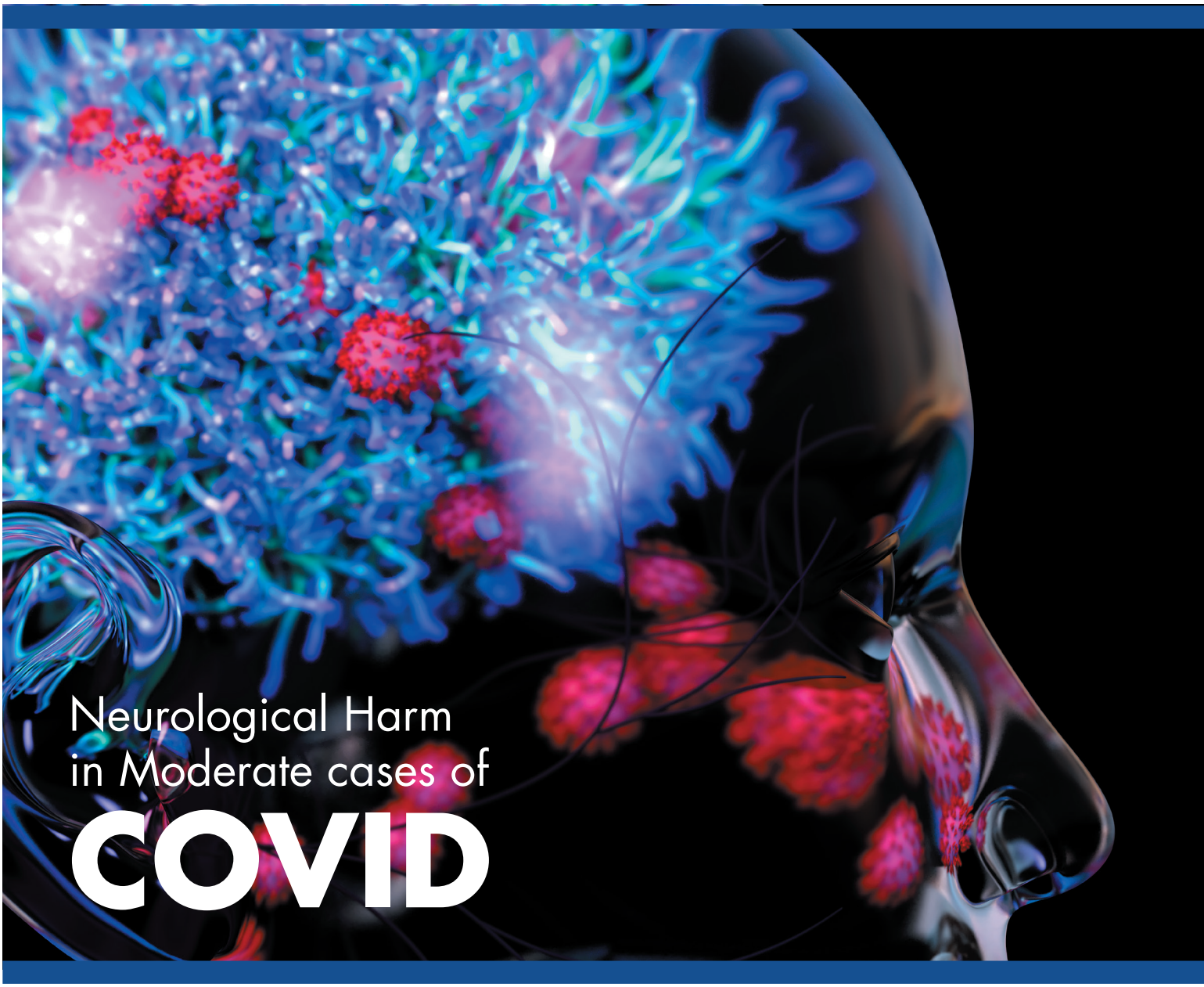
INSIDE VIEW

Issue 30.2
Spring 2021

A Quarterly Magazine Dedicated to the Field of Acquired Brain Injury



Published by Centre for Neuro Skills
insideview@neuroskills.com
neuroskills.com

ISSN# 1065-7320

How COVID-19 Can Affect and Damage the Brain

by Dr. Mark Ashley

On December 1, 2020, the number of COVID-19 cases worldwide totaled over 63.6 million, with 13.6 million cases within the United States. Of this total, nearly 1.5 million deaths were attributed to COVID-19, with over 269,000 of the deaths occurring in the U.S.[1]

COVID-19 had primarily been thought to be a respiratory disease. In recent months, however, growing evidence shows that the disease may likely be a disease of the epithelium of the lungs, or the lining of the respiratory tract, and the endothelium, the lining of arteries and veins throughout the body.[2]

Because of this, complications of COVID-19 tend to strike some organ systems more frequently than others. Respiratory, cardiovascular, renal, gastrointestinal, and neurological systems appear to be the most commonly impacted. Infection can present a loss of the sense of smell (anosmia) or taste (ageusia), Guillain-Barre syndrome, encephalopathy, encephalitis, and acute cerebrovascular disease.[3,4]

While extensive longstanding research has not been conducted due to relative inexperience with the virus, information is emerging that strongly suggests the risk of neurologic damage. One study compared the rate of acute ischemic stroke in individuals with COVID-19 to a group of people with influenza, a known stroke trigger. The research found the likelihood of stroke with COVID-19 infection (1.6% of people) to be substantially higher than for influenza (0.2%). [3]

Another study examined the risk of developing cerebrovascular disease with COVID-19 infection, which refers to disorders that affect the blood vessels and blood supply to the brain. The categories of cerebrovascular disease examined included cerebral ischemia, intracerebral hemorrhage, and leukoencephalopathy of the posterior reversible encephalopathy type. In total, 1.4% of 1,683 cases developed neurological complications over 50 days.[2] Neurological injuries included arterial dissections, subarachnoid hemorrhage, microbleeds, and single or multiple hematomas -severe injuries that resulted in high rates of death or significant disability.

The study found that the injuries tended to occur in the vascular areas that serve the brainstem and posterior (back) portions of the brain. Blood clotting in these areas can be exceedingly significant and impact the arteries feeding blood to the brain.[5]

There is also emerging evidence that individuals with pre-existing neurological injury are at greater risk for developing neurological complications in the event of COVID-19 infection. A case report of post-COVID-19 autoimmune encephalitis, an inflammation of the brain and spinal cord, found potentially significant long-term neurological symptoms and consequences if undiagnosed or improperly treated. These included non-fluent aphasia, oculomotor dysfunction, myoclonus of the tongue and limbs, echolalia, perseveration, and hallucinations.[6]

Recovery patterns post-COVID-19 show symptom persistence at the time of follow-up visit to range from 5% to more than 50% for neurological symptoms ranging from myalgia, vertigo, lack of appetite, headache, loss of taste, loss of smell, and fatigue.[7]

For the time being, it is reasonable to exercise caution in prediction about recovery from neurological deficits that accompany COVID-19 infection. There is evidence of recovery in some symptoms, such as the loss of taste or smell and significant long-term deficits associated with other complications such as stroke. However, we remain in the earliest stages in regards to understanding the near- and longer-term neurological consequences of COVID-19 infection. Recovery and symptom severity in the presence of newer interventions that impact viral replication rates and address inflammatory processes may be different, and hopefully better, than the currently available data. ■

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2021 Calendar of Events

Apr

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

May

7-8
Scripps Annual Brain Injury Conference
San Diego, CA
cripps.org/for-health-care-professionals/continuing-medical-education-cme

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

28-29
10th International Conference on Stroke and Cerebrovascular Diseases
Paris, France
strokecongress.neurologyconference.com

Jul

10-14
Neurotrauma 2021
Austin, TX
neurotrauma.org

11-14
Neurotrauma 2021
Virtual
neurotrauma.org/symposium/2021-virtual/general-info-2021

28-30
2021 Virtual World Congress on Brain Injury
Virtual
internationalbrain.org/meetings-and-events/virtual-conference-2021

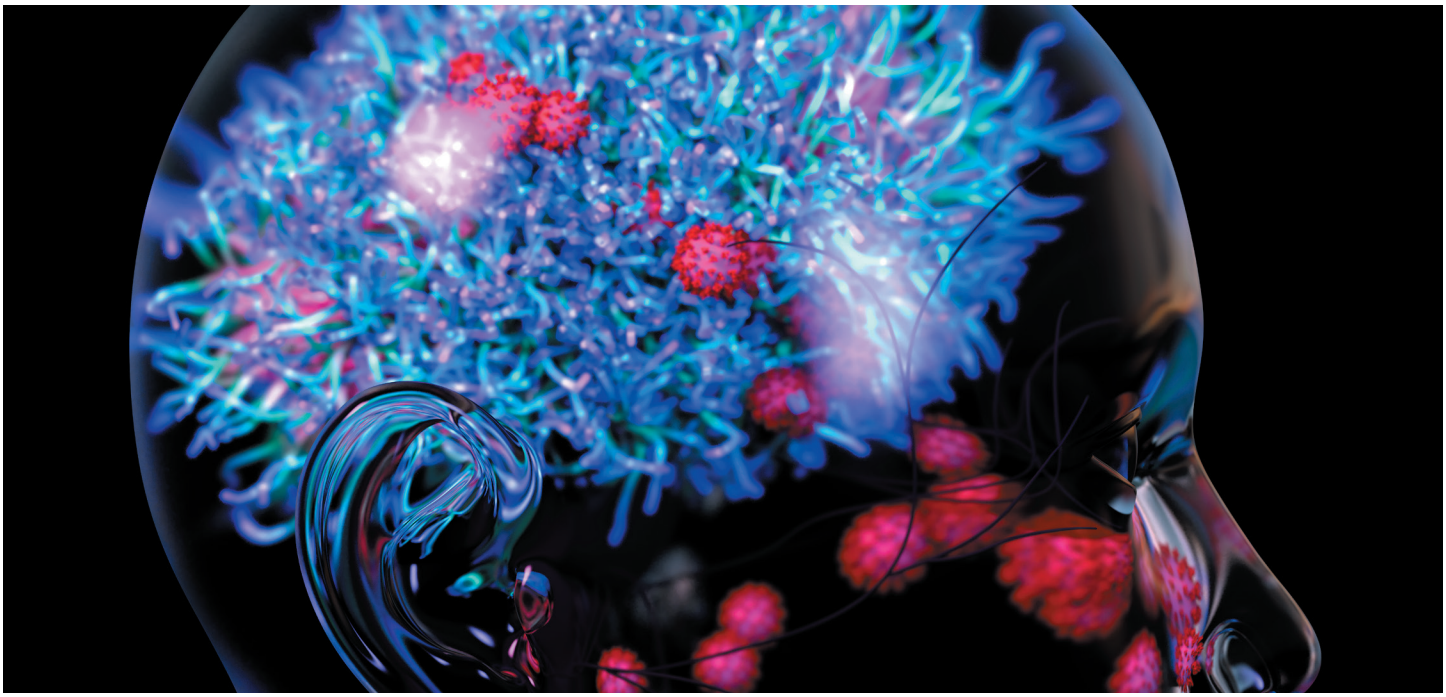
Sep

24-29
ACRM Annual Conference
Dallas, TX
acrm.org/meetings

Oct

4-5
11th Annual Traumatic Brain Injury Conference
Washington, D.C.
tbiconference.com/home

6-9
Pediatric Acquired Brain Injury Conference
New York, NY
ipbis2021.org



Even in Moderate Cases, COVID-19 is Causing Long-term Neurological Harm

Infection with SARS-CoV-2 can affect organ systems throughout the body including problems affecting the brain and nervous system—ranging from altered mental states to seizures to strokes.

COVID-19 can cause a wide range of neurological complications, even in patients who are not critically ill, a new study shows.

Since the start of the pandemic, it's become clear that infection with SARS-CoV-2 can affect organ systems throughout the body. That includes problems affecting the brain and nervous system—ranging from altered mental states to seizures to strokes.

In the new study, researchers found that among COVID patients at their safety-net hospital, neurological complications ran the gamut. And they were even seen in people who were more moderately ill with the infection.

Safety-net hospitals are obligated, by mandate or mission, to treat people regardless of their ability to pay. So, they typically have a large share of patients who are low-income,

minority and either uninsured or on Medicaid.

Those Americans have also been among the hardest hit by the COVID pandemic.

It's unclear at this point whether Black or Hispanic Americans are at increased risk of neurologic complications, according to lead researcher Dr. Pria Anand, from Boston Medical Center.

But it's important to document how the complications are showing up in hospitals serving low-income and minority patients, she said.

Anand and her colleagues studied the records of more than 900 COVID patients treated at their hospital between April 15 and July 1. Of that group, 74 needed a neurological consult or admission.

Overall, 18 patients suffered a stroke, 15 had seizures, and 26 were diagnosed with encephalopathy—a broad term for brain dysfunction, including confusion and delirium.

Some other patients developed nerve damage or movement problems. They included five with myoclonus, where muscles twitch or jerk involuntarily.

One patient showed signs of autoimmune encephalitis, a rare condition where the immune system attacks tissue in the spinal cord or brain, causing inflammation. The patient improved after treatment with anti-inflammatory corticosteroids.

In general, neurological complications of COVID seem to fall into a few different "buckets," said Anand, who is also an assistant professor at Boston University School of Medicine.

Some problems, she said, are related to an overactive immune response—such as Guillain-Barre syndrome, where the immune system attacks the body's nerves.

In other cases, Anand said, complications arise simply because a patient is critically ill in the hospital, and sometimes on a ventilator.

COVID does affect the vascular system in some patients—making the blood more prone to clotting, for example. And that can be behind complications like stroke.

Finally, Anand said, it's possible the virus itself invades the central nervous system in some patients. That's sometimes seen with certain other viruses, she noted—such as herpes and cytomegalovirus.

The findings, published in the journal Neurology Clinical Practice, are based on patients seen earlier in the pandemic.

At this point, doctors have learned more about managing COVID, in ways that can help prevent neurologic complications, said Dr. Aaron Glatt, a spokesperson for the Infectious Diseases Society of America.

That includes using medications like corticosteroids and Remdesivir, and drugs to prevent blood clots.

Glatt pointed out that the patients in this study were a select group—those sick enough to require a neurological consult in the hospital. And of the 74 patients, 47 had a history of neurological conditions.

"This isn't looking at all comers," noted Glatt, who wasn't part of the study.

That said, he also stressed that even people with milder COVID, who never enter the hospital, can have lasting neurologic symptoms. Doctors worldwide have been reporting seeing patients with lingering fatigue and what's been dubbed "brain fog"—problems with memory, concentration and other mental skills.

"There's a false sense of security among younger people, that COVID is only a risk to older people who end up in the hospital," Glatt said.

"I've taken care of many patients in their 30s and 40s," he added, "and they were very sick."

Anand agreed that people should be aware that death is not the only bad outcome of COVID, and people can face difficult recoveries.

In her study group, 10 patients died in the hospital. And while most left the hospital, the majority were released to skilled nursing facilities or other care to continue their recovery.

"Even after you leave the hospital," Anand said, "there can be a long road ahead." ■

"There's a false sense of security among younger people, that COVID is only a risk to older people who end up in the hospital."

Study Suggests Role of Sleep in Healing Traumatic Brain Injuries

Sound sleep plays a critical role in healing traumatic brain injury, a new study of military veterans suggests.

The study, published in the Journal of Neurotrauma, used a new technique involving magnetic resonance imaging developed at Oregon Health & Science University. Researchers used MRI to evaluate the enlargement of perivascular spaces that surround blood vessels in the brain. Enlargement of these spaces occurs in aging and is associated with the development of dementia.

Among veterans in the study, those who slept poorly had more evidence of these enlarged spaces and more post-concussive symptoms.

"This has huge implications for the armed forces as well as civilians," said lead author Juan Piantino, M.D., MCR, assistant professor of pediatrics (neurology) in the OHSU School of Medicine and Doernbecher Children's Hospital. "This study suggests sleep may play an important role in clearing waste from the brain after traumatic brain injury – and if you don't sleep very well, you might not clean your brain as efficiently."

Piantino, a physician-scientist with OHSU's Papé Family Pediatric Research Institute, studies the effects of poor sleep on recovery after traumatic brain injuries.

The new study benefited from a method of analyzing MRIs developed by study co-author Daniel Schwartz and Erin Boespflug, Ph.D., under the direction of Lisa Silbert, M.D., M.C.R., professor of neurology in the OHSU School of Medicine. The technique measures changes in the brain's perivascular spaces, which are part of the brain's waste clearance system known as the glymphatic system.

"We were able to very precisely measure this structure and count the number, location and diameter of channels," Piantino said.

Co-author Jeffrey Iliff, Ph.D., professor of psychiatry and behavioral sciences and of neurology at the University of Washington and a researcher at the VA Puget Sound Health Care System, has led scientific research into the glymphatic system and its role in neurodegenerative conditions such as Alzheimer's disease. During sleep, this brain-wide network clears away metabolic proteins that would otherwise build up in the brain.

The study used data collected from a group of 56 veterans enrolled by co-authors Elaine Peskind, M.D., and Murray Raskind, M.D., at the Mental Illness Research, Education and Clinical Center at the VA Puget Sound between 2011 and 2019.

"Imagine your brain is generating all this waste and everything is working fine," Piantino said. "Now you get a concussion. The brain generates much more waste that it has to remove, but the system becomes plugged."

Piantino said the new study suggests the technique developed by Silbert could be useful for older adults.

"Longer term, we can start thinking about using this method to predict who is going to be at higher risk for cognitive problems including dementia," he said.

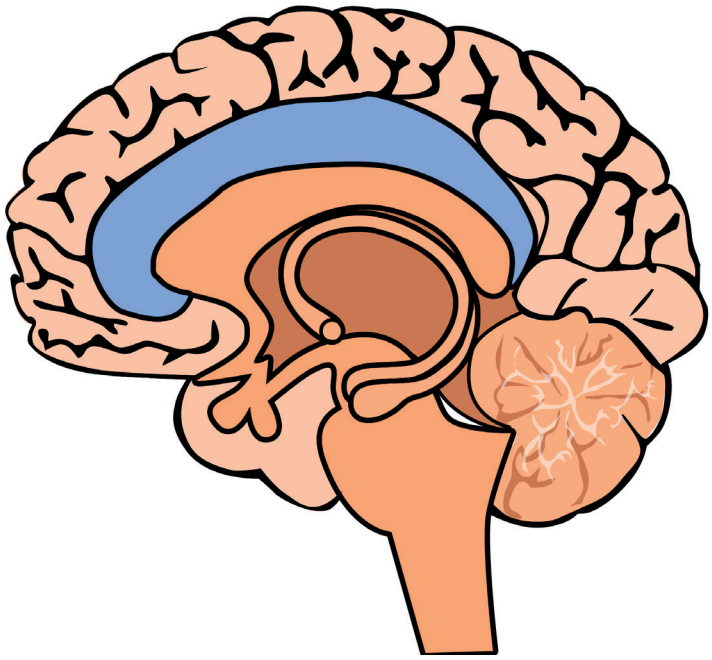
The study is the latest in a growing body of research highlighting the importance of sleep in brain health.

Improving sleep is a modifiable habit that can be improved through a variety of methods, Piantino said, including better sleep hygiene habits such as reducing screen time before bed. Improving sleep is a focus of research of other OHSU scientists, including Piantino's mentor, Miranda Lim, M.D., Ph.D., associate professor of neurology, medicine and behavioral neuroscience in the OHSU School of Medicine.

"This study puts sleep at the epicenter of recovery in traumatic brain injury," Piantino said. ■

"This study puts sleep at the epicenter of recovery in traumatic brain injury."

Brain Imaging Predicts PTSD After Brain Injury



Cingulate Cortex

Posttraumatic stress disorder (PTSD) is a complex psychiatric disorder brought on by physical and/or psychological trauma. How its symptoms, including anxiety, depression and cognitive disturbances arise remains incompletely understood and unpredictable. Treatments and outcomes could potentially be improved if doctors could better predict who would develop PTSD. Now, researchers using magnetic resonance imaging (MRI) have found potential brain biomarkers of PTSD in people with traumatic brain injury (TBI).

The study appears in a recent issue of Biological Psychiatry: Cognitive Neuroscience and Neuroimaging.

"The relationship between TBI and PTSD has garnered increased attention in recent years as studies have shown considerable overlap in risk factors and symptoms," said lead author Murray Stein, MD, MPH, FRCPC, a Distinguished Professor of Psychiatry and Family Medicine & Public Health at the University of California San Diego, San Diego, La Jolla, CA, USA. "In this study, we were able to use data from TRACK-TBI, a large longitudinal study of patients who present in the Emergency Department with TBIs serious enough to warrant CT (computed tomography) scans."

The researchers followed over 400 such TBI patients, assessing them for PTSD at 3 and 6 months after their brain injury. At 3 months, 77 participants, or 18 percent, had likely PTSD; at 6 months, 70 participants or 16 percent did. All subjects underwent brain imaging after injury.

"MRI studies conducted within two weeks of injury were used to measure volumes of key structures in the brain thought to be involved in PTSD," said Dr. Stein. "We found that the volume of several of these structures were predictive of PTSD 3-months post-injury."

Specifically, smaller volume in brain regions called the cingulate cortex, the superior frontal cortex, and the insula predicted PTSD at 3 months. The regions are associated with arousal, attention and emotional regulation. The structural imaging did not predict PTSD at 6 months.

The findings are in line with previous studies showing smaller volume in several of these brain regions in people with PTSD and studies suggesting that the reduced cortical volume may be a risk factor for developing PTSD. Together, the findings suggest that a "brain reserve," or higher cortical volumes, may provide some resilience against PTSD.

Although the biomarker of brain volume differences is not yet robust enough to provide clinical guidance, Dr. Stein said, "it does pave the way for future studies to look even more closely at how these brain regions may contribute to (or protect against) mental health problems such as PTSD."

Cameron Carter, MD, Editor of Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, said of the work, "This very important study uses magnetic resonance imaging to take the field a step closer to understanding why some people develop PTSD after trauma and others do not. It also lays the groundwork for future research aimed at using brain imaging to help predict that a person is at increased risk and may benefit from targeted interventions to reduce the clinical impact of a traumatic event." ■

Effects of Head Trauma from Intimate Partner Violence Largely Unrecognized

One in three women will experience intimate partner violence in her lifetime, and studies suggest that anywhere between 30% to 90% of women who experience physical abuse at the hands of an intimate partner experience head trauma.

While there is an abundant amount of research about traumatic brain injuries in athletes and those serving in the military, the same data is scarce when it comes to concussions and head and neck injuries sustained due to intimate partner violence.

Carrie Esopenko, assistant professor in the Department of Rehabilitation and Movement Sciences in the Rutgers School of Health Professions says that the World Health Organization estimates that one in three women will experience intimate partner violence (IPV) in her lifetime, and studies suggest that anywhere between 30% to 90% of women who experience physical abuse at the hands of an intimate partner experience head trauma. Yet not enough data is being collected to understand how this head trauma affects cognitive and psychological functioning as well as the underlying neural effects.

Esopenko is part of a new Intimate Partner Violence Working Group studying intimate partner violence–related head trauma as part of the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium, an international, multidisciplinary group that seeks to provide a collaborative framework for large-scale analysis and neuroimaging and genetic studies in patient groups. She discusses the effect that head trauma due to intimate partner violence can have on individuals and the challenges the working group faces in gathering data as recently published in the journal Brain Imaging and Behavior.

What is the risk for traumatic brain injury in those who suffer abuse?
Although intimate partner violence occurs at any age, it is most prevalent in the 18- to 24-year-old age group, and older adults are also vulnerable. Males and females experience IPV, but violence against women tends to result in more severe and chronic injuries. Due to the high degree of physical aggression associated with this type of abuse, there is a significant risk for traumatic brain injury caused by blunt force trauma, being violently shaken or pushed.

Another significant concern is anoxic brain injury, which can occur due strangulation or attempts to impede normal breathing. The prevalence of head injuries in women who have sustained IPV is estimated to be between 30 percent and 92 percent, with a high proportion of these women reporting injuries as a result of strangulation. It is estimated that more than 50 percent of women exposed to intimate partner violence suffer multiple brain injuries due to abuse-related head trauma.

What are the consequences of such injuries?
Past research suggests that IPV can impact cognitive and psychological functioning as well as have neurological effects. These seem to be compounded in those who suffer a brain injury as a result of trauma to the head, face, neck or body due to physical and/or sexual

violence. However, our understanding of the neurobehavioral and neurobiological effects of head trauma is limited.

Studies suggest that women who experience IPV report cognitive dysfunction, including impaired reaction time, response inhibition, working memory, attention and a range of other cognitive, behavioral and emotional difficulties. They often report a high degree of mental health disorders, such as depression, anxiety, substance use disorders, suicidal ideation and PTSD. There is evidence that intimate partner violence-related brain injury also alters brain function and structure.

What is unknown about traumatic brain injury in victims of domestic violence?

While research on traumatic brain injury in other populations, like athletes and the military, has dramatically increased over the past two decades, research on intimate partner–related brain injury is vastly understudied. We need to know more about the effect of sex, socioeconomic status, race and/or ethnicity, age at first exposure – including childhood trauma, duration and severity of IPV exposure, and psychiatric disorders on the neural, cognitive and psychological outcomes associated with IPV-related brain injuries. Knowing this can help us to predict outcomes and help personalize treatment and intervention strategies.

What are the working group's goals?

There remain important challenges to understanding the interaction between intimate partner-related brain injury and cognitive and psychosocial functioning, mental health and neural outcomes. Of importance is the identification and characterization of brain injury in this population, which is often difficult because brain trauma is often overlooked or not diagnosed in this population. By forming a global collaboration across disciplines — researchers, clinicians, first responders, community organizations and policymakers — we hope to help tailor measures that can be used across groups for consistent data collection that will enable us to combine large-scale datasets to answer these difficult questions and facilitate further translation of research outcomes to clinical care and community-based supports. ■

Studies suggest that women who experience IPV report impaired reaction time, response inhibition, working memory, attention and a range of other cognitive, behavioral and emotional difficulties.

NIH Study Uncovers Blood Vessel Damage and Inflammation in COVID-19 Patients' Brains but No Infection

Brains of patients who contract infection from SARS-CoV-2 may be susceptible to microvascular blood vessel damage that may be caused by the body's inflammatory response to the virus.

In an in-depth study of how COVID-19 affects a patient's brain, National Institutes of Health researchers consistently spotted hallmarks of damage caused by thinning and leaky brain blood vessels in tissue samples from patients who died shortly after contracting the disease. In addition, they saw no signs of SARS-CoV-2 in the tissue samples, suggesting the damage was not caused by a direct viral attack on the brain. The results were published as a correspondence in the New England Journal of Medicine.

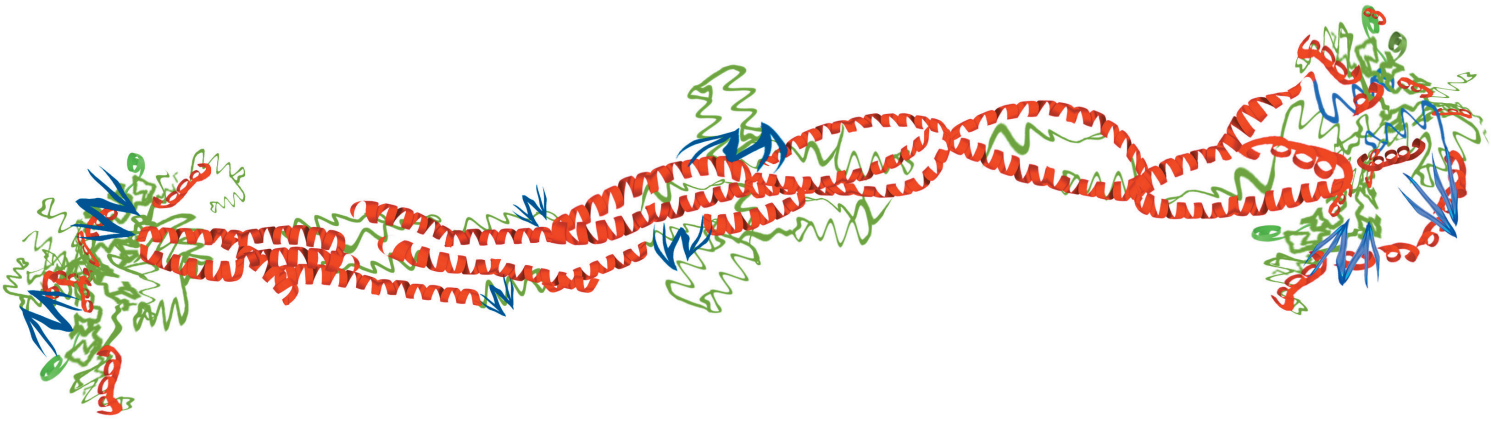
"We found that the brains of patients who contract infection from SARS-CoV-2 may be susceptible to microvascular blood vessel damage. Our results suggest that this may be caused by the body's inflammatory response to the virus" said Avindra Nath, M.D., clinical director at the NIH's National Institute of Neurological Disorders and Stroke (NINDS) and the senior author of the study. "We hope these results will help doctors understand the full spectrum of problems patients may suffer so that we can come up with better treatments."

Although COVID-19 is primarily a respiratory disease, patients often experience neurological problems including headaches, delirium, cognitive dysfunction, dizziness, fatigue, and loss of the sense of smell. The disease may also cause patients to suffer strokes and other neuropathologies.

Several studies have shown that the disease can cause inflammation and blood vessel damage. In one of these studies, the researchers found evidence of small amounts of SARS-CoV-2 in some patients' brains. Nevertheless, scientists are still trying to understand how the disease affects the brain.

In this study, the researchers conducted an in-depth examination of brain tissue samples from 19 patients who had died after experiencing COVID-19 between March and July 2020. Samples from 16 of the patients were provided by the Office of the Chief Medical Examiner in New York City while the other 3 cases were provided by the department of pathology at the University of Iowa College of Medicine, Iowa City. The patients died at a wide range of ages, from 5 to 73 years old. They died within a few hours to two months after reporting symptoms. Many patients had one or more risk factors, including diabetes, obesity, and cardiovascular disease. Eight of the patients were found dead at home or in public settings. Another three patients collapsed and died suddenly.

Initially, the researchers used a special, high-powered magnetic resonance imaging (MRI) scanner that is 4 to 10 times more sensitive than most MRI scanners, to examine samples of the olfactory bulbs and brainstems



Fibrinogen

from each patient. These regions are thought to be highly susceptible to COVID-19. Olfactory bulbs control our sense of smell while the brainstem controls our breathing and heart rate. The scans revealed that both regions had an abundance of bright spots, called hyperintensities, that often indicate inflammation, and dark spots, called hypointensities, that represent bleeding.

The researchers then used the scans as a guide to examine the spots more closely under a microscope. They found that the bright spots contained blood vessels that were thinner than normal and sometimes leaking blood proteins, like fibrinogen, into the brain. This appeared to trigger an immune reaction. The spots were surrounded by T cells from the blood and the brain's own immune cells called microglia. In contrast, the dark spots contained both clotted and leaky blood vessels but no immune response.

"We were completely surprised. Originally, we expected to see damage that is caused by a lack of oxygen. Instead, we saw multifocal areas of damage that is usually associated with strokes and neuroinflammatory diseases," said Dr. Nath.

Finally, the researchers saw no signs of infection in the brain tissue samples even though they used several methods for detecting genetic material or proteins from SARS-CoV-2.

"So far, our results suggest that the damage we saw may not have been not caused by the SARS-CoV-2 virus directly infecting the brain," said Dr. Nath. "In the future, we plan to study how COVID-19 harms the brain's blood vessels and whether that produces some of the short- and long-term symptoms we see in patients." ■

Researchers conducted an in-depth examination of brain tissue samples from 19 patients who had died after experiencing COVID-19

Timing May be Critical When Administering Treatment After Brain Injury

Researchers discovered Jekyll and Hyde immune cells in the brain that ultimately help with brain repair but early after injury can lead to fatal swelling.

Researchers from the National Institutes of Health have discovered Jekyll and Hyde immune cells in the brain that ultimately help with brain repair but early after injury can lead to fatal swelling, suggesting that timing may be critical when administering treatment. These dual-purpose cells, which are called myelomonocytic cells and which are carried to the brain by the blood, are just one type of brain immune cell that NIH researchers tracked, watching in real-time as the brain repaired itself after injury. The study, published in Nature Neuroscience, was supported by the National Institute of Neurological Disorders and Stroke (NINDS) Intramural Research Program at NIH.

Cerebrovascular injury, or damage to brain blood vessels, can occur following several conditions including traumatic brain injury or stroke. Dr. McGavern, along with Larry Latour, M.D., NINDS scientist, and their colleagues, observed that a subset of stroke patients developed bleeding and swelling in the brain after surgical removal of the blood vessel clot responsible

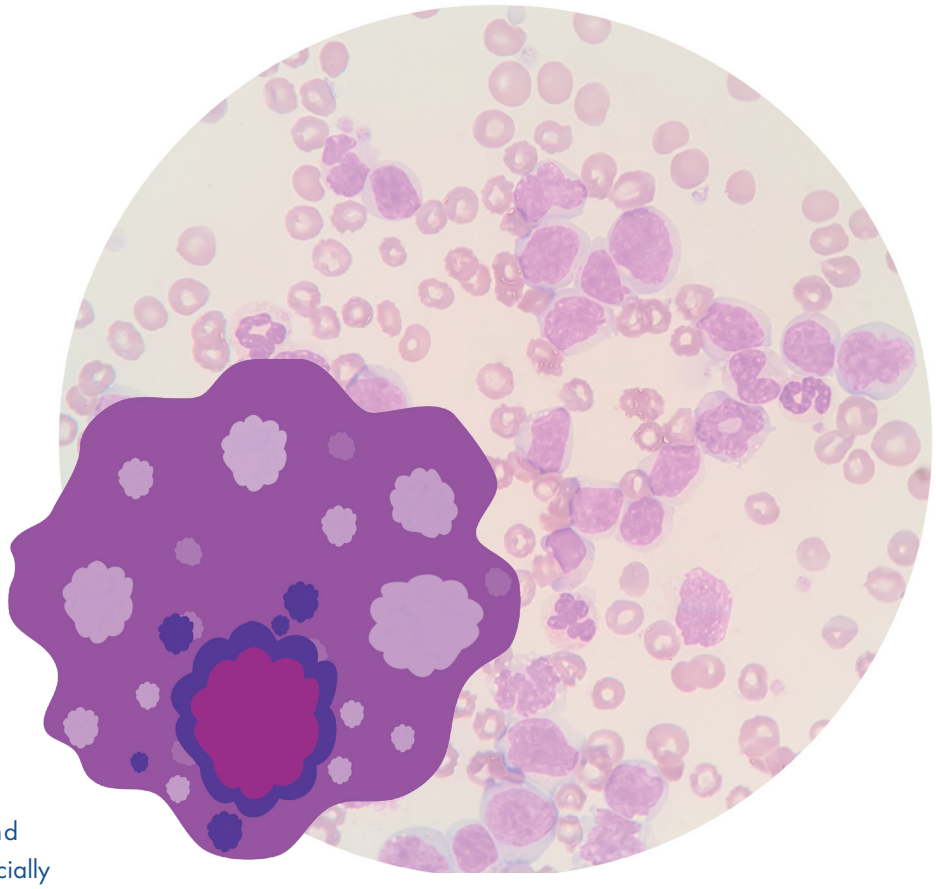
for the stroke. The swelling, also known as edema, results in poor outcomes and can even be fatal as brain structures become compressed and further damaged.

To understand how vessel injury can lead to swelling and to identify potential treatment strategies, Dr. McGavern and his team developed an animal model of cerebrovascular injury and used state-of-the-art microscopic imaging to watch how the brain responded to the damage in real-time.

Immediately after injury, brain immune cells known as microglia quickly mobilize to stop blood vessels from leaking. These "first responders" of the immune system extend out and wrap their arms around broken blood vessels. Dr. McGavern's group discovered that removing microglia causes irreparable bleeding and damage in the brain.

A few hours later, the damaged brain is invaded by circulating peripheral monocytes and neutrophils (or, myelomonocytic cells). As myelomonocytic cells move from the blood into the brain, they each open a small hole in the vasculature, causing a mist of fluid to enter the brain. When thousands of these cells rush into the brain simultaneously, a lot of fluid comes in all at once and results in swelling.

"The myelomonocytic cells at this stage of repair mean well, and do want to help, but they enter the brain with too much enthusiasm. This can lead to devastating tissue damage and swelling, especially if it occurs around the brain stem, which controls vital functions such as breathing," said Dr. McGavern.



Myelomonocytic Cell

After this initial surge, the monocytic subset of immune cells enter the brain at a slower, less damaging rate and get to work repairing the vessels. Monocytes work together with repair-associated microglia to rebuild the damaged vascular network, which is reconnected within 10 days of injury. The monocytes are required for this important repair process.

In the next set of experiments, Dr. McGavern and his colleagues tried to reduce secondary swelling and tissue damage by using a combination of therapeutic antibodies that stop myelomonocytic cells from entering the brain. The antibodies blocked two different adhesion molecules that myelomonocytic cells use to attach to inflamed blood vessels. These were effective at reducing brain swelling and improving outcomes when administered within six hours of injury.

Interestingly, the therapeutic antibodies did not work if given after six hours or if they were given for too long. In fact, treating mice over a series of days with these antibodies inhibited the proper repair of damaged blood vessels, leading to neuronal death and brain scarring.

"Timing is of the essence when trying to prevent fatal edema. You want to prevent the acute brain swelling and damage, but you do not want to block the monocytes from their beneficial repair work," said Dr. McGavern.

Plans are currently underway for clinical trials to see if administering treatments at specific timepoints will reduce edema and brain damage in a subset of stroke patients. Future research studies will examine additional aspects of the cerebrovascular repair process, with the hope of identifying other therapeutic interventions to promote reparative immune functions. ■

No Overall Difference in Concussion Recovery Time for Male and Female College Athletes

Researchers at Children's Hospital of Philadelphia (CHOP) and the University of Pennsylvania found female and male collegiate athletes take approximately the same amount of time to recover from a concussion, with subtle differences in recovery time depending on the type of sports being played and the division level of the sport. The findings suggest that equity in access to sports medical care among college athletes may be contributing to these similar outcomes.

The findings, derived as part of the CARE (Concussion Assessment, Research and Education) Consortium, were recently published online by the British Journal of Sports Medicine.

Some previous studies have indicated that female athletes may experience longer times to recovery and more lost time from sports due to sport-related concussions. However, other studies have found no differences, but many of these studies were conducted with smaller cohorts and may not have comprehensively accounted for a variety of additional extrinsic factors, including injury setting (practice vs. competition), mechanism of injury (person vs. equipment), and timing of reporting and seeking medical care.

In order to provide a more definitive picture of potential differences between the sexes in concussion injury and recovery, this study examined data collected by the CARE Consortium, funded jointly by the NCAA and the Department of Defense, representing the largest multi-center prospective study of concussion in collegiate athletes to date. In this study, colleges collected extensive pre- and post-injury data in a large, prospective cohort of thousands of collegiate athletes.

"I think many people are concerned that, based on intrinsic biological differences, female athletes may have longer paths to recovery from concussions than their male counterparts," said Christina L. Master, MD, a sports medicine pediatrician and Co-Director of the Minds Matter Concussion Program at CHOP and first author of the study. "However, to better understand any potential biologically-based sex differences in concussion injury and recovery, we needed a large study like this that could better account for extrinsic factors that are not biological."

The study collected data on 1,071 concussions that occurred between 2014 and 2017 across more than 30 colleges, universities and service academies participating in the CARE Consortium. Among those concussions, there was no statistically significant difference in recovery between males and females. Female athletes had a median of 13.5 days before returning to play compared with 11.8 days for males ($p=0.96$).

Subtle differences were seen between certain subgroups in the study. Females took slightly longer to recover than males from concussions sustained in contact sports (12.7 days for females vs 11 days for males, $p=0.00201$), while male athletes took longer to recover than females from concussions they experienced in limited contact sports (16.85 days for males vs 13.8 days for females, $p < 0.0001$). While there was no difference between the sexes seen among Division I collegiate athletes, female athletes in Division II/III sports had a longer recovery time than male athletes in the same division (13.0 days for females vs 10.6 days for males, $p = 0.0048$).

Master said these subtle differences could be attributed to a variety of factors, including differential access to athletic training and sports medical resources. For instance, Division I sports may have greater

"This study makes a strong case for equity in access to specialized athletic training and sports medical care."

levels of athletic training and sports medicine support compared with Division II and III sports. In the case of male athletes experiencing longer recovery time for limited contact sports, this may be related to fewer resources allocated to limited contact men's sports than contact men's sports where concussions are assumed to be more likely to occur. Another potential explanation may be that rules and regulations limiting exposure to impacts in men's contact sports may have had a mitigating effect on concussions in men's contact sports. This coupled with the fact that women took longer than men to recover in contact sports, but not in limited contact sports, suggests that these differences between men and women cannot be entirely accounted for simply on the basis of biological sex.

"This study makes a strong case for equity in access to specialized athletic training and sports medical care," Master said. "Title IX, which mandates equal access for both women and men to resources, such as sports, including athletic training and sports medical care, may have potentially helped to close any gap that exists in outcomes between the sexes. In the instances where recovery times did differ between the sexes, a re-examination of resource allocation might achieve a more equitable distribution to maximize outcomes for all athletes." ■

Title IX, which mandates equal access for both women and men to resources such as sports may have potentially helped to close any gap that exists in outcomes between the sexes.

Preventing Seizures After Brain Injury Could Stave Off Dementia

Blocking seizures after a head injury could slow or prevent the onset of dementia, according to new research by University of Alberta biologists.

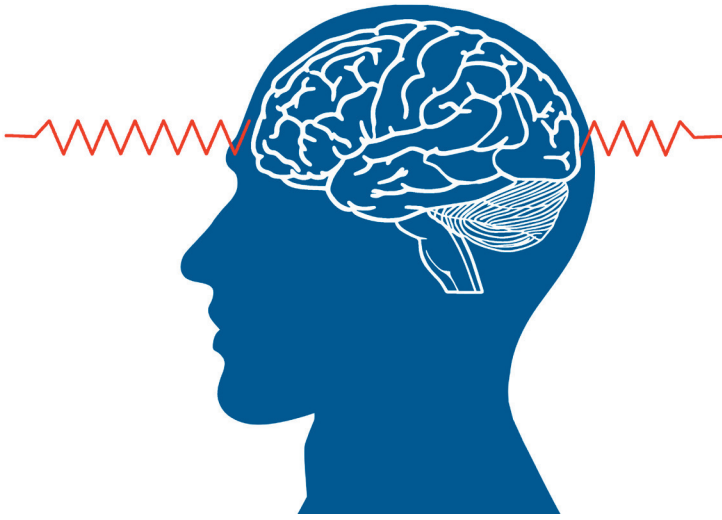
"Traumatic brain injury is a major risk factor for dementia, but the reason this is the case has remained mysterious," said Ted Allison, co-author and professor in the Department of Biological Sciences in the Faculty of Science. "Through this research, we have discovered one important way they are linked–namely, post-injury seizures."

"There is currently no treatment for the long-term effects of traumatic brain injury, which includes developing dementia," added lead author Hadeel Alyenbaawi, who recently completed her PhD dissertation on this topic in the Department of Medical Genetics in the Faculty of Medicine & Dentistry.

Traumatic brain injuries are a major risk factor for certain types of dementia, such as Alzheimer's disease and chronic traumatic encephalopathy. Because seizures are common for patients who have suffered these injuries, neurologists often prescribe anti-epileptic treatments to prevent the seizures.

Allison said the new research reveals the potential to refine this approach to treatment with the new goal of preventing dementia.

The study's lead author, Hadeel Alyenbaawi, says understanding the link between traumatic brain injury and dementia could help further research into preventive measures.



"Our data suggest that, at least in animal models, blocking these seizures also could have a benefit later in life by slowing or preventing the onset of dementia," he explained. "A prophylactic treatment to prevent dementia is an exciting possibility, though there is much work to be done to develop our concept."

"We are excited to see that our research and the tools we developed resolved some of the mystery around the link between traumatic brain injury and dementia."

Dementia affects more than 432,000 Canadians over the age of 65, two-thirds of whom are women. The Government of Canada estimates that by 2031, dementia will cost our health-care system $16.6 billion each year.

"Dementia is devastating for patients and families, and it is growing in prevalence in our aging demographics," added Allison. "These findings open the exciting possibility of refining the anti-epileptic treatments to be a prevention not only of seizures, but also dementia."

"We are excited to see that our research and the tools we developed resolved some of the mystery around the link between traumatic brain injury and dementia," added Alyenbaawi. "Our data regarding post-traumatic seizure could also help further investigation into promising preventive measures of these incurable diseases."

"Traumatic brain injury is a major risk factor for dementia, but the reason this is the case has remained mysterious."

MicroRNA May Serve as Therapeutic Targets for Traumatic Brain Injury

Scientists at the Walter Reed Army Institute for Research have shown that microRNA biomarkers related to Alzheimer's disease play a role in brain damage caused by traumatic brain injury.

TBI or brain trauma results from blows to the head, leading to chronic disruption of the brain and a cascade of long-term health conditions. Patients who suffer from TBI are at much higher risk of developing neurodegenerative disease or dementia, particularly Alzheimer's disease. The mechanism behind this relationship remains understudied, making the development effective therapeutics challenging.

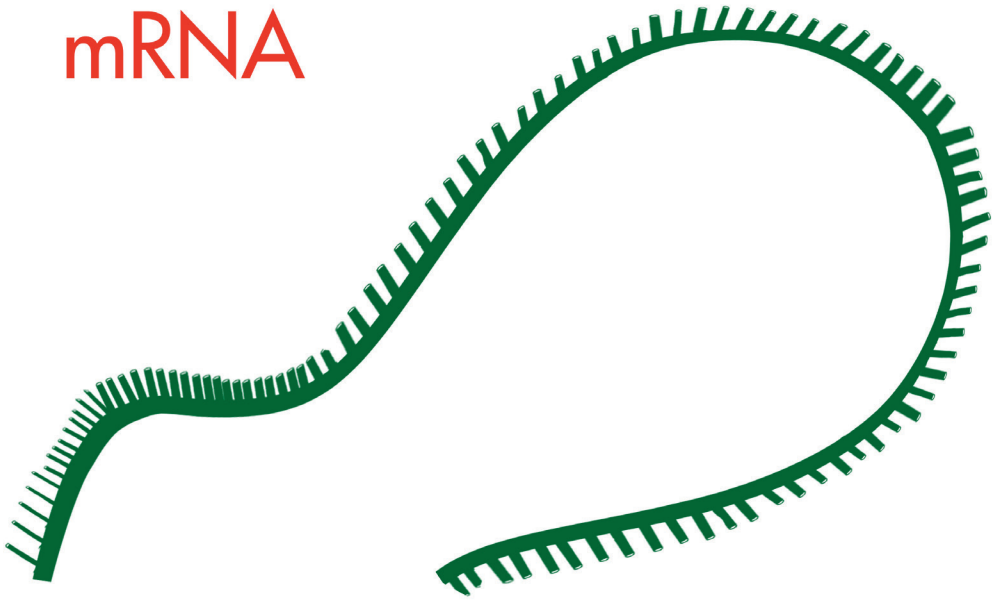
MiRNAs are small pieces of genetic material that play a critical role in normal gene expression. Yet, studies have also linked abnormal miRNA levels, or dysregulation, to a range of diseases including neurodegenerative disorders and cell death after TBI, making them a subject of great interest to researchers who hope to use them as biomarkers and novel targets of drug therapies.

In their publication in the Frontiers in Neuroscience, researchers evaluated more than 800 miRNAs in TBI models, showing that TBI caused coordinated miRNA dysregulation followed by increased amounts of the beta-site amyloid cleaving enzyme, or BACE1, and loss of amyloid precursor protein. BACE-1 cleaves APP to generate amyloid beta peptides, a hallmark of neurodegenerative disease pathology and brain cells loss, which are the focus of several clinical trials for Alzheimer's disease.

"The coordination of miRNAs, BACE1 and APP may serve as collective biomarkers reflecting the harm caused by TBI that is relevant to development of neurodegenerative disease," said Dr. Bharani Thangavelu and Dr. Bernard S. Wilfred, lead authors within Brain Trauma Neuroprotection Branch at WRAIR's Center for Military Psychiatry and Neuroscience.

"MiRNAs are increasingly recognized as mediators of injury. It is quite remarkable that BACE1 and APP are hubs for the miRNA affected by TBI. This work infers that there may be underlying common features of TBI and AD that have not been seen before without a genetic variant, which is more frequently studied, for models that explore the connections between TBI and neurodegenerative disease," remarked Dr. Angela M Boutte, section chief of molecular biology and proteomics within the BTN Branch.

Future research is planned to characterize the direct role of these miRNAs and their relationship to BACE1 within TBI. ■



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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