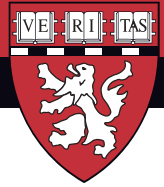


ON THE BRAIN

THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER



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City Life and the Brain

FOR THE first time in history, more people live in cities than in rural areas. According to the United Nations, that urban head count tallies up to more than half of the world's 6.7 billion people. While city life may offer many benefits—ready access to social and cultural events, more employment opportunities, and the promise of higher living standards, as examples—research does show that city life can have drawbacks. For one thing, it's hard on the brain.

Scientists who have begun to look at how the city affects our brains have uncovered some surprising findings, including evidence that city life can impair basic mental processes, such as memory and attention. A study conducted by University of Michigan researchers in 2008 found

that simply spending a few minutes on a busy city street can affect the brain's ability to focus and to help us manage self-control.

In that study, one group of participants strolled in a park, while another perambulated along busy city streets. After undergoing a battery of psychological tests, the people who walked the city streets scored significantly lower on attention and working-memory tests compared to those participants who ambled in the park. The researchers concluded that the stimuli of city life—traffic, neon lights, sirens, and pedestrian-packed sidewalks—direct our attention to things that are compelling, but only fleetingly so, and that

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Tribute to Ted Stevens, Recipient of David Mahoney Prize

TED STEVENS, the former U.S. senator from Alaska and winner of the 2004 David Mahoney Prize, died in a plane crash on August 9, 2010, at age 86. Stevens received the prize in recognition of his outstanding leadership and commitment to research on neurological disorders.

An important advocate of neuroscience research, Stevens helped promote the Decade of the Brain, a collaborative initiative begun in 1990 and co-sponsored by the Library of Congress and the National Institute of Mental Health of the National Institutes of Health.

It was Ted Stevens, above all others, who helped David Mahoney in his quest to make brain research a national priority. Stevens introduced Mahoney to many of his colleagues, which helped ensure the success of Mahoney's efforts to educate Congress on the need to support neuroscience research. Mahoney also fostered this educational initiative through HMNI, the Dana Alliance, and other organizations. The working relationship between Stevens and Mahoney grew into a strong friendship, one that included Mahoney's wife, Hildegarde and Stevens's wife, Catherine.

In his forty years in the Senate, Stevens rose to become the fifth most senior member of that chamber. He held appointments as chairman of both the Senate Appropriations Committee and the Senate Committee on Commerce, Science, and Transportation, which deals with science, engineering, and technology research.

From January 2003 to January 2007, Stevens served as Senate president pro tempore. He was one of only three senators to have held the title president pro tempore emeritus. ♥



this alteration of focus can occur at a pace that leaves us mentally exhausted.

“On a busy city street, it’s probably more adaptive to have a shorter attention span,” says Sara Lazar, PhD, an HMS instructor in psychology and director of the Massachusetts General Hospital Laboratory for Neuroscientific Investigation of Meditation. “If you’re too fixated on something, you might miss a car coming around the corner and fail to jump out of the way.”

“While city life may offer many benefits—ready access to social and cultural events, more employment opportunities, and the promise of higher living standards, as examples—research does show that city life can have drawbacks. For one thing, it’s hard on the brain.”

Some people might call these stimuli distractions, but as Lazar points out, they are actually vital pieces of information. Yet these stimuli do use up a lot of the brain’s natural processing power. The result is something called directed attention fatigue, a neurological symptom that occurs when our

voluntary attention system, the part of the brain that allows us to concentrate in spite of distractions, becomes worn down. People suffering from directed attention fatigue can experience short-term feelings of heightened distraction, impatience, or forgetfulness. When the condition is severe enough, people can exhibit poor judgment and feel increased levels of stress.

Fortunately, there are quick, easy fixes to help the brain restore its ability to focus. Studies show that spending a short period of time—even one as brief as 20 minutes—in a more natural setting can help the brain recover from the stresses of city life. That may be why urban greenways such as Central Park in New York City, Hyde Park in London, and the Emerald Necklace in Boston remain such popular venues—they allow city dwellers a place to escape the turbulence around them.

The benefits of a room with a verdant view can be found in studies involving hospitalized patients and residents of public housing complexes. Patients staying in hospital rooms that looked out on trees, for example, were found to recover more quickly than patients without an arboreal view. Similar results were found in studies involving women



Game Plan

residing in public housing projects; those whose apartments overlooked grassy areas reported they could more easily focus on the tasks of daily life.

This nature-brain symbiosis may be the result of a concept known as attention restoration theory, which was developed by environmental psychologists Rachel and Stephen Kaplan in their book, *The Experience of Nature: A Psychological Perspective*. According to this concept, people can concentrate better after spending time in nature or even after simply looking at pictures of nature. Watching a beautiful sunset or the nesting of birds in a tree doesn't demand the type of attention from the brain that filtering a multitude of competing stimuli on a bustling city street does. Natural vistas allow the brain's attention circuits to refresh.

In her laboratory at Mass General, Lazar is using neuroimaging techniques to study cognitive changes associated with meditation and yoga, practices that are, like nature, calming to mind and body. Lazar and her colleagues have found that people who meditate develop denser, thicker networks of neurons in the prefrontal cortex and right anterior insula of their brains. These areas govern attention and sensory processing.

She says such findings may help explain why urban life can affect our ability to hold things in memory. Memory, she says, relies on the hippocampus, a neural region that is sensitive to cortisol, a hormone secreted by the adrenal glands. Cortisol is linked with stress and secretion of it increases during the body's fight-or-flight response to fear or danger.

"If people are stressed about basic survival, they will have more cortisol and a smaller hippocampus, and thus potential difficulties with memory formation," says Lazar. "Moving to a quieter place could help reduce stress, which in turn can reduce cortisol levels and create conditions conducive to neuroplasticity." Neuroplasticity describes the brain's ability to form new neuronal connections to compensate for injury or changes in one's environment.

If you could use a break from the strain of city life, but don't see your future including a move to a less demanding environment, Lazar says you may want to consider taking up—or increasing your practice of—yoga or meditation. Your brain, and your lifestyle, could benefit immensely. ♥

This is the sixth in a series on how internal and external forces affect the brain.

WARM AND FUZZY, they are not. Even their names evoke dread: *Dead Rising*, *Resident Evil 5*, *Mortal Kombat*, *Thrill Kill*. Mature-rated video games may captivate players with their stunning, lifelike graphics and sophisticated depictions of place and story, but they also provide less attractive features such as violent, gory scenes and wanton killing.

Violent video games have been considered as possible spurs to school shootings, bullying behaviors, and violence toward women. Critics say these games desensitize players to violence. Advocates, by contrast, argue that no causal relationships have been found between video games and violence.

Do violent video games cause players, especially adolescents and young children, to exhibit aggressive behavior? Or do the benefits ascribed to these games, including sharpened coordination and cognitive skills, outweigh any harm? As research on the subject continues, the answer seems to be "yes" to both.

"There's no reason to think that video games can't teach both violence and cognitive skills," says David Bickham, PhD, an HMS instructor in pediatrics and a staff scientist at the Center on Media and Child Health at Children's Hospital Boston. "We know that they can do both, but much more research is needed to answer definitively."

Controversy escalates as violence increases

As a genre, video games date back to the late 1940s, when missile defense systems were "played" on early cathode-ray-tube monitors. The first documented computer game, *Noughts and Crosses*, did not become commercially available until 1952. More than two decades would pass before controversy over the violence of such games began. The release in 1976 of *Death Race*, a game in which players try to hit zombie pedestrians with cars, is now considered a catalyst to that debate. Four years later, game violence reached a new intensity with the release of *Mortal Kombat*, which featured digitized images of real actors as characters bent on ripping out their opponents' hearts. The more recent, and popular, *Grand Theft Auto* series has incited a new round of discussion of the possible link between violence and video games. In this game series, participants play big-city criminals who kill people, pick up prostitutes, steal cars, and join gangs.

As research into links between video-game violence and behavior ramps up, so too do the

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revenues of the video game industry. According to the Electronic Software Association, in 2009 the U.S. industry took in \$19.6 billion. While mature-rated games accounted for only 17 percent of those sales, six of the ten best sellers had violent themes, according to CNBC.

Cause and effect

What do past studies tell us about how the brain processes video-game violence? A 2006 study by scientists at Indiana University found that certain areas of teens' brains become active while violent video games are viewed and that regions that govern self-control remain less engaged. A 2010 review of 130 video game studies, conducted by researchers at Iowa State University, suggested that playing violent video games increases aggressive thoughts and decreases empathy.

Despite such findings, we still don't have a lot of information about cause and effect, says Cheryl Olson, ScD, an HMS assistant clinical professor in psychiatry and co-author of the 2008 book *Grand Theft Childhood: The Surprising Truth About Violent Video Games and What Parents Can Do*, which centers on middle-school children. "Violent video games are not causing mass violence in society," Olson says, "which suggests that these games may have little effect on violent crimes. On the other hand, playing mature-rated games statistically predicts a greater risk for bullying and fighting."

Individual risk for violent behavior, therefore, may be a separate concern. Researchers have found that children go through a variety of physical and mental changes when they play video games with violent content. In testimony before the Senate Committee on the Judiciary in 2006, Bickham described these effects: "They begin to think aggressively and to solve problems with violence. In this heightened and primed state, children are more likely to perceive other people's behaviors as aggressive, and they are more likely to respond aggressively."

Over time, he continued, exposure to this violent media can lead children to "adopt aggressive skills, beliefs, and attitudes; desensitize them to violence; and take aggressive approaches to interactions with other people. Using violent media as a child predicts aggressive behavior in adulthood."

Parent, beware

That doesn't mean that playing violent video games would be the sole catalyst for such behavior. Biology and environmental factors each play a role too.

"We each have a lifetime of experience to draw on," says Bickham. "The brain reaches for a solution and some of these solutions originate in different spheres of neurological influence. That's why some kids who play violent video games become violent, while others don't."

Bickham says children act on their beliefs and attitudes about violence based on the strength of competing beliefs, such as those from family and classmates, and the environment in which they live.

One issue that has not yet been thoroughly assessed, says Olson, is whether children understand the difference between real violence and fantasy. Children do report that TV news bothers them more than violent movies or video games; they know video games are "fake," while news is real. Children do not, however, understand satire until about age 12, she says, adding that satire underlies the *Grand Theft Auto* games. Nor do children realize that the casual racism in many such games can be intended to suggest that racism is hurtful.

While much more attention has been paid to how violent video games hurt rather than help, both Olson and Bickham say that these and other video games can have real-life benefits, including improving planning and problem-solving skills. Studies show that video-game playing can also help develop visual skills, spatial reasoning, higher-level thinking, and strategizing. Other research suggests that playing video games may have mental health benefits, including easing the symptoms of depression. This area, however, has not been studied extensively.

While Olson and Bickham have slightly different takes on the controversy, both agree that much needs to be sorted out through research and that parental involvement in this type of child's play is key. Parents need to be engaged in decisions on which video games to purchase. Olson notes that the Electronic Software Rating Board (www.esrb.org) has expanded its descriptions of games to include plot summaries and specific details on objectionable content. And Bickham, who suggests www.common sense media.org as a pre-purchase resource for information about games, says parents also need to watch for patterns in their children's behavior that can hint at problems. Playing mostly mature-rated games for more than 15 hours per week, for example, has been shown to be a risk factor for aggression.

"All media, including video games, should be on the parental radar," Bickham says. "It's when we don't pay attention that kids get in trouble." ♥

Harvard Mahoney Neuroscience Institute at Harvard Medical School

CELEBRATES ITS TWENTIETH ANNIVERSARY 1990–2010



SINCE ITS FOUNDING in 1990—the inaugural year of what former President George H.W. Bush designated would be the Decade of the Brain—The Harvard Mahoney Neuroscience Institute has helped advance neuroscience at Harvard Medical School by promoting public awareness of the importance of brain research and by helping to fund research at the School's Department of Neurobiology. The Institute was created by an agreement between David and Hildegarde Mahoney and Harvard Medical School.

David Mahoney was one of the youngest and brightest stars in the world of advertising and public relations, and he rose to become the Chief Executive Officer of Norton Simon, Inc., a conglomerate that owned or controlled several well-known international brands. After Norton Simon was acquired by the Esmark Company, David intensified his charitable activities in such organizations as The American Health Foundation, which he helped found, and the Phoenix House. Working with these groups, David discovered that few members of the general public, or officials in government, recognized the role of the brain in many disorders, the more noteworthy being depression, addiction, anxiety, stroke, and neurodegenerative disorders such as dementia, Alzheimer's disease, and Parkinson's disease.

Mahoney's realization of the need to promote brain research coincided with that of Daniel Tosteson, then the dean of Harvard Medical School and a noted innovator in medical education. Tosteson understood the need for telling the story of the exciting research findings that were being generated at Harvard Medical School, and he enthusiastically endorsed David and Hillie's idea for an organization like HMNI. The Mahoneys and Tosteson agreed that HMNI should have three distinct objectives. First, it should carry out educational activities not only through print media, such as *On the Brain*, the Institute's tri-annual newsletter, but also through conferences and symposia, each of which would be geared to the general public and legislators. Second, it should recognize those individuals who had done or were doing exemplary work in promoting an understanding of the brain, through the biennial awarding of the David Mahoney Prize. And third, HMNI should make fellowship funding available to the School's Department of Neurobiology, enabling gifted young investigators to work with outstanding senior scientists in the department.

Over the past twenty years HMNI has been an unqualified winner in achieving these three goals. It continues to be committed to its mission.

"When my late husband David and I established the HMNI with the late Dean Tosteson, we hoped it would be a major factor in creating brain awareness. Little did they nor I know, how very successful it would really become."

Hildegarde Mahoney – October 2010



David Mahoney



Hildegarde Mahoney



Daniel Tosteson

Photo: Magdalena Tosteson

The Mahoney Fellows Program— Progress in Neuroscience

The Mahoney Fellows Program has supported the research of promising young neuroscientists for nearly two decades. In doing so, the Program upholds a key part of the mission of the Harvard Mahoney Neuroscience Institute: to enable gifted young investigators to work with outstanding senior scientists in the Department of Neurobiology at Harvard Medical School. This year, three researchers have been nominated as Fellows. It is their research—as well as that of former Fellows such as the five included here—that spurs progress in neuroscience and advances our understanding—and appreciation—of the human brain.

2010 Mahoney Fellow Nominees



Katharina Cosker, PhD, will continue her work in the laboratory of Rosalind Segal, where Cosker investigates the role of neurotrophins, proteins important to maintaining the health and survival of nerve cells and their axons.



Jonathan Nassi, PhD, will continue research he has begun in Richard Born's laboratory. Nassi studies the role of feedback processing in the cerebral cortex, a function that appears to go awry in some psychiatric diseases, such as schizophrenia.



Kiran Padmanabhan, PhD, working in the laboratory of Charles Weitz, will advance his pioneering work on the role of proteins associated with the circadian clock mechanism, which drives fundamental physiological and metabolic rhythms and optimally coordinates them with the light–dark cycles of the 24-hour day.



Photo: Graham Gordon Ramsay

David Cardozo, PhD
1993 Mahoney Fellow
Assistant Professor of Neurobiology, Department of Neurobiology; Associate Dean of Graduate Studies, Division of Medical Sciences, Harvard Medical School

HMNI Mentor: Bruce Bean, Harvard Medical School

Research: Cardozo's current interests involve both the laboratory and the classroom. His laboratory research concentrates on finding new sources of neural stem cells and on investigating the potential these cells hold as treatment for patients with neurodegenerative disorders. His education research focuses on fine-tuning a tutorial process that brings greater rigor to small-group learning. For more than a decade, he has taught the Human Nervous System and Behavior course for Harvard's second-year medical and dental students. He also serves as Associate Dean for all of the graduate students in the Division of Medical Sciences at Harvard Medical School. While an HMNI fellow, Cardozo studied how calcium channels function in dopamine-producing neurons, and how their function may change in Parkinson's disease.

Reflection: "What I learned while a fellow I pass on to the graduate students I now work with: Follow your heart, pursue your passion, and be the best scientist you can be. The rest will follow."



Bevil Conway, PhD
2003 Mahoney Fellow
Knafel Assistant Professor of Natural Sciences, Program in Neuroscience, Wellesley College; Lecturer in Neurobiology, Harvard Medical School

HMNI Mentor: David Hubel, Harvard Medical School

Research: Conway explores how cells in the brain’s cerebral cortex encode color. In his PhD research with Margaret Livingstone, Conway investigated neural mechanisms for color and motion in the primary visual cortex. Using functional magnetic resonance imaging, he and his colleagues have since describe a dedicated “architecture” of brain regions that are specialized for processing color. His lab currently uses a multi-pronged approach of color psychophysics, computational modeling, and fMRI-guided single-neuron recording to decipher the transformation of cone signals that underlie color perception. Conway is also a visual artist and occasionally gives public presentations on the intersection of neuroscience and art.

Reflection: “Support from the Mahoney Fellowship came at a pivotal point in my career. It gave me the flexibility to pursue my interests using a range of techniques and approaches.”



Kyung-Dall Lee, PhD
1993–94 Mahoney Fellow
Professor of Pharmaceutical Sciences, College of Pharmacy, University of Michigan

HMNI Mentors: Peter Hollenbeck, now at Purdue University; Joel Swanson, now at the University of Michigan

Research: While an HMNI fellow, Lee focused on the role of kinesins, a class of proteins, in nerve cells and investigated how their function is regulated. These proteins attach to saclike structures called vesicles and act like motors, moving the vesicles and their contents—molecules vital to cellular function—throughout a neuron. Following his research at HMS, Lee pursued a career as a pharmaceutical scientist. He now studies other delivery mechanisms, with the aim of developing improved or new ways to deliver drugs to cells, particularly cancer cells.

Reflection: “I came to Harvard with a background in biophysics and cancer research. Harvard Medical was able to develop a position that would allow someone with my background to work there. I think this ability to build hybrid projects is one of the strengths of the School. I was able to work in two different departments on related research—and to apply successfully for an NIH grant. That experience cemented my interest in academic research and launched my independent career.”



Emily Liman, PhD
1993–95 Mahoney Fellow
Associate Professor of Biological Sciences, Department of Biological Sciences, Neurobiology Section, University of Southern California

HMNI Mentor: Linda Buck, now at the Fred Hutchinson Cancer Research Center and the University of Washington in Seattle

Research: Liman explores how our senses function by focusing on the cellular and molecular mechanisms by which primary sensory neurons transduce signals in the environment into electrical impulses. Working in Buck’s laboratory on the heels of her Nobel Prize–winning discovery of odorant receptors, Liman extended Buck’s work by identifying molecules that form part of the olfactory signaling pathway downstream of the receptors. Liman now studies how sensory neurons in the tongue and skin respond to chemosensory input to signal taste or pain. Her work has shown how a single class of ion channels can contribute to a variety of sensory responses from pheromone detection to the tingling effects of carbonation.

Reflection: “My work in Linda Buck’s lab taught me to pay attention to the details, stay close to the data, and, most of all, to keep my eye on the big questions.”



Kenton Swartz, PhD
1993 Mahoney Fellow
Senior Investigator, National Institute of Neurological Disorders and Stroke, National Institutes of Health

HMNI Mentors: Bruce Bean, Harvard Medical School; Roderick MacKinnon, now at Rockefeller University

Research: Swartz studies the molecular basis of nerve-impulse generation by investigating how changes in voltage along the nerve cell membrane help calcium and potassium ions move across synapses. Swartz began by studying how two classes of proteins, G-proteins and kinases, affected calcium channels and the passage of calcium ions, and how naturally occurring toxins, such as the tarantula’s hanatoxin, influenced potassium channels and the passage of potassium ions. By understanding how voltage regulation helps these ions move, scientists may be able to design drugs that control the propagation of nerve impulses.

Reflection: “The HMNI fellowship came at a critical stage, allowing me to develop a project that I could use to initiate an independent research career. I worked with a fantastic group of scientists. They influenced the way I think about scientific problems and the approach I take to answering them.”

David Mahoney Prize Recipients

The Harvard Mahoney Neuroscience Institute's David Mahoney Prize is awarded every two years to individuals who excel at "building a bridge between the public and the scientists dedicated to brain research." Eight people have received the award since its inception in 1995. This year's recipient is Kay Jamison, professor of psychiatry at The Johns Hopkins University School of Medicine.



**1995
President and Mrs. Ronald Reagan**

For their openness regarding the former President's fight against Alzheimer's disease



**1996
Mike Wallace**

former correspondent for the CBS News show *60 Minutes*

For his efforts to remove the stigma associated with depression



**1998
Roone Arledge**
former chairman of ABC News

For his role in raising awareness of neuroscience research by bringing the latest news of brain research to the public

Support HMNI and Neuroscience Research

The Harvard Mahoney Neuroscience Institute has supported laboratory research at Harvard Medical School and promoted public awareness of neuroscience research for twenty years. If you would like to join us in this mission, we would welcome your support in the form of a contribution to the Harvard Mahoney Neuroscience Endowment.

Checks may be made payable to Harvard Medical School and mailed to:

Harvard Medical School
attn: HMNI Ms. Alexandra Chase
401 Park Drive, Suite 22 West
Boston, MA 02215

To give online by credit card, visit the Harvard Medical School web site at www.hms.harvard.edu and click on **Make a Gift**. Please indicate HMNI in the Note field provided with the form.

You may also call the Office of Resource Development at 617-384-8500 and ask for **Gift Processing**.



**2000
Larry King**

Emmy Award-winning talk show host for CNN
For presenting information on brain health and brain disorders to his television audience and for keeping the public informed on the role brain research plays in finding effective treatments and therapies



**2002
William Safire**

former Pulitzer Prize-winning author and columnist for the *New York Times*
For his journalistic efforts to bring neuroscience to the world's attention, which included highlighting the importance of brain research



**2004
Ted Stevens**

former U.S. Senator from Alaska
For his advocacy among policy makers in Washington, D.C., for research on neurological disorders and for his pivotal contributions toward instituting the Decade of the Brain



**2006
James Watson**

Nobel Prize recipient for the co-discovery of the structure of DNA
For being a leader among his peers by helping to identify ten achievable goals for brain research during the Decade of the Brain



**2008
Charlie Rose**

Emmy Award-winning journalist and talk show host for PBS
For helping to enlighten the nation on the importance of brain research through his frequent interviews with dedicated scientists in the field



**2010
Kay Jamison**

professor of psychiatry, The Johns Hopkins University School of Medicine
For her outstanding research in manic-depressive illness and her candor over her struggles with the illness

Taming Delirium After Surgery

EACH YEAR, up to 56 percent of all hospitalized seniors over age 65 in the United States—more than 2.5 million people—experience delirium. The condition often follows fast on the heels of surgery, anesthesia, or serious illness, complicating hospital stays and delaying patients' return to home, family, and friends. Typically acute at onset, delirium is marked by a constellation of neuropsychiatric abnormalities, chief of which are decreased attention span and a waxing and waning state of confusion. At best, delirium reverses quickly; at worst, its symptoms trigger serious, even fatal, consequences.

Now, funded by a five-year, \$11 million grant from the National Institute on Aging, a team of scientists from Harvard Medical School, the Institute for Aging Research at Hebrew SeniorLife, Beth Israel Deaconess Medical Center, and Brigham and Women's Hospital will examine the causes and outcomes of delirium, with the goal of finding new approaches to preventing it and its long-term consequences. Called SAGES (Successful AGing after Elective Surgery), the study will follow 500 surgery patients over the age of 70 for 18 to 36 months to assess their post-surgery cognitive and functional status.

"Delirium is a common complication of surgery, but it's also preventable," says co-principal investigator Sharon K. Inouye, MD, an HMS professor of medicine and director of the Aging Brain Center at the Institute for Aging Research who has studied delirium and its manifestations for more than two decades. "SAGES will advance our understanding of the short- and long-term outcomes of delirium and, ultimately, help us improve care for older surgical patients," she adds.

Proper diagnosis is crucial

The confusion of delirium is accompanied by rapid changes in brain function. In addition to the symptoms described earlier, patients typically manifest altered levels of alertness, consciousness, and awareness. And research also has found that they show decreases in short-term memory and recall, disrupted attention, and disorganized thinking.

While delirium's exact cause remains unknown, many experts think a variety of structural and physiological mechanisms, including multiple neurotransmitter disorders, can cause it.

"While most seniors who suffer an episode of delirium go on to a full recovery," Inouye says, "nearly 20 percent experience complications, including death.

Up to 40 percent of delirium episodes, however, are preventable, which makes taking steps to avoid or correctly diagnose this condition crucial."

Delirium, says Edward Marcantonio, MD, an HMS associate professor of medicine at BIDMC and co-principal investigator on the study, can go unrecognized by physicians and nurses because it is episodic and often manifests simultaneously with dementia. In addition, its clinical consequences are largely underappreciated. Misdiagnosing delirium, he adds, leads to longer hospital stays, missed opportunities for treatment, unnecessary medications, or an overall poorer quality of life.

To treat delirium, physicians may look first at a patient's medications, stopping or changing any that could contribute to the condition. Disorders that exacerbate delirium, such as anemia, low or inadequate oxygen levels in body tissues, infection, and kidney or heart failure, should be treated promptly.



Study aims to stem problems after surgery

The SAGES study will bring together medical experts in surgery, psychiatry, anesthesiology, neurology, neuropsychology, medicine, epidemiology, and biostatistics to examine a host of delirium-related issues. Epidemiologists, for example, will examine the factors that enable a person to avoid delirium after surgery and exposure to anesthesia. Others will investigate inflammatory biomarkers and proteins to determine whether molecular changes can predict who is at risk for the condition. MRI testing, administered both pre- and postoperatively, will help determine whether delirium has long-

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Guiding Light to Parkinson's Treatment

IT MAY SEEM unusual to bring up the crystal jellyfish in a discussion of Parkinson's disease. This luminescent marine creature seems a world removed from a neurodegenerative disorder linked with a decrease in the production of the neurotransmitter dopamine.

They do have a link, though: a protein known as GFP, green fluorescent protein. GFP is used defensively by the crystal jellyfish; when disturbed,

the creature triggers production of the protein and bathes itself in the green-blue glow the protein emits. Scientists also use that glow to their advantage. By linking the color-producing protein to one of its more subdued cousins, they can use GFP's bright green glow as a beacon and monitor protein movement and activity in a cell. For a group of scientists at Massachusetts General Hospital, GFP is key to experiments designed to assess potential Parkinson's treatments.

"The GFP is a tool that allows us to follow the misfolding of proteins that is endemic to Parkinson's," says Pamela McLean, PhD, an HMS assistant professor of neurology. McLean is a member of the MassGeneral Institute for Neurodegenerative Disease (MIND), where she focuses on researching Parkinson's disease.

The protein that most interests McLean is alpha-synuclein, which is found primarily in neural tissue. Clumps of alpha-synuclein form brain lesions that are the hallmark of Parkinson's disease and other neurodegenerative disorders.

Signaling problems

Parkinson's disease occurs when dopamine-producing cells in the brain's substantia nigra, a central-brain structure, begin to malfunction and die. Dopamine



Taming Delirium After Surgery

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term impacts on brain function. Investigators also will use sophisticated assessment tools to determine whether certain levels of pre-surgery cognitive and physical health protect an individual from delirium's onset.

Inouye will assess participants 1.5 to 3 years after they've had elective surgery for such conditions as total hip or knee replacement, lower extremity arterial bypass, open abdominal aortic aneurysm repair, and lower extremity amputation. The evaluations will occur in the hospital or at the patient's home.

"As the population ages and surgical interventions expand for older people, this study will advance our knowledge about delirium's long-term effects," says Selwyn Rogers, MD, an HMS associate professor of surgery, chief of the Division of Trauma, Burns and Surgical Critical Care at BWH, and a SAGES co-principal investigator. "By doing so, we may improve our ability to diagnose delirium in a timely manner and potentially treat it to mitigate its effects."

Negotiating delirium's maze

In the late 1980s, Inouye developed the Confusion Assessment Method to help physicians identify and recognize delirium and to standardize the assessment used by clinicians who are not trained in psychiatry. In addition, Inouye developed an innovative, hospital-based approach for combating delirium. The Hospital Elder Life Program, or HELP, works to keep hospitalized older patients oriented to their surroundings and mobile within the limits of their physical condition.

Despite the considerable progress that she and her colleagues have made, Inouye says much work remains. At the Aging Brain Center, Inouye and her team are investigating whether delirium alters the course of dementia and whether it leads to longstanding cognitive impairment and pathologic changes in the brain. The SAGES study should provide insight, along with clues to interventions that can stem delirium's damage. ♥

helps orchestrate parts of the brain that contribute to movement and coordination. When these dopamine-producing cells die, the signals that tell the body to move are diminished, leaving people unable to initiate or control their movements in a normal way.

The development of Lewy bodies, which are abnormal clumps of proteins, primarily alpha-synuclein proteins, has been linked to the death of dopaminergic cells. The clumping interferes with the protein's efforts to fold into conformations that allow it to function properly—resulting in the movement disruptions that are the telltales of Parkinson's: tremors; muscle rigidity; slowed, or bradykinetic, movements; and impaired balance and coordination.

"If you look at the brains of Parkinson's disease patients after they die," says McLean, "the major pathology you will find is Lewy bodies. But we don't yet know why misfolded alpha-synuclein ends up in Lewy bodies."

Misfolding is not the only mystery that surrounds alpha-synuclein. Researchers aren't sure what the protein's exact function is, either. Some studies suggest that the protein can be neuroprotective *or* neurotoxic, depending on how much of it is present in brain cells.

Glowing proteins

In the lab at MIND, McLean and her colleagues are using a cloned version of GFP to identify damaged alpha-synuclein in brain cells, with the goal of developing drugs that stop the misfolding. To do this, the scientists split GFP in half, attaching one half to the end of one alpha-synuclein protein and the other half to another. As the two proteins come together during misfolding, the fluorescent ends of the GFP join and give off the characteristic green-blue glow.

McLean and her team think groups of several alpha-synuclein molecules are the culprits in killing off dopaminergic cells in Parkinson's patients. "If we think these groupings are critical to the formation of toxic species," she says, "we can look at ways to keep alpha-synuclein from clumping together in the first place. GFP gives us a read-out for misfolding. More green means more groupings; less green means fewer."

McLean, together with other scientists at MIND, has identified a natural avenue for preventing protein misfolding: heat-shock proteins. Heat-shock proteins guide other proteins into forming functional three-dimensional shapes. When activated in the brain, these proteins either correctly refold

alpha-synuclein or whisk away the clumped proteins to the cells' recycling system. "We are studying whether drugs might activate additional heat-shock proteins so as to protect the brain against misfolded alpha-synucleins," McLean says.

Heat-shock therapy

One such protein, known as HSP70, has been shown to prevent the huntingtin protein from bunching together. This protein is implicated in Huntington's disease, a neurodegenerative disorder that affects muscle coordination and leads to cognitive decline, dementia, and death. McLean and her colleagues are conducting tests to see whether HSP70 might also prevent alpha-synuclein from misfolding and damaging dopaminergic cells.

Geldanamycin, a compound used to degrade cancer proteins, has been found to block a protein that inhibits HSP70's production. Researchers are investigating whether it can raise HSP70 to levels sufficient to prevent alpha-synuclein from misfolding in animal models.

In laboratory experiments, the MIND researchers created an in-vitro model in which alpha-synuclein was overproduced by cultivated cells, causing them to clump and die. When, however, the researchers increased the number of heat-shock proteins in the cultivated cells, the cells did not die. The clues to these live-or-die happenings came from GFP: Cells that were treated and healthy remained dark while untreated cells glowed when the alpha-synuclein proteins clumped together.

"Our studies tell us that targeting heat-shock proteins, especially HSP70, may be a useful therapeutic strategy for Parkinson's disease," says McLean. "But it's not a cure. By the time someone is diagnosed, they've already lost about 50 percent of the cells in the substantia nigra—and you can't get those cells back. This type of drug, however, could halt the progression of the disease and give patients a fairly good quality of life."

The next step is getting a drug company interested in taking this information and developing a drug for Parkinson's. The end result, however, would still be a long way off, cautions McLean. It can take up to two decades and millions of dollars to develop and test a drug before it can be used in humans.

Until then, she says, the best bet is to develop a good biomarker for the disease. That way, when an effective drug is developed, clinicians will be able to identify Parkinson's patients early, perhaps even before symptoms appear, and start a therapy before too many brain cells die. ♥

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