# INSIDE VIEW

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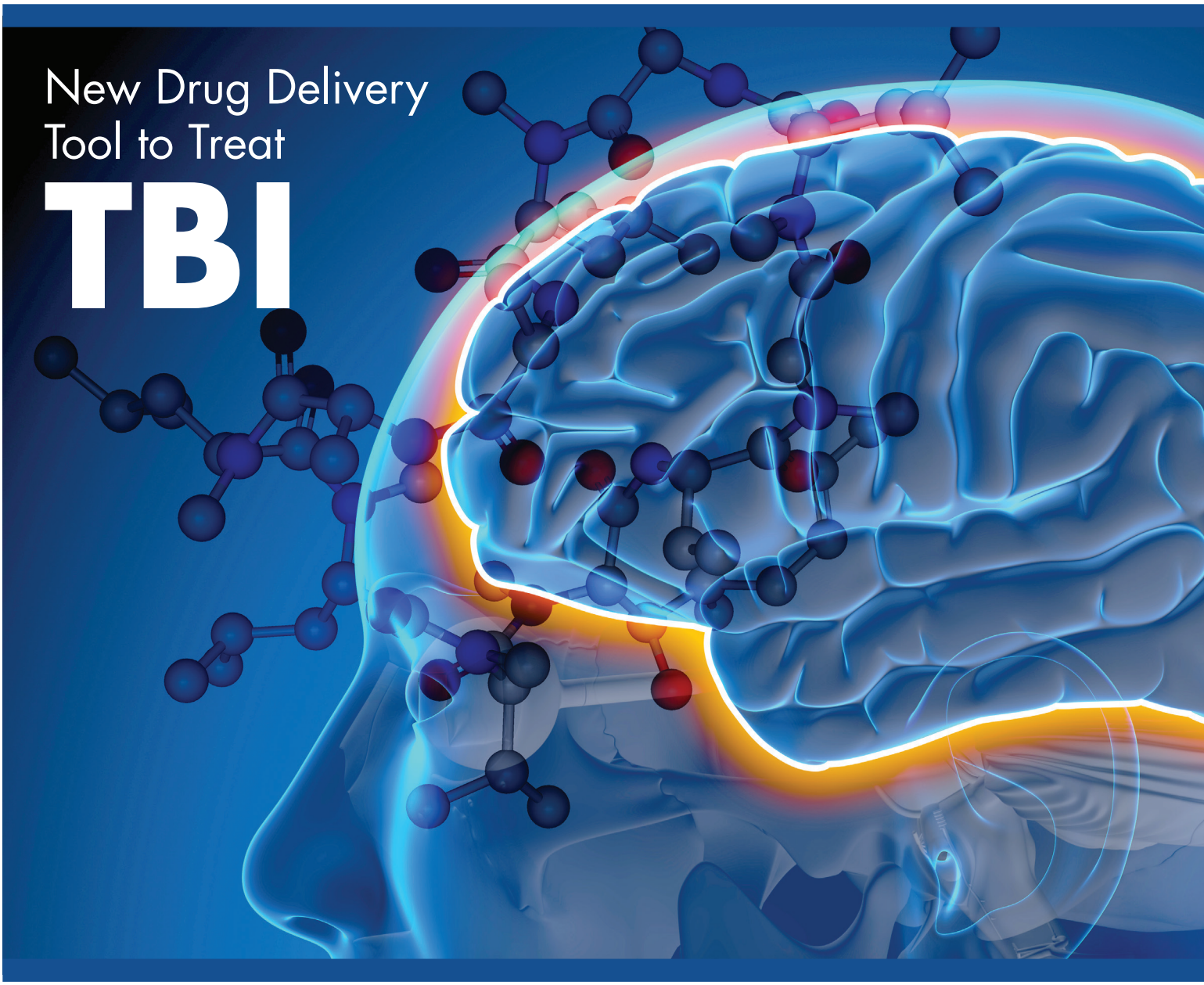


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# Concerns Surrounding Stroke Treatment in the Era of COVID-19

## by Dr. Mark Ashley

Stroke is an acquired brain injury and is a leading cause of long-term disability in the United States. Almost 800,000 people in America will experience a new onset or recurrent stroke each year. Worldwide, stroke is the second leading cause of death and disability.

Stroke is often thought of as a disease that occurs in older people. While this is often the case, the incidence of ischemic stroke in people aged 20-54 has increased.

Slightly over one-third of people who experience a stroke are functionally dependent or die by three months post-discharge. Recovery after stroke can require the care of a team of individuals, including physicians, nurses, physical and occupational therapists, speech-language pathologists, recreational therapists, psychologists, nutritionists, social workers, and others.

**Stroke rehabilitation in the era of COVID-19**

As we consider the impact of the recent COVID-19 pandemic, a number of concerns arise regarding the rehabilitation dosing afforded to individuals who sustain a stroke.

Hospitals have, necessarily, reduced lengths of stay for non-COVID-19 diagnoses as they attempt to free up bed space for COVID-19 cases. As a consequence, rehabilitation therapies have become shortened or non-existent. Further, outpatient rehabilitation services have been suspended in many locations, leaving one to wonder how people who suffer from stroke will receive crucial treatment.

**Factors impacting stroke recovery**

We know that many factors impact a person's functional outcome after a stroke. These include age, where a younger age is associated with a better outcome, and the timing of therapy, which is essential because therapy that is provided too early can be detrimental, and therapy that is delayed can negatively affect the outcome. The exact window of opportunity is not clear and most likely varies with several patient-specific factors.

We also know that the degree of the expertise of rehabilitation treatment impacts outcome; with more expertise comes better outcomes. And we know that both the frequency and intensity of therapy affect the degree of recovery of function a person will achieve and reduce the likelihood of hospital readmission. Simply put, more therapy is associated with better outcomes. Furthermore, higher intensity therapy is associated with more recovery.

Several factors seem to merge around interfering with a person's ability to recover to their fullest potential. One factor is bundling payments, wherein a hospital is incentivized to discharge a person quickly and to attempt to reduce rehospitalization. It has been demonstrated that bundled payment arrangements result in less use of tertiary care settings, such as rehabilitation. As well, payers have become accustomed to very short inpatient rehabilitation stays, followed by simple outpatient rehabilitation services.

It is clear that more attention must be paid to scientific evidence that strongly links better outcomes with more frequent therapy, therapy of higher intensity, therapy that is properly timed and of sufficient duration, and therapy that is provided by properly trained specialists in neurorehabilitation.

Finally, great care in payment structuring should be taken to avoid skimping on care for this vulnerable population. ■

# 2021 Calendar of Events

**Mar**

**11-13**
TBI Med Legal Conference
*San Diego, CA*
tbimedlegalcon.com

**24-25**
Brain Injury Association of Massachusetts Annual Conference
*Marlborough, MA*
biama.org/annualconference.html

**Apr**

**7-9**
American Society for Neuroscience Conference
*St. Louis, MO*
asnr.com/i4a/pages/index.cfm?pageid=1

**May**

**3-5**
2021 Insurance Rehabilitation Synergy Group Annual Conference
*Baltimore, MD*
*irsghome.org*

**22-27**
American Society of Neuroradiology Annual Conference
*San Francisco, CA*
asnr.org/annualmeeting

**Jun**

**2-4**
Brain Injury Canada Conference
*Ottawa, Canada*
braininjurycanada.ca/ottawa-conference

**27-29**
BIA of Pennsylvania Annual Conference
*Lancaster, PA*
biapa.org

**Jul**

**10-14**
Neurotrauma 2021
*Austin, TX*
neurotrauma.org

**Sep**

American Congress of Rehabilitation Medicine Annual Conference
*Dallas, TX*
acrm.org/meetings/

# Development of Precision Drug Delivery Tool to Treat Traumatic Brain Injury

This nanoscale drug carrier works by caging therapeutic agents—in this case, drugs such as gabapentin and cyclosporine A—to carry them within the body

An interdisciplinary team of researchers at the University of Southern California has developed a precision drug delivery tool to selectively treat areas of the brain damaged during a traumatic brain injury (TBI). The researchers anticipate that their rapidly deployable intervention could potentially help prevent long-term brain damage in the millions of Americans who sustain a TBI each year.

This invention has been tested using two different therapeutics, and the results appear in the journals Frontiers in Chemistry and Molecular Pharmaceutics.

**Stopping the damage before it's too late**

The effects of TBIs on the American populace are nothing short of staggering. TBIs annually cause more deaths and lifelong disabilities than HIV/AIDS, breast cancer, multiple sclerosis and spinal cord injuries combined. Approximately one third of patients die due to secondary complications related to their TBIs, and in 2014, an average of 155 Americans died following a TBI each day. To compound this dramatic human toll, the economic burden of treating TBIs and their long-term side effects is estimated to be $60-76.5 billion each year.

The causes of TBIs range from falls and forceful sports collisions to car accidents and severe blows to the head. Side effects vary widely, from cognitive challenges and dizziness to emotional changes and depression that can endure for days, weeks, or even years after the initial trauma. If effective treatments are not rapidly deployed, a TBI can trigger biochemical changes and inflammatory responses that progressively worsen a patient's brain damage. To prevent serious side effects, doctors recommend that patients receive treatment within the "golden hour" after sustaining the injury.

Despite the pressing need for effective and rapidly deployable therapies, there are currently no FDA-approved treatments specifically designed for TBIs. Some existing treatments rely on locating the injury within the skull and assessing the damage before proceeding, but this approach can rob precious time from clinicians attempting to stave off permanent brain damage.

**A nanoscale solution to a widespread problem**

An ideal treatment approach for TBIs would involve a fast-acting, safe, transportable and easily administered drug that could permeate the brain's protective barrier at the site of damage. A team of USC scientists, led by researchers at the USC Dr. Allen and Charlotte Ginsburg Institute for Biomedical Therapeutics, has mobilized to meet this urgent clinical need: they recently developed a novel drug delivery tool

designed to safely and rapidly treat regions of the brain damaged during a TBI.

The tool itself is known as a nanocage. As the name suggests, this nanoscale drug carrier works by caging therapeutic agents—in this case, drugs such as gabapentin and cyclosporine A—to carry them within the body. Once a caged drug has migrated through a patient's circulatory system and made its way to the brain, doctors can beam near-infrared (NIR) light through the patient's skull to energize the molecule and "open" the cage.

The beauty of this approach is multifold. Caging the drug before releasing it at the site of injury minimizes the side effects that one would expect from delivering an active drug throughout the entire body. Moreover, because the brain's barrier is weakest where it experienced the most trauma, higher concentrations of the drug will enter the brain precisely at the site of damage—thus circumventing the need for time-consuming imaging to locate the damage before proceeding with first-line treatment.

The researchers chose NIR frequency specifically for its ability to safely permeate human tissue without residual side effects, and they designed the nanocage itself to be biodegradable and non-toxic. This emerging intervention is still in its preclinical stages, but the researchers anticipate that it can be packaged as a portable intervention for first responders to immediately administer within a patient's "golden hour."

"I'm very hopeful for the impact this drug delivery tool could ultimately have on the millions of patients who experience TBIs each year," said Mark Humayun, MD, Ph.D., director of the USC Ginsburg Institute for Biomedical Therapeutics, who is the study's principal investigator. "A rapid intervention like this could significantly improve patient outcomes, and our team is excited to continue testing this approach to hopefully bring it to the clinic soon."

Caroline Black, Ph.D., lead author on the study, says this research was made all the more meaningful because of her personal connection to TBI within her family. "My dad had a severe TBI when he was 17 and I've seen how the effects of secondary injury can persist decades after the initial trauma," said Black, who is a USC-AbbVie postdoctoral fellow specializing in drug delivery sciences at the biopharmaceutical company AbbVie. "Our drug delivery tool has the potential to open new possibilities for rapid treatment of TBI, and I'm excited to see the impact it could have on improving patient outcomes." ■

# Concussion Discovery Reveals Dire, Unknown Effect of Even Mild Brain Injuries

Even mild concussions may seed the brain for Alzheimer's disease, dementia and other neurodegenerative problems

Even mild concussions cause severe and long-lasting impairments in the brain's ability to clean itself of toxins, and this may seed it for Alzheimer's disease, dementia and other neurodegenerative problems, new research from the University of Virginia School of Medicine reveals.

The discovery offers important insights into traumatic brain injury (TBI), a poorly understood condition that has become a major public concern, particularly in sports and for the military. The findings help explain why TBI is so harmful and why it can have such long-term effects. The research also suggests that certain patients are at greater risk of a decline in brain function later in life, and it paves the way for new and better treatments.

"This provides some of the best evidence yet that if you haven't recovered from a brain injury and you get hit in the head again, you're going to have even more severe consequences," said John Lukens, PhD, of UVA's Department of Neuroscience and the Center for Brain Immunology and Glia (BIG). "This reinforces the idea that you have to give

people an opportunity to heal. And if you don't, you're putting yourself at a much higher risk for long-term consequences that you might not see in a year but could see in a couple of decades."

### New Understanding of TBI

Lukens' research identifies a previously unknown consequence of TBI that can have long-lasting effects. When the brain swells, it presses against the skull; trapped in-between are tiny lymphatic vessels that clean the brain. This pressure on the vessels, the UVA researchers found, causes serious and long-lasting impairment of the brain's ability to purge itself of toxins. Working with lab mice, one of the best models of TBI available, the scientists found the impairment could last at least two weeks–a long time for mice–and possibly much longer.

These lymphatic vessels were identified by Jonathan Kipnis, PhD, and his collaborators at UVA in 2015. Until then, medical textbooks insisted the vessels did not exist and that the brain was "immune privileged," meaning that it did not interact with the immune system. Kipnis' discovery changed all that, and he has since determined the vessels play important roles in both Alzheimer's and the cognitive decline that comes with age.

Now they emerge as an important player in TBI. "We know that traumatic brain injury carries an increased risk for a bunch of long-term issues like dementia, Alzheimer's disease and CTE [chronic traumatic encephalopathy], and this has really been made extra public because of the NFL," said researcher Ashley C. Bolte, an MD/PhD student. "Then there's also anxiety, depression, suicide. The reasons why TBI results in increased risk for this isn't totally known, and we think that our findings might provide a mechanism as to why."

### People Most at Risk

The research suggests that people who have pre-existing problems with their brain drainage, either from prior concussions or naturally, are likely to suffer much more severe consequences from TBI. In mice, this led to more brain inflammation and worse outcomes, including memory impairment. "If you have a pre-existing kink in the pipes and you get hit in the head, then everything is taken to a higher level—the impacts on memory, the neuroinflammation," Lukens said. "There are a lot of implications to it."

Emerging imaging technology may eventually make it possible for doctors to identify people who will suffer the greatest consequences of TBI. More good news: Lukens also believes that doctors may one day be able to rejuvenate the impaired lymphatic vessels with drugs to improve patients' outcomes and possibly stave off long-term consequences. (This also may prove useful in the battle against the cognitive decline that naturally occurs with age.)

In addition, Lukens said, it eventually may be possible for doctors to evaluate brain drainage after injury to determine when it is safest for patients to return to action.

"Right now, we really don't know what to tell these kids who want to get back out on the field, or even members of the military," Lukens said. "It would be important to have empirical tests to say you can continue or never to do those things ever again." ■

People who have problems with brain drainage, either from prior concussions or naturally, are likely to suffer more severe consequences from TBI

# Rapid Blood Test Could Detect Brain Injury in Minutes

A blood protein test could detect the severity of head trauma in under 15 minutes, according to research published recently in the Journal of Neurotrauma.

By showing that glial fibrillary acidic protein (w) can accurately determine the severity of a brain injury through a blood test, the research team working on this study, led by author David Okonkwo, M.D., Ph.D., director of the Neurotrauma Clinical Trials Center at UPMC and professor of neurological surgery at the University of Pittsburgh School of Medicine, advanced the development of a point-of-care testing device designed to help clinicians assess traumatic brain injury (TBI) in minutes.

For the rapid test, the vision included using a hand-held device with a cartridge that would measure GFAP in a patient's blood. Researchers at Abbott Laboratories, a global health care company, will need to finalize the test for the i-STAT device, which already is used by the military and health care providers around the world to perform several common blood tests within minutes. The blood test would reveal a patient's GFAP level.

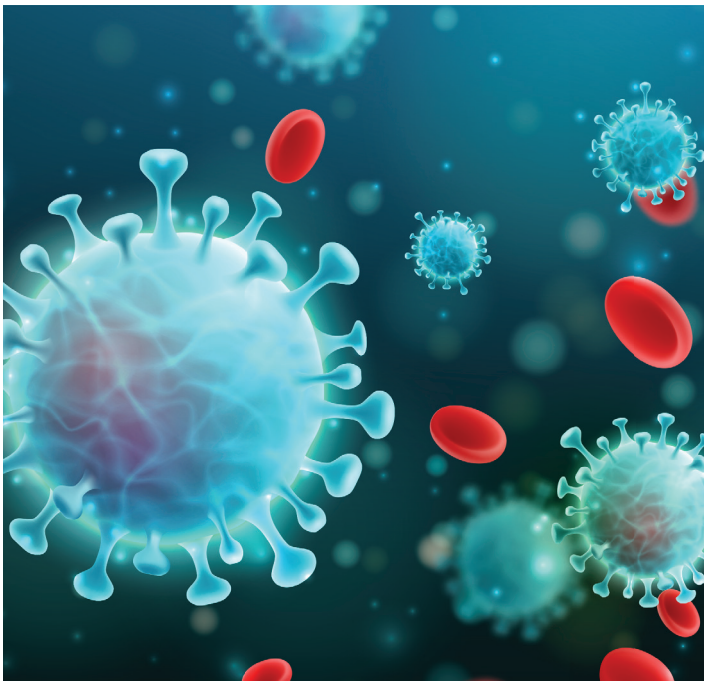
"This would eliminate guesswork in diagnosing TBIs and learn whether a person needs further treatment," said Okonkwo. "Whether you're testing a soldier injured in combat or testing a patient in a small rural hospital with limited resources, health care providers could have critical information they need—in minutes—to treat each patient's brain injury."

For this study, which expanded upon previous GFAP findings, researchers enrolled 1,497 people who sought care at one of the 18 Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) level 1 trauma centers nationwide over four years. GFAP is a Food and Drug Administration-approved marker for ruling out whether a patient needs a head computed tomography (CT) scan within 12 hours after a mild TBI.

For years, scientists have studied blood tests involving GFAP. They also have studied a similar protein called S100B. Both proteins are released in the bloodstream in response to specific injuries, including TBI. But this study showed that GFAP substantially outperformed S100B as a TBI diagnostic marker.

"Knowing this protein can show the severity of a TBI through a simple blood test is promising when considering we can use a device that already is in widespread use in hospitals, doctors' offices and urgent care facilities. All we would need to do is add an extra cartridge to the device to analyze blood for the GFAP protein," said Okonkwo. He estimates this device could potentially decrease unnecessary CT scans by 20% or more, saving nearly $100 million in medical expenses annually. ■

# 8 in 10 COVID-19 Patients Suffer Neurological Symptoms



Research has revealed concerning new COVID-19 findings: Neurological symptoms occur in 8 of 10 hospitalized COVID-19 patients.

These symptoms include muscle pain, headaches, dizziness, encephalopathy and "brain fog."

"Encephalopathy, which is characterized by altered mental function ranging from mild confusion to coma, is the most severe neurologic manifestation of COVID-19," said study co-author Dr. Igor Koralnik. He oversees the Neuro COVID-19 Clinic at Northwestern Memorial Hospital in Chicago.

For this new study, the researchers analyzed the charts of more than 500 patients hospitalized for COVID-19 within the Chicago-based Northwestern Medicine health system. The investigators identified neurological symptoms in 42% of patients when their COVID-19 symptoms surfaced, 63% of patients when hospitalized, and 82% of patients at any time during the course of COVID-19.

Many patients reported muscle pain (45%) and headaches (38%). Encephalopathy and dizziness were seen in almost one-third of patients. The study also found 16% had taste disorders and 11% had smell disorders.

Encephalopathy, characterized by altered mental function, is the most severe neurologic manifestation of COVID-19

After discharge from the hospital, only 32% of patients with encephalopathy were able to care for their own affairs, compared to 89% of those who didn't develop encephalopathy, the findings showed.

Also, the death rate in patients with encephalopathy was much higher (about 22%) than in those without encephalopathy (3%), according to the study.

"We are now looking to characterize the long-term neurologic effects of COVID-19 and the cognitive outcomes in patients with COVID-19-associated encephalopathy," Koralnik said in a hospital news release. He is chief of neuro-infectious diseases and global neurology at Northwestern Medicine.

"We're studying this in patients who are discharged from the hospital, as well as in COVID-19 'long-haulers,' who have never been hospitalized but also suffer from a similar range of neurological problems, including brain fog," he added.

The report was published a recent Annals of Clinical and Translational Neurology. The findings will help shape long-term care for people who suffer from neurological complications of COVID-19, Koralnik said.

"Patients and clinicians need to be aware of the high frequency of neurologic manifestations of COVID-19 and the severity of altered mental function associated with this disease," he noted. ■

# Researchers Discover Neuroprotective Treatment for Chronic Traumatic Brain Injury

Traumatic brain injury (TBI) is a leading cause of cognitive impairment that affects millions of people worldwide. Despite growing awareness about the debilitating and lifelong progressive consequences of TBI, there are currently no treatments that slow the deteriorative process. TBI survivors are currently treated with extensive physical and cognitive rehabilitation, accompanied by medications that may mitigate symptoms yet do not halt or slow neurodegeneration.

Now, researchers have found for the first time that this process can be pharmacologically reversed in an animal model of this chronic health condition, offering an important proof of principle in the field and a potential path to new therapy. The findings from Harrington Discovery Institute at University Hospitals (UH), Case Western Reserve University (CWRU) School of Medicine, and Louis Stokes Cleveland VA Medical Center were recently published in the Proceedings of the National Academy of Sciences (PNAS).

"TBI can lead to lifelong detrimental effects on multiple aspects of health," explains Andrew A. Pieper, MD, Ph.D., senior author on the study and Director of the Harrington Discovery Institute at UH Neurotherapeutics Center, Morley-Mather Chair in Neuropsychiatry, Professor of Psychiatry at CWRU, and Psychiatrist at the Louis Stokes Cleveland VA Medical Center Geriatrics Research Education and Clinical Center (GRECC). "Adverse long-term outcomes of TBI commonly include sensorimotor impairment, cognitive dysfunction, or emotional dysregulation, such as depression and anxiety, including worsened post-traumatic stress disorder. In addition, TBI significantly increases the risk of later developing aging-related forms of dementia, such as Alzheimer's and Parkinson's diseases."

Dr. Pieper and his team set out to test whether it was possible to reverse the lifelong chronic neurodegeneration and associated cognitive deficits after TBI, which had never been demonstrated before. They utilized a mouse model that mimicked concussive impact in middleaged people suffering a TBI decades prior, and administered an energy-elevating neuroprotective compound, known as P7C3-A20, that they had previously shown to have therapeutic value in acute TBI. The research team waited for one year after injury and then administered the compound daily to mice for one month.

Strikingly, this brief treatment with P7C3-A20 restored normal cognitive function. They continued to observe the mice for an additional four months, during which time they did not administer any more compound. Remarkably, at the end of this period the mice still showed normal cognitive function. Thus, after just one month of treatment, cognitive function remained improved four months later.

"When we examined the brains under the microscope, we saw that chronic neurodegeneration after TBI had completely stopped in the mice that had been briefly treated with P7C3-A20," said Edwin Vázquez-Rosa, Ph.D., co-first author on the study. "Then, under electron microscopy we discovered that P7C3-A20 had also facilitated repair of the endothelial cells lining the blood vessels of the brain."

"This is the first time we've seen that P7C3-A20 can protect endothelial cells at the interface of the cardiovascular system and the brain, known as the neurovascular unit (NVU)," explains Min-Kyoo Shin, Ph.D., co-first author on the study. Deterioration of the NVU occurs

"When we examined the brains under the microscope, we saw that chronic neurodegeneration after TBI had completely stopped in the mice that had been briefly treated with P7C3-A20"

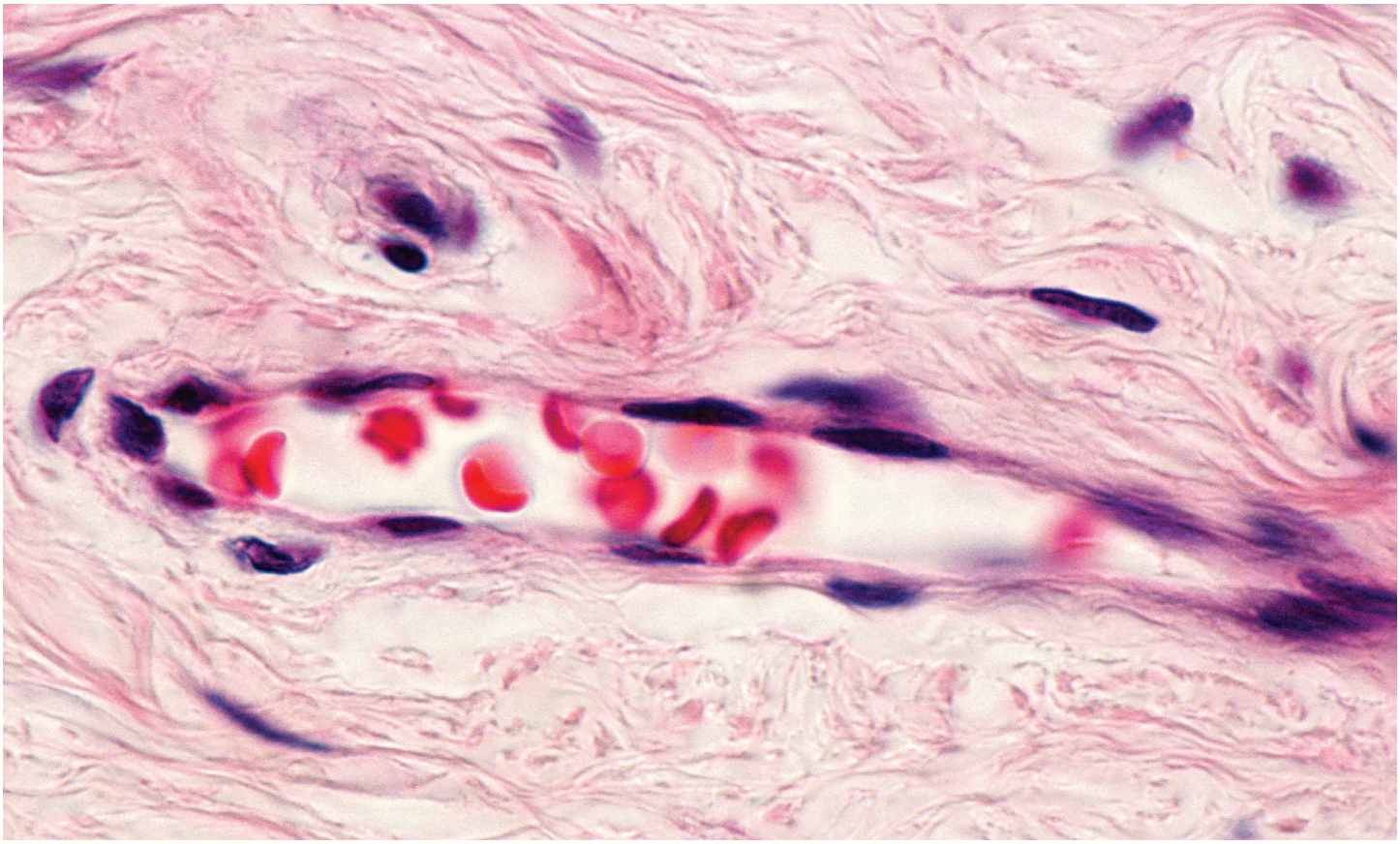
in almost all types of brain injury and disease, and is a well-known early and chronic feature of Alzheimer's disease. The team also showed that P7C3-A20 directly protects human brain microvascular endothelial cells cultured in the laboratory as well.

"Except for aging and genetics, TBI is the greatest risk factor for developing Alzheimer's disease," explains Matasha Dhar, Ph.D., co-first author on the study. "We speculate that preserving the blood-brain barrier at the NVU might be a way to protect TBI patients from this increased risk."

Robert A. Bonomo, MD, Associate Chief of Staff and Director of the Cleveland GRECC asserts, "These seminal findings have tremendous long-term impact on our veteran population that suffers from TBI."

There are currently no medicines available to patients that directly protect the blood brain barrier. A medicine with this property, such as might be derived from the P7C3 series of compounds, would have broad applicability to numerous conditions of the brain, including TBI and Alzheimer's disease. ■

"This is the first time we've seen that P7C3-A20 can protect endothelial cells at the interface of the cardiovascular system and the brain, known as the neurovascular unit"



# Saliva May Hold key to Concussion Diagnosis and Management

## Researchers discovered that a noninvasive saliva test demonstrated similar diagnostic accuracy to neurocognitive and balance tests commonly used today

A simple saliva swab may hold the key to diagnosing and managing mild traumatic brain injury (i.e., concussions), according to a study recently published in the journal Clinical and Translational Medicine. In a paper titled "Diagnosing mild traumatic brain injury using saliva RNA compared to cognitive and balance testing," researchers discovered that a noninvasive saliva test demonstrated similar diagnostic accuracy to neurocognitive and balance tests commonly used today, and greater diagnostic utility when combined with standardized symptom assessment. Moreover, the researchers from Penn State College of Medicine, SUNY Buffalo Jacobs School of Medicine, SUNY Upstate Medical and Quadrant Biosciences Inc., suggest that the saliva test may have additional clinical utility in predicting the type and duration of symptoms.

More than 3 million concussions occur each year, the majority occurring among children and young adults. Despite the prevalence of the injury, there are

few clinically valid methods for its diagnosis or prognosis. As a result, there is great value in an objective biomarker that is not only accurate, but easily collected and measured.

"Currently, the diagnosis of concussion relies largely on subjective symptom reports from patients," explains Steven Hicks, MD, Ph.D., FAAP, Associate Professor of Pediatrics, Penn State Hershey Medical Center and one of the co-authors in this study. "The lack of objective tools for concussion assessment is problematic because symptom reports can be manipulated to expedite, or delay, return to activities. As a result, studies have shown that concussion is often under-diagnosed."

Quadrant Biosciences has been working the past several years with researchers from Penn State Medical Center and SUNY Upstate Medical University to explore the use of saliva biomarkers to objectively diagnose concussion. This earlier research, published in the Journal of the American Medical Association Pediatrics in 2018, identified a panel of small, non-coding molecules ("ncRNA") in the saliva that acted as a "molecular signature" to not only diagnose concussion, but predict the duration and character of concussion symptoms. The present study was designed, in part, to test that diagnostic and prognostic utility in a larger cohort of patients.

In this study of 538 individuals across 11 test sites, the researchers compared the ability of saliva RNA to identify mTBI, relative to a commonly used symptom scale, balance test, and neurocognitive assessment. Saliva was collected using the ORAcollect®·RNA (OR-100) device from OraSure Technologies. The saliva test identified participants who had suffered mTBI with similar accuracy to standard clinical tools. The best performing predictive model included symptom reports combined with saliva RNA measures.

These results suggest that saliva RNA represents a noninvasive, biologic measure with the potential to aid concussion diagnosis. Hicks said predicting the length of concussions as early as possible would help ensure patients get the right care, and advise patients and parents on how long to expect symptoms to continue. "With that knowledge," Hicks explained, "physicians could make more informed decisions about how long to hold a child out of sports, whether starting more aggressive medication regimens might be warranted, or whether involving a concussion specialist might be appropriate. Anytime we can use accurate, objective measures to guide medical care, I think that represents an opportunity to improve concussion treatment."

"Physicians could make more informed decisions about how long to hold a child out of sports, whether starting more aggressive medication regimens might be warranted, or whether involving a concussion specialist might be appropriate"

While more studies are needed, Hicks said he is hopeful that measuring microRNAs in saliva could one day be an accurate, quick way to diagnose and manage concussions.

"The ultimate goal is to be able to objectively identify that a concussion has happened and then predict how long the symptoms will go on for," Hicks said. "Then we can use that knowledge to improve the care that we provide for children who have concussions, either by starting medicine earlier or holding them out of activities for longer." ■

# Could A Nasal Spray Of "Nanovesicles" Repair Brain Cells?

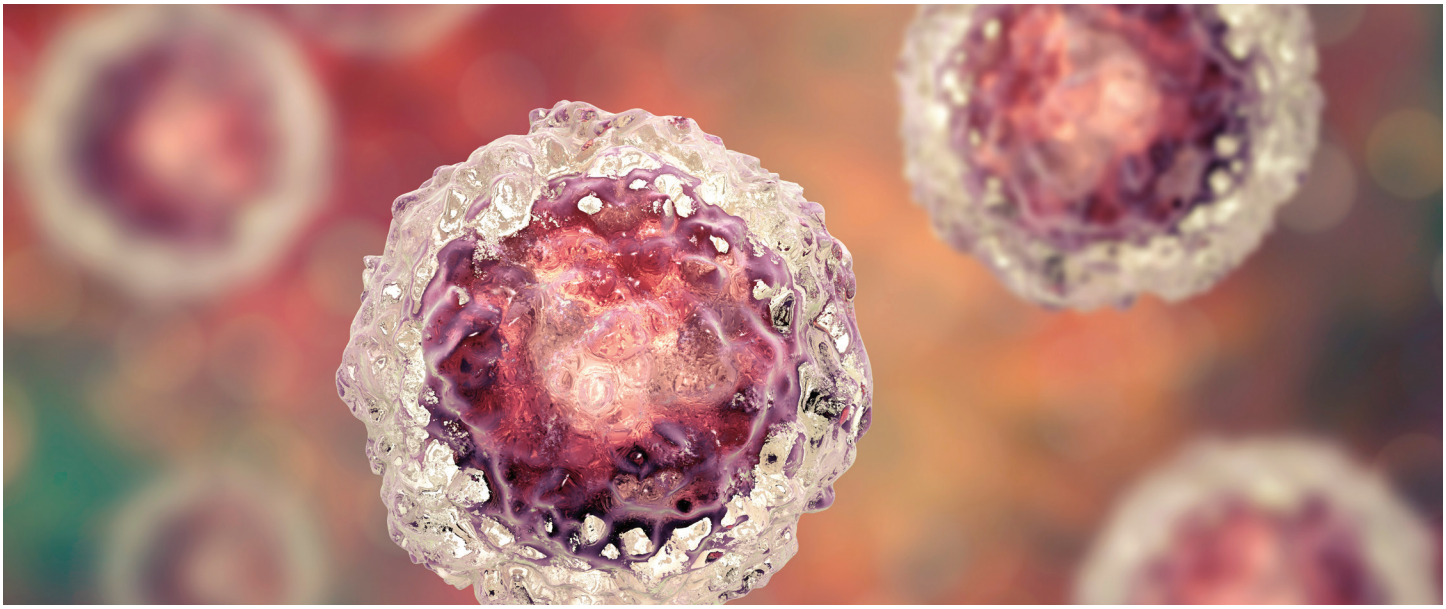
Extracellular Vesicles, derived from stem cells in the nervous system, can repair damaged cells and block proteins that cause both acute and chronic brain inflammation

An inexpensive, accessible and noninvasive therapy for diseases and injuries of the brain may be slowly emerging: tiny particles called extracellular vesicles (EVs). Unlike stem cell therapies for repairing brain damage — which can be unsafe when tested in humans — EVs may safely regenerate brain cells and reduce inflammation, according to a recent study conducted by researchers at the Texas A&M University College of Medicine.

The study, published in the Journal of Extracellular Vesicles, found that EVs derived from stem cells in the nervous system can repair damaged cells and block proteins that cause both acute and chronic brain inflammation. EVs, which under an electron microscope look like rain droplets on a windowpane, help with communication between cells. Pinching off from a cell into nano-sized globules, EVs then latch onto other cells and share their contents. Working like microscopic messenger pigeons between cells, EVs might be able to quickly deliver brain therapies.

But before this study was conducted in animal models, little was known about how to best separate therapeutic EVs from neural stem cells. Likewise, research had not pinpointed exactly which proteins and microRNAs (small fragments of RNA that regulate the production of proteins) the EVs carry throughout the brain. Ashok Shetty associate director of the Institute for Regenerative Medicine and professor in the Department of Molecular and Cellular Medicine, and his colleagues established a method for isolating EVs from neural stem cells and identified some of the EVs' cargo.

They found that EVs carry along proteins and microRNAs that can regenerate brain cells in the hippocampus — the



learning and memory center of the brain — and promote new connections between nerve cells and curb inflammation, among other neuroprotective functions. A few of these proteins or microRNAs might even help reduce amyloid-beta plaques and alpha-synuclein on the brain, which are key features of dementia (like Alzheimer's) and Parkinson's disease. Shetty says that with this knowledge, "we could use EVs to intervene very early and slow down these diseases, for example."

These findings suggest "there are a lot of other proteins in EVs that have to be studied," said Leelavathi Madhu, a College of Medicine associate research scientist and one of the first co-authors of the paper reporting the research. Future research, Madhu says, should directly investigate other brain conditions — such as Alzheimer's disease and traumatic brain injury.

Unlike therapy that uses neural stem cells, Shetty says EV therapy might pose few health risks. For example, EVs are too tiny to block blood flow or cause an immune response, and such a small quantity would need to be administered that there "likely won't be any side effects," said the other first co-author, Raghavendra Upadhya, associate research scientist at the College of Medicine.

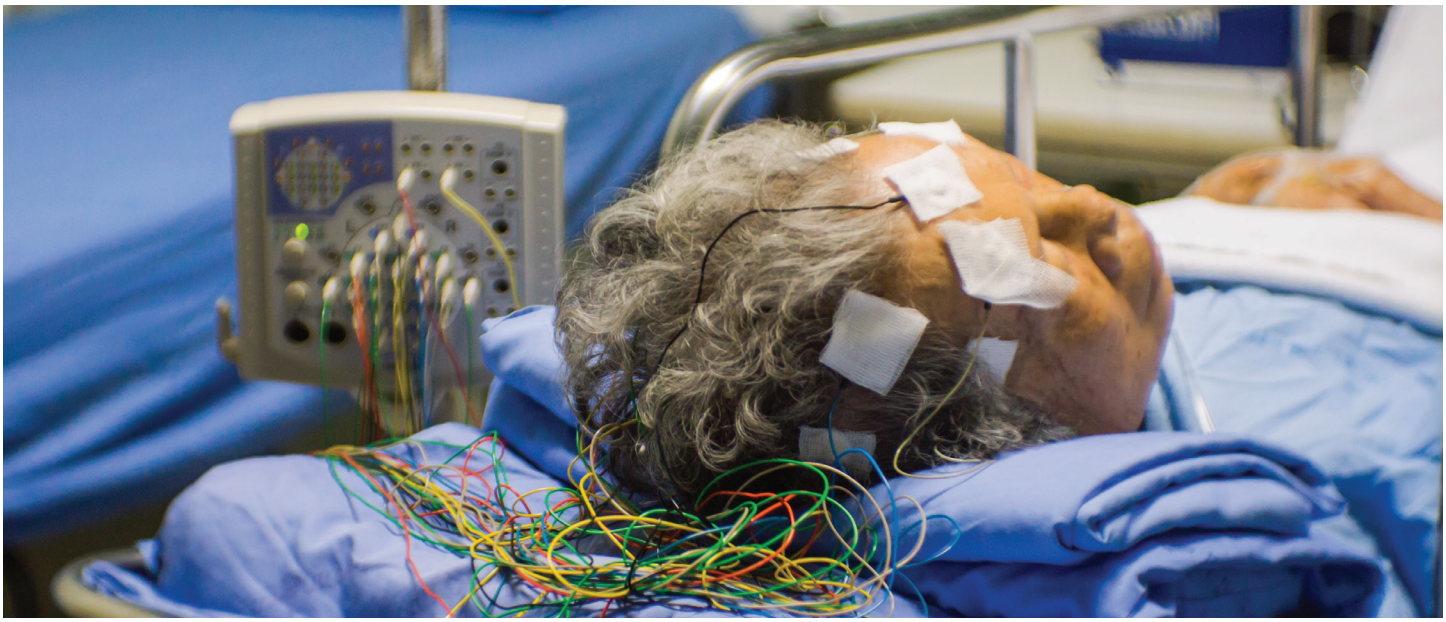
Therapeutic EVs, when administered through the nose, can enter brain cells (such as neurons and glia) in nearly all regions of the brain within six hours. This administration method makes them a potentially low-cost, non-surgical therapy for neurodegenerative diseases or brain injuries. An EV nasal spray, Shetty proposes, could be used as a therapy in almost all settings.

"Imagine a football player who has a concussion," he said. "You just have to give him a nasal spray of EVs to prevent long-term adverse effects such as cognitive and mood dysfunction."

EVs can be extracted from almost any cell, but because these researchers were interested in a brain treatment, they used EVs extracted from stem cells of the nervous system, or neural stem cells. Stem cells are produced from "master" cells, known as human induced pluripotent stem cells, which can make any type of cell or tissue. To produce master cells — and, subsequently, EVs derived from neural stem cells — researchers need only reprogram skin or blood cells. And these cells already fill shelves in cell banks, facilities that house cells for research projects.

However, such easy and effective therapies might take years to reach the public, if at all. The United States Food and Drug Administration (FDA) must first approve EVs for therapeutic use through human clinical trials, but Shetty notes that EV therapy research for brain disorders is currently restricted to animals. In the United States, no clinical trials have investigated brain disorder therapies that use neural stem cells generated from human induced pluripotent stem cells due to safety concerns, including abnormal immune responses and the development of tumors.

"That's why many groups are working on perfecting the isolation of therapeutic EVs from different types of neural cells, including neural stem cells," Shetty said. ■



# What EEGs tell us about COVID-19 and the brain

Researchers found that about one-third of patients who were given an EEG had abnormal neuroimaging localized in the frontal lobe of the brain

Throughout the pandemic, healthcare workers have seen more than just the lungs affected by COVID-19. Doctors have reported neurological complications including stroke, headache and seizures, but the information is limited to a number of individual reports that are not reflective of a larger population.

Researchers from Baylor College of Medicine and the University of Pittsburgh have gathered more than 80 studies, reviewed the data, and identified commonalities that are helping to paint a broader picture of how COVID-19 affects the brain.

The findings, published in Seizure: European Journal of Epilepsy, focused on electroencephalogram (EEG) abnormalities of the brain. EEG is a test used to evaluate the electrical activity in the brain. Researchers found that about one-third of patients who were given an EEG had abnormal neuroimaging localized in the frontal lobe of the brain.

"We found more than 600 patients that were affected in this way. Before, when we saw this in small groups we weren't sure if this was just a coincidence, but now we can confidently say there is a connection," said Dr. Zulfi Haneef, assistant professor of neurology/neurophysiology at Baylor.

The main reason a patient would be given an EEG is if altered mentation is noted, meaning a patient might have a slowed reaction to stimuli, followed by seizure-like events, speech issues, confusion or inability to wake up after sedation. The most common findings

from the EEG were slowing or abnormal electrical discharge, mostly in the frontal lobe.

Some of the EEG alterations found in COVID-19 patients may indicate damage to the brain that might not be able to be repaired after recovering from the disease.

"As we know, the brain is an organ that cannot regenerate, so if you have any damage it will more than likely be permanent or you will not fully recover," Haneef said.

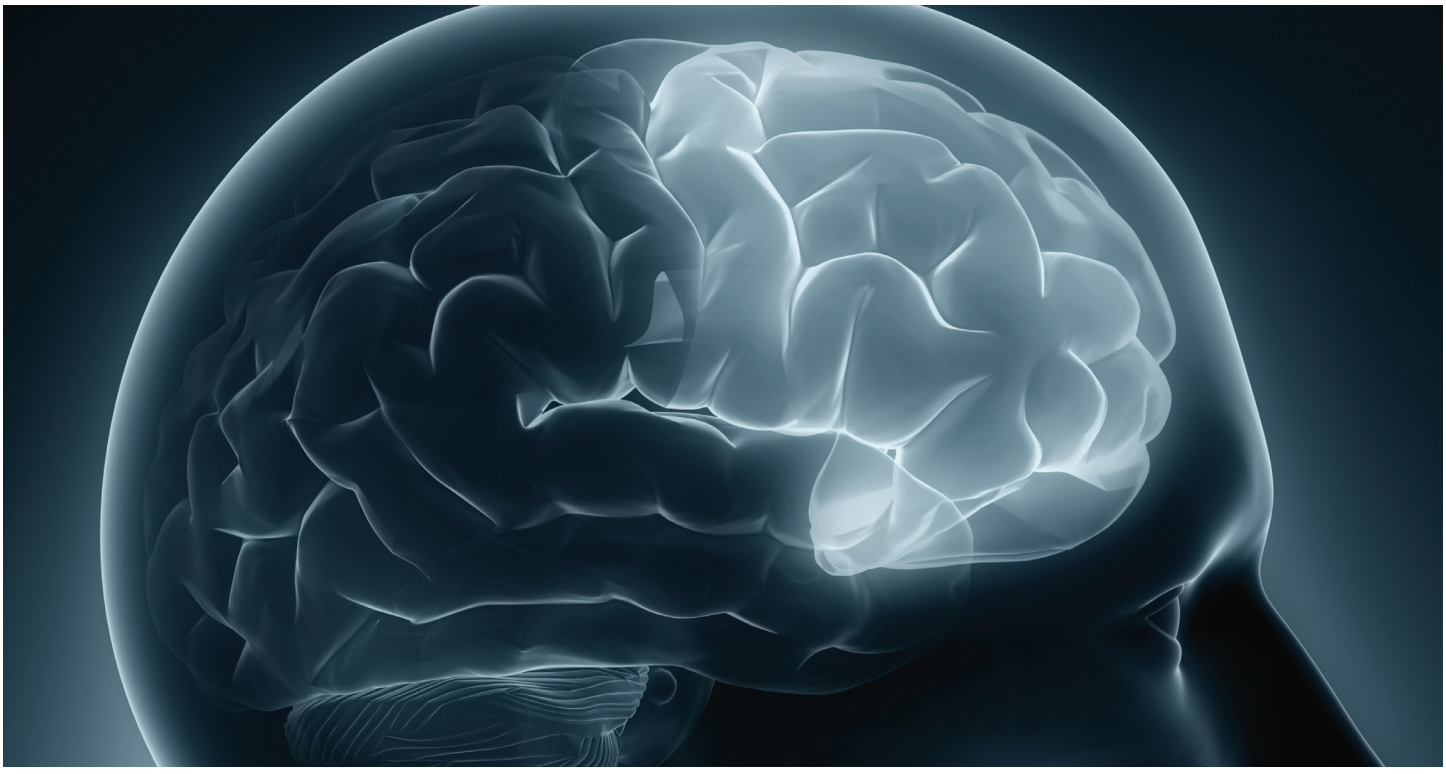
Haneef found the location of the abnormal activity interesting.

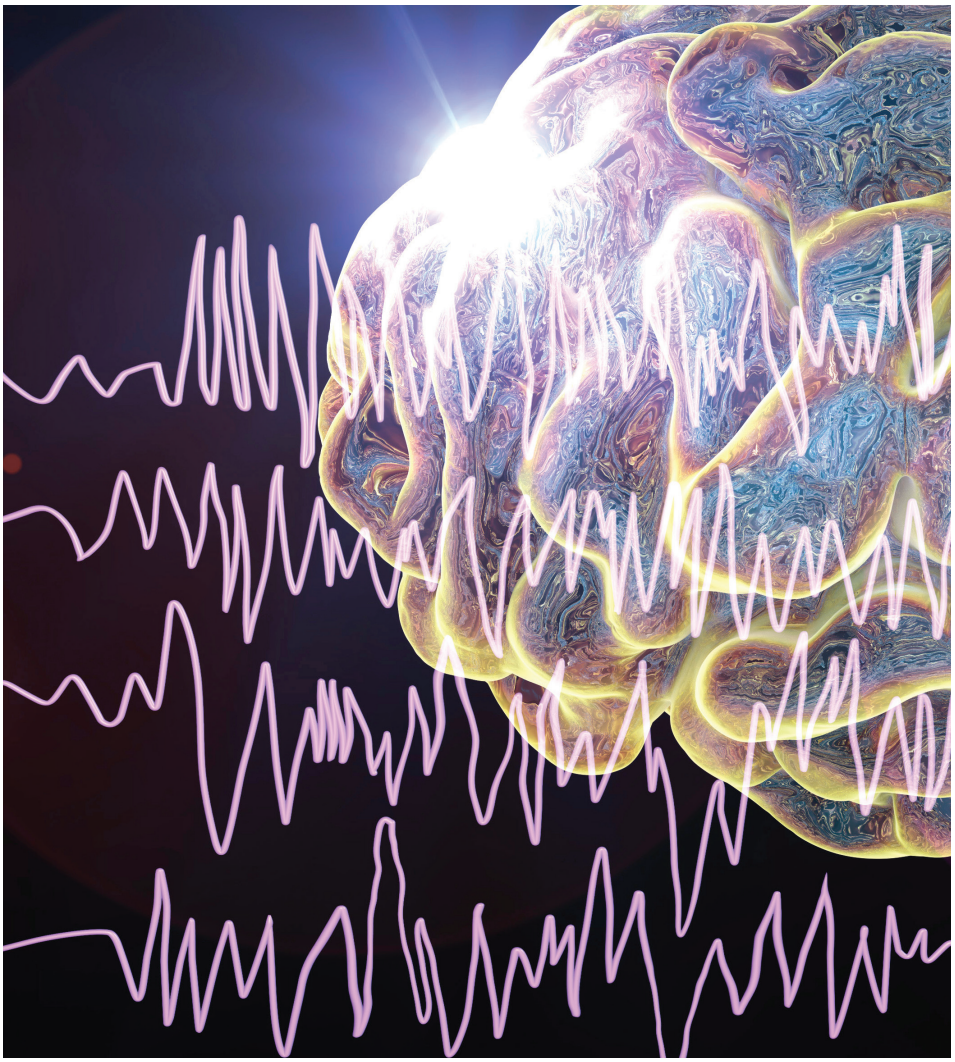
"We know that the most likely entry point for the virus is the nose, so there seems to be a connection between the part of the brain that is located directly next to that entry point," he said. "Another interesting observation was that the average age of those affected was 61, one-third were female and two-thirds were males. This suggests that brain involvement in COVID-19 could be more common in older males. More research is needed but these findings show us these are areas to focus on as we move forward."

It may not always be the virus acting directly on the brain causing the abnormal EEG readings, Haneef said. It could be the oxygen intake, heart problems related to COVID-19 or another type of side effect, which is why he says that comprehensive patient care should include more imaging of the brain or EEG testing as necessary.

"These findings tell us that we need to try EEG on a wider range of patients, as well as other types of brain imaging, such as MRI or CT scans, that will give us a closer look at the frontal lobe," Haneef said. "A lot of people think they will get the illness, get well and everything will go back to normal, but these findings tell us that there might be long-term issues, which is something we have suspected and now we are finding more evidence to back that up." ■

Some of the EEG alterations found in COVID-19 patients may indicate damage to the brain that might not be able to be repaired after recovering from the disease





# Individualized Brain Stimulation Therapy Improves Language Performance in Stroke Survivors

Baycrest scientists are pioneering the use of individualized brain stimulation therapy to treat aphasia in recovering stroke patients.

Aphasia is a debilitating language disorder that impacts all forms of verbal communication, including speech, language comprehension, and reading and writing abilities. It affects around one-third of stroke survivors, but can also be present in those with dementia, especially in the form of primary progressive aphasia.

"Aphasia can be very isolating," says Dr. Jed Meltzer, Baycrest's Canada Research Chair in Interventional Cognitive Neuroscience and a neurorehabilitation scientist at Baycrest's Rotman Research Institute (RRI). "It can negatively affect people's personal relationships, and it often determines whether or not someone can continue working."

In a recent study published in the journal Scientific Reports, Dr. Meltzer and his team tested language performance and used magnetoencephalography (MEG) to measure brain waves in 11 stroke survivors with aphasia before and after they underwent brain stimulation therapy.

The scientists found that the participants had abnormal electrical activity in brain regions close to but outside the area destroyed by the stroke. This abnormal activity was mainly a shift to slower brain waves, a pattern they have also observed in individuals with dementia.

"We mapped that abnormal activity and targeted it using noninvasive brain stimulation," says Dr. Meltzer. "We found that the stimulation made the activity more normal—that is, faster—and improved language performance in the short term."

Previous research has demonstrated that brain stimulation can improve language performance in aphasia patients. However, this study is one of the first to link this perfor-

We mapped abnormal activity, targeted it using noninvasive brain stimulation, and found that it made the activity more normal—that is, faster—and improved language performance

mance improvement to changes in the brain activity surrounding the tissue destroyed by stroke. In other words, this study suggests not only that brain stimulation works in aphasia patients, but also that the reason it works may be because it addresses abnormalities in the brain surrounding the destroyed tissue.

Another novel aspect of this work is that the scientists targeted each individual's abnormal brain activity with the stimulation treatment. In contrast, the standard approach in previous studies has been to use the exact same treatment, targeting the same brain areas, on every patient.

"Our results demonstrate a promising method to personalize brain stimulation by targeting the dysfunctional activity outside of the destroyed brain tissue," says Dr. Meltzer. "Aphasia patients are highly variable in terms of where their brain damage is and what part of the brain should be stimulated for therapy. By mapping individuals' brain waves, we are finding ways to target the right area to improve their language performance."

While the participants in this study were stroke survivors, individuals with dementia have similar dysfunctional tissue in their brains, and the scientists are also examining the use of brain stimulation in this group.

Dr. Meltzer and his team looked at the immediate effects of single stimulation sessions in this study. As a next step, they have received funding from the Heart and Stroke Foundation to conduct a full-scale clinical trial looking at the longer-term impacts of repeated stimulation for stroke survivors with aphasia. However, this study has been suspended because of the restrictions on in-person research participation due to the COVID-19 pandemic. In the meantime, the scientists have pivoted to optimize other aspects of aphasia treatment.

With additional funding, the researchers could test different types of stimulation with more patients over more sessions, allowing them to make faster progress in developing this treatment for individuals with aphasia.■

# INSIDE VIEW

A Quarterly Magazine Dedicated to the Field of Acquired Brain Injury


## Our Mission

Centre for Neuro Skills is committed to helping those who have sustained a brain injury achieve the maximum possible quality of life and has served clients from around the world since 1980. CNS offers cost-effective, outcome-driven, community-based rehabilitation programs that focus on environmental validity, a normal rhythm of living, and obtaining the highest level of functioning for each client.

## Locations

CNS programs are located in Bakersfield, Los Angeles and San Francisco, California, Dallas, Fort Worth, and Houston, Texas. For more information about our services please email us at cns@neuroskills.com or call our toll free number 800.922.4994 or from outside the US at 661.872.3408.

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