Brain SCAN

McGOVERN INSTITUTE
FOR BRAIN RESEARCH AT MIT

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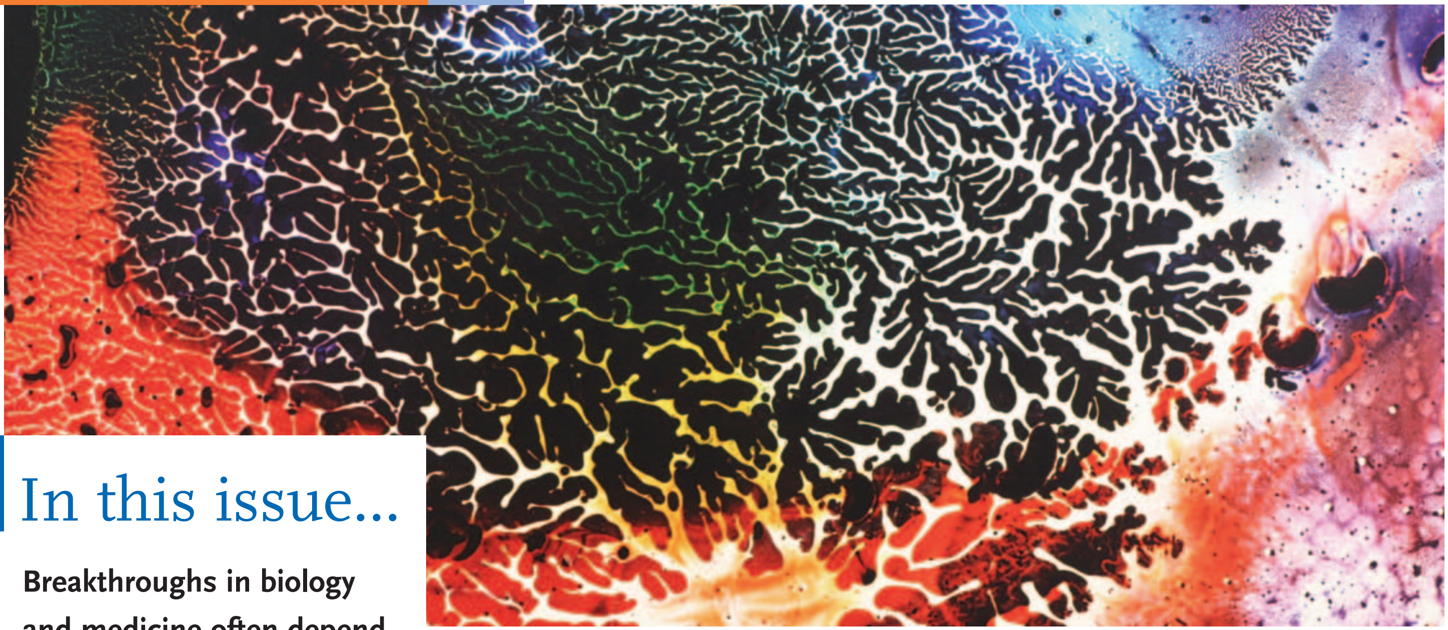


In this issue...

Breakthroughs in biology and medicine often depend on the development of new technologies.

I believe that neuroscience is now poised to take advantage of rapid advances in engineering, nanotechnology, genetics, molecular biology, and brain imaging devices. Those technologies will greatly enhance our ability to understand and treat major brain disorders. For those reasons, we at the McGovern Institute are excited about our new McGovern Institute Neurotechnology (MINT) program. The MINT program seeks to develop and implement advanced technologies in neuroscience and clinical research.

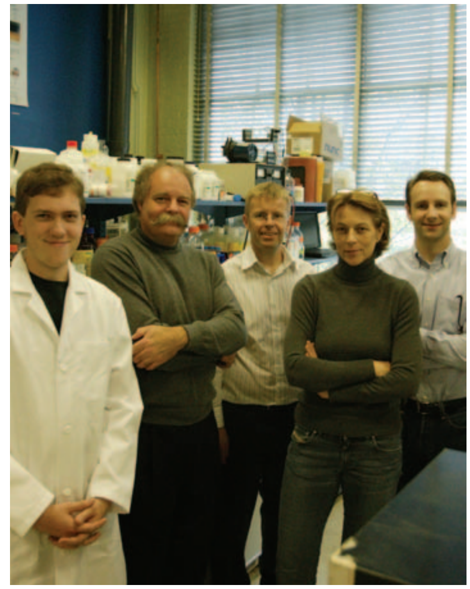
The McGovern Institute is embedded in a community with not only the most advanced technology available in the world, but also unparalleled clinical centers for investigating new approaches to brain disorders. The McGovern Institute does not itself contain a human genetics or clinical research component. However, we are developing relationships with the Harvard/MIT Broad Institute, the home of leading researchers in genetics, and with clinical sites such as McLean Hospital and Massachusetts General Hospital (MGH). These relationships give us the links we need to bridge genetic defects to clinical treatment. Likewise, our growing collaborations with engineering and material science departments at MIT give us access to people working at the cutting edge of areas such as nanotechnology, which will play a critical role in the medical devices of the future.

In this issue of *Brain Scan*, our feature article focuses on one of our first MINT collaborations, one with the Laboratory for BioInstrumentation at MIT under the direction of Professor Ian Hunter. Ian is a mechanical engineer who is keenly interested in applying nanotechnology and new materials to neuroscience and to drug development for neurological and psychiatric diseases.

The McGovern Institute is supporting graduate students and research scientists who are working with Ian and some of our McGovern Institute faculty in this nanotechnology effort. We believe this support can not only create revolutionary new neuroscience technologies, but also train the next generation of scientists who seek to bring these technologies to bear on important clinical problems.

Bob Desimone, Director

Above: Art inspired by cerebral cortex; Carol Pfeffer ©2006



The BioInstrumentation Laboratory Nanowire Team: Bryan Ruddy, Prof. Ian Hunter, Dr. Andrew Taberner, Dr. Cathy Hogan, and Dr. Patrick Anquetil. Absent: Giovanni Franzes.

NANOWIRES AND NEUROSCIENCE

Plastics. In the 1967 movie *The Graduate*, the young Dustin Hoffman listened skeptically to advice that plastics heralded the future of business and industry. Fast forward 40 years, and now plastics, technically called polymers, may mold the future of neuroscience.

That's thanks to the first McGovern Institute Neurotechnology (MINT) program, a collaboration between the McGovern Institute and MIT's Laboratory for BioInstrumentation, which is directed by Ian Hunter, the Hatsopoulos Professor of Mechanical Engineering. Three McGovern Institute investigators are currently involved in this program: Emilio Bizzi, Michale Fee, and Martha Constantine-Paton.

The collaborators are using tissue-like conductive polymers, dubbed nanowires, to study how learning and memory occur and how neural circuits are mis-wired in diseases like ALS or schizophrenia. They also hope these materials can help develop highly efficient and accurate drug screening and testing methods. These methods that may lead to new and long sought after therapies for developmental and degenerative diseases, mental illness, stroke, paralysis, and many other pressing needs.

Nanowires: Conductive Polymers

Conductive polymers are ultra-thin polymer threads that can carry electrical currents, forming a more flexible "wire" than any made out of metal. They have found their way into many fields, and Professor Hunter realized that they could benefit neuroscientists, too. Professors Bizzi, Fee, and Constantine-Paton hope these pliable wires can solve long-standing technical challenges in their labs.

"All advances in neuroscience have depended on advances in technology and engineering," said Bizzi. "Only by promot-

Emilio Bizzi

ing technological innovations for neuroscience can researchers make progress towards long-awaited treatments for brain disorders."

Recording Learning

For many decades, researchers have used electrodes for studying brain activity in living animals as they perform tasks. An electrode consists of a thin metal rod that rests on the neural tissue, where it detects changes in the electrical charges within neurons. It can also send a pulse into neurons to stimulate neural activity.

Electrode recordings work well when studying events that happen over the course of minutes or hours. As an example, Bizzi records from the motor cortex of frogs, turtles, and rats to learn how motor neurons orchestrate commands to move a subset of muscles with just the right force and torque to jump, swim, or run. He studies a phenomenon that's summed up in the adage: it's hard to learn to ride a bike, but once you learn, you never forget how. Bizzi investigates the changes that occur in the brain as we struggle to master complex motor skills that eventually become second nature. This process is not only handy, but at root it is key to any animal's survival. What if you had to think about how to put one foot in front of the other when running away from a lion?

Michale Fee uses electrodes to investigate something many people never associate with a motor skill: how youngsters learn to mimic the language of the parents. Think of how a baby's babbling gradually becomes recognizable syllables and then intelligible speech. To study the brain mechanisms involved in this process, he uses a rare animal model where neuroscientists can study learned behavior similar to language in humans: songbirds.

But conventional electrodes don't allow investigators to study longer-term events involved in learned behaviors. Electrodes don't stay near the same neuron very long, so it's impossible to track how that neuron's activity changes as an animal masters a skill. That's because, as Fee explained, the brain is floating in fluid and "sloshes" around inside the skull, while the electrodes are held rigidly to the skull. When the brain moves, the electrodes stay put and lose contact with the neurons they had been recording.

If investigators could record from the same neuron over longer periods of time, they could ask such question as: Where does learning actually occur? What happens to patterns of neural activity as a function of learning? Are the neurons completely devoted to a new function or do they multi-task? How long do they devote themselves to a new task?

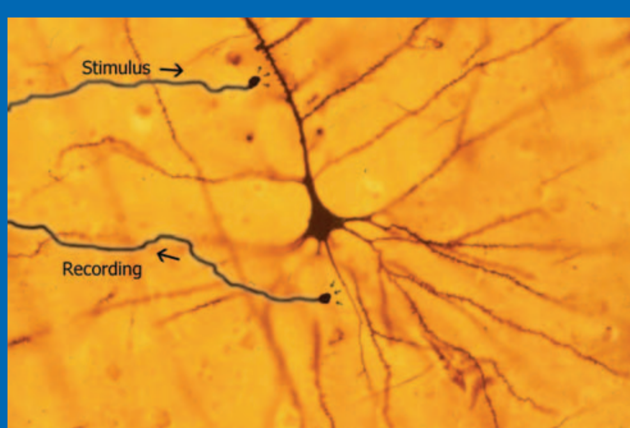
Neuroscientists can't attack these questions with current technology, but perhaps the new nanowire technology can help. Because they are flexible like brain tissue, nanowires can slosh around with the brain and maintain contact with the same neuron for weeks, month, or years.

Prof. Hunter's lab custom-makes the nanowires, which are spun from a brew of component molecules called monomers in a machine resembling a washing machine. Induced by the right chemical reactions, monomers combine to form longer, complex polymers. During an afternoon, the process produces a 100 x 100 millimeter cylinder that is sliced into "wires" about 1/10th the diameter of a human hair. Shorter wires go to Fee's for bird recordings, longer ones to Bizzi, who uses them in rats.

Michale Fee

Nanowire with neuron

An artist's conception of how one nanowire stimulates a neuron while a second records the neuron's response.



Composite image by Bryan Ruddy, Laboratory for BioInstrumentation, MIT.

Stimulating Patterns

A different challenge occupies Martha Constantine-Paton's lab. Her goal is to understand neural circuit formation during development and in plasticity: How does neuronal connectivity change over time in response to different temporal patterns of impulse activity? How do those patterns produce the structural changes that connect individual neurons into neural circuits?

Those structural changes occur at the synapses, the gaps between neurons. The changes are readily observable in tissue culture but difficult to discern in an intact brain. Much is known about how synapses are strengthened or weakened, but how circuits are achieved remains mysterious. The Constantine-Paton lab works to demystify the process.

That goal compliments one in Prof. Hunter's lab: producing a machine for screening potential small-molecule drugs

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Martha Constantine-Paton

Circuits and synapses

Martha Constantine-Paton focuses on what happens at the synapse, the site of communication between two neurons.

Graphics by Constantine-Paton, McGovern Institute at MIT.

that target specific aspects of synaptic function. Such drugs could be used to prevent neurodegenerative diseases or to enhance recovery after brain trauma or stroke. They could also be used in rapidly developing technologies, such as effectively incorporating stem cells into existing neural circuits.

Presently, researchers use electrodes to stimulate neurons in slices of brain tissue, in different patterns and in varying intensities, to see how the activity strengthens or weakens the synapses between neurons.

Constantine-Paton would like to create an even more powerful tool: predictable circuits in tissue culture that replicate actual brain circuits. Then she could learn more about how brain circuits are reorganized in brain disorders and also how drugs affect specific brain circuitry. However, the present technology for creating neural circuits is very time consuming, expensive, and difficult to use.

That's how the BioInstrumentation lab can help. The collaborators are molding electrically conducting polymers into nanowire arrays that fit over an aligned array of electrically exciting inputs on a stimulating plate. They can grow small populations of neurons on these electrically conducting arrays. They will then fit the arrays onto the stimulating plates that are programmed with specific patterns of electrical current pulses.

Constantine-Paton's lab will follow known spike-timing rules to produce predictable neuron circuits among the active neurons in the dish. When the plated neurons are loaded with dyes that fluoresce in response to membrane voltage changes, the researchers can digitally record the patterns as changes in fluorescence. With these new tools, investigators could begin to answer many basic research questions about neural plasticity and brain development.

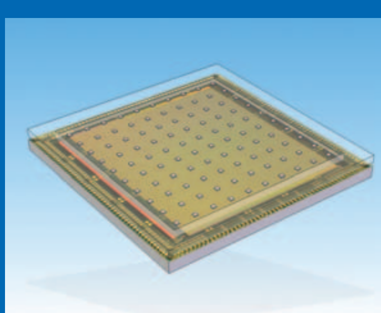
The collaborators further envision growing neural circuits that incorporate both normal and genetically diseased neurons on large numbers of disposable arrays. The plates will enter a Ferris wheel-like conveyor belt around an optical detector system. The detector could record the baseline pattern for each circuit. Then, like a farmer's crop duster, a device could spray small molecules over each plate to see what effect each has on each pattern of neural activity.

Such a system could systematically identify new families of drug candidates, as well as side-effects that otherwise may not show up until drugs are in expensive clinical trials or already on the market.

How the Future May Look

Eventually, the "nanoneurotechnolgy" being developed here could create brain-friendly neuroprosthetics that may help people recover from stroke and paralysis, allow blind people to see, or even regulate brain functions involved in neuropsychiatric disorders. As mentioned, the technology may also accelerate the discovery and design of drugs to intervene in developmental diseases like autism and schizophrenia, or neuro-degenerative diseases like ALS and Huntington's.

Perhaps "plastics" was the right advice, after all. ■



Conductive polymer array

Computer model of an array, showing a plate with posts of conductive polymers that conduct electricity. Neurons will grow in between the posts.

CAD image of Direct Imaging Polymer Coated Neural Electrode Array by Andrew Taberner, BioInstrumentation Laboratory, MIT

$1 Million Razin Gift for Graduate Fellowships Meets $500,000 Anonymous Challenge

Leadership Board member Sheldon Razin ('59) and his wife Janet have created a $1 million endowed fellowship in support of research at the McGovern Institute.

In creating this perpetual fund, the Razins have also met an anonymous challenge grant of $500,000 in support of the new Martinos Imaging Center at the McGovern Institute, which serves the entire MIT community and beyond.

"Shelly and Janet Razin have made a generous contribution to graduate training that will attract more and better students into neuroscience research," said Robert Desimone, Director. "I received a privately endowed fellowship such as this when I was a graduate student at Princeton, and I know how important this can be for someone just getting started in the field. In endowing a fellowship for graduate training, Shelly and Janet put their finger on one of the most pressing challenges in the field today, and they stepped right in and did something about it."

Shelly Razin, who grew up in nearby Everett, MA, credits MIT with opening up his early geographic and cultural horizons. He is still awed by its world-class excellence, brilliant minds, and cosmopolitanism.

After receiving a SB in mathematics from MIT in 1959, Shelly joined Northrop, working in operations research and then with computer systems. He joined Autonetics Division of North American Aviation, designing and implementing avionics systems. While there, he developed the mathematics for Loran navigation systems, now in all receivers worldwide. In 1973, he founded his own company in his garage with $2,000 and no venture capital. That company, Quality Systems, went public in 1982 and enjoys a market value of in excess of $1 billion.

"I'm lucky at this point in my life to be able to give back to MIT and help other people," Shelly reflected. "I wanted to provide fellowships to help people who don't have funds, because when I came here, I didn't have any. I hope the fellowships can attract the top-notch graduate students who might not otherwise come to MIT, and that some of them will go on to create breakthroughs in the field of mental health. I have a tremendous belief in brainpower at MIT. If we fertilize that brainpower with fellowship funds, great things can happen. These fellowships can help bridge the gap between research and applications that are valuable to all mankind."

Shelly Razin

Shelly knows first hand the impact of mental illness. His mother suffered from severe depression, and his brother and an uncle had schizophrenia.

"I remember asking my brother if he realized he had schizophrenia. He said, 'Yeah, but what can you do about it?' That was a ringing statement. I hope to have a different answer emanating from what we do here at the McGovern Institute."

Jim DiCarlo, Chris Moore, Shelly Razin, Bob Desimone, Martha Constantine-Paton, Ki-Ann Goosens, Emilio Bizzi, and John Gabrieli

Leadership Board and Friends of the Institute

The McGovern Institute hosted a joint meeting of the Leadership Board and the Friends of the Institute on Thursday, November 9, 2006. In the morning, the Board met to discuss the current and future directions of the Institute. McGovern Institute investigators Emilio Bizzi and Martha Constantine-Paton also discussed their work with nanowires in the first McGovern Institute Neurotechnology (MINT) program. (See article on page 2).

At lunch, the Friends of the Institute joined the Board and faculty members. Dr. Edward Scolnick of the Broad Institute spoke about how collaborating with the McGovern Institute is a natural outgrowth of his research on the genetic basic of psychiatric disorders. (See "The Genetics of Psychiatric Disease" on next page.) After lunch, Board members and Friends visited with individual faculty and toured the laboratories. Later, Professors John Gabrieli, Nancy Kanwisher, and Alan Jasanoff talked about their exciting findings in brain imaging.

Finally, the Martinos Imaging Center scanned one of the most interesting brains of his generation—Ethernet inventor and Chairman of the Leadership Board, Bob Metcalfe—as the guests watched through a window and observed his brain on a monitor. During the scanning, Bob performed a task requiring self-reflection. Self-reflection refers to contemplating your own attributes, such as whether you are humble or arrogant, outgoing or shy, lazy or ambitious. Gabrieli hypothesizes that some of the features of autism arise from dysfunctions in self-reflection and, by extension, reflecting on the thoughts and intentions of others. The tentative diagnosis? At least in this study, Bob's sense of self appears normal.

Friends Co-Chairs, Tom and Regina Pyle

Tom and Regina Pyle and their guest, Bikui Chen

Tom and Regina Pyle, co-chairs of the Friends of the McGovern Institute, welcomed other Friends and members of the Leadership Board at the joint daylong meeting on November 9th.

The Pyles are generous donors to the Institute and have established the *Regina S. and Thomas O. Pyle Fund* in support of graduate students. They have also made a gift in honor of Dr. Nicholas T. Zervas, Higgins Professor of Neurosurgery at Harvard Medical School and President ex-officio of the Boston Symphony Orchestra, in support of McGovern researchers studying the potential positive effect of music on cognitive development.

Inside Bob Metcalfe's Brain

Functional magnetic resonance imaging (fMRI) shows the area of Bob's brain that becomes active while reflecting on whether a trait adjective refers to him.

Image courtesy of Joe Moran and Susan Whitfield-Gabrieli, Martinos Imaging Center at the McGovern Institute.

Self-Reflection
"Am I smart? Kind? Generous?"

The Genetics of Psychiatric Disease

According to Dr. Edward Scolnick of the Broad Institute, schizophrenia, bipolar disease, and depression exemplify the overarching problem with psychiatric diseases: There is no basic understanding of the diseases, unlike in most other fields of medicine.

The paradigm for drug discovery is to identify a molecular target, do biochemical assays of candidate drugs, and take the best candidate to animal tests and then human clinical trials. This paradigm has never been applied to a psychiatric disease. Instead, through serendipity, a drug is found to have psycho-active properties. A human clinical trial follows, then animal studies, and finally biochemical assays to discover the drug's molecular target.

The genetic revolution has had a tremendous impact on clinical treatment for cancer and immune diseases, and has spawned numerous new drugs working in novel mechanisms. In stark contrast, it has had no impact on psychiatric diseases.

We have had no new classes of psychiatric drugs in the past 50 years, with the exception of two for schizophrenia. Lithium, for example, is still the mainstay for bipolar disease, and researchers are just now gathering inklings of how it may work.

"We've got to change that," Scolnick exclaimed. With the advent of new whole genome scanning at the Broad Institute, he hopes to identify genetic risk factors that may predispose one person more than another to mental illness.

"But that's just the start," he said. Researchers also need to understand the neurobiological effects of those genes. That's why collaborating with the McGovern Institute is so appealing. "Together we can crack this major unknown in medicine."

On Graduate Fellowships

No matter how long-term an investigator's research goals, bringing in graduate students who can focus on a specific project can make a difference right away. Supporting young researchers with fellowships can stimulate innovative research on newly conceived problems.

Rosa Cao

Rosa Cao, a 4th year PhD student who received the Shoemaker Fellowship for 2006-2007, is a case in point. Her graduate project evolved out of an idea regarding the hemodynamics in the brain that Investigator Christopher Moore had been considering but never had an opportunity to pursue. They hope to publish preliminary results soon.

"Fellowships are important when you work on a project that is not just the next step in what the lab has been doing," said Rosa. "When you start something brand new, it's hard to get traditional grants because you have no data, and with budget cutbacks, the NIH is less willing to take risks with their grants. To some extent, my project is risky for both Chris and me because we don't know how it will turn out. But if our theory is true, it could be big. Fellowships make it possible to work on totally new projects rather than stick with you know works."

Marnie Phillips, last year's recipient of the Shoemaker Fellowship, adds: "The fellowship allowed me to focus on my work rather than on time-consuming applications for government fellowships. And we've made great progress this year, for which I am extremely grateful."

SPECIAL SEMINAR

John Allman (CalTech): The Neurobiology of Intuition

Professor of Biology John Allman gave a special seminar at the McGovern Institute on September 28, 2006. He described intuition as a form of cognition that is highly developed in human beings compared to even our closest evolutionary ancestors. We owe our intuitions to large, bipolar Von Economo Neurons (VEN), a recently evolved specialization in large-brained animals that are nevertheless much more abundant in humans than in great apes, whales, and elephants. They emerge mainly after birth, with a growth spurt in childhood years that then tapers off. Allman hypothesized that VENs may help us learn social norms, and that "kinks" in the system lead to common psychosocial disorders like fronto-temporal dementia, autism, anorexia, depression, and sociopathy. If so, it's an example of how evolutionary development may provide clues to understanding neuropsychiatric disorders.

NEW FACULTY MEMBER: KI ANN GOOSENS

Ki Ann Goosens, PhD, joined the McGovern Institute as a principle investigator this year, 2006. She adds a new area of faculty expertise, studying the brain mechanisms that underlie fear, stress, and anxiety. These mental states are key components of cognition, one of the major research topics of the McGovern Institute.

"We are thrilled to have Ki Ann Goosens join us in the McGovern Institute and the Department of Brain and Cognitive Sciences," director Robert Desimone said. "Ki Ann is using the very latest molecular tools for manipulating specific neural circuits that are likely to play a key role in several forms of mental illness. The opportunities for making real progress in her field have never been better."

"I'm incredibly excited to have joined the McGovern Institute and the Department of Brain and Cognitive Sciences," Goosens said. "I look forward to working with the world-class students and investigators, and for the opportunity to contribute to the amazing science community at MIT."

Goosens uses interdisciplinary approaches to study the effects of stress on the "fear system" in the normal brain so that she can appreciate what goes wrong in the brains of people with depression, for example, for whom stress may trigger pathological fear and anxiety. Indeed, stress may play a role in many forms of mental illness. She has also developed techniques that overcome the "specificity problems" of many psychoactive medicines. Those medicines act on traditional neurotransmitters, which affect numerous brain systems other than the ones intended. She hopes her research will lead to new therapeutic approaches in treating mental illness.

Ki Ann Goosens

Goosens joined the McGovern Institute after completing her post-doctoral research with Dr. Robert Sapolsky at Stanford University. She is currently setting up her laboratory and will begin teaching in MIT's Brain and Cognitive Sciences department next year.

The McGovern Institute at MIT is a neuroscience research institute committed to improving human welfare and advancing communications. Led by a team of world-renowned, multi-disciplinary neuroscientists, The McGovern Institute was established in February 2000 by Lore Harp McGovern and Patrick J. McGovern to meet one of the great challenges of modern science the development of a deep understanding of thought and emotion in terms of their realization in the human brain.

Additional information is available at: http://web.mit.edu/mcgovern/

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