Sleep It Off

How Sleep Quality Influences Outcomes of Traumatic Brain Injury

By Greg Boyer

On March 16, 2009, actress Natasha Richardson suffered a traumatic brain injury (TBI) when she fell while skiing. She claimed to be fine; however, she started to experience severe headaches a couple hours after the fall. Two days later she died from a hematoma, or bleeding in the brain, induced by a TBI. In 2014, the latest year the CDC has published statistics, there were 56,800 deaths related to TBI in the US. Additionally, there were 2,870,000 emergency room, urgent care, and hospital visits for TBIs in the US.[1] While the term TBI may not be a part of everyone's lexicon, concussion, which describes a mild traumatic brain injury (mTBI), most likely is. Due in large part to a rapidly increasing scientific understanding of concussions, it has become quite the hot button issue. While contact sports have captured much of the notoriety, there is a risk of TBI among all populations. It is true that there is a heightened risk of sustaining a TBI in contact sport athletes, however, 72% of hospitalizations for TBI in 2014 were from falls and motor vehicle accidents, displaying the significance of TBI among all populations. Professional football, which has come under fire for the many former athletes who are suffering the consequences of brain trauma years later, has spent a great deal of effort reforming rules, safety equipment, and awareness to protect players. This dedication to improve the lives of those who suffer TBIs has not been seen, however, outside the realm of

sports. This is in part from TBI being thought to only affect athletes, which, as explained, is not the case.

One of the most enigmatic clinical discussions revolves around concussion protocol. While there is still no consensus regarding all aspects of how to treat, manage, and mitigate symptoms experienced following TBI, there has been extensive research in recent years into best practices. The reason for the difficulty in studying TBI is that there is immense individual difference in severity, symptomatology, location of injury, and outcomes of TBI patients. This has created opportunities for misinformation concerning treatments to be perpetuated.

We've all heard it: Don't fall asleep after a concussion. Like all myths, there is a reason that this has been considered good form. Brain imaging has only been in our scientific repertoire for a few decades. Meanwhile, humans have been experiencing TBI since the beginning of our existence. Thus, assumptions have been made on observation. It is not wholly uncommon in TBI patients to suffer head trauma, feel fine for a few hours, then suffer seizures, strokes, or death when they go to bed that night. This is precisely what happened to Natasha Richardson. In the hours following her accident, she was experiencing bleeding on the brain, but unfortunately did not experience severe headaches until the critical window of time for treatment had passed, and ultimately Richardson succumbed to her injuries.[2]

A severe impact to the brain can cause brain movement within the skull, which sometimes leads to bleeding. This, along with neuroinflammation, which is a result of the immune response to the injury, leads to increased intracranial pressure. The buildup of pressure occurs over a period of time, which is why patients may not experience a deterioration of symptoms until several hours later. If that time when symptoms deteriorate occurs when one is asleep, then the patient would not be able to reach out for medical attention when it is needed. This timeline could easily be misinterpreted as sleep itself being the culprit for a deterioration in symptoms; however, the true criminal is hematoma.

While there is no inherent risk of sleeping following a concussion, it is understandable why the opposite was believed to be true. If a TBI may have caused a hematoma, then it is crucial to seek treatment as soon as possible. Therefore, it is important to know the signs. Some symptoms, including confusion, headaches, blurred vision, and nausea, often overlap with that of a concussion. Most concussions are not medical emergencies; however, if there is an improvement of symptoms, followed by a sudden deterioration, then medical attention should be sought immediately. Seizures are also a tell-tale sign of hematomas. During the night after the TBI, it is good practice to have a relative or friend check on you throughout the night to ensure that all is well. In short, be alert of worsening symptoms, but sleeping is not the cause of mortality following TBI. After 24 hours, this precaution is not really necessary because if bleeding were a concern, then the complications would have already risen. Thus, the goal should then be to recover quickly and completely.

The thought that sleep could hurt recovery is not only wrong, but the opposite effect is actually true. Falling asleep after a concussion will not kill you, but preventing yourself from having a good night's sleep will only make it worse. Not only will poor sleep quality worsen your immediate symptoms, but also lead to worse long-term outcomes. There are many reasons to believe quality sleep is beneficial to TBI outcomes. This is because sleep mediates brain plasticity, the ability to learn new information, which is very important in the brain's memory as well as the ability to heal itself. The problem is that TBI symptoms make sleeping well difficult. One of the most common complaints in patients is poor sleep. This is obviously problematic. Poor sleep exacerbates feedback from TBI symptoms disrupting sleep, and disrupted sleep, in turn, worsens symptoms of TBI, which makes it all the more difficult to achieve a healthy sleep routine, also known as a circadian rhythm.

What Is Your Circadian Clock, and How Does It Affect Your Sleep?

Almost all living organisms follow a circadian rhythm, which is an internal clock that aids sleep-wake cycles. This is why most people feel tired at night and alert during the day. In healthy people, there is a complex system of biological processes that aim to normalize your sleep routines. There is a combination of internal cues, such as stress levels, and external cues, such as sunlight, that the body uses to determine when it is time to get some z's. However, this system is based on routines, which is why disruptions to our daily routines can easily affect our circadian clock. Common examples of disruptors include jetlag, staying up late studying for a test, or binge watching your favorite new TV show until 4 a.m.

There are many benefits to a good night's sleep, such as boosting the immune system, improving memory and attention, and regulating metabolism, which is the ability to convert food into energy.[3] The best outcomes in adults occur

from going to bed at the same time each night and having roughly 8 hours of uninterrupted sleep. Obviously, this is difficult to achieve in practice, but it is something to consider when debating whether to press play on that next Netflix episode.

Poor sleep quality or duration, however, has the inverse effect. Furthermore, when there is a disruption to your sleep routine, it can be quite difficult to get back on schedule. It can take days or even weeks to recover from your overseas vacation or the all-nighter you pulled.

While these examples are due to external disturbances, there are a variety of mechanisms the body uses internally to regulate sleep. In fact, there are even genes that are responsible for regulating sleep. These genes can have varying levels throughout the day, too, telling neurons when to be active, and when it is time for sleep. One of these genes, Per1, is responsible for making the internal clock 24 hours long. Per1 follows a daily, predictable pattern of expressing at high levels at dusk, and low levels at dawn. When there is too much Per1 released in the brain, the internal clock becomes too long.[4] This would make someone sleep for too long and then be awake for too long, as opposed to the ideal situation of waking up and going to sleep at the same time each day. Per1, in addition to external cues such as brightness, help us to sleep during the night and be awake during the day.

The Immune System Is also Hard at Work

The purpose of the immune system is often thought to be to fight viruses. While this is one of its functions, there are many methods the immune system utilizes to repair and protect the body. When you get a bruise or catch a cold, the immune system works overtime to nurse everything back to health. In addition to repairing vulnerabilities, the immune system is always playing an active role in maintaining homeostasis in the brain. There are immune cells that respond to unwanted changes in the brain by secreting small molecules that latch onto receptors throughout the brain to communicate information between cells. One family of these molecules are known as proinflammatory cytokines, which are regulators of inflammation. There is always some amount of these floating around the brain. However, levels of proinflammatory cytokines skyrocket when there is stress on the immune system. Proinflammatory cytokines have the ability to interact with neurons in a localized area or throughout the brain as a whole, such as when they induce a fever.

Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are two types of proinflammatory cytokines that play a key role in sleep regulation. While they both have very similar sleep regulatory effects, there are a couple differences between IL-1 and TNF. One of the main functions of IL-1 is to regulate temperature. Overnight, we actually sleep at a lower body temperature than we function at during the day. This is in part why it is especially difficult to fall asleep on those scorching hot summer nights. Increased concentration of IL-1 in the brain decreases temperature, thus IL-1 levels dip during the night.5 TNF, on the other hand, plays more of a role in regulating inflammation in the brain. More TNF in the brain results in more neuroinflammation. While these are the primary roles of IL-1 and TNF, they each overlap in function to a great degree, so they really can be paired together when talking about their effects on sleep regulation. The quantity of both IL-1 and TNF peaks during the night, and reaches a trough during the day. To determine the effects of IL-1 and TNF, studies have injected these substances in the brain, which resulted in sleepiness, fatigue, poor cognition, and other symptoms as a consequence of sleep loss.17 This shows that regulation of these cytokines is necessary for healthy maintenance of circadian rhythms.

Hormone Regulation

Despite their reputation for orchestrating puberty, hormones are used as a method of communication in the brain and body for a wide variety of tasks. In fact, hormones often work in a very similar manner to cytokines, which has led to quarrels among scientists over when to classify certain molecules as cytokines or hormones.[6] Still, there are a couple characteristic differences. Unlike cytokines, hormones exclusively communicate over long distances. While cytokines can be released by a variety of immune cells, hormones are released only by glands in the endocrine system. The endocrine system regulates a variety of human functions including physical and sexual development, metabolism, mood, and—you guessed it—sleep.

The three hormones that are most involved with sleep regulation are melatonin, progesterone, and histamine. The quantity of each of these actually varies cyclically throughout the day, helping to contribute to circadian rhythms. Each of these hormones plays a significant, specific role in regulating sleep. Melatonin is a hormone that promotes sleep by delivering messages to neurons all over the brain to power down. Therefore, in people with healthy circadian rhythms, melatonin levels are highest overnight, and lowest during the day. Due in part to societal pressures for maintaining health, dietary supplements, including melatonin, have become increasingly popular in recent years. While there is reason to believe melatonin supplements could help improve sleep quality and duration, it is important to take these supplements at the roughly the same time each day to achieve the intended benefits.[7]

Progesterone also aids in sleep, though in a slightly different manner. Progesterone diminishes the effects of sleep disturbances. Heightened progesterone levels are correlated with a better quality of sleep, due to this reduction in sleep disturbances. For example, you are less likely to be awakened by a loud noise if your progesterone levels are higher. Like melatonin, progesterone levels should peak overnight. Considering the natural effect of progesterone in aiding sleep quality, it is not wholly unsurprising that progesterone supplements will also reduce sleep disturbances.[8] While also contributing to sleep wake cycles, histamine has the inverse effect of melatonin and progesterone, as histamine promotes wakefulness and arousal.[9] Thus, histamine levels should peak during the day and decrease at night. Given the importance of these three hormones in regulating sleep, any unwanted changes to the quantity each hormone in the brain will have troubling consequences.

What Goes Wrong in TBI?

If there is anything to take away from Richardson's tragic death, it's that the potential risks of concussions should not be taken lightly. Without a doubt, immediate medical attention should be sought if you think you are concussed. Establishing there is no risk of immediate health complications should be the primary concern. Nevertheless, taking the appropriate steps to ensure a timely and full recovery is essential. Before discussing what those steps look like, the mechanisms by which TBI harms the brain should be understood.

There is an interaction between TBI and all three mentioned components of sleep: circadian clock, immune response, and hormone regulation. Recent studies have found Per1, the circadian rhythm gene, to upregulate following mTBI.[4] The

overproduction of Per1 results in longer circadian rhythms, increased light sensitivity, and an overall reduction in movement for mice models. Mice are good model organisms for TBI as mice brains are affected by head trauma in a way very similar to humans. The increase in light sensitivity can be explained by disturbances to the internal clock. We are naturally more sensitive to light at night when Per1 levels are high. We've all experienced this when needing to turn down the brightness of your phone at night. Given that heightened Per1 levels at night increase light sensitivity, the same increase in sensitivity is to be expected so long as Per1 levels are elevated.

Hormones are just as susceptible to dysfunction from TBI. Following injury, patients experienced a decrease in all three previously mentioned hormones: melatonin, progesterone, and histamine.[10] These hormones all play a role in sleep-wake cycles, so their deterioration is evidence of the effects of TBI on sleep. While the circadian clock is disrupted directly from Per1, the disruption of sleep due to dysregulation of hormones also negatively affects circadian rhythms. However, there is a great deal of individual difference. Not everyone is going to respond to TBI in the same manner. With that said, recent studies have explored methods to predict an individual's response to a TBI. Some of the variability can be attributed to gender. Given that hormone regulation plays an integral role in the effects of TBI, it is not surprising that there will be sex differences. Evidence suggests that males with TBI may have a greater memory deficit than females with TBI. Also, TBI affected mitochondrial respiration, which is related to the development of oxidative stress, in males only. Females face their own set of challenges and are more likely than men to report depression and anxiety following TBI. Furthermore, TBI is very prevalent among adolescents, especially those in athletics. Age may play a factor in treatment as well due to the changes in hormone production during development, but more research needs to be done to understand the ins and outs of these differences.[11]

Understanding the role of TNF in TBI is even trickier. In the days right after suffering a TBI, TNF is thought to be a necessary part of the immune response, helping to prevent some of the more serious and fatal symptoms that can occur. However, prolonged increases of TNF that are present in TBI can lead to the detrimental sleep effects described from injection of TNF into the brain. Since TNF and IL-1 go hand in hand, IL-1 also upregulates following TBI. Recent studies have used antibodies that aim to decrease IL-1 levels. This treatment

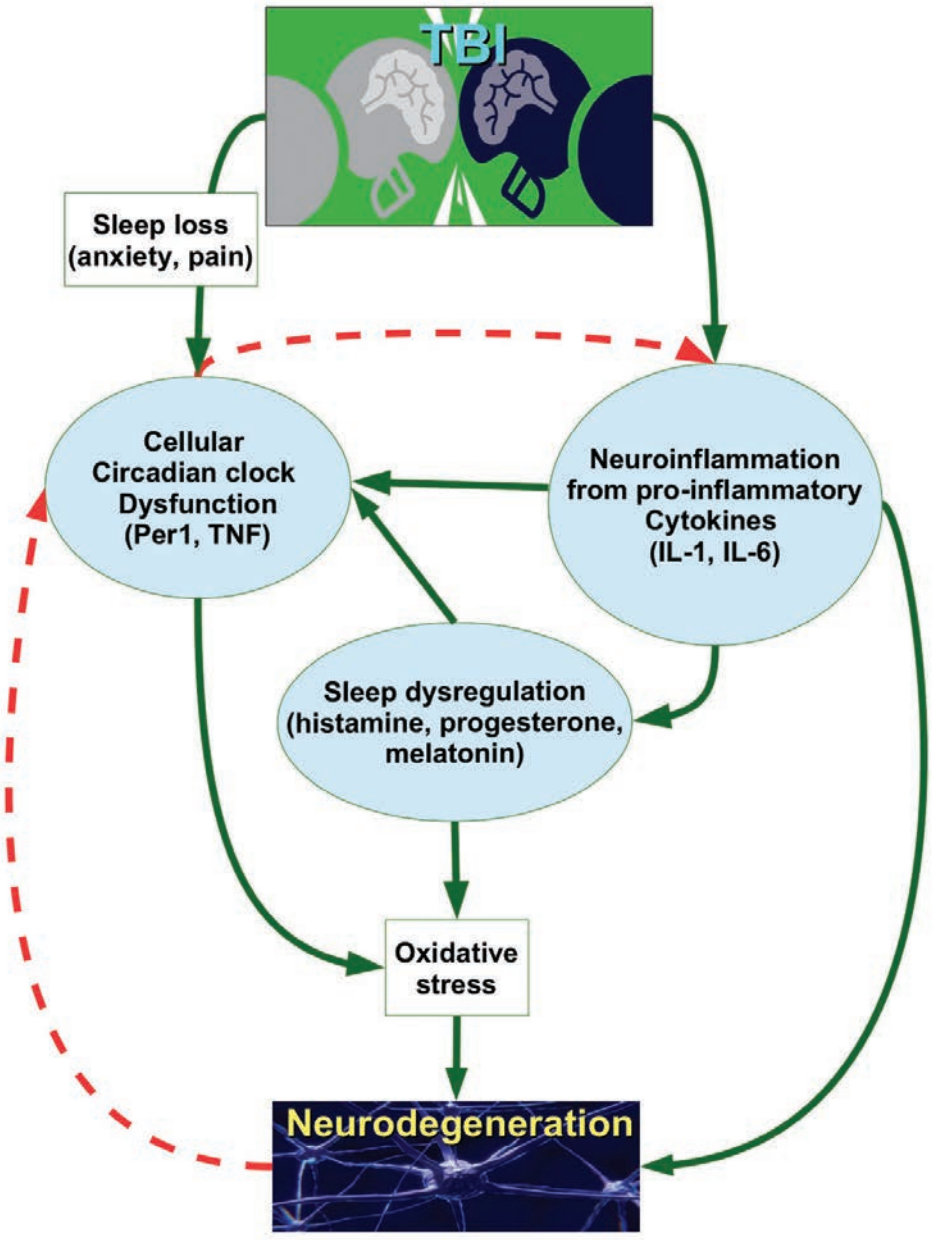

Figure 1. The effects sleep regulation can have on mTBI consequences and symptomatology. Green lines indicate primary effects and dotted red lines represent delayed effects.
"CES illustration" by Lorie Shaull from Flickr (CC BY-SA 2.0). Adapted by Greg Boyer

has shown promise as mice with this treatment show memory and cognitive improvements. Heightened levels of both TNF and IL-1 are responsible for increases in neuroinflammation that is characteristic of TBI.[17]

While there are short term consequences of each of these sleep disruptors, long term consequences are just as problematic. The experience of TBI, especially multiple TBIs, is correlated with increased likelihood of developing several neurodegenerative diseases, including Chronic Traumatic Encephalopathy (CTE), Alzheimer's Disease, and Parkinson's Disease.[12] Thus, it is crucial to treat TBI as early and effectively as possible. The goal is to prevent neurodegeneration, a fancy term for neuron death. The primary causes of this neurodegeneration are from the neuroinflammation and the downstream effects of oxidative stress.

Oxidative stress occurs when excess reactive oxygen species (ROS) exceed healthy levels. These are simply waste products that occur naturally. In healthy people, they do not cause much harm, as antioxidants clear them away. You may have heard of antioxidants advertised as a must-have super nutrient, present in blueberries, kale, dark chocolate, and more. Whether intaking more antioxidants though diet truly prevents these diseases is open for debate, however, the role that antioxidants play is most definitely vital. When there is more ROS than can be processed by antioxidants, it can be toxic for the brain. This excess ROS binds to and attacks lipids, protein, and DNA in the brain. ROS, in the absence of antioxidants, essentially go on a killing spree, attacking molecules and neurons in the brain.[9] As it turns out, hormones play an important role in regulating ROS, so the changes to hormone levels in TBI also have adverse effects on oxidative stress.

Neuroinflammation, as previously described, is the result of the immune response. The consequences of inflammation are much more straightforward. Increases in neuroinflammation essentially suffocate neurons, as the inflammatory tissue occupies the space in the brain that is typically reserved for neurons. Imagine the brain inside the skull as a full glass of water, and the inflammatory response as a golf ball that is dropped in. There just isn't enough room for both.

While the intercorrelations between all aspects of sleep in TBI make it easy for the entire system to be disrupted, the bright side is that treatments that target one area can often have widespread benefits throughout the system shown in Figure 1.

Sleep Disorders

In case it has not been made clear, sleep is necessary to recover after TBI. Unfortunately, it is difficult to maintain healthy circadian rhythms without intervention, as patients recovering from TBI often have poor sleep quality. Research in developing treatments is still very young, meaning there is often a lack of knowledge in how sleep should be regulated following mTBI. Additionally, symptoms of TBI, including anxiety, fatigue and headaches, further disrupt sleep. In fact, many TBI patients develop specific sleep disorders. Following TBI, 50% of patients experience sleep disturbances in general, 29% develop insomnia, 28% develop hypersomnia, and 25% acquire sleep apnea.[10] Given that TBI patients frequently develop sleep conditions that they previously did not have, it is logical that TBI will exacerbate pre-existing sleep conditions.

Studies exploring sleep disruptions alone have shown that there are shared consequences to those of TBI, including neuroinflammation, cerebrovascular dysfunction, and dysregulation of hormones associated with circadian rhythms. Chronic insomnia, for example, can alter the timing of when TNF is secreted in the brain.[13] One of the most dangerous sleep disorders, especially if left untreated, is sleep apnea. Sleep apnea is characterized by repeated stops in breathing while you sleep. This, too, results in oxidative stress. A common treatment of sleep apnea is continuous positive airway pressure (CPAP). Studies have shown CPAP's effectiveness in reducing oxidative stress in those with sleep apnea.[14] Considering the overlapping mechanisms of disfunction, it can only be assumed that the combination of TBI and sleep apnea would exacerbate all symptoms. Given that one in four TBI patients develop sleep apnea, more research should be dedicated to preventing the onset of sleep apnea in TBI patients and exploring treatments that would remedy both conditions simultaneously.

What Can Be Done?

A few treatments have been mentioned, but if you are hoping for a comprehensive overview of TBI treatments, you are in luck. First, let's take a step back. The ultimate goals of TBI treatments is to aid recovery and prevent neurodegeneration. Sleep aids recovery through its effect on brain plasticity. With that said, there is such a thing as too much sleep. Too much sleep can further disrupt circadian rhythms, as most adults' circadian clock is designed to have 7-9 hours of sleep. Sleeping all day and not partaking in daily activities will actually limit brain plasticity. In short, finding balance, and

returning to normalcy will provide the best results.[15]

This is easier said than done, especially due to the prevalence of sleep disruptors in our lives. Alcohol, high stress environments, and bright light from your phone, all can have effects on your circadian rhythms.[19] Alcohol use, which inhibits quality sleep and increases inflammation, has also been found to increase oxidative stress.[16] So, consuming alcohol while you are recovering from a TBI will have negative effects. Furthermore, bright light exposure at specific times during the day has shown to be beneficial for some sleep conditions that are characterized by irregular circadian rhythms.[20] However, bright light exposure right before bed, which can come from your phone or laptop, will have the opposite effect.

"Mental Maintenance; Tools to keep the mind fit"
By Staff Sgt. Micaiah Anthony from Royal Air Force Mildenhal

As mentioned, hormone supplements have shown promise for their ability to regulate circadian rhythms. Studies involving rats have shown that treatment of progesterone diminishes cognitive and sensorimotor deficits that are present in untreated rats induced with TBI. Furthermore, progesterone reduces the effects of oxidative stress and neuroinflammation. The efficacy of progesterone in treating TBI symptoms displays that circadian hormones, oxidative stress, and neuroinflammation are all relevant to the progression of neurodegeneration due to rmTBI.[21] Studies using animal models have also shown the benefits of histamine and melatonin supplements, however, researchers have had difficulty replicating findings in human subjects.[18] One potential problem of hormone focused treatment is that hormones can act differently in men and women. Progesterone, in particular, is expressed differently between sexes. Progesterone supplements have shown an ability to treat certain symptoms in females alone, including reduced tissue loss. Nevertheless, progesterone was able to treat the mitochondrial respiration dysfunction that exclusively affects males.[11] There is still more research that needs to be done to better understand all the moving parts of this condition.

One surprising direction research has traveled is into cannabis. Tetrahydrocannabinol, commonly known as THC, excites certain receptors in the brain, one being CRB-1. Studies are often conducted with compounds that bind to the same receptors as THC, but do not share the same psychoactive effects. Agonists of the cannabinoid receptor have shown a variety of promising effects. These range from increasing histamine production,[22] to suppressing IL-1, to decreasing neuroinflammation.[23] This does not necessarily mean that consuming marijuana will solve all of your problems, but it is interesting to note the potential benefits of certain compounds in this commonly used substance.

While Natasha Richardson will not be able to reap the benefits of the many recent advances in knowledge regarding TBI, she will be remembered for sparking a conversation. Advances in treatments of TBI have already saved countless lives, and will only continue to be more and more effective. Although it is usually treatable, traumatic brain injuries should not be taken lightly.

Whether it be societal pressure or desire to show grit, the 'tough it out' culture that often persists is not beneficial to anyone. This pressure to keep playing is highly prevalent in athletics; however, continuing physical exertion immediately after sustaining a brain injury only serves to increase the recovery time you face. The same way that a physical injury would be treated, like a broken arm with a cast, traumatic brain injuries need time to heal. As much as you may want to get back on with your life, trust your gut and get some rest. ■

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