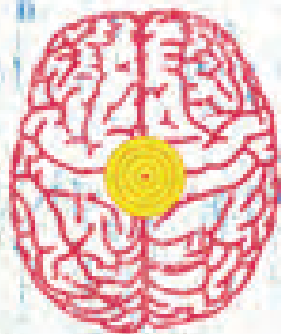


# neurotransmitter

A MAGAZINE OF THE GEORGE WASHINGTON INSTITUTE FOR NEUROSCIENCE AND  
THE GEORGE WASHINGTON UNIVERSITY HOSPITAL'S NEUROLOGICAL INSTITUTE

winter 2014-15



# Spanning the Synapse Between Cause and Cure



Welcome to the first edition of the *Neurotransmitter*, a semiannual publication of the George Washington University (GW) School of Medicine and Health Sciences (SMHS), George Washington Institute for Neuroscience (GWIN), and the George Washington University Hospital's Neurological Institute. For many years, GW has been well known for its expertise in the treatment of patients with disorders of the brain, spinal cord, peripheral nerve, and muscle, but now GW has established a greater mission in response to growing needs. Diseases of the nervous system are expanding as the older population increases, the consequences of sedentary lifestyles and obesity are realized, and new toxins and pathogens emerge. Declarations in the news media that stunning discoveries in the understanding and treatment of brain disorders are occurring at a rapid pace are simply not true.

SMHS has made a commitment to help reverse this trend through bold expansion of basic and clinical research with the intent to turn laboratory discoveries into improved patient care. For the last decade, Anthony Caputy, M.D., and his team of neurosurgeons have provided innovative care for patients with complex brain tumors, vascular disease, and epilepsy. Four years ago, Anthony LaMantia, Ph.D., one of the world's leading developmental neuroscientists, joined SMHS to lead GWIN, and thus far he has recruited four young scientists who are uncovering the mechanisms behind brain disorders including autism, seizure disorders, and neural degeneration. In late 2011, Henry J. Kaminski, M.D., came to SMHS to serve as Meta Amalia Neumann Professor and chair of the Department of Neurology. Kaminski has dedicated his career to understanding myasthenia gravis, a rare autoimmune disease that damages nerve and muscle communication. His laboratory is poised to move several therapies to the patients. This year James Griffith, M.D., was selected to serve as Leon Yochelson Professor of Psychiatry and Behavioral Sciences, and chair, Department of Psychiatry and Behavioral Sciences. He has already begun expanding GW's position in global mental health and simultaneously reaching out to address the needs of our underserved Washington, D.C., metropolitan community. These leaders share the goal of easing the burden of nervous system disease on individuals and society.

Neurotransmitters are molecules that signal nerve cell communication. In the same manner, *Neurotransmitter* will serve to inform you about the activities of the neuroscientists here at GW. Within these pages you will see the amazing breakthroughs that GW scientists and clinicians are making to improve the lives of patients with devastating neurological disorders. In this issue, we focus on epilepsy, which affects 5 percent of the world population, and stroke, which is the leading cause of disability in the United States and most industrialized nations. As you will see, we have broken down silos. No one works in isolation. We collaborate.

**HENRY J. KAMINSKI, M.D.**, Meta Amalia  
Neumann Professor of Neurology and  
Chair, Department of Neurology

**ANTHONY CAPUTY, M.D.**, Rizzoli  
Professor of Neurological Surgery and  
Chair, Department of Neurosurgery

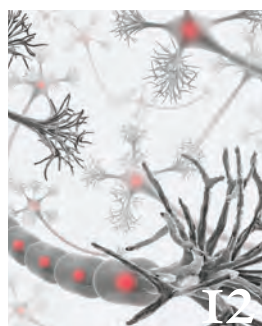
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Psychiatry and Behavioral Sciences

**ANTHONY LAMANTIA, Ph.D.**, Professor  
of Pharmacology and Physiology Director,  
GW Institute for Neuroscience

# neurotransmitter *fall 2014*

# contents

- 2 IN THE NEWS**  
GW University Makes Headlines in Research
- 6 THE EPICENTER OF EPILEPSY**  
A Historical Overview of the Disorder
- 8 SHOCK TO THE SYSTEM**  
Deep Brain Stimulation Offers Hope



- I2 CLOCK MANAGEMENT**  
A Team Approach Shortens the Time from Door to Treatment
- I6 SPOTTING STROKE IN THE COMMUNITY**  
The Prevalence of Stroke in Washington, D.C., is Higher than the National Average
- I7 SHORT-CIRCUITING FEAR AND THE FIGHT AGAINST PTSD**  
How Stress Influences Brain and Immune System Functions

**THE NEUROSCIENCES INSTITUTE** (NI) at The George Washington University Hospital is a premier neurological center. Patients come for comprehensive interdisciplinary care by the Institute's internationally recognized team of experts. The team treats patients for a wide range of neurological problems and provides expert care for patients with the most complex disorders that affect the nervous system. The NI consists of neurosurgeons, neurologists, emergency room physicians, critical care specialists, physiatrists, psychiatrists, neuro-radiologists, neuro-pathologists, and neuro-interventional specialists as well as outstanding allied health service providers in nursing, speech therapy, physical therapy, occupational therapy, and neuro-rehabilitation. The NI combines medical and surgical services, along with research and education, under unified leadership to optimize the health of our patients now and into the future through a multidisciplinary approach, state-of-the-art technology, and innovative treatment trials. To learn more visit [gwhospital.com/neuro](http://gwhospital.com/neuro).

Co-Directors: **ANTHONY CAPUTY**, M.D., FACS; **HENRY KAMINSKI**, M.D.; and **KIMBERLY RUSSO** M.S., M.B.A.

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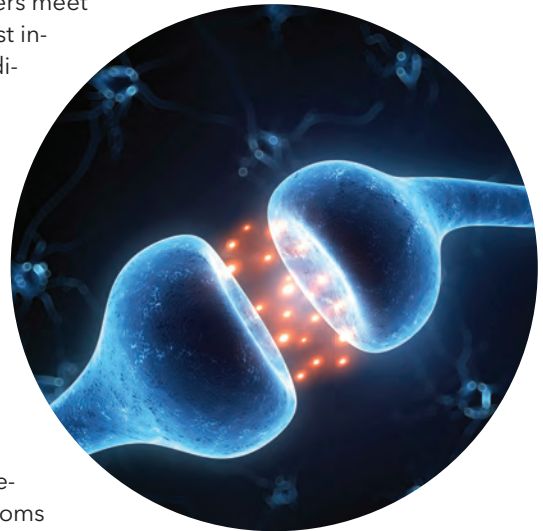
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## ON THE LEVEL

The George Washington University Hospital (GW Hospital) Epilepsy Center recently earned the highest certification in the field, a Level 4 Epilepsy Center designation from the National Association of Epilepsy Centers (NAEC). Level 4 centers meet the highest standard of care according to the NAEC, providing the most intensive neurodiagnostic monitoring, as well as the most extensive medical, neuropsychological, and psychosocial treatments available.

The specialists at GW Hospital understand the need for personalized epilepsy treatments. To accurately and effectively make a diagnosis, the center provides inpatient and outpatient facilities equipped with imaging and electroencephalogram (EEG) technologies that map out the locations of abnormal brain activity. The center features 24-hour video-EEG monitoring of seizures, so patients may quickly begin treatment following a detailed analysis and diagnosis of their condition.

In addition to treating epilepsy, GW physicians are pioneering the use of technologically advanced approaches for diagnosis and treatment, including surgical interventions and deep brain stimulation (DBS), for movement disorders such as Parkinson's. By stimulating particular regions of the brain through DBS, physicians can improve the major symptoms of some movement disorders and may help reduce the amount of medication needed to manage symptoms more effectively. For more information or to make an appointment, visit [www.gwdocs.com/epilepsy-center](http://www.gwdocs.com/epilepsy-center) or call 202-741-2700.

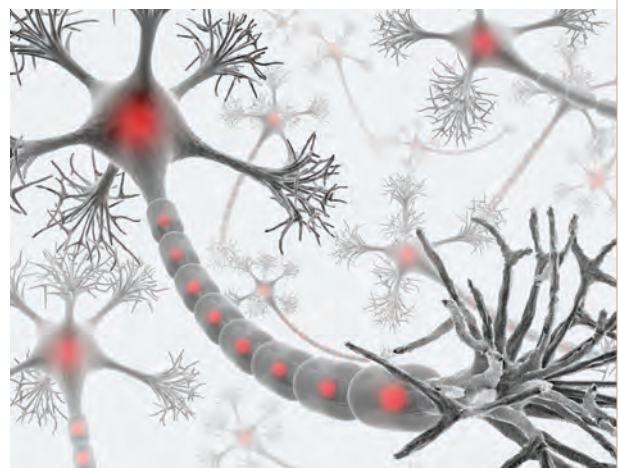


## GW ID'S PROTEIN THAT IMPEDES BRAIN CELL REPAIR

Vittorio Gallo, Ph.D., director of the Center for Neuroscience Research at Children's National Health System, recently uncovered a "potentially novel therapeutic target" to reduce the rate of deterioration and to promote the growth of brain cells damaged by multiple sclerosis (MS). Current MS therapies can be effective in patients with relapsing MS, but have little impact in promoting tissue growth.

The brain produces new cells to repair the damage from MS for years after symptoms of the disorder first appear. However, in most cases unknown factors limit the cells' ability to complete the repairs. In patients with MS, random patches of brain inflammation, or lesions, lead to destruction of myelin, a protective fatty covering that insulates nerve cell fibers in the brain. Myelin damage is a hallmark of MS.

Gallo, who is also a professor of pediatrics at the George Washington University School of Medicine and Health Sciences (SMHS), reported identifying a small protein, Endothelin-1 (ET-1), which has been shown to inhibit the repair of myelin. The study demonstrates the therapeutic potential of blocking ET-1 pharmacologically, or by using a genetic approach, which could promote repair of damaged myelin tissue. The research titled "Astrocyte-Derived Endothelin-1 Inhibits Remyelination through Notch Activation," was published in the February 2014 edition of *Neuron*, 81(3), pp. 588-602, available at <http://ow.ly/Ca0E3>.



## INTELLECTUAL DISABILITY AND AUTISM

As part of a national focus to better understand child health and development, Chiara Manzini, Ph.D., assistant professor of pharmacology and physiology at GW's School of Medicine and Health Sciences, was awarded a \$747,000 grant to research the causes of severe intellectual disability and autism.

"We are exploring the function of the gene and of the mutation that causes disease, by both using cell-based systems – analysis of neurons generated from animal models – and studying the behavior in mouse models to better understand the pathogenesis of the disease," says Manzini. "This gene regulates multiple signaling mechanisms inside the cells, and we are hoping to understand these mechanisms first, then figure out ways to modulate them to have an impact on the disease."

The Eunice Kennedy Shriver National Institute of Child Health and Human Development presented the grant, which started as a career-development grant during Manzini's postdoctoral career, was awarded for her project titled "Intracellular Signaling in the Development of Human Cognitive Function."



**"This gene regulates multiple signaling mechanisms inside the cells."**

**CHIARA MANZINI, Ph.D.**



**"Everybody agrees that sometime during development, the way the cerebral cortex is wired gets disrupted in autistic patients."**

**ANTHONY-SAMUEL LAMANTIA, Ph.D.**

## AUTISM AND EARLY BRAIN DEVELOPMENT

The link between autism and disrupted brain development is an essential part of the puzzle of the disease, and is poorly understood. However, thanks to funding from the Simons Foundation Autism Research Initiative (SFARI), GW School of Medicine and Health Sciences (SMHS) researcher Anthony-Samuel LaMantia, Ph.D., may be able to offer truly integrative and in-depth answers to these key questions in the field of autism research.

LaMantia, director of the GW Institute for Neuroscience and professor of pharmacology and physiology at SMHS, was awarded \$739,000 grant from SFARI for his promising research on a key class of nerve cells found in the cerebral cortex, which is the part of the brain that performs many key functions disrupted in autism, particularly social interaction, communication, and cognition.

SFARI is a leading funder of autism research in the United States. The prestigious SFARI research grants support cutting-edge investigations at several institutions. The SFARI research grant received by LaMantia and colleagues is the first such award at GW.

LaMantia and his research team, which includes interdisciplinary collaborators from GW and the University of Pennsylvania Perelman School of Medicine, will first look at how these nerve cells are generated from cortical stem cells during prenatal development. They will then look at connections made between these nerve cells in one cortical area and nerve cells in other cortical areas. The connections between these nerve cells have been suggested to be either diminished or increased based on imaging studies in patients with autism spectrum disorders (ASD). There is no clear indication, however, which cortical neurons make the abnormal connections, and whether under- or over-connectivity is related to autism pathology.

"Everybody agrees that sometime during development, the way the cerebral cortex is wired gets disrupted in autistic patients and that this is a key reason for the difficulties in behavioral regulation that these patients encounter," says LaMantia. "But no one really knows how that happens and what the end point is. We have the capacity to actually work out a key part of that question in a valid animal model."

## CONNECTING EARLY EATING PROBLEMS WITH NEURODEVELOPMENTAL DISORDERS

Collaborative research coming out of the George Washington University School of Medicine and Health Sciences (SMHS) reveals new information on the feeding and swallowing difficulties often found in children with neurodevelopmental disorders, such as autism. Using an animal model of DiGeorge/22q11 deletion syndrome, a genetic disorder that causes autism and intellectual disability, GW scientists found clear signs of early feeding and swallowing disruption, and underlying changes in brain development. The research, featured on the cover of a recent edition of *Disease Models & Mechanisms*, may even lead to a cure for these difficulties, which are known as pediatric dysphagia.

"We found that the same mechanisms causing neurodevelopmental disorders are disrupting development in parts of the nervous system that control swallowing and feeding," says Anthony-Samuel LaMantia, Ph.D., professor of pharmacology and physiology at SMHS and



director of the GW Institute for Neuroscience. "Cranial nerves, which control food intake and swallowing, aren't developing correctly, which likely contributes to failed coordination. This is good news. This is something we can fix."

Up to 80 percent of children with developmental disorders have difficulty ingesting, chewing, or swallowing food, difficulties that can lead to food aspiration, choking, or life-threatening respiratory infections. Despite its high co-incidence with developmental disorders, little was previously known about pediatric dysphagia.

Children with pediatric dysphagia tend to be sicker from birth onward. "Making the health of these kids as stable as possible from birth onward would allow clinicians to pick up on developmental signs sooner, which are often masked by more immediate problems like having ear or respiratory infections, not sleeping, or not gaining weight," says LaMantia.

The study, titled "Dysphagia and Disrupted Cranial Nerve Development in a Mouse Model of DiGeorge (22q11) Deletion Syndrome," was a collaborative effort between LaMantia and Sally Moody, Ph.D., professor of anatomy and regenerative biology at SMHS, with important contributions from Beverly Karpinski, a research scientist who works jointly with LaMantia and Moody; Thomas Maynard, Ph.D., associate research professor of pharmacology and physiology at SMHS and director of the GW Institute for Neuroscience Biomarkers Core; and Irene Zohn, Ph.D., associate professor of pediatrics, and of pharmacology and physiology and investigator in the Center for Neuroscience Research at Children's National Health System. The study was published in the February 2014 edition of *PubMed*, 7(2):245-57, available at <http://ow.ly/Ca2gn>.



## VISUAL ALERTNESS IN CORTICAL NETWORKS

Matthew Colonnese, Ph.D., assistant professor of pharmacology and physiology at GW's School of Medicine and Health Sciences, received a grant from the National Eye Institute to study developmental origins of wakefulness in the cerebral cortex. His project will investigate how circuit properties and computational structures change in the cerebral cortex – the region of the brain responsible for cognition and perception – between the fetal and postnatal periods.

"The fetal brain appears to be incapable of processing sensory information until just before birth – we are studying the mechanism of this critical shift," says Colonnese.

This research can help to better understand the critical developmental checkpoints that determine if an infant will develop a healthy, functional brain.

## THE ROAD TO RECOVERY STARTS WITH PT

Emily Main, DPT, PT, and Latasha Thomas, DPT, PT, became the first-ever graduates of the George Washington University School of Medicine and Health Sciences (SMHS) Neurologic Physical Therapy Residency Program on July 24.

Following a welcome and introduction by Elizabeth Ruckert, DPT, PT, NCS, GCS, assistant professor of physical therapy and residency program director, Main and Thomas presented results from their Resident Scholarly Projects. Main discussed “The self-efficacy of nurses in the mobilization of patients post stroke: A quality improvement project at Washington Hospital Center,” while Thomas presented “Hypertrophic Olivary Degeneration: A Case Study.”

The event marked the conclusion of an intensive year-long training and mentorship program for Main and Thomas, but it also signaled the completion of the residency program’s pilot year, a critical step before applying for certification from the American Board of Physical Therapy Residency and Fellowship Education.

Over the course of the year, Main and Thomas immersed themselves in four components of neurologic specialty practice – clinical practice, teaching, research, and didactic education. In addition to their teaching and research responsibilities, they logged 20 hours a week of clinical care.

The experiences – first focused on acute care, then acute rehabilitation, and finally outpatient rehabilitation, helped them develop advanced neurologic physical therapy – cemented their patient-centered, evidence-based, and collaborative care abilities. “Emily and Latasha have proven themselves to be ideal candidates during this first year of the residency program,” says Ruckert. As the two honed their skills working with patients with movement problems, adds Ruckert, the PT faculty gained valuable insight to help refine the program.



### FIRST CLASS

In July, Emily Main, DPT, PT, and Latasha Thomas, DPT, PT, became the first-ever graduates of the George Washington University School of Medicine and Health Sciences (SMHS) Neurologic Physical Therapy Residency Program.

## AT THE HEART OF SLEEP APNEA

Sufferers of a common sleep-breathing disorder have diminished activity among neurons responsible for keeping heart rate low. David Mendelowitz, Ph.D., vice chair and professor of pharmacology and physiology at GW’s School of Medicine and Health Sciences, discovered that in obstructive sleep apnea (OSA), neurons in the brainstem that control heart rate experience a blunting of their activity. The reduction of neuronal activity likely contributes to the increased heart rate, blood pressure, and risk of adverse cardiovascular events that occur in patients with OSA.

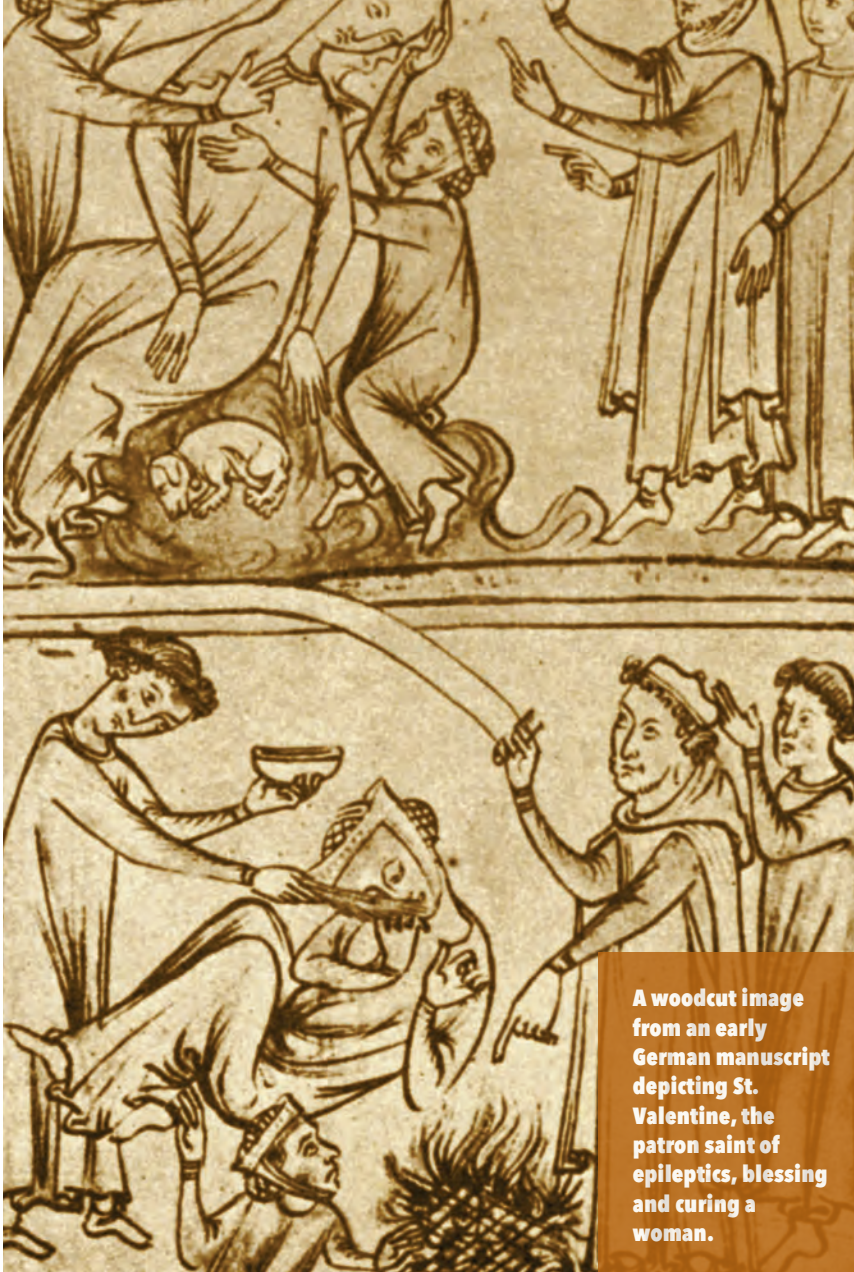
“Lack of sleep leaves the mind and body tired, leading to poor mental and physical performance, and if untreated OSA increases a person’s risk of developing hypertension and irregular heartbeats,” says Mendelowitz. “Therefore, it is very important that we have discovered some of the underlying mechanisms that could injure the heart and other cardiovascular tissues.”

OSA is a common cardiovascular disease, occurring in 24 percent of adult males and 9 percent of adult females, that causes repetitive interruptions of breathing during sleep. Lack of oxygen during these episodes brings the person to a lighter state of sleep or brief wakefulness to restore normal breathing. Cycles of interrupted breathing and arousal from sleep can occur as frequently as once per minute.

The study, published in the *Journal of Physiology*, shows that progression of blunted cardiovascular reflexes is accompanied by, and likely maintained by, inhibition of neurons in the brainstem that protect the heart and normally maintain a low resting heart rate. For more information about The Center for Sleep Disorders, visit [www.gwdocs.com/sleep-center](http://www.gwdocs.com/sleep-center), or for an appointment call 202-741-3430.

**“Lack of sleep leaves the mind and body tired, leading to poor performance., and if untreated obstructive sleep apnoea increases a person’s risk of developing hypertension and irregular heartbeats.”**

**DAVID MENDELOWITZ, Ph.D.**



A woodcut image from an early German manuscript depicting St. Valentine, the patron saint of epileptics, blessing and curing a woman.

# The Epicenter of Epilepsy

ANTHONY CAPUTY, M.D.  
SAMUEL POTOLICCHIO, M.D.

Today, medication is the first line of treatment for epilepsy; however, adverse reactions and resistance to the most common drugs have been reported in up to 90 percent of epilepsy patients.

Early history is full of accounts of individuals affected by epilepsy. Many cultures considered the common neurological disorder to be an affliction in which the person was possessed or “seized” by a spiritual force. The ancient Greeks thought of epilepsy as a divine state. Hippocrates, however, rejected this theory of a spiritual origin and proposed that epilepsy was a medical condition originating in the brain. Today we know that epilepsy is a disorder of the nervous system, which causes irregular cellular activity in the brain that can produce abnormal behavior. Epileptic seizures can be manifested in many ways, from brief focal motor movements to generalized prolonged convulsions. More than 1 percent of the global population has some form of epilepsy. In the United States, one out of 100 people will experience a seizure at least once, 3 million Americans have been diagnosed with



epilepsy, and as many as 20 percent of cases are not controlled by medications. The physical effects of epilepsy affect many aspects of an individual's life, including employment and the ability to drive a motor vehicle — and the social stigma of epilepsy can have an even broader influence. Intractable epilepsy has been associated with an increased risk of depression, memory problems, and sudden death.

### Essentials of Epilepsy

Epileptic seizures are defined as either convulsive or nonconvulsive. Generalized nonconvulsive seizures can involve complex behaviors such as staring and a loss of awareness, whereas focal convulsive seizures produce isolated motor movements, the stereotypical jerking responses. These symptoms of epilepsy can result from many causes. There may be a structural or metabolic cause for the seizure disorder. Epilepsy may result from previous trauma, stroke, infection, or tumors. The disorder may even be the result of congenital, developmental, or genetic conditions. Frustratingly, the great majority of epilepsy cases have no known cause.

The most common type of focal epilepsy in the adult is temporal lobe epilepsy, which accounts for 80 percent of complex seizures. Temporal lobe epilepsy is distinguished by partial seizures or memory deficits. The diagnostic findings include abnormalities on the electroencephalograph (EEG) and imaging that localize the seizure activity to the temporal lobe. Temporal lobe epilepsy has multiple etiologies, including trauma, infections, perinatal hypoxia, complex febrile seizures, malignancies, and vascular malformations. Symptoms may be familial or idiopathic. Genetic causes have recently been thought to be involved in the majority of cases.

### History of Treatment

In the 1800s, the first effective medical treatment for epilepsy was bromide, a chemical compound that was used in headache remedies late into the 20th century. In the 1900s, phenobarbital, a powerful barbiturate, and Dilantin, a

chemical cousin of barbiturates, came into use.

Around that period, John Hughlings Jackson introduced surgery as a treatment for epilepsy. Jackson studied the signs of these sudden, pulsating attacks and correlated his observations with postmortem cerebral lesions. By 1886, Victor Horsley, a pioneer in neurosurgery who developed a system to precisely map each brain structure, associated the seizure pattern in patients with epilepsy to skull injuries and successfully removed the seizure-inducing lesions using intraoperative electrical stimulation. Three years later, Scottish surgeon William Macewen performed the first successful brain surgery to remove a meningioma — a dural-based, slow-growing, typically benign tumor — to treat focal epileptic symptoms. In 1928, the Montreal Neurological Institute, under the direction of Wilder Penfield and Herbert Jasper, successfully treated epilepsy-producing lesions using stimulation mapping in awake craniotomies.

### Medicine vs. Surgery

Today, medication is the first line of treatment for epilepsy; however, adverse reactions and resistance to the most common drugs have been reported in up to 90 percent of epilepsy patients. When focal epilepsy becomes resistant to medications, surgery becomes a patient's best option. Surgical procedures include resections of portions of the temporal lobe or extratemporal foci. In addition, multiple subpial transections, hemispherectomy, corpus callosotomy, and gamma knife stereotactic radiosurgery may be used to treat intractable seizures. Other surgical treatment options involve electrical stimulation, including stimulation of the vagus nerve; NeuroPace-responsive neurostimulation; and deep brain stimulation.

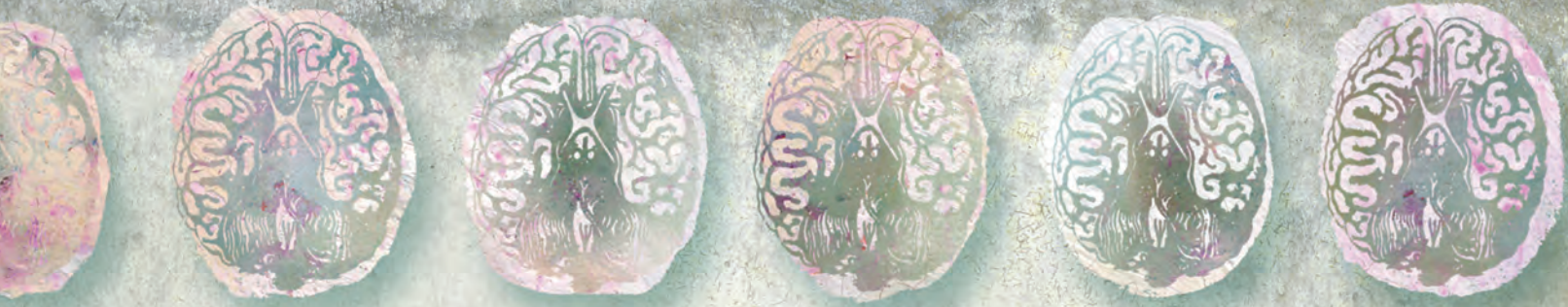
In the only Class I randomized trial to determine the effectiveness of surgical versus medical treatment, titled "A Randomized, Controlled Trial of Surgery for Temporal-Lobe Epilepsy" and published in the *New England*

*Journal of Medicine* 345 (5:311-8, 2001), Samuel Wiebe, M.D., professor of clinical neurosciences at the University of Calgary, demonstrated that surgery is superior to prolonged medical therapy for patients suffering from temporal-lobe epilepsy. After one year, 58 percent of the patients in the surgical group were free of disabling seizures, in comparison with just 8 percent of those in the medical group.

The George Washington University's clinical epilepsy team has performed more than 600 surgical procedures for intractable epilepsy. The technique employed, selective temporal lobe resection, is similar to that promoted by the Montreal Neurological Institute. Physicians record brain activity directly from the cortex during surgery using an EEG. The abnormal areas are defined and located by recording the stimulation mapping in the cortex, as well as in the amygdala and hippocampus, and those readings direct the surgical resection.

The selection of a candidate for surgery at GW involves a multidisciplinary team of neurologists, neurosurgeons, neuropsychologists, psychiatrists, radiologists, nurses, and social workers. This team employs structural, electrophysiological, and functional techniques to localize the seizures and define a discrete focus for surgery. An MRI will define any abnormal areas in the brain, including abnormalities of the hippocampus such as scarring in the inner portions of the temporal lobe, known as mesial temporal sclerosis. By using tests including electrophysiological tools such as EEGs to record the seizure pattern, both interictal and ictal, as well as positron emission tomography (PET) or single photon emission computed tomography (SPECT) imaging; functional MRI; and neuropsychological and Wada testing, physicians have a wealth of information at their disposal, providing a more accurate view of the problem and greater opportunity for surgical success.

For more information or to make an appointment, visit [www.gwdocs.com/epilepsy-center](http://www.gwdocs.com/epilepsy-center) or call 202-741-2700.



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# Shock to the System

DEEP BRAIN STIMULATION OFFERS HOPE TO THOSE FALLING OUTSIDE THE NORMAL STANDARD OF CARE

MARLENE CIMONS

# H

Healers have relied on electricity throughout history to treat human ailments and ease pain. The ancient Greeks used shocks from the electric torpedo fish to relieve gout and headaches. Centuries later, in a famous 1964 experiment, Yale University neurophysiologist José Delgado stepped into a Spanish bullring and stopped a charging bull from attacking him by remotely delivering an electric jolt from a device implanted earlier in the animal's brain. In the 1970s, New York neurosurgeon Irving S. Cooper began using electric brain stimulation in patients with cerebral palsy, spasticity, and epilepsy.

"Treating human disease by electrical stimulation is thousands of years old," says Mohamad Z. Koubeissi, M.D., FAAN, FANA, associate professor of neurology and director of the George Washington University School of Medicine and Health Sciences (SMHS) Epilepsy Center. "It has led to some very good results."

Koubeissi, who has served as director of GW's Epilepsy Center since 2012, believes that deep brain stimulation has real potential to help the vast number of epilepsy patients who are unable to stop their seizures with standard medications, or who are not candidates for surgery. Already he has initiated several new lines of research in the field, with promising results.

"Finding new therapies for epilepsy can make major changes in the lives of many people," Koubeissi says. "It's a very common disease, and it can be horrible. When uncontrolled, it can have a serious impact on people's social and professional lives."

Koubeissi, who was born in Beirut, earned his bachelor's degree in mathematics and his M.D. from the American University of Beirut. He then spent another year in Beirut as a postdoctoral research fellow in a neuro-pharmacology laboratory investigating the mechanisms of epilepsy in animals, before pursuing his medical internship at SUNY Upstate Medical University in Syracuse, N.Y., followed by more neurology training at New York University. Later, Koubeissi joined Johns Hopkins University, where he completed a clinical and research epilepsy fellowship. Before joining GW, he spent six years at the University Hospitals of Case Western Reserve University in Cleveland, where he was assistant professor of neurology.

"I have long been interested in studying the biological basis of behavior, and went to medical school to become a neurologist," he says, adding that he soon decided to make epilepsy his focus. "Epilepsy is one specialty that facilitates studying the functional localization of the human brain through electrical mapping, allowing explorations of the biological basis of behavior."

According to the World Health Organization and the Centers for Disease Control and Prevention, an estimated 50 million people worldwide, including nearly 3 million in the United States, suffer from the disease, characterized by uncontrollable and often disabling seizures. In the United States, roughly 150,000 new patients are diagnosed annually. One-third of all epilepsy patients live with these uncontrollable seizures because for them, medications do not work, and surgery – which involves removing portions of the brain – might impair cognitive function or movement.

**"Treating human disease by electrical stimulation is thousands of years old. It has led to some very good results."**

**MOHAMAD Z. KOUBEISSI, M.D.**

## SIGNS OF HOPE

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MOHAMAD Z. KOUBEISSI, M.D.

“Medication alone can control seizures in only two-thirds of patients, and many of the remaining one-third are not candidates for surgery,” Koubeissi says. “This means that about 1 million Americans will continue to have seizures, highlighting the need to come up with something new.”

The brain’s temporal lobe, located behind the ears on both sides, often is the site of epileptic seizures. However, surgery is not always possible when there is involvement of the hippocampus, an area within the temporal lobe that is critical for memory processing. Even without surgery, many epilepsy patients whose seizures originate in the hippocampus suffer from memory problems.

“There’s a huge unmet need in the care of patients with epilepsy, particularly for patients who, despite numerous new medications, still have uncontrolled seizures,” says Henry Kaminski, M.D., Meta Amalia Neumann Professor of Neurology, chair of the Department of Neurology, and professor of pharmacology and physiology at SMHS. “Those not responding to drugs need to look for newer ways to treat them.”

In recent years, deep brain stimulation has become an established treatment for a number of conditions, including Parkinson’s disease, essential tremor, and dystonia – a disorder characterized by involuntary muscle contractions that cause slow repetitive movements or abnormal postures – and more recently, for obsessive-compulsive disorder. Researchers also are studying deep brain stimulation in epilepsy, cluster headaches, Tourette syndrome, chronic pain, and major depression.

In epilepsy, clinicians have used deep brain stimulation, with mixed results, when standard treatments have failed. The procedure involves implanting electrodes within certain areas of the brain to produce electrical impulses that control excess electrical activity in the brain; a pacemaker-like device placed under the skin of the upper chest delivers electrical signals through a wire running under the skin and connecting to the electrodes. The idea is to regulate abnormal brain activity in order to control movement or, in the case of epilepsy, seizures.

The central nervous system has two kinds of tissue, gray matter and white matter. Gray matter, pinkish-gray tissue in the living brain, includes nerve cells called neurons that communicate with other nerve cells. White matter is made up of axons, the

pathways along which the neurons send those signals.

In the past, clinicians have tried stimulating gray matter brain structures using high-frequency electrical signals, with limited success. Koubeissi wondered whether a different approach, stimulating the white matter using low-frequency signals, might work better against seizures. He tried it in animals and was excited to see them experience a dramatic reduction in seizures.

Koubeissi next tested the approach on 11 human subjects who were undergoing evaluation for traditional surgery; these patients already had electrodes implanted in the brain in order to identify the site of their seizures, including electrodes in white matter regions.

“When we stimulated the white matter tract at low frequencies and studied the number of seizures, we discovered that each stimulation session reduced the odds of seizure by 92 percent over the course of the following two days,” he says. “The patients did not know they were being stimulated, and had no memory or cognitive problems during the stimulation.”

Results of Koubeissi’s study appeared online Sept. 4, 2013, in the *Annals of Neurology*.

Koubeissi and colleagues such as Donald Shields, M.D., Ph.D., FACS, assistant professor of neurological surgery, are now in the process of recruiting 16 additional epilepsy patients for a safety trial that will evaluate the long-term effects of an implanted pulse generator that delivers low-frequency stimulation to the temporal lobe white matter. The procedure is geared toward people for whom neither drug therapies nor surgery are an option, such as those who can’t have their hippocampus removed because it’s dominant for memory or speech. Koubeissi and Shields place electrodes in the hippocampus itself to stimulate that area of the brain. The whole process, says Shields, is about as minimally invasive as brain surgery gets – smaller than many craniotomies for other brain disorders.

“We use a stereotactic process to place the electrodes – small wires with contacts that discharge the electric stimulation – precisely, even though they’re centered deep in the brain,” explains Shields. The electrodes are inserted roughly 6 to 7 centimeters deep into the brain tissue, so precision is critical. “We take special, thin-cut magnetic resonance images, and use those to create a three dimensional image of the brain.”

## FROM BEIRUT TO WASHINGTON

Mohamad Z. Koubeissi earned his M.D. from the American University of Beirut. After a year as a postdoctoral research fellow in a neuro-pharmacology laboratory in Beirut he pursued his medical internship at SUNY Upstate Medical University in Syracuse, N.Y., followed by more neurology training at New York University. Later, Koubeissi joined Johns Hopkins University. Before joining GW, he spent six years at the University Hospitals of Case Western Reserve University in Cleveland, where he was assistant professor of neurology.



Before beginning surgery Shields and his surgical team plot their course to the target area for the electrode after defining the insertion point “because accurate placement of the electrodes is critical for success.”

The initial study of 11 patients demonstrated proof of principle, says Koubeissi, but because the patients did not undergo prolonged stimulation, their dramatic results were short-lived. In the upcoming clinical trial, Koubeissi and Shields plan to implant the pulse generator, where it will chronically stimulate electrodes implanted in the brain, with the long-term goal of reducing seizures without affecting memory. “Indeed, it is even expected that stimulation may improve memory,” he says.

The voltage used is relatively low, but can vary from patient to patient. “We are able to vary the voltage, frequency, and pulse width depending upon the needs of the patient,” explains Shields. “Electrodes are locked into position on the skull and connected to the pulse generator, much like a pacemaker.”

The U.S. Food and Drug Administration has approved the protocol through its Investigational Device Exemption, which allows researchers to study a device’s safety and efficacy. If it is deemed safe, the investigators will then launch a much larger study to see whether it is effective.

Koubeissi is exploring other approaches to epilepsy treatment, including an investigational surgical technique that involves using precise incisions in the hippocampus designed to eliminate the connections to seizures, while preserving those that affect memory.

“One of the most common sources of seizures is the hippocampus,” he says. “There is some suggestion that the longitudinal connections, which run the length of the hippocampus from anterior to posterior – front to back – are important for synchronizing the seizure discharges and indispensable for the clinical presentation of seizures. By ‘disconnecting’ these, we hope it will have an impact on seizures, but be much less detrimental to memory than typical resection, which removes the whole hippocampus.”

The surgery is not widely available, but GW Hospital is “one of the rare centers in the United States that offers this as an alternative,” he says. Once more individuals have undergone the procedure, “we will evaluate the outcomes,” he adds.

In another finding, Koubeissi and his colleagues, trying to determine the origin of an epilepsy patient’s seizures, discovered they actually could turn off her consciousness by stimulating the claustrum, a thin, irregular, sheetlike neuronal structure hidden below the inner surface of the neocortex, the top layer of the brain. Probing different areas of her brain with electrodes, they positioned one of them next to the claustrum, a site that had never received stimulation before. It knocked the patient out. She was unconscious, although still awake. She stopped reading and stared blankly into space, her breathing slowed, and she failed to respond to visual or auditory requests. Once the electrical stimulation stopped, she regained consciousness and couldn’t remember what had happened.

The discovery – the first to show that stimulating the claustrum can interrupt awareness – suggests that this part of the brain plays an important role in conscious experience and could have significant implications in treating coma and epilepsy patients.

“Our findings suggest that the claustrum is connected to the widely distributed neural networks that mediate consciousness,” Koubeissi says. “Thus, while high-frequency stimulation at a high electric current can disrupt consciousness – as we have shown – lower-frequency stimulations with lower currents may be of therapeutic value when applied chronically, because this is likely to activate all of the widely distributed networks of consciousness.”

Beyond the more familiar form of epilepsy, individuals can also suffer chronic seizures from traumatic brain injury resulting from automobile, sports, and other accidents, as well as from combat. All of these patients, potentially, could benefit from Koubeissi’s work.

“To be sure, right now Dr. Koubeissi is looking at people with classic epilepsy who are treatment resistant,” Kaminski says. “But there is no question his research ultimately will lead to a better understanding of seizures with a wide array of causes.”

For more information or to make an appointment, visit [www.gwdocs.com/epilepsy-center](http://www.gwdocs.com/epilepsy-center) or call 202-741-2700. To learn more about deep brain stimulation, visit [www.gwdocs.com/neurosurgery/deep-brain-stimulation](http://www.gwdocs.com/neurosurgery/deep-brain-stimulation).

# Clock Management

TAKING A TEAM APPROACH TO SHORTENING THE TIME FROM DOOR TO TREATMENT

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“Our goal is to administer ‘clot-busting’ medication within an hour upon a patient’s arrival.”

KATHLEEN BURGER, D.O.

hen it comes to treating a stroke, every second counts. With each tick of the clock, more than 32,000 brain cells die, making time the most critical element of stroke therapy.

“The saying goes ‘time is brain,’” says Henry J. Kaminski, Meta Amalia Neumann Professor and chair of the Department of Neurology at the GW School of Medicine and Health Sciences (SMHS). “The longer you wait, the greater the likelihood that you’ll have permanent damage.”

Although clinicians have little control over how quickly patients get to the hospital, “what we do have control over is what’s called ‘door-to-needle’ time,” says Kaminski. With this in mind, SMHS, the George Washington University Hospital (GW Hospital), and the George Washington Medical Faculty Associates (MFA) created a stroke team to provide essential treatment the moment patients arrive, 24 hours a day.

“Here at GW Hospital, Kathleen Burger has led an initiative that has experienced phenomenal results, with a door-to-needle time of around 60 minutes,” says Kaminski. “That puts us in the top tier of centers across the country, the top 2 percent, and it’s certainly the best in the Washington, D.C., metro area,” he adds.

“Our goal is to administer ‘clot-busting’ medication within an hour upon a patient’s arrival,” says Kathleen Burger, D.O., assistant professor of neurology at SMHS, who coordinates the stroke team. “The faster you give the medication, the more brain you’re able to save, and the less likely the patient is to have complications from the medication or the stroke,” she says.

Providing high-quality stroke care quickly isn’t easy; it took constant refinements in treatment methods and a concerted effort from many different departments. But the efforts have paid dividends, earning numerous awards in the process.

## WORKING AGAINST THE CLOCK

The longer you wait before treating a stroke, the greater the likelihood that the patient will have permanent damage. With each tick of the clock, more than 32,000 brain cells die, making time the most critical element of stroke therapy.

## Focusing on Speedy Treatment

Stroke is a major cause of death and disability worldwide. In the United States, someone suffers a stroke every 40 seconds, adding up to roughly 800,000 strokes each year. An American dies from stroke every four minutes, making it the fourth leading cause of death in the country. Even when it doesn’t lead to mortality, stroke is a leading cause of long-term disability, causing problems with thinking, talking, and walking.

Stroke is the general term for an interruption in the flow of blood to the brain. There are two basic types: ischemic, involving a blockage in the vessel supplying the brain with oxygen-rich blood; and hemorrhagic, caused by bleeding among the brain’s vessels. “The outcome of treatment depends on how quickly doctors can restore the blood flow to the brain, while minimizing the risk to patients,” says Wayne Olan, M.D., associate professor of neurological surgery and director of interventional and endovascular neurosurgery at GW Hospital.



**“Stroke is one of the ultimate multi-specialty endeavors in medicine. It represents a significant level of commitment from the institution, the medical staff, and the ancillary services, and we take a lot of pride in the service we’re able to provide.”**

**WAYNE OLAN, M.D.**

The most common type of strokes, called acute ischemic strokes, are treated using a thrombolytic, or “clot-dissolving,” drug called tissue plasminogen activator (t-PA), which can open a clogged artery, improve blood flow to the brain, and increase the patient’s chances of recovery. How long doctors have to treat the stroke depends on where the clot is located. Ideally patients should receive treatment within three hours of stroke onset. The GW Hospital stroke team’s ability to administer t-PA to the majority of patients in less than an hour has contributed to a lower rate of ischemic stroke mortality in comparison with most hospitals in the region as well as the rest of the country, Burger says.

These efforts earned the stroke team multiple American Heart Association/American Stroke Association (AHA/ASA) Target: Stroke Honor Roll awards. “It’s one of the hardest awards to obtain from the American Heart Association,” Burger says. “We’ve earned it three years in a row, something we’re really proud of.” She adds that GW Hospital is the only facility in the area to receive the award that many times, let alone over three consecutive years.

### **A United Effort**

“Stroke is one of the ultimate multi-specialty endeavors in medicine,” says Olan. Treating strokes requires cooperation across almost the entire institution, from emergency medical services (EMS) to the emergency department (ED), nurses, neurologists, the intensive care unit, neurosurgery, radiology, and the rehabilitation unit, among others. “It represents a significant level of commitment from the institution, the medical staff, and the ancillary services, and we take a lot of pride in the service we’re able to provide,” he says.

The team approach begins with EMS notifying the ED and the stroke unit that there’s a potential “brain attack” candidate. GW Hospital has a rapid initial evaluation protocol set up that helps doctors and nurses quickly identify patients who might have had a stroke, and begin initial treatment while they wait for the stroke team.

A single call goes out to several members of the stroke team. Once they’re notified, team members race to the ED to evaluate the patient. “The team approach that was developed

allows us to arrive in the emergency room to assess any potential brain attack patients within minutes,” says Burger.

Assessing the patient quickly also requires coordination with the neuroradiology department, which conducts a CT scan of the patient, and laboratory technicians, who conduct required lab tests. “As soon as it’s determined that this patient is a candidate for thrombolytic therapy, we go ahead and start treatment,” says Burger.

The stroke unit continues to monitor the patient throughout the care and rehabilitation process. “The same team that greets patients in the ED takes care of them until they’re discharged. They get immediate attention followed by continued care,” she says. “No matter what happens, we’re there with the patient.” The specialized stroke nurses are particularly valuable in this continued care.

Although most stroke patients are eligible for thrombolytic treatment, there are cases where dissolving the clot is not an option. That’s where the neurosurgical team comes in.

“Some blockages are better treated through a mechanical removal of the clot,” says Olan. “It involves going into the patient’s head to get the clot out using a mechanical device, a clot-breaking medication, a suction, or a stent,” he explains. “We have multiple different technologies available to us.”

Technological moves almost as quickly as the clinicians, so serving at a teaching hospital has its benefits. “One of the nice things about GW Hospital is that we see all the newest technologies available for stroke treatment,” Olan says. “For example, initially, all that was available for these patients was administering clot-breaking medication, but over the course of time different mechanical devices have evolved for direct removal of the clot, rather than waiting for it to melt away.”

### **Rising to the Challenge**

GW Hospital is working toward being certified as a Comprehensive Stroke Center. The designation requires a steady process of improvement, and requires buy-in from both the administration and clinical staff, says Henry Kaminski. For example, nurses in a Comprehensive Stroke Center are expected to be able to recognize stroke, skills that require hours of specialized education, Kaminski says.



“If you have signs of stroke — facial droop, change in speech, weakness of one arm — don’t think about it, immediately go to an emergency room. Ultimately what we want to do is to make the entire population here safer from stroke.”

HENRY KAMINSKI, M.D.



Wayne Olan, M.D., assistant professor of neurological surgery

“That’s a lot of hours that the personnel could be doing something else, but we figured out novel ways to place coursework online, and it’s being accomplished,” he says. “So those are the kind of challenges that the AHA is putting out for institutions, and we’ve been able to rise to hit those challenges.”

Training nurses across the hospital about stroke has already shown benefits, Kaminski says. A patient admitted with a transient ischemic attack (TIA), a sort of “mini-stroke,” suddenly showed signs of a full stroke while in the hospital and was promptly given treatment. “That’s because our nurses easily identified the problem and did the right thing, and that person had the thrombolytic treatment in less than an hour,” Kaminski says.

GW Hospital has already expanded its stroke data collection to meet the needs of a Comprehensive Stroke Center. Data helps the stroke team in their efforts to constantly refine their stroke treatment protocols, and the team also conducts monthly meetings and peer review sessions to elicit feedback and improve their performance. “Three to four years ago we did not have a door-to-needle time of 60 minutes,” Kaminski says. “Our challenge has been to build systems that allow us to educate ourselves about where the slow-downs are, and how we can continue to do better.”

### Working with the D.C. Community

GW Hospital’s stroke team has a particularly important role to play in an area such as Washington, D.C., which has high incidences of stroke, Kaminski says. According to the Centers for Disease Control and Prevention, the age-adjusted prevalence of stroke in Washington, D.C. is 3.3

percent, almost a full percentage point higher than the national average. “Although the 30-day mortality and acute mortality rate from stroke is very low, it does still lead to significant disability,” he says.

Getting patients to the hospital sooner would go a long way toward minimizing the effects of stroke. GW Hospital is working to increase stroke awareness in the community, so that patients recognize symptoms of stroke and quickly call emergency services. “If you have signs of stroke — facial droop, change in speech, weakness of one arm — don’t think about it, immediately go to an emergency room,” Kaminski says. “Ultimately what we want to do is to make the entire population here safer from stroke.”

To learn more about our rapid stroke treatment, visit [www.gwhospital.com/hospital-services/neurosciences-institute/rapid-stroke-treatment](http://www.gwhospital.com/hospital-services/neurosciences-institute/rapid-stroke-treatment).



**KATHLEEN BURGER, D.O.**, during a stroke screening event. The age-adjusted prevalence of stroke in Washington, D.C., is 3.3 percent, almost a full percentage point higher than the national average.

## Spotting Stroke in the Community

"I didn't know I had high blood pressure until today," said lifelong Washington, D.C., resident Angela Sanders. The news was a wake-up call for Sanders. "I would never have known about my increased risk factor for stroke if I [hadn't had] a screening," she said. Sanders was one of many members of the D.C. community who stopped by the Foggy Bottom metro station for Stroke Screening Day. The annual event, hosted by GW's School of Medicine and Health Sciences (SMHS), the GW Hospital, and the GW Medical Faculty Associates (MFA), is designed to help individuals identify their risk factors for stroke. Sanders' screening results prompted her to be more proactive about her health. "I'm scheduling a follow-up appointment with my doctor this afternoon," she added.

This was the first time that third-year medical student Justin Palanci had participated in Stroke Screening Day. "Education is the most important thing for patients," said Palanci. "I want to help people understand their risk factors so they can make changes in their lives to better their health."

"Today we are reaching out to the community and making sure people know that stroke is preventable," said Kathleen Burger, D.O., assistant professor of neurology at SMHS, stroke program director at GW Hospital, and director of cerebrovascular neurology at the MFA. Being able to identify the warning signs of a stroke is vital, explains Burger. "Facial droop, arm weakness, and slurred speech are just some of the warning signs," she said. If a person is experiencing these symptoms, it's "time to act and call 911."

Burger and her fellow GW physicians, nurses, residents, and medical students screened roughly 244 people during the event. The team checked pulse and blood pressure, reviewed the participants' personal and family medical history, and shared information about how to recognize and respond to stroke. Clinicians advised participants exhibiting high blood pressure to follow up with their primary care doctor. Those without doctors were given contact information for physicians at GW's MFA.

**"Today we are reaching out to the community and making sure people know that stroke is preventable."**

**KATHLEEN BURGER, D.O.**

# Short-Circuiting Fear and the Fight Against PTSD

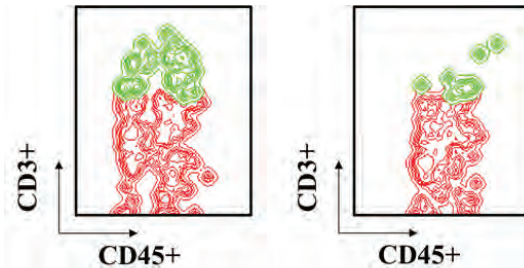
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aul Marvar, Ph.D., assistant professor of pharmacology and physiology at GW's School of Medicine and Health Sciences, studies how stress influences brain and immune system functions. The central nervous system plays an essential role in the regulation of blood pressure and has long been known to have two-way communication with the immune system.

"Chronic psychological stress and specific stress disorders such as post-traumatic stress disorder (PTSD) are strong predictors for the development of hypertension, which is a leading cause of stroke," says Marvar. "The immune system plays an important role in the development of high blood pressure and recently has been found to influence psychological stress-related and depression-related diseases."

## STRESS AND THE BRAIN

A flow cytometry plot showing CD45+ total leukocytes (red) and CD3+ T cells (green) in the vasculature of hypertensive mice. On the left is the control and on the right is a mouse whose central signals to angiotensin II were clocked. Note the reduced number of CD3+ and CD45+ cells in right panel. Marvar et al., *Exp. Physiol.* 2012 Nov; 97 (11): 1161-7.



Marvar and his team of researchers map neurocircuits that connect to immune signals in hypertension and stress-related disorders. They have shown that the hypothalamic region of the brain involved in the control of blood pressure is also critical for activation of the adaptive immune system (T lymphocytes) and peripheral blood vessel inflammation that occurs with high blood pressure. The hypothalamus is a tiny portion of the brain – roughly the size of an almond – found near the brain stem, which links the nervous system with the endocrine system via the pituitary gland. It is the same area of the brain that integrates stress information, fear memory, and blood pressure regulation.

Marvar recently published findings about these underlying mechanisms of PTSD in the journal *Biological Psychiatry*. Research, according to Marvar, suggests that individuals diagnosed with PTSD and treated with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) exhibited fewer PTSD-like symptoms. This research comes at a crucial time, when new medications for PTSD treatment are greatly needed. Currently, only two FDA-approved medications are available for the treatment of PTSD in the United States.

"Our current preclinical results show that the ARB losartan, given acutely or chronically to mice, enhances the extinction of fear memory, a process that is disrupted in individuals with PTSD," says Marvar. "Overall these data provide further support that this class of medications may have beneficial effects on fear memory in PTSD patients."

Fear extinction is a process by which a memory associated with fear is gradually "overwritten" in the brain by a new memory with no such association. For example, exposure therapy is a form of fear extinction whereby repeatedly exposing a patient in a safe manner to a feared object or situation slowly reduces or eliminates his or her fear. A medication that could potentially enhance the extinction of fear would be welcome to the millions of individuals who continue to suffer from symptoms of PTSD.

Overall, these studies provide an understanding for the link between the negative impact of stress and stress-related disorders such as PTSD on high blood pressure and lead to better treatments; in the long run, they can reduce the frequency of stroke, heart attack, and kidney failure.

To read Marvar's publications, see *Biol Psychiatry* 2014 Jun 1;75(11):864-72.

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