

MCGOVERN INSTITUTE

FOR BRAIN RESEARCH AT MIT

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A Sense of Timing

Behavioral experiments, brain recordings and computer models are all helping to explain how the brain processes time



FROM THE DIRECTOR

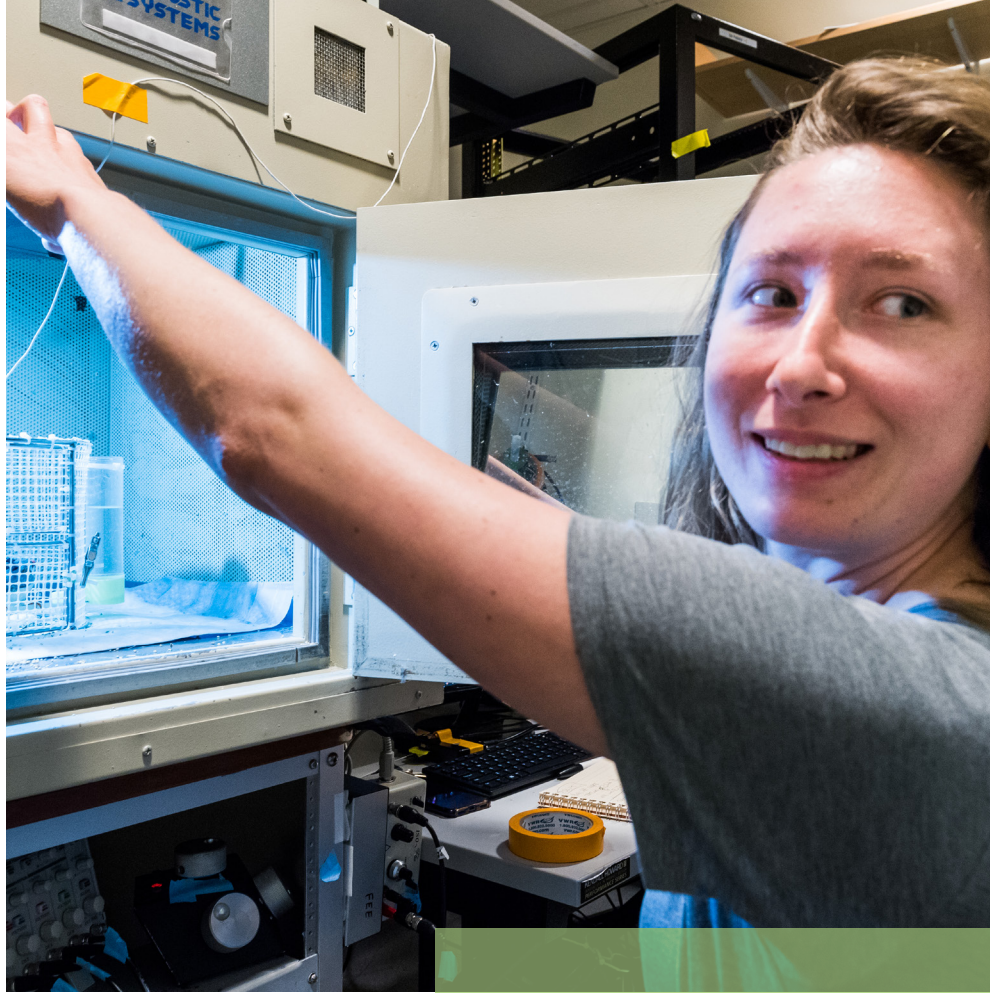
We know a great deal about how the brain detects physical stimuli—light, sound, touch, and so on—but how we sense the passage of time is still largely mysterious. As you can read in this issue, Michale Fee and Mehrdad Jazayeri are tackling this question, and are starting to uncover brain circuits that measure time and control the timing of actions. The two groups are studying different species using different techniques, but Michale and Mehrdad both come from engineering backgrounds, and in both cases their work illustrates the power of combining experiments with computational models—a trend that is becoming increasingly important as we grapple with the brain's enormous complexity.

In other news, we thank our longtime supporters Ted and Kay Poitras, who have made a new gift to support Ed Boyden's work (see page 6 of this issue). Ed and his colleagues have recently developed a new method for noninvasive brain stimulation, with potential clinical applications for many different disorders. Ed's original work was performed in mice, and the new funding will enable him to collaborate with clinical colleagues to begin testing in humans. Ed's study was published only a few months ago, and Ted and Kay's gift provides a wonderful example of how philanthropic support allows us to respond quickly to new opportunities as they arise.

Bob Desimone, Director
Doris and Don Berkey Professor
of Neuroscience

*On the cover:
Musical performance, like many skilled actions, involves complex and precisely timed movements. McGovern researchers are studying the circuits that underlie the brain's ability to process time.*

Image credit: Shutterstock / isaxar



How we sense the passage of time and control the timing of our actions is one of the great mysteries of brain science. McGovern Investigators are working on multiple approaches to solve this challenge.

The ability to measure time and to control the timing of actions is critical for almost every aspect of behavior. Yet the mechanisms by which our brains process time are still largely mysterious.

We experience time on many different scales—from milliseconds to years—but of particular interest is the middle range, the scale of seconds over which we perceive time directly, and over which many of our actions and thoughts unfold.

"We speak of a sense of time, yet unlike our other senses there is no sensory organ for time," says McGovern Investigator Mehrdad Jazayeri. "It seems to come

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entirely from within. So if we understand time, we should be getting close to understanding mental processes.”

Singing in the Brain

Emily Mackevicius comes to work in the early morning because that’s when her birds are most likely to sing. A graduate student in the lab of McGovern Investigator Michale Fee, she is studying zebra finches, songbirds that learn to sing by copying their fathers. Bird song involves a complex and precisely timed set of movements, and Mackevicius, who plays the cello in her spare time, likens it to musical performance. “With every phrase you have to learn a sequence of finger movements and bowing movements, and put it all together with exact timing. The birds are doing something very similar with their vocal muscles.”

A typical zebra finch song lasts about one second, and consists of several syllables, produced at a rate similar to the syllables in human speech. Each song syllable involves a precisely timed sequence of muscle commands, and

understanding how the bird’s brain generates this sequence is a central goal for Fee’s lab. Birds learn it naturally without any need for training, making it an ideal model for understanding the complex action sequences that represent the fundamental “building blocks” of behavior.

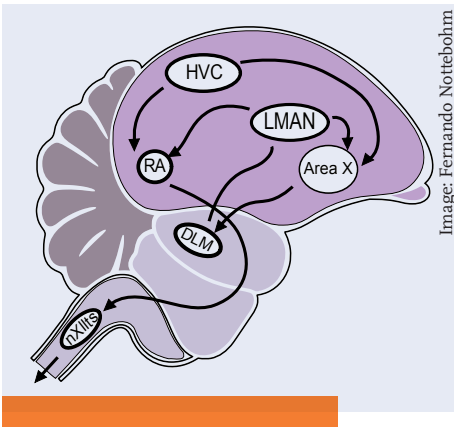
Some years ago Fee and colleagues made a surprising discovery that has shaped their thinking ever since. Within a part of the bird brain called HVC, they found neurons that fire a single short burst of pulses at exactly the same point on every repetition of the song. Each burst lasts about a hundredth of a second, and different neurons fire at different times within the song. With about 20,000 neurons in HVC, it was easy to imagine that there would be specific neurons active at every point in the song, meaning that each time point could be represented by the activity of a handful of individual neurons.

Proving this was not easy—“we had to wait about ten years for the technology to catch up,” says Fee—but they finally



Photo: Justin Knight

Emily Mackevicius (top), a graduate student in the lab of Michale Fee, studies how young zebra finches (below) learn to produce the precisely timed movements required for singing.



When a bird sings, a brain structure known as HVC sends precisely timed signals to downstream regions that control the vocal muscles.

succeeded last year, when students Tatsuo Okubo and Galen Lynch analyzed recordings from hundreds of individual HVC neurons, and found that they do indeed fire in a fixed sequence, covering the entire song period.

“We think it’s like a row of falling dominoes,” says Fee. “The neurons are connected to each other so that when one fires it triggers the next one in the chain.” It’s an appealing model, because it’s easy to see how a chain of activity could control complex action sequences, simply by connecting individual time-stamp neurons to downstream motor neurons. With the correct connections, each movement is triggered at the right time in the sequence. Fee believes these motor connections are learned through trial and error—like babies babbling as they learn to speak—and a separate project in his lab aims to understand how this learning occurs.

But the domino metaphor also begs another question: who sets up the dominoes in the first place? Mackevicius and Okubo, along with summer student Hannah Payne, set out to answer this question, asking how HVC becomes wired to produce these precisely timed chain reactions.

Mackevicius, who studied math as an undergraduate before turning to neuroscience, developed computer simulations of the HVC neuronal network, and Okubo ran experiments to test the predictions, recording from young birds at different stages in the learning process. “We found that setting

up a chain is surprisingly easy,” says Mackevicius. “If we start with a randomly connected network, and some realistic assumptions about the “plasticity rules” by which synapses change with repeated use, we found that these chains emerge spontaneously. All you need is to give them a push—like knocking over the first domino.”

Their results also suggested how a young bird learns to produce different syllables, as it progresses from repetitive babbling to a more adult-like song. “At first, there’s just one big burst of neural activity, but as the song becomes more complex, the activity gradually spreads out in time and splits into different sequences, each controlling a different syllable. It’s as if you started with lots of dominos all clumped together, and then gradually they become sorted into different rows.”

Does something similar happen in the human brain? “It seems very likely,” says Fee. “Many of our movements are precisely timed—think about speaking a sentence or performing a musical instrument or delivering a tennis serve. Even our thoughts often happen in sequences. Things happen faster in birds than mammals, but we suspect the underlying mechanisms will be very similar.”

Speed Control

One floor above the Fee lab, Mehrdad Jazayeri is also studying how time controls actions, using humans and monkeys rather than birds. Like Fee, Jazayeri comes from an engineering background, and his goal is to understand, with an engineer’s level of detail, how we perceive time and use it flexibly to control our actions.

To begin to answer this question, Jazayeri trained monkeys to remember time intervals of a few seconds or less, and to reproduce them by pressing a button or making an eye movement at the correct time after a visual cue appears on a screen. He then recorded brain activity as the monkeys perform this task, to find out how the brain measures elapsed time. “There were two prominent ideas in the field,” he explains. “One idea was that there is an internal clock, and that the brain can somehow count the

accumulating ticks. Another class of models had proposed that there are multiple oscillators that come in and out of phase at different times.”

When they examined the recordings, however, the results did not fit either model. Despite searching across multiple brain areas, Jazayeri and his colleagues found no sign of ticking or oscillations. Instead, their recordings revealed complex patterns of activity, distributed across populations of neurons; moreover, as the monkey produced longer or shorter intervals, these activity patterns were stretched or compressed in time, to fit the overall duration of each interval. In other words, says Jazayeri, the brain circuits were able to adjust the speed with which neural signals evolve over time. He compares it to a group of musicians performing a complex piece of music. “Each player has their own part, which they can play faster or slower depending on the overall tempo of the music.”

Ready-Set-Go

Jazayeri is also using time as a window onto a broader question—how our perceptions and decisions are shaped by past experience. “It’s one of the great questions in neuroscience, but it’s not easy to study. One of the great advantages of studying timing is that it’s easy to measure precisely, so we can frame our questions in precise mathematical ways.”



Graduate student Emily Mackevicius and Michale Fee.



Photo: Justin Knight

Merhdad Jazayeri studies the dynamic patterns of brain activity that underlie the perception of time.

The starting point for this work was a deceptively simple task, which Jazayeri calls “Ready-Set-Go.” In this task, the subject is given the first two beats of a regular rhythm (“Ready, Set”) and must then generate the third beat (“Go”) at the correct time. To perform this task, the brain must measure the duration between Ready and Set and then immediately reproduce it.

Humans can do this fairly accurately, but not perfectly—their response times are imprecise, presumably because there is some “noise” in the neural signals that convey timing information within the brain. In the face of this uncertainty, the optimal strategy (known mathematically as Bayesian Inference) is to bias the time estimates based on prior expectations, and this is exactly what happened in Jazayeri’s experiments. If the intervals in previous trials were shorter, then people tend to under-estimate the next interval, whereas if the previous intervals were longer, they will over-estimate. In other words, people use their memory to improve their time estimates.

Monkeys can also learn this task and show similar biases, providing an opportunity to study how the brain establishes and stores these prior expectations, and how these expectations influence subsequent behavior. Again, Jazayeri and colleagues recorded from large numbers of neurons during the task. These patterns are complex and not easily described in words, but in mathematical terms, the activity forms a geometric structure known as a manifold. “Think of it as a curved surface, analogous to a cylinder,” he says. “In the past, people could not see it because they could only record from one or a few neurons

at a time. We have to measure activity across large numbers of neurons simultaneously if we want to understand the workings of the system.”

Computing Time

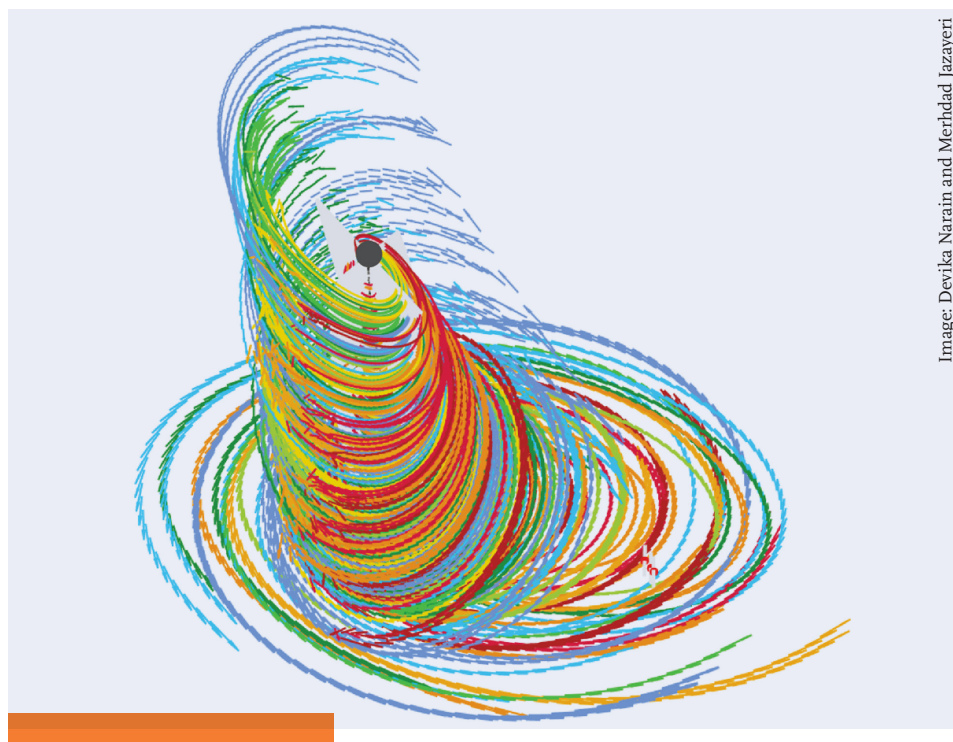
To interpret their data, Jazayeri and his team often turn to computer models based on artificial neural networks. “These models are a powerful tool in our work because we can fully reverse-engineer them and gain insight into the underlying mechanisms,” he explains. His lab has now succeeded in training a recurrent neural network that can perform the Ready-Set-Go task, and they have found that the model develops a manifold similar to the real brain data. This has led to the intriguing conjecture that memory of past experiences can be embedded in the structure of the manifold. Jazayeri concludes: “We haven’t connected all the dots, but I suspect that many questions about brain and behavior will find their answers in the geometry and dynamics of neural activity.”

Jazayeri’s long-term ambition is to develop predictive models of brain function. As an analogy, he says, think of a pendulum. “If we know its current state—its position and speed—we can predict with complete

confidence what it will do next, and how it will respond to a perturbation. We don’t have anything like that for the brain—nobody has been able to do that, not even the simplest brain functions. But that’s where we’d eventually like to be.”

A Clock Within the Brain?

It is not yet clear how the mechanisms studied by Fee and Jazayeri are related. “We talk together often, but we are still guessing how the pieces fit together,” says Fee. But one thing they both agree on is the lack of evidence for any central clock within the brain. “Most people have this intuitive feeling that time is a unitary thing, and that there must be some central clock inside our head, coordinating everything like the conductor of the orchestra or the clock inside your computer,” says Jazayeri. “Even many experts in the field believe this, but we don’t think it’s right.” Rather, his work and Fee’s both point to the existence of separate circuits for different time-related behaviors, such as singing. If there is no clock, how do the different systems work together to create our apparently seamless perception of time? “It’s still a big mystery,” says Jazayeri. “Questions like that are what make neuroscience so interesting.” ■



Devika Narain, a former postdoc in the Jazayeri lab, analyzed a neural network model that simulates brain activity during a timing task. The activity of a population of neurons can be described mathematically as a manifold, shown here in a 2D graphical representation.

Image: Devika Narain and Merhdad Jazayeri



Kay and Ted Poitras (center) with McGovern Institute director Bob Desimone.



Photo: Vilcek Foundation

Michael Halassa will join the McGovern Institute as an associate member in the fall of 2017.

New Fund to Support Non-Invasive Brain Stimulation

Our longtime friends and supporters Ted and Kay Poitras have created a new seed fund to support research into a novel method for brain stimulation, recently developed in the lab of Ed Boyden. This method, known as temporal interference, allows researchers to stimulate brain regions precisely and non-invasively, through the targeted application of rapidly changing electrical fields delivered to the surface of the head. The initial study, published in June, was conducted in mice,

and the new seed fund will enable Boyden to partner with clinical researchers to test it in human subjects. Temporal interference may offer an alternative to current techniques for deep brain stimulation, which require surgical implantation of intracranial electrodes. If successful, Boyden hopes the method could eventually form the basis of new treatments for disorders such as Parkinson's, depression and epilepsy. ■

Emilio Bizzi Becomes Emeritus Professor

We congratulate Emilio Bizzi on becoming an Institute Professor Emeritus at MIT. Bizzi is a founding member of the McGovern Institute, an elected member of the National Academies of Science and of Medicine,



Photo: Kent Dayton

Emilio Bizzi has become an Institute Professor Emeritus.

and a past president of the American Academy of Arts and Sciences. In a long and distinguished career, he has been a pioneer in the field of motor control, including the neural mechanisms that control eye movements, limb posture and motor learning. He has also played an important leadership role at MIT, overseeing the 1986 merger of the psychology department and the neuroscience program to form what is now the Department of Brain and Cognitive Sciences—one of the first university departments anywhere to reflect the deep connection between psychology and brain research. Although retiring from laboratory research, Bizzi will maintain an office at MIT, where he plans to write about his findings and theoretical insights from his many years of neuroscience research. He intends to remain actively involved with the McGovern Institute. ■

McGovern Institute to Welcome New Associate Member

Michael Halassa, who is currently a faculty member at New York University, joins MIT this fall. He will become an assistant professor in the Department of Brain and Cognitive Sciences, and will also join the McGovern Institute as an associate member.

Halassa's research is focused on the neural control of behavior, in particular the neural basis of attention and executive control. To study these questions, he has developed behavioral models of executive function in mice, allowing him to probe the underlying neural circuitry using a combination of behavioral testing, neurophysiological recordings and genetic manipulations. One of his current areas of interest is the thalamus, traditionally considered a "relay station" for sending sensory information to the cortex, but which is also important for the control of executive function, as Halassa's work has revealed.

Halassa, who is originally from Jordan, received his PhD from the University of Pennsylvania, and was a postdoc in the laboratory of Matt Wilson at MIT, while also doing a residency in psychiatry at Massachusetts General Hospital. He joined the NYU faculty in 2013. Halassa has received many awards, including the 2017 Vilcek Prize for Creative Promise, a national award given to immigrants who early in their careers have made "lasting contributions to American society through their extraordinary achievements in biomedical research." ■

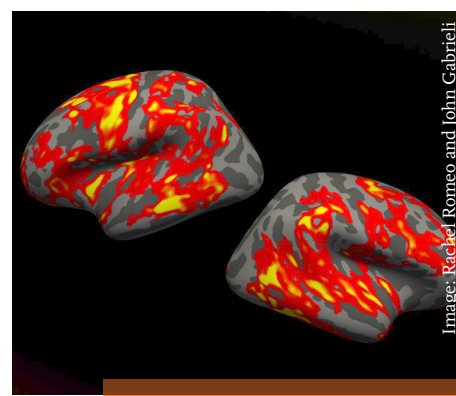
RESEARCH NEWS

Nancy Kanwisher has collaborated with clinical colleagues at Boston Children's Hospital to examine intracranial recordings in human patients undergoing epilepsy surgery. In this study, led by postdoc Leyla Isik, the researchers analyzed neural activity recorded via a grid of electrodes on the surface of the brain, as subjects watched movies. Based on these signals, the researchers could decode what the person was seeing at a given time—for example, whether there was an animal in the scene. By using movies rather than static images, Kanwisher and colleagues hope to come closer to understanding how the brain processes natural stimuli in an ever-changing real world.

Ed Boyden and colleagues have devised a way to image biopsy samples with much higher resolution than conventional methods—an advance that could help doctors develop more accurate and inexpensive diagnostic tests. The new technique, termed “ExPath,” relies on

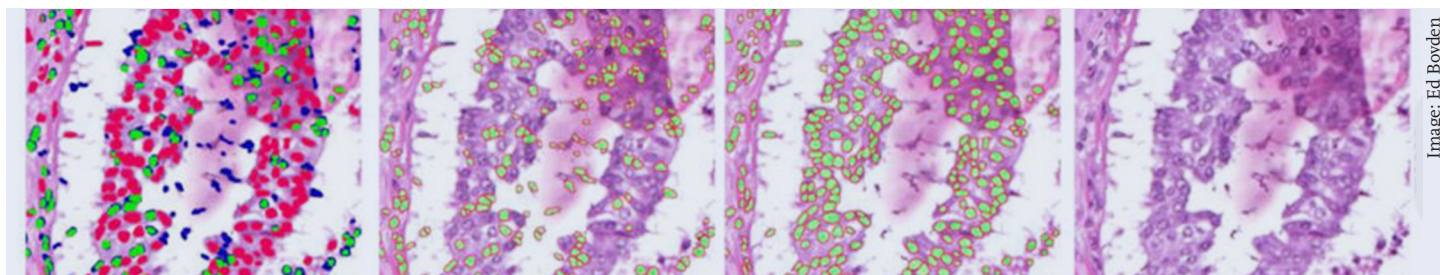
an approach known as expansion microscopy in which researchers expand a tissue sample to 100 times its original volume before imaging it. In their study, Boyden and his colleagues combine the ExPath technique with computational image analysis to distinguish early-stage breast lesions with high or low risk of progressing to cancer—a task that is difficult for pathologists using conventional microscopic methods.

Educators have devised a variety of interventions to try to help children with reading difficulties. Not every program helps every student, however, in part because the origins of their struggles are not identical. McGovern neuroscientist **John Gabrieli** is trying to identify factors that may help to predict individual children's responses to different types of interventions. He recently found that children from lower-income families responded much better to a summer reading program than children from a higher socioeconomic background. ■



Above: Red and yellow regions indicate brain regions that grew significantly thicker in reading-disabled children whose reading improved after an intensive summer treatment program.

Below: The ExPath technique reveals molecular information in biopsy samples that electron microscopes cannot provide.



AWARDS & HONORS



McGovern Investigator Feng Zhang.

Feng Zhang has been named a 2017 Laureate of the Blavatnik National Awards for Young Scientists. Established in 2007, the awards recognize the most promising scientific researchers aged 42 years and younger. Zhang is among three laureates who will each receive \$250,000 the largest unrestricted award of its kind for early career scientists. Zhang was recognized “for his role in developing the CRISPR-Cas9 gene-editing system and demonstrating pioneering uses in mammalian cells, and for his development of revolutionary technologies in neuroscience.”

Zhang has also been named a winner of the 2017 Albany Medical Prize, a \$500,000 award that is given annually “to those who have altered the course of medical research.” Zhang will share the prize with four other CRISPR researchers: Emmanuelle Charpentier of the Max Planck Institute; Jennifer Doudna of the University of California at Berkeley; Luciano Marraffini of The Rockefeller University; and Francisco Mojica of the University of Alicante. ■

EVENTS



McGovern researchers and staff roast marshmallows at the annual retreat in Newport, Rhode Island.

McGovern Institute Annual Retreat

On June 5–6, McGovern researchers and staff gathered in Newport, Rhode Island for the annual McGovern Institute retreat. The overnight event featured talks, a poster session, a Newport Harbor cruise (for those willing to brave the cool, wet weather) and a dance party. ■



Mentalist Jim Karol.

Famed Memory Expert Visits Institute

Jim Karol, the self-proclaimed “man with the world’s best memory,” visited the McGovern Institute on August 1 with USA Memory Championship founder Tony Dottino. Karol and Dottino participated in an entertaining seminar on memory organized by McGovern scientist Robert Ajemian. Video of this event can be viewed on our website. ■

■ *The McGovern Institute for Brain Research at MIT is led by a team of world-renowned neuroscientists committed to meeting two great challenges of modern science: understanding how the brain works and discovering new ways to prevent or treat brain disorders. The McGovern Institute was established in 2000 by Lore Harp McGovern and the late Patrick J. McGovern, with the goal of improving human welfare, communication and understanding through their support for neuroscience research. The director is Robert Desimone, who is the Doris and Don Berkey Professor of Neuroscience at MIT and former head of intramural research at the National Institute of Mental Health.*

Further information is available at: <http://mcgovern.mit.edu>

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