on—synaptic plasticity or how experience changes the connections between neurons in the brain, is essentially how our daily experience changes who we really are, because it changes the circuitry in our brain. It was something that is incredibly compelling to me. It's very challenging because our neural circuitry is so complex. But just trying to understand how our basic biology gives rise to cognition and memory felt like a very worthwhile endeavor," said Dr. Martin.

After being recruited to UCLA and joining the BRI in 1999, she continued her studies in synaptic plasticity.

The central mystery Dr. Martin seeks to unravel is how memories are formed. She explains that the neurons in our brain each have thousands of synapses that are present on cellular extensions that can reach quite a distance from the nucleus of the cell. In neuronal terms, a memory is formed when a particular sub-set of synapses is changed by a repeated pattern or strong stimulus. That change is caused by particular proteins, which in turn are manufactured by RNA. The RNA, however, comes from the cell's nucleus, which is, in cellular terms, both miles away and at the interchange of hundreds of synaptic highways. How does the RNA get activated over that distance and to the right target?

Dr. Martin enlists the help of *Aplysia californica*, a kind of sea slug. The relatively simple neuroanatomy of the marine creature, plus the large size of its neurons, makes it an ideal subject for studying synaptic plasticity. To study memory formation, she and her team use a simple reflex called the gill withdrawal reflex, for which the underlying neural circuit is well-known.

"If you shock the animal, the reflex is sensitized, and the animal has an enhanced gill withdrawal reflex," she said. The shock leads to the release of the neurotransmitter serotonin.

"The great thing is that we can put that whole mechanism in a dish, with a motor neuron and a sensory neuron, and they will form circuits.

Cont'd page 5

About the Magoun Lecture

The annual H.W. Magoun Lecture is the highest distinction the BRI bestows on its members. It is named in honor of the driving force behind the 1959 founder of the BRI, Dr. Horace "Tid" Magoun (1907-1991). Dr. Magoun is still fondly remembered as being deeply supportive of the work of others, while being reluctant to ever claim the limelight for himself. A respected neuroanatomist, he arrived in Los Angeles from the Neurological Institute at Northwestern University's School of Medicine. He was a firm believer in interdisciplinary research and teaching.

SPECIAL FEATURE ON LEARNING AND MEMORY

Martin, cont'd

And instead of shocking the animal, we can just put serotonin in the bath and get synaptic strengthening."

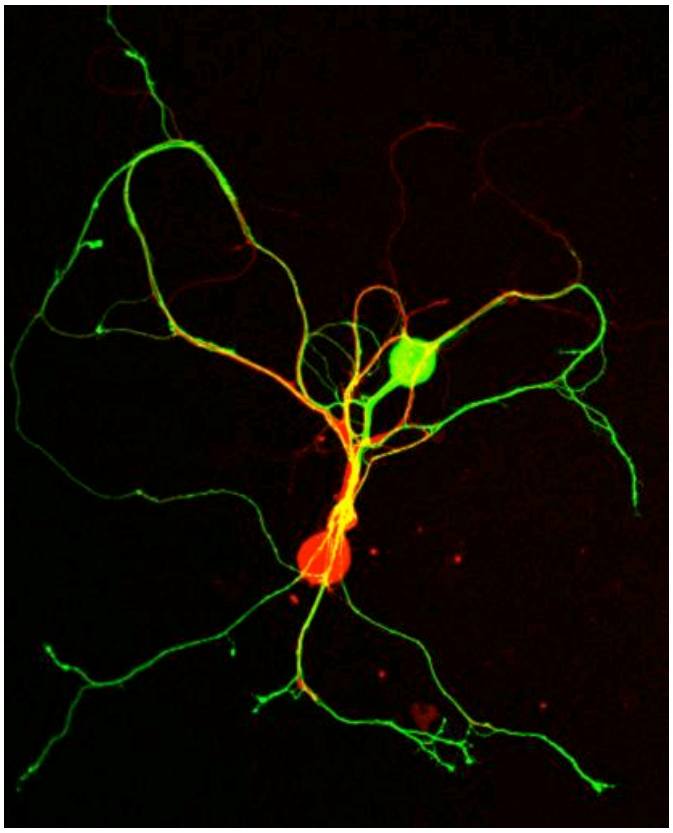
One of the more important discoveries to come out of the lab is the identification of a transcription factor that travels from stimulated synapses to the nucleus of the neuron in order to regulate RNA synthesis. "That's a very direct way of having the synapse communicate with the nucleus," said Dr. Martin.

It is not the only mechanism by which synapses will encode a memory. The neuron can cut out the nuclear middleman, so to speak. There are populations of RNAs that lurk in the synapses, and she has demonstrated that they can synthesize proteins in a highly localized fashion, which creates synaptic specificity in memory formation. "That you can get local protein synthesis at a particular site had not been shown previously," said Dr. Martin.

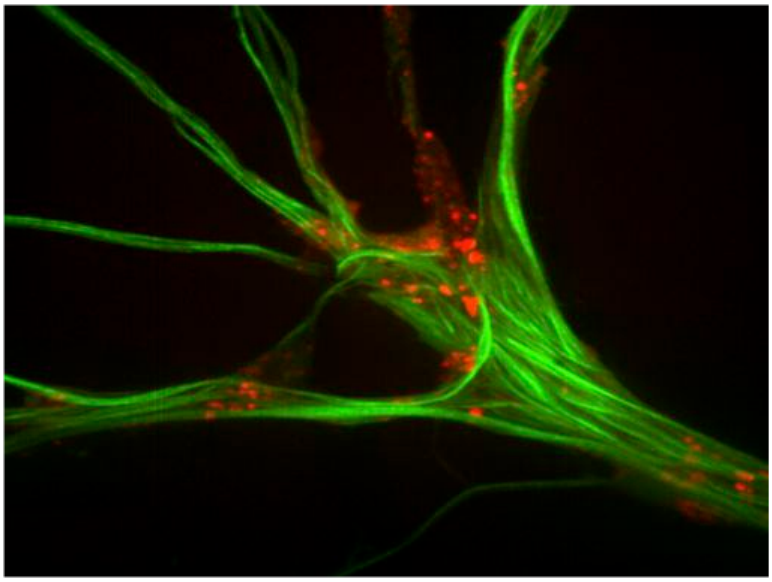
Every answer leads to new questions, and the investigators are busy trying to identify the specific proteins and molecules that are involved in the nuts and bolts of these processes—the RNA coding that controls delivery and signaling, the "train tracks" that shuttle the messengers around the cell. It's fine detail work, but Dr. Martin sees the forest through the synaptic branches and neuronal trees.

"I think it's important because we know from our experience it requires a certain plasticity in the brain to learn knew things: Part of the underlying mechanisms require that all of the parts of the neuron are able to communicate signals from the site of stimulation back to the cell body and that all the transport pathways work well," she said.

"We really want to identify what all of those molecules are, so that we can then see, for example, if any aspects of this intracellular communication are impaired in the aging brain. If we know how each step of communication happens, maybe we can target certain components of it."



A cultured *Aplysia* sensory neuron labeled in green makes synaptic contact with a motor neuron, which is labeled in red. Application of serotonin to this culture will strengthen the synaptic connection.



A high-magnification image of a cultured *Aplysia* sensory neuron in which the microtubules are labeled in green and a synaptically localized protein (VAMP) is labeled in red.

Microtubules are cytoskeletal elements that form tracks upon which molecular motor proteins transport proteins and RNAs throughout the neuron.

BRI drew Martin to UCLA

Dr. Kelsey Martin has been a member of the BRI as long as she has been at UCLA. The community and collaboration fostered within the BRI through the affinity groups, now being transformed into INCs, have had a direct impact on her work.

"The Learning and Memory Journal Club is one of the things that drew me here. There are more than 10 labs that participate, and it's an incredibly high-energy and interactive meeting," said Dr. Martin. "I have ended up collaborating with a lot of people in the journal club, like Dr. Tom O'Dell. When I need electrophysiology work conducted in the rodent brain, I can go to him, and in turn, he's taken advantage of our expertise in molecular biology."

Due to her enthusiasm for the Learning and Memory (L&M) Affinity Group, she established a group with BRI member Dr. Lawrence Zipursky called Synapse to Circuit (S2C). While the L&M affinity group is journal club in which the participants discuss published papers relating to cognition, the S2C involves the presentation and discussion of primary research data from the participating labs. The BRI creates an environment that encourages both approaches.

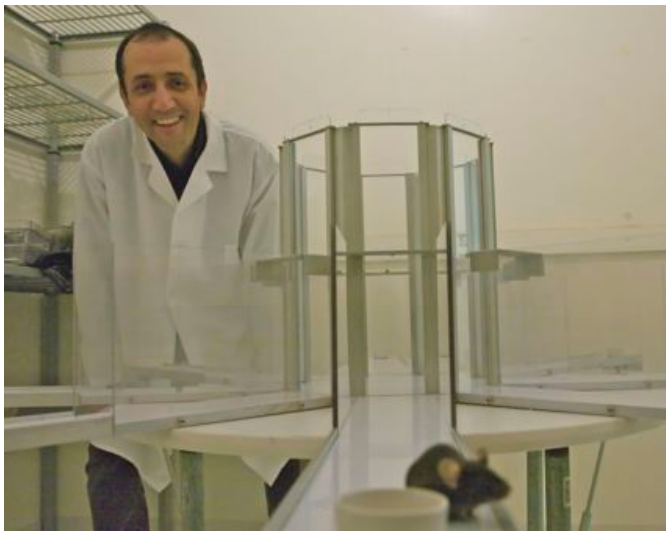
"Intellectually, for me and my lab, it's a great way to have a large and diverse community talk about what we're doing, get input on our research, and to learn from our colleagues," said Dr. Martin.

SPECIAL FEATURE ON LEARNING AND MEMORY

Silva lining: Working to Reverse Cognitive Impairments

There are few medical conditions more universally feared than mental impairments. To lose your ability to think or to remember is to lose something essential about you. That inherited versions of cognitive impairments are currently untreatable only adds to their menace.

Perhaps not for much longer, though, according to Dr. Alcino Silva. A pioneer in the field of molecular-cellular cognition, he believes that cognitive impairments are something that will be conquered. And he should know. His lab has developed treatments for two common inherited cognitive diseases, neurofibromatosis type 1 (NF1) and tuberous sclerosis (TS), now undergoing clinical trials.



"Yes we will be able to understand cognitive disorders. Yes we will be able to treat them," says Silva confidently. "If we can treat two neurological disorders, we might be able to treat many of them."

NF1 affects one in 3,000 people. It has a number of symptoms, including cognitive impairments. Patients experience spatial learning deficits, as well as difficulties in organizing information, attention problems, and motor deficits.

The gene that causes NF1 was identified in the lab where Dr. Silva was a postdoctoral fellow. Building on that discovery, he has studied a genetically modified mouse model that expresses the NF1 gene and shows a number of the same cognitive deficiencies as found in human NF1 patients.

Believing that this research might lead to a treatment for NF1's cognitive effects was going out on a limb. As Dr. Silva explains, "It was widely thought that neurological impairments were developmental and irreversible." His breakthrough came in treating them as a molecular-cellular problem of the adult brain. "Our work showed that we can reverse the learning problems of NF1 even when we treat adults. We do not have to start treatment during development," he stated.

"What we now know is that cognition is about genes and molecular, cellular, and systems processes, as well as the interaction between biology and environmental factors such as nutrition, exercise, and toxins," says Silva. "We are starting to understand cognition in the way that we understand immunology, that we understand development. There's a mechanistic basis to cognition."

In the case of NF1, study of the mutant mouse showed that the gene encoded a protein called neurofibromin. This protein regulates another protein called Ras, and this regulation is critical for the release of GABA, an inhibitory neurotransmitter, (a stop signal for synapses). Too much of it constrains the brain's plasticity and thus the ability to learn and adapt.

With this insight, Dr. Silva had a target, and was able to find a potential treatment that was already Food and Drug Administration (FDA)-approved. The drug was not psychopharmacological, but rather a statin—an anti-cholesterol medication, which decreases the lipids that are used to form cholesterol. Similar lipids are also used to modify the Ras protein that neurofibromin regulates, allowing Ras to attach to the neuronal cell membrane. Without those lipids, it cannot be where it needs to be to modulate GABA release, the ultimate cause for the cognitive impairments.

In Dr. Silva's mouse model, the statin treatment reversed the cognitive impairments caused by the NF1 mutation. Because statins are already approved as a safe drug for cholesterol reduction, clinical trials are already underway in the U.S. and Europe to test their efficacy in human NF1 patients.

Dr. Silva's success with NF1 led him to use a similar approach to investigate other diseases with cognitive impairment components. A treatment for tuberous sclerosis, also developed in his lab, is now undergoing clinical trials. He says that researchers are using a similar strategy to explore treatments for the cognitive deficits of common chromosomal disorders Fragile X and Down's syndrome, while he is investigating the roots of schizophrenia's cognitive effects.

Dr. Silva points out that as our population gets older, age-related cognitive deficits will become an increasingly important social and medical issue. There is no reason, he said, that molecular-cellular approaches to these deficits won't lead to solutions.

"It's just another piece of biology. If we can understand it, we can treat it. There's nothing mysterious about it," said Dr. Silva. "These diseases are horrible—schizophrenia, depression, Alzheimer's, Parkinson's. But I don't think it will be long before we have treatments that tackle the major causes of these disorders."

Support Behind the Science

Dr. Silva says that his breakthroughs in molecular-cellular cognition may not have been possible without support from Carol Moss Spivak. She directly underwrote his work on neurofibromatosis, buttressing the funding he received from the Children's Tumor Foundation and government sources. Ms. Spivak was part of his team in other ways as well; the UCLA alumna was a major supporter of the BRI's imaging facility, which bears her name. Through this specialized facility, researchers, including Dr. Silva and his team, are able to have access to equipment such as a two-photon microscope that allows the observation of how individual molecules are processed within single cells.

The imaging facility also boasts a number of other sophisticated equipment, including confocal and laser-scanning microscopes.

Neurofibromatosis type 1 (NF1): An inherited disease that affects one in 3,000 people worldwide. Patients typically have skin discolorations, larger-than-normal head sizes, skeletal abnormalities, and benign tumors called neurofibromas that appear under the skin. People with the condition are at higher risk for malignant tumors as well, including leukemia and they usually have learning disorders and a higher occurrence of attention deficit hyperactivity disorder (ADHD).

Tuberous Sclerosis (TS): An inherited disease caused by mutations in genes that encode tumor-suppressing proteins. It is characterized by tumor formation in the brain and other major organs. Roughly half of all TS patients also exhibit learning disabilities and autism.

GABA: An inhibitory neurotransmitter, whose purpose is to limit the firing of synapses in the brain.

Lipids: A type of molecule with a wide variety of functions involving energy storage, structural component of cell membrane, and cell signaling.

SPECIAL FEATURE ON LEARNING AND MEMORY

Aplysia Amnesia

Erasing Memories Could Help Victims of Trauma

Could veterans of war, rape victims and other people who have seen horrific crimes someday have the traumatic memories that haunt them weakened in their brains? In a new study, UCLA life scientists report a discovery that may make the reduction of such memories a reality.

"I think we will be able to alter memories someday to reduce the trauma from our brains," said the study's senior author, David Glanzman, a UCLA professor of integrative biology and physiology and of neurobiology.

The Eternal Sunshine of the Spotless Aplysia

The study appears in the April 27 issue of the *Journal of Neuroscience*, a premier neuroscience journal.

Glanzman, a cellular neuroscientist, and his colleagues report that they have eliminated, or at least substantially weakened, a long-term memory in both the marine snail known as *Aplysia* and neurons in a Petri dish. The researchers say they are gaining important insights into the cell biology of long-term memory.

They discovered that the long-term memory for sensitization in the marine snail can be erased by inhibiting the activity of a specific protein kinase — a class of molecules that modifies proteins by chemically adding to them a phosphate (an inorganic chemical), which changes the proteins' structure and activity. The protein kinase is called PKM (protein kinase M), a member of the class known as protein kinase C (PKC), which is associated with memory.

The research has important potential implications for the treatment of post-traumatic stress disorder, as well as drug addiction, in which memory plays an important role, and perhaps Alzheimer's disease and other long-term memory disorders.

"Almost all the processes that are involved in memory in the snail also have been shown to be involved in memory in the brains of mammals," said Glanzman, who added that the human brain is far too complicated to study directly.

PKM is rare in that while most protein kinases have both a catalytic domain, which is the part of the molecule that does its work, and a regulatory domain, akin to an on–off switch that can be used by other signaling pathways to shut off the activity of the kinase, PKM has only the catalytic domain — not the regulatory domain.

"This means that once PKM is formed, there is no way to shut it off," said Glanzman, who is a member of UCLA's Brain Research Institute. "Once it is activated, PKM's continual activity maintains a memory until PKM degrades."

Glanzman decided to study PKM in the marine snail, which has simple forms of learning and a simple nervous system, so that he could understand in precise detail how PKM's activity maintains a long-term memory, a process that is not well understood.

Glanzman and his colleagues — researchers Diancai Cai, lead author of the study; Kaycey Pearce; and Shanping Chen, all of whom work in his laboratory — studied a simple kind of memory called sensitization. If marine snails are attacked by a predator, the attack heightens their sensitivity to environmental stimuli — a "fundamental form of learning that is necessary for survival and is very robust in the marine snail," Glanzman said.

"The advantage of Aplysia," he said, "is that we know the neurons that produce this reflex; we know where they are in the nervous system."

The scientists removed the key neurons from the snail's nervous system and put them in a Petri dish, thereby recreating in the dish the two-neuron "circuit" — a sensory neuron and a motor neuron — that produces the reflex.

"The point is to reduce the problem so we can study on a fundamental biological level how PKM is maintaining long-term memory," Glanzman said.

They succeeded in erasing a long-term memory, both in the snail itself and in the circuit in the dish. They are the first scientists to show that long-term memory can be erased at a connection between just two neurons.

More here: http://newsroom.ucla.edu/portal/ucla/can-traumatic-memories-be-erased-202146.aspx

The Integrative Neuroscience Centers

The BRI is often called an umbrella organization for neuroscience on campus, but umbrellas can sometimes cast a shadow that hides those sheltered beneath it. "The planned launch of six new INCs is a step toward bringing the BRI's areas of particular research excellence into the light and highlighting the specific strengths of UCLA's neuroscience activities, said BRI Director Dr. Evans.

"The BRI is very big, and research is spread out between a large number of schools, institutes, departments and Organized Research Units, which sometimes makes it very difficult to see how all the components are contributing to the whole," said Dr. Evans. The INCs, by giving an institutional "face" to different areas of neuroscience, are designed to remedy this situation.

The proposed INCs have self-assembled either via the BRI's many affinity groups or by programs in other neuroscience-related departments. There are 21 BRI Affinity Groups, representing communities of scientists who share an interest in similar topics or techniques. Their activities include journal clubs, data presentations, and symposia but are largely informal in nature. Six INCs proposed at this point correspond roughly to the Focused Areas of Research (FARs) that guide curriculum options for the NSIDP. Dr. Evans explains that the new centers will be introduced in the coming years.

Evans explained that each INC will be able to develop their own identity. Each will have its own Website, and receive endowment support to organize symposia and seminars, as well as facilitate coordination and cooperation in their particular fields.

"The creation of the Websites will provide a more structured framework to understand and showcase the neuroscience community at UCLA," said Dr. Evans.

"The purpose of the INCs is to provide a working profile highlighting the diverse activities of the neuroscience community to potential students and the public."

Centers to Come

- Integrative Center for Learning and Memory
- Integrative Center for Neural Development, Degeneration, and Repair
- Integrative Center for Neurogenetics
- Integrative Center for Neuroimaging/Cognitive
- Integrative Center for Synapses, Cells, and Circuits
- Integrative Center for Addiction Neurobiology

Jason Stein: ARCS Scholar and 2011 Samuel Eiduson Lecturer

If Dr Jason Stein needed tips on delivering the 19th Eiduson Lecture, he needn't look far for advice. His supervisor, Dr. Paul Thompson, was the student honoree for the same award in 1998. As the BRI's chosen recipient of recognition for meritorious contributions to neuroscience by a graduate student, Dr. Stein is thrilled.

"It's such an honor. Paul gave this lecture when he was a student, so it means a lot to me. It's great to get this recognition. Most of your day is spent sitting in a lab, so this is a really nice reward," he said.

Dr Stein was scheduled to defend his doctoral thesis two weeks after this lecture, understates the reach of his work. Dr. Stein is collaborating with scientists around the world – from Australia to Norway to Indianapolis, using mathematical models to measure changes in brain structure that might identify genes responsible for neurodegenerative diseases.

"We're looking for changes across the entire genome and how they relate to changes in brain structure," said Dr. Stein. To do so, a consortium of researchers from 18 different sites around the world is performing detailed MRI scans of patients' brains, analyzed together with genetic samples from each individual.

Specifically, they are looking at the "endophenotype" of disease. By seeking correlations between specific genes and the volume of the hippocampus, they hope to identify genes implicated in brain disorders like Alzheimer's. The idea is a little bit like looking for levels of viral antibodies in the blood level to determine if someone has a cold virus, rather than looking for the sniffles.

"The hypothesis is that brain traits will be better for finding genes related to neurological disease than will the disease characteristics themselves. Diseases can be very heterogeneous – we don't know what makes up schizophrenia. We don't know what makes up Alzheimer's. So instead of looking at the disease entity itself, we're looking at hippocampal volume," explained Dr. Stein.

As it stands, to identify genes linked to disease takes roughly 20,000 samples. Dr. Stein hopes that the endophenotyping can cut this number by more than half, and thus speed up the process. Already, there has been some success; Dr. Stein has linked the GRIN2B gene to Alzheimer's through temporal-lobe volume, though that discovery is still awaiting replication.

Dr. Stein, a native of Ohio, studied at Northwestern University before working at the National Institute of Mental Health in Bethesda. It was there that he became familiar with the work of Professor Thompson and applied to conduct his Ph.D. studies at UCLA.

"Dr. Thompson really has the ability to combine new mathematical methods for analyzing images with a strong understanding of the underlying biology," said Dr. Stein, who was supported in his doctoral studies by the ARCS (Achievement Rewards for College Scientists) Foundation that provides scholarships to students with exceptional promise in areas of science, engineering, and medical research.

The **Samuel Eiduson Student Lectureship,** initiated in 1993, was named in honor of Dr. Samuel Eiduson (1918-2007) for his many years of dedication to the Interdepartmental Graduate Program in Neuroscience (NSIDP) and the BRI. A UCLA graduate and early member of the BRI, Dr. Eiduson was a driving force behind the establishment of the NSIDP and served as its chairman from its inception in 1972 until 1985. He is fondly remembered for championing many of the UCLA neuroscientists and graduates he knew, aiding them significantly in their careers. Each year, one student who has conducted especially commendable work during his/her thesis study delivers the BRI Eiduson lecture describing his/her work. Dr. Eiduson's support of such activities continues in the form of a planned gift to the BRI.

BRI Research Briefs Excerpted from the UCLA Newsroom

Potential Therapeutic Applications of Nanoscale Vaults

Jennifer Marcus| There's no question, drugs work in treating disease. But can they work better, and safer?

In recent years, researchers have grappled with the challenge of administering therapeutics in a way that boosts their effectiveness by targeting specific cells in the body while minimizing their potential damage to healthy tissue.

The development of new methods that use engineered nanomaterials to transport drugs and release them directly into cells holds great potential in this area. And while several such drug-delivery systems — including some that use dendrimers, liposomes or polyethylene glycol — have won approval for clinical use, they have been hampered by size limitations and ineffectiveness in accurately targeting tissues.

Now, researchers at UCLA have developed a new and potentially far more effective means of targeted drug delivery using nanotechnology.

In a study to be published in the May 23 print issue of the journal Small (and currently available online), they demonstrate the ability to package drug-loaded "nanodisks" into vault nanoparticles, naturally occurring nanoscale capsules that have been engineered for therapeutic drug delivery. The study is the first example of using vaults for this goal.

The UCLA research team was led by Leonard H. Rome and included his colleagues Daniel C. Buehler and Valerie Kickhoefer from the UCLA Department of Biological Chemistry; Daniel B. Toso and Z. Hong Zhou from the UCLA Department of Microbiology, Immunology and Molecular Genetics; and the California NanoSystems Institute (CNSI) at UCLA.

See More: http://newsroom.ucla.edu/portal/ucla/ucla-scientists-engineer-vaults-201567.aspx

Tobacco Smoking Affects Teens' Brains

Mark Wheeler| Tobacco smoking is the leading preventable cause of death and disease in the U.S., with more than 400,000 deaths each year attributable to smoking or its consequences. And yet teens still smoke. Indeed, smoking usually begins in the teen years, and approximately 80 percent of adult smokers became hooked by the time they were 18. Meanwhile, teens who don't take up smoking usually never do.

While studies have linked cigarette smoking to deficits in attention and memory in adults, UCLA researchers wanted to compare brain function in adolescent smokers and non-smokers, with a focus on the prefrontal cortex, the area of the brain that guides "executive functions" like decision-making and that is still developing in adolescents.

They found a disturbing correlation: The greater a teen's addiction to nicotine, the less active the prefrontal cortex was, suggesting that smoking can affect brain function.

The research appears in the current online edition of the journal *Neuropsychopharmacology*.

The finding is obviously not good news for smokers, said the study's senior author, Edythe London, a professor of psychiatry at the Semel Institute for Neuroscience and Human Behavior at UCLA.

"As the prefrontal cortex continues to develop during the critical period of adolescence, smoking may influence the trajectory of brain development and affect the function of the prefrontal cortex," London said.

In addition to London, study authors included lead author Adriana Galván, Christine M. Baker and Kristine M. McGlennen of UCLA and Dr. Russell A. Poldrack of the University of Texas at Austin.

See more: http://www.uclahealth.org/body.cfm?id=561&action=detail&ref=1611

BRI *After-hours*

Zombies party for bra-a-a-ins

Donations to the BRI come from many different people but certainly not flesh-eating undead creatures of horror. That fact changed on February 12 of this year, when the BRI was both proud and frightened to be a charitable partner of the third annual Zombie Prom.

Hosted by Los Angeles pop-rock band Saint Motel, the Zombie Prom is a rock concert for the post-mortal set, where music fans are encouraged to dress up in their finest prom dresses and gore-makeup. Saint Motel front man AJ Jackson says that the event was conceived as an alternative to Valentine's Day and has become bigger and bigger each year. "Turning it into a fundraiser for the BRI was a logical step," said Mr. Jackson.

"We thought 'zombies and brains.' It was a perfect connection," said the singer.

On the night of the concert, held in the historic Palm Court Ballroom of the Alexandria Hotel downtown, a sold-out crowd of 500 shuffling, bloody ghouls in search of skull gizzards and monster riffs showed up. They were met at the door by several students from the NSIDP who were overseeing a table stocked with a model brain and handouts about the brain.

Students and Saint Motel singer AJ Jackson, (fourth from left). Photo Angela Holtzen

The students were into the sprit of the event, dressed in fancy clothes and faux viscera. Several concert-goers stopped by the BRI table to check out the display, and many left contributions. Others made their donations through the purchase of premium VIP tickets, which earned them a goodie bag containing BRI-themed pencils, brain-shaped stress balls, and a calendar.

"We really enjoyed working with the BRI," said AJ, "We're looking forward to doing it again next year." The singer stopped by the table for a photo with the students and gave several shout-outs to the BRI from the stage.

Every Wednesday, students, staff, and researchers from the BRI-affiliated labs play a pick-up game of ultimate Frisbee on the intra-mural fields on the UCLA campus. Games are casual and a great way to build team spirit. Male and female players are welcome to come out. Contact Anna Taylor, ataylor1@ucla.edu, if interested.

Keep up-to-date on BRI-related news and discoveries by following us on Facebook: http://www.facebook.com/Brain.Research.Institute.UCLA and on Twitter: www.twitter.com/BRI_UCLA

BRI NEWSROOM

Excerpted from UCLA Newsroom

How Brain Corrects Perceptual Errors has Implications for Brain Injuries, Robotics

Stuart Wolpert |New research provides the first evidence that sensory recalibration — the brain's automatic correcting of errors in our sensory or perceptual systems — can occur instantly.

"Until recently, neuroscientists thought of sensory recalibration as a mechanism that is primarily used for coping with long-term changes, such as growth during development, brain injury or stroke," said Ladan Shams, a UCLA assistant professor of psychology and an expert on perception and cognitive neuroscience. "It appeared that extensive time, and thus many repetitions of error, were needed for mechanisms of recalibration to kick in. However, our findings indicate we don't need weeks, days, or even minutes or seconds to adapt. To some degree, we adapt instantaneously.

"If recalibration can occur in milliseconds, as we now think, then we can adapt even to transient changes in the environment and in our bodies."

In Shams' study, reported in the March 23 issue of the Journal of Neuroscience, 146 individuals, primarily UCLA undergraduates, performed what is known as a fundamental perceptual task. They looked at the center of a large screen that had eight speakers hidden behind it. Sometimes they heard only a brief burst of sound somewhat like radio static; sometimes they saw only a quick flash of light; and sometimes they both heard a sound and saw a light. They were asked to determine where the sound was and where the light was.

They participants, the researchers found, were much more accurate in determining where the light was than where the sound was.

While the subjects seemed to be *making* perceptual errors rather than *correcting* them, Shams stressed that this was an unnatural environment in which researchers artificially created a discrepancy between auditory and visual stimuli to show how quickly recalibration could occur.

In the real world, she said, recalibration would actually result in a *reduction* in errors in a person experiencing an auditory-visual discrepency due to a flaw in one of their senses.

This research could have implications for rehabilitation from brain injuries and could help in the development of prosthesis, when, for example, people get hearing devices and can use vision to guide their learning of how to localize sound. It also has implications for the design of robotic recalibration, which could be useful for aircraft as well as robots.

See more: http://newsroom.ucla.edu/portal/ucla/new-insights-into-brain-s-correction-193476.aspx

Lab safety Center a First

Phil Hampton | UCLA has created the University of California Center for Laboratory Safety to support research in this emerging field and facilitate the translation of results into best practices on the campus, as well as at other universities and research organizations.

The new center — believed to be the first of its kind in the country — aims to serve as a resource for other institutions, as UCLA emerges as a leader in developing programs intended to ensure safety in research labs. In recent months, dozens of universities, regulatory agencies, private research operations and trade organizations have sought detailed information about UCLA's lab safety programs and have requested presentations by campus personnel.

"At UCLA, our goal is nothing less than laboratory safety programs that are emulated by other major research universities, and the UC Center for Laboratory Safety is an important step forward on that path," Chancellor Gene Block said. "By developing and sharing best practices, we aid not only our own efforts but those of other University of California campuses and other institutions across the country."

One example of research to be conducted is an analysis of the effects of enhanced inspection, training and regulatory efforts on accidents and injuries at UCLA and other campuses, utilizing before-and-after data from multiple campuses.

"While we've made great progress in enhancing our lab safety programs, we need empirical data to demonstrate the impact on what's most important — the conditions in labs and the safety of those who work in them," said Nancy Wayne, UCLA associate vice chancellor for research overseeing laboratory safety, a position created in 2010 to enhance coordination between faculty researchers and campus regulators.

See more: http://newsroom.ucla.edu/portal/ucla/new-lab-safety-center-underscores-199640.aspx

In Memoriam: Fritiof S. Sjostrand, M.D., Ph.D. (1912 – 2011)

Dr. Fritiof S. Sjostrand, professor emeritus of molecular, cell and developmental biology, died April 6 at his home in Los Angeles at the age of 98. He was born in Stockholm and earned his M.D. degree in 1941 and his Ph.D. degree in 1945 from the Karolinska Institute.

Professor Sjostrand was an internationally recognized star in the area of electron microscopy and ultrastructural research. His work in the field of biological electron microscopy led to several pioneering developments and discoveries, the founding of a leading journal on the subject, and the development of strong research groups both in Stockholm and Los Angeles. A visiting professor at UCLA in 1959, Professor Sjostrand joined the Zoology Department faculty as a full professor in 1960. He used the electron microscope to describe details of cellular structure that anchor the current field of cell biology. Sjostrand dramatically improved techniques for ultrathin sectioning with minimal distortion and contributed the first high-resolution pictures of mitochondria and extensive 3-D reconstructions of the neural network in the retina.

Fritiof Sjöstrand became Fellow of the American Academy of Arts and Sciences in 1965. Among his many awards and recognitions over the years were the Anders Retzius Gold Medal in 1967, the Paul Ehrlich and Ludwig Darmstaedter Prize in 1971, and the Distinguished Scientist Award from the Electron Microscopy Society of America, which was presented to him on its 50th anniversary in 1992.

He is survived by his wife Birgitta, who currently works in the BRI's Electron Microscopy Services Center.