UNDERSTANDING TRAUMATIC INJURY TO THE HUMAN BRAIN

EDITED BY: Robert Knight and Amy Markowitz
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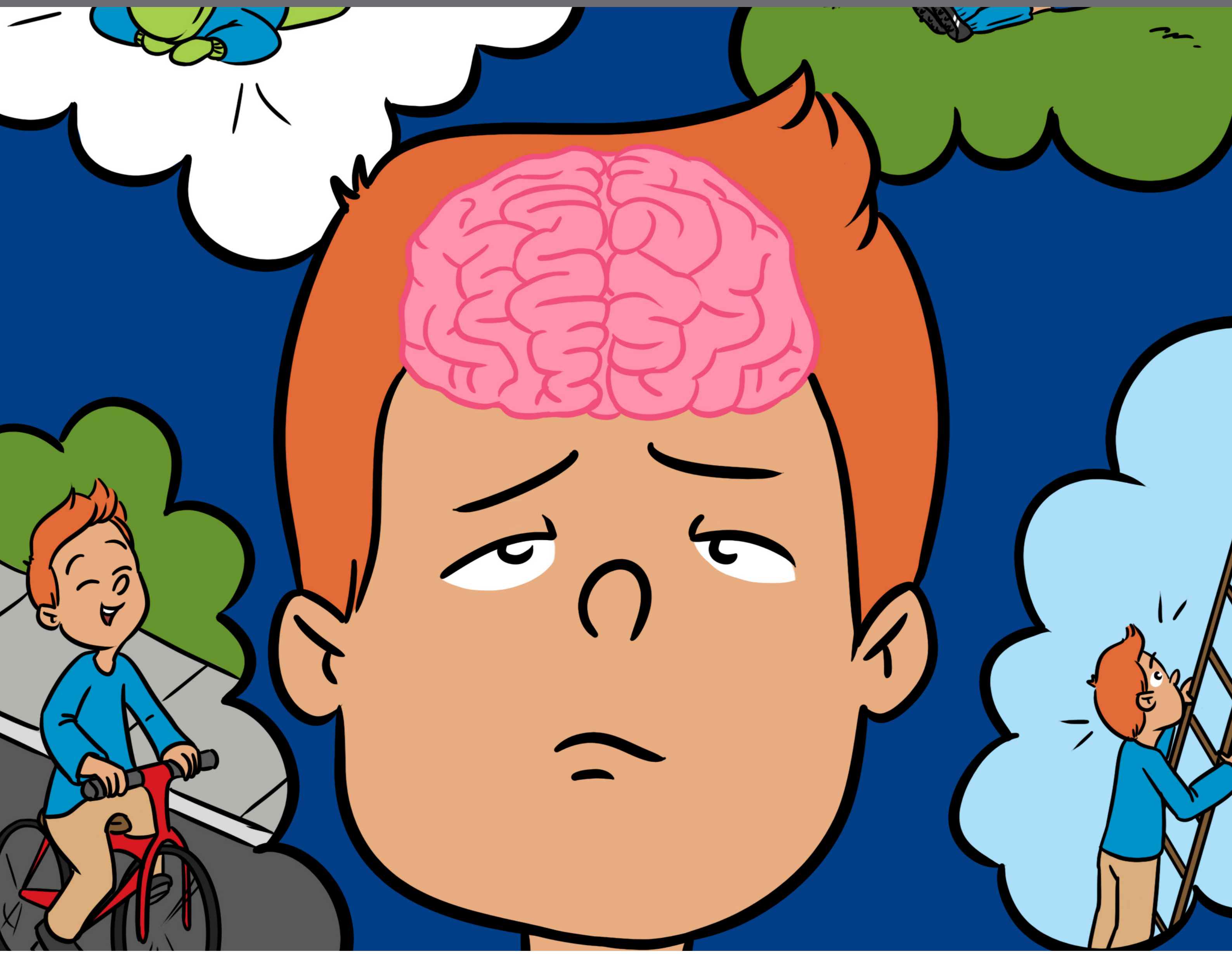

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UNDERSTANDING TRAUMATIC INJURY TO THE HUMAN BRAIN

Topic Editor:
Robert Knight, University of California, United States
Amy Markowitz, University of California, United States

Your noggin, your noodle, your coconut, your bean! There are many terms for your brain, that fantastic organ that sits inside of your skull, and runs, well, everything, whether you are thinking about it or not. Although the skull is a hard, purpose-built case to protect the brain, we live in an active environment, in which expected events and unexpected accidents may cause what we call a "traumatic brain injury" – everything from concussion on the sport field, to falls from a bike or a ladder or a snowboard, to car accidents and everything in between. These different mechanisms of injury may cause contusions or bruises to the brain, like a bruise to a muscle, and may also result in bleeds in or around the brain, called hemorrhages.

All of these types of brain injuries can result in damage to the actual brain tissue as well as cause interruptions to the complex electronic circuitry of the brain, causing symptoms like headaches, dizziness, fuzzy thinking, upset balance, memory loss, and poor sleep, to name just a few. Doctors are very good at treating the acute problems from a brain injury but we currently have no effective treatments for the actual injury to your brain and have to wait and see how the injury resolves on its own. While most people do recover spontaneously, for some, kids and adults alike, the symptoms can persist for a very long time, from months to years and sometimes permanently.

If there is any positive that can come from injuring the brain, it is that sometimes the only way to understand how something works is to "break" it, and watch how it puts itself back to together. In this collection of articles, we'll study the way we diagnose where and how the brain has been injured, how we treat the acute injury and discuss new models to enhance recovery of brain function. The first steps in our roadmap require a careful assessment of the details of the person's accident, examining the person thoroughly, and then reviewing special imaging studies called computed tomography (CT) or Magnetic Resonance Imaging (MRI) that show us the structures of the brain, and how they are connected or disconnected following the injury. New blood tests can identify the presence of special biomarkers that indicate that there has been an injury to the brain itself, rather than just to the bony skull. Other important information can come from electroencephalography (EEG), which uses small sensors attached to the skull to capture and measure electronic signals traveling around the brain, to see where the interruptions may be occurring.

We'll learn about special surgeries, including hemicraniotomy, where the neurosurgeon "pops your top", sometimes to relieve pressure on the brain, or to stop a hemorrhage from bleeding further, or to insert a protective metal plate. Surgeries and imaging studies give us a great deal of insight about the injured brain, but then what? Studies of other mammals, like rats and mice, can help us, but how, for instance, do we study a rat's memory? We'll find out how scientists accomplish this, and see how this knowledge might help patients recover memory after a brain injury.

Importantly, we'll also learn how can we protect our brains from injury, even when we can't avoid the accidents that come with everyday life. We'll explore emerging design of sports helmets and other gear, and learn how a strong neck and back can help prevent injury to the brain and spinal cord.

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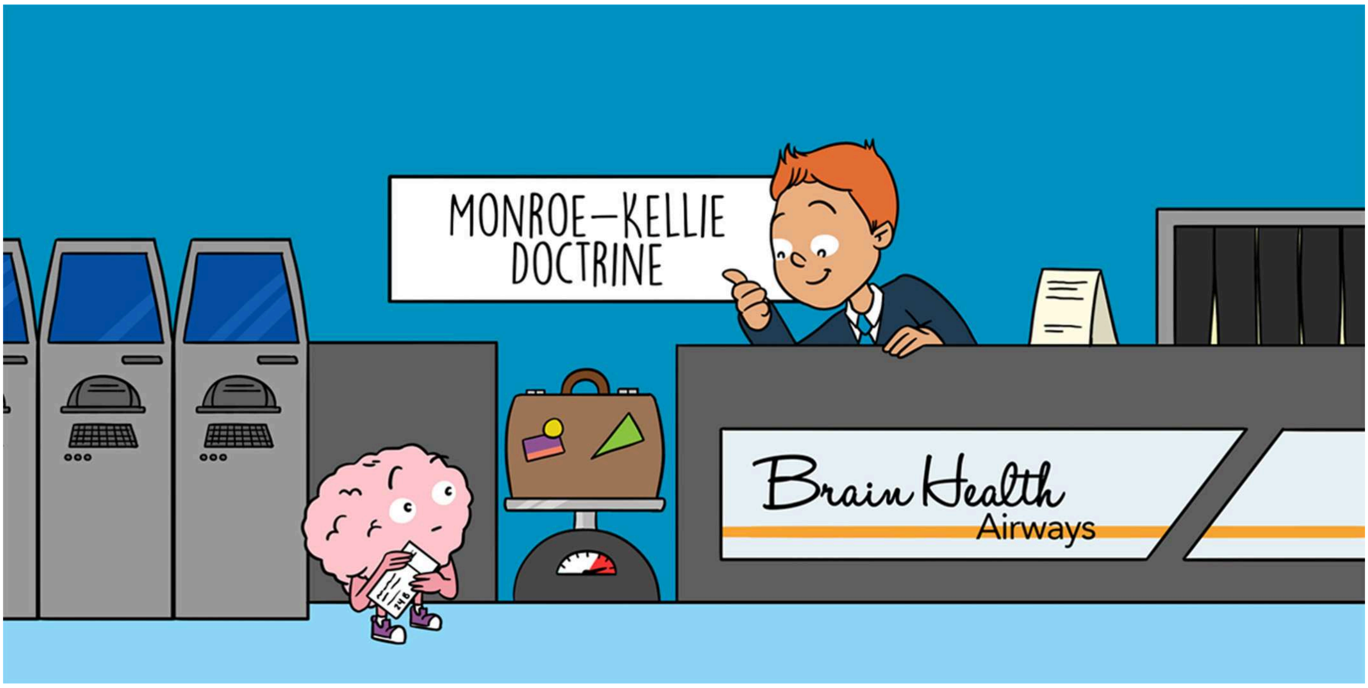

WHAT HAPPENS WHEN YOU HIT YOUR HEAD?

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YOUNG REVIEWERS:

CAITLYN
AGE: 14

CLEMENT
AGE: 13

DANIEL
AGE: 10

MARILIA
AGE: 12

Traumatic brain injury, or TBI, is an injury to the brain caused by a bump or hit to the head. It is a common injury in children and can cause lasting symptoms and disabilities. There are different causes of TBI, such as car accidents, falls, or football tackles. Fortunately, there are ways we can reduce TBI by making safe choices, such as buckling our seatbelts and wearing helmets while playing sports.

INTRODUCTION

Before we dive into talking about brain injury, we want to introduce something scientists call the Monroe-Kellie Doctrine, which is important for understanding how **traumatic brain injury (TBI)** happens. Think about your skull like a suitcase. If you are packing for a trip, you can only fit in a certain number of items. So, if you pack too many clothes, you would not be able to pack other things, like your favorite book. The Monroe-Kellie Doctrine states that there is a limited amount of space in the skull to hold all of the cells that make up the brain tissue, the blood that supplies oxygen to the tissue, and a special type of fluid that cushions the brain, called cerebrospinal fluid.

Figure 1

The brain is divided into different sections, called lobes, shown in different colors in this diagram. Lobes control things like movement, speech, and behavior. When a head injury occurs to a certain lobe or brain structure, then the functions that lobe or structure is responsible for can be impaired. For example, an injury to the temporal lobe can result in memory loss.

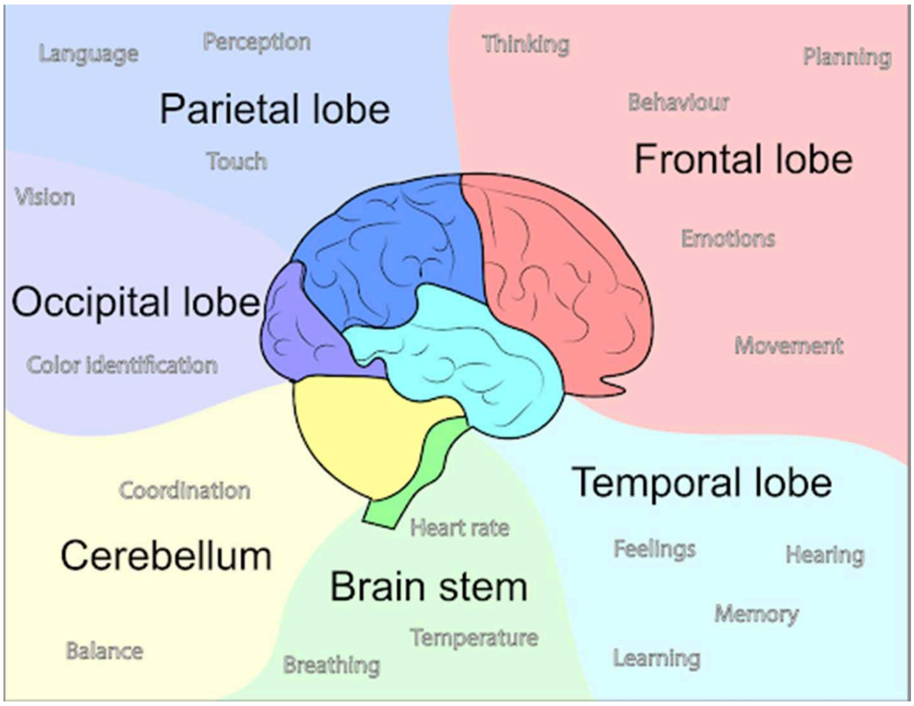


Figure 1

TRAUMATIC BRAIN INJURY (TBI)

A brain injury caused by a bump or hit to the head.

So, because the space is limited, if there is an increase in any one of these three things, one or both of the other two will have to decrease. That means that if you hit your head and the brain swells, there will be less room for blood, which could mean the brain will become even more injured. Or, if you hit your head and the blood vessels in your brain start to bleed, the brain tissue may end up getting squished to make room for the blood.

Types of Head Injuries

There are different types of TBI. First, we will talk about primary vs. secondary injuries. A primary injury is the initial injury; we will discuss what you can do to prevent a primary injury from happening. After the primary injury, secondary injury can cause even more damage to the cells and tissues. Some common examples of secondary injuries include inflammation (where brain tissue and blood vessels swell), hypoxia (when there is less oxygen going to the brain), and cellular death [1].

FOCAL INJURY

A brain injury that occurs in a specific part of the brain.

MENINGES

The membranes covering the brain and spinal cord.

TBIs can also be grouped into two types: focal vs. diffuse. Focal means that the injury occurred in a specific part of the brain. As you can see in Figure 1, the brain is divided into different parts, each with a different job.

Many **focal injuries** occur in the membranes covering the brain and spinal cord, which are called the **meninges** (see Figure 2). For instance, blood can collect between the two outermost membranes. We call this type of bleeding a hemorrhage or hematoma [2]. This takes us back to

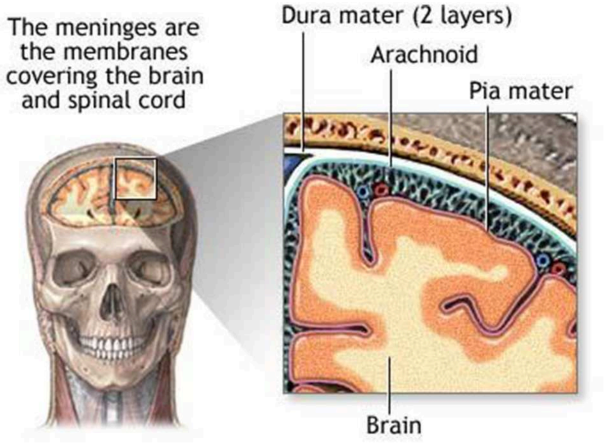


Figure 2

Figure 2

The membranes covering the brain and spinal cord are called the meninges. The three meninges are called the dura, arachnoid, and pia mater. Bleeding most commonly occurs between the dura and the arachnoid layers. Public domain image obtained from Wikimedia Commons: `https://commons.wikimedia.org/wiki/File:Meninges_diagram.jpg`.

the Monroe-Kellie Doctrine. In hemorrhage, if too much blood builds up in the skull, the amount of brain tissue and/or cerebrospinal fluid must decrease. Compression of brain tissue can damage or kill brain cells, and this can prevent a person from functioning normally.

DIFFUSE INJURY

A brain injury that occurs over a wider area of the brain.

Diffuse injuries occur over a larger area of the brain. In many of these injuries, less oxygen flows into the brain, similar to what happens in hypoxia [3]. Another common type of diffuse brain injury involves damage to the axons, which are the parts of brain cells that transport signals between the brain cells and the body. Axon damage can lead to the inability to move normally [2].

Brain injuries can have many other symptoms besides movement problems. Speaking normally, understanding what other people are saying, memorizing things, and eating can become difficult. Sometimes, mood swings and even depression can occur. Fortunately, patients can re-learn some of these tasks with therapy. The type of therapy a patient needs will depend on the location and severity of the injury, but might include physical therapy (to help with muscle weakness), occupational therapy (to help adapt to challenges in fine motor skills like brushing your teeth or cutting up your food), psychological counseling (to help with depression and anxiety), or appointments with a learning specialist (to help with problems reading and focusing).

Now that you have a general idea of what TBI is, we will discuss how these injuries occur and, more importantly, how you can prevent one from happening.

CAUSES, MECHANISMS, AND PREVENTIONS

In children and teenagers, the brain and skull continue to grow and more complex brain functions develop [4]. Because of these changes, TBIs can affect children at different ages in distinct ways.

Table 1

A summary of the most common mechanisms of TBI, and some easy prevention strategies to practice.

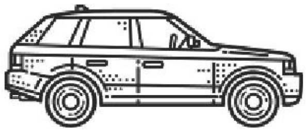
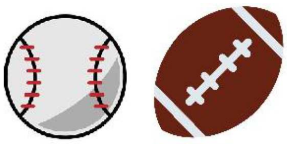
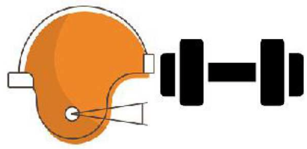
Mechanism	Prevention	What you should do
		• Talk to a doctor about which car seat is right for you or your sibling, based on height and weight. • Always wear a seatbelt while in a moving vehicle.
		• Talk to your coach about ways to protect yourself, such as wearing a helmet or improving your muscle strength. • Notify an adult if you ever hurt yourself during a game or practice.
		• Hold onto handrails and keep your shoes tied. • Let an adult know if you hurt yourself after a fall—small or big.

Table 1

For instance, a brain injury could cause more harm to a baby than it would a teenager, by interfering with normal brain growth and development.

Unfortunately, TBIs can occur during many fun activities (such as sports, running, or walking) and/or other things that we spend a lot of time doing (such as driving/riding in a car). Fortunately, however, there are ways to reduce our risk of TBI! Table 1 includes the common causes of TBI. Scientists have learned a lot about how TBI happens, by studying it in humans as well as modeling the condition in animals. While it may seem strange to give an animal like a mouse a TBI, it is a great opportunity for TBI researchers because, by using animals, variations that occur in humans, like diet, sleep cycles, and genetics, can be tightly controlled so that we know which factors contribute to TBI. From the human and animal studies, scientists have learned that TBIs activate a number of processes in the body, such as inflammation, cellular stress, and cell death.

Sports-Related Injuries

A hit to the head can occur while playing tackle football, skateboarding, doing gymnastics, or playing softball; thankfully, most are of these head injuries are mild injuries, such as concussion [5, 6]. But there is a good reason that parents, coaches, and other grownups always tell us to wear our helmets! Helmets protect the head, brain, and face from injuries while we play the sports we love. A helmet works best when it is the right size, when the chin strap is buckled tightly, and when there is padding on the inside. If a helmet is too big, not buckled, or is not cushioned, then when a player is tackled or a skateboarder wipes out, a TBI is more likely to occur [7]. While helmets typically do a great job of protecting us, TBIs can still happen even when we wear them. You should always tell an adult (a parent, guardian, or coach) if you hit your head, so that the adult can check you out and take you to a doctor if needed! Researchers are trying to improve helmet design by making the outside and inside work together better to protect your head from TBI, so that you can keep participating safely in the sports and activities that you love [7].

Motor Vehicle Collisions

Motor Vehicle Collisions (MVCs) can result in many types of injuries, including TBI. Injuries from an MVC cannot always be avoided, but they can be minimized by practicing seat belt safety. Seat belts keep us from being jerked around during fast turns and sudden stops. If your seatbelt is not worn properly, it is more likely that you could hit your head on objects inside the car or even get thrown from the car in the case of a collision. Researchers have found that people who were properly wearing their seat belts during MVCs were less likely to have TBIs, and they also had lower rates of TBI complications, such as brain bleeds or memory loss [8]. This is just one of the reasons why it is always important to wear a seat belt, and to use additional restraints, such as booster seats, if needed. These safety measures apply whether you are just traveling down the street or all the way across the state. Kids are not always big enough to fit into their seat belts properly. If you can wiggle in the seat belt, then an additional restraint, like a car seat or booster cushion, is suggested [9]. This is usually the case for all kids, from babies to 11-years-old. It is important to remember that the type of car seat or booster seat needed depends on the child's height and weight. Be sure to check the manufacturer's guidelines or check with a doctor when choosing a product that will keep you safe in the event of an MVC.

Falls

An innocent slip and fall can result in serious injuries, including a TBI. Falls can happen anywhere: walking around the house (especially with socks on a tile floor), playing tag in the park, going up and down the stairs, or jumping on the bed [4]. To prevent falls from happening, always use a handrail when going up and down stairs, do not run inside the house, keep your shoes tied to avoid tripping, and refrain from standing or jumping on furniture.

What else can I do?

Other than taking the common safety measures we have described, there are other things that you can do every day to help make your brain more resistant to injury. It all begins with living an active and healthy lifestyle. This means that it is important to eat your green vegetables (especially spinach!) because they contains a lot of vitamin E, which helps your brain cells, and thus your brain, to stay in tip-top shape [10].

When your brain is performing at its best, it is more likely to recover from an injury. Junk foods like cheeseburgers, chips, and ice cream are good to eat on occasion, but it is important to remember that we need to keep our brains and bodies healthy. Exercise is also important for building your brain's resistance to injury [10]. You can go to the park to play with your siblings and friends a few times a week or play sports—wearing a helmet, of course!

CONCLUSION

Scientists have put a lot of time and effort into learning about how TBIs occur, their impact on the human body, and the ways we can better protect ourselves from TBI (such as better helmet design). Although there are multiple types of head injuries, all with different symptoms, the important thing to remember is that they all result in an imbalance of brain fluid, tissue, and blood within the skull.

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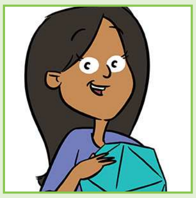
YOUNG REVIEWERS



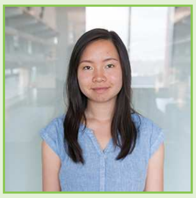
CAITLYN, AGE: 14
I like acting and singing! I love going to the movies with my friends. I go to a medical based school and want to be a psychologist.

CLEMENT, AGE: 13
I am an avid competitive fencer and orchestral violinist. That is all you need to know about me.

DANIEL, AGE: 10
Hi, I am Daniel and I really like cooking. I think cooking requires an open mind and that is useful in everyday life. I also play the saxophone. I enjoy it very much. I am also in Karate. A few days ago I found out that breaking a wooden board with a Karate strike is real and it is not only in the movies. Thank you for reading my bio.

MARILIA, AGE: 12
Hallo! My name is Marilia. I am in eighth class. I like to do sports, for example ice skating, rythmic gymnastics, and playing football. My favorite lessons in the school are biology, chemistry, sport, and Spanish. I enjoy to be with my friends and go swimming or watch a film with them. I have a small dog which I love!

AUTHORS



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NICOLE (NICO) OSIER

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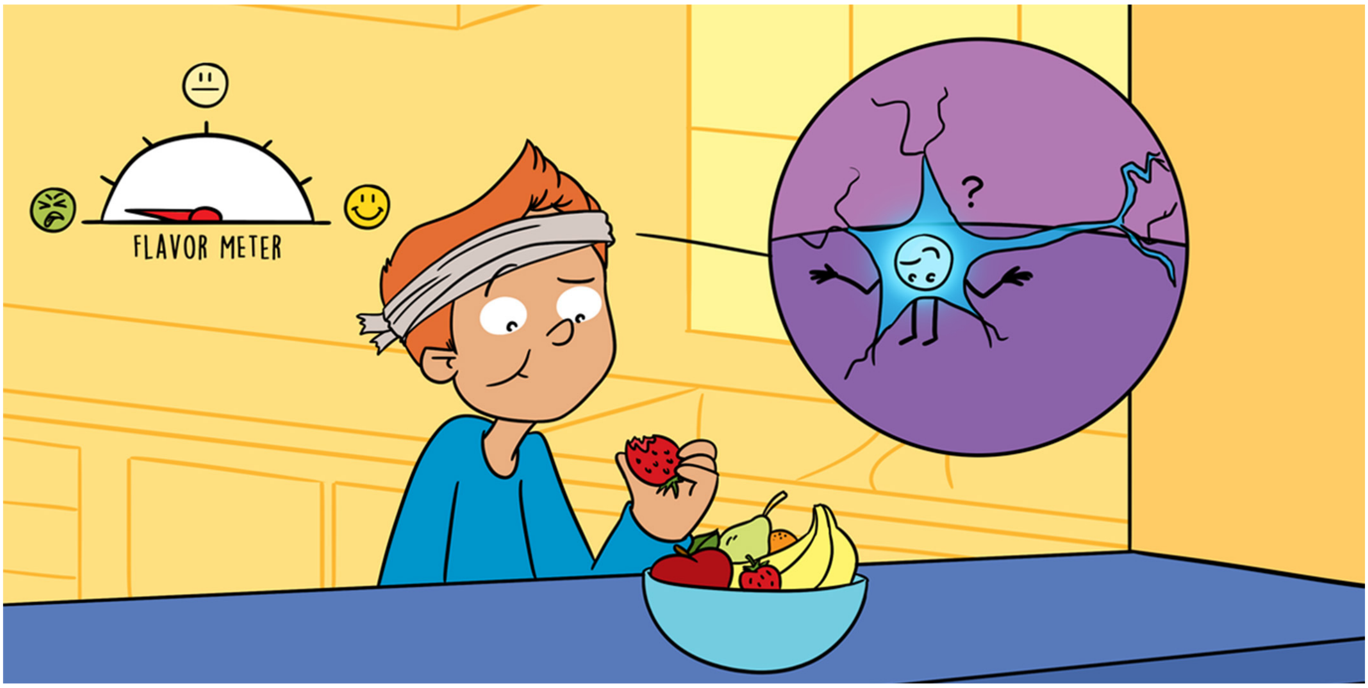

WHAT DO WE LEARN FROM STUDYING TRAUMATIC BRAIN INJURY?

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YOUNG REVIEWERS:

ELLA
AGE: 9

TOMOS
AGE: 12

A hard bump to the head can cause traumatic brain injury (TBI). Doctors treat more than 2 million Americans with TBI every year. Common causes of TBI are car crashes or hitting your head. Some TBIs are severe and some are milder. All TBIs can have serious effects, which include bleeding, brain swelling, or tearing of the brain's connections. It is important for researchers to study TBI, so that they can find ways to help those with a brain injury to get better. With this common goal in mind, scientists around the world are researching TBI. People with TBI often come to hospitals or clinics and some become part of research studies. TBI researchers follow athletes and military service members, too, because their activities increase the risk of TBI. In this paper, we review different types of TBI studies. We also discuss the groups helping scientists. We will also tell you how you could become a future TBI researcher!

Figure 1

Figure 1

A bump to the head while playing sports can cause a concussion.

TBI—WHAT IS THE BIG DEAL?

TRAUMATIC BRAIN INJURY (TBI)

A hit or jolt to the head that makes it difficult for the brain to work properly.

A **traumatic brain injury (TBI)** is caused by a hit to the head. This trauma makes it difficult for the brain to operate normally. Every hour, over 7,000 people worldwide experience a TBI [1]. It would take more than 100 school buses to carry them all! Some people are at higher risk for TBI. For example, TBI is more likely for babies and grandparents than parents. There are many causes of TBI. TBI can result from falling and hitting your head, or by something hitting your head with force. Jolting your head suddenly can cause a TBI as well. Car and other vehicle crashes are a common way people get TBIs, and you could also get a TBI from a crash on your bike or skateboard. Another common cause is playing sports, like soccer or football (Figure 1). Your head could collide with another player or with the ground while you are playing. Bomb blasts on the battlefield are a main cause of TBI for people in the armed forces.

WHAT HAPPENS TO THE BRAIN IN A TBI?

TBI can damage the brain in several ways, which is why one TBI can be very different from another. The injury could tear the skin or crack

Figure 2

Figure 2

Some TBIs result in a buildup of blood inside the skull, which can be very dangerous (Scientific Animations Inc. https://commons.wikimedia.org/wiki/File:Types_of_Intracranial_hematoma.jpg, Cropped by the authors to show subdural hematoma, https://creativecommons.org/licenses/by-sa/4.0/legalcode).

the skull at the site of impact. The damage to the brain might stay in one place or be spread across the brain. If blood or liquid builds up inside the skull, this can be very dangerous. Figure 2 shows a drawing of a head and brain and Figure 3 shows a brain scan of blood inside the skull after TBI. In Figures 2, 3, the red shows blood sitting inside the skull. This can be life threatening. A **neurosurgeon**, a doctor who performs surgery on the brain or spine, can stop the bleeding and fix the pressure building up in the brain.

Concussion means the same thing as mild TBI. The brain does not usually bleed after a concussion. The brain is made up of more than 60 billion **neurons**, which are very long nerve cells that send messages around the body using tiny chemicals [2]. A concussion can tear neurons or make it harder for neurons to work properly. The worse the injury, the longer it takes for the brain to return to normal. A TBI can damage the neurons that are responsible for senses like taste and smell. For example, a person might have a poor sense of smell after TBI.

NEUROSURGEON

A doctor who is trained to perform surgery on the brain or spine.

CONCUSSION

A mild traumatic brain injury, in which recovery happens within the first few weeks to months.

NEURONS

Brain cells that carry specialized messages.

HOW ARE PEOPLE AFFECTED BY TBI?

People can become unconscious, or "knocked out," for some time after a TBI. They might seem confused or have problems talking when they wake up. They will often not remember what happened to them. Recovery from a mild TBI can take a couple of days to a few weeks, and for some people with more serious TBI, it takes longer. Symptoms of TBI include difficulty thinking, remembering, or paying attention.

Figure 3

Brain scans can detect bleeding inside the skull after TBI.

Figure 3

Changes in the body, like headaches, feeling dizzy, or throwing up, are also common symptoms of TBI. Some people experience changes to their moods. They might feel more nervous or upset. To recover from a TBI, the injured person might need to stay home from work or school and take a break from sports, to let the brain rest. A doctor will be able to tell the TBI patient when it is safe to go back to these activities.

More severe TBIs have the potential for serious problems. These problems are often related to swelling and bleeding inside the skull. Emergency treatment for symptoms might be needed, such as help with breathing using a machine. Recovery from a moderate or severe TBI can take months to years. The symptoms of severe TBI can be very different from one person to the next, depending on the severity of the injury and the areas of the brain that are injured. In some cases, one side of the body may be in a paralyzed-like state, and the person may have a hard time moving his affected arm or leg. Therapists can help to re-train a patient's brain to control his or her limbs. Another common problem following TBI is difficulty with talking. Speech therapy helps patients with TBI communicate better.

WHY IS IT IMPORTANT TO STUDY TBI?

CLINICAL RESEARCH

The study of people or human tissue to better understand health and disease.

Clinical research is the study of people and how we function. This research aims to provide a better understanding of health and disease. Brain injury research is often about helping people with TBI. We want to understand exactly what happens to the brain after TBI so that we can develop better life-saving measures and prevent some of the serious consequences of TBI. Another important research focus is accurately diagnosing TBI, because a quick and accurate diagnosis allows doctors to act fast to help the injured person. Another goal of TBI research is understanding which kinds of treatments are best, and which things might help or harm a person during recovery. To study TBI, doctors often use brain scans, which can identify bleeding or other problems after injury. TBI researchers are always searching for new solutions, such as medicines and therapies, to help people make a good recovery after TBI.

WHAT IS TEAM-BASED RESEARCH ON TBI?

To study TBI, scientists work in teams made of different kinds of doctors. Each doctor can offer unique thoughts about how to set up the study. Scientists generally study three main groups of people with TBI. The first group is the general population, made of everyday people, like me and you, who might get injured. The second group is athletes who often get concussion from playing sports. The third group is military service members, because people in the armed forces are more likely to have a TBI when in combat.

The International Initiative for Traumatic Brain Injury Research (InTBIR) studies TBI on a global scale. This group includes countries in Europe, the U.S., and Canada. An example of an InTBIR study is called Transforming Research and Clinical Knowledge in TBI (TRACK-TBI). TRACK-TBI researchers see patients in clinics and emergency rooms right after their injuries. The researchers measure different forms of TBI, from mild concussion to coma. They follow up with the patients in the weeks to months after their injuries. The researchers want to see how things turn out for the patients after TBI. TRACK-TBI has made important discoveries about what happens to the brain after TBI, and they also have findings on the best ways to treat different forms of TBI [3, 4].

The National Collegiate Athletic Association and the Department of Defense have a study called the Concussion Assessment, Research and Education (CARE) Consortium [5]. CARE studies student athletes that attend U.S. colleges and military service academies. Before they start playing their sports, the athletes get tested for abilities that get worse after a concussion. Their abilities before they start playing sports are called the **baseline**. When athletes get concussions, they stop playing sports and their brain health is tested again several times, until they seem better. Then, CARE studies these tests to learn about the way the brain recovers from TBI. CARE answers important questions about how concussion affects the brain [5].

BASELINE

An athlete's abilities before the season starts, so that, if they get a TBI, researchers can measure their abilities again to see how they changed.

TRACK-TBI and CARE collect a variety of information about people and their TBIs, including details about the injuries and treatments. Researchers collect these data using brain scans, blood samples, brain function tests, and surveys. Helmet sensors can be used to measure how hard of a hit the athlete took. Did you know a concussion affects the movements of your eyes? Some sensors can measure eye movements, so researchers can track this information, too. Researchers are also exploring whether a person's genes play a role in recovery from TBI.

HOW MIGHT A PERSON BECOME A TBI SCIENTIST?

Do you want to become a future TBI researcher? Education is the most important step! To start, high school and college degrees are important. Most TBI researchers need lots of schooling to help build specialized skills. A medical degree or graduate degree is the most common. Other researchers choose a certificate program, such as one in clinical research. In these programs, students will often study research, the brain, or human behavior. Teachers and mentors train future scientists by working together with their students to prepare them for independent research. Formal programs are available to students interested in research [6]. Look for things like summer internships, which allow high school or college students to study science and practice research. You can learn about TBI on your own, too! Ask a librarian to help you search for scientific books or papers on TBI. Then read about the current TBI research that is being done. This will help you to better understand what studies you could explore next! Find something you are interested in. Then, reach out to the people doing that work. Tell them how interested you are and ask them if you can come visit or be involved with their research team. You never know where it might lead!

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YOUNG REVIEWERS

ELLA, AGE: 9
Hi, my name is Ella. I just started fourth grade and I really like it. I do gymnastics and am on the competitive team for Ninja Warriers.

TOMOS, AGE: 12
I am 12 years old and at high school in Scotland. I really enjoy STEM subjects but also history and politics. My hobbies are cricket, football stats, and watching TV.

AUTHORS

KRISTIN WILMOTH
I am a post-doctoral fellow in neuropsychology at the Medical College of Wisconsin. I earned my Ph.D. from the University of Texas Southwestern Medical Center in Dallas, where I also completed my internship training. I completed my dissertation on sport-related concussion in youth athletes. In addition to my clinical and research duties, I have enjoyed being involved in several professional organizations for

neuropsychology and brain injury. I love my work, but I also like to sing, volunteer, and travel to new places!

MICHAEL MCCREA

I am a professor in the Department of Neurosurgery at the Medical College of Wisconsin. I am an active researcher in the study of traumatic brain injury. I earned my Ph.D. from the University of Wisconsin–Milwaukee. Then I completed my internship training in neuropsychology at Vanderbilt University School of Medicine, followed by a post-doctoral fellowship in clinical neuropsychology at Northwestern University Medical School. I have served on several international expert panels related to research and clinical care for TBI. *mmccrea@mcw.edu

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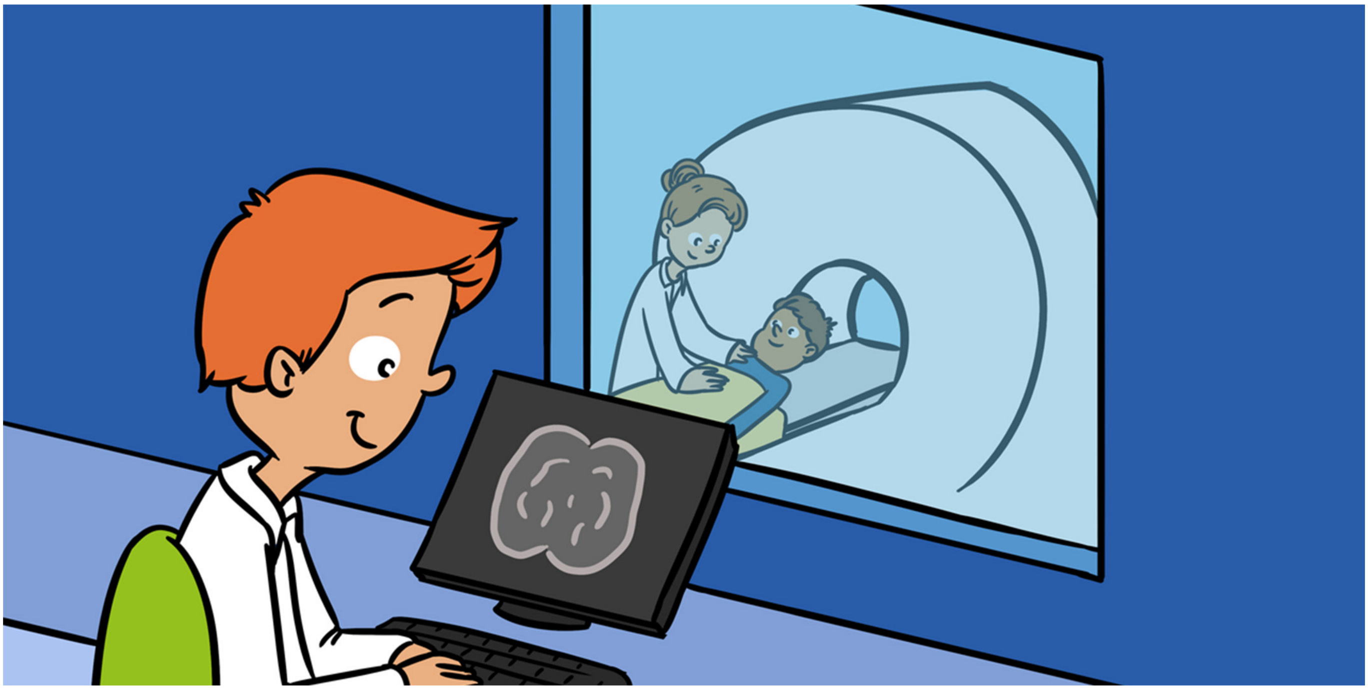

HOW TO SEE INTO THE BRAIN WITHOUT SURGERY!

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YOUNG REVIEWERS:

LAGUNA BLANCA
AGES: 14-16

Did you know that doctors look at the brains of thousands of people every day? In hospitals all over the nation, we are looking into patients' brains to see if something has gone wrong, so we can understand how to help treat each patient's condition. Brain imaging technology plays an important role in helping doctors diagnose and treat conditions like brain injuries. Behind the scenes, there are special cameras that allow us to see deep inside of the brains of patients every day.

INTRODUCTION

The field of medicine that is focused on capturing and analyzing images of the brain and all parts of the body is called radiology. The name radiology comes from the first type of "camera" or technology that was used to take these pictures, called the X-ray machine, which uses radiation. The word radiology was derived from the word parts "radio," for radiation, and "ology," from the Greek suffix meaning the scientific study of something. The invention of the X-ray is credited to German

Figure 1

Figure 1

An X-ray of the hand of Anna Ludwig taken on 22 December 1895 by her husband Wilhelm Röntgen. This is thought to be the first medical X-ray (Image credit: Otto Glasser, Wilhelm Conrad Röntgen and the early history of the Roentgen rays. London, 1933. National Library of Medicine).

mechanical engineer Wilhelm Conrad Röntgen who, in 1895, generated and detected the electromagnetic radiation that became the basis of the X-ray technology we still use today. In Figure 1, you can see the bones of Röntgen's wife's hand, thought to be the first X-ray image of a human body part. You can see the different finger bones, called phalanges, and a dark blob on the ring finger, which is her wedding ring. If you have ever broken a bone, you likely had an X-ray to determine where the break occurred.

HOW DO DOCTORS LOOK INSIDE THE BRAIN?

When a patient has a brain injury, one of the first things radiologists do in the emergency department of the hospital is to use a special kind of "camera," called a **computed tomography (CT)** scanner, to look at the patient's brain. The CT scanner, as it is known for short, is a machine that allows doctors to see into a patient's brain without surgery. The CT technology uses small bursts of radiation that pass through the body, similar to X-rays, and create different signals depending on the type of tissue they pass through, be it skin, bone, brain, or other tissue types. All of these signals are collected by a computer, which reconstructs them to form a three-dimensional image of the brain that the radiologist can analyze on a computer to look for injuries. The main difference between CT and X-ray is that X-ray just creates a single, two-dimensional image, similar to a picture you would take with your cell phone. While both the X-ray and CT can collect images in a matter of seconds, both techniques use radiation, and repeated radiation exposure can increase one's risk of various cancers. Radiology has even

CT

Computed tomography.

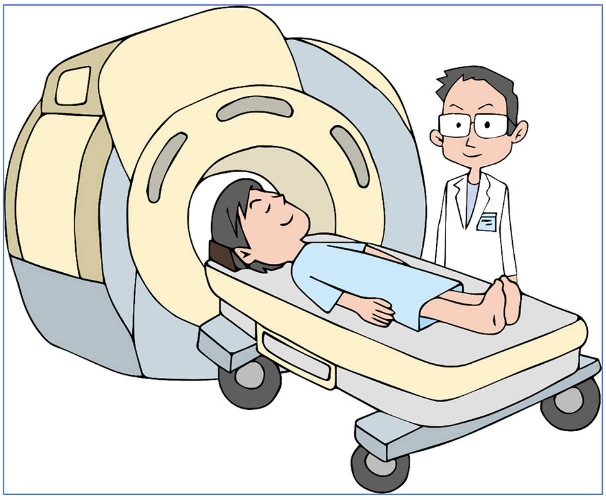

Figure 2

Figure 2

A patient being placed into a magnetic resonance imaging (MRI) scanner.

gone so far as to engineer what are called "low dose" CT scanners, used most often at children's hospitals, to try to reduce the amount of radiation young patients are exposed to.

MRI

Magnetic resonance imaging.

In addition to CT scans, another imaging technology called **magnetic resonance imaging (MRI)** can also be used to look inside the brain. MRI scanners use very strong magnets to look at the brain by using the "excitability" of the water molecules in our bodies. When we are young, our bodies are made up of 70–80% water and as we age, that proportion goes down to 50–60%, so there is a lot of water in our bodies to help with this kind of imaging! The magnets that MRI scanners use are measured in a unit called Tesla (T). These are very strong magnets, much stronger than the earth's magnetic field, which measures between 25 and 65 microTesla (μT, one millionth of a Tesla). The magnetic strength of clinical MRI scanners is 1.5–3 Tesla, 30,000–60,000 times stronger than the earth's magnetic pull! Because of these strong magnets, all patients are carefully screened for metal or implantable electronic devices, like cardiac pace makers, before they are put into an MRI scanner because the magnets could excite these materials and potentially cause harm to the patient. To date, no safety concerns have been identified with repeat MRI, as long as the patient does not have any MRI-incompatible devices or materials in his or her body.

For brain imaging with CT and MRI, the patients are most often asked to lie on their backs and then they are placed in the scanner, which is built like a tube. When imaging the brain, the patient's head is placed in the center of the tube where the machine has the best, most uniform, imaging strength (Figure 2).

COMMON BRAIN INJURIES THAT NEED IMAGING

Following a traumatic brain injury, there are various kinds of damage to the brain that imaging technologies can help doctors to see. Good imaging methods that let doctors see the entire brain are very important, in order to figure out exactly how the brain has been injured. The most common injuries are small bleeds in the brain, called microbleeds or microhemorrhages (see Figure 3), meaning a small ("micro") escape of blood from a torn blood vessel ("hemorrhage"). If you get a nosebleed, this is also a form of microhemorrhage—of the nasal membrane. The brain needs a continuous supply of oxygen from the blood to perform its everyday functions. The oxygen travels to the brain via blood vessels that come in a variety of sizes, from large arteries down to tiny capillaries. The smaller vessels are thought to be particularly vulnerable to brain injury, because they can stretch and compress as the brain gets jostled around in the skull during an injury. On a CT scan, these microhemorrhages look different from the surrounding brain tissue and have a clear "signature" as the blood pools in the area (see arrows pointing to dark dots in the left panel of Figure 3). MRI scanning is a more sensitive way to identify these microhemorrhages and other types of brain injury [1], but MRI takes longer than CT, so when there is severe trauma, CT is still more commonly used to get a quick image of what is going on in the brain. Another strength of MRI over CT is that it can be used to take different kinds of pictures, whereas the CT only takes one type of picture. With MRI, we can control the magnetic excitation properties of the molecules in ways that change the contrast on the images we collect. Where one type of MRI image may make blood show up brightly, another may make it show up dark, and these differences in contrast help radiologists more confidently determine that they are seeing something abnormal in the brain, like blood, or bruises to the brain tissue from an injury.

Another common brain injury is called a contusion (see arrows pointing to the bright spot in the lower left of the center panel in Figure 3), which is a bruise on the brain due to trauma. Like bruises that you get on your arm or leg from a fall, a brain contusion often includes a collection of

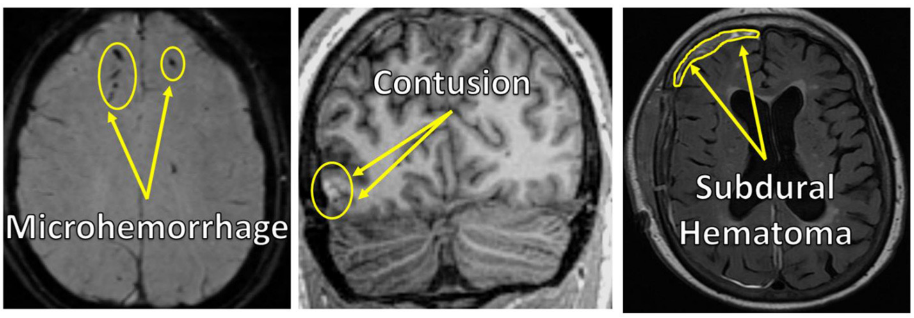

Figure 3

MRI images of brain injuries. Left to Right: microhemorrhage, contusion, subdural hematoma.

bleeds in a localized area. Unlike a bruise on your arm or leg, which heals over time, leaving no mark of the injury, brain contusions and the damage to the neighboring brain tissue can be more permanent. Looking inside the brain using CT or MRI imaging allows doctors to visualize brain contusions, which helps doctors determine how best to diagnose, treat, and care for patients with traumatic brain injury.

In addition to microhemorrhages and contusions, there are a variety of traumatic brain injuries that occur in what is called the "extra-axial space." The extra-axial space is the space between the surface of the brain and the inside of the skull. There are different compartments of the extra-axial space, called the subdural (see arrows pointing to the bright band in the upper left of the right panel in Figure 3), epidural, or subarachnoid extra-axial spaces. These compartments consist of different layers between the brain and the skull and they contain a variety of blood vessels that can break open, causing a pooling of blood termed hematoma. Hematomas most often occur with more severe head injuries that happen at a greater force and acceleration.

Lastly, just like with an ankle sprain, the brain can also swell following an injury or can contain a region of pooled fluid, which is called "edema." Doctors rely heavily on CT and MRI imaging to monitor the brain for edema because, unlike a sprained ankle where the skin can expand a bit as swelling occurs, the skull is a very stiff bony structure that does not expand when the brain swells, which may cause additional damage if the brain swelling is not treated quickly.

CONCLUSION

Advances in technology play an important role in the ability of doctors to diagnose and treat head injuries in a team approach. From emergency medicine physicians who make the initial evaluations, to radiologists who review and analyze the brain images, to neurosurgeons who may operate on a patient's brain, there is a diverse team of doctors who work together to provide the best treatment possible to each patient. And behind the scenes, there are these "special cameras," CT and MRI that allow them to see inside the brains of thousands of patients every day.

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YOUNG REVIEWERS

LAGUNA BLANCA, AGES: 14-16
Students enrolled in their first year of a 2-years science research program. Everyone in class has a different area of interest, so no matter what authors submitting to Frontiers of Young Minds write about, we would always be up for offering our input.

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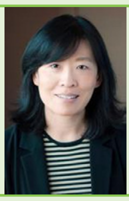

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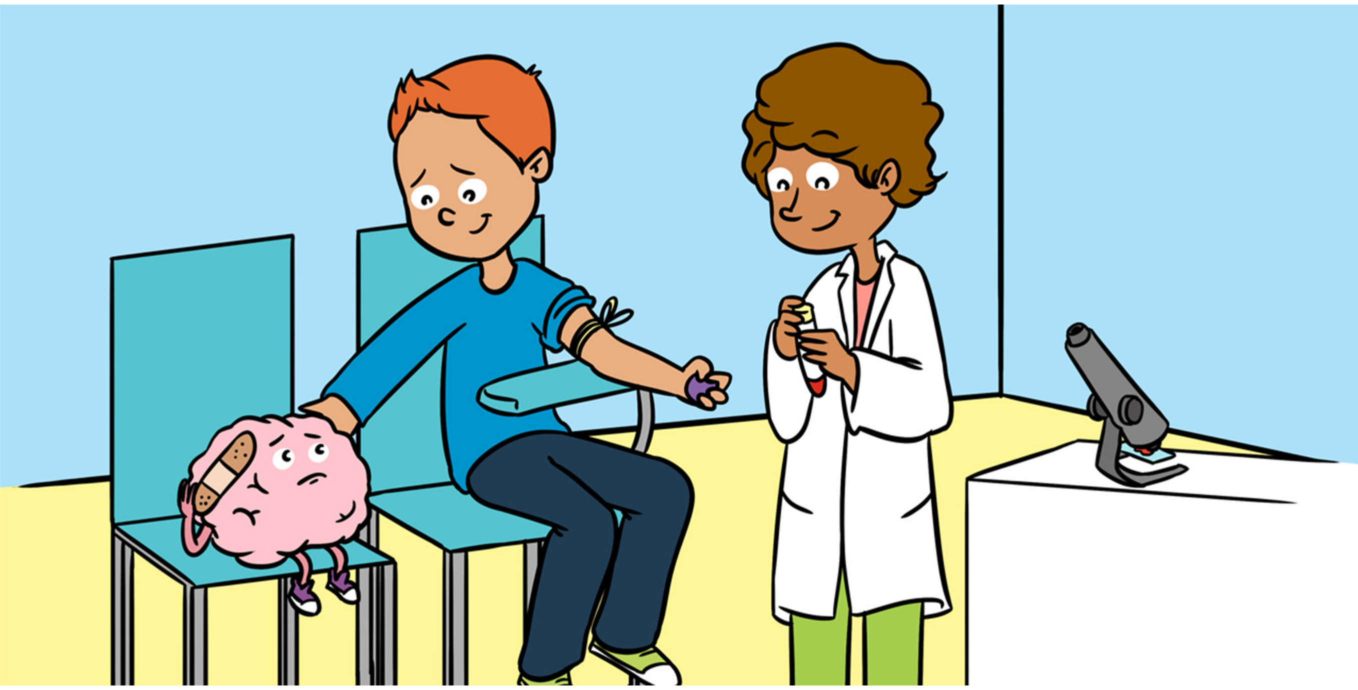

STUDYING BRAIN INJURY THROUGH THE BLOOD: THE PROMISE OF BIOMARKERS

Stephany Kim[1,2], Preston Klein[1,2], Mindy Nguyen[1,2] and Nicole Osier[1,2]*

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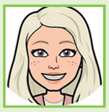

BRITT
AGE: 14

Scientists and doctors are trying to identify and develop new and better ways to diagnose brain injury, because brain injuries are hard to detect. Even when a brain is known to be injured, it is hard to treat. This is unfortunate, because traumatic brain injury (TBI) is the most common brain disorder in children. One of the ways to detect TBI is by looking at biomarkers in the blood. Biomarkers, ranging from protein to DNA, help scientists determine whether a part of the body is damaged. Different injuries produce different biomarkers, giving us information on the severity of the injury; and other biomarkers provide clues regarding injury location. Scientists are hoping to use these biomarkers in the blood to see how likely children with TBI are to have a good or bad outcome, and, more importantly, how doctors can better treat children for these injuries.

WHAT IS TRAUMATIC BRAIN INJURY (TBI)?

TRAUMATIC BRAIN INJURY

Physical trauma to the brain that can affect thinking and cognitive abilities.

Traumatic brain injury (TBI) is one of the most common brain disorders in children. TBI often occurs due to a strong blow to the head from getting hit by an object, running into an object, or falling on one's head. TBI can be very dangerous because it can severely damage the brain, which is critical for controlling the body and the personality, as well as speech, movement, and much more. Depending on what part of the brain is hurt, there can be serious consequences. Because of this, it is important to be able to diagnose a TBI as soon as it happens.

HOW DO WE CURRENTLY STUDY THE BRAIN AND WHAT ARE THE LIMITATIONS OF THESE METHODS?

When the brain is damaged, the consequences of the injury can be very serious. However, studying the brain is difficult, because the brain is enclosed in the skull. Therefore, it is hard to tell whether or not there is injury and how severe it is. Currently, the most common way to look inside the brain is through a process called imaging, with several types of images giving us different insights into the brain. Think of the different types of options on a camera. A panorama gives you a wide picture of what is happening. Other times, you take a video, so you can document the event in real time. Similarly, different imaging methods give us different information about brain injuries. The two most common types of imaging used on patients with TBI are shown in Figure 1.

Although imaging is currently the most used technique for diagnosing TBI, there are quite a few problems with these methods. First, the images often fail to detect problems in the brain after an injury. Moreover, medications, blood sugar levels, or even changes in the

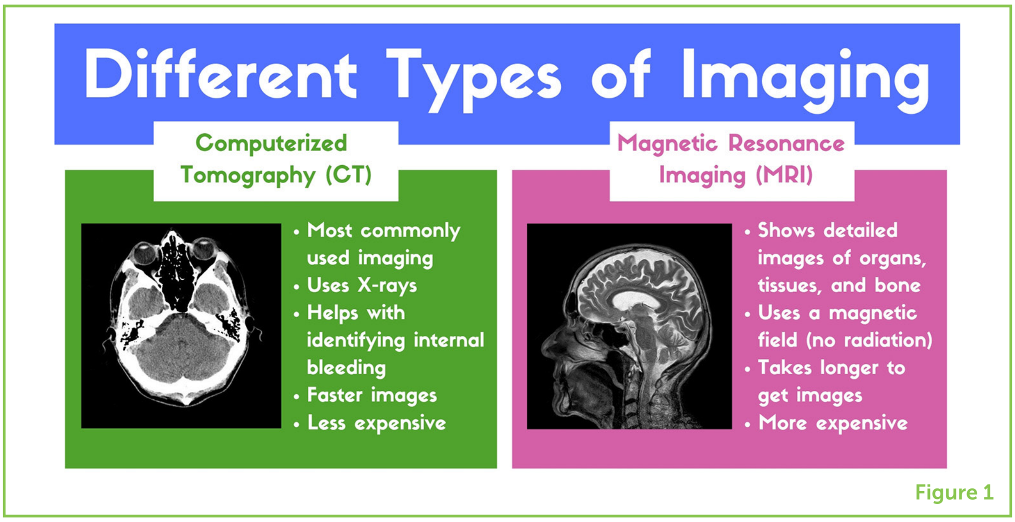

Figure 1

Two of the most commonly used imaging techniques for patients with TBI. (CT image: https://www.flickr.com/photos/ciscel/124548696/; MRI image: https://pixabay.com/en/mri-magnetic-x-ray-skull-head-782459/)

patient's emotional state can affect brain activity. This in turn can lead to inaccurate readings that look like a brain injury, leading to false conclusions. This is important, considering the second drawback: the fact that imaging is very expensive! The average cost to run scans can be a couple thousand dollars! Because of this, it is important for hospitals to minimize the number of scans that show no injuries, often referred to as negative scans. Also, because many of these methods essentially take pictures of the brain at a given moment in time, it is difficult to see how an injury develops, improves, or worsens over time without doing additional scans and spending more money [1]. And of course, some kinds of imaging, like CT scans and PET scans, use radiation or radioactive substances to look at the brain, and radiation is associated with a small risk of developing cancer.

WHY IS USING THE BLOOD A WORTHWHILE WAY TO STUDY THE BRAIN?

So, why are scientists looking at blood as a way to study brain injury? The first reason is that blood is easy to obtain from patients, using an IV line or through a simple blood draw from a vein in the hand. Since patients typically give blood to test for levels of other molecules in the body, such as glucose or iron, a blood test is an easy way to look for other markers in the blood that may tell us more about the brain injury. Second, drawing blood is a low-risk procedure, with the main risks being bruising, pain, and infection. Last, drawing blood is an inexpensive method for research and diagnostic tests! Compared with the thousands of dollars spent on expensive imaging, blood tests are a more affordable means of diagnostic testing, both for the hospitals and the patients.

WHAT CAN WE MEASURE IN THE BLOOD?

A **biomarker** is a molecule that can be analyzed to reveal information regarding the biological processes that are happening in the body [2]. For instance, your blood level of glucose is a biomarker that tells doctors if you are at risk for diabetes. Since diagnosing TBI quickly gives patients a better chance of recovery, discovering biomarkers that can be used to rapidly diagnose TBI would be extremely helpful. The three potential types of biomarkers being researched for diagnosing TBI are proteins, DNA/RNA, and **exosomes** (Figure 2).

Protein biomarkers are one of the most commonly studied [3]. Following TBI, the levels of certain proteins can increase or decrease, as a result of changes happening within brain cells that have been injured. Scientists can measure the levels of those specific proteins in a person's blood,

BIOMARKER

A biological molecule within the body that can be measured. Data from the presence and levels of biomarkers allows scientists to detect abnormalities and diseases in a patient.

EXOSOME

Vesicles that are released from cell and can travel through various bodily fluids. An exosome can contain molecules that indicate which cell it came from and what was happening in that cell.

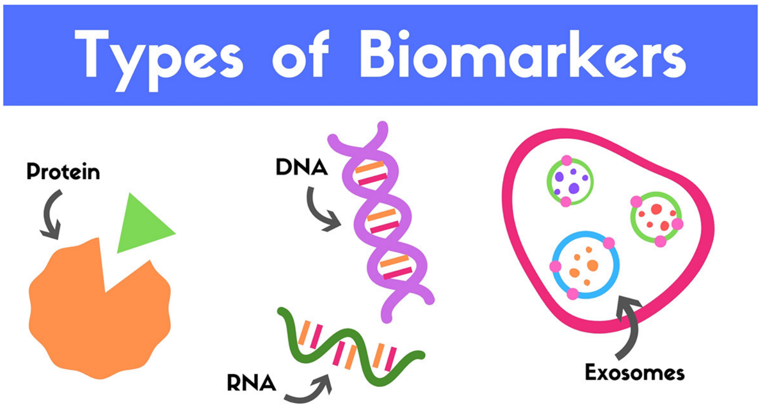

Figure 2

Figure 2

Biomarkers that are often used to detect TBI. Deoxyribonucleic acid (DNA) is the genetic material that tells each of our cells how to make all the proteins it needs. When cells are in the process of making proteins, DNA is first used to make ribonucleic acid (RNA). Both DNA and RNA can be used as biomarkers, as can the proteins they code for. An exosome is essentially a bubble (shown in blue and green) that is stored inside a cell with other exosomes, in a larger structure called a multivesicular body (shown in pink); each exosome contains various proteins, RNAs, and other molecules (as depicted in orange, red, and purple) that can be released outside the cell, often as a form of cell-to-cell communication.

saliva, urine, or other body fluids. Abnormal levels of these proteins can tell us if the patient has a TBI and how likely the patient is to recover. Despite progress, researchers are still searching for the ideal protein biomarker for TBI. Since many protein biomarkers are produced by other cells in addition to brain cells, it is difficult to use those protein biomarkers as definite indicators of brain injury. The different **half-life** of proteins also makes it difficult to reliably measure the levels of a specific protein. Half-life refers to how long it takes for the level of a protein to decrease by 50%. Some proteins break down quickly in blood, making them difficult to use for biomarker studies.

HALF-LIFE

The amount of time required for a substance to decrease to half of its initial level.

DNA and RNA are other types of biomarkers being studied. DNA is the molecule that makes up our genetic blueprint, and it is used to make RNA, which is then used to make proteins. The fact that DNA, RNA, and proteins are all related means that all three are potential biomarkers that can tell use slightly different things. As an example, damage to the brain can increase the production of certain proteins, including a protein called calcineurin. Interestingly, some people have slightly different versions of the calcineurin gene that are associated with worse outcomes following TBI [4]. If we can figure out which gene versions are associated with recovery from TBI, we may be able to discover new methods for diagnosis and treatment.

While DNA and proteins are promising potential biomarkers, we cannot really be sure whether they come from the brain or not, since all our cells contain DNA. This uncertainty has led scientists to use something called exosomes as biomarkers. Exosomes are a type of structure called extracellular vesicles (EVs), which are a hot topic in research [5]. Exosomes are stored inside cells in groups called multivesicular bodies, which are like bubbles that fuse with the plasma membrane, releasing the contents (the exosomes) outside of the cell (Figure 3). Think of the plasma membrane as the wall of a balloon. Since each cell has its own unique protein markers, when the multivesicular bodies fuse with the

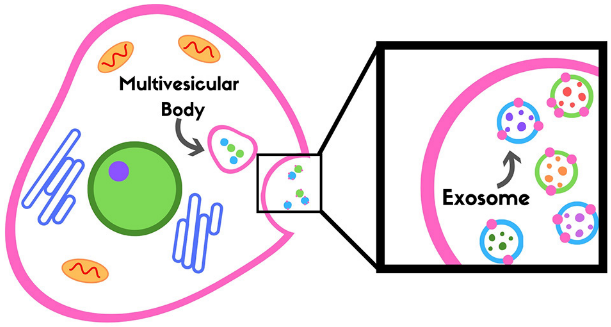

Figure 3

Figure 3

Exosomes are stored in a multivesicular body and released outside of the cell into the blood. Exosomes can show us what is happening in a particular cell type, because when they are released, they pick up pieces of the membrane from that cell (shown as pink dots on the outside of the blue and green exosomes in the black box, which have been released from the cell).

plasma membrane, the exosomes pick up these markers from the cell membrane. As a result, these markers tell us which type of cell the exosome came from and what was happening in that cell. In TBI, the markers present in exosomes might help us to understand what is happening in brain cells following brain injury.

EXAMPLES OF BIOMARKERS USED TO DETECT TBI

Researchers continue to study many biomarkers to see which ones might be the best for diagnosing TBI. Here are just a few of the potential TBI biomarkers and what they might tell us about brain injury.

GFAP is a protein biomarker that is found only in the cells of the brain and spinal cord. It is a structural protein, meaning it helps the cells maintain their shape. After brain injury, GFAP is released from damaged cells and it gets into the blood, where it can be measured in blood samples. GFAP increases in blood shortly after TBI and gradually decreases over time. GFAP may be helpful in determining how well patients will recover from TBI over time [6].

CYTOKINE

A general name for proteins of the immune system that participate in cell communication and affect how other cells behave.

Another protein biomarker that shows potential is a group of proteins called **cytokines**. Cytokines are released by the immune system after brain injury. Two cytokines that have shown promise in TBI research are called IL-10 and IL-6. One study found that patients who did not recover well from TBI had IL-10 levels about three times higher than patients who recovered well [7]. IL-6 has been shown to be beneficial immediately following TBI, but if the level of IL-6 stays elevated for too long, it can actually harm patient recovery [8]. Further research with IL-6 may allow us to track how well a patient is recovering after TBI.

Studies using DNA and RNA biomarkers have shown us that variations in certain genes, like one called PPP3CC, might predict how well a patient will recover from TBI [4]. This is promising, because DNA is easily accessible through the blood or saliva.

Currently, scientists are researching new ways to use exosomes to detect certain proteins or biomarkers in the blood. In one study, mice were exposed to mild or moderate TBI. When the researchers obtained exosomes from the brains of the mice, they observed that these exosomes had lower levels of certain RNA sequences and higher levels of other RNA sequences. Through these experiments, we can see the promise of using exosomes as a means of TBI diagnosis.

CONCLUSION

The recent attention that biomarkers have been receiving these past couple of years may lead to the identification of the first effective treatment for TBI! As we learn more about the brain and how it recovers from injuries, our hope is that we will be able to find better and faster ways to diagnose brain injuries and ultimately discover new methods to treat them. In the meantime, keep your brains safe and protected!

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YOUNG REVIEWER

BRITT, AGE: 14

Hey! I am Britt. At the moment, I go to Beacon Academy, a Montessori and IB high school. At school, I love Math, Science, and Spanish class. I also love doing dance, cheer, choir, and playing ukulele!

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I am a graduate of the University of California Los Angeles (UCLA) with a Bachelor of Science in Physiological Science and a Bachelor of Arts in Russian Language and Literature. Currently, I am pursuing a career in medicine, with hopes of specializing in either neurosurgery or cardiothoracic surgery. In my free time, I enjoy backpacking, snowboarding, reading, and, of course, searching for potential biomarkers.

PRESTON KLEIN

I am currently an undergraduate student at The University of Texas at Austin, pursuing a Bachelor of Science in Human Biology. After completion of this degree, I plan on attending medical school. In my free time, I enjoy running, reading, and exploring my local community.

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I am currently an undergraduate student at The University of Texas at Austin, pursuing a Bachelor of Science and Arts degree in Neuroscience with a minor in Forensic Science. I plan to attend graduate school to become a Physician's Assistant and specialize in Neurosurgery. When I am not in the lab or studying, I am out taking photos and adventuring in Austin, or playing tennis.

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I am a Principal Investigator at The University of Texas at Austin. I have a Bachelor's Degree in Nutritional Science and Nursing from Michigan State University and a Ph.D. from the University of Pittsburgh. My goal is to understand what makes some individuals recover better than others after head injury and apply this information to help doctors and nurses treat it. To learn more about my laboratory, visit my website: https://nicoleosier.wixsite.com/osierlaboratory/. In my free time I enjoy spending time with my spouse and cats and traveling the world. *nicoleosier@utexas.edu

frontiers FOR YOUNG MINDS

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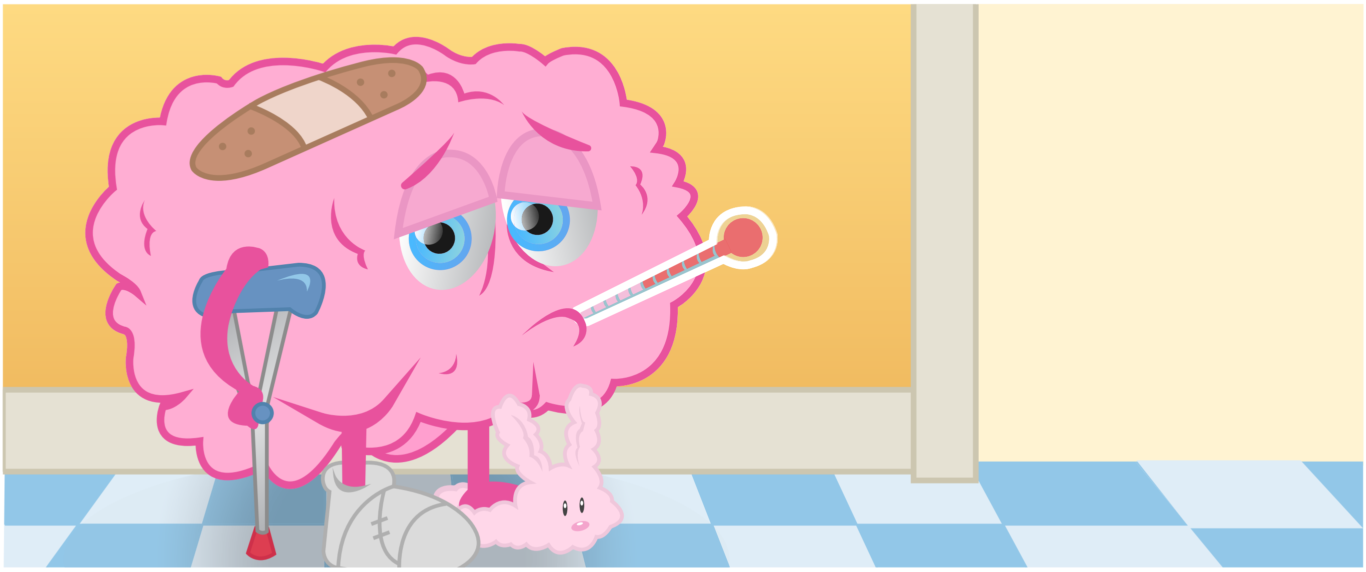

WHY DOESN'T YOUR BRAIN HEAL LIKE YOUR SKIN?

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[1]University of Western Ontario, London, ON, Canada, [2]McGill University, Montreal, QC, Canada

REVIEWED BY:

TRAFALGAR SCHOOL FOR GIRLS
12–13 YEARS OLD

Skin wounds like scrapes and cuts may be painful, but they usually heal perfectly. Worst case scenario, you may be left with a scar. In contrast, when the brain gets injured, we are often left with disabilities that stay with us for the rest of our lives. What is so different about the brain, and how does it repair itself? Brain cells face unique challenges when they get injured, for example, by a concussion or a stroke. And to cope with these challenges, the brain has an ingenious strategy to deal with injury.

THE BRAIN IS SUPER VULNERABLE

Your *brain* and your **spinal cord** together form what we call the central nervous system. Looking at a skeleton, have you ever asked yourself why the brain and spinal cord are the only organs in our body encased in bone? True, the lungs and the heart are also well protected by the rib cage. But when you look at the skull, it is basically a bony box with a few holes in it to let nerves leave the brain. The nervous system is unique compared to many other organs in that it does not expand or contract like your heart, lungs, and intestines do. Because there is no major movement, it is alright for the central nervous system to be entirely encased in bone. Why is the central nervous system so well protected? The answer is simple: because it is super sensitive and very vulnerable.

SPINAL CORD

The part of the central nervous system that sits in your spinal column, the bony structure along your back. The spinal cord is mainly responsible for picking up all kinds of feelings from your body and sending it to the brain for processing, as well as for sending movement commands from the brain to your arms and legs.

Which organ of your body do you think you're injuring most often? Probably, your skin. Think about a time when you fell, your skin broke open and you had a wound like a scrape or a cut for some time. If this injury happened a while ago, chances are you won't even see the spot on your skin any more. Or maybe you can see a scar, but basically your skin was able to repair itself almost perfectly. Unfortunately, the brain and spinal cord are fundamentally different. If your brain gets injured, some damage may persist throughout the rest of your life.

WHY CAN'T THE BRAIN REPAIR ITSELF LIKE YOUR SKIN CAN?

NERVE CELLS DO NOT RENEW THEMSELVES

Your skin cells keep dividing, they die and give birth to new cells all the time, even when you're not injured. After an injury, the skin makes a bunch of new cells and uses them to heal your wound. Yet, nerve cells in your brain, also called **neurons**, do not renew themselves. They do not divide at all. There are very few exceptions to this rule – only two special places in the brain can give birth to new neurons. For the most part though, the brain cannot replenish dead neurons. This is especially worrisome because neurons are very sensitive cells and they die for all sorts of reasons. When you bump your head and suffer a **concussion**, neurons die. When there is a glitch in the blood supply to the brain, also called a **stroke**, neurons die. Neurons also die when faced with changes in their own functions, which happens in the so-called **neurodegenerative diseases** like Parkinson's disease and Alzheimer's disease.

Here is the good news. Because loss of neurons is usually permanent, scientists are working on two important strategies to help the brain after injury. One way is to protect the nervous system immediately after the damage occurs. This damage could be a stroke, a severe concussion, or any kind of injury. If we can somehow limit the number of neurons that die early after injury, then we are keeping the damage to a minimum. To help with repair later on after the injury, after the damage is done, some scientists are trying to use **stem cells** as a treatment for neuronal loss in the brain.[1] These stem cells are young and immature cells that have not developed into "professional" cells yet. They have the capacity to develop into brand new neurons if scientists treat them with special molecules. This is a little like elementary school students who are not doctors or plumbers yet, but they have the capacity to become any professional in the future, given the right training. The biggest challenge with replacing dead neurons with stem cells is to have these newcomer neurons integrate, or fit into, the existing brain networks the right way. The new neurons can't just hang out in the brain, we need

[1] http://www.eurostemcell.org/commentanalysis/stem-cell-therapies-and-neurological-disorders-brain-what-truth

NEURONS

Nerve cells in the brain that receive signals from other nerve cells, process them, and then send along new signals to different nerve cells. This network of connected neurons is the basis of all the work that the central nervous system performs so you can think, move, and feel things.

CONCUSSION

A concussion happens when you hit your head hard and your brain bumps against your skull. If you have a bad concussion, you may see stars in front of your eyes, you may not remember what day it is, and you may feel nauseous.

STROKE

A stroke happens when the blood supply to a brain region is damaged. The nerve cells in that region die off quickly if they stop receiving essential things like sugar and oxygen from the blood.

NEURODEGENERATIVE DISEASES

A disease where neurons die off (or degenerate, which means they die) because they cannot deal with the challenges they face. Most of these challenges are complicated chemical processes.

STEM CELLS

Immature cells that have not developed into "professional" skin cells, or nerve cells, or any other cells in your body yet.

them to form connections with other cells and do the job that all neurons do: process signals.

NERVE CELLS HAVE TROUBLE REGROWING DAMAGED PARTS

Looking at the structure of a neuron, you will notice it has a cell body and several arms that it uses to connect and talk with other neurons (Figure 1, left). The really long arm that sends signals to other neurons is called *axon*, and axons can be really long. If an axon is damaged along its way to another cell, the damaged part of the axon will die (Figure 1, right), while the neuron itself may survive with a stump for an arm. The problem is neurons in the central nervous system have a hard time regrowing axons from stumps. Why do skin cells not have this problem? Skin cells are much simpler in structure. And because they can give birth to entirely new cells, they don't face the problem of having to repair parts of their cells.

So, why do damaged neurons have trouble regrowing axons?

First, they need motivation. There are special molecules that help activate growth in neurons. More of these motivating molecules are made when the neurons are active. So, if you keep your brain active, your neurons are more likely to grow. This is true both after injury and in the healthy brain.

Second, axons face a hostile environment that is full of molecular "stop signs" that signal "no trespassing" to axons. Some stop signs are part of the sheath, or covering, around neighboring axons, called **myelin sheath** (Figure 1, left). Some stop signs are part of a scar that gets built like a protective wall around an injury in an effort to keep the damage from spreading. These

STEM CELLS (CONTINUED)

They have the capacity to develop into any cell in your body, and their future "profession" is determined by what molecules they encounter as they mature. They can develop into any professional cell, including neurons, when scientists treat them with specific molecules.

MYELIN SHEATH

A fatty covering that envelops axons to make signals travel along axons as fast as possible. For example, this sheath is what allows you to react quickly when you hurt yourself, such as pulling back your hand from touching a hot stove top.

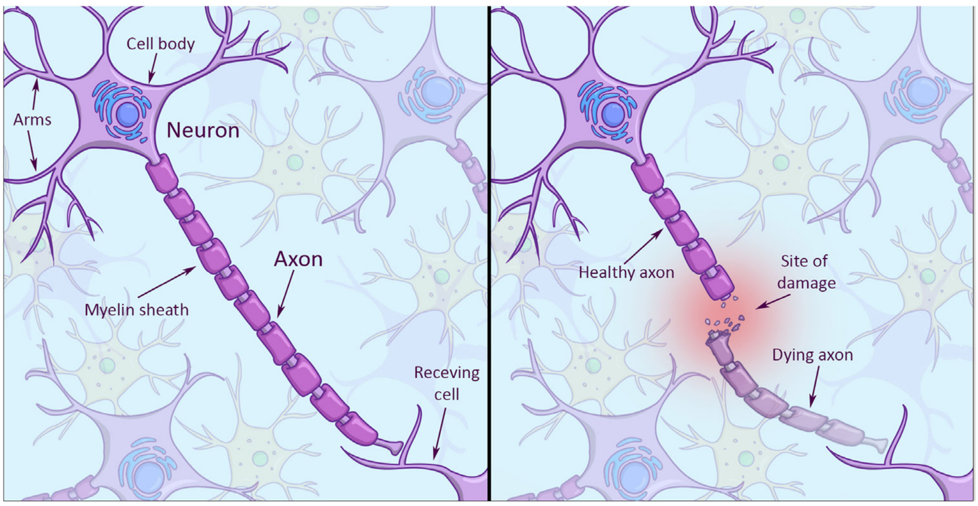

FIGURE 1

FIGURE 1

Left: the structure of a brain cell. Note the branch-like arms that extend from the cell body (top left corner). These arms receive incoming signals. The really long arm that extends to the bottom right is called the axon, which sends signals to a receiving cell. The axon is enveloped by a myelin sheath (in darker violet), which helps signals travel faster along the axon to the receiving cell. Right: when an axon gets injured, the end part dies off and leaves an axon stump. Stumps have a hard time to grow back after injury.

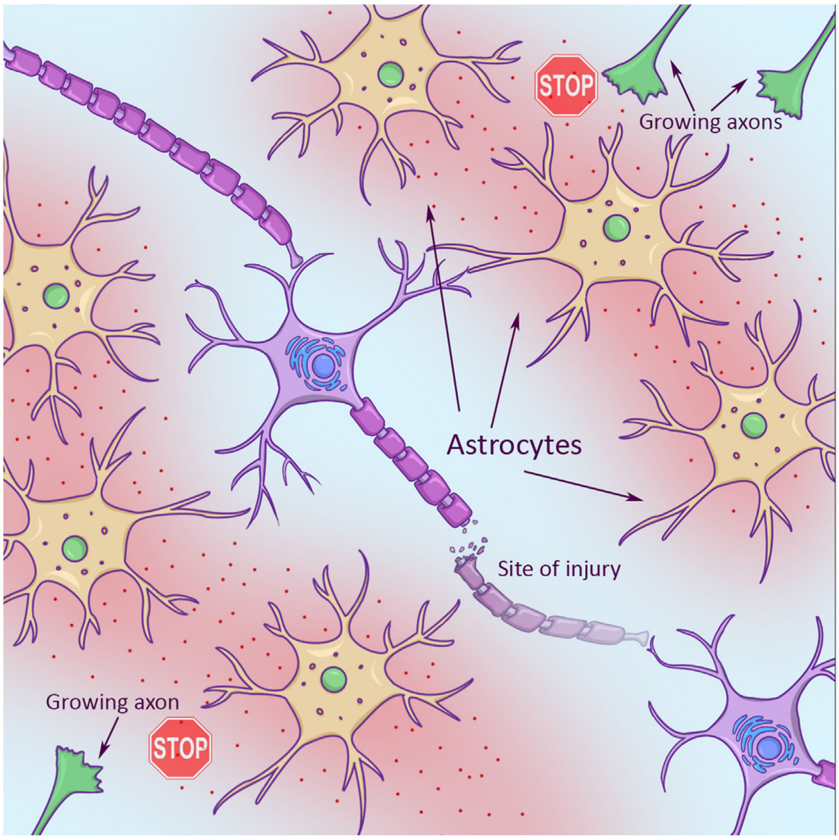

FIGURE 2

FIGURE 2

Growing axons (green in top right and bottom left corners) looking for new target cells to connect with have a hard time in an injury environment. This is partly due to star-shaped support cells (astrocytes, in yellow), which spit out chemicals (red). These chemicals stop axon growth.

ASTROCYTES

Translates into "star cells," due to the star-like shape of these cells. Astrocytes are support cells in the brain that are very different from neurons. They support neurons in many ways, such as by keeping harmful molecules away.

scars are made by brain cells called **astrocytes** (star cells, due to their star-like appearance). Scar-building astrocytes are just trying to help, but they also release a chemical into their environment that makes it hard for axons to grow (Figure 2).

But, there is good news here as well. Scientists are working on strategies to motivate injured neurons to grow by using special growth molecules and to eliminate stop signs for axons in order to make the injury environment more supportive for nerve cell growth [1].

THE IMMUNE RESPONSE IN THE BRAIN IS DIFFERENT FROM THAT IN SKIN

IMMUNE RESPONSE

Your body's reaction to injury. The immune response will send out specialized cells, some from the region of injury and some from the blood stream, to help clean up and repair.

The **immune response** plays an essential role in any kind of repair after injury. In injured skin, immune cells will rush to the site of injury from the blood and help the resident immune cells clean up debris from dead cells. Once the clean up is done, the immune cells die and stop the fight. The brain has specialized resident immune cells as well, and they will become activated when they sense danger or damage. A common problem in the brain is that the activated immune cells often don't know when to stop fighting. If they continue to spit out toxic chemicals over long periods, they can cause more harm than good, by killing healthy neurons. This is why scientists are trying to understand what switches brain immune cells on and off and trying to figure out how they can modify the response of these immune cells, so the cells can be helpful rather than harmful [2].

HOW THEN DOES THE BRAIN REPAIR ITSELF?

Learning about the limitations of neurons compared to skin cells, you may be disappointed that an organ as important as the brain seems to be unprepared for damaging events. The truth is, the central nervous system has an ingenious strategy to repair itself that is entirely different from the strategy used by other organs. The brain will never be the same as before the damage, but it will try to compensate for its losses. Neurons in the brain are able to change their connections with each other. This process is called **plasticity**, and it helps the brain to adapt to the loss of neurons. Forget for a moment about dying cells, the responsibility for plasticity lies entirely with the surviving cells. How does this work?

PLASTICITY

The ability of nerve cells to change their connections to other nerve cells. Plasticity is the process of neurons building new arms to connect with other neurons, or simply weakening or strengthening an existing connection with another nerve cell.

Because a neuron's primary job is to send out a signal, neurons are super good at sensing "free real estate," or other neurons, that they can connect with. Apart from growing new arms to connect with new cells, neurons can also modify the strength of existing connections with other neurons (Figure 3). They can either strengthen such connections or they can weaken them, resulting in a totally new network of connections in the brain. This

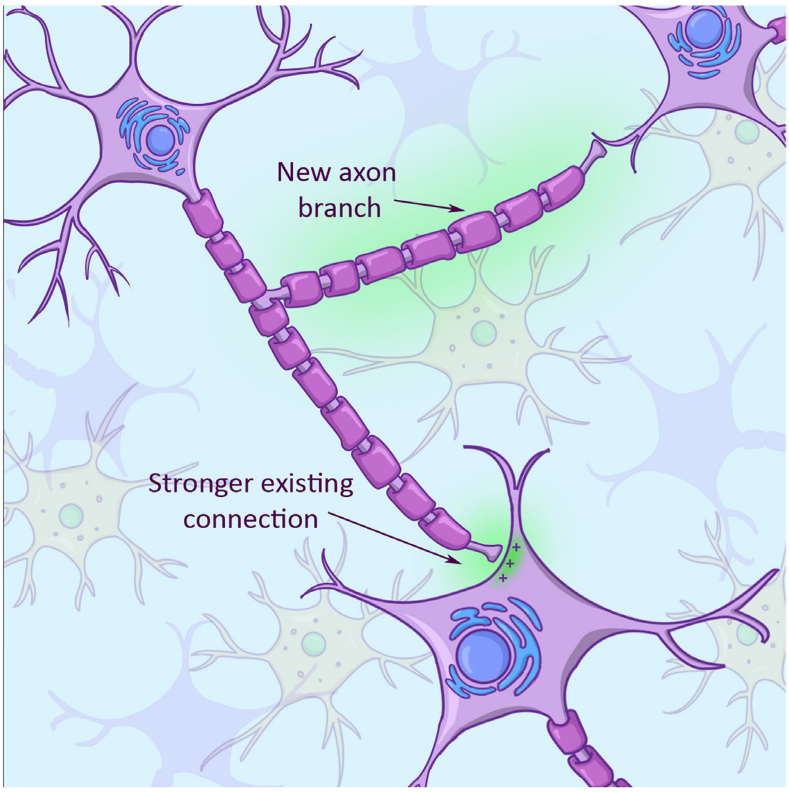

FIGURE 3

FIGURE 3

In response to an injury, a brain cell can adapt by growing new arms (axon branch with green background) and also by increasing or decreasing the strength of existing connections (connection between axon and receiving cell with green background in bottom right).

plasticity is driven and directed by activities that we perform. After a stroke or brain injury, patients usually improve to a certain extent doing some sort of physical therapy. The improvement is not so much due to growth of new neurons, as you learned above, but because these patients keep stimulating plasticity and, therefore, build new connections between surviving neurons in their brains!

Unfortunately, plasticity as a repair mechanism has its limits. Plasticity relies entirely on surviving cells, so the more surviving cells there are, the better. If someone suffers a severe brain injury, or a huge stroke that kills a substantial amount of brain cells, then there are less surviving neurons available for plasticity than following a mild concussion. The more cells available for plasticity to work with, the more plasticity can occur. This is why severe central nervous system injuries usually result in lasting disabilities. And because the consequences of these severe injuries are so dire, scientists are working hard to try to protect neurons from dying, to replace lost cells with stem cells, to help injured neurons grow, and to stimulate plasticity.

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REVIEWED BY

TRAFALGAR SCHOOL FOR GIRLS, 12–13 YEARS OLD

Seventeen young girls from Grade 7 participated in this review. Some of them are athletes and one of them had a concussion before. Some of them have family members/friends with mental illnesses. This group was very enthusiastic about the review process and everyone in the class participated and gave valuable feedbacks. Special mention to their science teacher Christianne Loupelle for being very motivating and considerate during the review process.

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ANGELA ZHANG

I am currently a masters' student at McGill University. In the past, I studied how distant parts of the brain are affected by stroke in another part of the brain. Now, I am interested in studying traumatic brain injury (concussion) and how the brain's visual system recovers afterward. Apart from research, I love travelling, playing piano, drawing, and skiing.

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INVESTIGATING TBI USING ANIMAL MODELS

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YOUNG REVIEWER:

MAXWELL
AGE: 12

In the USA, there are 2.8 million emergency room visits for traumatic brain injury (TBI) each year and about 1.2 million people are living with brain function problems due to TBI. Although much information has been gained from experimental and clinical studies showing how injuries happen, no effective treatments are currently available for TBI. To understand the effects of TBI on the brain and spinal cord, scientists use animal models as a cost-effective research method. Larger animal models, such as pigs or sheep, are closer in bodily functions to humans. However, the use of rodent models is preferred because they are easy to work with in the lab. Importantly, this also fits with the national recommendations to use the lowest mammalian species that can provide the answer to the scientific question. Using rodents, scientists can control specific details, such as the type of brain injury and the severity of the injury. There are ethical concerns about injuring in animals in scientific experiments, but scientists make substantial efforts to ensure the most humane treatment of these animals. Recently, animal models have been used to discover certain proteins, called biomarkers that are present in the brains of people

with TBI and could lead to the development of new therapies to prevent or reduce disability that can result from TBI.

TRAUMATIC BRAIN INJURY (TBI)

Brain damage caused by intense injuries directly targeted to the head, caused by accidents, sports, and other traumas.

CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE)

Brain deterioration caused by repetitive head injuries, leading to a progressive loss in memory and other brain skills.

TAU PROTEINS

Proteins present in brain cells called neurons that help the neurons keep their proper structure.

POST-MORTEM

After the death of a patient or subject.

ANIMAL MODEL

An animal that is used to study the development and progression of a disease and to test new treatments before they are given to humans.

ETHICAL

Involving questions of right and wrong.

WHY DO WE NEED TO UNDERSTAND TBI?

Traumatic brain injuries (TBIs) are one of the leading causes of injuries and death among people of all ages around the world. Deaths from TBI number in the hundreds of thousands and injuries in the millions. TBIs happen to children and adults through automobile accidents, falls, car-vs.-pedestrian injuries, blast injuries in the military, and sports injuries. TBIs can have life-long impacts on the quality of a person's life. Contact sports like football, soccer, boxing, and hockey can result in TBIs. Repetitive head trauma can lead to the development of **chronic traumatic encephalopathy (CTE)**, which is brain deterioration caused by repeated head injuries, leading to a loss of memory and other brain skills. CTE is associated with the accumulation of a substance called **tau protein** in the brain. CTE begins with mood and impulse-control problems and gradually develops into a devastating loss of brain function, similar to that observed in diseases like Alzheimer's and frontal-temporal dementia. Given that millions of people, including children, engage in contact sports, understanding TBI and CTE is a critical national health issue.

To learn about TBI, scientists would ideally like to study brain tissues from TBI patients. However, brain tissue samples are rarely available form patients. Brain samples from **post-mortem** (after death) cases of fatal TBI can be studied by scientists, but this is not enough to understand disease processes. **Animal models** provide a critical method for the study of TBI. Animal models help scientists study and find cures for diseases and disorders that are difficult or not **ethical** to study in humans [3, 4].

WHAT IS AN ANIMAL MODEL?

Animal models are non-human species which are studied and compared to understand common biological processes. Animal models play an important role in human TBI research. There are many types of animals used in testing. Although larger animals are more similar in bodily processes to humans, rodents are most often used as animal models due to their small size, lower cost, and the fact that it is easy to study multiple small animals in the same experiment. The animals used in TBI research include mice, brown rats, ferrets, and domestic pigs. Some of these animals have brains that are similar to humans and can be used to investigate the mechanisms and potential treatments for human TBI (Figure 1) [4].

In order to make the TBI animal models more like humans, scientists first inject the human tau gene into the animals. Please note that

Figure 1

Figure 1

This figure shows the anatomy of human, ferret, and mouse brains. Small animals share some structural characteristics with humans and are important in studying TBI, even though many animal brains are smaller than human brains. Human brains usually weigh about 1.4 kg, mice/rat brains are 0.002 kg, pig brains are 0.18 kg, cat brains are 0.03 kg, ferret brains are 0.84 kg, and sheep brains are 0.14 kg [1, 2, 5].

all the TBI research is conducted in anesthetized animals so they do not suffer any pain Then, scientists use different mechanisms to cause TBI in the animals. Unlike in humans where the severity of TBI is uncontrolled, when using animal models scientists have complete control over the type of injury they administer, and they can carefully measure the specific biological and behavioral responses of the animal to the TBI. Scientists use several methods to produce injuries the brain that mimics those that occur to humans. Different TBI models include producing a local injury to the brain, a more widespread injury as might happen in a concussion and a method to induce a blast injury as is often seen in soldiers. As noted, the animals feel no pain since they are under anesthesia and the scientist are safe from any possible injury while they are performing the experiments. After these injuries are administered to the animals, the scientists collect data on the animals' responses over a certain time span and compare them with human patient data [1, 4, 5].

BIOMARKER

A molecule that shows whether there is a disease or other problem.

FOCAL INJURY

Localized tissue damage caused by direct force.

WHAT DO WE LOOK AT IN THE BRAINS OF ANIMAL MODELS?

To study TBI, scientists often look at specific brain proteins called **biomarkers**. Biomarkers are a measure of a disease process, usually measured after **focal injury**? A typical biomarker would be the level of your blood glucose as a way to monitor diabetes. In TBI, the biomarkers we are interested in including tau proteins, glial fibrillary acidic protein, ubiquitin carboxy-terminal hydrolase L1, neuron-specific enolase. All of these proteins are part of the molecular structures that make up brain cells in both humans and the animal models, like the wood that holds up the framework of a house. When someone goes through a trauma or injury, these brain proteins break apart, resulting in brain cell deterioration, breaking down the framework of the brain. Let us focus on the example of tau proteins. In brain cells called neurons, tau proteins help make up the structure of the long, thin arms of the cells, called axons, which communicate with other neurons. The deposition of tau disrupts

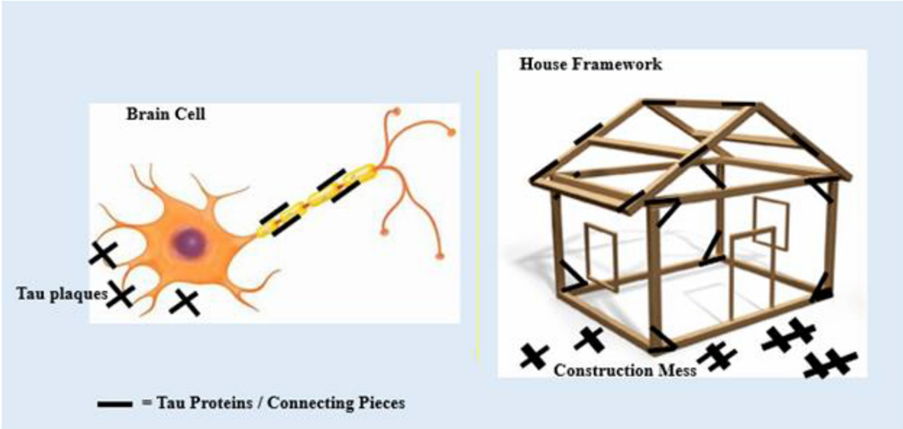

Figure 2

Figure 2

Tau proteins are like the nails that connect the framework of a wooden house. Tau proteins connect the microscopic parts of brain cells together to create their structure. During TBI, the impact of a hit can cause the tau proteins to react with other chemicals and fall off the structure. These tau fragments collect, and form buildups called tau plaques. These plaques cause a mess around the framework, like a construction mess. Plaques can cause malfunction of the brain and can lead to memory loss, movement issues, and other behavioral changes [4].

communication between brain cells, which leads to disordered thoughts and behaviors. The buildup of tau leads to memory loss, slow movement, loss of intellect, and other devastating behavioral changes. Similar to tau, all the other proteins listed also build up in the brain in a similar fashion and have similar devasting effects. Scientists have been trying to determine what leads to increases in the formation of these protein deposits and how to limit them (Figure 2) [3, 4].

WHAT ARE THE BENEFITS OF USING ANIMAL MODELS?

The use of animal models allows researchers to investigate diseases in ways that would be impossible in human patients because of ethical concerns. Humans and animals have similar basic cell processes, so the data collected from animals can reliably predict similar results in humans. Animal research also allows scientists to collect data from many different animals, which increases the reliability of the research findings. Some experimental animals, such as mice, reproduce in very large numbers, so there are lots of mice to use for research.

There is much discussion about whether it is right or wrong to use animals for research. and Some people argue that there is not enough solid evidence to compare animal models to human models. But other people argue that using animals in research is the only way to learn about some human diseases and to find solutions to those diseases. TBI research, such as the new study on tau biomarkers, helping us detect potentially better diagnosis for concussions, would not have provided a breakthrough in understanding TBI without the use of animal models. Using only post-mortem human samples does not provide enough data to test the scientific theories about the role biomarkers play in TBI. Animal models help us study the human system in faster and more efficient ways.

Many people fight for the ethical rights of animals, believing that animals should live without the distress of being experimental subjects. To maintain ethical practices, scientists have established regulatory boards to enforce a strict set of rules concerning animal research. There are things scientists can and cannot do, and rules about what types of research animal models can and cannot be used for. These rules support the three R's: replace, reduce, and refine. Scientists must organize their experiments so that they replace animals with other non-animal alternatives as often as possible. In addition, scientists must plan their experiment so that they reduce the number of animals used to the smallest possible number that will give them adequate evidence for their research question. Finally, scientist must refine the procedures done on the animals to reduce excessive harm or l distress to the animals. These rules and regulations allow scientists to get good results with the least consequences for the animals. There have been major breakthroughs in understanding human diseases using animal models, but hopefully, as technology advances, scientists will gradually be able to use fewer and fewer animals for their research [1, 5].

CONCLUSION

Animal models are an essential tool for many types of scientist research. For scientists like us who study the brain, animals help us investigate one of the most complex organs in the body. Animal models help us study key features of diseases that are hard to investigate using human subjects. These models have helped us understand the process by which the buildup of certain proteins, like tau, in the brain damages the brain's structure and function. With this information, scientists are working to discover methods to limit the amount of tau buildup, which in turn could decrease the effects of serious diseases like CTE, Alzheimer's, Parkinson's, and other disabling disorders of the brain.

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YOUNG REVIEWER

MAXWELL, AGE: 12
I am interested in a lot of different things and am curious about the world. I am humorous yet I can also be a bit dim at times.

AUTHORS

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Milin Kurup is a sophomore studying at the University of Florida, majoring in Microbiology and Cell Sciences. His Principle Investigator, Dr. Kevin Wang, and Ph.D. candidate Hamad Yadikar have been working with him on multiple experiments related to the buildup of tau plaques in the brain for the last 2 years. After experience in neurological research, he hopes to pursue a career in pediatric neurosurgery and hopes to inspire children in medical sciences. *milinkurup@ufl.edu

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Guriel Kim is a sophomore studying at the University of Florida, majoring in Health Science and International Studies. She is currently working in Dr. Kevin Wang's lab, doing experiments on samples sent from different companies all around the world. After graduation, she hopes to become a general surgeon with a focus in transplantation surgery.

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Lindsey Morrow is a sophomore studying at the University of Florida in the University Honors Program majoring in Biochemistry with a minor in Health Disparities in Society. Through Dr. Wang's lab, she is currently on a team that is working on the International Collaboration on Neuroinflammation Project, in which they explore the difference of severities and age ranges of TBI on a molecular level. After graduation she hopes to pursue a career in medicine.

SAMUEL RUIZ

Samuel Ruiz is a junior at the University of Florida majoring in Biology with a minor in Spanish. He is currently working with Dr. Wang's lab and is working on learning about the biochemical aspects of TBI through the animal model. In addition, he works with a non-profit organization known as Dream Team, where he helps pediatric cardiac patients. In the future, he hopes to become an orthopedic surgeon.

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frontiers FOR YOUNG MINDS

NEUROSCIENCE AND PSYCHOLOGY
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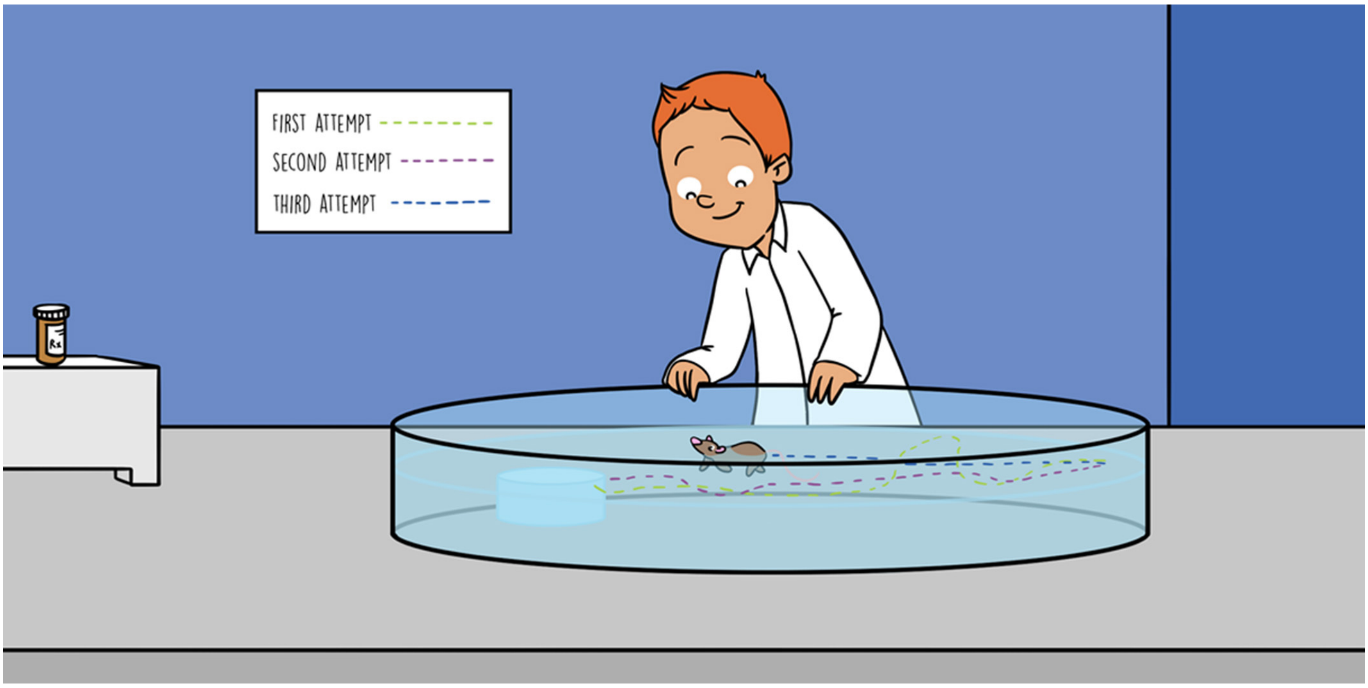

HOW DO YOU TEST A RAT'S MEMORY?

David W. Wright *

Emergency Medicine, School of Medicine, Emory University, Atlanta, GA, United States

YOUNG REVIEWERS:

DRUMMONDVILLE ELEMENTARY SCHOOL

AGES: 10–11

Brain injury often impairs a person's ability to remember. To find new drugs that improve memory after a brain injury, scientist must rely on experiments in animals such as rats. But how do you test the memory in rats? One way is to use a pool of colored water, called the Morris water maze. In this maze, rats have to "remember" where to go to get out of the water. The more a rat's memory has improved, the quicker it finds its way out of the water (rats do not like being in water). This test can also be used to compare two different drug treatments. It is an important tool for new drug discovery.

FINDING NEW TREATMENTS FOR BRAIN INJURY USING ANIMALS

MEMORY

The ability of the brain to recall past experiences or information.

One of the major purposes of the brain is **memory**. When a person suffers from a brain injury, memory is often damaged. In order to find new treatments to help bring memory back, scientist need to test many drugs. These tests are most often performed with animals because research on actual people is much more expensive and hard to do. Using animals allows the scientist to recreate the same type of

Figure 1

Figure 1

How do you test a rats memory? (Art by Jessica Forsstrom).

injury in every animal, run the tests several times to be sure the answer is correct, and try new drugs when the safety of the drug is not known. Rats and mice are the most common animals used because they are plentiful and easy to handle. To see if a new drug works to improve memory after a brain injury, the scientist would cause a brain injury in several rats and give the new drug to half of the rats. The other half would not get the drug (known as the control group). Then, they would set up a test to see if the memory in rats that got the new drug was better than the rats that did not.

HOW DO YOU TEST MEMORY IN A RAT?

This is a really good question! We have no idea what a rat thinks, much less what a rat remembers Figure 1. You cannot ask a rat questions; you cannot have it take a written test. A rat will not respond if you ask it to shake its head yes or no. In fact, it really will not respond to anything you ask at all.

So, how do we use rats in **experiments** to test the brain's function, such as whether a rat can learn new information or has developed a memory? How can we tell which rats have impaired memory, or are not thinking correctly? And how can we tell if a new drug works to help an injured rat's brain to recover more quickly?

EXPERIMENT

An action or process set up to find out whether something works or is true.

There are several ways to test whether a rat can learn new memories. One method is called the **Morris water maze** Figure 2. It is a type of puzzle for the rat—a test to see if the rat can get better at remembering its surroundings in order to avoid something unpleasant.

MORRIS WATER MAZE

One of the most widely used tasks in behavioral science for studying the processes and mechanisms of learning and memory.

Unpleasant? Well, rats can swim, but they do not like water. So, when placed into a round tank of water, a rat will eagerly swim to find a way out. In the case of the Morris water maze, the sides of the tank are too

Figure 2

A navigational memory test used mainly with rats and mice. A non-transparent liquid is placed in a tank with a submerged platform. Rats are put into the tank and swim until they find the platform. Each time they are put in, they learn how to get to the platform quicker using a shorter path. (Art by Jessica Forsstrom).

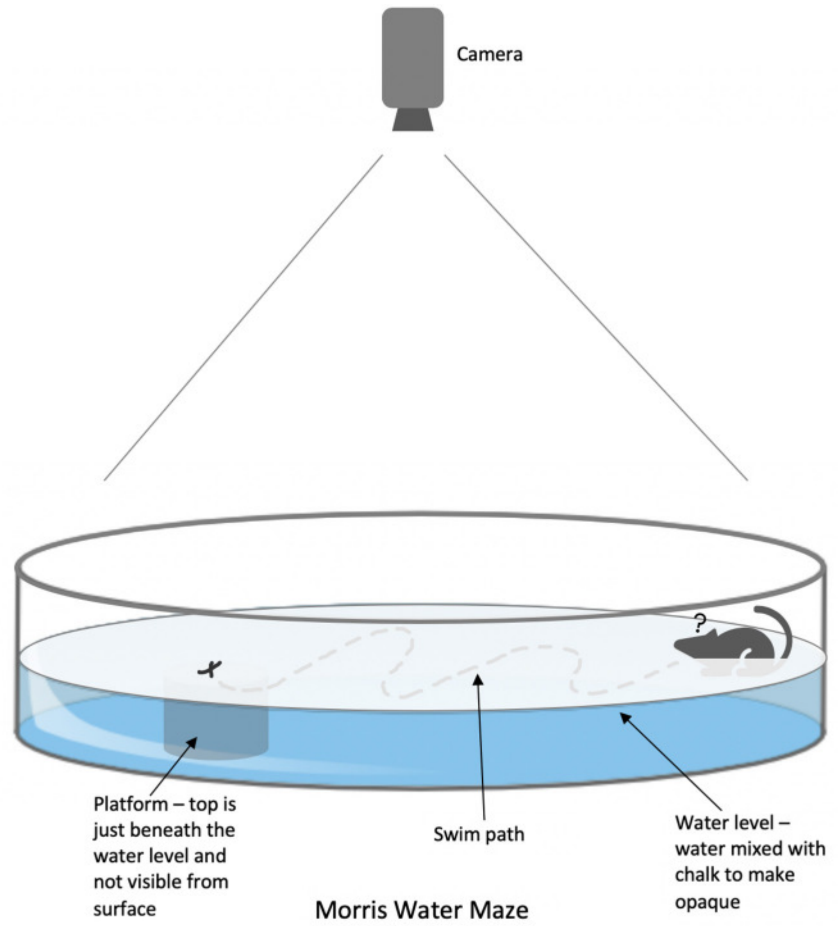

Figure 2

high for the rat to get out, so it swims around and around, looking for some other way out of the water.

In the Morris water maze tank, there is a platform placed just under the surface of the water. Once the rat finds the platform, it quickly climbs on. So, you would think that the next time the rat is put into the tank of water, it should just look for the platform and swim to it. *That is exactly what the rat tries to do*.

The Morris water maze is tricky, because the platform is hidden just *below* the surface of the water…and, to make it really hard, the water is colored with white chalk so that the rat cannot see the platform below the water's surface. So, even though the platform is always in the same location, it is actually hidden from the rat's view and the rat has to *remember* where the platform is located in the tank in order to find it quickly (Figure 2).

The first few times the rat is put into the tank, it learns where the platform is located in relation to the other objects that it can see in the room. Each time the rat is put into the tank, it searches quickly for the platform—remember, rats do not like to swim. The better the rat's memory and the better it learned from the last time it was put in the tank, the quicker and straighter it swims toward the platform.

We measure the distance of the path that the rat takes to the platform over several trials, to determine how "smart" a rat is, or how much memory the rat has.

THE FINAL TEST

In this experiment, the scientist tested several drugs to see if they could improve memory after a **traumatic brain injury**. First, they created a brain injury in a group of rats. These injured rats have trouble finding the platform each time they are put into the tank, even though they have been in the tank multiple times. This is because, due to memory problems caused by the brain injury, the rats were unable to learn or remember where the platform was located.

To test if the drugs improve memory, the rats are divided into groups based on which drug they got. For an example, the scientist used 10 animals per group (each animal within one group receives the same drug). If one of the drugs is working, then those rats will remember where the platform is located under the surface of the water and will swim straighter and faster to the platform. This is recorded as distance (how far the rat swam before it got to the platform) and time (how quickly it found the platform each time it was put in the maze). The distance (shorter path is better) and time (short time is better) are compared between each group of animals based on which drug they received and also compared with injured animals that did not received any drug (**control group**). If one of the groups did a lot better than the others and/or the control animals, then it means the drug improved the rats' memory and might be a new treatment for brain injury!

TRAUMATIC BRAIN INJURY

Any serious injury to the brain, often resulting from violence or an accident.

EXPERIMENTAL/ TREATMENT GROUP VS. CONTROL GROUP

In an experiment, two groups treated in the identical way except one group (treatment group) receives the intervention (drug or treatment) and the other does not (Control group).

CONCLUSION

So, now you know how scientist can use rats to do experiments testing new drugs to help improve recovery from brain injury. Measuring improvement in memory using a water maze is an important tool for studying how well a drug works in animals. Once scientist identify what drugs are safe and work best in animals, they can then design larger **clinical trials** to test the treatment in humans.

CLINICAL TRIAL

A research study in humans to test the safety and how well a treatment or intervention works.

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YOUNG REVIEWERS

DRUMMONDVILLE ELEMENTARY SCHOOL, AGES: 10–11
We are a grade 5 class, currently studying at Drummondville Elementary School (DES). We study in both English and French. Our class is very respectful of our planet and place great importance on recycling, and composting. We are a group of energetic students, who love sports, and love to move. Our classroom has a library filled with books that we love to read.

AUTHOR

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Wright is a tenured Professor and the Chair of the Department of Emergency Medicine at Emory University School of Medicine. He is a board certified emergency medicine physician practicing at Emory affiliated hospitals and Grady Memorial Hospital, Atlanta's premier Level 1 Trauma Center. He is actively involved in both the preclinical and clinical assessments of traumatic brain injury, stroke and other acute neurological conditions. He was the PI of the ProTECT III multicenter clinical trial of progesterone for acute traumatic brain injury and serves as the southeastern Hub PI of the Neurological Emergencies Treatment Trials network, Co-PI of the Georgia StrokeNet network, and Hub PI for the newly funded Strategies To Innovate Emergency Care Clinical Trials Network (SIREN). He has extensive clinical trial leadership and operational experience. He holds Adjunct appointments in the Department of Biomedical Engineering at the Georgia Institute of Technology, Rollins School of Public Health, and the Nell Hodgson Woodruff School of Nursing.
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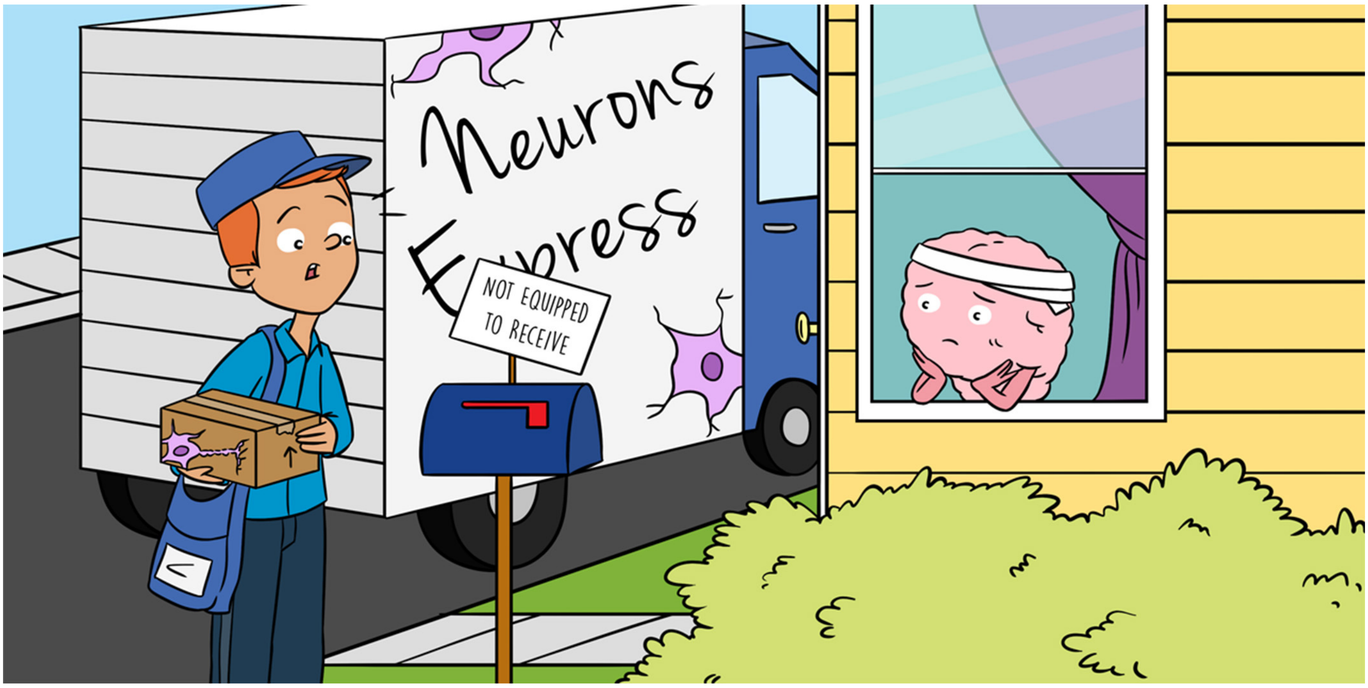

TUG OF WAR DURING TRAUMATIC BRAIN INJURY

Hiba Hasan[1,2†], Maha Tabet[1†], Samar Abdelhady[1,3], Sarah Halabi[4], Karl John Habashy[5], Firas Kobeissy[1*] and Abdullah Shaito[6*]

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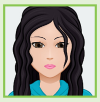

EUNBI
AGE: 13

Human behavior depends on the cooperation of about 100 billion brain cells, called neurons. The generation of new neurons occurs through a process called neurogenesis. Previously, scientists thought that neurogenesis stopped before birth. However, scientists have recently found that neurogenesis can still occur after birth and continues throughout life. Injuries to the brain can lead to the death of neurons, which is called neurodegeneration. Hence, one-time severe damage or repeated smaller injuries to brain neurons can lead to serious diseases called neurodegenerative disorders. Neurogenesis is important to replace damaged neurons, especially after brain injury. Scientists try to find ways to decrease the adverse effects of brain injury. One way is to help the brain to make more neurons following injury, by enhancing neurogenesis. This can help to treat brain injuries and neurodegenerative diseases.

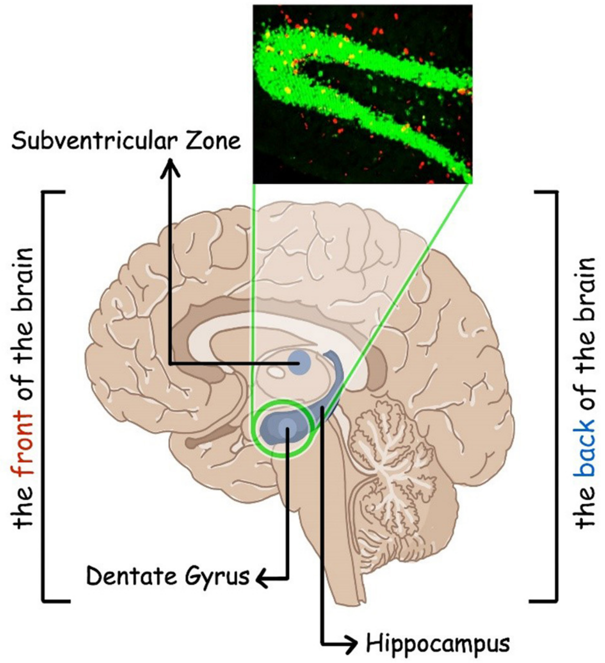

Figure 1

Figure 1

Sites of neurogenesis in the brain. This figure shows an adult human brain where neurogenesis, or the formation of new neurons, occurs in two regions. These two regions are the hippocampus and the sub-ventricular zone (shown in blue). In the hippocampus, neurogenesis specifically occurs in an area called the dentate gyrus. One way to detect newly formed neurons is to use BrdU staining. BrdU becomes part of the DNA of a new cell and can then be seen under the microscope using specific detector molecules. The picture in the upper left shows the neurons from the hippocampus of a mouse. The mature, old neurons show a green color, while the new neurons show an additional red color because they contain BrdU in their DNA.

NEURONS

Are fundamental cells of the brain that transmit information to other cells.

NEURAL STEM CELL

Are cells that can renew themselves and can form new neurons.

NEUROGENESIS

A process by which new neurons are produced.

NEURAL STEM CELLS: THE BENCH PLAYERS

The brain is the most complex organ in the body. Our brains allow us to think, observe, analyze, move, feel, and do many other tasks. Like other organs, the brain is made up of several types of cells. **Neurons** are the main cells of the brain. They are considered the main players in producing the wonderful range of human behavior. A neuron connects with other neurons to transmit messages. This message transmission allows us to do all the things we do. The brain also consists of other types of cells with different jobs, such as supporting and nourishing the neurons, helping the neurons to transmit their signals, or defending the brain against foreign organisms [1].

Not long ago, scientists believed that no new neurons could join the "team" of brain cells once it was formed before birth—it was thought that new neurons were not made after a person was born. Later, scientists discovered that two areas in the brain could make new neurons. These two brain areas contain special cells called **neural stem cells** (NSCs), which can generate new neurons through a process called **neurogenesis**. The two areas of the brain that contain NSCs and can perform neurogenesis throughout life are: (1) the sub-ventricular zone, which is the area of the brain where most of the neurogenesis happens; and (2) a region in the hippocampus, which is the part of the brain responsible for memory (Figure 1). Interestingly, it has also been found that NSCs can act as "bench players" that join the brain-cell team in case of injury, meaning that neurogenesis increases following damage to the brain [2].

HOW DO WE SPOT THE NEWBIES?

There are several ways to spot the neurons that have recently joined the team. BrdU staining is one method used to detect the new neurons, which are usually produced by NSCs. BrdU is a chemical that can be added to brain cells in the lab and then it becomes incorporated into the DNA of new neurons. BrdU becomes a part of and marks the DNA of new cells only, and the mature older cells do not get marked by BrdU. The staining by BrdU molecules in new cells can be detected under a microscope (Figure 1).

Another strategy to find newly formed neurons is to look for their mascot. Let us pretend that each type of cell in the brain has a specific mascot. If we can spot the mascot, then we will know the team and the team is the type of brain cell! But, what is the mascot of a neuron? Newly formed neurons will have specific molecules that are made only by them (their mascot). What scientists do is to look for the presence of these specific molecules. To find these specific molecules, scientists then use specific detector molecules that stick only to the mascot of new neurons and not to other mascots. The detector molecules can be seen under a special microscope.

Yet another method is to determine the age of the new neurons. This is possible because new neurons are much younger than the neurons that you were born with. Scientists do this by looking at the carbon content of neurons. Carbon is an element found in nature and is a building block of everything in life, including cells. The properties of carbon change over time, and we can know how old something is by looking at the type of carbon it has. Think of it this way: every year, the newcomers get a new bracelet as a welcome gift, which differs from bracelets distributed in the previous years. So, we can tell which year a member joined the team by looking at their bracelets. The bracelets are the type of carbon they have [2].

BRAIN INJURY AND NEURODEGENERATION

Most of us have bumped our heads once or twice in our lifetimes. We may have felt some sort of pain, but woken up the next day as if nothing happened. This is known as a head injury. Head injuries usually do not lead to long-term consequences. But, if the hit to the brain was repeated or if the initial bump was very severe, head injury can lead to a **traumatic brain injury (TBI)**. The worse the TBI, the more serious the outcome will be for the injured person and the more changes will occur in that person's brain.

TBI

An injury to the brain that disrupts normal brain functioning.

There are two stages to TBI, called primary injury and secondary injury (Figure 2). The primary injury involves changes in the brain that occur immediately after hitting our heads. There will be damage to cells,

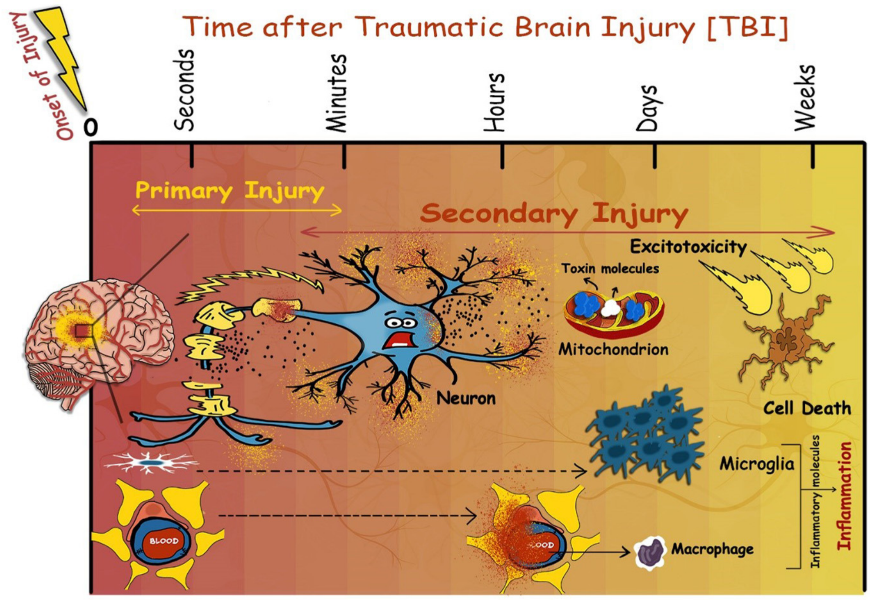

Figure 2

Figure 2

Events that occur following TBI. Traumatic brain injury consists of two phases: the primary injury and the secondary injury. The primary injury takes place within seconds to minutes following the onset of TBI. Primary injury involves direct damage to neurons caused by the blow to the head. The secondary injury takes place later, within minutes to weeks following the injury. The secondary injury involves the release of inflammatory molecules by microglia and other immune cells. In severe cases, microglia and other immune cells release a lot of inflammatory molecules during the secondary injury, which can lead to neuron death.

INFLAMMATION

It is a protective biological response that starts under harmful conditions, such as stress. It is one way your body fights infection, injury, or disease. It involves immune cells, blood vessels, and many molecules inside the cell.

MICROGLIA

A type of immune cell that is found in the brain.

NEURODEGENERATION

A process that causes neurons to die. It is a measure of neuron death.

NEURODEGENERATIVE DISEASES

Neurodegenerative diseases are a set of

bleeding near the area of injury, and pain. Hours or even days after the primary injury, the secondary injury takes place. The secondary injury involves more changes in the brain, including excitotoxicity (when neurons are damaged or even killed because of being highly active) and **inflammation**. Inflammation of neurons involves the activation of the immune cells of the brain that are called **microglia**. Activated microglia release inflammatory molecules, which recruit other types of immune cells to the location of the brain injury, thus increasing the inflammation even more. This increase in inflammation is a normal response to injury and is vital to the maintenance of health. However, an uncontrolled increase of inflammation is harmful to cells.

In addition, during the secondary injury, brain cells become stressed and start to accumulate toxin molecules that can eventually lead to the death of neurons, or what we call **neurodegeneration**. Therefore, it is often the secondary injury that causes the most damage and neurodegeneration, even though the actual hit to the head took place days or weeks earlier. The death of many neurons can be very dangerous and even lead to long-term problems called **neurodegenerative diseases** [3]. Scientists are trying to decrease the bad outcomes of TBI by increasing neurogenesis after the injury.

NEUROGENESIS AND NEURODEGENERATION: TUG OF WAR

Injury to the brain, as mentioned above, causes inflammation. Inflammation in the brain is caused by the activation of microglia and other immune cells called **macrophages**. These cells secrete

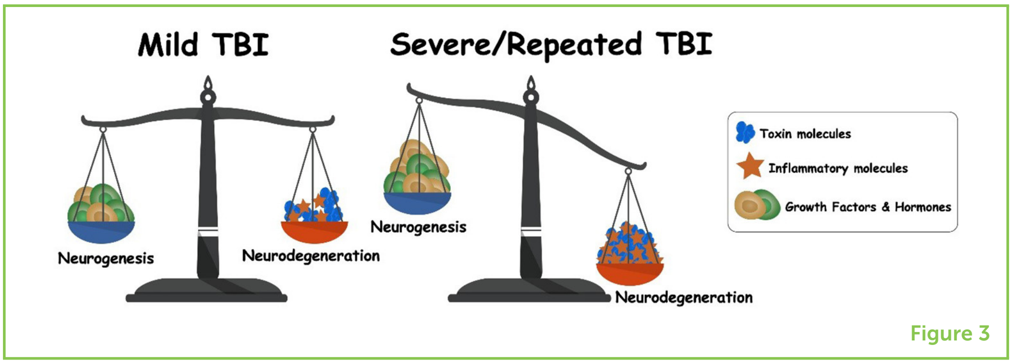

Figure 3

Balance between neurogenesis and neurodegeneration following TBI. The balance between neurogenesis and neurodegeneration is determined by the environment caused by the injury. In mild TBI, there is a balance between inflammatory molecules that favor neurogenesis and other inflammatory molecules that favor neurodegeneration. The inflammatory molecules that favor neurodegeneration act as toxin molecules that kill neurons. As a result, in the cases of severe or repeated TBI, the balance is disrupted and tips more toward neurodegeneration, since the production of toxin molecules is highly increased.

chemicals, such as the inflammatory molecules, that can promote either neurogenesis or neurodegeneration (Figure 3). But, how?

If the brain injury is very mild, controlled inflammation in the brain will occur. This controlled inflammation has a positive effect on neurogenesis, since it aims to replace the lost neurons. However, if the injury to the brain is very severe or if the brain injury is repeated, as often seen in certain sports activities, then this can lead to severe inflammation. Severe inflammation cannot be controlled. Some inflammatory molecules released during severe inflammation have a negative effect on neurogenesis and form a harsh environment for growth of new neurons. In the presence of these inflammatory molecules, even if newborn neurons form then they cannot survive. So, in the case of severe or repeated head injuries, there will be more neurodegeneration than neurogenesis.

This situation is like weighing two things on a pan balance. If there are equal weights on both sides, the balance is at equilibrium. This is what happens in the case of controlled inflammation: the amount of neurogenesis that occurs is somewhat equal to the amount of neurodegeneration that took place as a result of the injury. However, if one side of the balance is heavier than the other, this will cause the balance to tilt. In the case of severe brain injury, there is uncontrolled inflammation. This causes the amount of neurodegeneration to be greater than the amount of neurogenesis (Figure 3). In this situation, the balance tilts toward neurodegeneration and the secondary injury can lead to serious neurodegenerative diseases [4].

diseases characterized by the progressive loss of neurons or neural function. They lead to problems with movement, or mental functioning. Most of these diseases are not curable.

MACROPHAGE

A type of immune cell involved in the process of inflammation.

THE EFFECTS OF NEURODEGENERATION

Neurons work together to perform all brain functions. If neurons start to die, the functions of the brain are affected. People who suffer a mild or a moderate TBI may lose a few neurons. They may experience problems with their thinking or memory, or with their ability to pay attention.

Severe TBI occurs when the brain receives a severe injury, for example, during car crashes or hard falls. People who perform contact sports, such as football players, hockey players, soccer players, and boxers are examples of people who may be exposed to severe TBI or repeated TBI.

During severe TBI, many neurons die and this causes neurodegeneration to outweigh neurogenesis. Severe TBI or repeated hits on the head may put people at risk of developing neurodegenerative diseases because a great number of neurons die.

Neurodegenerative diseases can show up tens of years following TBI. Neurodegenerative diseases include Alzheimer's disease, which causes memory loss, and Parkinson's disease, in which people start to shake because they lose control of their muscles. Amyotrophic lateral sclerosis (ALS), a disease in which people lose control of their muscles, and chronic traumatic encephalopathy are other types of neurodegenerative diseases. Encephalopathy refers to diseases that affect the function or structure of the brain and in chronic traumatic encephalopathy the patients show problems in their behavior, mood, and thinking, leading to confusion and forgetfulness.

CONCLUSION

TBIs should always be taken seriously. The damage that occurs following TBI is not always visible immediately. If you experience a TBI, it can affect you in the long run. There are many factors that influence the outcome of TBI. If the injury is very severe, neurogenesis is not as effective, and this can shift the balance toward neurodegeneration. So, you should always protect your head when doing dangerous activities or when playing sports. Protecting your brain is a must [3, 5]!

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YOUNG REVIEWER

EUNBI, AGE: 13

My name is Eunbi and I am from San Francisco. I am currently in eighth grade. Reading science articles and discovering further wonders about the world and mechanisms of human diseases are very fascinating for me. I believe that even small discoveries could influence the future of this world.

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I acquired an M.Sc. in Neuroscience from the Neuroscience Research Centre at the Lebanese University and conducted my Master's research project in the department of Biochemistry and Molecular Genetics at the American University of Beirut (AUB). My project examined the role of mitochondria and oxidative stress in traumatic brain injury (TBI), with a focus on testing a possible antioxidant treatment. In addition to my love for research, I like reading, drawing, and writing.

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I am a medical doctor. I did a research internship in Dr. Kobeissy's lab at the American University of Beirut (AUB) to study traumatic brain injury [TBI] using animal models. In my free time, I love drawing scientific illustrations and brain art, watching movies that talk about the brain, and since I work for long hours at a desk, I enjoy going hiking to keep my body fit.

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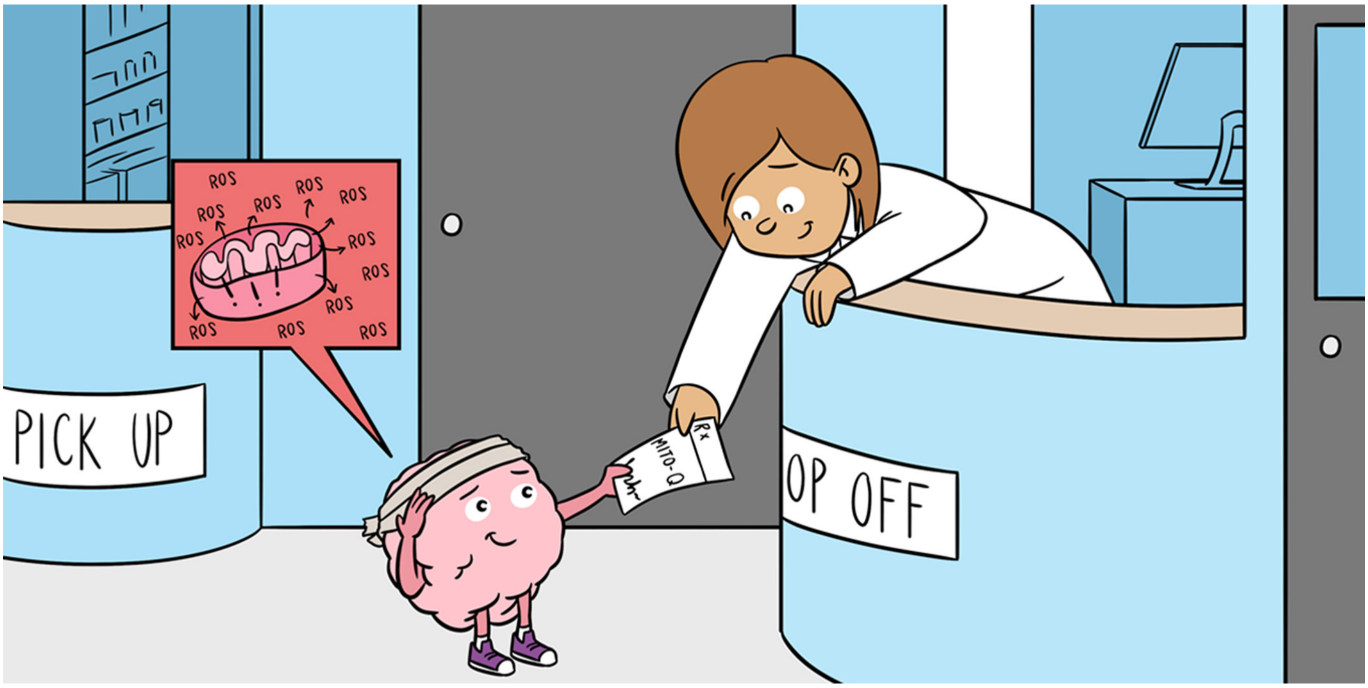

MITOCHONDRIA IN BRAIN INJURY: ANTIOXIDANTS TO THE RESCUE!

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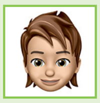
YOUNG REVIEWERS:



IAGO
AGE: 13

NOVA
AGE: 8

If you have ever bumped your head, then you may have experienced a traumatic brain injury (TBI). TBI is brain damage caused by an outside force. In the long run, TBI may weaken a person's ability to think, learn, or remember. In this article, we will learn how the mitochondria, tiny structures inside our cells, are partly responsible for the harmful effects of TBI. Mitochondria produce most of the energy our cells need to function properly. This, however, comes with a cost. Energy production is accompanied by the release of harmful substances, such as reactive oxygen species (ROS). ROS can damage components inside our cells and even lead to cell death. In TBI, damaged mitochondria produce high amounts of ROS. Drugs called antioxidants may protect the brain following TBI. Antioxidants

can destroy ROS. However, you should never use these drugs without medical guidance.

WHAT IS TRAUMATIC BRAIN INJURY?

Have you ever bumped your head? You most likely have. Your brain is vulnerable to impacts that can occur while you are practicing sports, if you have a bad fall, or if you are in a car accident. These impacts can result in a damage to the brain, which is called **traumatic brain injury** (TBI). TBIs can have varying levels of severity. Severe TBI causes the most damage to the brain. Mild TBI is the most common form of TBI and typically does not cause permanent symptoms. However, if you receive repeated mild TBIs, symptoms may persist. TBI may affect several brain functions, including a person's ability to think, concentrate, learn, and remember things. In the long run, repeated mild TBI may also increase the risk of some diseases caused by the death of main cells of the brain called **neurons**. Tiny structures inside our cells called **mitochondria** are partly responsible for these harmful long-term effects of TBI [1].

TRAUMATIC BRAIN INJURY

Damage caused to the brain by a bump to the head.

NEURON

The main type of cells in the brain. They serve to communicate messages within the brain and between the brain and other body organs.

MITOCHONDRIA

Structures found in our cells responsible for producing the energy our cells need.

WHAT ARE MITOCHONDRIA?

Mitochondria are special structures found inside all of body cells. The main function of mitochondria is the production of the energy our cells need to function. A mitochondrion is made of an outer membrane surrounding a space that contains an inner membrane. The inner membrane surrounds an inner cavity, called the matrix. The inner membrane contains the elements responsible for energy production.

Think of the mitochondria as the power generators of our cells. Similar to real generators that release pollutants as they generate power, mitochondria also produce harmful substances as by-products. Among those harmful by-products are **reactive oxygen species** (ROS). ROS can interact with and damage components of our cells. The cell has several systems to protect itself from excessive ROS. One protective system consists of substances called **antioxidants**. Antioxidants can control or remove extra amounts of ROS. Under stressful conditions, such as in TBI, damaged mitochondria generate huge amounts of ROS. The protective antioxidant systems become overwhelmed and fail to destroy the excessive ROS. As a result, many cell components may get damaged, which may lead to death of the cell [2] (Figure 1).

REACTIVE OXYGEN SPECIES

Substances produced by our cells. ROS, in very high levels, can interact with and damage components inside the cell.

ANTIOXIDANT

Molecules that can be man-made or found in nature, such as in fruits. They can protect the cell against the harmful effects of ROS.

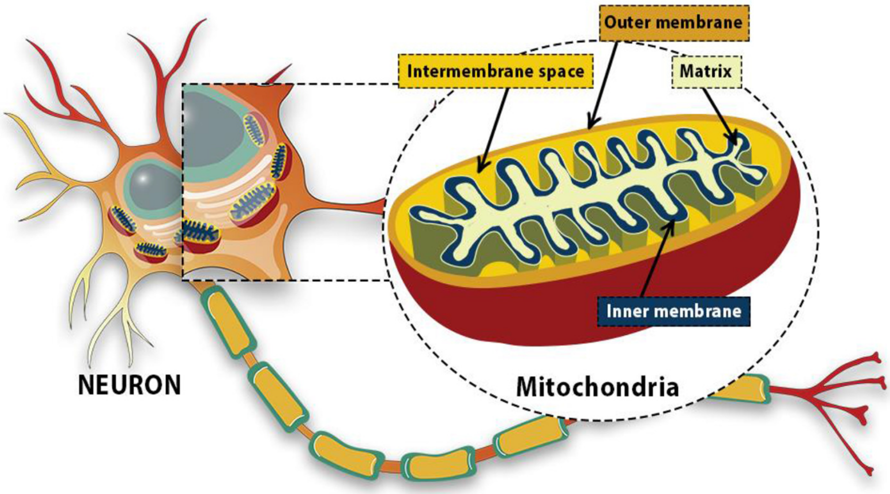


Figure 1

Figure 1

What are mitochondria? Mitochondria are organelles found in almost all of our cells, including neurons. A mitochondrion is made up of an outer membrane, an intermembrane space, an inner membrane, and a space in the middle called the matrix. Mitochondria are responsible for producing the energy our cells need.

WHAT DO MITOCHONDRIA DO DURING TRAUMATIC BRAIN INJURY?

The bump on the head is the mechanical force that leads to TBI. Think of it as the force that sets off the falling of a row of domino tiles. After the bump on the head, a series of events takes place in the brain. In the case of a TBI, the mechanical force first causes damage and injury to neurons and may, later, cause their death. The mechanical force also leads to the abnormal release of molecules, called **neurotransmitters**, used for communication between brain cells. When released, neurotransmitters knock down another domino tile: they cause the abnormal increase of certain substances inside neurons which, in turn, cause the mitochondria to increase production of ROS. ROS then interact with and damage several components inside neurons. Damage to cellular components leads to the impairment of cellular functions. One result of this damage is **inflammation** in the brain. Damaged cells are set to die [3]. Death of brain neurons is the main problem in TBI (Figure 2).

NEUROTRANSMITTER

A molecule used for communication between neurons.

INFLAMMATION

It is a protective biological response that starts under harmful conditions, such as stress. It is one way your body fights infection, injury, or disease. It involves immune cells, blood vessels, and many molecules inside the cell.

ANTIOXIDANTS: TO THE RESCUE!

ROS are one of the main culprits causing neuron dysfunction and death during TBI. If scientists can reduce the levels of ROS in the brain, they may be able to reduce the symptoms of TBI. Antioxidants can act like a sponge that absorbs the harmful amounts of ROS and make them inactive. This ability of antioxidants to reduce the harmful amounts of ROS, in the brain, prevents ROS from damaging the neurons.

So where do we find these antioxidants? Some antioxidants are naturally found in our cells. However, following TBI, antioxidants availability may decrease and our natural antioxidants become

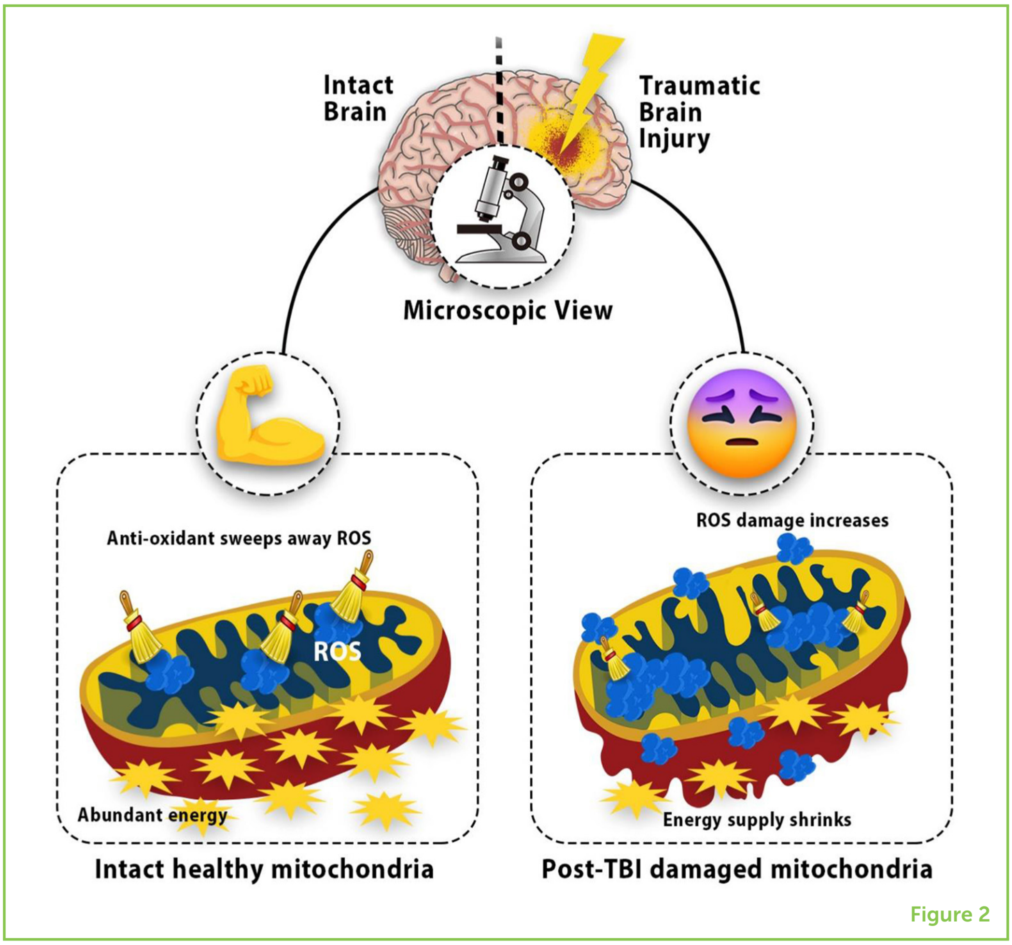


Figure 2

Mitochondria in TBI. In undamaged mitochondria, antioxidants help keep the mitochondria healthy and the cell's energy levels normal. However, in TBI, ROS are produced in large quantities and antioxidants get overwhelmed. The mitochondria get damaged and energy production decreases.

overwhelmed. Extra antioxidants can be provided from outside our body (external antioxidants) in the form of a drug or a supplement. In fact, several of these external antioxidants have been used in the treatment of TBI. Scientists have even found ways to guide the antioxidants to the mitochondria. This is important since mitochondria are the major source of ROS. For example, in our lab, we have used a powerful antioxidant called MitoQ for treating TBI. MitoQ is attached to special guide molecules that can take the antioxidant directly to the mitochondria where ROS are made. This increases the efficiency of the MitoQ drug [3, 4].

CAN HEROES BECOME VILLAINS?

Another way to look at antioxidants is to imagine antioxidants as heroes that chase the culprits (ROS) and put them in jail in order to save the cell.

Just like almost everything in life, balance is needed when it comes to taking antioxidants. Consuming too many antioxidants can be dangerous. If taken at high dosages, especially when ROS levels are normal, antioxidants may become toxic to cells. Excessive

Figure 3

Can heroes become villains? Despite the fact that they can protect neurons from harmful ROS, it has been shown that excessive consumption of antioxidants may cause serious diseases, such as cancer. So, we should never take any antioxidant without a doctor's permission.

consumption of antioxidants may increase the production of ROS instead of reducing it. Excessive antioxidants may also increase the occurrence of some diseases, including cancer. Therefore, antioxidants should be taken cautiously and under appropriate guidance from a doctor. We do not want our heroes to turn into villains [5, 6] (Figure 3)!

CONCLUSION

Traumatic brain injuries are very common. Finding a treatment is essential to limit their negative consequences. Mitochondria are the structures responsible for energy production inside our cells. In TBI, mitochondria become damaged and produce dangerous amounts of ROS. This can lead to the damage and even the death of the neurons in the brain. Antioxidants may represent a solution to reduce excessive amounts of ROS and reduce the harm of TBI. Scientists have developed ways to target certain antioxidants to the mitochondria to increase the effectiveness of these drugs. Although antioxidants are available without a prescription, it is always important to seek medical advice before consuming these powerful drugs.

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YOUNG REVIEWERS

IAGO, AGE: 13

My name is Iago and I am in seventh grade. My favorite subjects are writing, math, social studies, and science. My hobbies are acting, D&D, and fake-sword fighting. I think it is important for scientists to write for children, so that kids can learn how to think critically and ask questions about how the world works. My mom and dad are "mad" scientists because they stuck a playing card in a brain for a magic trick—good thing the brain was made of Jell-O!

NOVA, AGE: 8

My name is Nova and I am in third grade. My favorite subjects are writing, science, social studies, and reading. When I grow up, I would like to be an architect, because I like art and I also like building. I think it is important for kids to be curious so they can learn. Albert Einstein said that he did not have a special brain, but he wondered how the universe worked, so he went out and learned, so he could figure it out.

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I acquired an M.Sc. in Neuroscience from the Neuroscience Research Centre at the Lebanese University and conducted my Master's research project in the department of Biochemistry and Molecular Genetics at the American University of Beirut (AUB). My project examined the role of mitochondria and oxidative stress in traumatic brain injury (TBI), with a focus on testing a possible antioxidant treatment. In addition to my love for research, I like reading, drawing, and writing.

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I am currently a Masters Student majoring in Genomics and Health at the Lebanese University. My current research is about the effects of repetitive traumatic brain injury at the behavioral and proteomic levels. Later, I will join Dr. Firas Kobeissy's Lab at the American University of Beirut, with a focus on treating traumatic brain injury using stems cells in combination with drugs. I aim to acquire more experience in the field of neuroscience and to find neuroprotective therapies for neurodegenerative diseases.

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I am currently a PhD candidate in University of Giessen. Previously, I was a volunteer in the Biochemistry and Molecular Genetics department at the American University of Beirut. The lab focuses on understanding the pathological basis of brain injuries and tests cell- and drug-based therapies for traumatic brain injuries. I have a Master's in Biology with a specialization in Immunology, where I tested the anti-inflammatory and antioxidant activities of different natural agents on autoimmune diseases. I hope to pursue a Ph.D. focusing on the immunopathological basis of autoimmune disorders and hope to find a cure for such diseases.

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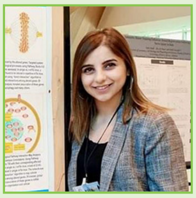

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I obtained my Ph.D. at the University of Texas Southwestern at Dallas (Texas, USA), where I studied microbiota interaction with intestinal cells. Currently, I am an Assistant Professor at the Lebanese International University (Beirut, Lebanon). The current research projects I am working on include the use of stem cells to treat TBI, and the cell–cell communication that happens in different cancers. I also teach several core Biology courses to undergraduates. Email me when you get into college and need help in your Biology courses. *abdshaito@gmail.com

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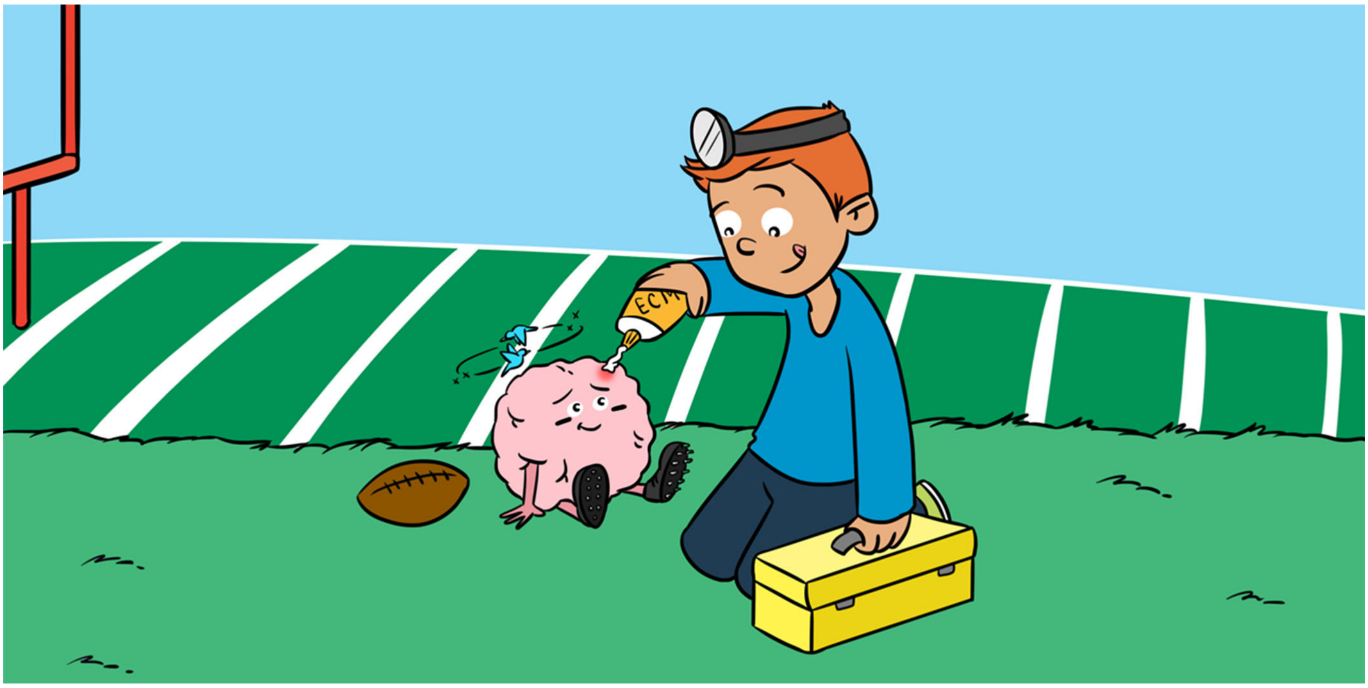

TISSUE ENGINEERING IN TRAUMATIC BRAIN INJURIES

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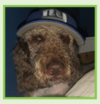
YOUNG REVIEWERS:

ARIANA

AGE: 12



LUCIEN

AGE: 12

NAOMI

AGE: 12

If the brain is injured due to traumatic brain injury (TBI), it will lose some of its cells. If our brain cells get damaged, we may be left with problems controlling our movement, our speech, or even our memory! In the future, tissue engineering may be able to help people with TBI. Tissue engineering involves building a piece of tissue outside of the body or assisting the damaged part of a tissue to grow again and function inside the body. Cells are the building blocks of the body, and they are surrounded by a matrix that supports them. This matrix is called the extracellular matrix (ECM). Scientists can make artificial mimics of the natural ECM. The artificial ECM helps a damaged tissue to regenerate. In this article, we discuss how Gel-MA, an artificial ECM, can have healing properties in injured brains.

INTRODUCTION

Did you know that a lizard can regrow its cut-off tail? This property is called regeneration. Regeneration is an ability that is not unique to lizards. Many animals can regenerate parts of their bodies to replace damaged ones. When a certain flatworm is cut into pieces, each piece of the flatworm can turn into a whole new worm! A starfish can regrow a new arm if it loses one, and sometimes an arm can grow into an entire starfish. Humans can also regenerate, but to a lesser level. For example, have you ever wondered why, when we accidentally cut ourselves with something sharp, we later find it healed with no marks of the injury, apart from occasional scarring? This is due to the **regenerative capacity** of the skin. Unfortunately, not all our body parts and tissues can repair themselves, and some never do so.

REGENERATIVE CAPACITY

The ability of the body to repair and replace cells, tissues, or organs lost due to injury or disease.

THE HUMAN BRAIN

Our brains are like machines that work day and night. We do not think about most of the things that our brains control, like breathing, regulating our heartbeats, and digesting the food that we eat by moving the muscles of the stomach.

The brain is a complex organ and is part of what we call the **central nervous system**. There are two main types of brain cells: neurons and glial cells (Figure 1). Neurons are the key players for information processing. There are around 100 billion neurons in your brain; equal to the number of the stars in the Milky Way Galaxy. Neurons are the cells that make you able to think, learn, memorize things, and transmit messages to other parts of your body. Glial cells are cells that support the neurons. They act like housekeepers or nurses of the brain; they provide neurons with adequate nourishment, they clean up dead neurons, and they protect the living neurons from infection by foreign organisms.

CENTRAL NERVOUS SYSTEM

The bodily system composed of nerve tissues. It controls the activities of the body. In vertebrates, it includes the brain and the spinal cord.

The neurons connect with each other to make a network that allows the brain to perform its functions. If only few neurons in the brain become damaged or dead, then such a small disruption in the neuron network may not be noticed by the affected person. However, if many neurons die, the affected person may suffer from problems with movement, memory, speech, or thinking, etc. When the brain loses too many neurons, it cannot replace them all. This is because the brain, unlike the skin, cannot regenerate. So, protecting this vital organ is a must!

One important thing to know about the brain is that if it shakes, it breaks. A head injury that results from a strong blow or a fall can traumatize the brain. This can disrupt the normal functions of the brain. Such an injury is called **traumatic brain injury** (TBI). Different bumps to the head can lead to different types of TBI, ranging from mild, to

TRAUMATIC BRAIN INJURY

Damage caused to the brain by a bump to the head. The injury usually disrupts normal brain functioning.

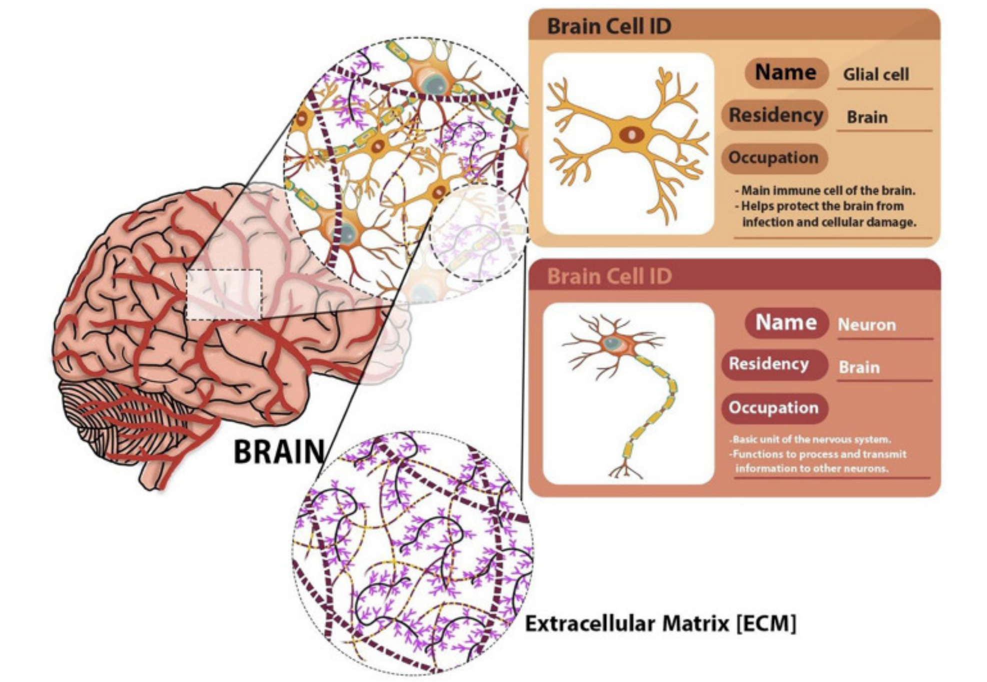


Figure 1

Figure 1

The 3D structure of brain cells: brain cells and their surrounding extracellular matrix (ECM). The human brain is made up of 2 main types of cells as shown in the enlarged area (upper right). The enlarged area also shows brain cells surrounded by the extracellular matrix (ECM). The ECM is made up of a network of biological molecules as shown in the enlarged circle (lower left). The ECM surrounds the neurons and makes a 3D structure around the cells, giving them their shapes and helping them to perform their functions. Two main types of brain cells, neurons and glial cells, are detailed in the enlarged area in the upper right. These cells vary in shape, structure, and function. Neurons process and transmit information to other body systems and organs. Glial cells support neurons with nutrients and protect the whole brain from cellular damage and infection by foreign organisms.

REGENERATIVE MEDICINE

Regenerative medicine is the branch of medicine that develops methods to replace or regenerate human cells, tissues or organs, in order to restore or establish normal function. The impaired function can be the result of any cause, including birth defects, disease, trauma, or aging.

moderate, to severe. The symptoms from a trauma to the brain depend on how severe and frequent the TBI is. In fact, these brain injuries are not rare. Concussions, which may happen when we fall off a bike, play sports, or get in a car accident, are one form of TBI.

REGENERATIVE MEDICINE TO THE RESCUE

A hit to the brain can injure some neurons and even cause them to die. The dead neurons cannot be properly replaced. This is similar to an explosion that causes some buildings to collapse. Obviously, buildings cannot reconstruct themselves. Engineers and workers are needed to fix the damage. If we apply the same concept to injured body parts (such as the brain), **regenerative medicine** can act as the engineers and workers and could save the day [1].

Thanks to regenerative medicine, restoration of body functions that are damaged due to an injury or a disease is now possible. Regenerative medicine can be used to treat diseases such as those of the nervous system and of the heart. Regenerative medicine can also replace or repair tissues and organs that are damaged by trauma (like TBI) or by aging. Regenerative medicine can help in two ways. First, it can use cells made outside the body to replace the lost or damaged cells in the body. Second, it can increase the production of new cells inside the body. These regenerative medicine approaches can enhance tissue function, reduce disabilities, and improve the quality of life [2].

TISSUE ENGINEERING AND THE MAGICAL GLUE

Tissue engineering is one new field of regenerative medicine. It combines life sciences with engineering and applies the principles of both fields. Tissue engineering focuses on developing tissues outside the living body that can be used to restore or maintain a body function or even to replace a whole organ.

TISSUE ENGINEERING

A sub-branch of regenerative medicine. It applies the principles of engineering and life sciences toward the development of biological substitutes that can restore, maintain, or improve tissue function or a whole organ. The biological substitutes include biomaterials, cells, and biologically active molecules. The biological substitutes can be used to create tissues or cellular products outside the body or help the repair of tissues within the body.

Cells are the building blocks of tissues, and they are connected using a sort of glue. This glue is called the **extracellular matrix** or ECM. The ECM makes a 3D structure around the cell, which helps to keep its shape (Figure 1). This 3D structure helps cells to communicate with each other and allows them to function properly. Each type of cell (brain cells, heart cells, etc.) has its unique kind of ECM. Only the ECM specific for a particular cell type can allow that cell type to function properly. One form of tissue engineering, tries to supply cells with a proper ECM glue to help repair damaged cells. The best glue is the one that most closely resembles the original ECM inside the tissue. For example, to have functional brain cells, we need to use an ECM similar to the natural ECM that surrounds brain cells inside the body. This is because only the brain ECM supplies the brain cells with their proper 3D structure.

EXTRACELLULAR MATRIX (ECM)

A three-dimensional network of biological molecules present around cells. It provides support to the cells it surrounds.

When engineering a tissue, scientists use cells that they grow in the lab and/ or an ECM glue. They can build the whole tissue in the lab and then implant it into the person who needs it. Another option is to directly provide the damaged tissue with the substances it needs to rebuild itself. In that case, the ECM glue can be added to the damaged tissues without the need to add cells [3].

GEL-MA, A PROPER ECM FOR TBI TREATMENT

One of the challenges of brain disorders such as TBI is that the damaged neurons are hard to replace. While it is hard for neurons to regenerate by themselves, scientists work hard to make that happen. Since it is not ethical to experiment on the brain of a living human being, scientists use cells growing in small plastic dishes called cell culture dishes (Figure 2A). In our lab, we grow special cells that perform similar functions to neurons. These special cells are cultured on an artificial ECM that we call Gel-MA. Gel-MA is a type of gel made up of gelatin (gelatin is what gives jelly its texture). We have tested the effects of Gel-MA to see if it can help the cells to grow. We grew the special cells with different amounts of Gel-MA. We cultured the cells in the cell culture dishes for one day and then checked how they were growing. We found that, as we increased the amount of Gel-MA, more cells lived. This means that the Gel-MA helped these special brain cells to grow better (Figure 2A).

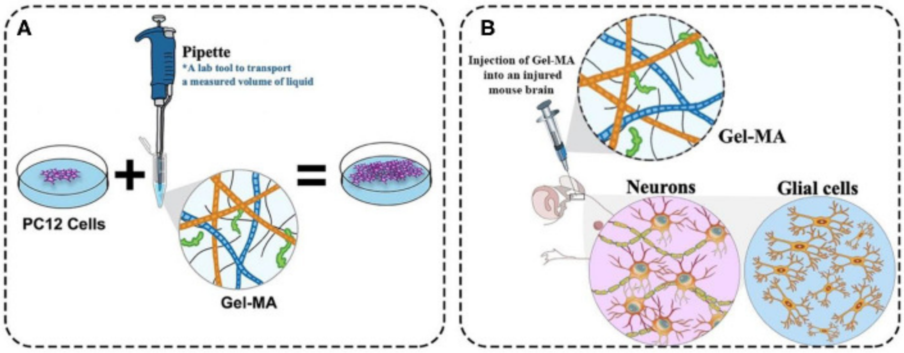


Figure 2

Figure 2

Gel-MA is a potential ECM for treating brain injuries. **(A)** Special cells called PC12, which are a lot like neurons, were grown in cell culture dishes. When Gel-MA was added to the cells, they increased in number. **(B)** Gel-MA was applied directly to the injured brains of mice, to study its beneficial and healing effects in TBI. Gel-MA decreased the size of the injury when applied to injured brains and helped the glial cells and neurons to function better.

In another experiment, we tested whether Gel-MA could protect neurons from damage by TBI. For this, we used mice that we subjected to TBI. We placed a drop of Gel-MA at the place of head injury. After a week, the mice were still alive, which means that the gel did not have toxic effects. When we checked the brains of the injured mice, we found that the injuries were almost gone 1 week after adding Gel-MA. Now, we are testing whether Gel-MA, added to the injured brains of mice, can improve the behavior of these mice or if they can perform mental tasks better. If we see an improvement, this means that Gel-MA helps to heal brain injuries and can restore brain functions (Figure 2B).

CONCLUSION: THE IMPACT OF GEL-MA

We use Gel-MA because it can help neurons establish their proper 3D structure. This is similar to what the natural ECM does in the brain. Another important point is that Gel-MA is not toxic to cells, on the contrary, it enhances their growth. This is exciting because it means that, by using an artificial ECM, we are now able to help the injured brain during its healing process [4]. We saw from our experiments that Gel-MA has healing properties during TBI. Our hope is that, in the future, scientists can improve TBI treatment using Gel-MA or other forms of tissue engineering. The brain, which was long thought to be irreparable, now has the promise of repair. Gel-MA could provide an exciting method for treating TBI. Now we must translate our findings from mice to humans, so that we will be able to deal with the important, worldwide issue of TBI!

ORIGINAL SOURCE ARTICLE

Al Rifai, N., Hasan, A., Kobeissy, F., Gazalah, H., and Charara, J. 2015. "Culture of PC12 neuronal cells in GelMA hydrogel for brain tissue engineering," in *2015 International Conference on Advances* *in Biomedical Engineering (ICABME)*. p. 254–7. doi: 10.1109/icabme.2015.7323300

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CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

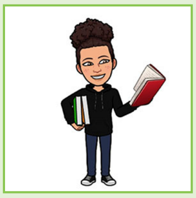
YOUNG REVIEWERS

ARIANA, AGE: 12

My name is Ariana and I am 12 years old. Some of my favorite hobbies are reading, ice hockey, and music. I play the clarinet and the piano. My favorite series is Harry Potter and I can read about a book a day! I also love doing fun science and art experiments.

LUCIEN, AGE: 12

My name is Lucien. I am a sixth grade student. My favorite subjects are math, science, and STEM. My favorite sports are hockey, tennis, and skiing. Other things I enjoy are 3D rendering, graphic design, gaming, and streaming on the PC that I built. I have two little sisters. When I am not picking on them I like cooking breakfast for them.



NAOMI, AGE: 12

My name is Naomi, and I am in sixth grade. In my free time I enjoy reading, playing sports, and playing piano and French horn. I am the oldest sibling and I have two younger brothers who are really annoying.

AUTHORS

JUDY TANIOS

I am currently a junior embryologist at an IVF clinic, committed to making miracles happen for those who lost hope of having children. I am also volunteering at Dr. Firas Kobeissy's lab at the American University of Beirut to fulfill my passion for research. I love to read scientific publications even in my free time. I also love watching movies and have at least one movie night with friends each week.

SARAH AL-HALABI

I graduated from the Lebanese International University with a degree in biochemistry. I am currently studying for my Master's degree in Biology at the American University of Beirut. My research interests include cancer, transcriptomics, proteomics, and microbiology. I want to eventually complete a Ph.D. in Biology or Biochemistry.

HIBA HASAN

I am currently a volunteer in the Biochemistry and Molecular Genetics department at the American University of Beirut. The lab focuses on understanding the pathological basis of brain injuries and tests cell- and drug-based therapies for traumatic brain injuries. I have a Master's in Biology with a specialization in Immunology, where I tested the anti-inflammatory and antioxidant activities of different natural agents on autoimmune diseases. I hope to pursue a Ph.D. focusing on the immunopathological basis of autoimmune disorders and hope to find a cure for such diseases.

SAMAR ABDELHADY

I am a medical doctor. I did a research internship in Dr. Kobeissy's lab at the American University of Beirut (AUB) to study traumatic brain injury [TBI] using animal models. In my free time, I love drawing scientific illustrations and brain art, watching movies that talk about the brain, and since I work for long hours at a desk, I enjoy going hiking to keep my body fit.

JOHN SALIBA

I am a Ph.D. candidate in biomedical engineering at the American University of Beirut. My research interest is in neuroscience, biomaterials, drug delivery, and cancer. I have a Master's degree in BioMEMS and a Bachelor's in Physics. I have a passion for learning new things and understanding how the world around me works. I hope that

I can contribute to improving patient healthcare through new scientific findings and new approaches to therapy.

ABDULLAH SHAITO

I obtained my Ph.D. at the University of Texas Southwestern at Dallas (Texas, USA), where I studied microbiota interaction with intestinal cells. Currently, I am an Assistant Professor at the Lebanese International University (Beirut, Lebanon). The current research projects I am working on include the use of stem cells to treat TBI, and the cell-cell communication that happens in different cancers. I also teach several core Biology courses to undergraduates. Email me when you get into college and need help in your Biology courses. *abdshaito@gmail.com

FIRAS KOBEISSY

I am a neuroscientist with extensive experience in experimental brain injury. I am an assistant Professor at the Department Biochemistry at the American University of Beirut. I obtained my Ph.D. from the University of Florida in the area of neuroscience. My current research focuses on identifying biomarkers for drug abuse toxicity and traumatic brain injury neuroproteomics. I am a member of the Center of Neuroproteomics and Biomarker Research and the Center for Traumatic Brain Injury Studies at the McKnight Brain Institute at the University of Florida. *firasko@gmail.com

†These authors have contributed equally to this work

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NEUROSCIENCE
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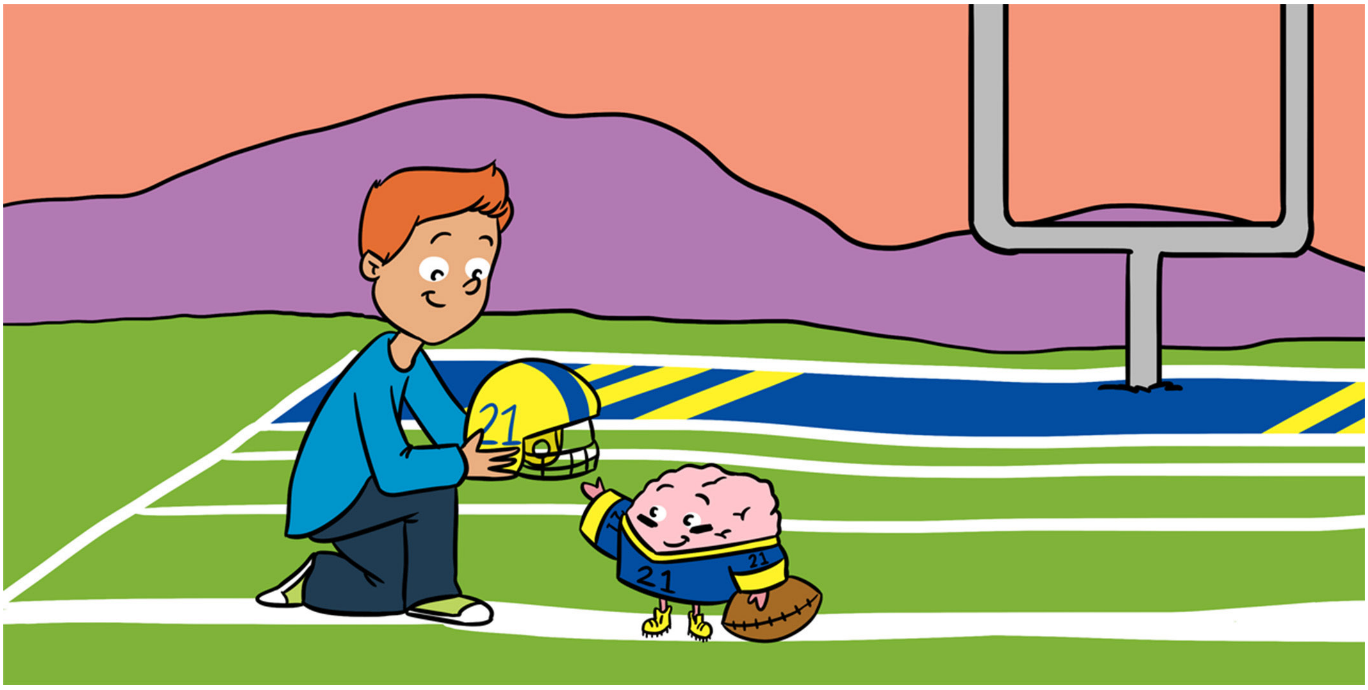

PREVENTING THE BRAIN FROM BEING INJURED

Daniela Flores*, Sabine Delouche and Gillian Hotz

Kidz Neuroscience Center at University of Miami, Miami, FL, United States

YOUNG REVIEWERS:

STEM CONNECT RESIDENTIAL CAMP

AGES: 14-15

The brain controls much of what we do in our everyday lives. Because the brain controls almost everything you do, it is important to protect it and prevent it from being injured. Injury prevention is important, because traumatic brain injuries can result in long-term negative effects when they are not diagnosed and treated properly. Often, children and even their parents are not aware of the symptoms resulting from a traumatic brain injury, and this can lead to a delay in treatment. By understanding how injury prevention works and the methods used, you can reduce your risk of injury and keep your brain healthy.

WHAT IS TRAUMATIC BRAIN INJURY?

Your brain controls everything you do and everything that goes on in your body. It controls how you walk, how you talk, and how you learn; it even controls how hungry you are! Like any other part of your body, sometimes your brain can get injured. When your brain gets injured, it is called a **traumatic brain injury** (TBI). TBI happens when something outside of your body hits you hard enough to hurt your brain.

TRAUMATIC BRAIN INJURY

A disruption in the normal function of the brain that can be caused by an external force such as a hit to the head.

When someone experiences TBI, that person can have problems that last a long time, sometimes even forever. TBI can change the way you think, remember things, and learn things. It can change the way you move and the way you speak, hear, or see. It can also change your emotions and your personality.

CONCUSSION

A mild traumatic brain injury caused by a bump, blow or jolt to the head causing the brain to move rapidly back and forth.

One type of TBI is called a **concussion**. You can get a concussion when something hits your head or body hard enough to knock your brain around inside of your skull [1]. In a concussion, the brain experiences an initial impact on the part of the skull that is hit, due to acceleration or quickly moving forward, and a second impact on the opposite side of the skull, from the deceleration or rebound from the initial impact, as shown in Figure 1. You can get a concussion from playing sports such as American football, ice hockey, boxing, skiing, or even soccer. A concussion can also happen if you crash while riding a bike without a helmet, or if you are in a car accident.

Some common symptoms of concussion include:

- Headaches
- Dizziness
- Trouble balancing
- Being bothered by light or noise
- Confusion
- Having a hard time concentrating
- Feeling nauseous (sick to the stomach)
- Having trouble remembering things
- Having trouble sleeping
- Personality changes

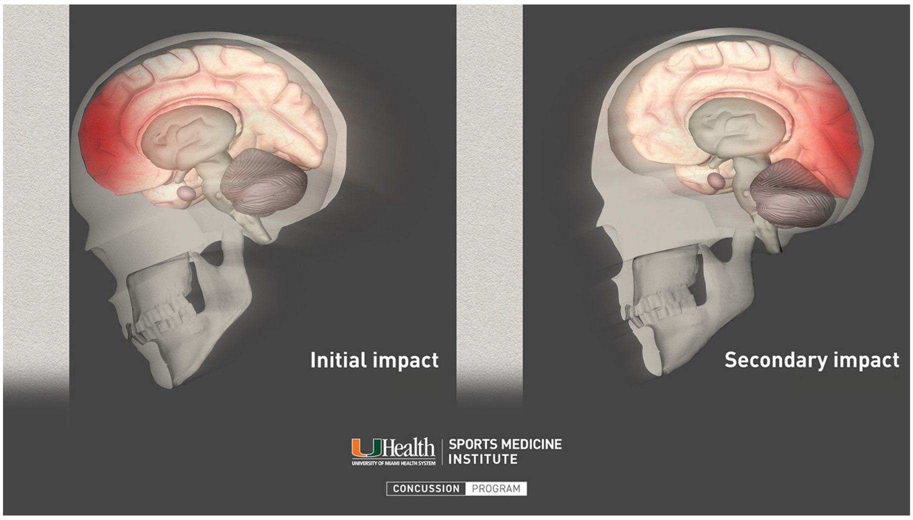

Figure 1

Figure 1

The red areas show where the brain impacts the skull during the initial impact and the secondary impact as a result of hitting your head or body hard enough.

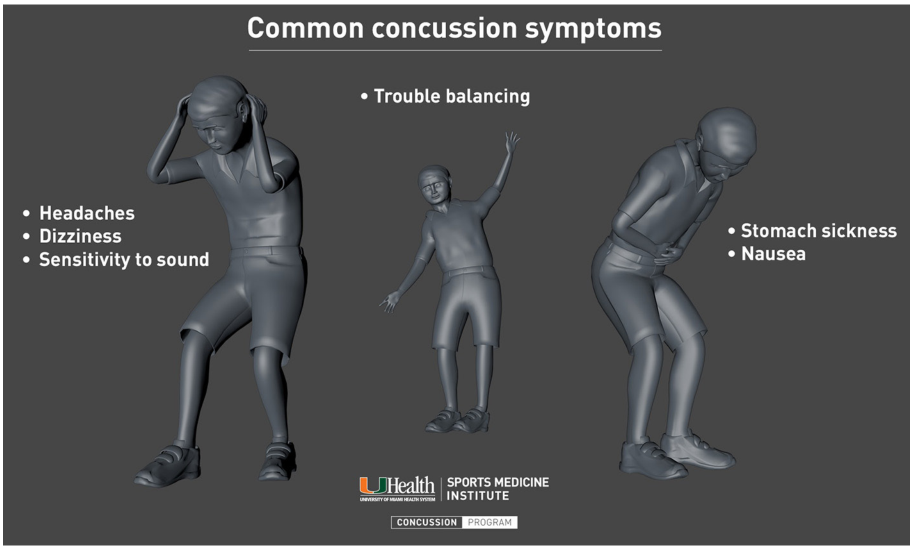

Figure 2

Figure 2

Common concussion symptoms.

These symptoms, which are also illustrated in Figure 2, are all pretty scary! If you hit your head and experience these symptoms, it is very important to seek medical attention.

The good news is that brain injuries like concussions are preventable, and they can be diagnosed and treated by a doctor. In fact, there are programs dedicated to treatment of concussions, like the KiDz Neuroscience Center at the University of Miami (KNC). KNC focuses on reducing the number of children and adolescents that experience brain and spinal cord injuries. Keep reading, to learn about different **injury prevention** models and how programs like KNC use these injury prevention models to reduce the incidences of TBI in their communities.

INJURY PREVENTION

Efforts focused on identifying and preventing the causes of injuries.

LEVELS OF BRAIN INJURY PREVENTION

Brain injury prevention focuses on ways to minimize these injuries in everyday life. There are three levels of prevention: primary (or first), secondary (or second), and tertiary (or third).

The goal of primary prevention is to stop a brain injury from happening in the first place. This is done by reducing the risk of exposure to an injury. An example of primary prevention is teaching athletes about tackling and heading techniques to prevent TBI while playing football.

If someone already has a brain injury, secondary prevention is used to keep that injury from getting worse. Having a doctor examine you for a concussion after a hit to the head, called "screening," is an example of secondary prevention.

The last level of prevention is tertiary. Tertiary prevention is used to lessen the effects of a brain injury. The CDC has new guidelines on mild traumatic brain injury (mTBI) among children, which include 19 recommendations relating to diagnosis, prognosis (outcome), and the management/treatment of pediatric mTBI [2]. These guidelines are examples of tertiary prevention. The recommendations include rest, assistance with school work (giving extra time to complete assignments), and proper sleep methods. All of these can help with recovery.

THE 6-E MODEL OF INJURY PREVENTION

Brain injury prevention programs use something called the "6-E Model" to make sure everything possible is being done to stop injuries from happening. The 6 E's stand for **education, engineering, enforcement, encouragement, equity, and evaluation**. When all of these pieces work together, more brain injuries are prevented.

Education is used to teach an individual what they can do to stay brain injury-free. Effective education about TBI prevention can include learning how to be safe while playing sports, like the football tackling techniques shown in Figure 3, learning how to properly ride a bicycle, and learning how to safely cross the street, as a pedestrian.

Engineering consists of making changes to the environment that will reduce the chances of someone getting hurt. The environment includes the places that you play and live in, the roads you travel on, or even the equipment you use. A newly designed helmet that absorbs

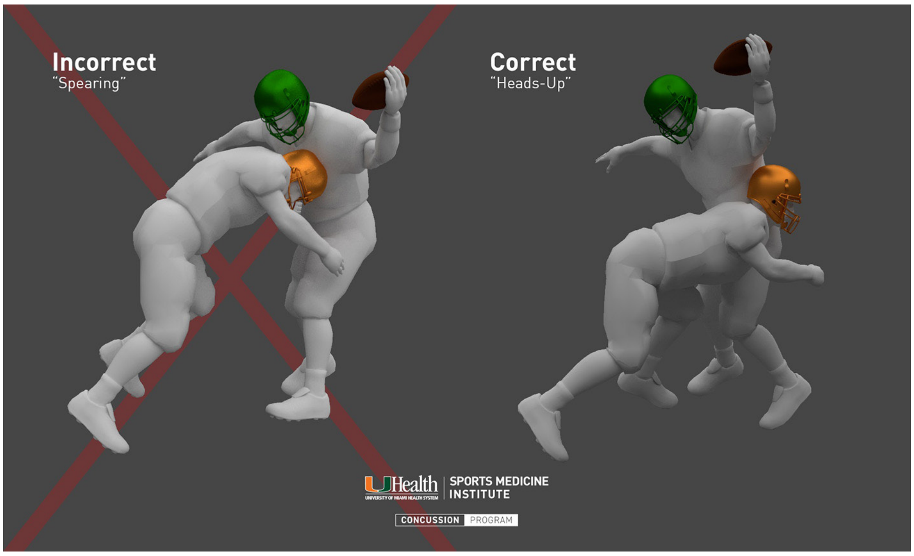

Figure 3

Figure 3

The figure shows two football tackling techniques: spearing and heads-up. It demonstrates the spearing technique as incorrect and the heads up technique as correct tackling technique. The heads up technique avoids direct contact with the head and decreases the chances of injury.

the shock of a hit, and bikes-only lanes on the road to lower the chances of being hit by a car are both examples of using engineering to prevent injuries.

Enforcement enlists the help of lawmakers and police officers to make and enforce policies that reduce TBI incidents. This includes passing laws that help keep everyone safe and using police officers to make sure people follow those laws. Examples of enforcement are police officers giving tickets to people who do not wear seat belts in their cars or requiring children to wear helmets while riding bicycles.

Encouragement creates awareness, by getting people excited about activities like walking and biking, especially when those activities are done in a safe way. Encouragement can be done by giving out prizes, like earning points, each time someone crosses the street safely using the crosswalk.

Equity means giving everyone a chance to benefit from an activity. It also means finding out which things keep people from being safe and trying to fix them. For example, if a child cannot afford a helmet, an injury prevention program can give that child a helmet for free.

Lastly, evaluation, like a report card, checks that safety and prevention programs are actually meeting the needs of the community and working the way they are supposed to. This evaluation step helps to address and fix the things that are not working well.

BRAIN INJURY PREVENTION PROGRAMS AT UNIVERSITY OF MIAMI

Now that you have learned about the levels of injury prevention and the 6-E model, let us take a look at some programs that exist. The KiDZ Neuroscience Center (KNC) at the University of Miami has three programs that work to reduce the number of brain and spinal cord injuries in children and teenagers. These programs were created in 2001 because of the high number of pediatric (ages 0–14) brain injuries seen at the Ryder Trauma Center. Each of these programs uses all three levels of injury prevention in Miami-Dade County, Florida.

1. The first program is UConcussion (www.uconcussion.com). This program includes two clinics, which focus on the secondary and tertiary levels of prevention. The Pediatric mTBI Concussion Clinic helps children 5–16 years old with all injuries that result in concussions. The Sports Concussion Clinic helps high school and college athletes who have a sports-related concussion.

2. The second program is WalkSafe (www.iwalksafe.org). This program teaches elementary school-age (5–10) children how to be safe pedestrians, by teaching them important skills like how to cross the street. This program falls under the primary level of prevention, because it focuses on education and tries to stop injuries before they happen. Children can practice the skills they learn from WalkSafe at school first, before using those skills in their day-to-day lives.

3. The last program is BikeSafe (www.ibikesafe.org). This program teaches middle school-age (10–14) children important bike safety skills. Children learn how to wear their helmets properly, how to check their bikes before going on a ride, rules of the road, and the different hand signals that should be used while bicycling. Just like the WalkSafe program, BikeSafe falls under the first level of prevention.

In addition to these programs that address all three levels of injury prevention, WalkSafe and BikeSafe also use the 6-E model. As result of the efforts of these programs, there has been a 78% decrease in pediatric pedestrians hit by cars and a 30% decrease in pediatric bicyclists hit by cars in Miami-Dade County. The programs have accomplished this by working together with local government officials (like the mayor), traffic planners, school districts, and communities. Strong relationships with these different partners help the programs work toward improvements to bike paths, roads, sidewalks, and school environments, to make the environment safer for young people like you!

CONCLUSION

You are now prepared to help prevent brain injuries from happening to you and to those around you. You have learned what a concussion is, what the symptoms are, and how concussions can happen. Even if you think you are not at risk for getting a TBI, accidents can happen, and this is valuable information to help keep your brain healthy.

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CONFLICT OF INTEREST STATEMENT: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

STEM CONNECT RESIDENTIAL CAMP, AGES: 14-15

The STEM Connect Residential Camp was an experiential education program offering Year 10 students from nine schools, 3 days of exposure to exciting and rewarding study of Science, Technology, Engineering, and Mathematics (STEM) on the Sunshine Coast. The STEM sessions targeted enterprise skills such as creative thinking and problem solving, digital proficiency, and science communication.

AUTHORS

DANIELA FLORES

I am most interested in working to improve the well-being of children. Before working for the University of Miami WalkSafe program, I worked in the Foster care system as an Advocate for children who were abused and neglected. Now that I have gained experience in injury prevention and brain injury research, I want to continue learning and exploring these topics. During my spare time, you can find me hanging out at the beach or trying out new restaurants around Miami. *dflores@med.miami.edu

SABINE DELOUCHE

I am a recent graduate of Public Health, and am learning so much about prevention and working to keep populations safe and healthy. My favorite part of public health is getting to interact with people of all different backgrounds and ages. When I am not at the office, you can find me dancing to salsa music, traveling, and trying out new foods! I love adventure, and enjoy getting to learn more about people, their environments, and what makes them happy.

GILLIAN HOTZ

I grew up in Ontario, Canada where most kids play hockey, skate, or ski. I was always getting injured myself from playing these sports and started thinking about what could be done to prevent these injuries. In college, I studied Neuroscience at Boston University where I learned all about the brain and brain injury. After I finished my Ph.D., I started working at the Ryder Trauma Center in Miami where I directed a Pediatric Brain Injury Program where we treated children with traumatic brain injuries. We put a multidisciplinary team together to figure out how to prevent these injuries of children that get hit by cars, are injured on a bicycles and skate boards and also playing sports.

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NEUROSCIENCE
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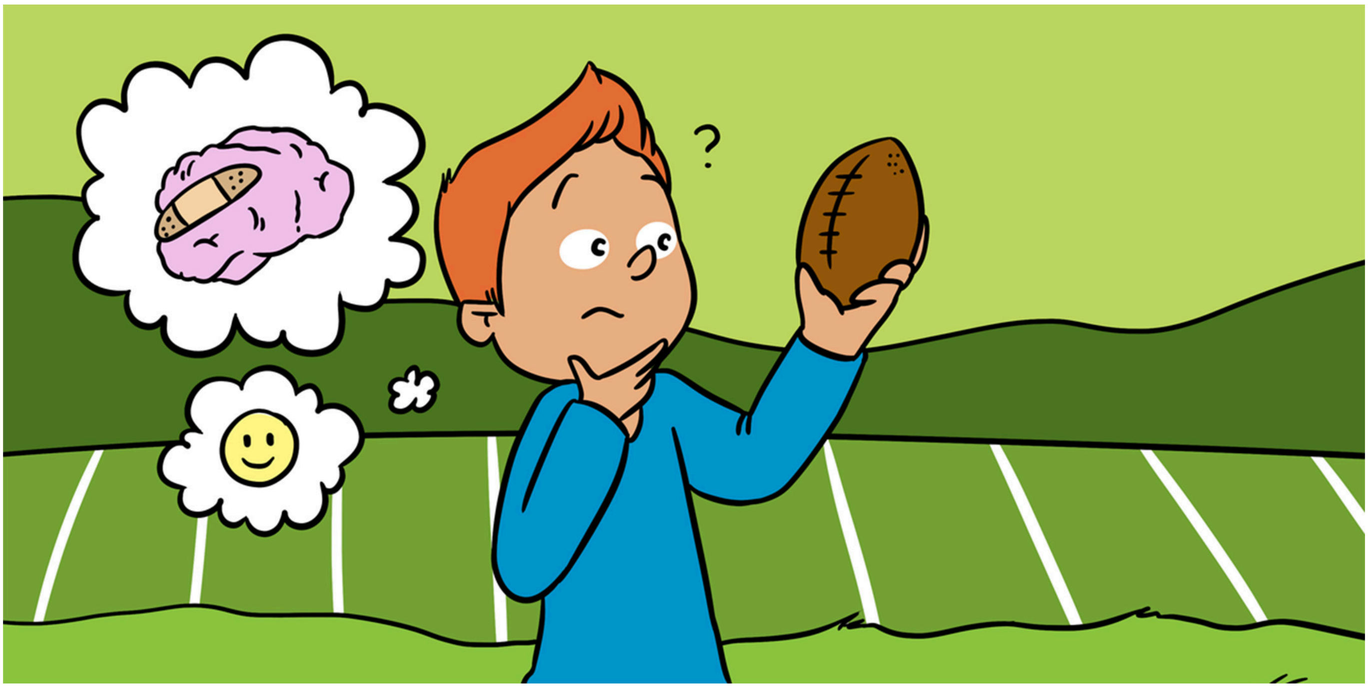

SPORTS ARE GOOD FOR YOUR MOOD, BUT A CONCUSSION IS NOT

Amanda Clacy[1], Daniel F. Hermens[1], Kathryn M. Broadhouse[1,2] and Jim Lagopoulos[1]*

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[2] Sydney Medical School, University of Sydney, Sydney, NSW, Australia

YOUNG REVIEWERS:


CHARLOTTE
AGE: 9


DARREN
AGE: 9


JOSIE
AGE: 9


NOAH
AGE: 14


VRISHAB
AGE: 9


WILL
AGE: 9

To play, or not to play, that is the question! We all know that sports are really good for your health. Did you know that playing in a team sport during adolescence has been shown to improve brain development and can protect you from developing a mood disorder? On the flip side, playing a sport can also place you at risk of getting an injury, like a concussion. Concussion is an injury to the brain that happens quite often when people play sports like football, netball, and soccer. The damage a concussion can do to someone's brain might increase their risk of developing a mood disorder later in life. In this article, we are going to discuss the benefits that participation in team sports can offer to healthy brain development and mental health, as well as the potential damage sports-related concussion can do to brain function and mood.

There are heaps of different things that can support healthy brain development during **adolescence** (ages 12–18), but there are also some things that might not be so good for our brains. In this paper, we

ADOLESCENCE

The stage of development between childhood and young adulthood, typically between 12 and 18 years of age.

MOOD DISORDERS

A psychological disorder in which a person's feelings and emotions remain either too active (such as anxiety) or not active enough (such as depression) over several weeks.

CONCUSSION

An injury to the brain that occurs when someone is hit in the head or body, causing the brain to be thrust forwards or backwards in the skull, which disrupts normal brain function.

will talk about why sports are good for the brain during adolescence, because they not only offer some protection against the development of **mood disorders** but can also help people who have mood disorders to feel better. But we will also talk about how getting a **concussion** while playing a sport might put someone at risk of developing a mood disorder later in life.

In this article we are going to talk about things like depression (feeling sad or empty), anxiety (feeling worried or stressed a lot of the time), and suicidality (not wanting to live anymore). If you are struggling with any feelings like this, or are worried about your mental health at all, please talk to a trusted adult, such as a parent, a teacher or counselor, or your doctor.

MOOD DISORDERS IN ADOLESCENTS

Mood disorders, such as depression and anxiety, are big mental health problems for young people all over the world. Having a mood disorder can make it difficult for a young person to develop positive relationships with friends and family, concentrate at school, or feel hopeful about the future. When someone feels these kinds of things over weeks or even months, that person may begin to experience depression (feeling really low and empty) or have thoughts of suicide (not wanting to live any more). Mood disorders, such as depression and anxiety play a part in the development of suicidal thoughts and behaviors (also called suicidality). It is really important that we look for ways to prevent the development of mood disorders and also ways to help young people who have mood disorders to feel better.

The brain goes through a *lot* of changes during adolescence. In regard to mental health in young people, these changes can make the brain quite sensitive to injuries. Let us start by talking about how the various areas of the brain are connected to each other. Regions of the brain need to communicate with each other so that we can think, plan, and carry out tasks in everyday life. The brain is made up of gray matter and white matter. Gray matter contains the cell bodies of neurons (which are the building blocks of the brain that process information). White matter consists of parts of neurons called axons, which are the connections that link different regions of gray matter together (see Figure 1). During adolescence, the white matter begins to decide which brain areas need to be connected the most. Think of this like a road map. Big cities get visited by more people more often, so highways are built to make sure that people can access these places quickly and easily. On the other hand, little country towns might only have dirt tracks connecting them, because they do not get visited as often. In the same way, as the brain develops throughout adolescence, it prioritizes building the white matter connections that we use the most and removes those that we do not use anymore (see Figure 2;

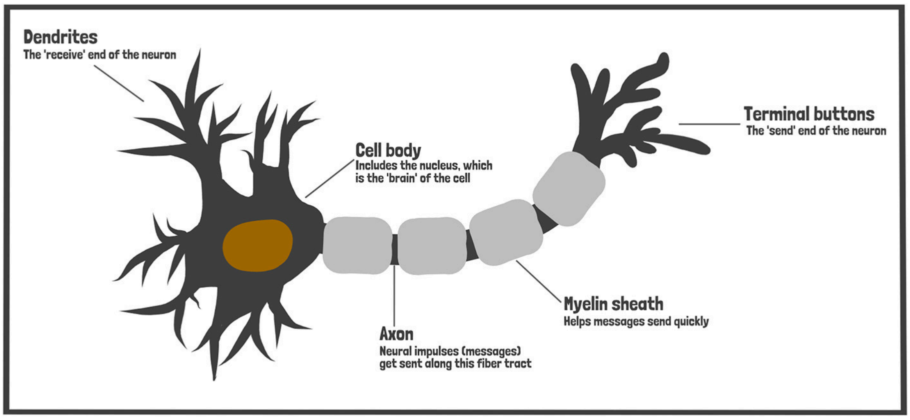

Figure 1

Figure 1

Our brains are made up of billions of neurons. Gray matter is made up of the cell bodies of neurons, and white matter is made up of the myelin-covered connections (known as axons) that link different regions of gray matter together.

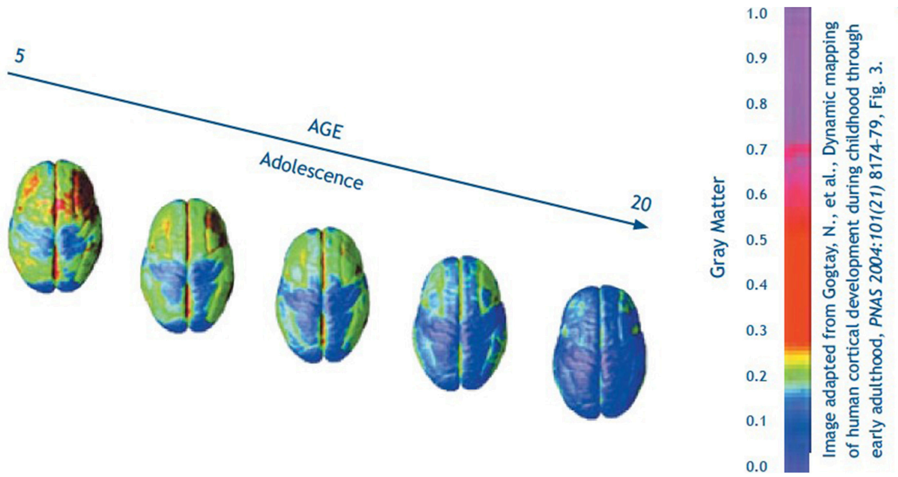

Figure 2

Figure 2

The white matter "road map" of our brains is shaped throughout adolescence to strengthen the highway connections between the regions of the brain we use most often and delete the dirt track connections we do not use. At the same time, our gray matter becomes more dense in the regions of the brain we use most. Think of it like little cities in the brain, where gray matter sky-scrapers and shopping centers are built so lots of business and activity can happen in one spot. By the end of adolescence, a healthy brain will have a well-formed network of white matter highways and dense gray matter cities, to help us process lots of information quickly and effectively.

[1]). This allows the brain to quickly respond to certain, common things without you having to think about them too much.

During adolescence, the prefrontal cortex (PFC) and the limbic system are two regions of the brain that are under major construction (see Figure 3). The PFC is involved in making decisions and in goal-directed behavior (thinking about what you want to do, how to do it, and then doing it). The limbic system controls our feelings, memories, and stimulation (which allows us to explore, learn, and discover interesting things). Research has found that young people who experience mental health issues like suicidality, anxiety, and depression during adolescence are at risk of their white matter highways failing to connect these important regions of the brain properly [2]. If the connections between the PFC and the limbic system are not healthy and strong, it is more difficult for someone to solve problems, set goals, and manage emotions in a healthy way. When they cannot do these important tasks, people can begin to feel sad, stressed, and overwhelmed. Unfortunately, these kinds of difficulties place young people at risk of developing a mental illness.

Figure 3

During adolescence, the prefrontal cortex (PFC) and limbic system are two regions of the brain that are under major construction; they are connected by the anterior cingulate cortex (ACC). The PFC helps us to make decisions and process information, and the limbic system helps us to process our emotions.

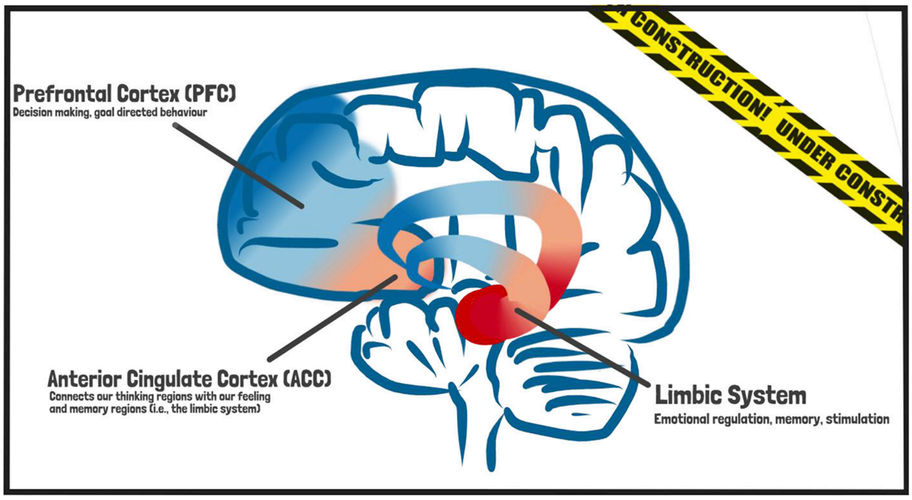

Figure 3

SPORTS ARE GOOD FOR THE DEVELOPING BRAIN

There are lots of different ways we can help support healthy brain development throughout adolescence. One of these is physical activity. Through its effect on how we think and feel, as well as its effect on the way our brains form, physical activity has been shown to significantly benefit adolescent mental health and development. How does this happen? Research has shown that physical activity improves brain development during adolescence through its positive effect on **neurogenesis** (the growth of neurons) and **brain plasticity** (the ability for the brain to change and adapt to new and different things) [3]. Playing a *team* sport can offer even more protection and developmental perks than just physical activity alone! Participating in a team sport exposes a person to both the benefits of physical activity on the brain, as well as to great social support and engagement with other people.

NEUROGENESIS

The growth of neurons. The opposite of this is **neurodegeneration**, which is the death of neurons.

BRAIN PLASTICITY

Our brain's ability to change and adapt to new and different things.

By participating in team sports, adolescents are more protected against mood disorders, because they feel more involved with their friends, they feel better about themselves and their skills, and they feel more confident in social settings [4]. This is exactly what we want to see, because young people who have strong relationships with their friends and family have been shown to be more resilient, hopeful, and positive about their lives, which is basically the opposite of having depression or thoughts of suicide. These effects of team sports can help the brain make strong, positive connections and provide lasting benefits to a young person's mental health.

CONCUSSION AND MOOD

Unfortunately, because many team sports involve a lot of people moving quickly, there is a risk that players might get injured.

Concussion is an injury to the brain that occurs when someone is hit in the head or body, causing the brain to be thrust forwards or backwards in the skull, which disrupts normal brain function. Concussions can feel and look different in different people. Some people with concussions might become forgetful, others might become grumpy or depressed; others might get a really bad headache or feel like they are going to be sick. Some people might even experience a combination of these different symptoms. Young athletes might feel these symptoms straight away or it might take hours or even days for the symptoms to emerge. If you *think* you have a concussion, you should visit your doctor to get checked out, just to be on the safe side. Most people will recover from a concussion in about 2 weeks without any ongoing symptoms or major disruptions to their brain development. However, there are some people who, following a concussion, continue to have problems with things like memory and emotions. This may be because of injury to the parts of the brain that control these functions.

The brain regions that have been shown to be most impacted by concussions include the PFC and the limbic regions of the brain. These are the same regions of the brain that are under a lot of construction during adolescent development, and the same regions that are involved in mood disorders like depression and suicidality. This might be why concussions and depression share so many symptoms (see Figure 4). The damage a concussion can do might actually place a young person at risk of developing a mood disorder later in life, because it impacts the same brain regions that are rewiring and developing during adolescence. In fact, adolescents with a history of concussion have been found to be over 3 times more likely to experience depression in their lifetime, compared with young people who have never had a concussion [5]. Research looking at depression and suicide in adult and retired athletes has begun to show us that concussion may undo a lot of the good things that sports do for the brain. For example, concussions have been linked with **neurodegeneration** (the early death of neurons), reduced brain plasticity, and the development of depression and suicidality [6]. Unfortunately, we do not yet know what the long-term emotional and developmental consequences are for young people who get a concussion.

TO PLAY, OR NOT TO PLAY?

A lot of research still needs to be done to improve our understanding of the interactions between participation in team sports, concussion risk, and long-term mental health outcomes for adolescents. Most of the research we have on concussions and how they relate to the development of depression and other mood disorders has not been looked at in adolescents. This makes it difficult to totally understand the long-term impact of concussions on youth mental health. As we have said, adolescence is a sensitive time in the development of the

Figure 4

These are some of the symptoms shared between concussion and depression. These similarities might occur because the PFC and the limbic system are shown to be affected in both conditions.

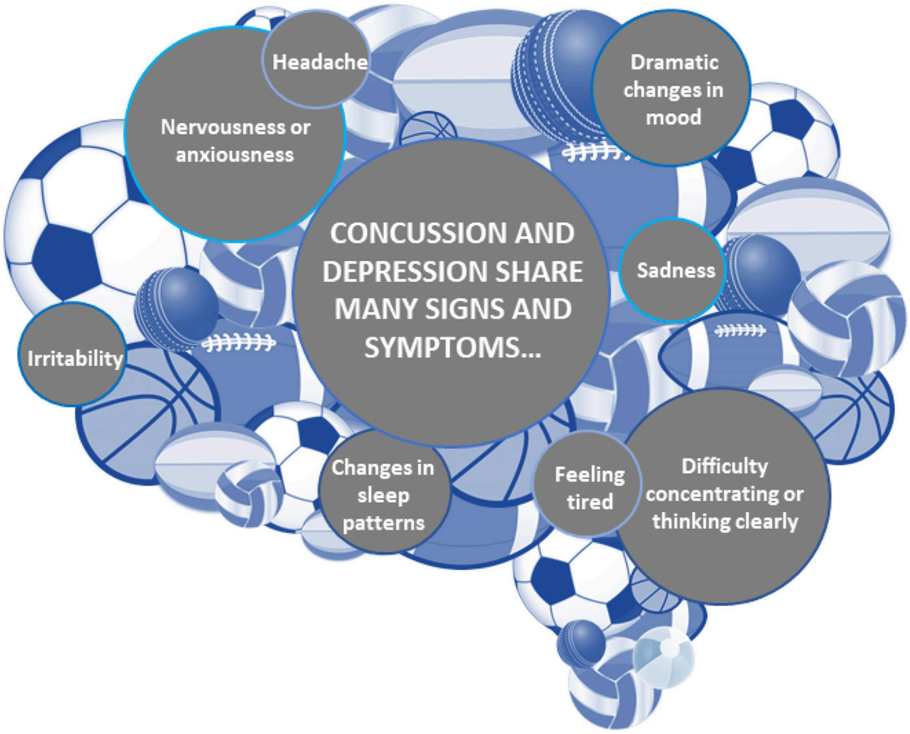

Figure 4

brain. We need to make sure we are doing everything we can to support happy, healthy development throughout this period, which includes being physically active with friends!

Remember, if you are struggling with feelings of sadness, anxiety, or stress, or if you are worried about your mental health at all, please talk to an adult that you trust.

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CONFLICT OF INTEREST STATEMENT: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

CHARLOTTE, AGE: 9
Charlotte is in fourth grade and loves playing soccer, mastering new math concepts, and reading books about adventurous kids. She sleeps on the top bunk and her favorite snack is pita chips. Charlotte barely tolerates her twin sister, but she adores her baby sister, who was born on Leap Day. Charlotte plans to study biology in college. She wants to attend a school where she can ride a Segway to visit her parents whenever she feels like it.

DARREN, AGE: 9
I like to do math, and reading in school. I am also very good at spelling.

JOSIE, AGE: 9

Josie is in fourth grade and loves playing soccer, eating Korean food, and reading books about adventurous kids. She sleeps on the bottom bunk and her favorite junky snack is chips. Josie's best frenemy is her twin sister, but she absolutely adores her baby sister, who loves to wear overalls. Josie plans to study music in college and become a famous singer.

NOAH, AGE: 14

I am halfway through high school and my favorite subject is lunchtime, closely followed by Music and Science. When I grow up, I want to be an astrophysicist. I like to read in my free time. I do parkour, crossfit, and Air Force cadets outside of school, and I am writing a book about Australian SAS soldiers. I like to eat, especially enchiladas and bacon, but not at the same time.

VRISHAB, AGE: 9

I play the violin and flute. I like sports. I am very passionate about the environment and started a composting club at my school.

WILL, AGE: 9

I am a fourth grader in Philadelphia, PA. I love playing and watching sports, especially my hometown Philadelphia teams. I also like school, especially reading, writing, math and social studies. I have been playing drums for 3 years. I like going on trips like to the beach or to visit my grandparents in Florida. I also really like playing games with my little sister and building sports stadiums with blocks and magnet tiles.

AUTHORS

AMANDA CLACY

In my research on head injuries and mood disorders, I use both neuroscience and community research methods to make sure that I am getting the facts about things that matter most to everyday people. My favorite part of my job is talking to people in the community about what is important to them. My goal as a researcher is to help create a world that brings out the best in people. In my spare time, I like climbing mountains, taking my dogs kayaking, and crocheting brains and fun critters.

*aclacy@usc.edu.au

DANIEL F. HERMENS

I am a brain scientist and I study mental disorders, including ADHD, depression and psychosis. My research has focused on adolescents and young adults, which I think is the most interesting and dynamic time of life in terms of brain changes. Currently, my favorite part of the brain is the hippocampus. When I am not doing research, I like to gaze at architecture, go on long bike rides or dance "robot-style" with my two daughters while we listen to Daft Punk.

KATHRYN M. BROADHOUSE

I decided I wanted to study science and more specifically Physics at high school as I loved to learn how things and the universe work. When deciding my career, it was really important for me to be doing what I love, but also feel my work was meaningful and helping society. I therefore decided to specialize in medical imaging as this field combines a lot of the fundamental principles of physics to investigate and understand disorders and disease.

JIM LAGOPOULOS

In my career as a brain scientist I have taken over a million pictures of brains and studied many different areas of mental health. One of my favorite parts of my job is sharing my passion for brain research with up-and-coming scientists. I believe the more we know about the brain, the more we can help people to live their best lives. When I am not researching brains, I like to go on adventures. Some of my favorite adventures are deep sea fishing, climbing big mountains, and being with my kids.

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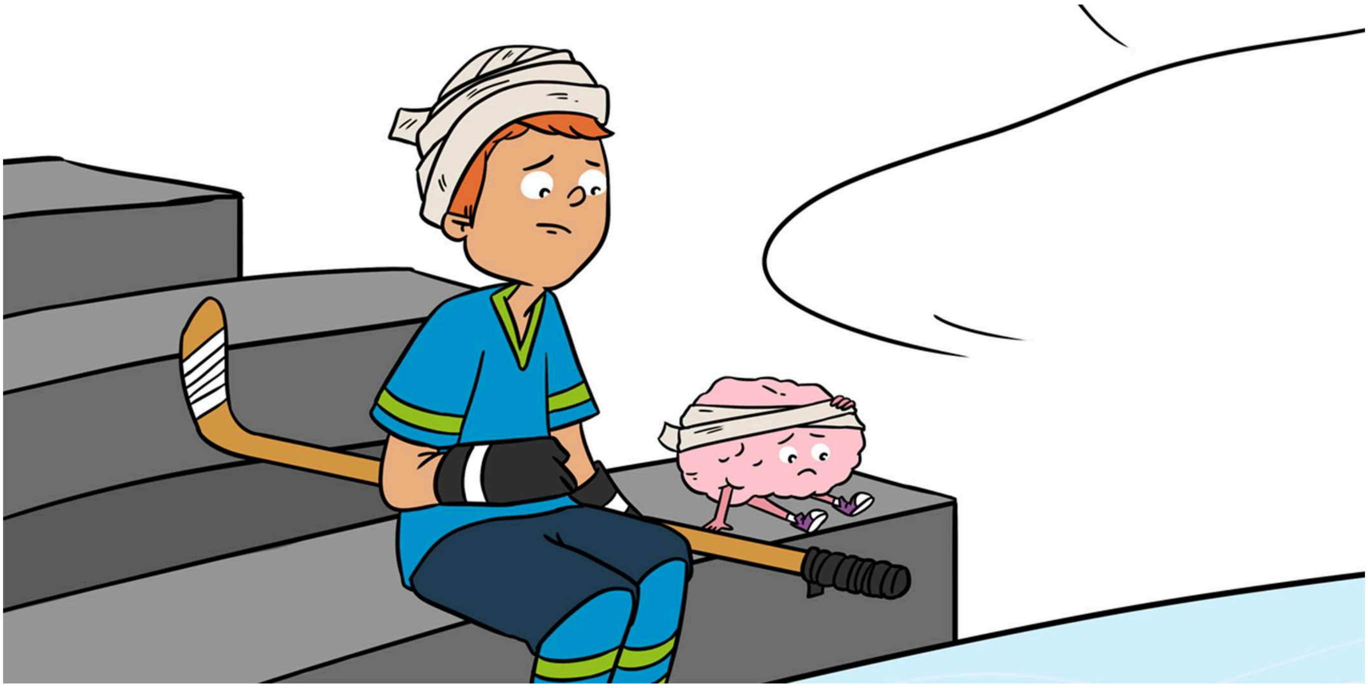

CTE: THE HIDDEN RISK OF PLAYING CONTACT SPORTS

Hamad Yadikar**, Connor Johnson, Edwin Mouhawasse, Milin Kurup, Lynn Nguyen, Niko Pafundi and Kevin K. W. Wang

Program for Neurotrauma, Neuroproteomics & Biomarkers Research, Departments of Emergency Medicine, Psychiatry, Neuroscience and Chemistry, University of Florida, Gainesville, FL, United States

YOUNG REVIEWERS:

MONICA
AGE: 5

WASHINGTON ELEMENTARY
AGES: 9–10

If you have ever played contact sports, you may have heard about chronic traumatic encephalopathy (CTE). CTE is caused by repetitive head injuries leading to a progressive loss in memory and other brain skills. The lack of proper skull protection has become a leading cause of brain problems in athletes. When playing sports, we focus on competition rather than the impact of repetitive injuries. Physical sports, like football, hockey, and boxing, have all been associated with CTE. When the brain hits the skull with an intense force, a substance in brain cells called tau proteins can malfunction in a way that leads to harmful changes in thinking, behavior, and mood. Tau proteins can collect between brain cells and form structures that disrupt normal communications between the cells. We can protect our brains from CTE by limiting the number of head injuries we experience. Giving ourselves adequate recovery time following an injury, receiving medical clearance before

Figure 1

Figure 1

Which sports can cause CTE? High-impact sports, such as soccer, football, boxing, and hockey, can lead to the development of CTE. Tackling in football, hitting the head on the ice in hockey, and hitting the ground or another person's head in soccer can all lead to head trauma and result in CTE if not appropriately treated. Although some protective gear has been created for sports, such as football and hockey, players are still susceptible to CTE. Sports administrators have added padding to arenas and courts to prevent head injuries. Additionally, coaches have emphasized good sportsmanship and proper techniques to avoid head injuries.

TRAUMATIC BRAIN INJURY (TBI)

Damage in the brain caused by a sudden hit to the head. TBIs can occur from accidents, sports, or other physical traumas.

CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE)

A disease developed after multiple traumatic brain injuries, through the breakdown of brain cells.

COUP AND COUNTERCOUP MODEL

A model representing how an initial injury (coup) can have enough force to cause damage on the opposite side of the brain (countercoup).

returning to normal activities, and keeping up with our social lives throughout recovery can help prevent or minimize the negative effects of CTE.

WHAT IS CTE?

Have you ever played a sport and hit your head by accident, maybe colliding with the ground or with another person? You might have experienced a ringing pain or a headache in the short term, but have you ever considered what repetitive hits to the head might do to your brain in the long term? When we play sports, we tend to focus on the fun parts, like the competition, teamwork, and the joy of winning. However, people usually do not consider the possible consequences of sports injuries on their mental health. Contact sports like football, soccer, boxing, as well as domestic violence and bomb blast waves, might damage the human brain more than expected, even after all the initial symptoms of the injury are gone (Figure 1) [1].

When a strong force hits the skull, the brain suffers damage. When the brain is damaged by a single injury, called a **traumatic brain injury (TBI)**, the body is affected in many different ways, depending on the intensity of the damage. When there are repeated injuries to the brain, those people are at a higher risk for developing something called **chronic traumatic encephalopathy (CTE)**. Chronic stands for "long-lasting," traumatic means "intense," and encephalopathy refers to any process that alters the function or the structure of the brain. Severe hits can injure opposite sides of the brain, through the **coup and countercoup model**. How do opposite sides of the brain get injured? Well, the coup is the initial injury that occurs from a hit, while the countercoup injury occurs on the opposite side of the brain as the brain hits the inside of the skull (Figure 2). When the injury is intense,

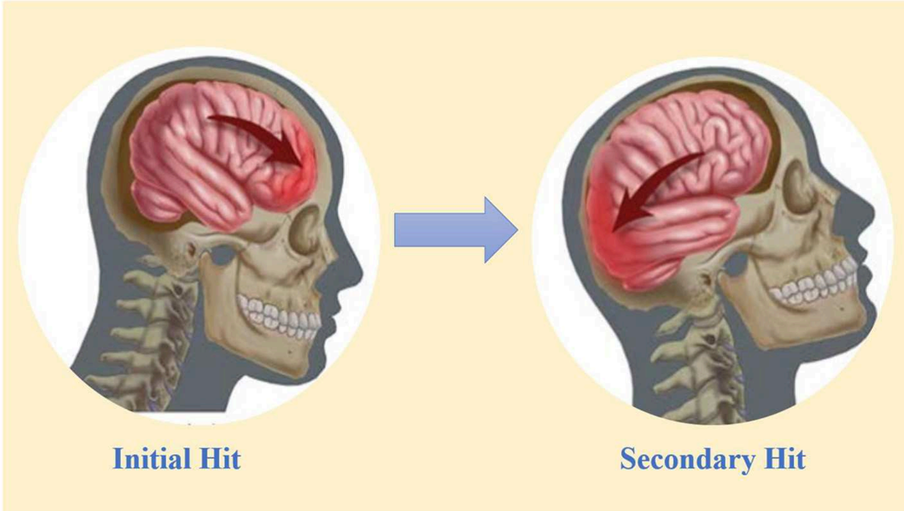

Figure 2

Figure 2

One hit can damage two parts of the brain: the coup and countercoup model. One hit to the brain results in a force on the skull that causes the brain to move back and forth. This motion leads to dual injuries, one in the location of the initial hit (coup) and a secondary hit on the opposite side, where the brain bounces off the inside of the skull (countercoup). Such injuries can be very damaging to the structure and function of the brain [1, 2].

the brain can develop long-term damage in multiple areas that can significantly impair brain function, possibly leading to memory loss and, in a few cases, even death.

So, it seems that repeated brain injuries will begin to damage the brain permanently. In sports like football, players can have contact on almost every play. Head contact is frequent in soccer, especially when players slide tackle to get possession; frequent head-to-head contact going for a ball can knock players out. In boxing, getting hit in the head repeatedly is inevitable. Looking at these sports from this perspective, it is easy to see why so many athletes are developing CTE, and most do not realize the consequences. Some sports have less of a risk for CTE, including swimming, tennis, and even basketball. We should all consider the risks and think about brain safety before we play any activity or sport. There are always emergencies that no one can control, like bike or car accidents, but when it comes to contact sports, we need to make the right decisions for a healthier life [1–4].

The level of intensity of each hit influences how quickly the brain starts to deteriorate. CTE can come from one strong hit or multiple smaller hits over time. Multiple factors influence the development of CTE in response to a head injury, including genes, diet, alcohol, drugs, etc. Different people are affected in different ways, and no specific number of hits dictates whether the CTE will develop [1].

WHAT HAPPENS IN THE BRAIN WHEN PEOPLE HIT THEIR HEADS PLAYING SPORTS?

The human brain needs healthy proteins for the brain cells to work and function properly. There are some proteins that we get from our diets and other proteins that are produced inside our bodies, such

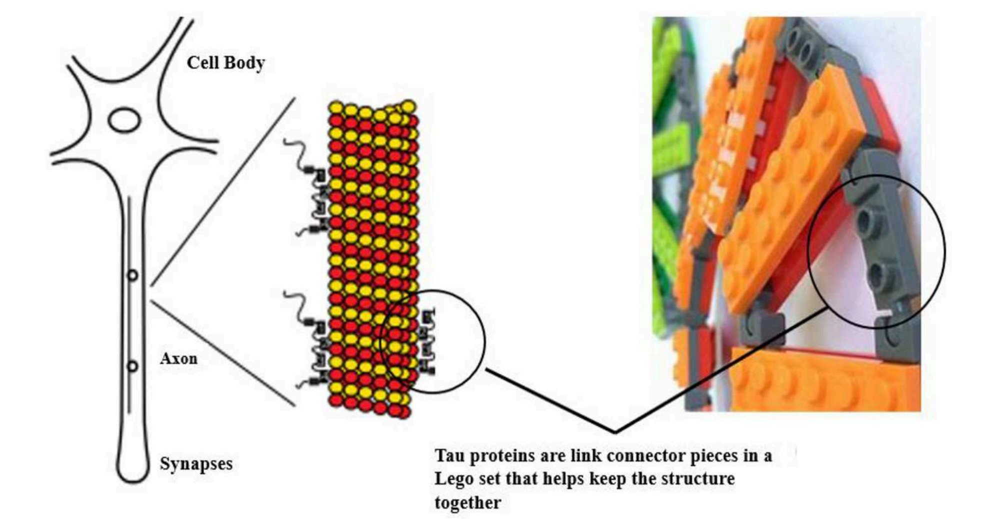

Figure 3

Figure 3

How do tau proteins relate to TBI/CTE? A brain sends messages (synapses) through brain cells or neurons. A neuron is made of a long central strand known as an axon, which helps carry synapses in the brain. An axon is made of smaller proteins (microtubules) represented by the red and yellow balls. Similar to Lego pieces, tau protein holds onto the microtubules to hold the neurons together. When tau proteins are broken down as in TBI or CTE, they cause destruction of the brain neuronal structure. These broken parts of tau form a mess. Too much destruction makes it hard for the body to clean up the mess. When the messes obstruct brain functions, this leads to memory loss and other problems.

TAU PROTEIN

A protein that holds brain cells together to keep the brain structure intact.

TAUOPATHIES

Diseases caused by the breakdown of tau proteins; Alzheimer's disease is an example.

as the **tau protein**. Tau proteins are the connecting pieces that hold brain cells together. Imagine the brain is a Lego city, with thousands of tall buildings, each one representing a brain cell. If a head injury occurs while playing sports, it disrupts the brain cell structures, like an earthquake causing the Lego buildings to fall apart. Continuous hits shake the brain cells, breaking them into smaller pieces and creating a mess that we call protein aggregates. When these aggregates collect within cells, it is difficult for the tau protein to function properly. Think of a traffic jam on the streets between the Lego buildings, caused by all the fallen debris. Over time, larger protein aggregates collect through the breakdown of other brain cells. As people age, these messes become so severe that the Lego city of brain cells in the brain can no longer function in a healthy way. Diseases related to problems with tau function are called "**tauopathies**." Tauopathies do not occur in an instant but happen after multiple brain injuries occur over time. Playing contact sports can speed up this process [1, 2, 5] (Figure 3).

HOW CAN I TELL IF I HAVE CTE?

CTE is hard to diagnose compared with other brain diseases. The methods usually used to look at the brain and diagnose brain diseases are called MRI and CT scans [6]. Unfortunately, these techniques are not able to show whether or not the brain has experienced CTE. You can predict that a person might have CTE if he or she has been a sports player for 10–15 years and suddenly starts acting differently or expressing unusual emotions, such as suicidal thoughts and depression. Scientists usually identify CTE after death because the brain has to be removed and examined for tau clusters to accurately diagnose CTE. Observation of degraded brain structures and decreased brain size may indicate that a person had CTE. Most of the symptoms associated with CTE also occur in people who suffer from diseases related to memory loss, including Alzheimer's disease.

Researchers are trying to find new and efficient ways to diagnose CTE in living patients so that these people can be treated. Many methods are being studied, but one of the most promising methods is a brain-scanning technique known as positron emission tomography (PET). PET scans the brain a radioactive substance is injected into a vein. The radioactive substance allows any problems with the brain tissues to be seen. PET researchers would like to discover a specific radioactive substance that can find issues with the tau proteins in the brain. Another important method for diagnosing CTE involves identifying broken-down forms of tau in body fluids, including blood, **cerebrospinal fluid (CSF)**, mucus, saliva, or urine. Detection of tau in these fluids could indicate whether CTE is likely in the patient.

CEREBROSPINAL FLUID (CSF)

The brain or spine fluid that scientist use to study tauopathies.

How can *you* know if you might have a brain injury from hitting your head? Immediate symptoms, which can happen right after the injury or take up to a day to occur, include: loss of consciousness, feeling dizzy, severe headaches, blurry vision, nausea/vomiting, fatigue, trouble speaking, difficulty sleeping, loud ringing in the ears, or even a bad taste in the mouth [3, 4].

CAN CTE BE TREATED?

CTE is a progressive, long-term, harmful process. At this point, there no reliable treatments for CTE. However, scientists are hoping to find some biological molecules, known as biomarkers that can be used to detect and decrease the chances of developing CTE. These biomarkers are produced by the cells of the brain, specifically when the brain is injured, and they may someday allow us to diagnose CTE and potentially cure the diseased brain.

HOW CAN I PREVENT MYSELF FROM GETTING CTE?

Since there is no cure for CTE, preventing it is the best way to stop yourself from getting it. Headgear and body pads are examples of preventative methods that are meant to lower the chances of head injuries in many sports and jobs. Although helmets do not fully prevent TBI, they reduce the amount of impact. Hard surfaces on the outside of helmets are used to prevent skull fractures, while inner sections contain padding to reduce the amount of shock that the head experiences when hit. Scientists and sports medicine analysts are working on improving helmet paddings to prevent coup and countercoup injuries.

In addition to protective gear, sports administrators continue to take preventative measures to ensure the safety of players. For example, placing pads on hard surfaces in wrestling arenas and on basketball courts, to prevent head injuries. Coaches also teach players how to respect each other through sportsmanship, to avoid aggression and unnecessary injuries. Coaches have also incorporated neck stretches before, during, and after practice, to release neck tension and provide head support.

CONCLUSION

Although preventative methods are used, brain injuries still occur on a daily basis. When these injuries do happen, they must be appropriately treated. Around 85% of TBIs need about 3 weeks of recovery. One should take care of oneself until fully recovered, to prevent additional injury. Cut back on physical activity, get plenty of rest, avoid computer time, write things down, and avoid drinking alcohol. During recovery, light exercise and brain-stimulating activities are recommended to help the brain and body heal. Some examples include stretching exercises and puzzles. Following the recovery process, your doctor may have you undergo physical and mental tests to make sure your brain has gone back to its original state. These tests will ensure that you have recovered enough before you to go back to your day-to-day activities [1, 2].

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YOUNG REVIEWERS

MONICA, AGE: 5

I like to draw pictures... because I want to express what is on my mind. I enjoy going to new cities and countries. I am extremely creative, and I love cooking. I also like to read books and learn things by children all over the world. I like sports like swimming and skating.

WASHINGTON ELEMENTARY, AGES: 9–10

This young group of science minded students love working together to solve problems think through issues and come up with solutions that make the world an even more awesome and science-y place!

AUTHORS

HAMAD YADIKAR

Hamad Yadikar is an Assistant Professor at Kuwait University, in the Department of Chemistry and Emergency Medicine. His research project involves understanding traumatic brain injuries (TBIs), and CTE. He is continuing his studies as a post-doc with Professor Wang at the University of Florida and hopes to aim to find a cure for people that suffers from different types if brain injuries. *hamadayadikar@chem.ufl.edu

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Connor Johnson is a fourth-year undergraduate at the University of Florida majoring in Chemistry with a focus on Biochemistry. He is a Researcher at the McKnight Brain Institute in Gainesville, Florida under the supervision of Dr. Kevin Wang, Ph.D. and Ph.D. candidate Hamad Yadikar. He hopes to attend medical school and ultimately become an emergency physician or a trauma surgeon.

EDWIN MOUHAWASSE

Edwin Mouhawasse is a third-year Health Science major at The University of Florida. He does research at the McKnight Brain Institute on traumatic brain injuries, under Ph.D. student Hamad Yadikar and Dr. Kevin Wang. He is a member of the volunteer organization Dream Team, where he volunteers in the pediatric intensive care unit and the pediatric cardiac intensive care unit. He is following the pre-medical track and would like to go to medical school and become a physician one day.

MILIN KURUP

Milin Kurup is a freshman studying at the University of Florida, majoring in Microbiology and Cell Sciences and minoring in Health Disparities. He has been working with Dr. Kevin Wang and Ph.D. candidate Hamad Yadikar on tauopathies for the last two years. After experience in neurological research, he hopes to pursue a career in Pediatric Neurosurgery and inspire children in medical sciences.

LYNN NGUYEN

Lynn Nguyen is in her fourth year studying at the University of Florida. She majors in Microbiology and Cell Science and minors in Environmental Sciences. She studies tauopathies at the McKnight Brain Institute under the supervision of Dr. Kevin Wang and Ph.D. candidate Hamad Yadikar. Once she graduates, she plans to apply to dental school and eventually become a prosthodontist.

NIKO PAFUNDI

Niko Pafundi graduated from the University of Florida with a B.S. in biology in 2018. Under the supervision of Dr. Kevin Wang and Ph.D. candidate Hamad Yadikar, he has assisted in experiments and analyzing the results to further understand tau protein. In May of 2018, he plans to apply to Pharmacy School.

KEVIN K. W. WANG

Dr. Kevin Wang is the Director of the Program for Neurotrauma, Neuroproteomics & Biomarkers Research and Associate Professor of Emergency Medicine at the University of Florida and the McKnight Brain Institute in Gainesville, Florida, USA. He is also Health Research Neuroscientist and Merit Award Principal Investigator at the Brain Rehabilitation Research Center at the Malcom Randall VA Medical Center (Gainesville, FL).

frontiers FOR YOUNG MINDS

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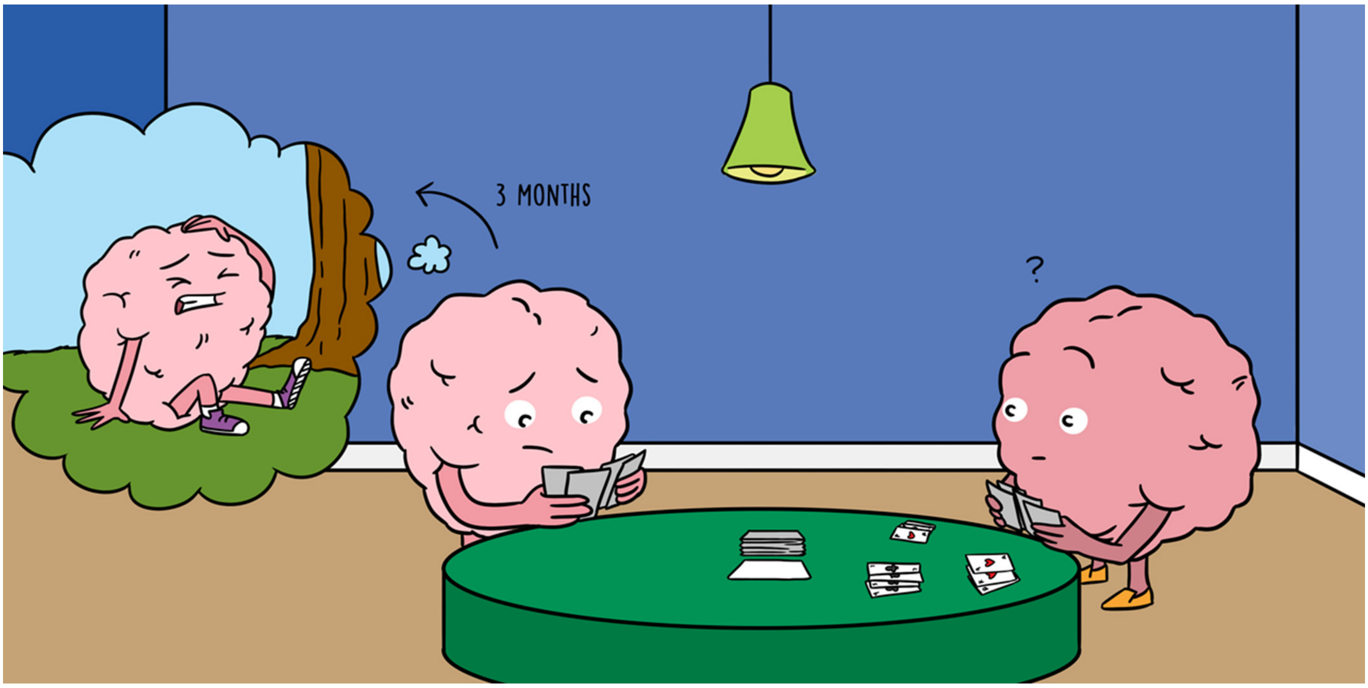

THE EFFECTS OF CONCUSSION CAN BE LONG-LASTING

*Alexandrea Kilgore-Gomez, Hector Arciniega and Marian E. Berryhill**

Programs in Cognitive and Brain Sciences, and Integrative Neuroscience, University of Nevada, Reno, Reno, NV, United States

YOUNG REVIEWERS:

MT. ROSE ELEMENTARY

AGES: 11–12

Have you ever felt "groggy" after hitting your head? We are learning more about how important it is to protect your brain from injuries, such as concussion. Concussion is also called mild traumatic brain injury (mTBI). After an mTBI, most people think patients recover within a few weeks. We noticed that some college students who had had an mTBI were struggling to remember information for a few seconds. This ability is called working memory and we need it for most thinking jobs, like remembering the name of someone you just met, or what you wanted to get from the fridge. In our experiments, we tested different groups of students to see if they could remember things for 1 s, like the color of squares. Participants with a history of mTBI (on average, more than 4 years after injury) performed worse than students without a history of mTBI. The take-home message is that there can be lasting effects of mTBI, even years after it happens.

WHAT HAPPENS AFTER A CONCUSSION?

Accidents happen all the time, due to falls, car accidents, and sports. Often, in accidents, people hit their heads. In the USA, **mild traumatic**

MILD TRAUMATIC BRAIN INJURY (MTBI)

Also known as concussion, a condition of brain damage due to force applied to the head.

brain injury (mTBI) results in >200,000 hospitalizations per year [1]. mTBI causes the brain to move, twist, or bounce against the inside of the skull. This can stretch and tear brain cells even though the brain is protected by a cushion of liquid called cerebrospinal fluid, several layers of tissue, and the skull. Some people even lose consciousness during an mTBI. People may not appear injured from the outside after an mTBI. Medical professionals have to diagnose an mTBI by physical examination and by asking questions. Soon after an mTBI, people often report symptoms including headaches, trouble with coordination and sleep, feeling slowed down ("mental fog"), difficulty concentrating, feeling emotional, and memory loss. A few weeks after an mTBI, symptoms usually go away and people slowly return to their daily activities, including school and sports.

Most research on mTBI includes people during the acute (0–7 days after injury) and subacute (up to 3 months after injury) stages of recovery. Only a little research studies what happens more than 3 months after injury. This is probably because of the assumption that everyone fully recovers. But there can be lasting problems with thinking, even years after an mTBI [2, 3]. This is an important point, because it means that some people do not fully recover after an mTBI.

CAN MTBI AFFECT BRAIN FUNCTIONS, LIKE MEMORY?

Executive functions are thinking abilities that allow us to achieve our goals. For example, executive functions allow you to stay on task, plan ahead, hold onto thoughts, solve problems, and refrain from inappropriate actions (like talking back to a teacher). In patients who had experienced TBI more than 4 years ago, we studied an executive function called **working memory**, which is the mental workspace that holds information for immediate use. For example, remembering the numbers the teacher writes on the board as you write down the problem in your notebook. Working memory differs from what is called long-term memory, which is what we use to remember events over years. For example, working memory helps us do addition in our heads, long-term memory is what allows us to remember our first day at school.

Working memory has three stages: **encoding** (putting information in), **maintenance** (holding on to that information), and **retrieval** (remembering that information and using it). Usually, people can hold about 3–5 things in working memory at a time. Working memory requires cooperation between regions in both the front and back of the brain. If brain cells in either of these regions are damaged, working memory could suffer. Although some researchers observed normal working memory shortly after mTBI [4], others saw that working memory is worse after mTBI, even years after injury [5, 6]. A problem

EXECUTIVE FUNCTION

Abilities that allow us to get our work done. These abilities include paying attention, planning ahead, staying on task until it is done, and not doing something we know is not allowed.

WORKING MEMORY

The "mental workspace" that holds on to a few pieces of information for immediate use. It includes three stages: encoding (putting information in), maintenance (holding onto information), and retrieval (remembering what was put in).

ENCODING

Putting something into working memory. For example, the colored squares are put into working memory during the encoding stage.

MAINTENANCE

Holding on to information in working memory.

RETRIEVAL

Remembering information that is in working memory. For example, knowing the color of the top squares after they disappear from the screen.

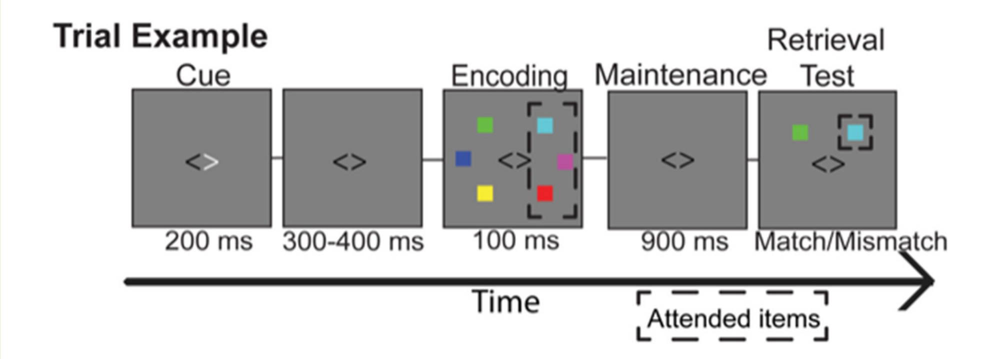

Figure 1

Figure 1

How did we test the three phases of working memory? Participants included students with a history of mTBI (averaging >4-years post-mTBI) and a control group, without a history of mTBI. The task was on a computer. Students kept their eyes on the center of the screen. First, a white cue (< or >) pointed to the side of the screen to attend to (dashed box indicates the attended items), while ignoring the squares on the other side. Then, colored squares flashed (100 milliseconds (ms), or 1/10 of a second). Students tried to encode (remember), the color of each square on the attended side. Next, during maintenance, students tried to remember each square's color. Finally, there was a retrieval test. Students judged whether one colored square (inside the dashed square) matched the color shown during encoding.

in understanding the lasting effects of mTBI is that injuries vary, and everyone's brain and recovery are different.

To study whether mTBI affects the executive function of working memory in patients who had mTBIs in the past we asked two questions. First, we asked whether college students with a history of mTBI performed differently on a working memory task compared with students without a history of mTBI. Second, we asked whether one of the stages of working memory—encoding, maintenance, or retrieval—was more hurt by the mTBI.

HOW DID WE TEST OUR QUESTIONS?

To determine whether working memory was affected by mTBI, we tested students with a history of mTBI, averaging 4 years post-injury, and a control group that was made up of students who had no history of mTBI. Participants had to use working memory to remember the colors of squares that were briefly flashed on a computer screen. The experiment asked students to do a lot of trials that went as follows. First, student focused on the center of the screen, a cue appeared (white >), indicating where the student should attend (outlined in dashed box)—either the left or the right side of fixation. Then, after a short pause, 1, 2, or 3 colored squares quickly flashed on each side of the screen. On one side they were attending (and on the side they were ignoring) the colored squares. This image was the working memory encoding phase which allowed some of the colored squares to enter working memory. Next, there was a short pause, or maintenance period, during which the student tried to hold in working memory the color of each square. Finally, the retrieval stage was a test of working memory. One square appeared on the attended side of the monitor and the student pressed keys to indicate whether it matched or mismatched the color shown during encoding. An example of one trial of this task is shown in Figure 1, and participants did hundreds of trials.

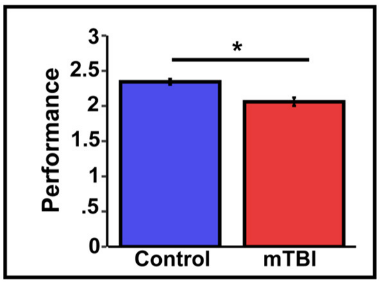

Figure 2

Figure 2

Students with a history of mTBI remember less than the control group. The control group (blue bar) remembered almost 2.5 (out of 3) colored squares, but the mTBI group (red bar) only remembered about 2. The * means this difference is statistically significant. We used mathematical tests to tell us if the difference between the two groups is more than would be expected by chance. We found that it did, so it is called significantly different. These results and others we performed told us that students with a history of mTBI are worn at working memory tasks.

Then, to see if one stage of working memory was more affected by mTBI than the others, we made each stage of working memory easier or harder. One way we did this was to change how long the stage lasted. For example, lengthening encoding by showing the squares longer makes it easier because there is more time to attend to the different colors. Even when we made the task easier the mTBI group still did worse. This told us that the problem is not with one particular stage of working memory. We think it is more likely that each stage is a little bit worse in the mTBI group.

WHAT DID WE FIND AND WHAT DO OUR RESULTS MEAN?

First, we found that, overall, students with a history of mTBI did worse on our working memory tasks than students without a history of mTBI (Figure 2). This is surprising because it was about 4 years since the students had had an mTBI and most people think that we get completely better after an mTBI. The results mean that there can be lasting changes after an mTBI. We found problems with working memory and we are now seeing problems with attention. We think there could be other problems, too, and we are now using more kinds of tasks to better understand what kinds of lasting changes are likely.

When we asked whether one stage of working memory was more affected by mTBI, we found that the encoding, maintenance, and retrieval stages of working memory seemed to be equally affected. Even when we made each stage of working memory easier, we still saw that the mTBI group performed worse. For example, making encoding longer did not help the mTBI group, nor did making the maintenance duration shorter. We do not think that just one stage of working memory is causing the problem; instead, problems can happen at each stage of working memory. This will probably make it harder to fix because we need to work on improving encoding, maintenance and retrieval in the mTBI group to help improve working memory.

So, what does this mean for you? Take care of your head! Having an mTBI can hurt a person's working memory for a long time, even years after the injury. Prevention is important because we do not know how to fix problems with thinking tasks, such as working memory. In our study, we learned that no single stage (encoding, maintenance, or retrieval) of working memory could explain the working memory problem in the mTBI group. We saw that college with a history of mTBI could not remember as many colored squares as students who did not have mTBI. This could mean that they have to study more to do well in their classes, and college is hard enough already. Preventing head injuries is important. Wearing a helmet protects you from head injuries today and protects you from the effects of mTBI months and years into the future.

WHY IS THIS RESEARCH IMPORTANT?

This research is important because mTBIs should be taken seriously. Right now there is no blood test or brain scan that can reliably detect an mTBI. mTBIs require medical attention, and mTBI sufferers should follow the medical advice of their doctors. Brain injuries need time to heal and we need to learn more about how to help people recover. Researchers must continue to study what is happening to the brain after an mTBI. For example, our group wants to find out why some people with a history of mTBI do not show impairments in working memory. Maybe this information will help us to find ways to help those patients who do have working memory problems, so that all mTBI survivors can return to a normal working memory capacity.

ORIGINAL SOURCE ARTICLE

Arciniega, H., Kilgore-Gomez, A., Harris, A., Peterson, D. J., McBride, J., Fox, E., et al. 2019. Visual working memory deficits in undergraduates with a history of mild traumatic brain injury. *Atten. Percept. Psychophys.* 81:2597–603. doi: 10.3758/s13414-019-01774-9

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YOUNG REVIEWERS

MT. ROSE ELEMENTARY, AGES: 11–12

We are an amazing group of students that LOVE Science class! We enjoy being challenged and seeing how real life research can connect to our lives. In our spare time we enjoy art, drawing, reading, eating, sleeping, video games, kickball, basketball, soccer, and spending time with our friends.

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Alexandrea Kilgore-Gomez is a senior in college at the University of Nevada, Reno majoring in Neuroscience and minoring in Analytical Chemistry. She started working in the Memory and Brain laboratory with Dr. Marian Berryhill during her first year in college. She has now conducted many experiments investigating mild traumatic brain injury. After graduation, she plans to go to attend medical school to become a doctor. In her free time, she likes to rock climb, try new restaurants, and watch movies.

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CARING FOR YOUR BRAIN: WHAT YOU NEED TO KNOW ABOUT CONCUSSIONS

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REVIEWED BY:

DARIUS
12 YEARS OLD

Concussions are an injury to the brain that can result in several kinds of changes in the way the brain functions: changes in the way you think (cognitive changes), in the way your brain works (neurological changes), and in the way you feel (physical and emotional changes). Concussions can be caused by accidents where you hit your head on something like the ground, a tree, or another person. It is important to know the signs and symptoms of a concussion and what you need to do to allow your brain to heal properly. It is also important to know how to prevent concussions.

INTRODUCTION

Five little monkeys jumping on the bed, one fell off and bumped his head – many activities we engage in involve running, jumping, and playing. Sometimes, activities are organized, for example, playing soccer or baseball. Other times you create games in your backyard with friends, go sledding when snow appears, or have other fun adventures in nature. All of these games and adventures are important for your body and your brain. Involvement in these activities is good for your body, as they make you stronger. These activities also help your brain learn to think and solve problems. Adventure and exploration are a big part of childhood, and it is good to grow up doing what you enjoy. Accidents happen though, including accidents to monkeys jumping on beds! Each year millions of kids are injured while riding bikes, sledding, or playing sports. Some of these injuries are visible, like a cut or a broken bone. However, the brain can be injured too, even though you cannot see it. It is important to know what you can do to protect your brain from serious injury and what you should do if you think you may have hurt your head. The best thing you can do if you hurt your head is take the time to recover appropriately and talk to others about how you are feeling. Then, you can get back to your adventures and exploration – because those things are important too.

WHAT IS A CONCUSSION?

A concussion is an injury to the brain that is caused by a sudden, abrupt movement of the head, typically because of a blow or jolt to the head or body that makes the brain move rapidly inside the skull (Figure 1).

The injury that results from this is called a mild traumatic brain injury, most commonly referred to as a concussion. There are many different definitions of concussion, but they all have some things in common. These common features include changes in brain function, including changes in the way you think (cognitive changes), in the way your brain works (neurological changes), and in the way you feel (physical and emotional changes). These changes may or may not be accompanied by a temporary loss of consciousness, also known as fainting or passing out [1]. The abrupt movement of the brain can stretch and injure brain cells, which can change the way these cells function. These

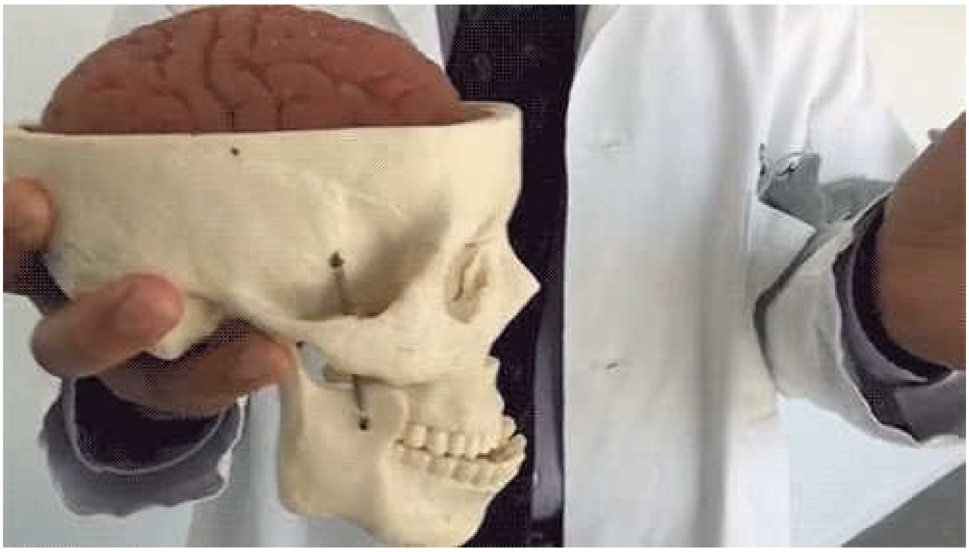

FIGURE 1

FIGURE 1

This is how your brain moves in your skull when you are hit (http://ucresearch.tumblr.com/post/131237007666/this-is-your-brain-experiencing-a-concussion-it).

changes can be short-lived or long-lived, but most of the time, the cells heal and function normally in 7–10 days [2].

Sometimes, it may take longer than 10 days for the brain to return to normal after a concussion, especially in children. Because it is not possible to "see" the changes that happen in your brain or how your brain is healing, it is very important to know the signs and symptoms of a concussion and to tell an adult what you are feeling. That way, everyone can get a better idea of how your brain is healing [3].

SYMPTOMS OF A CONCUSSION

When you hit your head, these signs and symptoms may happen right away, or they may take a few hours or even a day to start. How do you know if you have a concussion? Usually, people will report that they "don't feel right." These are some of the symptoms that you might notice in yourself if you have a concussion [4]:

- Headache or "pressure" in the head;
- Nausea or vomiting;
- Balance problems or dizziness, or double or blurry vision;
- Bothered by light or noise;
- Feeling sluggish, hazy, foggy, or groggy;
- Confusion, concentration, or memory problems;
- Just not "feeling right," or "feeling down."

Other people, such as friends, parents, and teammates, are also helpful in determining if you have a concussion, because they might notice certain signs or symptoms that you will not notice yourself. These are some of the common signs that they might observe in a child with a concussion:

- The child cannot recall events that happened *before* or *after* the hit or fall;
- The child appears dazed or stunned;
- The child forgets instructions, is confused about an assignment or position, or is unsure of the game, score, or opponent;
- The child moves clumsily;
- The child answers questions slowly;
- The child loses consciousness (*even briefly*);
- The child shows mood, behavior, or personality changes.

These signs and symptoms can be very serious, and they can make it hard to do the things that you want to do. Therefore, if you feel these symptoms or see them in someone else, it is very important to report them to an adult.

WHAT SHOULD I DO IF I HAVE A CONCUSSION?

If, after an accident, you are not feeling right and think you might have a concussion, it is very important that you report your symptoms to an adult. Depending on where you are when injury happens, this adult could a teacher, coach, or your parents. Sometimes, athletes do not want to report that they may have a concussion because they want to keep playing or they are afraid that they will let their team down. It is important to remember that you are injured and your health is more important than whether you win or lose a game! If you think a friend does not seem right after being hit in the head, you should also help them out by making sure that they tell an adult, or you can tell an adult what happened. Because it is often hard to see that a concussion has happened, parents and doctors will rely on you to be honest and tell them what symptoms you are having. If you start feeling worse, it is very important to tell someone.

WHAT SHOULD PARENTS AND COACHES DO IF THEY SUSPECT A CHILD HAS A CONCUSSION?

Concussions are especially dangerous because you cannot see the actual injury; therefore, adults must rely on the child to report that they have been hit in the head and ask them to describe any symptoms they have that might be related to a concussion. Adults should monitor the injured child to see if there are any signs of a concussion and to see if the child is acting differently or just does not seem quite right. If an adult suspects that a child has a concussion, the child should be removed from play or stop doing what they were doing, so that they can be monitored. It is then important to seek out appropriate medical attention to have the child evaluated, so that they can receive the proper treatment. Parents and coaches should provide a supportive environment, so that children will report that they have been hit in the head and possibly have a concussion. Also, adults should not let the injured child back to play until they have been cleared by a doctor.

WHEN CAN SOMEONE WITH A CONCUSSION RETURN TO PLAY OR SCHOOL?

Now, you know that it is important to let your brain heal after a concussion, before you go back to adventures and school. But how do you know if your brain is ready to go back? The signs and symptoms of a concussion are your best measure of how your brain is healing. The recommendation is at least 24–48 h of complete mental and physical rest. That means no screen time (e.g., texting, TV, and computer), and no running, jumping, spinning, or swinging. You will also need to stay out of school because thinking and problem solving is hard for your brain, too. After the first 24–48 h, you may work with your doctor to start adding back in activities to see how you feel when you do them. Do those symptoms return? For example, you might try to read for a bit or go for a walk. How do you feel? You should continue to increase the amount of work your brain does and what it is exposed to, including loud noises and bright lights. If at any point your symptoms increase, then take a break from that activity for a bit longer. This might mean telling your parents or a teacher that you do not feel right. Your brain is still healing. When reading, screen time, lights and noises do not seem to increase symptoms, then try getting your heart rate up and see how you feel. Go for a run or a bike ride and if symptoms return take a bit more time off. It is very easy to reinjure your brain while it is healing. So, make sure to let it heal all the way before you get back to adventures, exploration, and playing sports. During this recovery time, continue to be honest about your symptoms and listen to the recommendations of your doctor and parents [5].

HOW DO I PREVENT A CONCUSSION?

Since you now know that it is very important to protect your brain, but also know that it is important to be adventurous, how do you protect your brain? Hopefully, you wear a helmet when you ride your bike, skateboard, or ski. But do you wear it when you go sledding or on a zip line? These are also adventures that may lead to you hitting a tree or the ground hard enough to cause a concussion. A helmet is a great protector for your brain, although you can still get a concussion while wearing one. Some states have laws about the activities that require helmets and the required age for wearing a helmet (for example, biking under 16 years of age), but there is never a law that you cannot wear a helmet; so, be as safe as possible and wear a helmet whenever you do anything adventurous! You should also wear head protection during sports, like a helmet for football or head padding for martial arts. Wearing head protection may feel a little weird at first, but it is better to be safe than sorry. Some sports require helmets to be worn, and in these sports, it is helpful to make sure that your helmet fits you well. If your helmet does not fit snugly, see if you can find one that fits you better. If you notice any cracks or damage to the helmet, make sure to tell your coach, so that he can make sure it is replaced or fixed. It is also important to learn good mechanics and form when you play sports. Your coach will teach you how to tackle someone or to head a soccer ball. Listen carefully and use your strong body, not your head, to play. If you do not use proper technique, you might put yourself or someone else at risk for a concussion. Examples of proper form include making sure you tackle with your head up in football or not using your stick as a weapon in hockey or lacrosse. While you might see a lot of information on TV or in the news related to the long-term effects of concussions, scientists still have a lot to learn (for more information, see the CDC website [4]). There may be long-term effects of both single and multiple concussions, but we do not know for sure. We also know that playing sports is beneficial for you in other ways, so it is important to continue playing but to be as safe as you can, and remember to tell someone if you hit your head so appropriate care can be taken. A healthy healed brain gives you the best chance of doing all you love, and as mom always says, "no more monkeys jumping on the bed."

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REVIEWED BY

DARIUS, 12 YEARS OLD

I am 12 years old. In my free time, I enjoy reading and computer programming. As a hobby, I make useful objects and experiment with devices. I am very interested in the environment and was one of the founders of my school's green committee. I enjoy reading about science, particularly chemistry, biology, and neuroscience.

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NEUROSCIENCE
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WHAT IS RECOVERY LIKE AFTER TRAUMATIC BRAIN INJURY?

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YOUNG REVIEWER:

SOPHIA

AGE: 9

In the movies, many characters heal very quickly after getting hurt. Some, like Wolverine or Rapunzel, even have special healing powers. However, when a person gets hurt in real life, it may take a lot of patience and hard work to get better. People who are recovering from an injury may also need support from the community and care from healthcare and educational professionals. In particular, it takes time and hard work to recover after a traumatic brain injury (TBI). People with TBI work with a special group of professionals, called a rehabilitation team, to get better. In this article, we will learn about a boy named Dante, who had a TBI after falling off his bicycle. We will learn what happened in Dante's brain after he got hurt and how his rehabilitation team helped him after his TBI. We will finish up by talking about how you can help people with TBI in your community.

Even though you cannot see your brain, it is the most complicated part of your body. Your brain controls how you move, think, and experience the world. It controls things that you do intentionally, like the words

TRAUMATIC BRAIN INJURY (TBI)

Damage to the brain that is caused by an external force. TBI may result in changes in many different brain functions, including moving, thinking, or communicating.

you say. Your brain also controls things you do not even notice, like staying balanced when you are sitting in a chair. Considering how important the brain is, it makes sense that a brain injury could be a big deal. A **traumatic brain injury (TBI)**, which is an injury that happens when an external force damages the brain, may change every part of a person's life. Some disabilities after TBI are physical, like when someone has problems with balance and uses a wheelchair. However, many disabilities after TBI are not physical, but have to do with thinking or communication skills. These disabilities may be hard for others to recognize or understand. That is why TBI is sometimes called an "invisible injury."

WHAT HAPPENS WHEN THE BRAIN GETS HURT?

TBI happens when an external force damages the brain. Some common causes of TBI are car accidents, falls (like when riding a bike or playing sports), or getting hit on the head. TBI is quite common. More than 2 million Americans (including 800,000 children) seek medical care for a TBI every year [1].

One challenge in helping people with TBI is the fact that every single TBI is unique. There are many different types of damage to the brain. TBI may include damage that is focal, which means there is damage in a specific part of the brain. For example, a person may have a bruise in the frontal lobe, which is the front part of the brain. However, TBI is also diffuse, which means that it affects multiple parts of the brain. Your brain contains 60 billion neurons, or nerve cells, that have their own special functions to control. Those nerve cells connect through long fibers called axons. Axons allow different parts of the brain to work together. In **diffuse axonal injury**, some of the axons connecting different parts of the person's brain are damaged or die. This causes big changes in the connections and functions of the brain. Look at Figure 1 to learn more about how TBI might damage the connections between parts of the brain.

DIFFUSE AXONAL INJURY

Damage to axons (connections between brain cells) that results from TBI and may affect how the brain functions as a whole.

A person's TBI may also change over time. A person may have **primary injuries**, which happen immediately, such as a bruise in the frontal lobe. However, **secondary injuries** may happen from minutes to days after the primary injury. Secondary injuries may include brain swelling and bleeding, a lack of oxygen to the brain, or disturbance to electrical activities in the brain.

Because TBI results in damage all over the brain, it causes problems with the brain's many important functions. For example, a person with TBI may be in a coma because there is a change to the brain's ability to stay alert. After waking up from the coma, the person may notice changes to movement and balance, problems with senses like vision or hearing, headaches, and sensitivity to noise or lights. Some people may have problems with thinking, learning, and communicating. Some

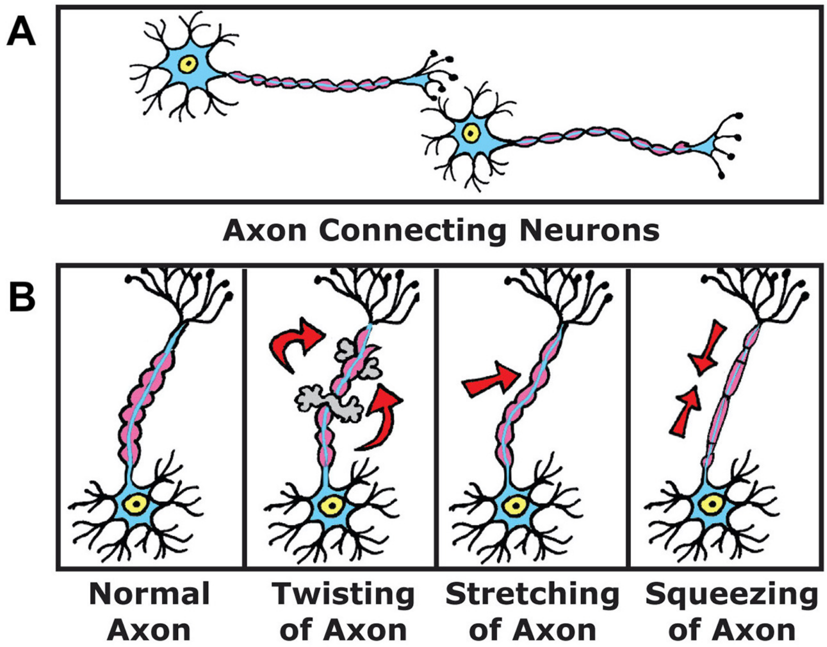

Figure 1

Figure 1

(A) Your brain's 60 billion nerve cells connect through long fibers called axons. Axons allow signals to travel through the brain so that different parts of the brain can work together. **(B)** In TBI, depending on the types of force on a person's brain, axons might be stretched, squeezed, or twisted. Afterwards, the axon may not work well or at all, which can impair the connections between brain cells.

may also notice changes in emotions and behaviors [2]. For example, a person who has problems with communication may have a hard time keeping up with conversation or understanding jokes or teasing. This may be especially challenging at school. It might be difficult to know where to fit in and who is a friend. People with TBI may also get frustrated or angry very quickly. Family, friends, and teachers might not understand that these problems relate to TBI and may not know how to help. When you think about how serious the effects of a TBI may be, it makes sense that there are special teams dedicated to helping people with TBI.

HOW CAN REHABILITATION HELP AFTER TRAUMATIC BRAIN INJURY?

After a TBI, a person may spend some time in the hospital recovering from severe medical problems. In some cases, the person may need help to breathe or eat. The hospital team will make sure that the person is safe and comfortable enough to leave hospital care so that the next part of the **rehabilitation** process can begin [3].

REHABILITATION

A special medical service focused on helping people to regain independence and get back to their lives after an injury or illness.

Rehabilitation is a medical service focused on helping people to regain independence and to take part in activities of daily life after an injury or illness. After leaving the hospital, some people may go home, and some may go to another facility for ongoing care. If a person is ready to take part in daily therapy, he or she may go to a special facility called inpatient rehabilitation. **Inpatient rehabilitation** is like a school

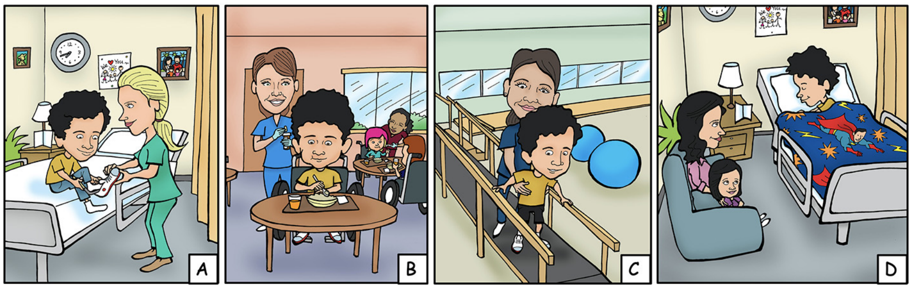

Figure 2

Figure 2

Dante's morning in inpatient rehabilitation. **(A)** First, Dante gets up and gets dressed with his occupational therapist. **(B)** Next, he has breakfast with the other kids in inpatient rehabilitation. **(C)** After breakfast, he practices walking with his physical therapist. **(D)** Finally, Dante needs to get some rest before lunch because his TBI makes him very tired. He wants to be ready for more therapy this afternoon!

or camp for people recovering after an injury or illness. A child with TBI may go to a special facility that is only for kids [3].

A TYPICAL DAY IN INPATIENT REHABILITATION

A child who has a TBI will be busy most of the day in inpatient rehabilitation. At first, inpatient rehabilitation may be really hard. People in inpatient rehabilitation go from spending most of the day in a hospital bed to getting up, moving around, and doing lots of activities every day. Some people with TBI may be very tired or frustrated, which makes therapy challenging. We are going to spend a day with Dante, who fell while riding his bike in his neighborhood. Dante was wearing a helmet when he had his accident. Wearing a helmet is important because, in some cases, it can prevent a TBI. In other cases, like Dante's, a helmet can reduce the severity of TBI or even save a person's life. Reviewing Dante's day will help us to learn about what a day in inpatient rehabilitation is like.

OCCUPATIONAL THERAPIST

A rehabilitation professional who helps people complete the daily activities they want and need to do after an injury or illness.

Dante wakes up early in the morning to get dressed with his **occupational therapist** (Figure 2A). Occupational therapists help people do the things they want and need to do after an injury. TBI may change how a person moves his or her hands, fingers, and arms. These changes may make it difficult to button a shirt, tie shoes, or hold a fork. Relearning these skills makes it possible to eat, dress, or complete schoolwork. Occupational therapists may use special tools to make these activities possible, like the shoehorn Dante uses to put on his sneakers.

Next, Dante will eat breakfast (Figure 2B). Today, he is eating in the meal room with other kids. Some of these kids have had TBIs, but others are recovering from other injuries or illnesses. Eating with the other kids allows Dante to practice communication in a social setting. Because Dante is still in a medical facility, his nurse may come by the breakfast room with medications to help with headaches, pain, or seizures.

PHYSICAL THERAPIST

A rehabilitation professional focused on helping people who have trouble moving and completing important activities after an injury or illness.

Next, Dante goes to the gym to work with his **physical therapist** (Figure 2C). Physical therapists focus on rehabilitation for people who have

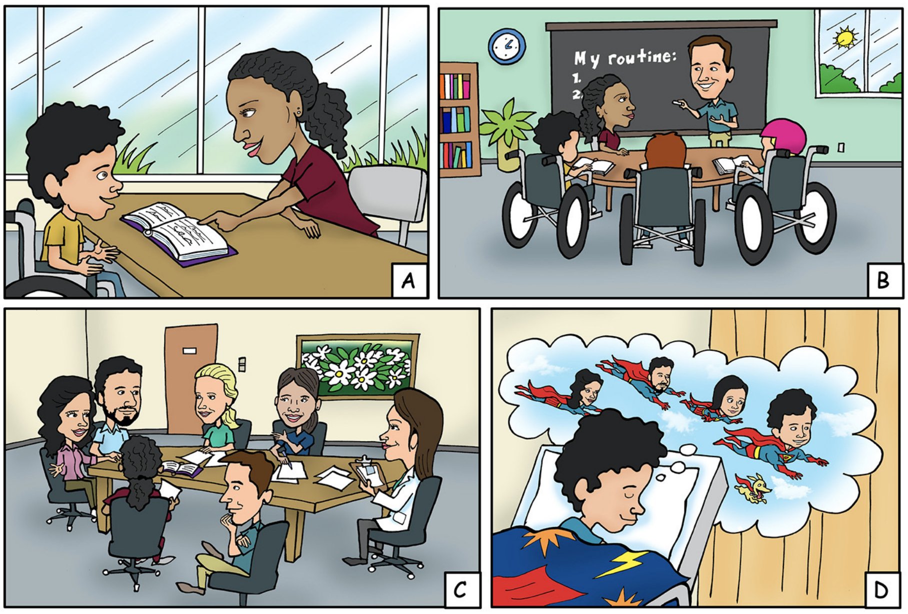

Figure 3

Figure 3

Dante's afternoon in inpatient rehabilitation. **(A)** After lunch, Dante has speech therapy. **(B)** Then, he attends rehabilitation school with his friends. **(C)** While Dante is resting, his parents attend a meeting with his rehabilitation team to learn about his progress and treatment plan. **(D)** Tonight, Dante will rest well and get ready for another day of hard work tomorrow!

trouble with movement. This may include strength and balance for standing, walking, and changing positions. Dante is walking well, but he has trouble with his balance and gets tired quickly. Today, he and his physical therapist are doing some exercises for standing upright and walking for longer periods of time. After this session, Dante will be tired. He will use his wheelchair for the rest of the day to keep him safe.

Dante has a break before lunch (Figure 2D). After a TBI, people are often very tired after even simple tasks. Dante needs breaks throughout the day!

After lunch, Dante goes to speech therapy (Figure 3A). **Speech-language pathologists** (also called speech therapists) help people with changes to thinking, communication, or swallowing. A speech-language pathologist may help a person with TBI to swallow and eat safely. You can see Dante's speech-language pathologist in Figure 2B. She stopped by the breakfast room to make sure that the kids were eating and drinking safely this morning.

SPEECH-LANGUAGE PATHOLOGIST

A rehabilitation professional who helps people with changes to thinking, communication, and swallowing after an injury or illness.

Speech-language pathologists also work through changes to speech or language and develop strategies to address communication and thinking problems [4]. In speech therapy today, Dante is working on strategies for his memory. He and his speech-language pathologist have created a memory book. In this book, Dante keeps information about himself, his injury, and his daily activities. Dante uses his book to tell his speech-language pathologist about his day so far. Dante's memory book helps him to track what he learns and to share information with the people he sees throughout the day.

Next, Dante will go to rehabilitation school with some of the other kids (Figure 3B). Rehabilitation school is important because many kids have trouble in school after TBI. Students need to use many of the skills affected by TBI, like thinking, communication, and social skills. Because TBI is an "invisible" injury, some challenges related to TBI might go unrecognized. TBI symptoms may also be diagnosed as something else, like behavior problems.

Everything Dante does in rehabilitation should matter for his daily life [4, 5]. Going to school is a great way for Dante and his friends to work on their therapy skills in a real-world setting. For example, Dante must pay attention to the teacher and remember his assignments. He must also use social skills to know when to talk and when to listen. During rehabilitation, kids and families may learn about supports, or **accommodations**, that will help with returning to school. These accommodations are not about changing what a person with TBI learns in school. Instead, they are about making changes to *how* a student learns so that he or she may get the most from the classroom. Some kids may need more breaks, quiet, or extra time to finish assignments. These types of changes help a student with TBI to stay in his or her regular environment as much as possible.

ACCOMMODATIONS

Changes at school (like more breaks, quiet time, or time to finish assignments) that help a student with a disability (like TBI) to be successful in the classroom.

While Dante rests after school, his parents meet with his rehabilitation team (Figure 3C). In inpatient rehabilitation, all of Dante's physicians, nurses, and therapists work together. This helps everyone to understand Dante's goals and progress [2]. Every person with TBI is different, and every TBI is different. It is hard to predict how much progress a person will make or how quickly a person will see progress. Many scientists are working on this problem. In the meantime, therapists must customize their plans to each person's strengths, needs, and daily life. That way, the person makes as much progress in therapy as possible.

At this meeting, the entire team updates Dante's parents on his progress in therapy and talks about what he will need when he goes home. This meeting is important because inpatient rehabilitation jump-starts Dante's return to his life after TBI, but it is only a small part of the recovery process [2, 3]. Dante and his family are the most important members of the rehabilitation team. When Dante goes home after a few weeks in inpatient rehabilitation, he and his family will continue his therapy every day!

WHAT IS MOST IMPORTANT TO KNOW ABOUT TBI IN YOUR COMMUNITY?

Using Dante's example, we can see that TBI is a serious injury resulting in many changes to brain functions. Although people with TBI may work very hard and see big improvements in therapy, many will have changes to thinking, movements, and communication for their whole lives.

People with TBI may have "hidden" disabilities that make it hard to know how and why they could use support. For example, people with TBI may find school and social settings to be difficult, but if others do not understand TBI, they may not know why. If you know someone like Dante who has a TBI, make sure to be a good listener, to ask how you can help, and to treat the person with understanding and respect.

Recovery from TBI is a long, challenging process. Returning to life after TBI takes hard work and help from rehabilitation professionals, family, friends, and the entire community. Even though people with TBI do not heal as quickly as characters in movies, we hope that this article has shown that getting back to life after TBI takes super hard work, super community, and super strength!

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YOUNG REVIEWER

SOPHIA, AGE: 9

I live in Tucson, Arizona. My favorite sports are swimming and fencing. I play the violin and love to bake. My best friends are my two little brothers. I love to climb trees and indoor rock climbing. My favorite pastime is spending time with my friends. I love to read, and my favorite book series is "Diary of a Wimpy Kid." I am really enjoying being an editor for Frontiers for Young Minds.

AUTHORS

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I am a brain injury researcher and speech-language pathologist. I love learning more about the brain and using what we know to help people get back to their lives after brain injury. When I am not in the lab or clinic, I enjoy reading, cooking, traveling, and spending time with family, friends, and my dog! *emily.l.morrow@vanderbilt.edu

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I am also a brain injury researcher and speech-language pathologist. I love conducting experiments on how we diagnose and treat people with brain injuries that may improve the rehabilitation process. When I am not in the lab, I like to read, play board games, and travel with my family.

frontiers FOR YOUNG MINDS

HEALTH
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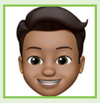
RETURNING TO SCHOOL AFTER A CONCUSSION

Melissa McCart**, Christina Karns, Meghan Ramirez, Matthew Dawson and Ann Glang

Center on Brain Injury Research and Training, University of Oregon, Eugene, OR, United States

YOUNG REVIEWERS:


JEANINE
AGE: 15


NAVIN
AGE: 13


RANJANA
AGE: 14

A concussion can occur when someone experiences a hard hit to the head that jars the soft brain. This is why concussions are also called traumatic brain injuries (TBIs). When a student gets a concussion, it often disrupts athletics, school grades, and social life. It can sometimes even cause personality changes. Researchers have learned that: (a) a team approach is best; (b) an individual plan should be developed to help a student return to school successfully; (c) extra supports for learning and play activities at school are important; and (d) parents and teachers need to check a student's progress frequently until there is a full recovery. Concussions can affect you or your friends. You need to know what to do to help yourself get back to play, school, and life. This article summarizes research-based practices for returning to school following concussion.

WHAT IS A CONCUSSION?

Hey students, skaters, athletes, and bikers! You already know that protecting your brain during any risky activity is important, but injuries happen. What do you do if you think you might have a **concussion**?

CONCUSSION

A blow or hit to the head that temporarily impairs brain function.

Figure 1

Figure 1

Average number of yearly trips to the emergency room for concussion, for people 19 years old or younger [1, 2]. *Vehicles include all types of vehicles (cars, dirt bikes, all-terrain vehicles, etc.). **Combative includes all types of fighting sports (wrestling, boxing, karate, etc.).

If you get a concussion, how soon should you go back to school and athletics? How long will the concussion affect you? What can teachers, parents, and doctors do to help you recover? In this article, we will give you the latest research-based information about how to get back into the game of life.

A concussion is a brain injury caused by a bump, blow, or jolt to the head or by a hit to the body that causes the brain to move rapidly back and forth inside the skull [1]. Which activities cause the most concussions? Figure 1 shows the number of children who go to the emergency room each year for specific sports and recreation activities that result in concussions. These activities are similar in that they can make the brain twist, bounce, or move violently back and forth in the

Figure 2

Common accommodations available at school.

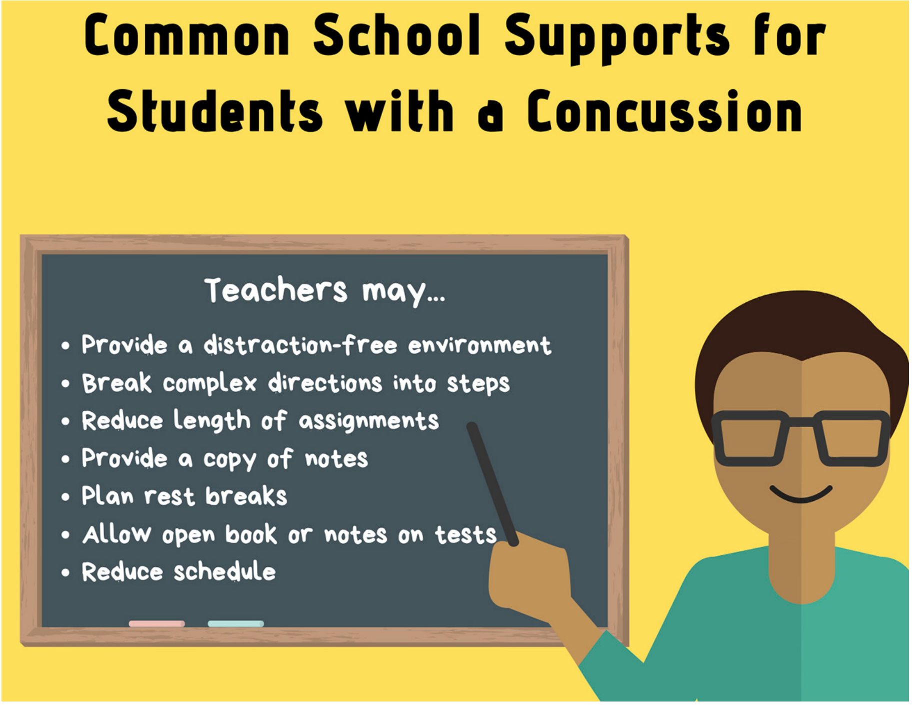


Figure 2

skull, injuring the brain. Concussions can happen in any activity, even on the playground or in your backyard.

Concussions are different from most other types of injuries. Often there is no bump, bruise, or mark when you get a concussion. A strong jolt to the body might not leave a mark. If you break your arm, a doctor will confirm it with an X-ray, but if you get a concussion, there is usually no physical sign of it. This can make it tough when you go back to school after a concussion—you may look fine, but you may feel pretty awful. The symptoms of concussion, which include fatigue, trouble concentrating, and headaches, may make it difficult to keep up on classwork or even to hang out with friends. The good news is that the effects of concussion usually do not last long and there are some strategies that can help you go back to your old self more quickly. Figure 2 lists the common signs of concussion that might be noticed by you or others, like friends, parents, or teachers. Learn more in the Frontiers for Young Minds article called Caring for Your Brain: What You Need to Know about Concussions [3].

EVERY CONCUSSION IS DIFFERENT

It can be tricky to know when it is ok to return to normal activities after a concussion. You may want to return to school quickly so you do not fall behind or miss important assignments. You may want to get right back to your favorite sports and time with friends. The problem is that it takes most people a few weeks to a month to fully recover from a concussion. Research has shown that gradually returning to usual activities like school and sports is important for recovery [4]. Doing too much too soon can make your recovery take longer. Taking it slow allows you, teachers, and parents to learn more about what you need for a successful recovery. Remember, every brain injury is different.

If your symptoms after concussion are manageable, you might just need to take it easy for a few weeks as you return to school. Taking it easy means staying on a regular schedule, going to bed at a reasonable time, and limiting time spent on anything intense, like video games. Just give yourself a mental break while your brain heals. In other words, being bored is a good way to recover from concussion!

A TEAM-BASED APPROACH WORKS BEST

It is important to tell someone at school right away if you hit your head hard or if a doctor has diagnosed you with a concussion. Working with your family and doctor, the school team can help you figure out the best plan for returning to school and activities. Your decision-making team should include you, your parents or guardians, your doctor, and a school counselor. Sometimes your teacher, administrator, school nurse, or athletic trainer can be on your team as well. The team should work together to create a plan so that everyone is on the same page about your return to school and activities.

EXTRA SUPPORTS ARE IMPORTANT

Taxing the brain at school with activities, academics, and friends can make recovery take longer.

So, what should a Return to School and Play Plan look like? Although every concussion is different, most students need just a few simple supports in place to help them as their brains recover. These supports are called **accommodations** and may include things like reduced homework, extra time for tests, or delaying big projects or tests until you are feeling better. You might need a special place at school to rest when you get tired, have a headache, or when things get stressful. Here is a detailed list of accommodations that your team can consider. Figure 3 also shows some of the most common accommodations you might get at school.

ACCOMMODATIONS

Accommodations are changes that help students learn when they have challenges. For example, sitting in the front of the classroom or only doing half of an assignment.

At home, you might need family support to keep to a low-key schedule. You might need your family to be sure you have a quiet space and to help you make it to your doctor appointments, get to sleep on time, and eat healthy meals. In sports, your coach will need to know how you are feeling and encourage you to take it easy so that you do not get worse or get another concussion.

Figure 3

Common signs of concussion.

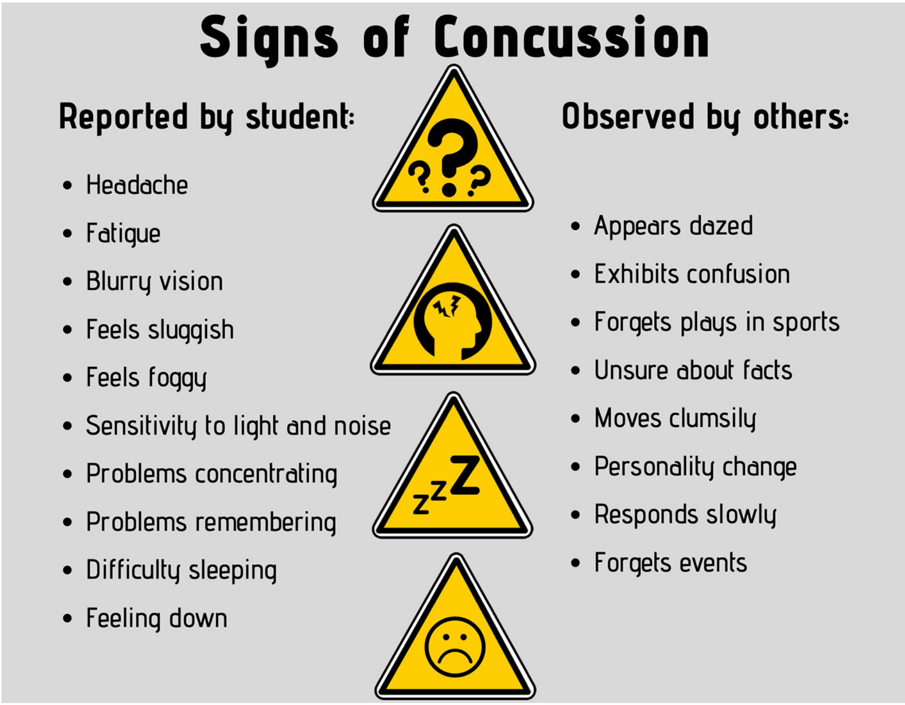


Figure 3

TRACK YOUR PROGRESS

It is important to track your progress so you, your family, your coaches, and your teachers know if you are getting better and what things you might need help with. There are lots of ways you can track your own progress and communicate how you are doing. You could keep a journal or do a daily survey. There are even apps specifically designed to help young people track their symptoms after a brain injury [5]. Something as simple as a happy-to-sad face rating system can give everyone a sense of how things are going for you each day.

Regardless of what kind of tracking system you use, it is important to let people know how you are doing. After a concussion, teachers might be not aware of what you are struggling with, because you look just like you did before your concussion. For example, your math teacher might not know that each night your homework takes over an hour, whereas before you could get it done in 15 min. This information helps your teachers and the rest of the team know what accommodations will be the best to help you.

WHAT IF I HAVE ONGOING PROBLEMS?

Most students will recover from a concussion within a few weeks, so accommodations will be temporary. In some cases, recovery takes longer and more accommodations might be needed. There are two programs to help you get the longer-term supports you might need. A **504 plan** is for students with a disability that limits major life activities like recreation and schoolwork. If you find you need ongoing accommodations but you can do most of your schoolwork and responsibilities by yourself, a 504 plan might be right for you. If you need more help, an **individualized education plan**, or IEP, could be best. Your team will need to work together to coordinate what kind of plan is best for you.

504 PLAN

A 504 plan is a formal legal plan that requires a student to be given the defined accommodations that are agreed upon by the students' team.

INDIVIDUALIZED EDUCATION PLAN (IEP)

A formal legal plan that provides for special instruction and is designed to specifically address a student's individual learning needs.

It is important to be informed about managing concussions so if it happens to you, you will know what to do to support your recovery. The most important thing to remember is that a gradual return to academics and activities, as long as it does not make things worse, is the best approach. If you follow this guideline, you will be back in the game of school, sports, and life as quickly as possible!

AUTHOR CONTRIBUTIONS

MM was the lead author. CK and AG were the contributing authors. MD and MR were students and contributed to the first draft of the manuscript. All authors contributed to the manuscript, read, and approved the submitted version.

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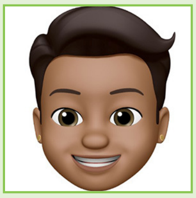
YOUNG REVIEWERS

JEANINE, AGE: 15

I am a junior at a very competitive school which means that I always have to be prepared for what comes next. My favorite subjects are molecular biology and chemistry even though I also enjoy math and art history. Also, I enjoy swimming and being a member of the environmental club and track and field team. In addition, I make time to have lots of fun. My hobbies include, reading fantasy books, watching documentaries, hanging out with my friends, and eating my favorite foods.



NAVIN, AGE: 13

I am interested in the medical field and aspire to become an anesthesiologist in the future. I enjoy reading and drawing cartoons. I have been playing ice hockey and love being on the rink. Tennis, swimming, and cross-country are also my favorite sports. I love eating anything that is vegetarian. I want to contribute to my community in any way I can and make a positive change.

RANJANA, AGE: 14

I love science and am especially into medicine. I am passionate about health and wellness. I enjoy reading and watching heist movies. I love spending time in labs, researching, and learning. I would like to learn more languages; right now, I can speak three. I hope to travel to more countries in the future!

AUTHORS

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Melissa McCart earned her doctorate, masters' degree, and administrator's licenses from the University of Oregon. She has worked with at-risk children and families as a behavior specialist and special education teacher. She is currently the director of the Oregon TBI Teams and works in the field of TBI research at the Center on Brain Injury Research and Training at the University of Oregon. Melissa has been a school administrator, behavioral consultant, and a special education teacher to students with emotional/behavioral disorders. Melissa currently is a member of the National Collaborative on Childhood Brain Injury and serves on multiple committees. *mccart@uoregon.edu

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Christina Karns received her doctorate in Neuroscience from the University of California, Berkeley. At the University of Oregon, she has directed neuroimaging projects with children, teens, and adults with and without disability to clarify how attention and self-regulation support healthy brain development. This work has provided foundation for evidence-based interventions that utilize the neuroplasticity of emotions and cognition to support people in positive and healthy interactions with society and each other.

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Meghan Ramirez is a student working with the Center on Brain Injury Research and Training in Eugene, Oregon. She is currently a senior at the University of Oregon studying psychology and minoring in anthropology and sociology. She is part of ongoing research with the Center on Brain Injury Research and Training as well as with the Brain Electrophysiology Lab. Her research interests are in the therapeutic benefits of sound and how they can be used as treatment for individuals with traumatic brain injuries.

MATTHEW DAWSON

Matthew Dawson is completing his final year as an undergraduate at the University of Oregon. Double majoring in biology and psychology, Matthew's focus has been in neuroscience. His undergraduate career has been spent working with Center on Brain Injury Research and Training on the TBI Teams project focused on providing evidenced-based practices for educators working with students who have experienced TBI. Matthew wants to further explore the implications of TBI on unaccompanied youth and adolescents experiencing homelessness.

ANN GLANG

Ann Glang is a Research Professor and Director of the Center on Brain Injury Research and Training at the University of Oregon. Since 1987, she has secured and directed or co-directed over 30 federally funded research projects focused on individuals with TBI. She has published numerous journal articles, edited two books on her work with children with TBI, and co-authored five manuals for educators serving children with TBI. Dr. Glang was awarded the 2011 Researcher of the Year award by the North American Brain Injury Society. Dr. Glang has also led the development of a range of SBIR-funded education programs, including Brain 101, a concussion education and management program for high schools.

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