

ON THE BRAIN

THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER



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Learning & Memory *HMNI's Neuroscience Symposium*

IN HER opening remarks at the Harvard Mahoney Neuroscience Institute (HMNI)'s "Symposium on Memory & Learning" in Palm Beach, Florida, Hillie Mahoney observed, "Our ability to learn and remember impacts the quality of our daily lives. Therefore, it is incumbent upon us to know what we can each do to maintain our ability to learn and remember."

Three leading scientists explained how the brain develops, learns, remembers, and forgets to a standing room only crowd at HMNI's symposium, held at the Colony Hotel in March. Their discussion included how the brain fails through progressive illnesses like Alzheimer's disease and what happens to it as we age.

An extraordinary computational machine

Carla Shatz, PhD, the new director of the Harvard Mahoney Neuroscience Institute and one of the world's foremost developmental neurobiologists, is widely known for her work on early brain function and the detailed connections between the eyes and the brain.

The brain is "probably the most extraordinary computational machine that we can imagine," Dr. Shatz said, with at least a trillion neurons and even more connections. "It's an extraordinary machine because it allows us to adapt to the environment, and this process of adaptation and learning and memory happens throughout life. It begins early in development and it persists well into our aging years."

Unlike a computer, which is hard-wired from the outset, Dr. Shatz explained that the brain is "actually building its own hardware. When the brain changes, the hardware changes. Literally, the circuits of the brain change. And this happens more in childhood than it does in adulthood."

Dr. Shatz illustrated the hard-wiring of the brain by discussing how the brain combines the visual

information from two eyes into layers and columns so that an individual nerve cell gets input from both eyes.

"Once that signal is present in the neurons," she said, "it's sent to the output neurons of the eye, and those connections from the output neurons are then sent to the higher brain centers, to visual centers, for information processing. The wiring is extremely elegant and precise in the sense that it's almost as if two separate views from the right eye and the left eye are knitted together somehow in these higher order centers."

Dr. Shatz added "it's as if nothing has been left to chance; everything is perfectly wired." However, some things [in the brain] are left to a process she calls "use it or lose it." Appropriate connections in the brain are strengthened by use and inappropriate ones are eliminated through disease. A baby's

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(L-R) Dr. David Sinclair, Dr. Carla Shatz, Mrs. David Mahoney, moderator, and Dr. Dennis Selkoe.

brain, then, is not just a smaller version of the adult brain; it is an evolving set of circuits, which develop based upon use.

This "use it or lose it" process, however, occurs in only certain parts of the brain. Connections in the visual system, for example, become hard-wired. Yet, in other parts of the brain, especially in areas responsible for learning and memory, the process persists throughout a person's lifetime.

"There are early critical periods when experience can influence brain wiring," Dr. Shatz told the audience. "Later, this adaptability is restricted to important parts of the brain that are famous for their roles in learning and memory, like the hippocampus, the frontal lobes and the cerebral cortex."

Dr. Shatz said this wiring begins during fetal development and continues throughout life. "The

fact of the matter is," she said, "that your brain, whether you like it or not, is different now than before I started talking, and that these changes, if you remember anything, are encoded in local changes in the circuits in your brain that are still able to adapt through experience."

Alzheimer's – a protein connection

Twenty-two years ago Dennis Selkoe, MD, and his colleagues broke new ground when they developed a method for isolat-

ing the abnormal neurofibrillary tangles that are a hallmark of Alzheimer's disease, discovered their unusual chemical properties, and developed the first antibodies to them.

Dr. Selkoe told the audience that amyloid parent proteins (APP) in the brain get cut by enzymes, with a large part of the protein "going off and doing good things," while the other, smaller part stays in the cell wall. The piece of protein remaining in the cell undergoes a second cut, which researchers believe releases a small fragment (called amyloid beta) that causes some people to develop Alzheimer's disease.

This cutting is normal and necessary for the function of APP. APP releases amyloid beta peptide, many hundreds of thousands of which make up senile plaques that are found in Alzheimer's.



Dr. Dennis Selkoe illustrates a concept to the crowd using a pen as his prop.

"We want to decrease the amount of this amyloid beta protein in the brain," said Dr. Selkoe. "We have to be careful, because numerous proteins need to be cut by the two enzymes. We therefore have to tune down one or other of the enzymes a little bit, so proteins can still function and get cut, but lower it enough that people don't build up plaques of amyloid beta peptide as they get older."

One way to clear out the amyloid, he said, is through an Alzheimer's vaccine. The vaccine includes a small amount of amyloid beta protein, to which the body makes antibodies. These antibodies circulate to the brain, where they latch onto the amyloid protein and start pulling it out of the brain and into the blood stream.

Alzheimer's researchers around the world, Dr. Selkoe said, are trying to determine just how this vaccine works. One trial at Harvard Medical School has shown the vaccine to be effective in animal models, and several companies have had trials with what Dr. Selkoe called "positives and negatives," the negative being brain inflammation in some individuals who received the vaccine. In addition, he said, a trial is now underway with a monoclonal antibody to amyloid beta that is being investigated in human patients.

Extending life, preventing disease

In his laboratory at Harvard Medical School, David Sinclair, PhD, is bringing science a little closer to a drug that extends life and prevents many diseases of aging. His lab and others have identified genes that regulate the pace of aging in many organisms and have shown that the same genes that control aging also control how well organisms defend

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Dr. Carla Shatz addressing a standing room only crowd at the Colony Hotel.

HMS-HMNI Dinner in Palm Beach



(L-R) Mrs. David Mahoney with Mr. Stanley Rumbough and Mrs. Richard Waterman



(L-R) Dr. David Sinclair, Mrs. William Hamm and Mr. Edward Rover



(L-R) Mrs. Dennis Selkoe and Dr. Dennis Selkoe with Mr. Donald Cronson

Following the symposium on *Memory & Learning* at the Colony Hotel, friends of Harvard Medical School and the Harvard Mahoney Neuroscience Institute gathered for a delightful evening of discussion at *Hilago*, the home of Hillie Mahoney. The three scientists, Drs. Shatz, Sinclair and Selkoe, shared with the guests an update on Harvard's progress to effectively wed basic neuroscience with neurological research in order to enhance their ability to apply the power of neuroscience to diseases of the brain.



Mrs. Henry Ford and Mr. Frank Chopin



Mr. and Mrs. George Gardner



Dr. Carla Shatz explains a point to Mr. Louis Cabot



The Right Honorable and Mrs. Brian Mulroney

Brain Plasticity, Dendritic Spines and Memory

Throughout the brain lay lollipop-looking structures called dendritic spines that are the source of synaptic contact and, some scientists believe, may be involved in the formation of memories.

Bernardo Sabatini, MD, PhD, assistant professor of Neurobiology at Harvard Medical School, studies these dendritic spines in his lab to determine if stimulating them induces synaptic plasticity. Part of the Hebbian theory of the neurochemical foundation of learning and memory, synaptic plasticity refers to the variability of the strength of a signal transmitted through a synapse.

Spines and memory

Each less than 2 microns long, dendritic spines are comprised of a spine head and a spine shaft. The spine head contains a synapse and represents a means by which new contacts between cells can be made and where existing contacts are strengthened. Because excitatory synapses are located on spines in the hippocampus (an area of the brain critically involved in some types of learning and memory), some scientists believe an increase in their number could relate to an increase in excitatory neurotransmission, a key element in memory formation. This hypothesis, however, has not yet been proven.

“The role of spines in memory is unclear,” says Dr. Sabatini. “Spines appear in development at the same time that synapses appear. They are motile early in life and their movement is affected by the sensory environment of the animal. Electrical stimuli of the type that produces changes in synaptic strength lead to the growth of new spines. Thus, there is a temptation to say that growth of dendritic spines correlates with the storage of information or the formation of memories, but the evidence is anecdotal at best.”

Researchers at Rutgers University recently reported that an increase in spine density accompanies associative memory formation. Their findings suggest that the formation and expression of associative memories increases the availability of dendritic spines, as well as the potential for synaptic connections. Associative memory stands as the most likely model for cognitive memory, as humans retrieve information best when it can be linked to other, related information.

Optical tools to study deep spines

The trouble with studying dendritic spines is that they are so small – some only tenths of a micron across – and so deep within the brain that they are hard to image. Further, the brain is so opaque that light from conventional imaging techniques cannot penetrate the brain well enough to see the spines.

By developing optical tools, Dr. Sabatini and his colleagues have been able to explore spines deep within brain tissues. This has allowed them to investigate how neurons establish communication channels and how the brain stores and recalls information. The researchers built and use a sensitive optical tool that includes a two-photon microscope with another microscope mounted on top of it to allow light to stimulate a specific synapse. The researchers combine this optical method with electrophysiological measurements of synaptic currents, as well as manipulation of neurons. Finally, they add computational approaches to better understand synapses and synaptic circuits.

“Studies have shown that different types of manipulation change spine density,” says Dr. Sabatini, “but we don’t know the role of this in memory. We do know that new spines house new synapses, but there is currently no tool available to interfere with spine growth without also interfering with synaptic plasticity.”

Synaptic regulation

In his lab, Dr. Sabatini is studying synaptic regulation, specifically the regulation of one synapse independent of its neighbor. Synaptic regulation is involved in the mechanisms underlying long-term potentiation, an experimental model for synaptic changes in the hippocampus that may be essential for learning and memory.

“We need to look at the mechanism of change in synapses, and most researchers who are looking at spines are doing it blindly,” explained Dr. Sabatini. “They don’t know what’s being stimulated [in the brain] so it’s hard to determine the level of synaptic plasticity. We are using optical tricks with the two-photon microscope to deliver a stimulus and read out the consequences relative to synaptic plasticity; we choose the synapse we want to study.”

In the end, he says, he thinks this will give him and his colleagues access to the mechanisms of synaptic plasticity and thus a better understanding of how we form memories and acquire new learning.

The 'Dirty' Drug

A 19-year-old "raver" posts his experience with the mind-altering drug Ecstasy on a drug-related Web site: "I first started feeling tingly sensations and sort of a constant vibe throughout my body. Completely euphoric, I was in a state of mind that could not be described by words for I have never known this feeling of joy before."

Bertha Madras, PhD, an addiction specialist at Harvard Medical School and the New England Primate Center, calls Ecstasy a "dirty" drug. Also known as MDMA for its chemical composition (3,4-methylenedioxymethamphetamine) – Ecstasy affects the brain by altering the activity of multiple neurotransmitters, including serotonin, dopamine, norepinephrine and acetylcholine, which enable nerve cells in the brain to communicate with one another.

Ecstasy is rapidly absorbed into the bloodstream. As a result, additional doses produce unexpectedly high blood levels, causing toxic effects.

The "positive" effects a person experiences after taking Ecstasy – feelings of mental stimulation, emotional warmth, empathy toward others, decreased anxiety – relate to the function of neurotransmitters in the brain, says Dr. Madras. Serotonin mediates mood and has some control over memory and cognitive function, while dopamine mediates a sense of energy, experiential salience and heightened mood.

"We know," said Dr. Madras, "that Ecstasy users experience impaired memory, attention deficits, and difficulties with problem solving. Studies indicate that regular users with relatively high doses have more sleep disorders and increased anxiety, impulsive behavior, and hostility. Moderate users also show persistent memory impairment and problems with working memory."

A study sponsored by the National Institute of Drug Abuse in the late 1990s provided the first direct evidence that chronic use of Ecstasy causes brain damage in humans. Subsequent studies found that, compared to non-users, heavy Ecstasy users had significant impairments in visual and verbal memory and that poorer memory performance by Ecstasy users is linked to loss of brain serotonin function. These and other studies support the conclusion, say researchers, that Ecstasy-induced brain serotonin neurotoxicity may account for the persistent memory impairment found in users.

Dr. Madras says that while some of these deficits may be partially ameliorated by abstaining from the drug, they are not totally eliminated. The problem with all Ecstasy-related studies, she adds, is

that "we don't know what the brains of users were like before they started."

In the early 1900s, German scientists developed MDMA as a parent compound to be used to synthesize other pharmaceuticals. Psychiatrists in the United States began using the drug in the 1970s as a psychotherapeutic tool even though it never received FDA approval for use in humans. It first became available on the street at this time, and its use has grown exponentially over the years. Today, the drug is popular at dance parties called raves.

According to the 2002 National Survey on Drug Use and Health, more than 10 million people over the age of 12 reported using Ecstasy at least once in their lifetime. There were an estimated 1.8 million new users in 2001. Between 1999 and 2001, hospital emergency department visits due (in part) to Ecstasy use rose 94 percent.

Dr. Madras, who is currently involved in two studies of Ecstasy, says that one problem with the drug is the amount of "junk" in each tablet. According to a limited U.S. study published in 2000, only 63 percent of all tablets sold as Ecstasy that they sampled actually contained Ecstasy; the other 37 percent contained ephedrine, caffeine and the over-the-counter cough suppressant dextromethorphan. Additionally, she says, LSD has been found in some tablets, added to produce hallucinogenic effects. Some of these additives are neurotoxic, including amphetamines, which can destroy nerve endings. Others, such as ephedrine, carry cardiac risks.

Dr. Madras and her colleagues are currently studying trace amine receptors, which were found in 2001 to be a target of the drug. The drug was previously thought to primarily target transporters. Her investigation is studying the activation of trace aiming receptors in primates using Ecstasy. Another study is geared toward determining what factors inside of cells determine the differential toxicity of Ecstasy.

While Ecstasy use has leveled off today, Dr. Madras says use of the drug is still disconcerting. "If neurotoxicity and irreversibility [of drug-related deficits] are confirmed," she says, "a generation of young, innocent, uninformed people may engage in behavior that could adversely affect their developing brains. Unfortunately, Ecstasy advocates only emphasize the positives and Ecstasy users believe the drug to be harmless."

Harvard Center for Neurodegeneration and Repair

A Center for Collaboration and Translation

The brain and central nervous system are phenomenally complex, as are the diseases that affect them – Alzheimer’s, Parkinson’s, amyotrophic lateral sclerosis (ALS), and others – making them difficult to identify and treat. For years, scientists at Harvard Medical School have been at the forefront of understanding the causes of these diseases.

However, until recently, says Dennis J. Selkoe, MD, a neurologist at Brigham and Women’s Hospital and the Vincent and Stella Coates Professor of Neurologic Diseases at HMS, “what was lacking was the ability of scientists to do something about them [neurological diseases] and move toward treatment.”

That’s where the Harvard Center for Neurodegeneration and Repair (HCNR) comes in. Established in 2001 with a five-year, \$57 million grant from an anonymous donor, the HCNR is a decentralized community of neuroscience and neurology researchers striving to reduce the impact of Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, ALS, and many other neurodegenerative diseases.

“There is a tremendous local resource of investigators interested in neurodegenerative diseases,” says HCNR director Adrian J. Ivinson, PhD, “MDs, PhDs, basic and clinical researchers, with an overlapping common interest in the diagnosis, treatment, and cure of these diseases.”

The HCNR brings these scientists together into a structure that Dr. Ivinson refers to as resembling a “three-legged stool”: a focus on neurodegenerative diseases, collaboration among researchers, and translating research findings into clinical applications.

Collaboration a key

At the end of the 1990s, says Dr. Selkoe, there was a desire among neuroscience researchers at Harvard to interact more directly with a wider range of scientific colleagues – chemists, electrophysiologists, animal behaviorists – to build a broader base of knowledge about neurodegenerative diseases. Joseph B. Martin, MD, PhD, Dean of the Faculty of Medicine at Harvard Medical School, neurobiologist Carla Shatz, PhD, Peter Lansbury, PhD, and Dr. Selkoe were the visionaries behind the HCNR and remain key players in the Center.

Today, more than 600 scientists from across the HMS community, including eight of its affiliated hospitals, are members of the HCNR. A series of twelve programs have replaced five original “cores.”

These programs include pre- and post-doctoral training, optical imaging, magnetic resonance imaging, image analysis, bioinformatics, a virtual brain bank, an advanced tissue resource center, genetics outreach, neurological clinical trials, drug discovery, and tissue regeneration.

“Collectively,” says Dr. Ivinson, “these resources extend our ability to translate understanding of the brain and its diseases into new and effective therapeutic interventions.”

A unique model

Unlike most of academic research, where the focus is typically on individual investigators, the HCNR model is based on collaboration among scientists to bring about discoveries in neurodegenerative diseases. Dr. Ivinson points to the HCNR’s Laboratory for Drug Discovery in Neurodegeneration (LDDN) as an example.

The largest of the HCNR’s programs, the LDDN’s mission is to discover new chemical agents that can be used either as research tools to probe the cellular mechanisms of disease or as lead structures for the development of new drugs. Dr. Ivinson says the HCNR hired 14 scientists, many from the pharmaceutical and biotechnology industries, to staff the LDDN. These individuals, he says, have the skill-sets to look at investigators’ targets, help the investigators develop assays, screen compound libraries to identify drug leads, and then test these leads in animal models.

“This is a new structure,” he says, “which is unusual inside of academia. We say, ‘bring us the idea, move it into our lab, we’ll give you the professionals to help with the work, but it’s still your project.’ A lot of what we do [at the HCNR] works in a similar way to LDDN.”

The memory and learning paradigm

Diseases that affect memory and learning permeate HCNR, from Alzheimer’s disease and dementia to stroke and multiple sclerosis. While Alzheimer’s is perhaps the “flagship disease of the HCNR,” says Dr. Selkoe, a great deal of research at the HCNR has a memory and learning component behind it.

“A neurodegenerative center like ours,” says Dr. Ivinson, “is never far from memory and learning. Some of our people are absolutely involved in synaptic function and memory. At the other end, we have clinical trials testing off-label uses [of drugs]

and chemical entities in memory clinical trials.”

Two scientists conducting leading research are Reisa Sperling, MD, and Andrew Budson, MD, both neurologists at Brigham and Women’s Hospital.

Dr. Sperling, who is director of clinical research at the Brigham’s Memory Disorders Unit, is involved in research on neuroimaging markers for early Alzheimer’s disease and, in particular, functional MRI studies of associative memory. Currently she is studying healthy seniors, Alzheimer’s patients, and older individuals with mild cognitive impairment (often a harbinger of Alzheimer’s disease), using functional MRI to study alterations in brain function underlying memory impairment. Her work has now expanded into using functional MRI to evaluate the effects of new treatments for Alzheimer’s disease.

In his lab, Dr. Budson is gaining an understanding of memory distortions in patients with Alzheimer’s disease. He has examined two different types of memory that are believed to involve different neuroanatomical systems: item-specific recollection (the specific details of a prior encounter) and gist memory (the general meaning of an idea conveyed by a collection of related items). His research has found that patients with Alzheimer’s show deficits in both types of memory; however, when information is repeated across multiple trials in Alzheimer’s patients, patients increase their gist memory but not their item-specific recollection, leading to an increase in false memories.

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HMNI’s Neuroscience Symposium

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against injury, how efficiently they repair it, and how well they survive.

For nearly 70 years, Dr. Sinclair said, scientists have known that the lifespans of mammals can be extended through calorie-restricted diets. More recently, researchers have found that a gene – SIR2 – is turned on by calorie restriction; all lifeforms possess the SIR2 gene.

“If you take any lifeform, any live organism – take a yeast cell, take a fly – and you put in extra copies of the SIR2 gene, they live longer,” said Dr. Sinclair. The SIR2 gene makes proteins that “chomp bits off other proteins,” allowing them to repair cells. “We believe,” Dr. Sinclair told the audience, “that, in its chomping, it could make ourselves and our bodies live longer.”

One of the proteins SIR2 makes is found in red wine, which Dr. Sinclair has isolated in its pure molecular form in his laboratory and given to animals and yeast cells. When administered the red wine molecule, called resveratrol, nematode worms live 35 percent longer through calorie restriction, as do flies.

Resveratrol is being tested as a treatment for certain diseases of aging, including cancer and diabetes. In mice, the molecule is a potent inhibitor of cancer. “Right now,” said Dr. Sinclair, “the research on this red wine molecule stops at rats, although people who have fed it to rats have only been looking at short-term effects on things like cancer, and even neurological disorders. It turns out that it prevents things like Alzheimer’s in mouse models.”

Dr. Sinclair’s lab is currently conducting studies in which resveratrol and resveratrol analogues are given to mice of various ages to see how long they live and what happens to their diseases of aging. He said if this science is correct a resveratrol pill may be on the market in the next five to ten years.

After a question-and-answer session with the audience, which included queries about stem cell research, Mrs. Mahoney closed the proceedings by saying, “Our brains leaving this room this afternoon will be different than they were when we walked in the door. And as I look back on the last 14 years [since HMNI’s founding], it is awesome to ponder on how far we have come in understanding the brain. Yet, it is almost overwhelming to think about how much we still have to learn.”



Ed Rover, president of the Dana Foundation, and Hildegarde Mahoney, chairman of the Harvard Mahoney Neuroscience Institute (HMNI) pose with a bust of the late David Mahoney, former chairman of the Dana Foundation and co-founder of the HMNI, at the Dana Centre in London. The centre, which opened in November 2003, was established with funding from four benefactors and combines science, art, and media into interactive experiences for an adult audience. The bust of Mr. Mahoney was unveiled at the opening event for the Dana Centre.

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Harvard Center for Neurodegeneration and Repair
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Dr. Budson recently received funding from the HCNR to examine the use of a false recognition paradigm as an outcome measure for clinical trials in patients with mild to moderate Alzheimer's, using memantine as a medication. This work will be combined with functional MRI in a study with Dr. Sperling on the efficacy of memantine in patients with mild Alzheimer's disease.

A time for translation

Over the last ten to 20 years, says Dr. Iverson, there has been a phenomenal improvement in our mechanistic understanding of neurodegenerative disease. Now, he adds, "it's time to translate that knowledge into new treatment for patients."

Driving translational research at the HCNR is the Neurological Clinical Trial Service (NCTS), which encourages, supports, and develops clinical trials

of treatments or procedures for neurodegenerative diseases. The program has had a significant impact on the community's ability to launch new trials and to develop successful pilot trials into full-size, well-funded studies. Since its inception, the NCTS has supported 63 neurodegenerative disease clinical trials, helping to secure more than \$8.5 million in external funding for follow-up studies at Massachusetts General Hospital, Beth Israel Deaconess Medical Center, McLean Hospital and Brigham and Women's Hospital.

"When we look across the gap, from bench to bedside," says Dr. Iverson, "we see that translation does not happen by chance. To do this you need a lot of components; no one entity can do it. Translational research is challenging; there's a huge range to cover. And the HCNR offers a better way to do it."

ON THE BRAIN

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