Qmetrics
TECHNOLOGIES

Is it Safe to Play Again? Understanding mTBI and Post-Concussive Microtrauma

"I know they are injured, but I can't see anything wrong."

Introduction

The human brain remains one of science and medicine's last frontiers. Advanced technologies have brought discovery and understanding to many brain regions and functions, but there is still an immense amount of knowledge to discover. However, one area where progress has been made is mild traumatic brain injury (mTBI) and the subsequent healing processes, including the duration of rest needed to resume everyday activities safely.

Brain injuries have many causes, are unpredictable, and have a detrimental impact on the injured individual. Additionally, family, friends, and employers can be affected by the injury, and there can be great cost involved with recovery.

Let's put this in perspective: Globally, the annual incidence of Traumatic Brain Injury (TBI) is variably estimated at **27 to 69 million individuals.** Many survivors live with significant cognitive and behavioral disabilities, resulting in both a personal and socioeconomic burden.[1,2]

In the United States, the annual cost to support disabilities and impairments is estimated at $60 billion dollars.[3]

Recovery from mTBI varies from patient to patient and can look different for each. It has been shown that physical activity is a key part of an affected person's rehabilitation. However, knowing when an individual is ready to return to their activities after mTBI following the injury, and at what level, is a critical piece of the puzzle.

Clinicians have lacked an objective measure to determine when a person has sufficiently recovered from mTBI to resume regular daily activities, and for athletes when to return to play. This is a distinct challenge compared to a physical injury, such as a fractured arm where one can directly monitor bone healing. MRI imaging and conventional review by the human eye does not consistently identify microtrauma. Consequently, the management of recovery is driven by testing and self-reported symptoms.

Qmetrics has developed the Concussion Index, a score between zero and one derived from multiple 3D features of a single conventional MRI exam, providing an objective indicator of post-concussive microtrauma severity. The higher the index, the more severe the post-concussive injury.

Types of TBI

There is a general consensus that there are eight types of TBI.[4] These include:

- Concussions (mTBI)
- Second impact syndrome
- Contusions
- Brain hemorrhages
- Intracranial hematomas
- Coup-contrecoup brain injury
- Diffuse axonal injury
- Penetrating brain injury

The severity of brain injuries varies from mild to severe, depending on the degree and type of damage to the brain.

Brain injury is broken down into its respective areas of activity in Table 1.

Table 1 Brain Injury Causes

Activity	Percentage of Total
Sports	~8%
Motor Vehicle	~20%
Falls	~28%
Collisions	~19%
Assaults	~11%
Other	~14%

Concussion or mild traumatic brain injury (mTBI) is one of the most common brain injuries and is one of Qmetrics' current emphasis. Concussions occur due to an impact to the head or body that transmits force to the brain, resulting in brain tissue impacting the skull or stretching and twisting inside the skull. These impact and twisting forces can damage neurons and axons, disrupt function and cause bleeding. Concussions are largely diagnosed via symptoms, which can include headaches, changes to vision, balance, concentration, or mood, and usually resolve within a couple of weeks.

Return to play or clearance to resume former activity is mostly managed by the resolution of symptoms. However, studies show that people who were recently concussed are more likely to incur another concussion and that despite "feeling

100%" they may have reductions in agility and reaction time.[5,6] More concerning are the potential long-term effects of multiple head hits or concussions and the growing concern that they may lead to Chronic Traumatic Encephalopathy (CTE).

While significant brain bleeds at the time of injury are life-threatening and detected and treated by emergency medical care, most concussions cause injuries or microtrauma that are too small to be seen by conventional radiology. Additionally, MRI studies are usually ordered only for patients who have not recovered as expected, in order to rule out other possible causes for the patient's symptoms. Typically, these tests appear negative because the radiologist can't see any visible injuries despite knowing the patient has persistent post-concussive symptoms. Qmetrics Concussion Index was developed out of a concern raised by Dr. Steven P. Meyers, a neuroradiologist who was frustrated by his inability to see post-concussive injuries on patients who he knew were still injured. Using radiomics, or mathematical algorithms measuring three-dimensional signal patterns and textures in the MRI data and Artificial Intelligence to discover the radiomic features present in post-concussive patients, but not in patients without diagnosed brain injuries, Qmetrics was able to build a formula to identify post-concussive microtrauma. This formula is applied to a single, conventional MRI exam to produce a number between zero and one that shows the severity of post-concussive microtrauma.

Sports-Related Trauma

Participation in sports is a voluntary decision. Among youth, the object is to have fun and enjoy the game. It is estimated that 5-10% of all athletes ultimately play at the professional or semi-professional level. An increased emphasis on player safety, along with high-profile media attention, has drawn attention to athletic injuries; among these, mTBI is receiving significant attention because of confirmed or suspected cases of Chronic Traumatic Encephalopathy (CTE). Some possible reasons for the prevalence of mTBI might include but are not limited to:

- More players across all sports
- Drive to become professional
- Pressure to stay in the game
- Burnout
- Protective equipment design

These factors reflect the "pressure cooker" of competitive sports today. The financial, legal, medical, and psychological risks are the highest they have ever

been. Achieving the player objective of maximizing safe, quality time on the field requires a concerted effort. Frequently, risk-adjusted benefit of any measure must be considered, i.e., the increased resilience of an upgraded helmet versus the greater momentum resulting from its increased weight.

Perceived risk in Sports Injuries is also starting to impact the level of involvement in sports like American Football. In fact, after interviewing a mix of six current or retired NFL players, it was unanimous that the majority of head injuries preceded their professional career.

"Most of my concussions were before the NFL in Pop Warner, high school, and college. I think several things contributed to that like conditioning, hitting as hard as we possibly could, and lack of experience." Junior Lee – Ex-NFL Player

Number of Tackle Football Participants in US from 2006-2018 (in millions)

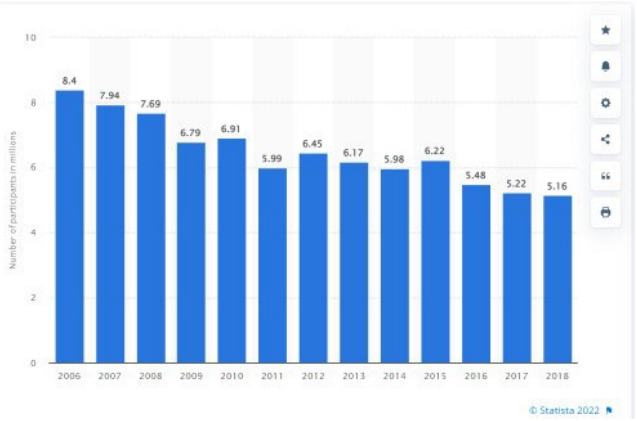

Figure 1: Tackle Football Participation

Interviews with multiple professional athletes provided very important insights. These elite players are dedicated/committed athletes and would choose to play while hurt or injured. They maybe thought they knew the consequences or were willing to take the chance. It sometimes gets reasoned by the "degree" of injury. You can still play if you are hurt or hurting like a headache from a hard hit to the head versus having an injury like a torn ACL where mobility becomes limited. Concerns about loss of time on the field or reduced visibility can overtake management of the unseen injury, from a player's perspective.

New and available technology and services can address the concern over recovery/return to play, mitigating the risk of long-term disability or cognitive

impairment due to premature return to activity. It shouldn't be assumed that a player is safe to return to the game (or normal activity) because he or she sat out for a period of time, or that self-reported symptoms went away.

To emphasize, the challenge today is the determination of readiness to return to play when a concussion is suspected or confirmed. Lacking understanding of the complexities of brain injury, a blanket and clinically arbitrary healing time of x days or x weeks is typically recommended. It is currently driven by symptoms, and "feeling ok" may not be proof that the brain is fully healed and as robust as it was before the injury.

Non-Sports-Related Trauma

The majority of head injuries are not sports-related but instead from everyday accidents, falls, and unfortunately, assaults. There is ample real-world evidence on the variable rate of healing across injury types and individuals. Since these injuries are more random and not associated with an organized sport, organization, or uniform treatment protocol it is critical to educate emergency room physicians, radiologists, neurologists, nurses, and staff about the need and opportunities for assessing and diagnosing mTBI.

Technology

The application of deep learning to MRIs has been Qmetrics' intellectual property and specialty for the past ten years, patented in 2021. Qmetrics' analysis has been repeatedly validated against extensive clinical data.

This technology illuminates trends and features in conventional MRIs that have historically escaped human interpretation.

First, differences are detected from multiple components of a single MRI exam, including diffusion tensor images, a key indicator of white matter microtrauma which can impact quality of life.

Second, the differences detected are three-dimensional patterns and textures. Conventional radiological review is done in 2D (doctors look at each picture, not at the data in 3D) and it is difficult/impossible for humans to aggregate subtleties from multiple sources simultaneously. Think of trying to tell which of two

fishbowls full of M&Ms has greater total contact between green & brown candies and greater total separation between red and orange candies.

Finally, post-concussive microtrauma is revealed through radiomic algorithms that detect subtle patterns and textures in the MRI data revealing the underlying abnormalities caused by the concussion. To understand how we can detect features too small to be seen, consider how sailors can tell where the wind is blowing because the water appears darker. The darker appearance is caused by changes in how light reflects off the rougher surface of the water. Sailors know the wind is stronger because the water is rougher due to its darker appearance, not because they can see the individual wavelets directly.

The Concussion Index (CI) usefully summarizes these indicators of microtrauma in an actionable way. The primary factors in CI describe the abnormal movement of water molecules in the brain. Much like water in a drinking straw is constrained to move only along the length of the straw, white matter fibers allow fluid to move only along the length of the fiber. If the fiber is damaged, fluid may leak, and these subtle changes in movement patterns are captured by MRI. Numerous peer-reviewed studies show white matter (axonal) injury in post-concussive patients is picked up by MRI imaging. Qmetrics permits the visualization of this information outside of the laboratory. [7,8,9,10,11,12]

Services

Concussion Index Assessments

Qmetrics is an exclusive provider of the Concussion Index to physicians and allied health providers for their patients. Our secure online portal makes it easy to provide the MRI and clinical data necessary to generate a Concussion Index report.

MRI Protocol Support

A conventional neurological MRI study that includes Diffusion Tensor (DTI) acquisitions is necessary for generating a Concussion Index report. Specific protocol examples can be found in Figure 2, and we are happy to work with you to tailor or optimize a protocol capable of supporting a Concussion Index report.

Secure Data Transfer

Our secure electronic data transfer portal, Osmosis, has been supporting clinical trials and studies using imaging worldwide for over 10 years. Osmosis makes it simple and easy to send your patients' data to us safely, securely, and quickly.

Validation

If you would like validation data specific to your site and patients, we would be happy to provide up to 10 Concussion Index reports for patients known to you to have sustained a concussion and those known to be free of recent concussive injury. We ask that you permit us to publish the anonymized results to better inform the medical community.

Scientific Collaboration

If you are researching pathophysiology or treatment of concussive injury, recovery and return to play, or other concussion-related research involving MRI imaging, we would be happy to work with you to add Concussion Index data to your project.

MRI Protocol:

AXIAL T1 MPRAGE – 1mm isotropic resolution, TR=1200ms, TE=2.29ms, TI=600ms, FOV=250mm, Flip angle=8 degrees

AXIAL Diffusion Tensor – 2mm isotropic resolution, minimum 12 diffusion directions, b-value 1: 0 s/mm^2, b-value 2: 1000 s/mm^2. This acquisition must include Fractional Anisotropy (FA) and Apparent Diffusion Coefficient (ADC) derivatives (typically automatically provided by the MRI scanner)

Figure 2: MRI Protocol

Summary

Qmetrics Technologies is passionate about improving player and patient outcomes with its expertise and technology. Conventional management of post-concussive injuries is lacking in objective information. Most often, patients return to activity based on self-reports of "feeling ok" with increasing levels of intensity. However, growing evidence suggests that multiple head hits, even blows that don't result in a concussion, are linked to prolonged recovery, longer-term impairment, and even CTE/death. The Concussion Index provides an objective assessment of brain

structure normality, enabling physicians and their patients to plan and track recovery from mTBI.

References

[1] GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019 Jan;18(1):56-87. doi: 10.1016/S1474-4422(18)30415-0. Epub 2018 Nov 26. Erratum in: Lancet Neurol. 2021 Dec;20(12):e7. PMID: 30497965; PMCID: PMC6291456.

[2] Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, Agrawal A, Adeleye AO, Shrime MG, Rubiano AM, Rosenfeld JV, Park KB. Estimating the global incidence of traumatic brain injury. J Neurosurg. 2018 Apr 1:1-18. doi: 10.3171/2017.10.JNS17352. Epub ahead of print. PMID: 29701556.

[3] Irwin, Kelley BS; Ede, Alison MS; Buddhadev, Harsh BPT; Driver, Simon PhD; Ronai, Peter MS, CSCS*D, NSCA-CPT*D, ACSM RCEP Physical Activity and Traumatic Brain Injury, Strength and Conditioning Journal: August 2011 - Volume 33 - Issue 4 - p 43-47 (doi: 10.1519/SSC.0b013e318210e899)

[4] https://www.hopkinsmedicine.org/health/conditions-and-diseases/traumatic-brain-injury

[5] Harmon KG, Drezner JA, Gammons M, Guskiewicz KM, Halstead M, Herring SA, Kutcher JS, Pana A, Putukian M, Roberts WO. American Medical Society for Sports Medicine position statement: concussion in sport. Br J Sports Med. 2013 Jan;47(1):15-26. doi: 10.1136/bjsports-2012-091941. Erratum in: Br J Sports Med. 2013 Feb;47(3):184. PMID: 23243113.

[6] Adam O, Mac Donald CL, Rivet D, Ritter J, May T, Barefield M, Duckworth J, LaBarge D, Asher D, Drinkwine B, Woods Y, Connor M, Brody DL. Clinical and imaging assessment of acute combat mild traumatic brain injury in Afghanistan. Neurology. 2015 Jul 21;85(3):219-27. doi: 10.1212/WNL.0000000000001758. Epub 2015 Jun 24. PMID: 26109715; PMCID: PMC4516289.

[7] Wu YC, Harezlak J, Elsaid NMH, Lin Z, Wen Q, Mustafi SM, Riggen LD, Koch KM, Nencka AS, Meier TB, Mayer AR, Wang Y, Giza CC, DiFiori JP, Guskiewicz KM, Mihalik JP, LaConte SM, Duma SM, Broglio SP, Saykin AJ, McCrea MA, McAllister TW. Longitudinal white-matter abnormalities in sports-related concussion: A diffusion MRI study. Neurology. 2020 Aug 18;95(7):e781-e792. doi: 10.1212/WNL.0000000000009930. Epub 2020 Jul 8. PMID: 32641518; PMCID: PMC7605507.

[8] Bartnik-Olson B, Holshouser B, Ghosh N, Oyoyo UE, Nichols JG, Pivonka-Jones J, Tong K, Ashwal S. Evolving White Matter Injury following Pediatric Traumatic Brain Injury. J Neurotrauma. 2021 Jan 1;38(1):111-121. doi: 10.1089/neu.2019.6574. Epub 2020 Aug 10. PMID: 32515269; PMCID: PMC7757530.

[9] Wilde EA, Goodrich-Hunsaker NJ, Ware AL, Taylor BA, Biekman BD, Hunter JV, Newman-Norlund R, Scarneo S, Casa DJ, Levin HS. Diffusion Tensor Imaging Indicators of White Matter Injury Are Correlated with a Multimodal Electroencephalography-Based Biomarker in Slow Recovering, Concussed Collegiate Athletes. J Neurotrauma. 2020 Oct 1;37(19):2093-2101. doi: 10.1089/neu.2018.6365. Epub 2020 Jun 9. PMID: 31931657.

[10] Lancaster MA, Olson DV, McCrea MA, Nelson LD, LaRoche AA, Muftuler LT. Acute white matter changes following sport-related concussion: A serial diffusion tensor and diffusion kurtosis tensor imaging study. Hum Brain Mapp. 2016 Nov;37(11):3821-3834. doi: 10.1002/hbm.23278. PMID: 27237455; PMCID: PMC6867350.

[11] Tamez-Peña J, Rosella P, Totterman S, et al. Post-concussive mTBI in Student Athletes: MRI Features and Machine Learning. Front Neurol. 2022;12:734329. doi:10.3389/fneur.2021.734329

[12] Martinez-Torteya A, Rodriguez-Rojas J, Celaya-Padilla JM, Galván-Tejada JI, Treviño V, Tamez-Peña J. Magnetization-prepared rapid acquisition with gradient echo magnetic resonance imaging signal and texture features for the prediction of mild cognitive impairment to Alzheimer's disease progression. J Med Imag. 2014;1(3):031005. doi:10.1117/1.JMI.1.3.031005