

ON THE BRAIN

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The “French Paradox” for the Brain

RESEARCHERS HAVE discovered that, in regions of France where the population enjoys a high-fat diet but regularly consumes red wine with meals, the incidence of heart attacks is distinctly lower than in other parts of the world. Now researchers say this phenomenon, commonly called the “French Paradox,” may extend to brain health, as well.

The key to the French Paradox is *resveratrol*, a compound found in a variety of plants as part of their defense system against disease – and in particularly high levels in grapes. Red wine has a relatively high concentration of resveratrol not only because it is made from grapes, but because of the winemaking process itself: the skin and seeds of grapes used to make the wine ferment in grape juice for long periods of time.

Studies have established that, in addition to the cardio-protective effects discovered in the early 1990s, resveratrol may have wide-ranging impacts including anti-cancer, antiviral, anti-aging, and anti-inflammatory benefits. Research conducted at Harvard Medical School suggests that resveratrol may even protect the brain from stroke, Alzheimer’s, and other neurodegenerative diseases.

David Sinclair, Ph.D., Associate Professor of Pathology at Harvard Medical School and Director of the Paul F. Glenn Laboratories for the Biological Mechanisms of Aging, has studied the mechanisms of human aging for over a decade. He developed what is called the theory of “xenohormesis,” which proposes that organisms have evolved to respond to stress-signaling molecules produced by other species in order to prepare themselves for a deteriorating environment or loss of food supply.

Sinclair says that plants produce compounds in response to adversity, and that humans pick up on these chemical cues. When we ingest these compounds, they activate our own defenses against adversity, or in our case, disease. Among

these compounds is a family of enzymes called *sirtuins*, which are found in almost every species of plant, as well as in mice and humans. There are seven different human sirtuins (SIRT 1–7) that, when activated, protect cells from damage and help keep them alive. One of these, SIRT1, is activated by resveratrol.

Resveratrol and neuroprotection

Sinclair’s research on resveratrol focuses on the concept that calorie restriction (CR) delays most age-related diseases and promotes healthy aging. More than 70 years ago, scientists found that rats fed 40 percent fewer calories lived longer and were healthier than better-fed rats. Subsequent studies have shown that CR delays many diseases, including cancer, atherosclerosis (hardening of the arteries), type II diabetes, and neurodegeneration. Some scientists say that CR is one of those events that triggers stress-signaling molecules.

In a recent study, scientists discovered that sirtuins, especially SIRT1, become more active in calorie-restricted diets. The study found that restricting calories, especially carbohydrates, prevents the formation of the brain-clogging amyloid-beta plaques that are common in Alzheimer’s disease. HMS researchers put Alzheimer’s-prone mice on diets that cut their caloric intake by 70 percent and found that these mice had less plaque-building activity than mice with unrestricted diets. When they put the gene for human SIRT1 into the brains of calorie-restricted mice, plaque-clearing activity rose.

Other studies have shown that giving mice with amyloid-beta plaques red wine slows down their memory loss and brain cell death, and that resveratrol lowers the levels of amyloid-beta peptides that cause these plaques. Sinclair suspects SIRT1 is involved.

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David Sinclair

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HARVARD MAHONEY NEUROSCIENCE INSTITUTE PRIZE DINNER

Seventh David Mahoney Prize Awarded to Nobel Laureate Dr. James D. Watson

ON TUESDAY, October 31, the Harvard Mahoney Neuroscience Institute (HMNI) awarded the seventh David Mahoney Prize to Nobel Laureate Dr. James D. Watson, Chancellor of the Cold Spring Harbor Laboratory, who successfully proposed the double helical structure for DNA in 1953. HMNI Chairman Hildegarde E. Mahoney presented the award to Dr. Watson at a dinner at The Pierre in New York City.

“This is an evening about celebration, about passion, about gratitude and about hope. ‘Celebration’ of the progress that has been made and the people who have helped make it possible; ‘passion’ for the work that has yet to be done;

‘gratitude’ for the many possibilities that are being discovered every day, and ‘hope’ for the future,” Mrs. Mahoney said to the approximately 170 guests attending.

The dinner followed a symposium with lively discussions between Dr. Watson and Emmy Award-winning journalist Charlie Rose. Topics ranged from autism diagnosis and treatment to exercises for brain health, and how to attract young scientists to the field of neuroscience. A comprehensive question and answer period moderated by Edward Rover, President of the Charles A. Dana Foundation and a council member of HMNI, concluded the symposium.

Mrs. Mahoney presented Dr. Watson with a Steuben crystal pillar engraved with his name, the year of the prize and “For building a bridge between the public and scientists dedicated to brain research by the Harvard Mahoney Neuroscience Institute.”

The David Mahoney Prize was established in 1995 to recognize individuals who have helped increase public awareness about brain science and disorders of the nervous system. Past recipients include President and Mrs. Ronald Reagan in 1995, Mike Wallace in 1996, Roone Arledge in 1998, Larry King in 2000, William Safire in 2002, and Senator Ted Stevens in 2004. The next prize will be awarded in 2008.



Photos:

(Above left) Charlie Rose at Symposium preceding 7th David Mahoney Prize dinner at the Pierre Hotel.

(Above right) Nobel Laureate Dr. James D. Watson at Symposium.

(Left) Edward Rover, an HMNI Council member, was the Moderator of the HMNI Symposium.



(l to r) Dr. Gerald Fischbach former Director of the Harvard Mahoney Neuroscience Institute and his wife, Dr. Ruth Fischbach of Columbia with Dr. James Watson, Hillel Mahoney and Harvard University Provost Dr. Steven Hyman, who was the keynote speaker.



Hillie Mahoney, Chairman of the Harvard Mahoney Neuroscience Institute, with Charlie Rose at the Symposium.



Bob Merrill (r) (Harvard '81) and his trio provided the music at the cocktail reception.



Toby (Mrs. Franklin D.) Roosevelt, Jr. and Dr. Joseph Hayes



Liz (Mrs. James D.) Watson with Gigi (Mrs. Roone) Arledge, whose late husband was the 1998 recipient of the David Mahoney Prize in Lausanne, Switzerland.



(l to r) Senator Ted Stevens of Alaska, 2004 recipient of the David Mahoney Prize, Hillie Mahoney, Dr. James D. Watson and Cathy (Mrs. Ted) Stevens.



Ms. London King and Didi (Mrs. James E.) Burke



Ambassador and Mrs. Edward Ney with Mr. George Kaufman



Mr. and Mrs. Charles A. Dana III



Harvard University Provost Dr. Steven Hyman, Dr. Lawrence Altman and Mr. William Safire, Chairman of the Dana Foundation and 2002 recipient of the David Mahoney Prize.

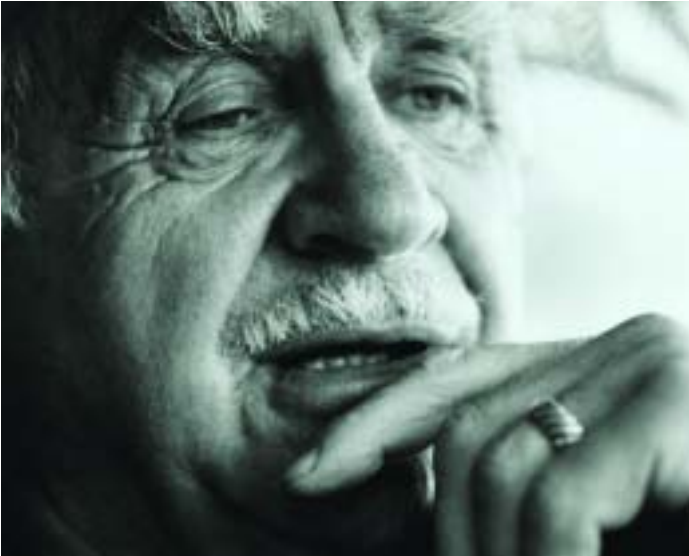


Carolyn (Mrs. Leonard) Firestone and Dr. Bruce Horton

Remember My Name?

Name and face recognition studies lead to better understanding of Alzheimer's progression

IF YOU'VE EVER been to a party and had trouble remembering the names of people you've met, you're not alone – many of us have difficulty remembering names, as well as faces. Dr. Reisa Sperling, Assistant Professor of Neurology at Harvard Medical School and a neurologist at Brigham and Women's Hospital, has been studying the reasons behind this phenomenon: "Names and faces are inherently difficult to remember because they are inherently unrelated. Names are particularly hard to remember because there's no context for remembering them. They're often mentioned once in a conversation, and then the conversation goes on."



Sperling, who studies memory as it relates to normal aging, mild cognitive impairment (also called MCI, a transitional stage between the cognitive changes of normal aging and the more serious problems of Alzheimer's disease) and Alzheimer's disease, became interested in name and face recognition because of her own inability to remember names. Her research has led to greater understanding of how memory function is impaired in the long decline to profound memory loss that is common in Alzheimer's.

The hippocampus is the key to a good memory

Memories are formed deep within the brain in a structure called the hippocampus. This region of the brain is critical for learning and remembering relationships – such as names and faces – in the context in which they were experienced. The hippocampus also connects memories with other, related memories and gives them meaning.

Remembering names and faces is a part of what is called *episodic memory*. Episodic memory is responsible for the recollection of events, including time, place and associated emotions (in contrast to semantic memory, the memory of facts and concepts). Associative memory (also called relational memory) is the ability to learn relationships between items, an essential property of human intelligence.

"Think of episodic memory as the ultimate in associative memory. We distill this to name and face recognition, a microcosm of episodic memory," Sperling says. The most common memory complaint with older people, she adds, is not being able to remember names, thus names and faces are a good paradigm for paired association.

A tool to gauge brain activity

Sperling has used functional magnetic resonance imaging (fMRI) to study the brains of patients who are aging healthfully, those with MCI, and those who have progressed to Alzheimer's disease. Functional MRI, an imaging technology that produces a snapshot of the brain in action, is a key tool in understanding how the brain works when tasks are being completed. Since the hippocampus plays an important role in forming new associations and is affected early on in the course of Alzheimer's disease, name/face recognition tests conducted with fMRI scans give scientists a lot of information about how certain areas of the brain – primarily the hippocampus – are affected during the progression of Alzheimer's.

In one study, Sperling compared the name and face association abilities of 10 healthy young people, 10 healthy older adults, and seven people with mild Alzheimer's. Using fMRI scans, she found that the hippocampus was turned on when the younger people correctly learned name and face pairs, while

the subjects with Alzheimer's showed little or no hippocampal activity. While researchers already knew that the hippocampus shrinks as a result of Alzheimer's disease, this was one of the first studies to show that its functionality is also impaired.

Another fMRI study found that the hippocampus works differently in patients with MCI than in those with Alzheimer's. The findings showed that people with mild functional difficulties resulting from MCI had greater hippocampal activity during memory task performance than older, healthy subjects. Conversely, patients with Alzheimer's showed significantly less hippocampal activation than either control subjects or those with MCI.

Sperling says that parts of the brain need to "turn off" to learn names and faces, while other areas need to turn on to remember them. "There is a reciprocal relationship to learning and memory," she adds, and this may be the reason why hippocampal activity changes as Alzheimer's progresses.

In a more recent study, Sperling found that people with early MCI are still able to compensate for memory problems through other parts of the brain, while they can't once Alzheimer's has progressed to its later stages. The main finding was that older people with memory impairments have less hippocampal activation than younger, healthy people. The older people, however, can still turn on the parts of the brain required for remembering names and faces but, as Alzheimer's progresses, this compensatory ability disappears.

Staying active is crucial!

While drugs cannot yet prevent Alzheimer's, Sperling says there are many things people can do to keep their brains healthy as they age, including staying engaged and socially active, and engaging in physical activity. "The best prevention," she says, "is to stay physically and mentally active. This won't fix underlying [memory] problems, but it may help slow the progression of memory loss."

The "French Paradox" for the Brain

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A number of studies have proven that resveratrol has beneficial effects in protecting people from stroke. Researchers in Taiwan found that resveratrol can improve blood flow to the brain by 30 percent, thereby reducing the risk of stroke. They believe that this neuroprotective effect occurs because resveratrol stimulates the formation or release of nitric oxide, which increases cerebral blood flow.

In addition to resveratrol, grapes and wine contain some 600 different compounds, including antioxidant molecules (chemicals that reduce disease-causing oxygen damage to cells). It is possible, Sinclair says, that resveratrol works in combination with some of these to protect brain cells. In his experiments, he has shown that *quercetin*, an antioxidant found in grapes and the skin of apples and red onions, extends lifespan by allowing resveratrol to circulate in the bloodstream longer.

How much is enough?

While resveratrol is found in nearly all dark red wines – merlot, cabernet, zinfandel, shiraz and pinot noir – a glass of wine with dinner is not necessarily a recipe for good health: "You might have to drink a glass or two for 20 years," says Sinclair. "No one knows how much is enough. In mice, a dose of 10 glasses a day seems to provide remarkable health benefits and may even extend lifespan."

Currently, researchers are conducting clinical trials in an attempt to develop a pill form of resveratrol, as well as other SIRT1 activators that may be even more potent. In the meantime, a glass of red wine at dinner just might help you live a longer and healthier life.

Calming the “Storm” of Epilepsy with Botanicals

EPILEPTIC SEIZURES are recognized by just about every culture in the world, both old and new: 500 years ago in China there was no such diagnosis as epilepsy, but medical texts from that era accurately describe certain types of seizures that characterize the disease. Today, scientists are turning to ancient cultures and the plants they used to treat epileptic patients to discover compounds that may control epileptic seizures more effectively than current therapies.

Steven Schachter, M.D., is a Professor of Neurology at Harvard Medical School and Associate Director of Clinical Research at HMS’s Division for Research and Education in Complementary and Integrative Medical Therapies. “The strategy,” he says, “is to study botanicals [plants and herbs] with a tradition of use and evaluate them as sources of potential new treatments for epilepsy.”

Schachter, a neurologist at Beth Israel Deaconess Medical Center, is consulting historical Chinese medical texts and sources from other cultures that recommend herbs or combinations of herbs to treat epileptic seizures. He then tests extracts of

these herbs, as well as compounds isolated from those extracts, in standard animal models of epilepsy and in laboratory assays to determine how they work and might be relevant to epilepsy.

An electrical storm in the brain

The brain works by continuously generating tiny electrical impulses in an orderly pattern. These impulses travel along nerve cells (neurons) in the brain and throughout the body via chemical messengers called neurotransmitters. Some neurotransmitters help to propagate this electrical activity, while others restrict it. A seizure occurs when neurons misfire and send a “storm” of abnormal electrical discharges to neurons throughout the brain.

While epilepsy can sometimes be traced to some form of brain injury or disease like trauma, strokes, or tumors, the cause in most cases is unknown. Clinicians divide seizures into partial seizures, in which abnormal electrical activity begins in just one part of the brain, and generalized seizures, which appear to involve most or all of the brain at their onset. Seizures do not often begin immediately after the brain has been injured; many occur months, or even years later, a phenomenon referred to as *epileptogenesis*.

Filling a pressing need

Botanicals, Schachter says, are an important source of therapeutic compounds and, potentially, of new antiepileptic drugs (AEDs). Since seizures in approximately 25 percent of patients do not respond to available pharmacological treatments – and only a small fraction of these patients qualify for or have access to therapeutic brain surgery – there continues to be a pressing need for new epilepsy treatments. “Many of today’s prescription drugs contain natural product derivatives,” he adds. “For example, one of the most recently approved drugs for Alzheimer’s disease is isolated from the snowdrop plant.”

Over the centuries, a large number of Asian, African, and South American herbal medicines have been used singly or in combinations to treat convulsive diseases. Other herbal medicine, including *Huperzine A* (which Schachter has just received a grant to study in patients with epilepsy), work in ways that are potentially relevant to the treatment of epilepsy. *Huperzine A* is a compound that comes



Steven Schachter



Huperzine A is a compound that comes from the Chinese moss plant *Huperzia serrata*, which has been used in Chinese folk medicine to treat fevers and inflammation.

from the Chinese moss plant *Huperzia serrata*, which has been used in Chinese folk medicine to treat fevers and inflammation. Schachter has found that it also has potent anticonvulsant effects in animal models of epilepsy, while other studies have shown that it may have neuro-protective properties.

In addition to Huperzine A, Schachter and his collaborators have studied nearly 20 other herbal medicine extracts and pure, extract-derived compounds isolated from Asian herbal medicines. Like Huperzine A, most have shown significant anti-seizure activity in animal models of epilepsy. "Compounds isolated from botanicals serve a role for plants that produce them," says Schachter. "They may ward off infection or serve as hormones for the plant. We believe that some of them may also have effects on brain cells that will inhibit seizures."

To study this, Schachter and his HMS colleagues examine the effects of herbal extracts and the compounds isolated from them, using the same assays that demonstrate how commonly prescribed AEDs work. Most of these drugs augment the inhibitory effects of GABA (gamma-aminobutyric acid), a neurotransmitter that binds to neurons and prevents the transmission of electrical activity across neurons, or reduce the excitatory effects of glutamate, which has the opposite effect of GABA.

To identify botanicals for study, Schachter has established a network of academic colleagues around the world, including herbal experts at Chinese University of Hong Kong, Keio University (Tokyo), Kyung Hee University (South Korea), Tzu Chi University (Taiwan), the University of Chile, and University Hospital of Dakar in Senegal. "This is a variation on the bench to bedside model," he said, where discoveries in the lab eventually have clinical applications. "[This is] a tradition-to-bench-to-bedside approach."

Only the beginning

Because side effects and drug interactions are common in seizure medications, and since animal models and laboratory assays are not fully predictive of efficacy in humans, compounds isolated from botanicals must go through rigorous testing

before they are used on patients, says Schachter. "Just because these compounds are natural," he says, "it certainly doesn't mean they are harmless or effective. All of this has to be carefully studied, in the same manner as synthesized pharmaceuticals. This is a multi-year effort."

To get from botanicals to pharmaceuticals, he adds, "our goals are to develop a pipeline of novel compounds isolated from herbal medicine extracts that show promising activity in animal models of epilepsy, conduct the necessary preclinical studies to allow us to proceed with early-stage clinical trials, perform these proof-of-concept studies, and then partner to develop these compounds as potential FDA-approved drugs for epilepsy."



One of the most recently approved drugs for Alzheimer's disease is isolated from the snowdrop plant.

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