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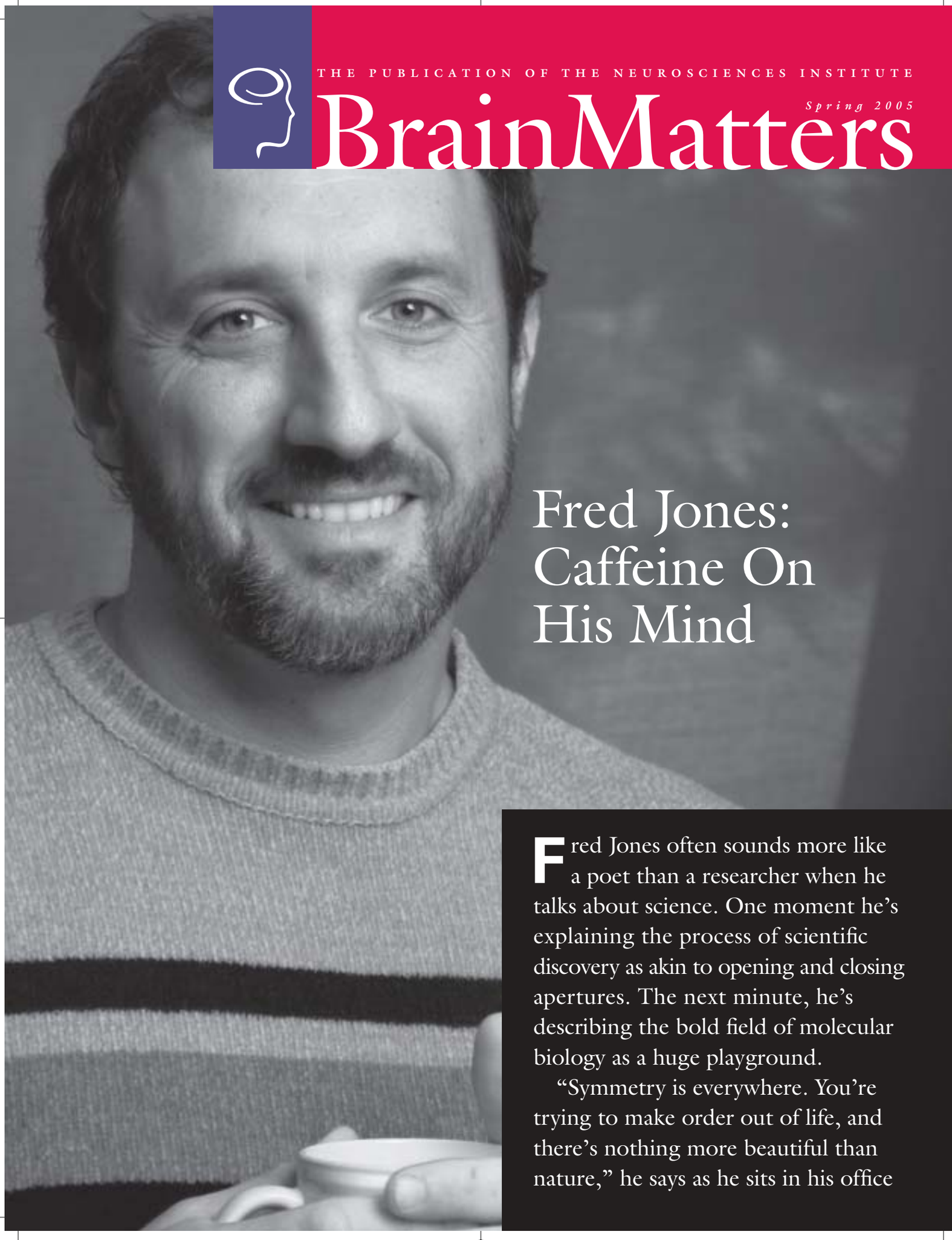


Fred Jones: Caffeine On His Mind

Fred Jones often sounds more like a poet than a researcher when he talks about science. One moment he's explaining the process of scientific discovery as akin to opening and closing apertures. The next minute, he's describing the bold field of molecular biology as a huge playground.

"Symmetry is everywhere. You're trying to make order out of life, and there's nothing more beautiful than nature," he says as he sits in his office

at The Neurosciences Institute. His passion and enthusiasm for his work are contagious.

"Science can be poetic. You're describing life. Whether you're a poet describing life through words or whether you're a scientist posing hypotheses and designing experiments to determine what nature has given you to observe," he says.

The Path to Neuroscience

Since he was a kid growing up in Massachusetts, Jones has been observing nature. He and his family spent many summers in Quissett Harbor, a community a mile or so north of the Woods Hole Oceanographic Institute. It was in this idyllic setting that he began to get an understanding of how a community of scientists could work together to tackle tough problems.

"I was privileged to be surrounded by academics, scruffy sailors, and patrons of the sciences. They all had in common a certain humility and reverence for nature. They were in awe, and they were all great at what they did," Jones recalls.

As an undergraduate at Yale University, Jones knew that he wanted to pursue a career addressing the big questions in science. He focused on how cells of the immune system communicate with each other at Yale, and then spent a few years after graduation working for a small biotechnology company in Westchester County, New York. "I knew that I needed to learn more about molecular biology to learn how to work with DNA," he says. "I wanted to understand how the cell surface talks to the DNA."

Jones's time at the biotech company piqued his interest to become an academic researcher. He was accepted to The Rockefeller University's graduate program in life sciences, and it was there that he first met Gerald Edelman, the founder and director of The Neurosciences Institute, who was also head of the laboratory of developmental and molecular biology at Rockefeller.

"I was drawn to Dr. Edelman's lab because he and his colleagues were focusing on a big question, namely, which molecules regulate cell-cell communication and determine the shape of the animal during development. He had won the Nobel Prize for his work in immunology in 1972, and he had branched out to explore arenas that required integrating several fields of inquiry," says Jones.

The two hit it off from the outset, and Jones became an integral member of Edelman's lab. "The collegial environment and fertile ground for discovery that Dr. Edelman fostered in the lab at Rockefeller brought back that same intense creativity I had seen as a boy in Cape Cod," says Jones. When the lab moved from New York to La Jolla in 1992, Jones moved with his colleagues, leaving his native East Coast for California to join The Scripps Research Institute as an assistant professor. Like his mentor Gerald Edelman, Jones was making connections between his work as a molecular biologist and the challenging field of neuroscience.

When The Neurosciences Institute asked Jones to become a research fellow in 2000, the answer was easy. For Jones, the Institute provides the ideal environment to pursue his far-reaching interests.

"It's a very interactive place. It gives me the opportunity to apply what I have learned thus far to explore different levels of neuroscience," he says. "Neuroscience is the synthesis of so many disciplines and you can learn so much every day."

"The large majority of drugs developed for Parkinson's don't work after awhile," says Jones. "Why do these drugs fail, and why do they fail in different ways for different people?"

Parkinson's Disease and Dopamine

At the Institute, Jones calls on his extensive background in molecular biology to understand how genes are expressed and regulated in the brain.

"Every day, ongoing events can influence your life. Since I'm a gene regulation person, that strikes me as very important," he says. "The big challenge for me is to try to understand how changes in environment or behavior or physiology have an impact on genes."

To understand the dynamic and complicated processes of gene regulation, Jones has chosen to focus on dopamine, a chemical that is produced by the body. As a chemical messenger, dopamine (similar to adrenaline) works by binding to specific receptor molecules on the nerve cell surface. Dopamine affects brain processes that control movement, emotional response, and the ability to experience pleasure and pain. Dopamine has also been connected to Parkinson's disease; people with Parkinson's have significant dopamine deficiencies.

Jones has a personal stake in deciphering the mysteries of dopamine and Parkinson's — his father has the disease.

"The large majority of drugs developed for Parkinson's don't work after awhile," says Jones. "Why do these drugs fail, and why do they fail in different ways for different people? If we understand how dopamine and its receptors are actually regulated, we might be better able to design better regimens for treatment."

The Caffeine Connection

With its connection to pleasure and pain, dopamine has been studied in the context of addiction and response to drugs ranging from heroin to cocaine. To get to the heart of understanding the complexity of dopamine on a systemic level, Jones chose to look at how caffeine — the world's most ubiquitous drug — affects regulation of the dopamine system. He's been working on the subject with Institute colleagues across a range of disciplines, from neurophysiology to gene expression.

"For the last three years, caffeine has been a major part of my interests," says Jones, who readily admits to having a morning cup of coffee. "It's the most widely used drug in the world, and we're using it more. And there are so many physiological associations you have with it. You can have euphoria, enhanced socialization, and creativity, or you can have anxiety if you have too much or if you're with the wrong group of people. It really changes the nervous system, depending on the behavioral context."

In studies with mice and cultured neurons, Jones and his colleagues have found that caffeine alters the number of dopamine receptors in the brain, and they believe that a thorough understanding of how caffeine affects the dopamine system could lead to new therapies for Parkinson's.

"The strategy of putting dopamine back into the system when Parkinson's patients don't have it can actually reduce the expression and signaling by the dopamine receptors. Dopamine replacement alone doesn't solve the problem — there's a balance here we don't understand," he says.

As Jones seeks to understand that balance, that symmetry in nature that he finds so challenging and elusive, he will continue to thrive at the Institute.

"I think that this Institute is uniquely poised to provide insights to basic but mind-blowing questions such as: 'How does the brain work?' We're humble enough to know that the answers may only be found in the chasms that exist between the knowledge of specialists. The only way to explore these gaps is to respect the unique paths we've all had to knowledge and always listen and learn from each other," he says.

For thousands of years, philosophers and scientists have been struggling with one of the most complex aspects of human behavior: sleep. "We must now proceed to inquire into the cause of why one sleeps and wakes, and into the particular nature of the sense-perception, or sense-perceptions, if there be several, on which these affections depend," Aristotle wrote in 350 B.C. It wasn't until 1953 that researchers identified rapid eye movement (REM) sleep, the state of sleep where we dream. Scientists across the world continue to seek to understand sleep, and they readily admit that there is a vast amount that we just don't know about this ubiquitous activity.

On a bright spring morning, four researchers at The Neurosciences Institute gathered to talk about sleep.

Institute fellows Joseph Gally, Ralph Greenspan, Douglas Nitz, and Bruno van Swinderen come from very different scientific backgrounds and bring divergent perspectives to the topic of sleep. *BrainMatters* asked them to have an informal, wide-ranging discussion about sleep, behavior, and consciousness.

Let's start with the big question. What are your theories about why organisms ranging from humans to flies need sleep?

Joseph Gally: Dr. Edelman and I have a proposed a theory called reapportionment, that is, that the day-to-day functioning of the nervous system requires movement of cellular components from one place to another, and that there needs to be a shutdown time when things get put back. What we'd like to know is what are the selective advantages of sleep. It seems so obvious that sleep is anti-advantageous. You would think that most organisms would do better if they could remain alert. However, it appears that over evolutionary time no animal has evolved a way of getting around sleep.

Ralph Greenspan: Or they have evolved to do other things while sleeping.

Gally: That's right.

Douglas Nitz: For me, one idea that I've been tossing around in my head for a number of years has to do with the strength of connectivity between cells in the brain. The combined slow wave type of electrical activity in the cortex during non-REM sleep results in an overall dampening of synaptic strength — the intensity of connections between nerve cells. If I wanted to be speculative, I would say that those changes produce the clarity of perception that one has upon waking from sleep. It's like moving the antenna around on a TV to get rid of that funky background.

Bruno van Swinderen: I would agree with a lot of what Doug is saying, but my angle is that I don't know much about the human brain. In a way it's a disadvantage because there's a lot of literature out there that I'm just not aware of in terms of its relation to sleep. But on the other hand it could be an advantage because maybe those things are not necessary for defining sleep in any organism. I see things on a much more operational level. You define sleep by an increased arousal threshold and decreased responsiveness to irritating stimuli. And sleep rebound (more sleeping than usual) follows sleep deprivation. That's pretty much it. I see sleep much more as an uncoupling of perception.

Greenspan: I have some ideas about sleep, but I wouldn't go so far as to call them theories. What interests me most about sleep is what it could tell us about the overall way that the brain organizes its function. If you consider sleep in the constellation of things that go on in the brain, there's a way of looking at what's happening during sleep that could actually shed light on what the brain is doing at other times.

The Z Factor

Among all human activities, our need to sleep remains, for the most part, a mystery. But Institute scientists are making steady progress in the quest to decipher the function of sleep.

What are the challenges for scientists who study sleep? How do you gather information about a process that is, by definition, unconscious?

van Swinderen: You introduced that word unconscious. The way I've been thinking about it lately is that when you sleep you're suppressing everything to a higher degree in terms of perception. And when you're awake, you're still suppressing everything except that one dynamic window of attention.

Nitz: But you do go from being conscious of something to conscious of nothing. There is a qualitative jump there.

van Swinderen: But now, when you're talking, you're completely unconscious of Joe. How's that lack of consciousness different than the lack of consciousness that comes out of sleep?

Nitz: I see your point, but I still think there is a qualitative jump when you go to sleep.

Greenspan: The notion of being cut off from the world is both a major qualitative and quantitative difference. What sleep may reveal to us is what goes on when the brain is talking to itself, which it does all the time. So maybe in REM sleep what you see is a kind of sampling of what it would be like if the brain were only talking to itself and not responding to the outside world at the same time.

What are the pragmatic benefits of studying sleep? How will your research shed light on our understanding of diseases and medical conditions?

Greenspan: There are two aspects of that question. One is what's it going to do for things having to do with sleep per se. And secondly what will it do for larger global questions about brain function and so on. Sleep gives you a different angle on understanding the way things are done in the brain. Chronic insomnia is a fairly major problem in the population and a fairly major component of things like chronic depression.

Nitz: With mood disorders, nearly every drug that's on the market today is something that alters the activity of neuromodulatory systems. There's definitely a link there to our studies of sleep and these systems. Another connection between sleep research and medical treatment will likely come from studies of how emotional memories are re-experienced in REM sleep. Here, it may be possible to determine the origins of REM sleep disturbance in those suffering from Post-Traumatic Stress Disorder.

What is distinctive and unique about the way The Neurosciences Institute approaches this complex topic of sleep?

Greenspan: We tend to think about sleep on all of these different levels at the same time. That's certainly a general feature of the way we approach things here, and it applies pretty well to this topic. We aren't satisfied with looking at just the molecular or the systems or the behavioral level. We really want to understand how these levels are linked and integrated.

Nitz: Here, one can have a conversation about consciousness and how sleep is a window to understanding it. Right in the same building is someone else who can talk about how particular neurons are firing and how that is compatible, or not, with your idea. To some extent, you can get that from reading a bunch of different scientific papers, but the give and take of science is much better in person.

van Swinderen: What makes this place different is that there's at least one representative from several different areas — somebody doing math, somebody recording from rat brains, somebody working on flies, somebody doing molecular biology. You're going to feel more comfortable collaborating with a friend than with someone to whom you're afraid you might look like an idiot. And when you break bread with colleagues here every day, that's conducive to that kind of collaboration.

Gally: Essentially all I know about nervous systems is what I learn from the people around me. With my background in biochemistry, I learn all that I can at this place about biology and behavior.

SPRING 2005

News & Events

"Minding the Arts"

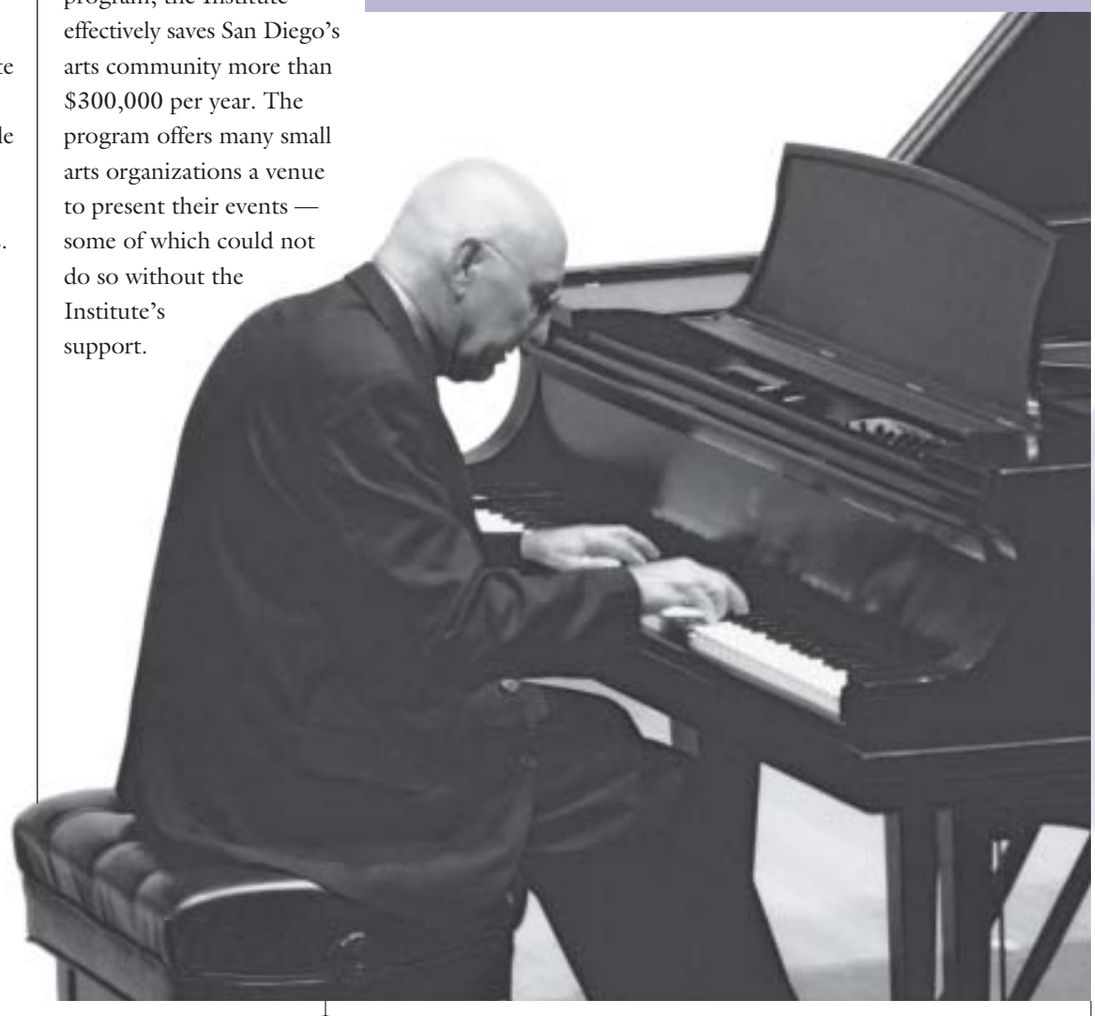
The Neurosciences Institute will hold its third annual "Minding the Arts" fundraising event to support its performing arts program on Sunday, September 25, 2005. Chaired by Linda Satz, with Audrey Geisel and Alexander Butterfield as honorary chairs, the 4–8 p.m. event will raise funds to allow the Institute to continue making its superb auditorium available at no charge to local not-for-profit arts and educational organizations. San Diego newscaster Michael Tuck will act as master of ceremonies.

"Minding the Arts" will include an outdoor cocktail reception amidst the stunning architecture of the Institute's campus on Torrey Pines Mesa, followed by a concert in the auditorium featuring the San Diego Opera Ensemble, Westwind Brass, and the Second Avenue Klezmer Ensemble. Local chefs will provide food and beverage stations.

Tickets to "Minding The Arts" are $150, and all proceeds from the event will be used to cover the costs associated with lending out the auditorium, including maintenance, security, energy, and staff support. Through its "Performing Arts at The Neurosciences Institute" program, the Institute effectively saves San Diego's arts community more than $300,000 per year. The program offers many small arts organizations a venue to present their events — some of which could not do so without the Institute's support.

Neurosciences Research Program

Every spring, the meeting of the members of the Neurosciences Research Program provides a unique opportunity for some of the world's preeminent researchers to converge at The Neurosciences Institute for three days of discussion about challenging issues in brain science. On March 6–9, scientists from as far away as Sweden, Mexico City, and Japan gathered at the Institute to talk about topics ranging from memory in primates to the neural systems underlying American Sign Language.



Storing Our Memories

Where are memories stored? Is a specific part of the brain responsible for our knowledge about a book you read last week or an experience you had as a first-grader? Or does the brain store memories in widely distributed networks?

Joaquin Fuster, M.D., Ph.D. (above), a pioneer in the field of memory, provided insights to these questions and others during a talk on March 15 at The Neurosciences Institute's Library Roundtable.

Fuster, a professor of psychiatry and biobehavioral sciences at the UCLA School of Medicine, has been making major contributions to our understanding of memory for more than four decades. In 1971 he described the first "memory cells" ever found in the primate brain. During his Roundtable discussion, Fuster made the case for a systems approach to memory, explaining that an interactive, overlapping network of nerve cells throughout the brain stores memories.

Fuster's research has wide-ranging implications for knowledge of the brain. By gaining a better understanding of these mechanisms, he argues, scientists can gain insights into the disorders of cognition at the foundation of many neurological and psychiatric disorders, including stroke, brain trauma, Alzheimer's disease, and schizophrenia.

Offered two to three times per year to the public, the Library Roundtable lectures at the Institute are delivered by leading figures in science and technology as well as in other fields that pertain to brain science.

From the Director

Scientists have been tempted to compare the operations of the brain to those of digital computers. A little thought on the matter suggests that this comparison is strained. In the first place, the number and combinations of signals coming from the environment are enormously more variable than most of those that we send into a computer. Moreover, the kinds and combinations of signals coming into our brains depend on both our body and our environment. At the Institute, we like to say that the brain is embodied and the body is embedded in the world around us. Unlike the unambiguous input to a computer, input to the brain is highly variable. Furthermore, as the brain develops, the establishment of its refined cellular wiring and connectivity is, to a large degree, individual — neurons that fire together wire together in enormous networks. All of this suggests that no two human brains, even those of twins, are identical: each brain reflects the history of an individual's path of experience. Those properties are products of evolution, which does not design such structures but selects them. Understanding the brain in these terms is an exciting challenge.

Research at the Institute explores the workings of the brain with freedom to inquire and excitement to find. As discussed in this issue, whether it is caffeine (which keeps you up as it alters your reward systems) or sleep in humans and insects, the world of neurobiology opens us up to the pursuit of marvelous trails of discovery.

Gerald M. Edelman, M.D., Ph.D.
Director

DONOR PROFILE

A Meeting of Minds

For Linda and Joe Satz of La Jolla, The Neurosciences Institute was a well-kept secret.

They knew little about the Institute until they met director and founder Gerald Edelman at an Institute function about three years ago. Dr. Edelman later took them on a tour of the Institute and began to talk with them about the organization's far-ranging research programs. For Joe, a tax attorney and member of The Price Group LLC, that conversation was the beginning of his relationship with the Institute.

"I was impressed with the creativity and the breadth of research taking place here," says Joe, who now serves on the board of the Neurosciences Research Foundation. "You need to have a flexible, innovative science institute that can explore basic questions about the brain."

For Linda, the Institute has a unique appeal — the connection between the arts and science. Active in the San Diego arts community, Linda has become integrally involved in the Institute's performing arts program. For two years, she has served as chair of "Minding the Arts," the Institute's annual fundraising event that attracts an eclectic blend of performers (see story on page 6).

"By offering its superb auditorium free-of-charge to the arts community, the Institute is truly providing an important gift to San Diego," she says.

Linda and Joe have clearly connected with the Institute, and they are committed to enhancing awareness about the Institute and its mission in San Diego and beyond. "We have had a chance to talk with the scientists, and they are doing research in areas that are very unique," says Joe. "We believe that there are great opportunities at the Institute for discoveries that will have important impacts on humanity."

Linda and Joe Satz

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