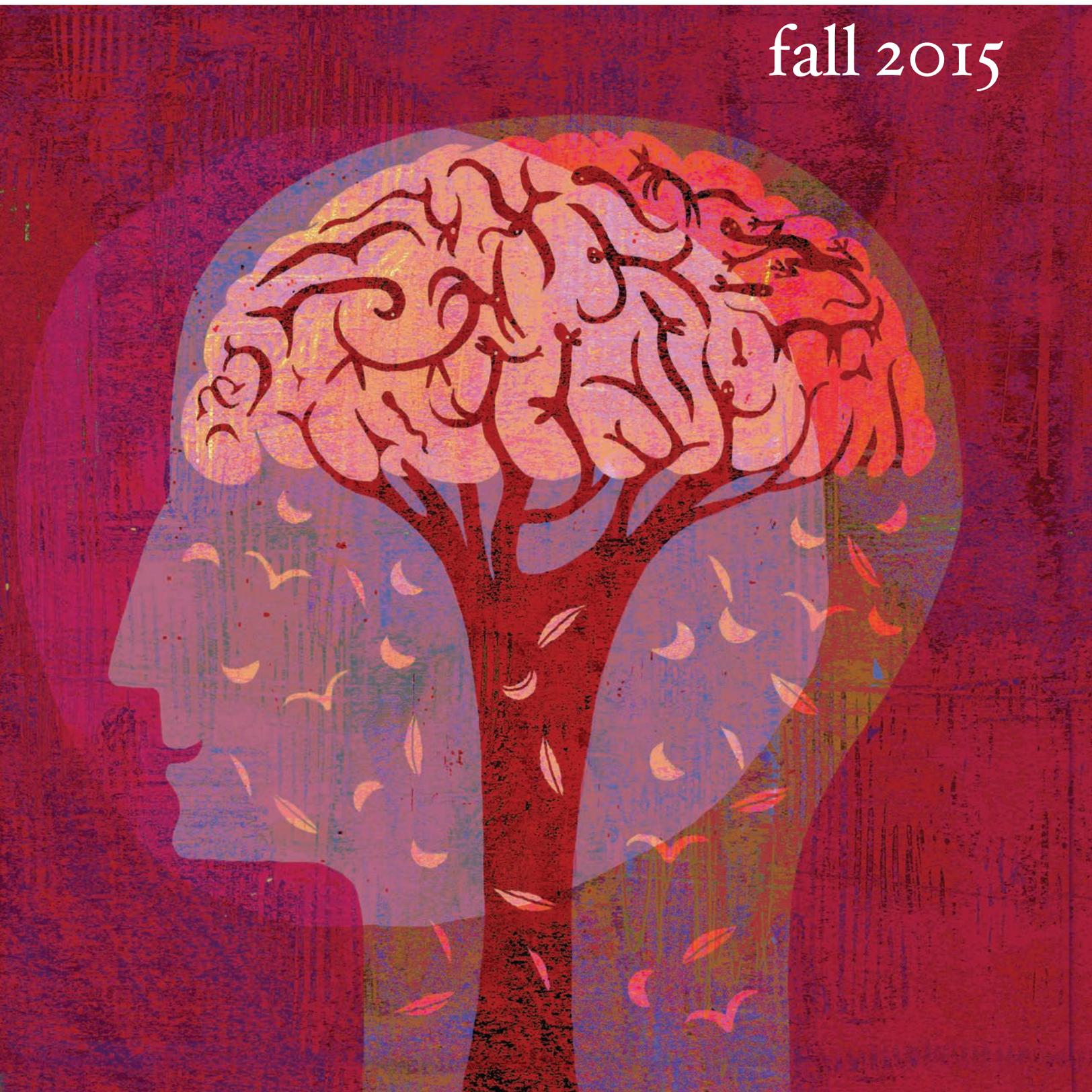


neurotransmitter

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

fall 2015



T

he second edition of *Neurotransmitter* continues our mission to provide you with a glimpse of the breadth of work being performed across our member institutions – George Washington Institute for Neurosciences (GWIN), part of the GW School of Medicine and Health Sciences (SMHS); the George Washington University Hospital’s Neurological Institute; and the GW Medical Faculty Associates.

This issue describes many of our investigations into neurological disorders at the molecular-cellular level. One of the newest members of the SMHS research community, Robert H. Miller, Ph.D., senior associate dean for research, Vivian Gill Distinguished Research Professor, and professor of anatomy and regenerative biology at SMHS, has devoted decades to understanding the myelin coating of nerve cells in the brain. His studies have led to the identification of drugs that enhance the repair of myelin and suppress the immune system injury produced in models of the devastating human disease, multiple sclerosis. Anthony-Samuel LaMantia, Ph.D., professor of pharmacology and physiology at SMHS and director of GWIN, and colleagues take novel approaches that link animal and human studies to understand dysphagia – an under-appreciated, devastating disorder that prevents normal eating and swallowing.

Moving to patient care, Veronica Slootsky, M.D., RESD ’15, assistant professor of psychiatry and behavioral sciences at SMHS, discusses multiple treatment options for severe depression using state-of-the-art brain stimulation methods (see also special section on stimulation procedures for severe epilepsy). Jonathan Sherman, M.D., assistant professor of neurological surgery at SMHS, reports on treatment for the glioblastoma brain tumor. Despite decades of attempts to improve treatment, the tumor remains lethal. Sherman describes his work to alleviate the suffering of patients. In addition to these major features, we have added brief descriptions on a few of the many activities between SMHS and its clinical partners. Our investigators have provided insights into two aspects of autism. One may explain why boys are more likely to suffer from autism, while the other describes how nerve cells move during brain development, and how this protein may also contribute to autism. Other stories feature neurologists and scientists who care for patients with a spectrum of diseases that affect nerve and muscle. Two of the members of the neuroscience institute, Mohamad Z. Koubeissi, M.D., FAAN, FANA, associate professor of neurology and director of the SMHS Epilepsy Center, and Donald Shields, M.D., Ph.D., FACS, assistant professor of neurological surgery at SMHS, were recently featured in a National Geographic documentary series, “Breakthrough,” for their work in the treatment of intractable epilepsy. They have proposed a novel surgical approach that uses deep brain stimulation to provide low-frequency stimulation to deep brain structures to treat the seizures. The preliminary results in the two patients treated thus far are encouraging.

As emphasized in the introduction to the first *Neurotransmitter* (visit smhs.gwu.edu/neurotransmitter to view a copy), a common theme among the features is to advance care for individuals challenged with brain disorders, and the driving force is collaboration. The more brains working together, the better. We hope *Neurotransmitter* will stimulate your neurons.

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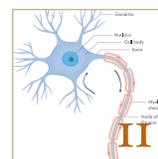
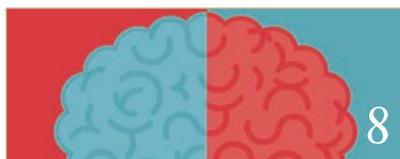
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THE NEUROSCIENCES INSTITUTE (NI) at The George Washington University Hospital is a premier neurological center. Patients come for comprehensive interdisciplinary care by the Institute's internationally recognized team of experts. The team treats patients 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 www.gwhospital.com/hospital-services/the-neurosciences-institute-at-the-george-washington-university-hospital.

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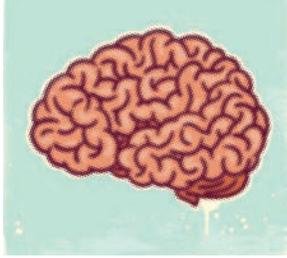
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“...we will have greater opportunity to educate and improve knowledge...”

MOHAMAD KOUBEISSI, M.D.

WORDS TO THE WORLD

The George Washington University (GW) Epilepsy Center’s “Epilepsy Grand Rounds,” a monthly seminar series that began in January 2013, has found a new home with epilepsy.com, the Epilepsy Foundation’s website.

“Thanks to our partnership with epilepsy.com, this series will now be visible to hundreds of thousands of physicians, health care providers, and laypersons from all over the world,” said Mohamad Koubeissi, M.D., director of the GW Epilepsy Center and associate professor of neurology at the GW School of Medicine and Health Sciences. “With this exposure, we will have greater opportunity to educate and improve knowledge, competence, and clinical performance for larger numbers of attendees.”

The series appears on epilepsy.com/professionals, a branch of the site that houses a forum for innovative voices in the field. The GW lectures are also live-streamed, which allows attendees to pose questions in real time, and are archived for future viewing. The series provides continuing medical education for participating physicians, as well.

Epilepsy.com is a primary resource for those living with epilepsy; their caregivers; and experts in the treatment, care, and research of the neurological condition. Visit smhs.gwu.edu/epilepsy/ for more information.

RORA PROTEIN A FACTOR IN AUTISM SEX BIAS

Sifting through the potential reasons behind sex bias in autism, Valerie Hu, Ph.D., professor of biochemistry and molecular medicine at the GW School of Medicine and Health Sciences, has uncovered an important factor: the sex-dependent difference in the protein levels of the gene retinoic acid-related orphan receptor-alpha (*RORA*), a nuclear hormone receptor that functions as a transcription factor.

“According to the Centers for Disease Control and Prevention, males are nearly four times as likely as females to have autism, but the reason for this sex bias is still a mystery,” explained Hu. “Our research suggests that deficiencies in *RORA* expression in the brain may have a greater impact on males, which may contribute to the known sex bias in autism in several ways.”

Looking at genetically identical mouse models, Hu and her research team found a twofold higher level of *RORA* expression in the frontal cortex of female mice than in male mice. They also determined that the correlation between *RORA* and target gene expression in the cortex was higher in male mice than female mice. On the human side, the team found a strong positive correlation between the levels of *RORA* and aromatase protein – an enzyme that converts male to female hormones – in the frontal cortex in males and females without autism spectrum disorder, and in males with autism. That correlation didn’t appear in females with autism, suggesting that they may have compensatory mechanisms for regulating *RORA* target genes to offset *RORA* deficiency.

“Overall, this study suggests that *RORA* deficiency may have a greater impact on males, not only because males have lower baseline levels of *RORA* in the brain to start with, but also because the expression of autism-associated genes may be more highly correlated with the lower expression of *RORA* in males,” said Hu. “This provides yet another plausible explanation for sex differences in autism susceptibility.”

Hu’s study, “Investigation of sex differences in the expression of *RORA* and its transcriptional targets in the brain as a potential contributor to the sex bias in autism,” appeared in the May 2015 edition of *Molecular Autism*.



EVOLVING BRAINS: GENOMES, CONNECTOMES, AND DIVERSITY

A rapt audience of neuroscientists and students ringed the tables filling the George Washington University's (GW) Marvin Center for the fifth annual Neuroscience Symposium, titled "Evolving Brains: Genomes, Connectomes, and Diversity," in the spring of 2015.

Presenters at the GW Institute for Neuroscience (GWIN)-sponsored symposium included students and faculty members from GW's School of Medicine and Health Sciences (SMHS) and Children's National Health System (Children's National), as well as three renowned keynote speakers: Yoav Gilad, Ph.D., professor of human genetics at the University of Chicago; David Van Essen, Ph.D., Alumni Endowed Professor of Anatomy and Neurobiology at Washington University; and Jon Kaas, Ph.D., Distinguished Centennial Professor of Psychology, associate professor of cell and developmental biology, and professor of radiology and radiological sciences at Vanderbilt University.

"[Our keynote speakers] really provided us with a diverse, but nevertheless coherent, view of how to think about the brain, the underlying genomic constraints of building it, the way that it may be connected to ensure diverse forms of behavior, and finally, how throughout evolution, these final patterns of connectivity to ensure optimal function have emerged," said Anthony-Samuel LaMantia, Ph.D., professor of pharmacology and physiology at SMHS and director of GWIN.



GW SMHS faculty and student topics included the genetics and biology of cognitive disorders and non-invasive neuroimaging of brain organization, among others. This year's symposium also featured poster presentations by students from both GW and neighboring institutions, such as George Mason University, American University, and the National Institutes of Health.

Although a date has not yet been set, plans are already underway for the 2016 event.



FRANÇOIS BOLLER, M.D., Ph.D., professor of neurology at GW's School of Medicine and Health Sciences, and past president of the International Society for the History of the Neurosciences

PERSONALITIES PEPPER PRESENTATIONS AT NEUROSCIENCE CONFERENCE

The personalities at the heart of the lectures at the 20th annual International Society for the History of the Neurosciences (ISHN) meeting spanned centuries, encompassing the worlds of music, art, literature, and pop culture. Gathered under the umbrella of neuroscience, the characters – some revolutionary, some infamous – not only contributed to the art and science of medicine, but also provided great fodder for the lecturers and participants gathered at the George Washington University (GW) in early June.

"The schedule was stocked with a lot of interesting things," said Henry Kaminski, M.D., chair and professor of neurology at the GW School of Medicine and Health Sciences, who chaired the introductory session of this year's ISHN conference.

Topics and accompanying personalities included mechanical neuroscience in opera – a short, light form of opera popularized by composer Jacques Offenbach and lyricist-composer duo W.S. Gilbert and Arthur Sullivan; color theory; depictions of multiple sclerosis in literature; and the storied tale of physician Walter Freeman, prolific performer and enthusiastic promoter of lobotomies.

The weeklong event, sponsored by the GW departments of history and neurology, also featured a trio of symposia, poster presentations, and a keynote speech by Daniel Drachman, M.D., who discussed the history of myasthenia gravis.

A PIECE OF THE PUZZLE

GW School of Medicine and Health Sciences (SMHS) researchers have fit another piece into the complex puzzle of a genetic developmental disorder that leads to behavioral diseases.

Anthony-Samuel LaMantia, Ph.D., professor of pharmacology and physiology at SMHS and director of the GW Institute for Neuroscience (GWIN), along with Thomas Maynard, Ph.D., associate research professor of pharmacology and physiology at SMHS, and post-doctoral fellow Daniel Meechan, Ph.D., has spent the last nine years investigating how behavioral disorders such as autism, attention deficit hyperactivity disorder, and schizophrenia emerge during early brain development. In their most recent study, the research team showed how autism-related genetic lesions interfere with cellular and molecular mechanisms that ensure the development of interneurons.

Interneurons, a critical type of cortical neuron, appeared in the correct number outside the cortex but were not able to move properly into the cortex, where they normally help control cortical circuit activity. The

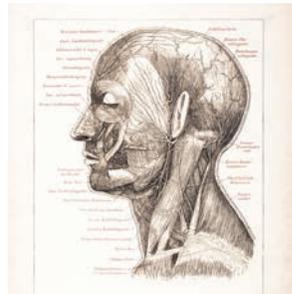


reason, according to the research, was a diminished expression of activity of a key regulatory pathway for migration – the Cxcr4 cytokine receptor. Earlier, LaMantia had determined that another critical neuron, the projection neuron, was not generated in appropriate numbers during development in a 22q11.2 Deletion Syndrome mouse model.

“This gives us two pieces of the puzzle for this genetic developmental disorder,” said LaMantia. “These two pieces tell us that in very early development, those with 22q11.2 Deletion Syndrome do not make enough cells in one case, and do not put the other cells in the right place.

This occurs not because of some degenerative change, but because the mechanisms that make these cells and put them in the right place during the first step of development have gone awry due to mutation.”

The study, “Cxcr4 regulation of interneuron migration is disrupted in 22q11.2 deletion syndrome,” appears in the Proceedings of the National Academy of Sciences journal.



“The conference was a pivotal moment in myasthenia gravis research. We no longer want to simply use medications developed for other diseases and adapt them for myasthenia gravis patients.”

HENRY KAMINSKI, M.D.

GW RESEARCHERS SEEK HIGHER RESEARCH STANDARDS FOR MYASTHENIA GRAVIS

For those suffering from myasthenia gravis, a rare, debilitating autoimmune disorder, effective medication is lacking, owing to a high failure rate of potential drug compounds. Soon, however, patients may have recourse; Linda Kusner, Ph.D., associate research professor of pharmacology and physiology at the GW School of Medicine and Health Sciences (SMHS), is taking concrete steps toward a solution.

In September 2014, Kusner organized a two-day workshop, “Standards for Preclinical Efficacy Evaluations for Myasthenia Gravis,” at the National Institute of Neurological Disorders and Stroke (NINDS), with support from NINDS, SMHS, and the Myasthenia Gravis Foundation. The goal: tackling the failure rate by looking at deficiencies in preclinical assessments of possible therapies.

“The conference was a pivotal moment in myasthenia gravis research,” said Henry Kaminski, M.D., Meta Amalia Neumann Professor, chair of the Department of Neurology, and conference participant. “We no longer want to simply use medications developed for other diseases and adapt them for myasthenia gravis patients. This conference focused specifically on drug development for myasthenia gravis.”

Myasthenia gravis experts discussed raising research standards and updating consensus guidelines for experimental methods, outcome assessments, and statistical requirements to be used worldwide. Experts also identified important variables to control, such as the phenotype of laboratory animals.

A follow-up meeting, part of the Association of British Neurologists-hosted “Myasthenia Gravis & Related Disorders” conference, will take place in Oxford, England in January 2016. Both Kusner and Kaminski will assist with event organization.

In August 2015, Experimental Neurology published a special edition dedicated to summaries of the September 2014 conference as well as reviews of other topics related to therapy evaluations for myasthenia gravis.

For more information visit www.gwdocs.com/neurology/myasthenia-gravis-center.

SPOTTING THE SOURCE OF STRESS

Stress is the bane of the modern world. Bills, demands at work, even laundry can trigger pressure sensors that leave the heartiest among us full of anguish and anxiety. Stress, particularly in the animal kingdom, on the other hand, developed as a life-saving mechanism. The fight or flight instinct keeps us on our game when faced with challenges, and it keeps prey animals on their toes when sensing danger.

A team of researchers, led by Joshua Corbin, Ph.D., principal investigator in the Center for Neuroscience Research at Children's National Health System, and associate professor of pediatrics and of pharmacology and physiology at GW's School of Medicine and Health Sciences, recently uncovered a gene common in a range of species that plays an essential role in the developing nervous system, particularly in specifying neurons required for the brain's stress system. The investigators identified a gene known as *Dbx1*, which is only active during the early embryonic stages, yet has long-lasting effects after its limited window of activity has closed.

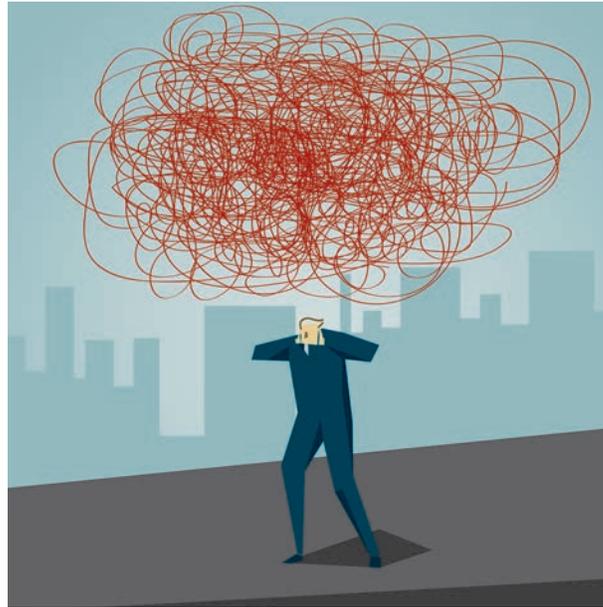
This discovery enables science to take a big step toward understanding gene processes and how they affect behavior. The research, published in the April 2015 edition of the journal *Neuron*, shows that while *Dbx1* is only expressed for a brief period during brain development, it unleashes a cascade of events that impact the expression of other genes critical for proper brain development.

Mice models reveal that this embryonic gene is critical for establishment of the brain's stress axis; removal of the gene before birth virtually eliminates the specific aspects of the animals' stress response later in life. When investigators genetically removed *Dbx1* from the mice, they were surprised to discover just how selective the effects of a lack of *Dbx1* were to both developmental programs and behavior. Without the gene, stimulus, such as the scent of a natural predator, failed to trigger the appropriate response.

"The *Dbx1* gene has a very specific function to developing and building circuits and behavior," explained Corbin. With the removal of the *Dbx1* gene, "basically the mice don't have the normal stress response because they lack this gene. The circuitry of the stress system was not really there.

"Now we have a piece of information that sheds light on the genetic programs that drive innate behavior circuit formation," Corbin said. "We now understand much better how this system is established from early stages of brain development. How that development unfolds has been, up to now, poorly understood – a kind of black box."

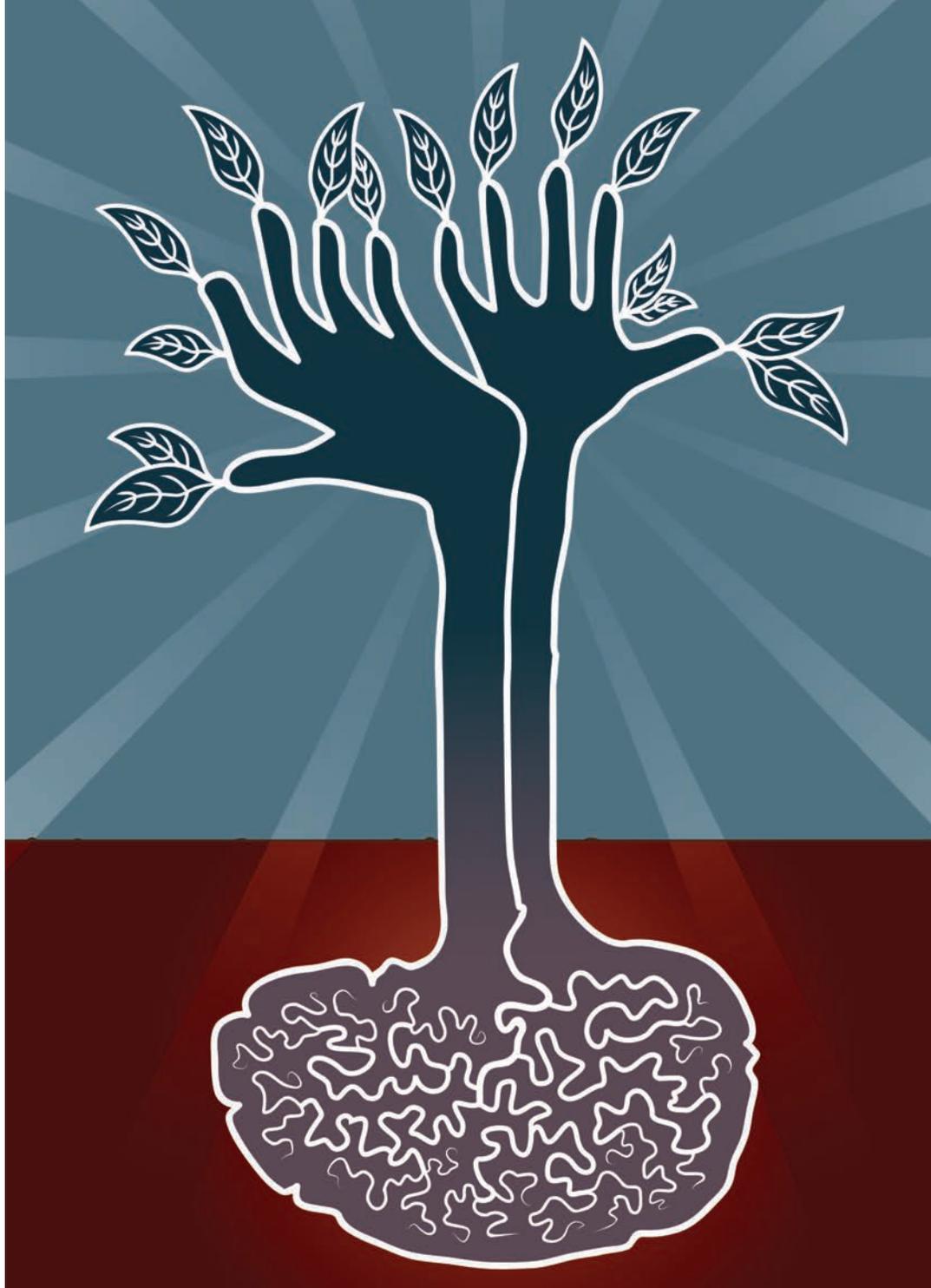
The findings, he said, open the door to understanding how similar evolutionarily conserved brain structures are formed in humans. The long-term impact of specific genetic mutations may affect these developmental processes, areas of investigation that would demand further study.



Stress, particularly in the animal kingdom, developed as a life-saving mechanism. The fight or flight instinct keeps us on our game when faced with challenges, and it keeps prey animals on their toes when sensing danger.



A team of researchers, led by Joshua Corbin, Ph.D., recently uncovered a gene common in a range of species that plays an essential role in the developing nervous system, particularly in specifying neurons required for the brain's stress system.



Illuminating Pediatric Dysphagia

GENETIC MOUSE MODEL TAKES CENTER STAGE AS RESEARCHERS
INVESTIGATE FEEDING AND SWALLOWING DISORDER

CAROLINE TRENT-GURBUZ

“Can you imagine,” said Anthony-Samuel LaMantia, Ph.D., director of the GW Institute for Neuroscience

and professor of pharmacology and physiology at the GW School of Medicine and Health Sciences (SMHS), “you’re an infant, and one of the key behaviors you have to learn is to ingest food. Someone comes at you with food, and it hurts!” That pain, a product of pediatric dysphagia, is at the heart of what LaMantia and his team are working to solve. With a five-year, three-pronged plan and a \$6.2 million program project grant (PPG) from the National Institute of Child Health and Human Development, PPG director LaMantia is determined to tackle the problem where it begins: in the brain.

Act One: The Basics

Pediatric dysphagia presents as a mostly mechanical problem; infants and children are unable to chew and swallow and may aspirate or choke on what they try to consume. Complications include ear and sinus infections and dribbles of liquid that settle in the lungs.

Today, dysphagia is treated symptomatically. There is no cure, and researchers understand little about a disorder that ranges from mild to severe. What researchers do know is that it can appear in as many as one in four children, and up to 80 percent of those with neurodevelopmental disorders, such as autism, have dysphagia. “This is a real-life disease,” LaMantia said.

Dysphagia is also a tricky disease. As LaMantia pointed out, delving deeper into the “whys” and “hows” of a disorder that appears in babies has limitations; researchers and physicians would prefer using minimally invasive techniques with infants. The ideal solution, therefore, is an animal model.

Act Two: The Mouse Model

LaMantia has dedicated the past 15 years to DiGeorge Syndrome, or 22q11.2 Deletion Syndrome, which occurs when a small part of chromosome 22’s long arm is missing. The effects are far-reaching, and patients suffer from a medley of complications. LaMantia’s

research on DiGeorge Syndrome — and the genetic mouse model he and his team use — unlocked the link between the deletion and the resulting dysphagia.

“It is remarkable how good a model this is,” LaMantia said. “The insight that we were initially able to get supported our basic hypothesis.”

Their hypothesis was that dysphagia emerges when fundamental mechanisms in early brain development are disrupted, causing defects in the neurons that become part of the cranial nerve system. The discovery also revealed that dysphagia develops embryonically. With that in mind, the researchers at SMHS and clinical partner institution Children’s National Health System (Children’s National) decided to use the mouse model to further understand dysphagia.

Act Three: The Team

To best tackle the causes of dysphagia, LaMantia and PPG associate director Sally Moody, Ph.D., professor of anatomy and regenerative biology at SMHS, assembled a cast of experts in mouse genetics, bioinformatics, maternal nutrition, and neuronal functioning.

“The project was put together to try to attack the problem, or at least analyze the problem, from a multidisciplinary perspective,” Moody explained. “It’s the combination of expertise that we think will allow us to make progress.”

Act Four: The Project

The investigation is divided into three parts: the origin of dysphagia, the pathology, and a possible path to prevention, all of which researchers will pursue simultaneously while informing one another of their progress.

Part one, headed by David Mendelowitz, Ph.D., vice chair and professor of pharmacology and physiology, with Norman Lee, Ph.D., professor of pharmacology and physiology; Thomas Maynard, Ph.D., associate research professor of pharmacology and physiology; and Anastas Popratiloff, M.D.,

Ph.D., adjunct professor of anatomy and regenerative biology, focuses on dysphagia in newborns. More specifically, the researchers will assess any abnormalities in the neuroanatomical connections that control the muscles an animal uses to feed and swallow.

In part two, LaMantia, Moody, and Lee are zeroing in on the development of the embryonic hindbrain. In early developmental stages, a population of cells migrates from the hindbrain into the periphery to make craniofacial structures. For infants with dysphagia, somewhere along the way the mechanisms controlling how these cells develop into peripheral neurons and the facial skeleton go awry. “The brain has to have a code, and the periphery has to have a code, and they have to match,” LaMantia said. When they don’t match, messaging between the two becomes garbled. A second important goal of the part-two team is to identify the genes that are altered in the hindbrain, which can then lead to the motor and sensory mismatches.

The third part of the project is what LaMantia and Moody termed the most adventurous. Retinoic acid, a derivative of Vitamin A, is one of the signaling factors strongly affected by the 22q11.2 deletion. Hypothesizing that maternal nutrition — in particular retinoic acid as it plays a role in the development of the hindbrain — could influence the severity of dysphagia, Maynard and Irene Zohn, Ph.D., associate professor of pediatrics at SMHS and a researcher at Children’s National, are experimenting with maternal diets.

Act Five: The Goals

Although the team is still a few years away from the project’s conclusion, the researchers’ goals could have long-lasting consequences for dysphagia sufferers, some of whom cope with the disease well into adulthood.

“We’re hoping that there might be ways of regulating [dysphagia] either prenatally via diet or postnatally through pharmacological therapies to help the kids overcome this behavioral deficit that really impacts their lives,” Moody said.

Getting to Glioblastoma

ERIC BUTTERMAN

It can start with something as severe as a speech problem or a seizure, or as subtle as a headache – but if it turns out to be glioblastoma, it unfortunately won't end so differently. Roughly a decade ago, the drug temozolomide added to treatment at least upped the two-year survival rate to 25 percent, according to Jonathan Sherman, M.D., assistant professor of neurological surgery at the George Washington University (GW) School of Medicine and Health Sciences (SMHS) and director of surgical neuro-oncology. But like his fellow researchers, Sherman is striving to add more than just time. He is hoping for a true breakthrough, even teaming up with a mechanical engineer as one of his strategies.

"These are typically middle-aged men and women who you may see die in a year or two after [a glioblastoma] diagnosis," he said. "We've seen so many good people go through this. We're working on many things, and we're driven."

For Sherman, an important challenge came from the need to understand brain tumors from the basic science perspective. It was no easy task. "That meant time on the bench learning cell culture and how it related to treatment – it was a huge learning experience," he said. "I began this work studying cancer stem cells and developing a technique to more easily localize them within the tumors. I next looked at treating these cancer stem cells in an effort to treat the entire tumor. I thought this [area of research] could be rewarding if I collaborated with the right people to grow my science knowledge. Studying cancer stem cells takes time and, bottom line, you need good collaborators around you."

TREATING GLIOBLASTOMA

In search of a new treatment for glioblastoma, which typically affects middle-aged men and women, Jonathan Sherman, M.D., assistant professor of neurological surgery at the George Washington University School of Medicine and Health Sciences, is even teaming up with a mechanical engineer as one of his strategies.

Into Action

In understanding stem cells, his recent work, collaborating with SMHS faculty members Anthony-Samuel LaMantia, Ph.D., professor of pharmacology and physiology, and Sally Moody, Ph.D., professor of anatomy and regenerative biology, involves the study of Fox genes in relation to tumor formation. Fox genes are a family of transcription factors, some of which have been implicated in glioblastoma. Therefore, SMHS has been looking at how glioblastoma tumor cells form in relation to specific Fox genes. "They play a role in gene expression," Sherman said, "but, the question is: Will it impact treatment? Only time will tell." With a differentiation model, he and his collaborators "look to further characterize the relationship of these genes to glioblastoma formation in an effort to develop new treatment targets." More results will be shared in an upcoming paper.

Another project he couldn't have predicted involved cold atmospheric plasma – and teaming with a mechanical engineer. "I started working with Michael Keidar, Ph.D., professor of mechanical and aerospace engineering at GW's School of Engineering and Applied Sciences, around four or five years ago. He developed a device that generates cold atmospheric plasma from electrified helium. We partnered up to look at glioblastoma on cell-level models," said Sherman. "It was about understanding how this cold plasma,



“We have to remember that it’s been a tough battle with glioblastoma for 40 years. The outcomes have been frustrating in the past for the medical community, but that means it takes being committed to making strides and keeping an open mind. We’re in this for a more hopeful conclusion. Patients are depending on this work and for us to continue to be creative in our approach.”

JONATHAN SHERMAN, M.D.

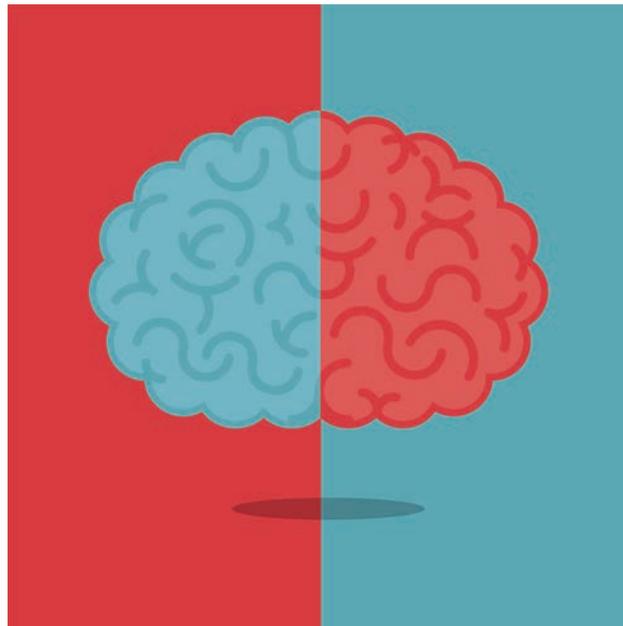
through generation of oxygen free radicals, will affect tumor death and not normal cells. You use it on the cells, and it treats the cells – but the question is: How do we get it into the brain? Our initial data indicates that we don’t necessarily have to treat the whole tumor and may only need to treat part of the tumor, and this could be a significant result in bringing this technology to clinical trial.”

The idea is, by implanting a probe into the tumor, to treat the tumor through a tube with cold atmospheric plasma treatment directly on the tumor. “There is actually a different technique where you don’t treat tumors directly, but you treat media, and then that media forms these free radicals,” Sherman said. “Then the media can be placed into the resection cavity to treat residual tumor cells. We’re trying to figure out the right animal study. It has exciting possibilities.”

From Different Angles

Sherman’s glioblastoma work is aided through specialized imaging, which includes functional MR imaging and diffusion tensor imaging. These modalities allow researchers to look at the relationship of the tumor to fiber tracts and eloquent cortex, where movements and speech are recorded during the imaging. “For movement tasks, the hand, face, and leg motor regions are identified,” he said. “For speech tasks, the expressive [Broca’s] and receptive [Wernicke’s] speech regions are identified. The latter information can also be invaluable in determining which side of the brain serves as the dominant hemisphere.”

There is also the assistance of the awake craniotomy program at the SMHS. This method involves securing the patient’s



head and subsequent exposure of the brain. The subject is conscious (albeit provided with anesthesia) so that motor and speech areas can be mapped through stimulation with relation to the tumor. “Typically, the tumor is then resected through continuous testing while the patient is conscious,” Sherman explained. “The published literature [describes] an increased degree of tumor resection with decreased morbidity or permanent neurological deficits using awake surgical resection.” Without hurting the patient, the more you can remove of the tumor, the greater the potential to increase length of survival.

Even infrastructure improvements are on the radar, as GW is looking to soon build one of the first intraoperative MRIs in the area. “This technology allows the surgeon to perform an MRI of the brain during the surgical resection to assess for residual tumor,” Sherman said. “The literature supports the use of this technology with a statistical increase in degree of tumor resection.”

The Fight Continues

For Sherman, he’s optimistic about having several present and possibly future treatment options to fight against this disease, but cautions that patience will be critical. “We have to remember that it’s been a tough battle with glioblastoma for over 40 years,” he said. “The outcomes have been frustrating in the past for the medical community, but that means it takes being committed to making strides and keeping an open mind. We’re in this for a more hopeful conclusion. Patients are depending on this work and for us to continue to be creative in our approach.” For more information visit gwdocs.com/neurosurgery.

Researchers Gain Ground in Treating Multiple Sclerosis

THOMAS KOHOUT AND CAROLINE TRENT-GURBUZ

Researchers, including Robert Miller, Ph.D., senior associate dean for research, Vivian Gill Distinguished Research Professor, and professor of anatomy and regenerative biology at the George Washington University School of Medicine and Health Sciences (SMHS), have taken another step forward in tackling multiple sclerosis (MS).

MS develops when the immune system, namely T-cells, attacks the myelin sheath, the fatty insulation that surrounds axons; consequently, communication between the brain and the body is disrupted, and nerve deterioration occurs. Preventing this neural degeneration requires remyelination through new oligodendrocytes, cells that create the myelin sheath. That's where Miller and his fellow researcher, Paul Tesar, Ph.D., a professor in Case Western Reserve's Department of Genetics and Genome Sciences, come in.

"Current therapies focus on stopping immune system attacks, slowing the progression of the disease," said Miller, who joined SMHS at the start of the 2014 academic year. "Our goal is not to try to stop the immune attack, because we can do that quite well. The goal is to try to actually repair the brain itself."

Over the years, Miller explained, there has been marked success in the development of a number of immunosuppressant therapies that target the central nervous system T-cells. The most effective therapies actually block T-cell entry into the brain and spinal cord. "Those work incredibly well," he said. "The problem is they don't actually regulate the disease at all. The disease is still ongoing in the brain

and spinal cord, even though the patients feel better because they have fewer attacks."

Contrary to conventional wisdom, the body – through brain and spinal cord neural stem cells – is capable of creating new neurons, as well as new oligodendrocytes. Through screening a library of bioactive small molecules, researchers discovered therapeutic compounds for

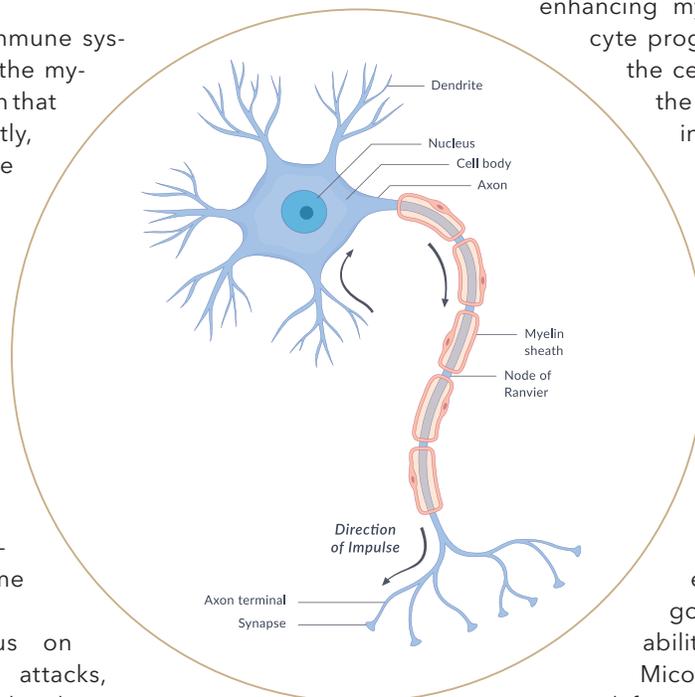
enhancing myelination from oligodendrocyte progenitor cells, the stem cells in the central nervous system that are the primary source for myelinating oligodendrocytes. From that development, Miller and Tesar found two drugs, miconazole and clobetasol, that could have a significant impact on reversing the severity of MS.

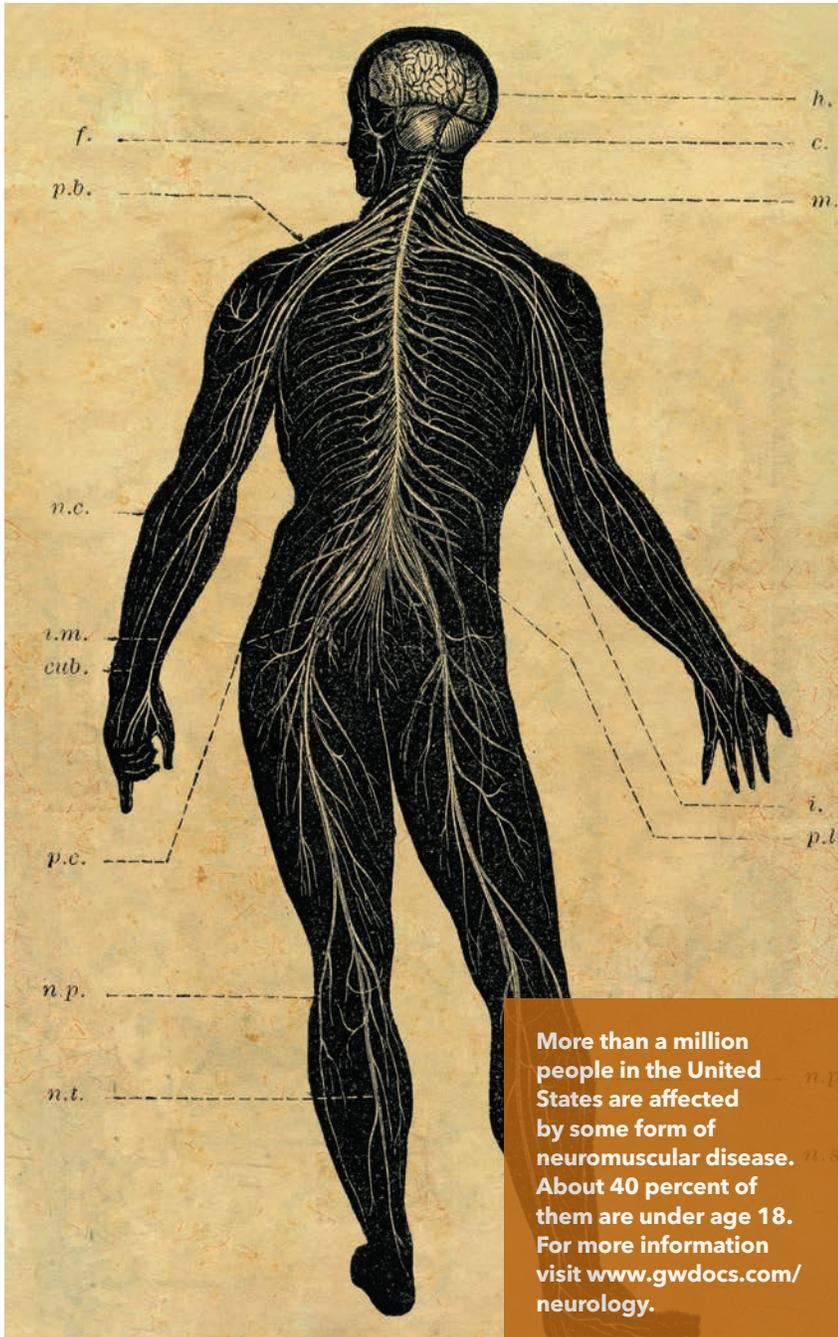
"We asked if we could find a faster and less invasive approach by using drugs to activate native stem cells already in the adult nervous system and direct them to form new myelin," Tesar said. "Our ultimate goal was to enhance the body's ability to repair itself."

Miconazole, the scientists discovered, functions directly as a remyelinating drug, enabling the body to repair the protective myelin coating over the nerves without affecting the immune system. Clobetasol, which serves as a powerful immunosuppressant, also functions as a remyelinating agent.

"While successful in vivo, we're looking forward to continuing our research through further testing of miconazole and clobetasol, taking the next steps to finding treatments for MS," Miller said.

Miller and Tesar's report, "Drug-based modulation of endogenous stem cells promotes functional remyelination in vivo," was published in the spring 2015 edition of *Nature*.





Putting Muscle Behind Neuromuscular Disease Research

STEVE GOLDSTEIN

Neurology begins with the brain, but that's hardly the end of it. Neurological diseases as a whole involve the brain, the central nervous system, the spinal cord, the nerve roots, and peripheral nerves and connect with muscles – and there's disease at each of those points.

The George Washington University has a “muscular” advantage in treating some of the most common – as well as rare – disorders.

According to the Muscular Dystrophy Association, more than a million people in the United States are affected by some form of neuromuscular disease, and about 40 percent of them are under age 18. These diseases are rare acquired or inherited (genetic) conditions that affect some part of the neuromuscular system such as the muscles, the peripheral motor nerves (in the arms, legs, neck, or face), the neuromuscular junction where the nerves and muscles meet, or the muscle-controlling nerve cells (motor neurons) in the spinal cord.

Diseases such as myasthenia gravis and amyotrophic lateral sclerosis (ALS) are rare but well known due to their devastating consequences. Far more common conditions include sciatica, carpal tunnel syndrome, and other peripheral neuropathies. Within GW's Department of Neurology is the Neuromuscular Disease Division, whose highly skilled clinicians care for patients with peripheral nerve diseases, motor neuron disorders, and muscle and neuromuscular transmission disorders.

“Neuromuscular experts form a subset of neurologists,” said Henry Kaminski, M.D., Meta Amalia Neumann Professor and chair of the Department of Neurology at GW's School of

Medicine and Health Sciences (SMHS). “We’re looking at the output of the brain and how dysfunction to those systems leads to disease.”

A Muscular Team

The division team includes director Perry Richardson, M.D. ’84, professor of neurology and of neurological surgery; assistant professors of neurology Elham Bayat, M.D., RESD ’06, and Karim Salame, M.D.; and Kaminski. The ALS Clinic is the only one in the Washington, D.C. metro area supported by the ALS Society. The diagnosis of neuromuscular disorders is facilitated by an advanced electrodiagnostic laboratory, which has received the highest possible accreditation with exemplary status from the American Association of Neuromuscular and Electrodiagnostic Medicine.

“There is no other center in the D.C. area with the breadth of expertise in neuromuscular disease, with independent validation, coupled with the research done in conjunction with national organizations and the innovative translational research being done on the GW campus,” Kaminski said.

Kaminski’s NIH-supported research has focused on myasthenia gravis. “One of the most exciting things we did here at GW is identify in patients with myasthenia gravis a unique expression of a protein called survivin, which is also found in cancer cells and helps keep them alive,” Kaminski explained. “This protein is expressed in the immune cells of patients, and we think survivin is responsible for keeping these cells alive. Since these cells are responsible for the disease, we’re going to develop a treatment that eliminates the expression of the protein in these cells. So far, in animals, it’s worked very well!”

Richardson recently completed a study, sponsored by Pfizer, Inc., to assess the efficacy and safety of pregabalin treatment in subjects with chronic post-traumatic peripheral neuropathic pain. “Neuromuscular disease is in kind of a growth spurt of use of therapeutics, especially as we define many

of them as autoimmune,” Richardson explained. “Immune-mediated diseases lend themselves to treatment by drugs.”

Richardson also said there may be new treatment options on the horizon for CIDP — Chronic Inflammatory Demyelinating Polyneuropathy — which has a fatality rate exceeding 10 percent. “CIDP is the disorder that starts out looking like Guillain-Barre syndrome [a treatable autoimmune disease sometimes triggered by an infection that leads the body to attack the nerves, leading to sudden onset of muscle weakness and pain], but it doesn’t go away,” Richardson said. “We’re very excited that some of the hitherto undiagnosed neuropathies are now attributed to CIDP and therefore treatable. Multi-focal motor neuropathy is a cousin of that, where instead of sensory and motor loss, there’s just motor problems.”

ALS on Trial

Research trials for ALS, popularly known as Lou Gehrig’s disease, are being pursued by Bayat, director of the ALS Clinic, who completed her neurology residency at GW, where she served as a chief neurology resident. She then went on to complete her clinical neurophysiology fellowship, which also included Electromyography (EMG) and neuromuscular disorders, at GW.

The newest member of the division, Salame, is researching the muscle aspect of the nerve in neuromuscular diseases. He most recently co-authored a chapter in the new edition of *Neuromuscular Disorders in Clinical Practice*, one of the only comprehensive books in the field of neuromuscular disease, which was co-edited by Kaminski.

Diagnostic Science

Richardson stresses that diagnostic capability is crucial for effective treatment. “Our lab stands in two rooms with EMG instruments, and these instruments measure biological signals to interrogate nerve function and muscle function,” Richardson said. “It’s a tremendous extension of the neurological

exam because you generate a hypothesis from the history and exam and the lab can verify the hypothesis. It detects disease, it locates whether the problem is coming from the limb nerve or the spinal nerve root or the motor neuron — or just the muscle, as a myopathy instead of a neuropathy. And it can tell us something about the prognosis and whether surgery is really necessary.”

Kaminski said the lab has detected erroneous diagnoses from tests performed elsewhere. “The lab testing is absolutely critical for coming to an appropriate diagnosis,” he asserted. “We often have patients where we have to repeat the study because the previous tests were not done in a rigorous fashion.” He added that one of his lab technicians has written a book on performing electrodiagnosis.

The division also performs diagnostic muscle and skin biopsies, the best way to diagnose peripheral neuropathies. “These are capabilities that most community neurologists and, quite frankly, most centers in the area do not have,” said Kaminski.

Physical Medicine and Rehab

Richardson also cited the importance of the GW Medical Faculty Associates’ relatively new Division of Physical Medicine and Rehabilitation (PM&R) created by Kaminski. “Many of the patients we see do not have nerve issues, but rather muscular-skeletal issues, and PM&R is very valuable,” said Richardson.

“We’re able to marry up patients with the right treatment, including medications for neuropathic pain, and we help decide when to get surgery for spinal root problems and when to get injections into peripheral nerve territory,” said Richardson. Innovative treatments include steroids for carpal tunnel syndrome and botulinum toxin (Botox) for spasticity and to reduce drooling for ALS patients.

“The value of our division,” concluded Richardson, “is we see a huge number of conditions that are common, and we have the ability and experience to be precise about unraveling difficult diagnoses of conditions that are not.”



Neuromodulation for Treating Depression

ELECTRICAL AND MAGNETIC STIMULATION OFFER NEW WAYS TO TREAT DEPRESSION

SANDEEP RAVINDRAN

I

magine feeling constantly tired and sad, being unable to concentrate, and losing interest in activities you previously enjoyed. These are just some of the symptoms of depression, a disorder that affects about 15 million people in the United States at any one time.

Left untreated, depression can have severe consequences, affecting work and personal relationships, and potentially contributing to suicide. Although antidepressant medication and psychotherapy can be effective at treating depression, up to a third of patients fail to respond even after multiple courses of medication.

There is hope for patients with treatment-resistant depression, in the form of neuromodulation, which uses electrical or magnetic stimulation to modify brain circuitry. "Neurons use electricity to communicate, and we can modulate that without the use of medication," said Veronica Slootsky, M.D., RESD '15, assistant professor of psychiatry and behavioral sciences at the George Washington University School of Medicine and Health Sciences (SMHS).

Some of these neuromodulatory therapies have been used for decades; others are still experimental. With current advances in neuromodulation, these treatments provide useful alternatives for patients for whom antidepressants and psychotherapy aren't sufficient. "It's nice to have another tool in our toolbox," Slootsky said.

Neuromodulation Has Come a Long Way

Neuromodulation encompasses a wide range of techniques. Although all of them use either electrical or magnetic stimulation to affect the brain, the precise mechanism by which they work is still not completely understood. There are several hypotheses for how the stimulation works: It may alter levels of signaling molecules in the brain, or cause the release of certain hormones, or increase levels of growth factors that promote the growth and survival of neurons.

Regardless of the specifics, some of these therapies affect the whole brain, whereas others are used to target particular regions. "The reason that we choose these different regions is that prior studies using functional MRI have determined that those regions are implicated in certain disorders, such as depression," said Slootsky.

Probably the best-known neuromodulation technique is electroconvulsive therapy (ECT), which has been used to treat psychiatric illnesses since 1938. ECT uses electric currents passed through the brain to trigger a brief seizure, and can quickly reverse symptoms of some mental illnesses.

Current ECT treatments use low doses of electricity in conjunction with modern anesthesia and muscle relaxants, reducing the risk of side effects such as memory loss or confusion. "In general, it's a very safe treatment, and for many patients it can be lifesaving," said Slootsky.

Despite being one of the most effective and safe treatments for severe mental illnesses, ECT still has negative associations due to its early incarnations, which used high doses of electricity and were administered without anesthesia. "This is a great, great method,

"Neurons use electricity to communicate, and we can modulate that without the use of medication."

VERONICA SLOOTSKY, M.D.

FEELING BLUE

Depression is a disorder that affects about 15 million people in the United States at any one time.

which unfortunately suffers from a lot of stigma, so it's really underutilized," Slootsky said.

ECT is very useful for treating patients with severe depression, especially those who have failed to respond to other treatments. "For patients with depression with psychotic seizures, it can be up to 95 percent effective, which is huge," said Slootsky. The therapy generally provides much quicker relief than medications, and is therefore helpful in patients who are at acute risk of suicide or are catatonic. "For some disorders it's really one of the best treatments we have, and it's often the only treatment."

Slootsky recalls an early experience witnessing the difference ECT can make on a severely depressed patient. Before the treatment the patient was "minimally interactive, was cognitively very slow and dull, and had a lot of the typical symptoms of very severe depression," she said. "After two weeks, she was like a different person when I saw her. She was joking around; she was smiling, interactive; she just looked much more animated, and it was a marked difference."

Different Ways to Stimulate Brain Circuitry

ECT is invaluable for treating severe depression, but those with mild depression can use two other neuromodulatory techniques that utilize much weaker electrical currents: transcranial direct current stimulation (TDCS) and transcranial alternating current stimulation (TACS). These therapies are cheaper, safer, and easier to administer than ECT. "These are things that people can probably do at home if they buy the unit with a doctor's prescription and direction," said Slootsky.

TDCS delivers very mild electrical currents through electrodes placed on the scalp, and can excite or reduce neuronal activity in specific brain regions. The technique is still experimental and has not yet been FDA-approved, but has shown promising results. TACS uses the same principle, but with alternating current instead of direct current, and is FDA-approved for treating depression.

Slootsky is preparing a study to test the effectiveness of a TACS technology called Alpha-Stim on women with postpartum depression. The condition is "extremely common, and some women don't want to take medication," said Slootsky. The Alpha-Stim technology consists of cellphone-sized units with electrodes attached. "They can actually take these units home, and the electrodes are clipped to their earlobe," she said. "This could be a great method for patients who have postpartum depression and would like some treatment."

Not all neuromodulation techniques are quite as easy to use; some require a pacemaker-like device to be surgically implanted in patients. One such technique is called vagal nerve stimulation (VNS), and it uses the implanted pacemaker to deliver electrical signals to the vagus nerve. VNS has been shown to improve mood, and the method is FDA-approved for treating chronic depression.

Another technique, called deep brain stimulation, uses the pacemaker-like device to deliver a current to electrodes

implanted in specific brain regions, to control excessive or abnormal electrical activity. This method has been used successfully in patients for whom multiple attempts at treatment have failed. However, the technique is not yet FDA-approved.

Some neuromodulation techniques use magnets rather than electrodes. One of them, transcranial magnetic stimulation (TMS), uses a large electromagnetic coil placed against the scalp to generate an electric field and stimulate brain cells. TMS is able to target certain brain structures and improve the symptoms of depression.

"TMS is currently FDA-approved for people who have failed their medication for depression," said Slootsky. Unlike ECT, TMS requires no anesthesia and has no cognitive side effects, but it is also not as effective for people who have found multiple antidepressant treatments unsuccessful, she said. "It's being [thoroughly] researched right now to see if we can make it more effective for those kinds of patients."

For treating severe depression, another technique, called magnetic seizure therapy, has emerged over the last decade and a half. Magnetic seizure therapy is similar to ECT, but uses strong magnetic fields instead of electricity to induce electrical currents in the brain. It is still experimental, but appears to have the same benefits as ECT, with fewer side effects.

A Bright Future

As noted, several of these neuromodulatory therapies are currently FDA-approved for treating different types of depression, and others are still experimental but appear very promising. SMHS is currently working on getting new ECT and TMS machines, and Slootsky hopes to begin her Alpha-Stim research study in the near future. Physicians will soon have a variety of neuromodulation tools at their disposal, and more research will help them understand how best to administer these therapies, Slootsky said. Further studies will also help uncover the mechanisms behind neuromodulation.

Slootsky wants to use neuromodulation in conjunction with other treatments to help patients with treatment-resistant depression. "We're constantly improving psychotherapy and medication management techniques as well, and I think that we have to use a multimodal approach, and we're refining everything," said Slootsky. "So I think that the future looks pretty bright."

"Electroconvulsive therapy is a very safe treatment, and for many patients it can be lifesaving."

VERONICA SLOOTSKY, M.D.

The Future Caught on Camera

DONALD SHIELDS, M.D., Ph.D., FACS
ASSISTANT PROFESSOR OF NEUROLOGICAL SURGERY

Futurist Ray Kurzweil predicts that by the 2030s humans will have the ability to connect their brains directly to cloud computing. Many of Kurzweil's other bold predictions have indeed come true, but new technologies such as brain-machine interface devices will need to be perfected for this one to take shape. The human brain is the most complex system in the known physical universe. Some have suggested it's so complicated we can never really understand it. Others believe if we can understand the mathematics that define brain function, we can make real progress.

On a basic level, the brain functions electrically, so neurosurgeons can stimulate and modify its function with electrical current. Electromagnetic force is one of the four fundamental forces of our universe. Previous human brains, like those of James Clerk Maxwell in the 19th century, began to delineate the mathematics of electricity (electromagnetic fields). Based in part on these principles, Thomas Edison subsequently designed the first electrical grid in New York City and Albert Einstein devised the theory of relativity. In addition, the electrical currents in the brains of these and other scientists/engineers over the past decades were instrumental in developing electrically powered computers used today to plan the trajectories of electrodes for

stimulation of the brains of human patients. Recording these results in turn helps physicians to understand how the brain works, and hopefully the mathematical equations that govern brain function.

Recently, film crews for *National Geographic* filmed surgeries and subsequent epilepsy monitoring at George Washington University Hospital in two patients who underwent deep brain stimulation (DBS) for treatment-resistant seizure disorders. Unlike DBS for movement disorders, this procedure is designed to stimulate deep brain structures with low frequencies. Mohamad Z. Koubeissi, M.D., FAAN, FANA, associate professor of neurology and director of the George Washington University School of Medicine and Health Sciences' Epilepsy Center, reports preliminary results showed "each stimulation session reduced the odds of seizure by 92 percent over the course of the following two days. The patients did not know they were being stimulated and had no memory or cognitive problems during the stimulation."

During the surgery, I also placed small recording depth electrodes in the frontal, temporal and parietal lobes in order to determine where each patient's seizures originated. The recording depth electrodes also allow Koubeissi to evaluate what happens to seizure activity in these areas during and after stimulation with the DBS electrode. This technique is considered in patients who cannot safely undergo resection of the seizure focus and continue to have seizures despite multiple anti-epileptic medications. Each of the electrodes is placed into the brain with a minimally invasive approach, using 3-D models of the patient's brain to plan the procedure in advance.

National Geographic will broadcast this documentary, titled "Breakthrough," beginning this fall, as part of a series describing innovative procedures impacting the treatment of human disease.



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