INSIDE VIEW

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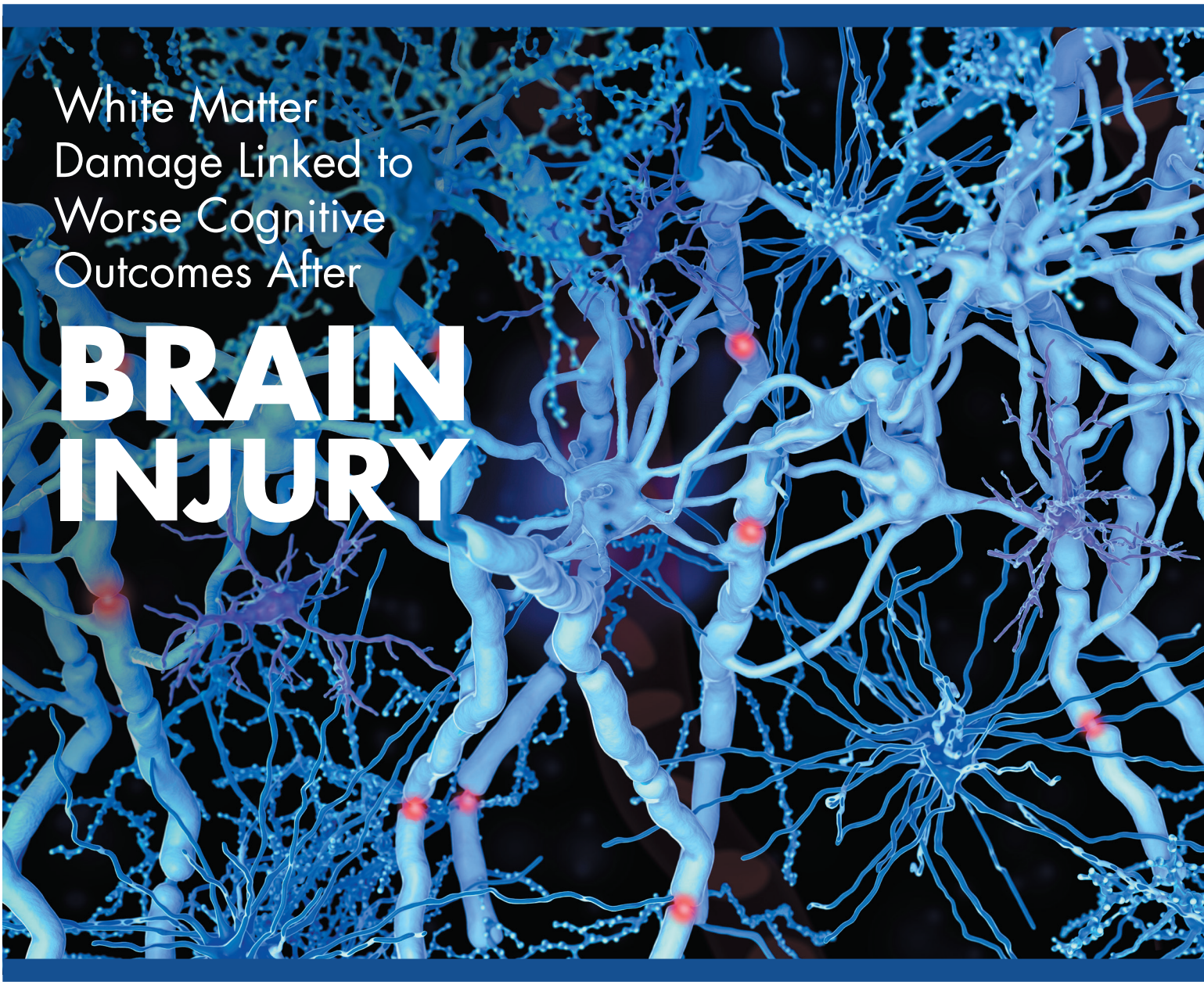

White Matter Damage Linked to Worse Cognitive Outcomes After

BRAIN INJURY

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Light Therapy Helps Treat Traumatic Brain Injury

A new study by researchers at the VA Portland Health Care System in Oregon found that augmenting traditional treatment for traumatic brain injury (TBI) with morning bright light therapy (MBLT) improved physical and mental symptoms for participants. The team will present their work at the American Physiological Society's (APS) annual meeting at Experimental Biology 2021.

According to the U.S. Department of Veterans Affairs (VA), over 185,000 veterans have been diagnosed with at least one TBI. TBI is both a common and complex injury. Because of the circumstances surrounding the brain injury, TBI frequently coincides with posttraumatic stress disorder (PTSD). Cognitive and memory impairments and poor sleep quality often result from these paired conditions. Unfortunately, the current treatment methods for TBI, which focus on improving the cognitive symptoms, have inconsistent results.

Noting the reciprocal relationship between sleep disruption and cognitive function, the research team focused on addressing the sleep quality in the experimental group. Over the course of eight weeks, one group received group cognitive therapy, while the other received cognitive therapy as well as 60 minutes of MBLT within two hours of waking each day.

The MBLT group reported improvements to cognitive function, sleep, depression and neuropsychiatric trauma symptoms. The traditional therapy group did not report improvements in any of these areas.

Jonathan Elliott, PhD, a member of the research team, said that the study "demonstrates a highly feasible mechanism to improve cognitive function and the efficacy of [current treatment] … and ultimately overall quality of life in U.S. veterans." ■

The MBLT study group reported cognitive function, sleep, depression and neuropsychiatric trauma symptom improvements.

2021 Calendar of Events

Jul

10-14
Neurotrauma 2021
Austin, TX
neurotrauma.org

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

19-20
International Conference on Functional Neuroanatomy, Neurological Disorders and Brain Injury
Toronto, Canada
waset.org/functional-neuroanatomy-neurological-disorders-and-brain-injury-conference-in-july-2021-in-toronto

23
2021 Virtual NABIS Medical and Legal Conference on Brain Injury
Virtual
internationalbrain.org/meetings-and-events/2021-virtual-nabis-medical-and-legal-conference-on-brain-injury

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

Aug

6-8
Abilities Expo Houston
Houston, TX
abilities.com/houston/

13-14
10th International Conference on Stroke and Cerebrovascular Diseases
Paris, France
strokecongress.neurologyconference.com

Sep

9-10
BIA Michigan Annual Conference
Virtual
biami.org/afc-3/

20-24
State of the States in Head Injury Conference
Virtual
nashia.org/sos-2021

23-26
TBI Med Legal Conference
San Diego, CA
tbimedlegalcon.com

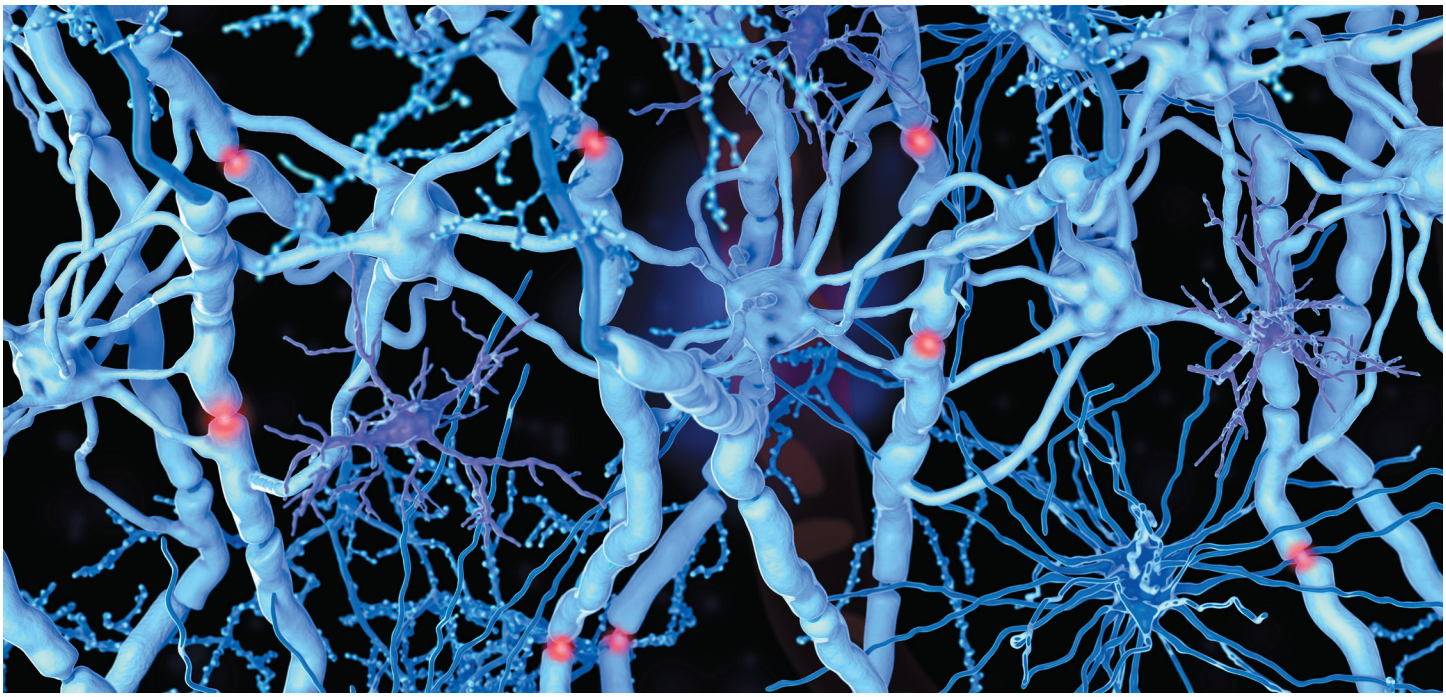
24-29
ACRM Annual Conference
Dallas, TX
acrm.org/meetings

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

Articles are sourced from scientific journals, universities and publications that contribute to the ongoing research of brain injury.



Damage to White Matter is Linked to Worse Cognitive Outcomes After Brain Injury

"This study is a reminder that connections between brain regions might matter just as much as those regions themselves, if not more so."

A new University of Iowa study challenges the idea that gray matter (the neurons that form the cerebral cortex) is more important than white matter (the myelin covered axons that physically connect neuronal regions) when it comes to cognitive health and function. The findings may help neurologists better predict the long-term effects of strokes and other forms of traumatic brain injury.

"The most unexpected aspect of our findings was that damage to gray matter hubs of the brain that are really interconnected with other regions didn't really tell us much about how poorly people would do on cognitive tests after brain damage. On the other hand, people with damage to the densest white matter connections did much worse on those tests," explains Justin Reber, PhD, a UI postdoctoral research fellow in psychology and first author on the study. "This is important because both scientists and clinicians often focus almost exclusively on the role of gray matter. This study is a reminder that connections between brain regions might matter just as much

as those regions themselves, if not more so."

The new study, published in PNAS, analyzes brain scans and cognitive function tests from over 500 people with localized areas of brain damage caused by strokes or other forms of brain injury. Looking at the location of the brain damage, also known as lesions, the UI team led by Reber and Aaron Boes, MD, PhD, correlated the level of connectedness of the damaged areas with the level of cognitive disability the patient experienced. The findings suggest that damage to highly connected regions of white matter is more predictive of cognitive impairment than damage to highly connected gray matter hubs.

Network hubs and brain function

Research on cognition often focuses on networks within the brain, and how different network configurations contribute to different aspects of cognition. Various mathematical models have been developed to measure the connectedness of networks and to identify hubs, or highly connected brain regions, that appear to be important in coordinating processing in brain networks.

The UI team used these well accepted mathematical models to identify the location of hubs within both gray and white matter from brain imaging of normal healthy individuals. The researchers then used brain scans from patients with brain lesions to find cases where areas of damage coincided with hubs. Using data from multiple cognitive tests for those patients, they were also able to measure the effect hub damage had on cognitive outcomes. Surprisingly, damage to highly connected gray matter hubs did not have a strong association with poor cognitive outcomes. In contrast, damage to dense white matter hubs was strongly linked to impaired cognition.

"The brain isn't a blank canvas where all regions are equivalent; a small lesion in one region of the brain may have very minimal impact on cognition, whereas another one may have a huge impact. These findings might help us better predict, based on the location of the damage, which patients are at risk for cognitive impairment after stroke or other brain injury," says Boes, UI professor of pediatrics, neurology, and psychiatry, and a member of the Iowa Neuroscience Institute. "It's better to know those things in advance as it gives patients and family members a more realistic prognosis and helps target rehabilitation more effectively."

UI registry is a unique resource for neuroscientists

Importantly, the new findings were based on data from over 500 individual patients, which is a large number compared to previous studies and suggests the findings are robust. The data came from two registries; one from Washington University in St. Louis, which provided data from 102 patients, and the Iowa Neurological Registry based at the UI, which provided data from 402 patients. The Iowa registry is over 40 years old and is one of the best characterized patient registries in the world, with close to 1000 subjects with well characterized cognition derived from hours of paper and pencil neuropsychological tests, and detailed brain imaging to map brain lesions. The registry is directed by Daniel Tranel, PhD, UI professor of neurology, and one of the study authors.

"When we look at how strokes and other brain damage actually affect people, it turns out that you can predict much more from damage to white matter."

Reber notes that the study also illustrates the value of working with clinical patients as well as healthy individuals in terms of understanding relationships between brain structure and function.

"There is a lot of really excellent research using functional brain imaging with healthy participants or computer simulations that tell us that these gray matter hubs are critical to how the brain works, and that you can use them to predict how well healthy people will perform on cognitive tests. But when we look at how strokes and other brain damage actually affect people, it turns out that you can predict much more from damage to white matter," he says. "Research with people who have survived strokes or other brain damage is messy, complicated, and absolutely essential, because it builds a bridge between basic scientific theory and clinical practice, and it can improve both.

I cannot stress enough how grateful we are that these patients have volunteered their time to help us; without them, a lot of important research would be impossible," he adds. ■

Brain Changes Following Traumatic Brain Injury Share Similarities with Alzheimer's Disease

Researchers hypothesized that comparing these patterns could reveal not only how the degenerative trajectories of the two conditions are similar but also which features of brain atrophy could predict Alzheimer's risk after TBI.

Brain changes in people with Alzheimer's disease and in those with mild traumatic brain injuries (TBIs) have significant similarities, a new USC study shows, suggesting new ways to identify patients at high risk for Alzheimer's. The findings appear in *GeroScience*.

TBIs, which affect over 1.7 million Americans every year, are often followed by changes in brain structure and function and by cognitive problems such as memory deficits, impaired social function and difficulty with decision-making. Although mild TBI—also known as concussion—is a known risk factor for Alzheimer's disease, prior studies haven't quantified the extent to which these conditions share patterns of neural degeneration in the brain.

USC researchers hypothesized that comparing these patterns could reveal not only how the degenerative trajectories of the two conditions are similar but also which features of brain atrophy could predict Alzheimer's risk after TBI.

The study included 33 study participants with TBIs due to a fall, another 66 participants who had been diagnosed with Alzheimer's disease and 81 healthy control participants without either TBI or Alzheimer's. The researchers analyzed MRIs of the patients' brains and created additional computer-generated models to compare dozens of different brain structures, ultimately mapping similarities and differences between the three different groups.

In multiple brain areas of both TBI and Alzheimer's participants, the researchers found reduced cortical thickness when compared to the healthy controls. Cortical thickness is roughly correlated with brain age and its thinning is often associated with reductions in attention, memory and verbal fluency, as well as with decreased ability to make decisions, integrate new information and adapt one's behavior to new situations, among other deficits.

"These findings are the first to suggest that cognitive impairment following a traumatic brain injury is useful for predicting the magnitude of Alzheimer's-like brain degradation," said study author Andrei Irimia, an assistant professor of gerontology, neuroscience and biomedical engineering at the USC Leonard Davis School of Gerontology and the USC Viterbi School of Engineering. "The results may help health professionals to identify TBI victims who are at greater risk for Alzheimer's disease."

Using MRIs, the study identified significant similarities between TBI and Alzheimer's disease in how the brain's gray and white matter degrade after injury. In gray matter – the part of the brain that contains neuron cell bodies and their short-range connections – the most exten-

sive similarities were in areas involved in memory (temporal lobes) and decision-making (orbitofrontal cortices).

In white matter—which connects different brain regions and allows their neurons to communicate across longer distances—the researchers found comparable degeneration patterns in structures such as the fornix, corpus callosum and corona radiata. Whereas the fornix is involved in memory function, the corpus callosum facilitates information exchange between brain hemispheres. The corona radiata is involved in limb movement, and its injury can lead to poorer coordination and balance.

The scientists also used machine learning techniques to accurately predict the severity of Alzheimer's-like brain changes observed during the chronic stage of mild TBI based on cognitive assessments conducted shortly after such injuries.

At least 15% of Americans have a history of TBI. Chronic TBI effects on cognitive function may be particularly severe in older people, who are approximately three times more likely to sustain a TBI than other age groups.

Studies of TBI effects on brain structure have identified both amyloid plaques and neurofibrillary tangles—twisted fibers found inside the brain's cells—which resemble those observed in Alzheimer's disease. Despite this evidence, the study authors said, few studies have investigated whether TBI can alter brain trajectories toward Alzheimer's, particularly at older ages.

The new findings do not establish a cause-and-effect relationship between TBI and Alzheimer's disease but do add to the evidence that the two conditions share common trajectories, researchers said. The study, which was co-authored by USC alumnus Kenneth Rostowsky, is a follow-up to the team's earlier study outlining TBI-related changes in brain function. ■

New findings add to the evidence that the two conditions share common trajectories.

New Finding Suggests Cognitive Problems Caused by Repeat Mild Head Hits Could be Treated with Drug Therapy

"Our goal was to understand how the brain changes in response to the low-level head impacts that many young football players, for example, are regularly experiencing."

A neurologic pathway by which non-damaging but high frequency brain impact blunts normal brain function and causes long-term problems with learning and memory has been identified. The finding suggests that tailored drug therapy can be designed and developed to reactivate and normalize cognitive function, say neuroscientists at Georgetown University Medical Center.

The investigators, working with collaborators at the National Institutes of Health, had previously found that infrequent mild head impacts did not have an effect on learning and memory, but in their new study, reported recently in *Nature Communications*, the investigators found that when the frequency of these non-damaging head impacts are increased, the brain adapts and changes how it functions. The investigators have found the molecular pathway responsible for this down-tuning of the brain that can prevent this adaptation from occurring.

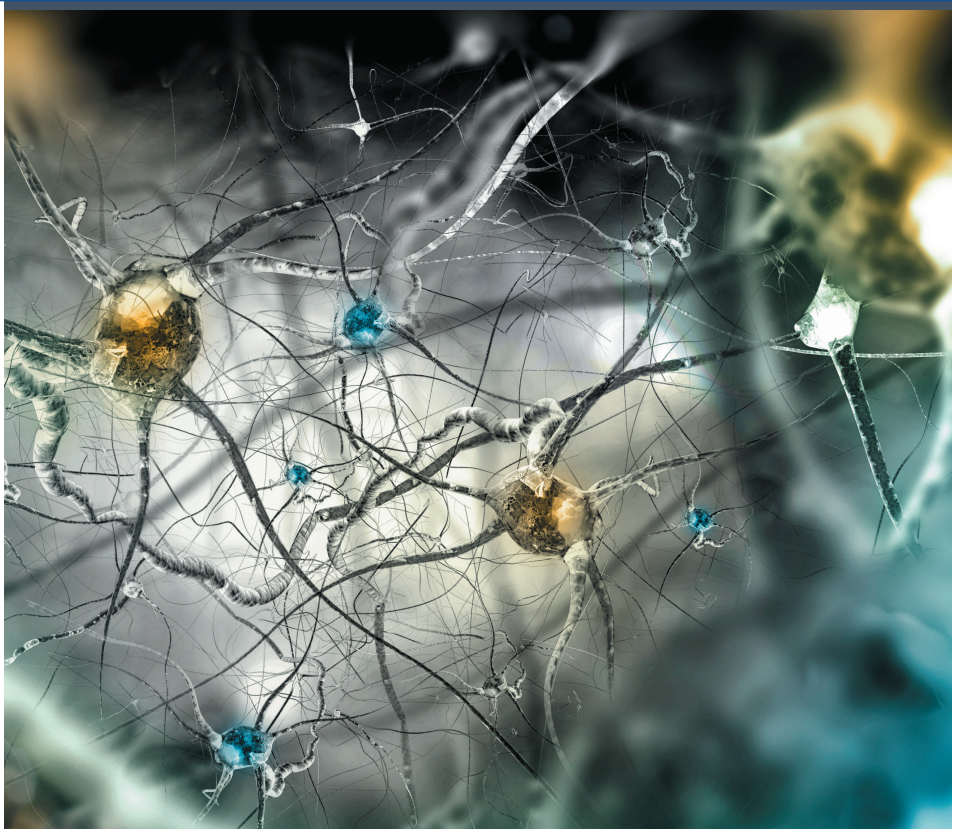
This study is the first to offer a detailed molecular analysis of what happens in the brain after highly repetitive and very mild blows to the head, using mice as an animal model, says the study's senior investigator, Mark Burns, PhD, an associate professor in Georgetown's Department of Neuroscience and head of the Laboratory for Brain Injury and Dementia.

"Most research in this area has been in mouse models with more severe brain injury, or in human brains with chronic traumatic encephalopathy (CTE)," he says. CTE is a degenerative brain disease found in people with a history of repetitive head impact. "This means that we have been focusing only on how CTE pathology develops. Our goal was to understand how the brain changes in response to the low-level head impacts that many young football players, for example, are regularly experiencing."

Researchers have found that the average high school and college football player receives 21 head impacts per week, while some specialized players, such as defensive ends, experience twice as many. Behavioral issues believed to come from head impact have been reported in athletes with exposure to repeated head impacts. Issues range from mild learning and memory deficits to behavioral changes that include aggression, impulsivity and sleep disorders.

"These findings represent a message of hope to athletes and their families who worry that a change in behavior and memory means that CTE is in their future," says Burns.

In this study with mice, researchers mimicked the mild head impacts experienced by



football players. The mice showed slower learning and impaired memory recall at timepoints long after the head impacts had stopped. After the experiment, a detailed analysis of their brains showed that there was no inflammation or tau pathology, as is usually seen in the brains of brain trauma or people with CTE.

To understand the physiology underlying these memory changes, the study's co-first author, Bevan Main, PhD, assistant professor of neuroscience at Georgetown, conducted RNA sequencing of the brain. "There are many things that this type of analysis can point you to, such as issues with energy usage or CTE-like pathways being activated in nerve cells, and so on," Main says. "All of our sequencing studies kept pointing to the same thing – the synapses that provide communication between neurons."

The next step was to figure out how synaptic function was altered. Stephanie Sloley, PhD, a graduate of Georgetown's Interdisciplinary Program for Neuroscience and the study's other first co-author, conducted electrophysiology studies of different neurons charged with releasing varied neurotransmitters – chemicals passed between neurons, via synapses, that carry functional instructions. "The brain is wired via synaptic communication pathways, and while we found that these wires were intact, the way that they communicated using glutamate was blunted, repressed," says Sloley.

Glutamate is the most abundant neurotransmitter in the brain, and is found in more than 60% of brain synapses. It plays a role in synaptic plasticity, which is the way the brain strengthens or weaken signals between neurons over time to shape learning and memory.

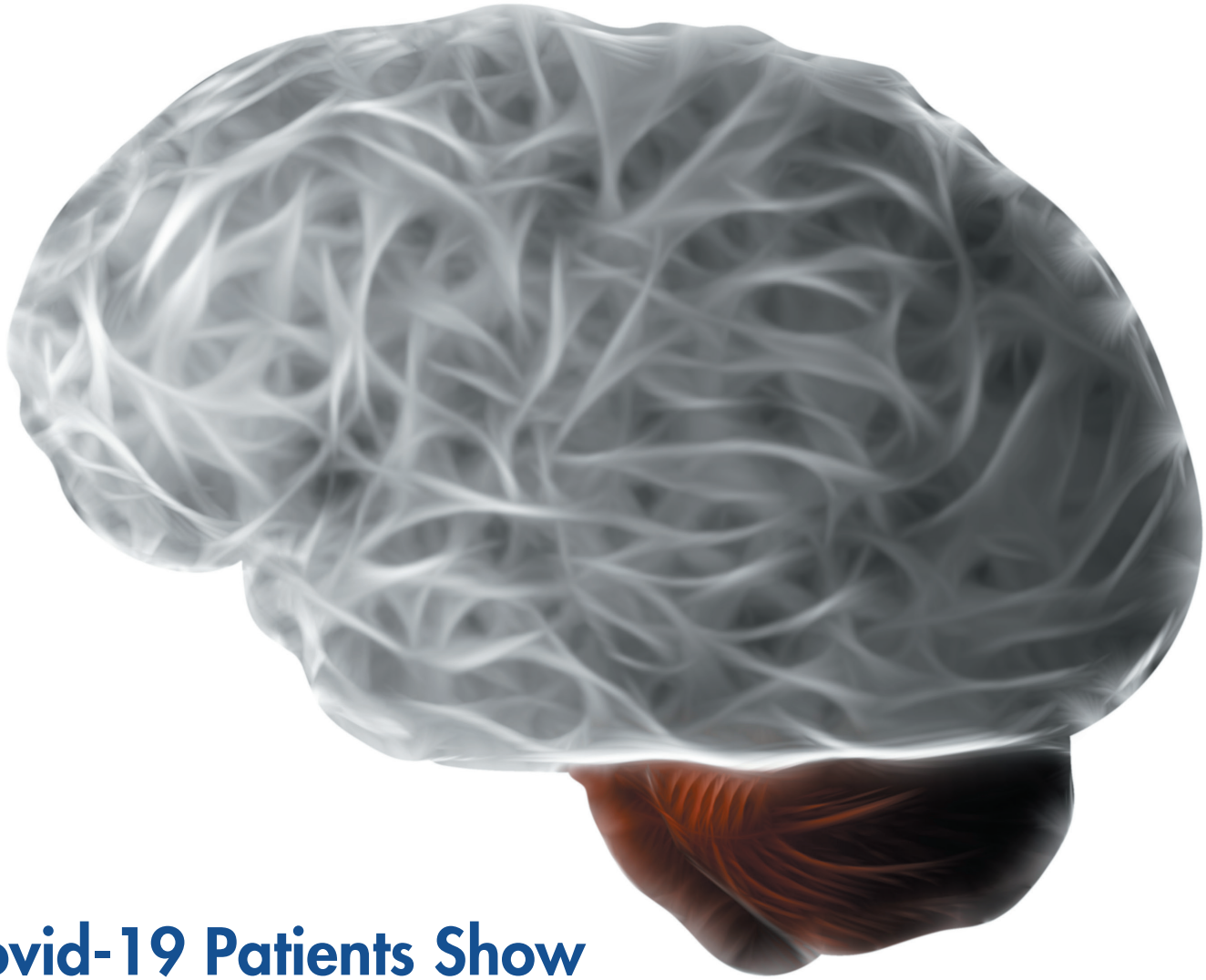
"Glutamate is usually very tightly regulated in the brain, but we know that head impacts cause a burst of glutamate to be released. We believe that brain is adapting to the repeated bursts of glutamate caused by high frequency head impact, and dampens its normal response to glutamate, perhaps as a way to protect the neurons," explains Sloley. She found that there was a shift in the way that neurons detected and responded to glutamate release, which reduced the neurons ability to learn new information.

With a single head hit or infrequent hits, the synapses do not go through this readjustment, Burns says. But after only a week of frequent mild hits, glutamate detection remained blunted for at least a month after the impacts ended. The affected mice showed deficits in learning and memory, compared to a placebo group of animals.

The authors confirmed that the changes in cognition were due to glutamate by giving a group of mice a drug to block glutamate transmission before they experienced the series of head knocks. This drug is FDA-approved for the treatment of Alzheimer's disease. Despite being exposed to the hits, these mice did not develop adaptations in their synapses or neurotransmission, and did not develop cognitive problems.

"This tells us that the cognitive issues we see in our head impact mice are occurring due to a change in the way the brain is working, and not because we have irreparable brain damage or CTE," Main says. "It would be very unlikely that we would use a drug like this in young players as a neuroprotectant before they play sports, because not all players will develop cognitive disorders," he says. "More much likely is that we can use our findings to develop treatments that target the synapses and reverse this condition. That work is already underway"

Burns believes that CTE and this newly discovered mechanism is different. "I believe that CTE is a real concern for athletes exposed to head impact, but I also believe that our newly discovered communication issue is independent of CTE. While it is concerning that head impacts can change the way the brain works, this study reveals that learning and memory deficits after repeated head impacts do not automatically mean a future with an untreatable neurodegenerative disease." ■



Covid-19 Patients Show Reduced Gray Matter Volume in the Brain

The study found lower gray matter volume in the frontal-temporal network was associated with a higher level of disability among Covid-19 patients.

Covid-19 patients who receive oxygen therapy or experience fever show reduced gray matter volume in the frontal-temporal network of the brain, according to a new study led by researchers at Georgia State University and the Georgia Institute of Technology.

The study found lower gray matter volume in this brain region was associated with a higher level of disability among Covid-19 patients, even six months after hospital discharge.

Gray matter is vital for processing information in the brain and gray matter abnormality may affect how well neurons function and communicate. The study, published in the May 2021 issue of *Neurobiology of Stress*, indicates gray matter in the frontal network could represent a

core region for brain involvement in Covid-19, even beyond damage related to clinical manifestations of the disease, such as stroke.

The researchers, who are affiliated with the Center for Translational Research in Neuroimaging and Data Science (TReNDS), analyzed computed tomography scans in 120 neurological patients, including 58 with acute Covid-19 and 62 without Covid-19, matched for age, gender and disease. They used source-based morphometry analysis, which boosts the statistical power for studies with a moderate sample size.

"Previous studies have examined how the brain is affected by Covid-19 using a univariate approach, but ours is the first to use a multivariate, data-driven approach to link these changes to specific Covid-19 characteristics (for example fever and lack of oxygen) and outcome (disability level)."

The analysis showed patients with higher levels of disability had lower gray matter volume in the superior, medial and middle frontal gyri at discharge and six months later, even when controlling for cerebrovascular diseases.

Gray matter volume in this region was also significantly reduced in patients receiving oxygen therapy compared to patients not receiving oxygen therapy. Patients with fever had a significant reduction in gray matter volume in the inferior and middle temporal gyri and the fusiform gyrus compared to patients without fever. The results suggest Covid-19 may affect the frontal-temporal network through fever or lack of oxygen.

Reduced gray matter in the superior, medial and middle frontal gyri was also present in patients with agitation compared to patients without agitation. This implies that gray matter changes in the frontal region of the brain may underlie the mood disturbances commonly exhibited by Covid-19 patients.

"Neurological complications are increasingly documented for patients with Covid-19," said Vince Calhoun, senior author of the study and director of TReNDS. Calhoun is Distinguished University Professor of Psychology at Georgia State and holds appointments in the School of Electrical and Computer Engineering at Georgia Tech and in neurology and psychiatry at Emory University.

"A reduction of gray matter has also been shown to be present in other mood disorders such as schizophrenia and is likely related to the way that gray matter influences neuron function."

The study's findings demonstrate changes to the frontal-temporal network could be used as a biomarker to determine the likely prognosis of Covid-19 or evaluate treatment options for the disease. Next, the researchers hope to replicate the study on a larger sample size that includes many types of brain scans and different populations of Covid-19 patients. ■

“Previous studies have examined how the brain is affected by Covid-19 using a univariate approach, but ours is the first to use a multivariate, data-driven approach to link these changes to specific Covid-19 characteristics (for example fever and lack of oxygen) and outcome (disability level).”

Researchers Identify Mechanism That May Lead to New Therapies for Strokes and Brain Injuries

In a surprising discovery, researchers at Massachusetts General Hospital (MGH) identified a mechanism that protects the brain from the effects of hypoxia, a potentially lethal deprivation of oxygen.

This serendipitous finding, which they report in *Nature Communications*, could aid in the development of therapies for strokes, as well as brain injury that can result from cardiac arrest, among other conditions.

However, this study began with a very different objective, explains senior author Fumito Ichinose, MD, PhD, an attending physician in the Department of Anesthesia, Critical Care and Pain Medicine at MGH, and principal investigator in the Anesthesia Center for Critical Care Research.

One area of focus for Ichinose and his team is developing techniques for inducing suspended animation, that is, putting a human's vital functions on temporary hold, with the ability to "reawaken" them later. This state of being would be similar to what bears and other animals experience during hibernation.

Ichinose believes that the ability to safely induce suspended animation could have valuable medical applications, such as pausing the life processes of a patient with an incurable disease until an effective therapy is found. It could also allow humans to travel long distances in space (which has frequently been depicted in science fiction).

Ichinose believes that the ability to safely induce suspended animation could have valuable medical applications, such as pausing the life processes of a patient with an incurable disease until an effective therapy is found.

A 2005 study found that inhaling a gas called hydrogen sulfide caused mice to enter a state of suspended animation. Hydrogen sulfide, which has the odor of rotten eggs, is sometimes called "sewer gas." Oxygen deprivation in a mammal's brain leads to increased production of hydrogen sulfide. As this gas accumulates in the tissue, hydrogen sulfide can halt energy metabolism in neurons and cause them to die. Oxygen deprivation is a hallmark of ischemic stroke, the most common type of stroke, and other injuries to the brain.

In the *Nature Communications* study, Ichinose and his team initially set out to learn what happens when mice are exposed to hydrogen sulfide repeatedly, over an extended period. At first, the mice entered a suspended-animation-like state--their body temperatures dropped and they were immobile.

Interestingly, the mice that became tolerant to hydrogen sulfide were also able to tolerate severe hypoxia. What protected these mice from hypoxia? Ichinose's group suspected that enzymes in the brain that metabolize sulfide might be responsible. They found that levels of one enzyme, called sulfide:quinone oxidoreductase (SQOR), rose in the brains of mice when they breathed hydrogen sulfide several days in a row. They hypothesized that SQOR plays a part in resistance to hypoxia.

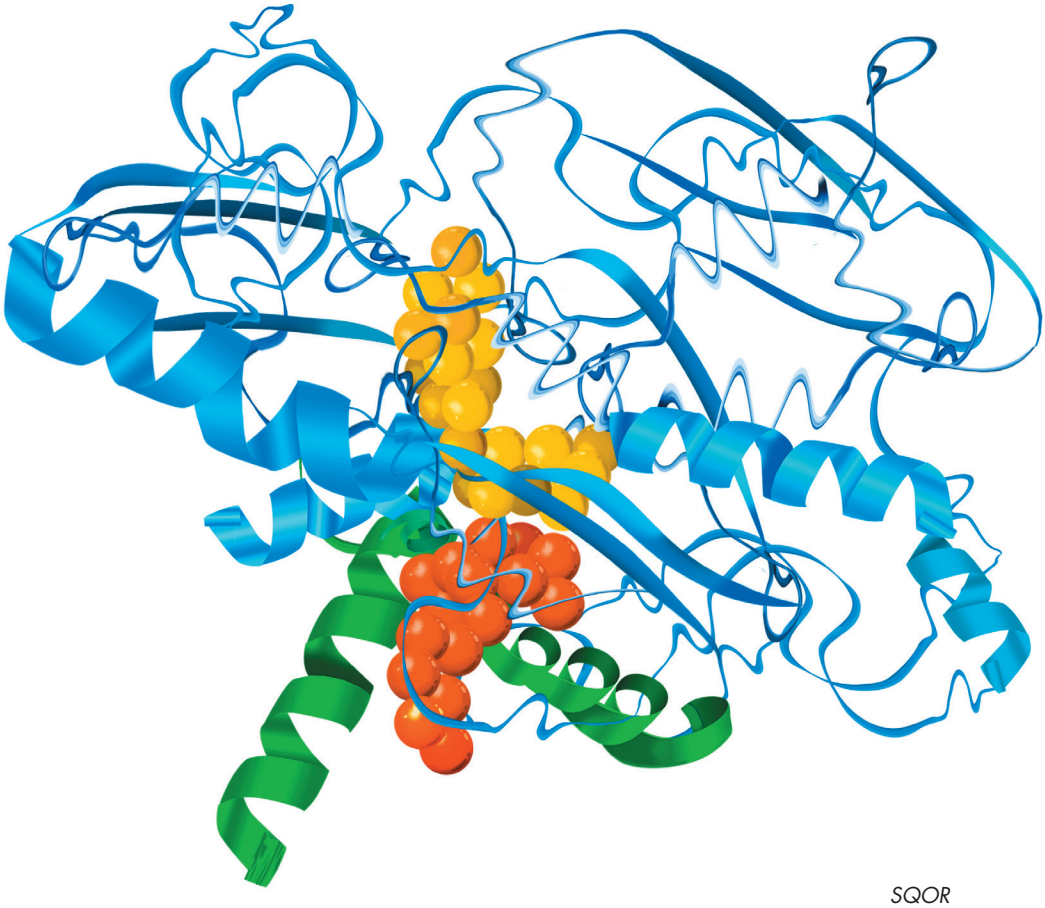
There was strong evidence for this hypothesis in nature. For example, female mammals are known to be more resistant than males to the effects of hypoxia–and the former have higher levels of SQOR. When SQOR levels are artificially reduced in females, they become more vulnerable to hypoxia. (Estrogen may be responsible for the observed increase in SQOR,

since protection from the adverse effects of hypoxia is lost when a female mammal's estrogen-producing ovaries are removed.)

Moreover, some hibernating animals, such as the thirteen-lined ground squirrel, are highly tolerant of hypoxia, which allows them to survive as their bodies' metabolism slows down during the winter. A typical ground squirrel's brain has 100 times more SQOR than that of a similar-sized rat. However, when Ichinose and colleagues "turned off" expression of SQOR in the squirrels' brains, their protection against the effects of hypoxia vanished.

Meanwhile, when Ichinose and colleagues artificially increased SQOR levels in the brains of mice, "they developed a robust defense against hypoxia," explains Ichinose. His team increased the level of SQOR using gene therapy, an approach that is technically complex and not practical at this point. On the other hand, Ichinose and his colleagues demonstrated that "scavenging" sulfide, by using an experiment drug called SS-20, reduced levels of the gas, thereby sparing the brains of mice when they were deprived of oxygen.

Human brains have very low levels of SQOR, meaning that even a modest accumulation of hydrogen sulfide can be harmful, says Ichinose. "We hope that someday we'll have drugs that could work like SQOR in the body," he says, noting that his lab is studying SS-20 and several other candidates. Such medications could be used to treat ischemic strokes, as well as patients who have suffered cardiac arrest, which can lead to hypoxia. Ichinose's lab is also investigating how hydrogen sulfide affects other parts of the body. For example, hydrogen sulfide is known to accumulate in other conditions, such as certain types of Leigh syndrome, a rare but severe neurological disorder that usually leads to early death. "For some patients," says Ichinose, "treatment with a sulfide scavenger might be life-saving." ■



SQOR

When sulfide:quinone oxidoreductase (SQOR) levels were artificially increased in the brains of mice, "they developed a robust defense against hypoxia."

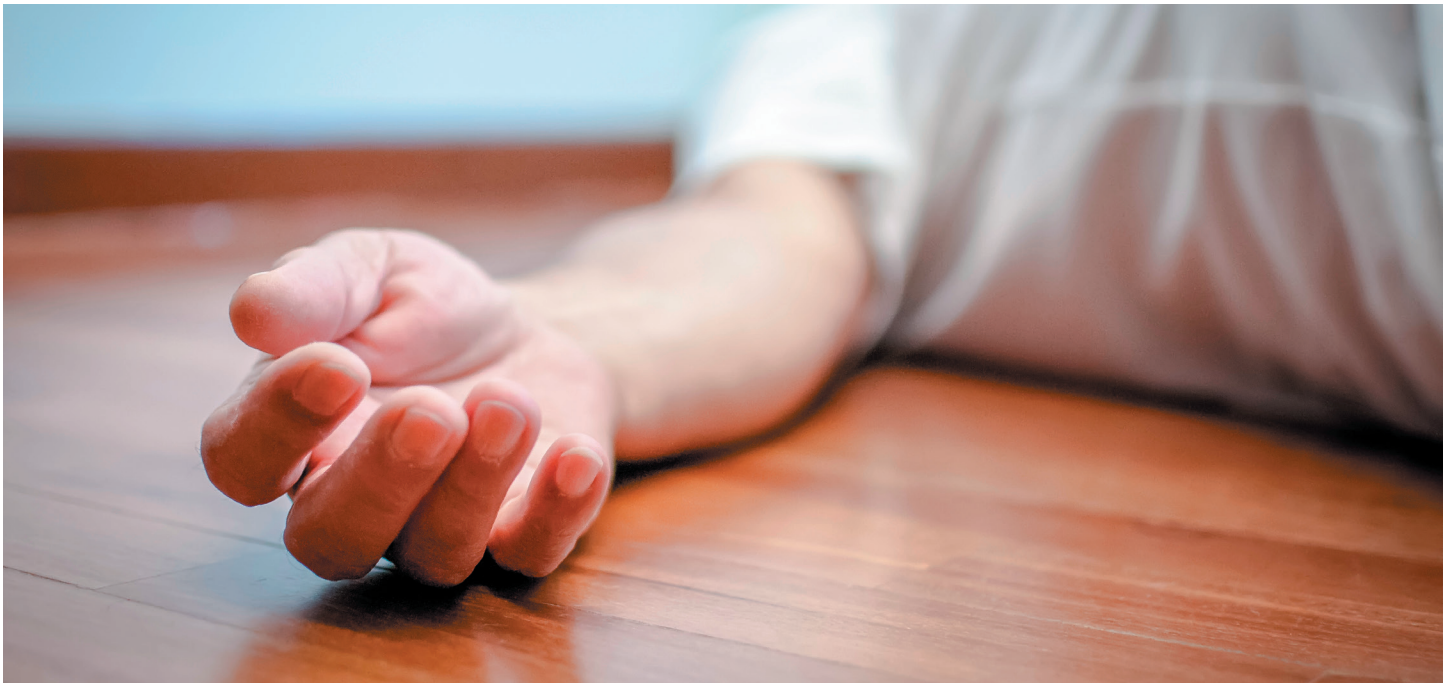
Concussion with Loss of Consciousness May be Linked to Life with Some Disability

"About 16% of all adults have experienced a concussion with loss of consciousness, and our study found that nearly half of those people are living with disability."

People who have had a concussion where they lost consciousness may be more likely to have some disability or limitations later in life–such as difficulty walking or limitations in the amount or type of work they can do–than people who have never had a concussion, according to a study recently published in the online issue of *Neurology*®, the medical journal of the American Academy of Neurology.

"About 16% of all adults have experienced a concussion with loss of consciousness, and our study found that nearly half of those people are living with disability," said study author Andrea L.C. Schneider, MD, PhD, of the University of Pennsylvania Perelman School of Medicine in Philadelphia and a member of the American Academy of Neurology. "This substantial burden of disability suggests that research into how to better care for and improve the functioning of people with concussions over the long term should be a priority for both public health and for planning for individuals."

The study involved 7,390 people with an average age of 58. People were asked if they had ever had a concussion with loss of consciousness. They were also asked questions about their ability to do daily activities such as eating and dressing, preparing meals and doing household chores, walking up steps and carrying heavy objects. Their grip strength was also tested to check for any disability in their



arms. Disability was defined as having "some difficulty" or greater difficulty in an area.

People were also asked whether a physical, mental or emotional problem keeps them from working at a job or limits the kind or amount of work they can do. An answer of "yes" was defined as having a disability in that area.

A total of 16% of people had experienced a concussion with loss of consciousness. Of those, 47% had some disability in at least one area of functioning, compared to 37% of people with no history of concussion.

"This corresponds to 11.4 million people in the United States with a history of concussion with loss of consciousness and disability in at least one area," Schneider said. "And it's possible that this is an underestimation, as the study did not include people in the military, nursing facilities or prisons who may have be more likely to experience concussions and disability."

The study found the area with the greatest amount of disability was in mobility, such as being able to walk up 10 steps or stand up from an armless chair, with 38% experiencing at least some difficulty. About 36% said they had at least some difficulty in general physical activities such as carrying heavy objects or standing for long periods. About 35% of people said they were limited in the amount or type of work they could do.

The results were much the same after researchers adjusted for other factors that could affect disability, such as age, amount of physical activity, high blood pressure, amount of sleep and depression. The only area that did not show a link between concussion and disability was grip strength.

Schneider noted that the study was not designed to show cause and effect. It only shows an association between past concussion with loss of consciousness and disability. ■

"This corresponds to 11.4 million people in the United States with a history of concussion with loss of consciousness and disability in at least one area."

Obsessive Compulsive Disorder Linked to Increased Ischemic Stroke Risk Later in Life

Adults who have obsessive-compulsive disorder (OCD) were more than three times as likely to have an ischemic stroke later in life compared to adults who do not have OCD, according to new research published today in Stroke, a journal of the American Stroke Association, a division of the American Heart Association.

"The results of our study should encourage people with OCD to maintain a healthy lifestyle, such as quitting or not smoking, getting regular physical activity and managing a healthy weight to avoid stroke-related risk factors," said study senior author Ya-Mei Bai, M.D., Ph.D., a professor in the department of psychiatry at Taipei Veterans General Hospital and National Yang Ming Chiao Tung University College of Medicine, both in Taiwan.

Worldwide, stroke is the second-leading cause of death after heart disease. Stroke is a medical emergency that occurs when blood and oxygen flow to the brain are interrupted, usually by a blood clot (ischemic stroke). Less common is stroke from a burst blood vessel that causes bleeding in the brain (hemorrhagic stroke). In both types of stroke, immediate treatment is critical to prevent brain damage, disability or death. The abbreviation F.A.S.T. can help people remember the warning signs and what to do: F-face drooping, A-arm weakness, S-speech difficulty, T-time to call 9-1-1.

OCD is a common, sometimes debilitating, mental health condition characterized by intrusive, unwanted thoughts, ideas or sensations (obsessions) that make a person feel driven to do something repetitively (compulsions). The repetitive behaviors characteristic of OCD, such as hand washing, checking on things or continuously cleaning, can significantly interfere with a person's daily activities and social interactions. Previous research found that OCD often occurs after stroke or other brain injury. What remained unclear

was whether the reverse is true: can OCD increase stroke risk?

To find out, researchers examined health records from 2001-2010 from the Taiwan National Health Insurance Research Database to compare stroke risk between 28,064 adults with OCD and 28,064 adults who did not have OCD. The average age at diagnosis with OCD was 37 years, and women and men were nearly equally represented in the data. Researchers compared stroke risk between the two groups for up to 11 years.

The analysis found:

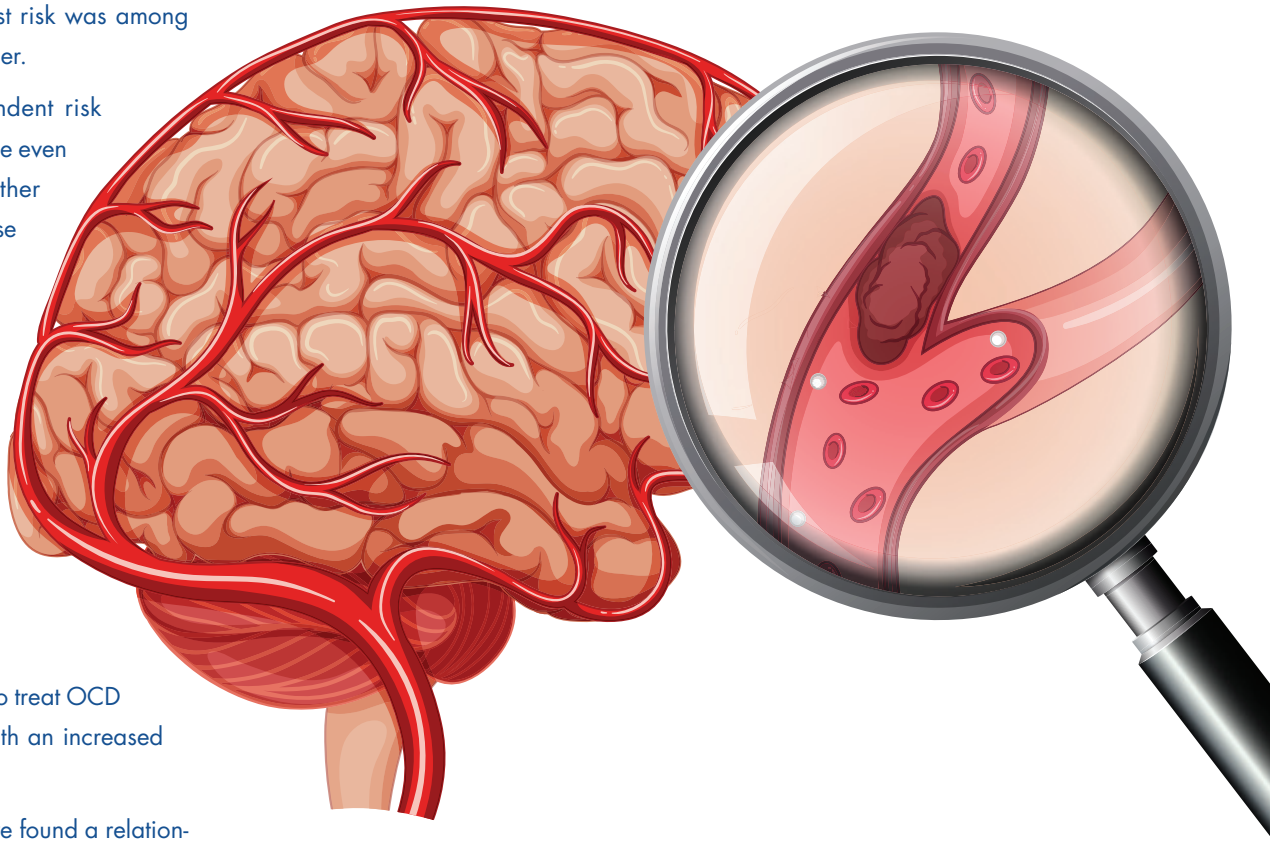
- Adults with OCD were more than three times as likely to have a stroke from a blood clot compared to adults who did not have OCD; the greatest risk was among adults ages 60 and older.
- OCD was an independent risk factor for ischemic stroke even after controlling for other factors known to increase stroke risk, including obesity, heart disease, smoking, high blood pressure, high cholesterol and Type 2 diabetes.
- No difference in risk was found for a hemorrhagic stroke (burst blood vessel).
- Similarly, medications to treat OCD were not associated with an increased risk of stroke.

"For decades, studies have found a relationship between stroke first and OCD later," Bai said. "Our findings remind clinicians to closely monitor blood pressure and lipid profiles, which are known to be related to stroke in patients with OCD."

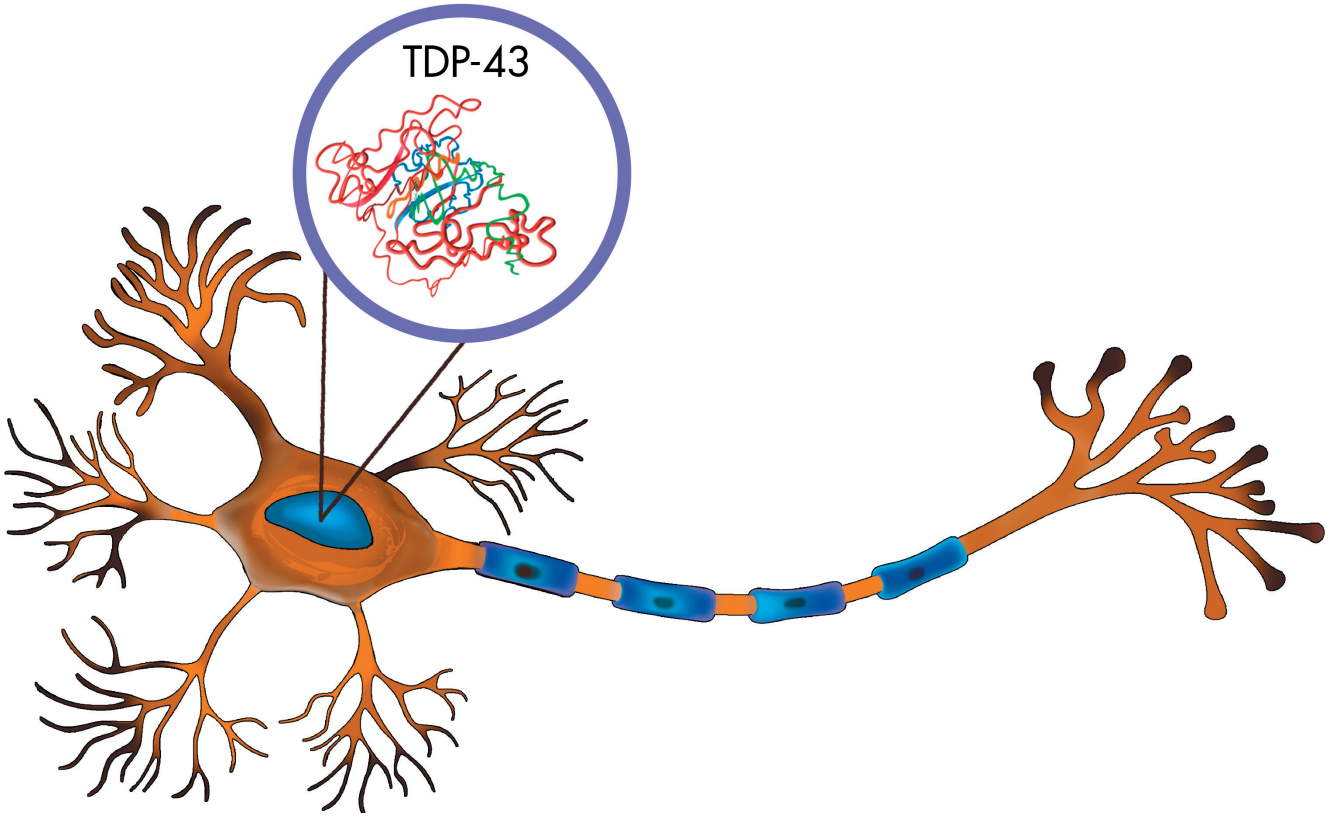
Limitations of the study were that only stroke among patients who sought health care were included, so some cases may have been missed; and information on disease severity was not included along with family medical history or environmental influences. The study also was observational, so it could only show an association between OCD and later stroke; it does not prove cause and effect.

"More research is needed to understand how the mental processes connected to OCD may increase the risk of ischemic stroke," Bai said.

Adults with OCD were more than three times as likely to have a stroke from a blood clot compared to adults who did not have OCD.



Ischemic Stroke



Scientists Identify Mechanism Linking Traumatic Brain Injury to Neurodegenerative Disease

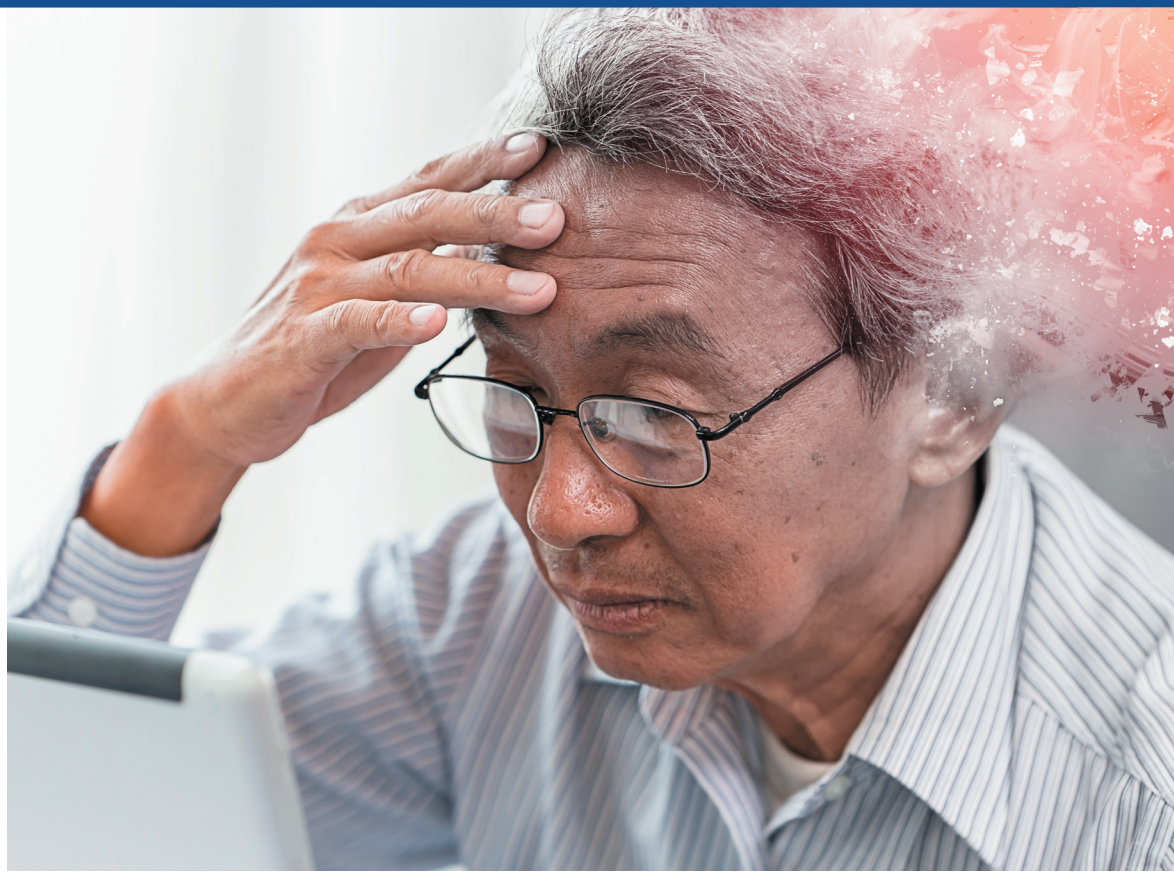
Study results could aid the development of treatments that halt the progression of cell damage after brain injury, which can otherwise lead to neurological diseases.

Scientists have revealed a potential mechanism for how traumatic brain injury leads to neurodegenerative diseases, according to a study in fruit flies, and rat and human brain tissue, published recently in eLife.

The results could aid the development of treatments that halt the progression of cell damage after brain injury, which can otherwise lead to neurological diseases such as amyotrophic lateral sclerosis (ALS), and Alzheimer's and Parkinson's disease.

Repeated head trauma is linked to a progressive neurodegenerative syndrome called chronic traumatic encephalopathy (CTE). Postmortem tissues from patients with CTE show dysfunctional levels of a molecule called TDP-43, which is also found in ALS, Alzheimer's disease and frontotemporal dementia.

"Although TDP-43 is a known indicator of neurodegeneration, it was not clear how repeated trauma promotes the build-up of



TDP-43 in the brain," explains first author Eric Anderson, Postdoctoral Research Associate at the Department of Pediatrics at the University of Pittsburgh, Pennsylvania, US. "We have shown that repetitive brain trauma in fruit flies leads to a build-up of TDP-43. In this study we measured the changes of proteins in the fruit fly brain post injury to identify the molecular pathways that cause this."

From an analysis of 2,000 proteins, the team identified 361 that significantly changed in response to injury. These included components of the nuclear pore complex (NPC) involved in nucleocytoplasmic transport - the shuttling of important cargoes between the cell nucleus and the rest of the cell.

They found that a family of molecules that make up the NPC called nucleoporins (Nups) were increased in both larval and adult flies after injury. When they looked at the distribution pattern of Nups around the edge of the nucleus in fruit fly nerve cord cells, they found it was altered after brain trauma: there were gaps in the nuclear membrane and clumps of Nups. They also found changes in a key enzyme involved in transporting molecules in and out of the nucleus in injured brains. As a result, the transport of fluorescently labelled cargo in and out of the nucleus was impaired.

Having established that brain injury impairs the transport machinery between the nucleus and the rest of the cell, the team looked at whether the build-up of Nups leads to the aggregation of TDP-43 seen in neurodegenerative diseases. They created fruit flies that produce excess Nup protein and then stained the brain cells for the fruit fly version of TDP-43, called Tbph. They found a significant increase in the number of Tbph deposits in brains that had too much Nup compared with normal brains. Moreover, these high levels of Nups were also toxic to the flies, causing decreased motor function and reducing the distance they could climb in a certain timeframe. When the level of Nups was reduced in cells after injury, this improved the flies' climbing ability and lifespan, highlighting an avenue to explore for new treatments.

Finally, the team looked at whether the increased build-up of a Nup molecule (Nup62) was also seen in human brain tissue after injury. They examined postmortem brain tissue from patients with mild and severe CTE matched to healthy tissue from people of the same age. All mild and severe patients were involved in sports, while healthier cases were not. They found that Nup62 was present in large amounts in the wrong place in patients with mild and severe disease, but not in the healthy group, and the degree of Nup62 aggregation increased with the severity of disease. They also saw similar changes in the distribution of Nup62 in a rat model of traumatic brain injury.

"Our study reveals that traumatic brain injury can disrupt nuclear transport machinery of the cells, which plays an essential role in normal cell functions such as communication," concludes senior author Udai Pandey, associate professor of pediatrics, human genetics and neurology at the University of Pittsburgh School of Medicine. "This suggests that the accumulation of neurodegenerative hallmark proteins caused by injury begins with these nuclear transport defects, and that targeting these defects could be a strategy for preventing trauma-induced neurological disorders."■

Study Illuminates How COVID-19 Worms Its Way into the Brain

New research offers an up-close view of how SARS-CoV-2, the virus that causes COVID-19, can spread to the brain. The study helps explain the alarming array of neurological symptoms reported in some patients with COVID-19, as well as why some patients suffer severe neurological effects while others experience none at all.

The researchers report evidence that SARS-CoV-2 can infect both the nerve cells that power our brains (neurons), and the cells in the brain and spinal cord that support and protect neurons (astrocytes).

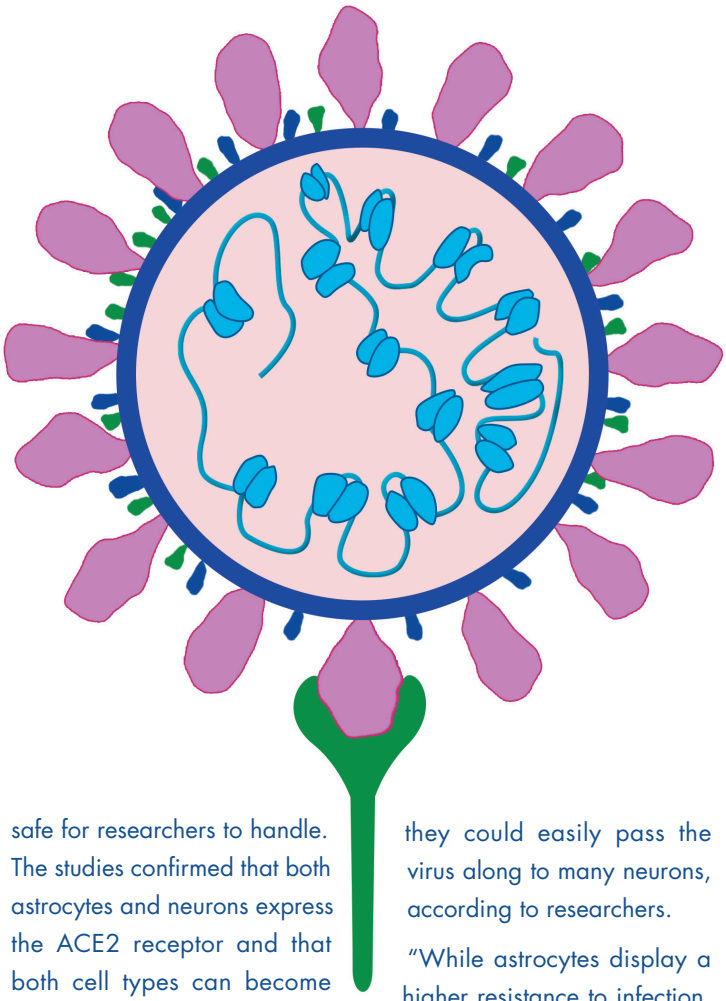
"Our findings suggest that astrocytes are a pathway through which COVID-19 causes neurological damage," said Ricardo Costa, PhD, a postdoctoral fellow at the Louisiana State University (LSU) Health Shreveport and the study's first author. "This could explain many of the neurologic symptoms we see in COVID-19 patients, which include loss of sense of smell and taste, disorientation, psychosis and stroke."

Costa will present the research at the American Physiological Society annual meeting during the Experimental Biology (EB) 2021 meeting, held virtually April 27-30. The study is led by Diana Cruz-Topete, assistant professor of molecular and cellular biology at LSU Health Shreveport, and includes collaborators Oscar Gomez-Torres, PhD, and Emma Burgos-Ramos, PhD, from Universidad de Castilla-La Mancha in Spain.

In the respiratory system, SARS-CoV-2 is known to infect a person's cells by grabbing hold of proteins on the cell surface called angiotensin-converting enzyme-2 (ACE2) receptors. It has been unclear whether brain cells have this receptor.

For the study, Costa and colleagues examined RNA and proteins to determine whether cell cultures of human astrocytes and neurons expressed ACE2. They then exposed the cells to a version of the SARS-CoV-2 virus that had been modified to be safe for researchers to handle. The studies confirmed that both astrocytes and neurons express the ACE2 receptor and that both cell types can become infected with SARS-CoV-2, though astrocytes were less likely to become infected.

SARS-Cov-2 spike protein binding to ACE2



Astrocytes are the main gateway to the brain, responsible for shuttling nutrients from the bloodstream to the neurons while keeping harmful particles out. By resisting infection, astrocytes could help keep SARS-CoV-2 out of the brain, but once infected, they could easily pass the virus along to many neurons, according to researchers.

"While astrocytes display a higher resistance to infection, neurons seem to be more susceptible," said Costa. "This suggests that only few astrocytes getting infected could be sufficient for the infection to quickly spread to neurons and multiply quickly. These observations could explain why while some patients do not have any neurological symptoms, others seem to have severe ones." ■

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