

ON THE BRAIN

THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER

Involuntary Speech

WHAT DO King George VI, Winston Churchill, Wilt Chamberlain, Marilyn Monroe, and Joe Biden have in common? At one time or another, each has struggled with stuttering, sometimes painfully, and, sometimes, publicly.

Stuttering, also referred to as stammering, is a communication disorder in which the normal flow of speech is interrupted by involuntarily repetitions (th, th, th, the); prolongations of sounds, syllables, words, or phrases (ththththis); or by pauses during which a person is unable to formulate words. After years of attributing stuttering to childhood emotional trauma, poor parenting, or excessive anxiety, the scientific community is now gaining a clearer understanding of the neural basis of this condition. Their findings are shattering the conventional wisdom about stuttering.

"There's ample evidence that stuttering is a brain disorder," says Peter Rosenberger, a former HMS assistant professor of neurology who also founded and, for 30 years, directed the Learning

Disorders Unit at Massachusetts General Hospital. This evidence has put to rest the misconception that those who stutter are not as intelligent or capable as fluent speakers.

According to the Stuttering Foundation, a national, nonprofit organization working toward the prevention and improved treatment of stuttering, nearly 68 million people worldwide stutter. In the United States, there are more than 3 million people who speak with a stutter. Approximately 5 percent of all children (boys more often than girls) go through a period of stuttering that lasts six months or more. Nearly three-quarters of them no longer stutter by late childhood, while others carry their struggle—and such potential consequences as low self-esteem, the effects of ridicule, and social anxiety disorder—into adulthood.

The most common form of stuttering, developmental stuttering, occurs as a child is developing speech and language skills. According

continued on page 2

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CONTENTS

- 1 *Involuntary Speech*
- 3 *Sleep Deprivation and the Brain*
- 5 *Diabetes: A Link to Cognitive Function?*
- 7 *HMNI Fellows: The Future of Neuroscience*



to some scientists, the stuttering is triggered because those skills have not developed enough to meet the child's verbal needs. This form of stuttering tends to run in families. In 2010, scientists at the National Institute on Deafness and Other Communication Disorders (NIDCD) discovered three genes implicated in developmental stuttering. Another form, neurogenic stuttering, often follows an injury to the brain such as stroke, trauma, or tumor. Psychogenic stuttering, another, albeit rare, form of the disorder, is identified most often in people suffering some form of mental illness.

Left side, right side

While much of stuttering remains a mystery to scientists, they do know, based on imaging studies, that the brains of people who stutter are structurally different for those of people who do not stutter; these differences could affect behavior.

Positron emission tomography studies of people who stutter show decreased activity in cortical areas associated with language processing, such as Broca's area, which controls motor functions linked with speech production. People with damage to Broca's area can understand language but cannot successfully form words or produce speech. These same studies show hyperactivity in the motor areas of the brain, including the basal ganglia, a structure deep in the brain's gray matter that helps control muscle and nerve function.

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Previously, scientists had found evidence of rewiring in the brains of people who began stuttering as children. Fluent speakers use the left side of their brain to integrate what they hear with word formation. People who stutter, however, transfer this workload to the right hemisphere; a defect in the left hemisphere prevents the motor cortex, which controls movement, from generating the instructions that coordinate the muscles of the throat and mouth to aid in speech production. The brain compensates by shifting speech-related tasks to the right hemisphere. Thus, even though an individual who stutters knows what words to say,

those words are produced with a struggle and as halting, stammering speech.

Slow and deliberate does it

Some 80 percent of children who stutter recover spontaneously. For other children and adults who stutter, behavioral therapies to teach specific skills can lead to improved oral communication. For very young children, early intervention and treatment may help prevent stuttering from becoming a lifelong problem. There is, however, no cure for the condition.

According to NIDCD, many of the current behavioral therapies used to treat stuttering teach the person how to minimize the expression of the disorder by speaking slowly, regulating breathing, or gradually progressing from single-syllable responses to longer words and more complex sentences. One technique, called delayed auditory feedback, takes an artificially modified version of the original acoustic speech signal and feeds it back to the individual through headphones. This technique and other behavioral therapies, says Rosenberger, have been effective in helping stutters become fluent speakers.

In the 1970s, Rosenberger and others investigated using haloperidol, a powerful anti-dopaminergic drug, to treat stuttering. Although they found the drug could effectively help those who stutter to become more fluent, the drug's side effects overpowered its benefits so its use was discontinued.

The Food and Drug Administration has yet to approve any drugs for stuttering, but some drugs approved to treat other problems are now being tested for the condition. Pagoclone, an anti-anxiety medication, and asenapine, an atypical antipsychotic drug, have shown some promise. The former enhances the activity of the neurotransmitter GABA, which may be disrupted in people who stutter, while the latter blocks dopamine receptors in the brain. Both potential treatments require further study.

Two years ago, the obstacles facing those who stutter received popular attention when the movie *The King's Speech* won the Academy Award for Best Picture. The film depicted how England's King George VI struggled with and overcame stuttering with the help of a speech therapist.

"The movie is quite good," opines Rosenberger. "It provides an intelligent look at stuttering and sobers people's attitudes toward people who struggle with stuttering." ♥

Sleep Deprivation and the Brain

This article is part of a series on the internal and external forces that affect the brain.

SLEEP IS ONE of the body's most important functions. It is essential for cellular renewal and tissue maintenance, for the removal of cellular debris, and for neural processing and archiving, including the firm establishment of memories. In addition, deep, restorative sleep stimulates brain regions used in learning.

Unfortunately, though, many people in this country average less than the seven to nine hours of sleep per night recommended by the National Sleep Foundation—and by many physicians and sleep researchers. This shortfall has consequences: Millions are sleep deprived and thousands suffer the unexpected effects of sleep loss.

Sleep deprivation is simply the condition of not getting enough sleep and can be either acute (a single night of poor sleep) or chronic (a string of nights with insufficient sleep). Most of us know the effects of a bad night's sleep: We're irritable, clumsy, and our cognition and recall are just a bit off. Even one night of sleep deprivation can lead to difficulty concentrating, impaired judgment, and diminished cognitive function. Over time, repeated periods of sleep loss can lead to such deleterious mental effects as hallucinations or mania.

"Every function of the brain that has been tested is affected by sleep loss—mood, learning, reaction time," says Elizabeth Klerman, an HMS associate professor of medicine and a sleep researcher at Brigham and Women's Hospital.

How sleep works

Our understanding of sleep has developed over decades as researchers, including those in Harvard Medical School's Division of Sleep Medicine, have deciphered its biological basis. The human sleep-wake cycle is controlled by two complementary mechanisms. Our circadian clock, which regulates the body's internal processes and alertness levels, is located in the hypothalamus, a region of the brain that also produces hormones that control such processes as sleep, mood, and hunger. Governed by light-dark cycles, this clock is key to controlling the timing of our sleep. Circadian rhythms alone, however, are not enough to regulate our sleep. Sleep-wake homeostasis, or the accumulation of sleep-inducing substances in the brain, essentially reminds our body that it needs to sleep after a certain period of being awake.

continued on page 4



Neurotransmitters in the brain also play an important role in helping us fall asleep, remain asleep, and wake up. One of these chemical messengers is the neurotransmitter melatonin. During the day, the pineal gland, a small gland, located just above the middle of the brain, that produces melatonin, is inactive. Daytime levels of melatonin, in fact, are barely detectable. When the sun sets, or our exposure to light is lost, the pineal gland releases melatonin into the bloodstream, making us feel sleepy. Melatonin levels stay elevated throughout the night, but decrease as the levels of light increase with the new day.

The researchers found that areas of the prefrontal cortex, a center for working memory and reasoning, are more active in people who are sleep deprived. This indicates that, for a given task, the prefrontal cortex has to work harder in sleep-deprived people than in those who've had sufficient sleep.

During the hours we are awake, the neurotransmitter adenosine attaches to receptors in the brain. The longer we are awake, the greater the amount of adenosine that attaches to these receptors and accumulates in the brain. When we sleep, adenosine is broken down and its levels in the brain fall. If we don't get enough sleep, adenosine remains in the brain, causing grogginess.

Sleepyhead

A number of studies show how sleep deprivation affects brain function. A University of California, San Diego, study used functional MRI to monitor activity in sleep-deprived brains. The researchers found that areas of the prefrontal cortex, a center for working memory and reasoning, are more active in people who are sleep deprived. This indicates that, for a given task, the prefrontal cortex has to work harder in sleep-deprived people than in those who've had sufficient sleep. In 2011, researchers at the University of Wisconsin found that the brains of rats kept awake for extended periods began to shut down, neuron by neuron, even though the rats were still awake. They found that the most-used neurons were the first to shut off. Such results may help explain why we function less well the longer we stay awake or when we have inadequate sleep. Other researchers have observed genetic changes in the sleep-deprived

brain that could lead to health problems such as heart failure, stroke, and depression and mood disorders.

Shifting schedules

Sleep deprivation, says Klerman, is often self-imposed, a function of our hectic work schedules and the presence of electronic devices and 24-hour entertainment sources that keep us occupied at all hours.

Without adequate sleep, some people's performance suffers. "After a couple of days without adequate sleep, many of these folks say they are not tired, but their performance worsens," says Klerman, who has conducted performance studies on the sleep deprived. "The brain is not accurately conveying alertness and tiredness and this affects self-assessment of performance."

By some estimates, excessive sleepiness contributes to a greater-than-twofold risk of sustaining an occupational injury. The National Highway Traffic Safety Administration estimates that drowsy driving, often a reflection of the lack of sleep, is responsible for at least 100,000 automobile crashes (about 1 every 6 minutes), 71,000 injuries, and 1,550 deaths each year. Much of this mayhem and loss could be eradicated if drivers got adequate amounts of sleep.

As part of her work for the U.S. space program, Klerman led a National Space Biomedical Research Institute (NSBRI) team that developed computer software that uses sophisticated mathematical modeling to help astronauts and ground personnel adjust to shifting work-sleep schedules. The software uses a complex mathematical formula to predict how a person will react to specific conditions and to allow users to interactively design better work schedules. The software also features a "shifter," a component that prescribes when to use light to reset, or shift, a person's circadian clock to improve performance at critical times, such as during a space mission.

Klerman says the software can be adapted for people who work night shifts, including medical personnel and first responders.

"Our lives, including our safety," she said in an NSBRI press release announcing the software, "are impacted by people who have jobs requiring shift work or extremely long hours and who may be at increased risk of accidents affecting themselves or others."

To diminish that risk, we should all say, "Sweet dreams." ♥

Diabetes: A Link to Cognitive Function?

THE COMPLICATIONS OF uncontrolled diabetes are well recognized: nerve damage, kidney disease, blindness, and circulation problems that affect the extremities. The disease's impact on the brain, however, is often overlooked. This oversight could spell trouble for millions of Americans who face the daily challenge of controlling their blood sugar.

According to the American Diabetes Association, an estimated 26 million Americans have diabetes. Another 79 million have prediabetes, a condition in which blood sugar levels are higher than normal but not high enough for a diabetes diagnosis.

A growing body of evidence suggests that the cognitive health of millions with the disease is as much at risk as are other body systems from the effects of out-of-control blood sugar. "Unlike for certain other diseases, scientists originally didn't know where to look in the brain for the effects of diabetes," says Gail Musen, an HMS assistant professor of psychiatry and assistant investigator in the Section on Clinical, Behavioral, and Outcomes Research at Joslin Diabetes Center. "We knew, theoretically, that because it affects so much else in the body, it also could affect the brain." Since Musen's first study of diabetes and brain



More recently, Gail Musen and her colleagues discovered reduced white matter integrity and cortical thickness in patients with long-standing type 1 diabetes. "It's not clear," she says, "whether such changes to the brain will have a more profound effect as a patient ages."

function nearly a decade ago, the scientific community has gained a greater understanding of how diabetes—primarily type 1 diabetes—affects brain function.

Shrinking brain

Musen's 2006 study, reported in the journal *Diabetes*, was the first comprehensive study of density changes in the brain's gray matter as a result of type 1 diabetes. Its findings suggested that persistent hyperglycemia, or high blood sugar, and acute severe hypoglycemia, or low blood sugar, have an effect on brain structure. The gray matter reductions were small and did not necessarily show any clinically significant cognitive impairment, but the brain regions involved included the memory, attention, and language

processing centers. More recently, Musen and her colleagues discovered reduced white matter integrity and cortical thickness in patients with long-standing type 1 diabetes. "It's not clear," she says, "whether such changes to the brain will have a more profound effect as a patient ages."

Currently, Musen is using functional MRI, which measures the brain in action, to determine whether regions of the brain with gray matter density loss show impaired function. Even though people with diabetes may show normal performance in terms of accuracy or processing speed on cognitive tasks, their brain activity may differ from that of patients without diabetes. Such changes, she said, may precede clinically relevant cognitive issues, such as memory loss and

continued on page 6

mild cognitive impairment, a precursor to Alzheimer's disease.

Another study, led by neurophysiologist Vera Novak, an HMS associate professor of medicine and a neurophysiologist at Beth Israel Deaconess Medical Center, identified a key mechanism that can lead to memory loss, depression, and other types of cognitive impairment in older adults with type 2 diabetes. In a study published in 2011 in *Diabetes Care*, Novak reported that two molecules, sVCAM and sICAM, cause inflammation in the brain. Novak found that gray matter in the brain's frontal and temporal regions—areas responsible for such critical cognitive functions as decision making, verbal memory, and complex task performance—were most affected.

The long-term stress and strain of diabetes management can lead to a decreased quality of life and an increased likelihood of depression. Working with colleagues at Joslin Diabetes Center, Nicolas Bolo is studying whether impaired glucose metabolism can explain the increased prevalence of depression in people with type 1 diabetes.

"It appears that chronic hyperglycemia and insulin resistance—the hallmarks of diabetes—trigger the release of these adhesion molecules and set off a cascade of events leading to the development of chronic inflammation," says Novak. "Once chronic inflammation sets in, blood vessels constrict, blood flow is reduced, and brain tissue is damaged."

Some scientists have begun calling Alzheimer's disease "type 3 diabetes" because of its characteristic complications of profound memory loss and severe cognitive decline. Musen is cautious about this label. "It's a good hypothesis and has generated a lot of science," she says, "but we need better studies" before drawing firm conclusions.

A chicken-or-egg question

For some time, clinicians have known that diabetes and depression often go hand in hand, but now the mechanism behind this relationship is becoming more evident. A 2010 Harvard School of Public Health study in the *Archives of Internal Medicine* found a biological link between the two:

depression increases the risk for diabetes and diabetes increases the risk for depression.

"We've thought for a long time that the burden of type 1 diabetes is enough to increase depression," says Nicolas Bolo, an HMS lecturer on psychiatry and the director of neuroimaging in psychiatry at Beth Israel Deaconess, who is studying the link between diabetes and depression. The long-term stress and strain of diabetes management—multiple finger sticks to check blood sugar levels, daily injections of insulin, and the worry of complications—can lead to a decreased quality of life and an increased likelihood of depression.

Working with colleagues at Joslin Diabetes Center, Bolo is studying whether impaired glucose metabolism can explain the increased prevalence of depression in people with type 1 diabetes. The team is using high-tech magnetic resonance spectroscopy to noninvasively measure metabolites in the brain.

One of these metabolites is glutamate, the principal excitatory neurotransmitter. Early results showed that brain glucose levels, as expected, are higher in people with type 1 diabetes. Glutamate is higher as well in the brains of these patients, especially in emotion centers such as the anterior cingulate cortex. "High glucose levels in the brain increase glutamate in regions involved in emotional control, which means increased depression among people with type 1 diabetes," says Bolo.

Bolo's research may lead to specific treatments that target the glutamate pathway in the brain and, thus, offer relief for diabetes patients suffering depression. Studies show that one such drug, ketamine, holds promise as an antidepressant that would act by blocking the action of a key protein involved in glutamate signaling in the brain. Researchers say this drug could be potentially life-saving for people with depression; unlike antidepressants such as Prozac and mood stabilizers, ketamine becomes effective in hours instead of weeks.

Although the findings of Musen, Novak, and Bolo shed light on how diabetes can affect the brain, the standard advice for warding off complications, including cognitive decline, remains the same: control your blood sugar, maintain a healthful diet, and take care of yourself. "We know that following this advice can improve peripheral systems, like vision," says Musen, "but it can help cognition as well." ♥

HMNI Fellows: The Future of Neuroscience

TO ENCOURAGE young scientists to pursue neuroscience research, the Harvard Mahoney Neuroscience Institute supports fellowships at Harvard Medical School. For more than two decades, partial or complete fellowships have been provided to more than 60 HMNI fellows, supporting a variety of neuroscience investigations, including research into the molecular biology of circadian rhythms, visual processing in primates, the development of olfactory systems in mammals, and gene expression and memory.

Three HMNI fellows are currently working in laboratories in the Department of Neurobiology at HMS.



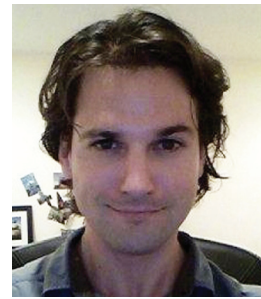
Gabriella Boulting

Neuroscientists know that for neurons to function properly, they must be able to “see” and “hear” signals in the brain. As the brain develops, cells in the brain physically change how they are wired and how they integrate the signals they receive. “This is what makes us cognitive beings,” says Gabriella Boulting, an HMNI fellow in the laboratory of Michael Greenberg, the Nathan Marsh Pusey Professor of Neurobiology and chair of the Department of Neurobiology at HMS.

In Greenberg’s laboratory, Boulting is studying enhancer sequences, the regulatory elements that control gene expression. Enhancers are poorly understood; they have been difficult to study because they can be located far away from the genes they influence. Boulting is hoping to develop methods that will ease the study of these sequences; she’s adapting technologies that use specially tailored proteins to target and repress enhancer function.

Boulting is engineering these proteins to recognize brain-derived neurotrophic factor (BDNF) genes in mice. These genes play a crucial role in regulating neuronal synapse function, thus allowing neurons to adapt their responses to stimuli and to guide behavior accordingly. “By focusing on well-characterized genes, such as those for BDNF,” she says, “I can examine the regulatory role that enhancer sequences play in the basic neuron functions that underlie memory and learning.”

Prior to her fellowship, Boulting earned a doctorate in molecular and cell biology at Harvard University and worked in the laboratory of Kevin Eggan, an HMS professor of stem cell and regenerative biology, studying mouse models of motor neurons to better understand cognitive and neurodevelopmental disorders in humans.



Noah Druckenbrod

The ability to detect, interpret, and respond to complex sounds in the environment depends on the precise functioning of neural circuits in the inner ear. Spiral ganglia, the primary neurons involved in hearing, receive input from sensory hair cells and transmit this information rapidly and accurately to auditory processing centers in the central nervous system. In addition, the cochlea, the portion of each inner ear that is shaped like a snail’s shell, are innervated by a small population of motor neurons that provide reverse feedback; that is, signals that run from the brain to the ear.

In the laboratory of Lisa Goodrich, an HMS associate professor of neurobiology, HMNI fellow Noah Druckenbrod is studying both the development of the neural circuits that connect the inner ear to the brain and the neurons in the spiral ganglion. “Our work,” he says, “aims to understand how these two populations of neurons interact to create the circuits that underlie the perception of sound.”

Druckenbrod uses novel imaging and molecular techniques to distinguish the critical cellular and molecular events that “influence the final wiring decision to form a functional cochlea.” He says that understanding how the wiring of the inner ear occurs will give scientists a better understanding of neurodevelopment and diseases of the nervous system that disrupt proper wiring, such as amyotrophic lateral sclerosis (Lou Gehrig’s disease) and progressive muscular atrophy, as well as the obstacles involved in motor neuron regeneration.

Before he joined HMNI as a fellow, Druckenbrod earned both his bachelor’s degree and his doctorate in neuroscience at the University of Wisconsin–Madison.

continued on page 8



Zihua Liu

Each night as we sleep, extraordinary changes occur in our brains: our memories reorganize and our mind rejuvenates. The process of sleep, and particularly how and why the brain switches from a waking to a sleeping state and back again, has long intrigued scientists. In the laboratory of Dragana Rogulja, an HMS assistant professor of neurobiology, HMNI fellow Zihua Liu is studying these questions. And he's looking into why we need to sleep at all.

Using *Drosophila melanogaster*, the common fruit fly, as a model system, Liu is characterizing genes identified through large-scale genetic screening to reveal the molecular pathways they use to shut the brain down during a good night's sleep. Among the genes Rogulja identified in a previous study is cyclin A, a regulator of the cell cycle process. She discovered that cyclin A functions in neurons to promote sleep in *Drosophila*, and found that reducing the amount of cyclin A in the flies' neurons delayed the sleep-wake transition and caused multiple arousals from sleep.

Liu is examining discrete populations of neurons that are active sleep centers. Fruit flies tend to sleep all night, as do humans, so finding sleep mechanisms in *Drosophila* may have implications for the study of human sleep. "What's interesting," Liu says, "is that cyclin A is expressed in only a few cells in the *Drosophila* brain. This small number greatly facilitates the mapping of sleep-regulating neuronal circuits in which cyclin A acts."

Liu and Rogulja also want to understand how cyclin A regulates sleep on a molecular basis. They say many clues are provided by the thorough characterization of the gene in the context of cell cycle regulation.

Prior to his HMNI fellowship, Liu earned his doctorate at the Chinese Academy of Sciences' Institute of Genetics and Developmental Biology in Beijing. ♥

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