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Introduction

Mild Traumatic Brain Injury (MTBI), commonly referred to as “concussion”, affects over 1.7 million in the United States annually, with costs of nearly $17 billion. Despite the name, these injuries should not be considered to be “mild”, as approximately 15% of patients suffer persistent symptoms beyond three months. Until recently, no consistent correlation existed between clinical symptoms and radiological evidence of structural damage to the brain.

Conventional imaging methods have had relatively little to contribute in the evaluation of patients with MTBI. Traditionally, only a small minority underwent imaging- usually patients with atypical symptoms, in order to exclude a more serious injury. Occasionally, MRI would demonstrate micro hemorrhages, which were of unclear clinical significance. The advent of Diffusion Tensor Imaging (DTI) has opened a new role for MRI in the diagnosis of MTBI. DTI offers a method to noninvasively assess the microstructural integrity of white matter, and coherence of the white matter fiber tracts. Both of these anatomical concerns can be affected by MTBI. DTI has evolved to the point that it is understood that MTBI patients with a given symptom demonstrate a unique white matter injury pattern.

Diffusion Kurtosis Imaging (DKI) is an emerging technique that provides independent and complementary information to that acquired with DTI. DKI information is thought to indicate the complexity of the microstructural environment of the imaged tissue.

Functional MRI (fMRI) is also being utilized to show brain changes in patients with MTBI. Changes in brain activation have been seen when subjects perform memory tasks at the time of injury, and again six weeks (or longer) after injury. Differences between male and female subjects and older and younger subjects have also been noted.

Susceptibility-Weighted Imaging (SWI), which is termed Blood Sensitive Imaging (BSI) on Hitachi MR systems, has enhanced recognition of microhemorrhages from MTBI. These lesions are often missed on CT, T1- and T2-weighted MRI, and routine gradient echo sequences. Studies have shown that the locations of microhemorrhages correlate with regions of patient complaints.

Magnetic Resonance Spectroscopy (MRS) is being used in research to develop a non-invasive test that can provide a straightforward diagnosis for Post-Traumatic Stress Disorder (PTSD) or MTBI, or both. These two conditions have many overlapping symptoms. Researchers suspect that they may find a “suite” of metabolites that make up the chemical signature associated with MTBI and PTSD.

These various MRI techniques are being used by researchers to better understand brain injuries in a variety of populations- those suffering from mild traumatic brain injuries due to trauma, brain injuries suffered by military members, pediatric brain injuries, as well as brain injuries due to sports, including those who suffer from Chronic Traumatic Encephalopathy (CTE). In this module, we will be discussing each of these categories of brain injuries, and examining research results obtained through the use of various MRI techniques.
Mild Traumatic Brain Injuries

An estimated 1.5 million individuals sustain a Traumatic Brain Injury (TBI) each year, with approximately 75% of these injuries classified as an MTBI. An MTBI sufferer is classified by the American Congress of Rehabilitation Medicine as a patient “who has had a traumatically induced physiological disruption of brain function, as manifested by at least one of the following:

1. Any period of loss of consciousness
2. Any loss of memory for events immediately before or after the accident
3. Any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused)
4. Focal neurological deficit (s) that may or may not be transient

but where the severity of the injury does not exceed the following:

1. Loss of consciousness approximately 30 minutes or less
2. After 30 minutes, an initial Glasgow Coma Scale (GCS) score of 13-15
3. Post-traumatic amnesia not greater than 24 hours

MTBI has been termed a “silent epidemic”, as many patients do not have visible physical signs. Rather, they have disabling cognitive, psychological, and/or behavioral impairments, and employment disabilities that are often unnoticed or misdiagnosed. Patients may receive a head CT or MRI of the brain if they had loss of consciousness, post-traumatic amnesia, focal neurological deficits, physical signs of a skull fracture, were involved in a dangerous mechanism of injury, or are older than age 65. However, these tests are neither sensitive nor specific enough to identify individuals who have sustained an MTBI. These patients may not receive the proper diagnosis, leading to a lack of precise and appropriate clinical management. An accurate diagnosis is important in order to distinguish those truly suffering from MTBI sequelae, as opposed to those with malingering symptoms.

Patients may receive a more accurate diagnosis of MTBI if they undergo more recently researched imaging tests that aid in the diagnosis of MTBI, such as DTI and Susceptibility-Weighted Imaging (Blood Sensitive Imaging, or BSI on Hitachi systems). These imaging tests are better at identifying microstructural damage such as Diffuse Axonal Injury (DAI), and microhemorrhages that occur in MTBI. It is important to establish a diagnosis of MTBI in order to appropriately treat those most affected by this injury.

Structural MRI

Structural, or standard, MRI has improved detection of small hemorrhages, herniation, midline shift, and brain edema compared to the use of CT. Increased use of MRI following MTBI is uncovering the nature and location of specific lesions characteristic of these injuries, and helping to elucidate treatment possibilities. Two different types of lesions (microbleeds and linear lesions) have been identified histopathologically in post mortem exams of patients with severe TBI, but imaging correlates were not previously demonstrated in MTBI.
A total of 256 patients with acute TBI were evaluated over a 2-year period. Over 90% of these patients had a GCS score between 13 and 15. Imaging evidence of hemorrhage in the brain was seen in 104 patients, with 67% of them reporting a loss of consciousness, and 65% of the 104 reporting amnesia or temporary forgetfulness. MRI was performed within an average time frame of 17 hours after the injury, which included T2-weighted sequences, FLAIR sequences, and Diffusion Weighted Imaging (DWI). Cerebral punctate microbleeds were found in 20% of the patients, in areas such as the gray matter-white matter junction, corpus callosum, and brainstem. These lesions are characteristic of DAI. Distinct and different from the microbleeds were the tube-shaped linear lesions found in 33% of the patients, primarily in the frontal lobes and parasagittal white matter. Additional findings in association with the linear lesions included ischemia and edema, with 68% of the linear lesions classified as severe. The microbleeds were distributed throughout the brain, while the linear lesions were found mainly in one area, and more likely to be associated with injury to adjacent brain tissue. It is hypothesized that the linear lesions may represent a type of vascular injury that is seen in brain tissue studies of people with more severe TBI. This finding may provide an opportunity to develop treatment strategies for people who have suffered a MTBI. MRI may become more of a standard practice after MTBI, offering patients with primary vascular injury in the brain more appropriate acute treatment.

**Diffusion Tensor Imaging**

DTI has become the preferred MRI test to evaluate DAI associated with MTBI. DTI has four times improved sensitivity over CT for detecting non-hemorrhagic DAI, and can evaluate for other intracranial pathology, as it is twice as sensitive as CT for detecting contusions. DTI permits the evaluation of white matter and nerve fibers, and can assess myelin sheaths and nerve cell membranes. While both DWI and DTI detect changes in diffusion between different groups of water molecules, DTI has the additional capability of assessing the direction of the water diffusion. DTI can also identify microscopic tissue damage and examine white matter tracts.

DTI assesses the parameters of *Fractional Anisotropy* (FA), *Apparent Diffusion Coefficient* (ADC), and *Mean Diffusivity* (MD). DTI uses FA as an index of local coherence of fibers. Normally, water molecules in white matter tracts align along the direction of the tract and move faster along an axon, therefore termed anisotropic. Decreased structural integrity of brain tissue leads to increased random motion of water molecules in all directions, which is a reduction in FA. FA is measured on a scale of 0 to 1. In areas of highly restricted diffusion, such as the corpus callosum, the FA is high. FA is moderate in gray matter, as the diffusion of fluids through this tissue is somewhat restricted. In areas of low restriction, such as cerebral spinal fluid, the FA approaches zero. ADC is the average of the diffusion of water measured in the x, y, and z planes. MD measures average diffusion.

DTI studies have shown that even one MTBI can show damage to the white matter tracts in the acute, sub-acute, and chronic phases post-injury. The main areas significantly affected in MTBI include the internal capsule, corpus callosum, and subcortical white matter. DTI studies performed on patients in the acute and sub-acute phases have reported contrasting findings, with some studies reporting increased FA while others reported decreased FA in areas affected by MTBI. Increased FA in the posterior corpus callosum was reported in one study, with another study reporting increased FA in the corpus callosum and various left hemispheric tracts 3 weeks post-injury, with normalization of FA after 3-5 months. Conversely, a study reported decreased FA in the internal capsule and corpus callosum within 24 hours of injury, and normalization in 2 of 5 patients at 30 days. Another study that examined mild, moderate, and severe TBI found that patients with MTBI had lower FA and significantly higher ADC
in the genu of the corpus callosum at less than 3 months post-injury, but no significant differences were found between the groups after 3 months. Although FA was different in these studies, the areas affected by MTBI were similar. It is hypothesized that the differing FA values may represent different pathophysiological processes - increased FA may represent axonal swelling or cytotoxic edema, while decreased FA may represent axonal degradation and discontinuity with water between the spaces. Serial DTI studies may provide a way to monitor the resolution of various deficits in MTBI patients.

Researchers are corroborating areas of altered function seen on advanced imaging, such as DTI, with deficits in cognitive function seen on neuropsychological testing. Regions of altered function seen on DTI included the frontal cortex, corpus callosum, uncinate fasciculus, superior longitudinal fasciculus, anterior corona radiate, thalamus, and cerebellum. Neuropsychological testing has shown an association of executive function with the frontal white matter and the superior longitudinal fasciculus. Information processing corresponded with the cingulum, corona radiata, inferior longitudinal fasciculus, parietal white matter, and thalamus. Memory was localized to changes in the temporal, frontal, cingulate and parahippocampal regions. Establishing these structure-function associations may be used to predict persistent cognitive deficits, as well as to improve the precision with which various cognitive deficits can be diagnosed.

Investigations into specific anatomy of the brain found that 26% of MTBI participants had decreased FA in the corpus callosum, which connects with various regions in the brain, as well as directly connecting the two hemispheres of the brain. The extent to which the corpus callosum is damaged appears to correlate with total IQ. A moderate TBI group had significantly decreased FA in the genu, stem, and splenium of the corpus callosum, while the MTBI group showed decreased FA only in the splenium of the corpus callosum. Neuropsychological testing performed in a time frame with a mean of 560 days post-injury showed a positive correlation between FA in the splenium and total IQ.

DTI examinations on MTBI subjects have also found abnormalities in FA values in the uncinate fasciculus, which is a white matter tract that connects the orbitofrontal cortex to the temporal pole. Its proposed function has been related to emotion and memory, but recent research has revealed that it is also involved in language and attention. Studies have shown that MTBI subjects with deficits in the uncinate fasciculus have shown impairment in verbal learning. One study showed that males with MTBI had significantly decreased FA values in the uncinate fasciculus compared to females. The males also took more than twice as long to recover from MTBI than the females, regardless of the initial severity of symptoms. The decreased FA in the uncinate fasciculus was felt to be the most substantial risk factor for a recovery time longer than three months. Researchers feel that DTI and the uncinate fasciculus FA value could offer a metric for evaluating the severity of MTBI and predicting clinical outcomes.
Researchers are also looking at MTBI patients to determine if specific injuries are associated with a given symptom, with their research theme being that patients with concussions should be treated individually, based on their symptoms. The electronic medical records of 45 patients with MTBI and neuropsychiatric symptoms were selected from throughout an 8-year period. Of this group, 84% exhibited irritability, 71% had depression, 40% had anxiety, and 22% met the criteria for all three conditions. DTI showed decreased FA in the superior longitudinal fasciculus, in the white matter around the nucleus accumbens, and in the anterior limb of the internal capsule in patients with MTBI and depression (Figure 1). The regions that were abnormal in patients with depression after trauma were very similar to regions that are abnormal in patients with nontraumatic major depressive disorder. Injury in the nucleus accumbens region was also associated with recovery time in concussed patients with depression. The more severe the injury was in this region, the longer it took for patients to return to their baseline. The nucleus accumbens serves as the brain’s reward center, and is often abnormal in patients with a major depressive disorder. These results suggest that the nucleus accumbens plays an important role in any sort of depressive symptoms.

![Figure 1 DTI shows how patients with depression have significantly decreased FA in the region of the right nucleus accumbens (white arrow in A), anterior limb of the internal capsule (white arrow in B), and superior longitudinal fasciculus (white arrow in C); these regions are involved in depressive disorders in non-traumatic and traumatic settings (Images courtesy of Radiology)](image)

Concussed patients with anxiety had diminished FA in the vermis, compared with control subjects who had MTBI but no neuropsychiatric symptoms. While irritability is a common symptom after concussion, researchers found no regions of significantly decreased FA in the concussed patients with irritability. They hypothesized that while some post-concussion symptoms may be associated with a specific focal injury, perhaps not all of them are. These results may have been influenced by a component of organic brain injury, as well as the patient’s ability to deal with the injury.

Clinically, studies show that treatments already being used in the non-traumatic setting could potentially help MTBI patients, at least for depression. However, medications used for non-traumatic anxiety patients may not be as effective in patients who have anxiety after MTBI. The results received through the use of DTI contribute significantly to studies that compare traumatic (MTBI) and non-traumatic patient groups.
Many MTBI patients suffer from vestibulopathy after their injuries, which is a debilitating condition that includes dizziness and/or vision problems. This condition puts them at increased risk for another injury, as well as affecting their everyday functions of living, and return to work or sports. This post-concussion “dizziness” was thought to be due to injury to the inner ear. However, researchers have employed DTI to identify parts of the brain that cause people with MTBI to become dizzy or have vision problems, meaning that the injuries are to the brain itself, rather than the inner ear. Patients with MTBI and vestibular symptoms had lower FA values in the cerebellum and fusiform gyri than the control subjects with no symptoms, indicating damage to the brain’s signal-transmitting white matter (Figure 2). The cerebellum is the part of the brain that is vital for balance, and the fusiform gyri integrate vision between the left and right eyes to create a 3D visual field. These brain regions were not previously suspected to be involved in post-traumatic vestibulopathy. Researchers are planning to continue to develop DTI as a way to diagnose patients with MTBI to predict their symptoms. Through these scans, physicians may be able to predict that an injured region of the brain is related to a certain symptom. It must be relayed to MTBI patients that dizziness is not merely a peripheral symptom of MTBI, but may actually indicate a more serious injury to the brain.

![Figure 2 DTI axial (left) and coronal (right) views of the fusiform gyri; vestibular abnormalities correlated with decreased FA values in cerebellar regions (responsible for sensorimotor processing and central and/or axial balance), as well as the fusiform gyrus, which is responsible for visually guided locomotion and stereoscopic vision (Images courtesy of Radiology)](image)

Persistent chronic changes in the white matter have been documented after even one MTBI episode. DTI studies performed after three months continued to reveal pathology in areas similar to those found in the acute and sub-acute phases of MTBI. In a study of patients with continued post-concussive symptoms, which included difficulty with attention, concentration, memory and poor job performance, participants with MTBI had significantly decreased FA in the corpus callosum, subcortical white matter, and internal capsules bilaterally, when compared to the control group. A decrease in FA in the corticospinal tract, sagittal stratum and superior longitudinal fasciculus was found in individuals with chronic MTBI. Long-term alterations in white matter can be found many years after an injury. The areas most commonly affected are the cerebral lobar white matter and the corpus callosum and internal capsule. Researchers utilizing fiber tracking have found discontinuity of the white fiber tracts, such as supratentorial projection fiber bundles and corpus callosum fibers. Approximately 19% of MTBI patients had discontinuity of the fronto-temporo-occipital fiber bundles. These findings support chronic visible changes demonstrated in the same areas as the subacute and acute stages of MTBI.
DTI may hold the key to predicting which MTBI patients are most likely to fully recover from their head injuries in as little as a year’s time. Prior to the increased use and popularity of DTI, physicians had no reliable way to differentiate in advance which patients might have lingering, long-term adverse effects from those who would have a complete recovery. It has been reported that as many as 15-30% of patients experience concussion symptoms indefinitely. DTI enables visualization of how the brain compensates for concussion damage, so appropriate therapy can begin quickly, resulting in more favorable outcomes.

A group of 39 patients diagnosed with MTBI had DTI performed within 16 days of their concussions. This study also included 40 healthy control subjects. Twenty six of the 39 concussed patients returned for follow-up assessments one year later. Compared to the healthy controls, the MTBI patients showed areas of abnormally low FA that correlate with nerve fiber damage and cognitive impairment. However, other brain areas with abnormally high FA may suggest that the MTBI patient’s brains were responding to their injuries by remyelinating, or repairing, injured tissue (Figure 3). Having a greater volume of white matter areas with higher FA correlated with better outcomes and recovery times for MTBI patients. Conversely, the areas of low FA, which indicate white matter damage, were not useful in predicting recovery from MTBI one year later. These findings suggest that, rather than trying to minimize the damage of an MTBI, therapy may be more effective if it targets the brain’s own ability to compensate or repair white matter damage.

Figure 3 DTI of a concussion patient’s brain; areas of low FA (in red) indicate injured white matter, while high FA (in blue) suggest more efficient white matter connections compensating for concussion damage; a large amount of high FA can predict recovery from a concussion (Image courtesy of Albert Einstein College of Medicine)
Diffusion Kurtosis Imaging

DKI is an emerging technique that provides independent and complementary information to that acquired with traditional diffusion techniques. The additional information is thought to indicate the complexity of the microstructural environment of the imaged tissue. DKI is an attempt to account for the variations in the diffusion of water molecules in the complex intracellular and extracellular in vivo environment. Both DWI and DTI are based on the premise of Gaussian distribution of water diffusion in biologic systems. In other words, the water molecules diffuse uniformly in a certain direction, as in a bucket of water, and would conform to a bell curve. In the reality of a complex cellular structure, water molecules diffuse through an environment that is highly heterogeneous in any direction, leading to deviation from the Gaussian distribution. Rather than a bell curve, non-Gaussian distribution on a graph is more peaked, with lighter or heavier “tails”. The term “kurtosis” refers to an alteration of a normative pattern of distribution. High peaks, or higher kurtosis values, imply more impediments to normal diffusion and greater complexity within the imaged system. Diffusion is always fast initially, slowing as water molecules interact more and more with cellular structures.

Since diffusion is directional, diffusion kurtosis also varies across directions being measured. The most commonly used DKI parameters are those that have more direct physical relevance to the diffusion tensor. They include:

- **Mean Kurtosis (MK)** - the average of the diffusion kurtosis along all diffusion directions
- **Axial Kurtosis (AK)** - the kurtosis along the axial direction of the diffusion ellipsoid
- **Radial Kurtosis (RK)** - the kurtosis along the radial direction of the diffusion ellipsoid

Reduced MK is associated with loss of cellular structures. In white matter, AK is typically low, because the diffusion along the axial direction of the axons is free and relatively unrestricted, leading to the least deviation from the Gaussian diffusion. RK is typically high in white matter, as cellular membranes and myelin sheaths cause highly nongaussian displacement distribution, and a heterogeneous diffusion pattern.

A study of patients who had sustained an MTBI within the past year utilized DKI to show white matter changes in the thalamus. The thalamus acts as a relay station, as it has reciprocal projections to the entire cerebral cortex. It is involved in processing and transmitting cognitive, sensory, and motor function information. The role of the thalamus is related to attention, concentration, and processing speed, with changes in this area accounting for variances in executive function, attention, and memory in MTBI patients. Reduced MK within the thalamus in these patients suggested that evaluation of this region may serve as an early predictor of brain damage.
The use of DKI in cases of MTBI is gaining momentum, especially after the successes found with DTI. Recent studies have focused more on the use of DKI in cases of severe TBI. Researchers feel that high MK values around lesions may indicate the formation of glial scars, which are not noticeable on conventional images or FA maps (Figure 4). Reduced MK values are associated with the loss of cellular structures. DKI may prove to be a more sensitive tool for identifying brain injury, and may prove helpful in predicting cognitive outcome among TBI patients.

![Figure 4 DKI parameter maps (MK, FA, and MD in top row) and conventional MR images (Flair, T2, Susceptibility-Weighted Image in bottom row) at same axial location on victim of severe TBI; high degrees of MK may indicate formation of glial scars around lesions (yellow arrows), which are otherwise not noticeable on conventional images or FA map; high MK regions are accompanied by restricted diffusion as indicated on MD map, but different degrees of contrast (red arrows) on MD and MK maps are evident](image)

**Functional MRI**

fMRI has been utilized to show brain changes in patients with mild traumatic brain injury. Approximately 2 million people suffer nonfatal traumatic brain injuries each year, with more than 75% of those cases classified as MTBI. Previous research considered MTBI as a temporary affliction, with full recovery typically occurring within three months. However, lingering health issues exist in as many as 10%-15% of MTBI patients, including headaches, interrupted sleep, loss of balance, memory and other cognitive impairments, and fatigue. Additional studies have found that a person’s reduced function may be due to structural changes in the brain from the MTBI incident, while results from neuropsychological tests, CT, or routine MRI still appear to be normal.

fMRI has shown changes in brain activation when subjects with MTBI performed memory tasks. In a study where fMRI was performed at the time of injury, and again six weeks after the initial MTBI, digit span and continuous performance tests were performed prior to the fMRI on MTBI and control subjects. The digit span is a short-term memory test of how many numbers a participant can remember in sequence, while the continuous performance test measures a person’s sustained and selective attention and impulsivity. Participants were given a series of numbers and were to respond when a number shown matched the previous number, the one shown two numbers ago, or the one shown three numbers ago. The working memory load was considered to be minimal for one number back, moderate for two numbers back, and high for three numbers back. The working memory test scores did not
significantly differ between the control and MTBI groups. However, different brain activation patterns between the groups were visualized on fMRI scans in response to increasing working memory loads. The control subjects were able to increase the activity of their working memory circuitry to perform the numbers tasks, while the MTBI patients found it more difficult to do so with the moderate and high working load conditions (Figure 5). Increased working memory load is typically associated with increased activation of the bilateral frontal and parietal regions, a circuitry overlap with regions vulnerable to damage in MTBI. The MTBI patients exhibited more activity in some areas outside and inside the working memory circuitry compared to the control subjects. In the six-week follow-up study, the MTBI patients showed improved activation in response to greater working memory loads. The authors of the study feel that fMRI may find a place in the evaluation and guidance of treatment strategies, specifically targeting brain areas involved in MTBI recovery.

Figure 5 fMRI shows activation maps of one-, two-, and three-back results upon initial scan and at six-week follow-up; improvement in the working memory circuitry was noted in the follow-up study, which was greater during two-back versus one-back conditions (green arrows), but less notable with three-back versus two-back conditions (Images courtesy of Radiology)
fMRI studies have been used to point out differences in recovery time from MTBI between men and women. Digit span and continuous performance tests, mentioned above, were performed before the working memory task fMRI studies. Male patients with MTBI showed no significant differences from male control subjects in digit span or continuous performance tests, but female MTBI patients had lower digit span scores than the female controls. Two working memory task fMRI studies were performed—one within a month of the MTBI injury, and one six weeks after the initial fMRI. The initial fMRI scans of the MTBI patients showed increased activation in working memory brain circuits in the men, and decreased activation in the women, compared with the controls (Figure 6). In the six-week follow-up fMRI scans, the female MTBI patients continued to show hypoactivation, which suggests ongoing working memory problems. However, the male MTBI patients showed regression of their hyperactivation, returning to a more normal activation level, similar to the male control subjects. Hypoactivation can be caused by more severe brain damage, which does not allow another area of the brain to compensate for the loss of function. The results of this limited study suggest that women may have worse working memory outcomes, suggesting the need for separate MTBI management strategies for patients of different sexes.

Figure 6 Images show increased activation in bilateral frontal and parietal regions, which is consistent with activation of working memory circuitry in each group; in control subjects (A), visual comparison of working memory activation patterns shows more activation in women than in men, especially in the frontal region; substantially less activation (hypoactivation) in female patients with MTBI (B) than in female control subjects, as well as substantially more activation (hyperactivation) in male patients with MTBI than in male control subjects; at six-week follow-up study (C), female patients with MTBI showed persistent hypoactivation patterns, whereas male MTBI patients showed regression of hyperactivation and activation levels similar to those of male control subjects (Image courtesy of Radiology)
Additional studies using fMRI have compared the recovery from MTBI in younger vs. older patients. The younger patients were in the age range from 21-30 years, while the older patients were in the age range between 51-68 years. Working memory activity on fMRI was compared between young and old MTBI patients within one month of injury, and again six weeks after the initial exam. In the initial exam, hyperactivation during memory tests was seen in the young MTBI patients in the right precuneus and right inferior parietal gyrus. The younger patients also showed increased working memory activity associated with greater post-concussion symptoms in the right precuneus and right inferior frontal gyrus, and poor working memory performance in the right precuneus (Figure 7). Since increased brain activation was associated with worse task performance and more severe post-concussion symptoms in the younger patients, researchers have theorized that the hyperactivation displayed on fMRI could indicate more severe brain injury. The older MTBI patients displayed hypoactivation in the right precuneus and right inferior frontal gyrus during their memory tasks. At the six-week follow-up, the younger patients displayed a partial rebound of working memory activation patterns, along with decreased post-concussion symptoms. These changes were not detected among the older patients with MTBI, providing evidence of better neural plasticity in younger patients. As with the different outcomes found between males and females, the different working memory activation patterns between younger and older patients may lead to different management strategies for their treatment after MTBI.

![Figure 7 Images show different working memory activation patterns in healthy control subjects and young and old patients with MTBI; young control subjects (top left) had increased activation in the frontal and parietal regions, predominantly at the left hemisphere; in the initial exam, young patients with MTBI (top middle) had bilateral hyperactivation in the frontal and parietal regions, compared with young control subjects; partial recovery of the activation pattern (top right) is seen at follow-up imaging; older control subjects (bottom left) had increased cerebral activation in bilateral frontal and parietal regions; in the initial exam, older MTBI patients (bottom middle) showed hypoactivation, compared with the older control subjects; older MTBI patients had even less activation at follow-up (bottom right) (Image courtesy of RSNA)
Susceptibility-Weighted Imaging

Susceptibility-Weighted Imaging has enhanced recognition of microhemorrhages in MTBI that may not be picked up on CT, T1- or T2-weighted MRI, or Gradient Echo MRI. This type of imaging is performed on Hitachi MR systems as Blood Sensitive Imaging (BSI). It involves the use of a 3D RSSG EPI sequence, set to BSI mode, to acquire T2*-weighted images that use deoxygenated blood as a “natural” contrast agent. In one study that utilized susceptibility-weighted imaging in MTBI patients, the locations of microhemorrhages were related to the patient complaints. Visual complaints correlated with microhemorrhages in occipital regions, and hearing deficits correlated with temporal hemorrhages. The microhemorrhages were not detected in 76% of patients using conventional MRI only. Another study found that children and adolescents who suffered mild to severe TBI showed a significant inverse relationship between the Glasgow Coma Scale score, and the number and size of hemorrhagic diffuse axonal injury lesions seen on susceptibility-weighted imaging. Those who suffered an MTBI had the lowest quantity and smallest volume of hemorrhagic lesions, while those with severe TBI (lower scores on the GCS) had the highest quantity and largest volume of hemorrhagic lesions. At 6- and 12-month follow-ups, a direct relationship was found between the degree of disability and the number and size of hemorrhagic lesions, suggesting a worse prognosis for those with greater number and size of hemorrhagic lesions.

Summary

A growing number of individuals sustain MTBI each year. Utilizing only CT or routine MRI to rule out acute brain injury may not be sufficient to make a precise diagnosis of MTBI. The use of DTI has shown that even one MTBI can cause damage to the white matter tracts in all phases post-injury. Decreased fractional anisotropy in specific regions of the brain has been linked to post-concussion symptoms that are associated with the same brain regions. Reduction in specific Diffusion Kurtosis Imaging parameters in certain brain regions may be an early predictor of brain damage. fMRI has demonstrated differences in working memory activation between males and females, as well as between younger and older patients. Susceptibility-weighted imaging has greatly improved our ability to see microhemorrhages that may not be recognized using other imaging modalities. The precision and timeliness of an accurate diagnosis of MTBI is critical for the patient to receive the medically necessary treatment to return to being a vital functioning member of society. Utilization of the variety of MRI testing that is now available for MTBI patients will accelerate the attainment of this goal.
Military Injuries

Mild Traumatic Brain Injuries

MTBI are very common among U.S. service members returning from the conflicts in Iraq and Afghanistan. These injuries are often referred to as concussions, and result from the head being hit or violently shaken. According to the Armed Forces Health Surveillance Center, more than 300,000 service members have been diagnosed with MTBI between 2000 and 2015. MRI has shown brain damage in a surprisingly high number of active duty military personnel who suffered blast-related MTBI.

Current assessment of MTBI relies heavily on behavioral observations and on patient recall of events, such as post-traumatic amnesia and loss of consciousness. The need for a more definitive marker for MTBI led Gerard Riedy, M.D., Ph.D. to look at advanced brain imaging with MRI as a tool for assessing MTBI. Dr. Riedy works at Walter Reed National Military Medical Center, and was able to study 834 military service members with MTBI related to blast injuries. Slightly more than 84 percent of the patients reported one or more blast-related incidents, and 63 percent reported loss of consciousness at the time of injury.

The MRI scans revealed the presence of white matter T2 hyperintensities in 52 percent of the MTBI patients. These hyperintensities can be thought of as brain “scars”. Dr. Riedy expressed surprise to find the amount of brain damage that was found in that number of patients, as it is typically expected that patients with MTBI will have normal MRI results. Pituitary abnormalities were also identified in almost a third of the MTBI patients. Previous research has shown a decline in pituitary function in soldiers who experienced MTBI, perhaps due to blast-related trauma.
### Susceptibility-Weighted Imaging

Approximately 23 percent of military service members serving in Afghanistan and Iraq sustain TBI. Microbleeding on the brain, which can sometimes trigger serious secondary health conditions such as brain swelling or stroke, has been seen after TBI amongst our military. Many military members who have suffered a TBI have not been imaged until many, many months after their injury occurred, resulting in lower rates of cerebral microhemorrhage detection, which further delays correct treatment. Bleeding becomes harder to diagnose with time, as changes occur in iron deposits in the brain. The use of susceptibility-weighted imaging provides greater visibility of blood, and is much more sensitive to bleeding than conventional MRI (Figure 8). Hitachi’s Oasis and Echelon Oval systems perform Susceptibility-Weighted Imaging with an option called Blood Sensitive Imaging, or BSI. BSI uses a 3D RSSG EPI sequence, set to BSI mode, to acquire T2*-weighted images that use deoxygenated blood as a “natural” contrast agent. T2* imaging is sensitive to differences in magnetic susceptibility of adjacent tissues allowing for high resolution venographic images.

![Figure 8 Susceptibility-Weighted Image showing extensive microhemorrhages (arrows) consistent with diffuse axonal injury - a brain injury in which damage in the form of extensive lesions in white matter tracts occurs over a widespread area - in a 25-year old male with blast-related MTBI (Image courtesy of RSNA)](image-url)
In a study led by the aforementioned Dr. Riedy, 603 military personnel diagnosed with TBI received MRI scans that included susceptibility-weighted imaging. The patients were divided into two groups—those who were injured within three months, and those whose injury occurred at least three months to more than a year earlier. Of the 603 military service members who participated in the study, 7 percent (approximately 42 patients) were found to have at least one occurrence of microbleeding on the brain. Those who underwent an MRI more than a year after they were injured had a lower rate of brain microbleeding than those scanned within 12 months following a TBI. Brain bleeding was detected in only 5.2 percent of those who had an MRI a year after their injury, while bleeding was found in 24 percent of those imaged three months after their injury. Early characterization of cerebral microhemorrhages may help to explain clinical symptoms of acute TBI, as well as to identify the severity of brain damage. Military service members who undergo specialized MR brain imaging (including susceptibility-weighted imaging) soon after suffering a TBI may then receive relevant treatment more promptly. Dr. Riedy endorses having access to MR imaging in the field to facilitate early detection of TBI, and provide timely treatment.

Dr. Riedy and his research team are working to build a database of advanced imaging data, hoping to link this data with the more subjective symptoms associated with MTBI. Currently, a key area of focus is PTSD, which is a mental health condition caused by a traumatic event or events. Symptoms of MTBI and PTSD overlap, but treatments for one are unlikely to work for the others. Findings such as brain “scars” on MRI are objective measures of mild traumatic brain injury, which, when combined with subjective symptoms, may lead to more appropriate therapies for our service men and women. MRI has made it possible for military personnel and their families to actually see what have previously been called the “invisible wounds of war”.
Magnetic Resonance Spectroscopy

MRS is being used in research to develop a non-invasive test that can provide a straightforward diagnosis for either PTSD or MTBI, or both. Many of the symptoms of PTSD and MTBI overlap, with patients in both groups showing signs of depression, difficulty concentrating, anxiety, fatigue, loss of interest, and more. There is currently no screening tool or instrument to reliably diagnose either condition, so many cases of each condition go undetected or misdiagnosed. The use of MRS allows researchers to detect levels of metabolites in the brains of veterans who have suffered from MTBI and/or PTSD. Each participant had four regions of their head scanned, which included the anterior cingulate, parietal white matter, temporal lobe, and posterior cingulate (Figure 9). In preliminary results, two potential biomarkers were identified in 18 patients. Patients with MTBI had lower levels of the metabolites N-acetyl aspartate and creatine compared to PTSD patients. N-acetyl aspartate is a marker of neuronal health, and creatine is a marker of cellular energetics. The research group plans to expand the study to include several hundred participants, and suspects that rather than one or two metabolites, a “suite” of metabolites may be found to make up the chemical signature associated with MTBI and PTSD. This “suite” of metabolites might include choline and lactate, as both showed elevated levels in non-military patients suffering from TBI that underwent MRS at Massachusetts General Hospital. The relative size of the choline peak increases with pathological changes in membrane turnover or rapid cell division. Lactate is not normally seen in the adult brain, and its presence can be detected in cases of cerebral infarction, high-grade malignance, or mitochondrial disorders. Validation of these chemical signatures may enable returning veterans to receive MRS and MRI of the brain as part of their routine care.

Figure 9 Example of metabolite levels found in various areas of the brain using MR Spectroscopy
Diffusion Tensor Imaging

DTI may play a key role in predicting military veterans’ functional post-deployment outcomes (i.e. how soon they return to work) following a MTBI during combat. Currently, it is difficult to differentiate between the effects of MTBI and other conditions, such as PTSD. MRI and DTI were used to study 57 military veterans who had a clinical diagnosis of MTBI following deployment. The average length of time between injury and post-deployment evaluation was 3.8 years, with an average follow-up duration of 1.4 years. DTI was used to detect abnormalities in the brain, particularly in the white matter, via measurements of water movement. Results were compared to clinical measures and patient outcomes six months to 2.5 years after the initial evaluation.

All conventional MR images were interpreted as normal. However, significant associations were found between initial post-deployment DTI measurements and neurobehavioral symptoms, timing of injury, and subsequent functional outcomes. Following the initial post-deployment evaluation, 34 study participants (60%) returned to work. The DTI images of the veterans who did not return to work displayed significantly lower fractional anisotropy and higher diffusivity, suggesting less structural integrity, in the left internal capsule (Figure 10). This area is associated with motor stimulation to the typically dominant right side of the body. There may be a connection between impairments in fine motor functioning and the injured veterans’ inability to return to work. The loss of white matter integrity has a direct, measurable effect, and the differences in white matter microstructure may partially account for the variance in functional outcomes among this population.

![DTI Image](image.png)

**Figure 10** DTI shows regions of brain (blue) in which lower fractional anisotropy correlates with more severe neurobehavioral symptoms; veterans with the most severe symptoms had lower microstructural integrity in these regions (Image courtesy of Radiology)
Summary

MRI has revealed the presence of white matter T2 hyperintensities, or “brain scars”, in a large number of military members who have suffered mild traumatic brain injuries during the conflicts in Iraq and Afghanistan. Research has shown a need for more timely MR imaging of military members returning from these conflicts with traumatic brain injuries, as microbleeding is easier to detect in the early months after injury. Susceptibility-weighted imaging can be used to provide greater visibility of blood in the brain. Magnetic Resonance Spectroscopy is being used to detect metabolite levels in the brains of military members suffering from MTBI and/or PTSD, in the hopes of finding biomarkers that would enable an easier diagnosis of both conditions. DTI has been used to associate losses of white matter integrity with variances in functional outcomes of military veterans.
Pediatric Injuries

Traumatic Injuries

Trauma is a leading cause of death in children older than one year, with head trauma representing 80% or more of the injuries. In approximately 5% of head trauma cases, patients die at the site of the accident. Head trauma has a high emotional, psychosocial, and economic impact, as these patients often have comparatively long hospital stays, with 5-10% requiring discharge to a long-term care facility.

The highest rate of traumatic head injury is among children ages 0-14. Long-term complications of head injury are common in children, and they are related to both primary and secondary injuries. Mechanism of injury appears to be a significant predictor of clinical and functional outcomes at discharge for equivalently injured patients. CT of the head remains the most useful imaging study for patients with severe head trauma. Indications for CT scanning in a patient with a head injury include GCS score less than 12, posttraumatic seizures, amnesia, progressive headache, loss of consciousness for longer than 5 minutes, physical signs of basilar skull fracture, repeated vomiting or vomiting for more than 8 hours after injury (Figure 11). MRI is useful for estimating the initial mechanism and extent of injury and predicting its outcome in the neurologically stable patient. MRI is not as practical for emergency situations, as monitors and life support equipment needed by unstable patients may not be safe within the magnetic field of the MR scanner.

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<td>Utters incoherent words</td>
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<td>Makes no movements</td>
<td>Extension to painful stimuli (decrebrate response)</td>
<td>Abnormal flexion to painful stimuli (decorticating response)</td>
<td>Flexion / Withdrawal to painful stimuli</td>
<td>Localizes to painful stimuli</td>
<td>Obey verbal commands</td>
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Figure 11 The scale is composed of three tests: eye, verbal, and motor responses; a motor response in any limb is acceptable; the three values separately as well as their sum are considered; the lowest possible GCS sum is 3 (deep coma or death); the highest sum is 15 (fully awake person)

One hundred pediatric patients with head trauma were included in a study of the relationship between initial GCS scores and admission brain CT and MRI findings (when MRI was indicated). All 100 patients received CT scans, while 10 of the patients also had MRI brain studies. These 10 patients had suspicious initial GCS scores that did not correlate with their CT findings, or were considered to have severe TBI. None of the patients received intravenous contrast for either CT or MRI examinations. Those aged 15-18 were the most affected age group in this pediatric study. The causes of head trauma were 52% due to motor vehicle accidents, 34% due to falling from a height, and 14% due to violence. The initial GCS scores when the patients arrived at the hospital showed 54% classified as mild TBI (GCS>13), 8% moderate TBI (GCS between 9 and 12), and 38% classified as severe TBI (GCS between 3 and 8). Positive CT imaging findings were found in 79% of the patients, with one or more imaging findings observed in 67.1% of the patients. Amongst the 10 patients that also received MRI scans, findings included 60% with subdural hematoma, 50% with brain contusions, 20% with intracerebral hemorrhage, and 20% with diffuse axonal injury.
Mild TBI

Amongst the 54 patients classified as mild TBI, 21 were considered to have normal CT findings. Of the remaining 33 cases, 14 cases had more than one abnormal finding. MRI was able to detect 2 cases of non-hemorrhagic contusions that were not detected on initial CT scans. The most common imaging findings in the mild TBI cases included subgaleal hematoma, skull fractures, and brain contusions.

Moderate TBI

Eight of the 100 patients in this study were classified as having moderate TBI. Six of these eight patients had more than one CT finding. MRI detected one large non-hemorrhagic brain contusion that was not shown on the initial CT examination (Figure 12). That patient’s initial GCS score was 9. The most common CT findings in moderate TBI cases were subgaleal hematoma (bleeding between the skull and the scalp), fracture, subdural hematoma, and brain contusions.

![Figure 12](image_url) Three-month old with moderate TBI and GCS score of 9; CT image on left shows subtle area of hypodensity at the right high parietal region (red arrow); T1-weighted axial MR image in center shows area of low signal intensity at the same region (green arrow); T2-weighted axial MR image on right shows high signal intensity in the same region, suggestive of non-hemorrhagic brain contusion with no significant mass effect (blue arrow)
Severe TBI

Thirty eight patients were classified as severe TBI, with 33 cases presenting with more than one CT finding. Five cases displayed diffuse axonal injury, with 3 of those cases having “suspicous” findings on their initial CT. Unfortunately, those three patients succumbed to their injuries before MRI could be performed. MRI confirmed the diagnosis of DAI in the remaining 2 cases, and detected the actual extent of the injury (Figure 13). The most common extra-axial findings in severe TBI included subgaleal hematoma, skull fractures, subdural hematoma, subarachnoid hemorrhage, epidural hematoma, and intraventricular hemorrhage. The most common intra-axial findings with severe TBI included brain edema, brain contusions, intracerebral hemorrhage, and diffuse axonal injury.

![Figure 13 Severe TBI in 18-year old with GCS score of 8; T1-weighted axial images in row A, T2-weighted axial images in row B, FLAIR axial images in row C; orange arrows indicate an area of hyperintensity on all sequences within the lateral aspect of the left cerebellar hemisphere corresponding to subacute hemorrhagic contusion; yellow arrows indicate foci of hyperintensity on all pulse sequences within the right dorsolateral midbrain; white arrows indicate thin subdural hematoma overlying the right cerebral hemisphere displaying high signal intensity on all pulse sequences; green arrows indicate areas of T1 and T2 hyperintensity in the right frontal lobe corresponding to subacute hemorrhagic contusion; all findings are suggestive of grade III diffuse axonal injury](image-url)
Diffuse Axonal Injury

DAI is a frequent result of traumatic acceleration/deceleration or rotational injuries, and a frequent cause of persistent vegetative state in patients. DAI represents approximately one half of all intra-axial traumatic lesions. These lesions are the most significant cause of morbidity in patients with TBI, which most commonly result from high-speed motor vehicle accidents. DAI typically consists of several focal white matter lesions in a characteristic distribution. Although DAI is considered a primary-type injury, with damage occurring at the time of the accident, research has shown that a delayed component exists, with secondary factors. Injury to the axons interrupts axonal transport, so transported materials accumulate. Secondary swelling can occur in various areas, which are termed axonal balls, or retraction balls or bulbs. These areas of swelling likely represent axonal disconnections. DAI is suggested in any patient who demonstrates clinical symptoms disproportionate to his or her CT findings, as the degree of microscopic injury is usually greater than that seen on diagnostic imaging. DAI results in instantaneous loss of consciousness, with more than 90% of patients remaining in a persistent vegetative state. DAI rarely causes death, as brainstem function typically remains unaffected.

MRI is the preferred examination for DAI, particularly with the use of gradient echo sequences. MRI may play a role in predicting the length of coma in DAI patients. DTI has also emerged as a promising technique for assessing white matter integrity via the measurement of the anisotropic diffusion of water molecules. DTI may be useful in assessing patients with even mild TBI. Traumatic microbleeds are considered to be a radiologic marker for DAI. The use of susceptibility-weighted imaging has been found to be sensitive and accurate for microbleed detection. Susceptibility-Weighted Imaging can be performed on Hitachi’s Oasis and Echelon Oval systems using BSI, as previously explained in the Military Injuries section.

Conclusions from this pediatric study stated that statistical significance was found between GCS scores and imaging findings. The lower the GCS score, the more severe were the TBI and the imaging findings. CT is often considered the modality of choice in the evaluation of acute head injury due to its speed, its wide availability, its sensitivity to acute blood, and its ease of use in the ER. MRI is indicated for patients with acute TBI when neurological findings are unexplained by CT and do not correlate with the GCS score. MRI has also been found to be superior to CT in the detection of non-hemorrhagic brain injury, and in cases of diffuse axonal injury. It is also more sensitive to brainstem injury, especially with the use of FLAIR sequences.
Sports-Related Injuries

When considering sports-related concussions in children, most CT and MRI scans are normal. However, the role of MRI may be gaining in importance in determining whether or not children are able to return to sporting activities. A retrospective review was performed on 151 pediatric patients who had received CT or MRI scans after diagnoses of sports-related concussions by a neurosurgeon. Twenty four patients received CT scans, nineteen of which were normal. Sixteen patients underwent MRI exams, with twelve normal results. However, MRI also detected signs of hemorrhagic and nonhemorrhagic traumatic lesions that prompted physicians to advise that the patients not return to contact sports.

There are limited, if any, clinical studies that have reviewed neuroimaging findings in pediatric patients with concussion. CT is often avoided outside the emergency setting for pediatric patients, due to radiation exposure. Researchers advise that CT should only be used to rule out intracranial hemorrhage in acutely injured patients. MRI has the advantage of no radiation exposure, and should be considered for pediatric patients with focal neurological deficits, worrisome symptoms, or abnormal or inconclusive CT findings. Researchers recommend development of standardized MRI protocols for concussion imaging, and better clinical practice guidelines to guide decision-making for pediatric patients with sport-related concussion who have traumatic lesions on imaging.

Utilization of MRI in Pediatrics

One recent study involving pediatric patients found increased utilization of MRI, with a decrease in CT usage in the emergency department of a New York City hospital. A majority of the MR procedures were performed for neurological reasons, such as headache, seizure, trauma, or weakness. MRI offers the benefits of avoiding ionizing radiation, as well as detecting additional pathologies that may not be seen on CT.

A four-year survey of over 18,000 MRI scans performed on outpatient pediatric patients showed an increased use of anesthesia despite stable MRI utilization. Sedation or general anesthesia are the standby strategies to successfully complete MR imaging studies. MR scans on the pediatric population are challenged by issues such as claustrophobia, the need for contrast injections, and a child’s tendency to move around. This study found that the frequency of sedation or anesthesia use increased from 21% of cases in 2011 to 28% of cases in 2014. The most pronounced increase was among the 1-6-year-old patients. The data for this study was from one Accountable Care Organization (ACO), whose goal is to provide quality care with cost containment to low-income children. The study is somewhat limited by the fact that all subjects were enrolled in Medicaid, and may have a higher disease burden and different rate of utilization of diagnostic testing compared with the general pediatric population.
Summary

MRI has been found to be superior to CT in the detection of non-hemorrhagic brain injury and in cases of DAI in patients with acute TBI. In pediatric patients with sports-related concussions, MRI has detected signs of hemorrhagic and nonhemorrhagic traumatic lesions, prompting physicians to advise their patients to not return to their contact sports. Limited studies on the utilization of MRI in the pediatric population have shown:

- An increase in MR usage and a decrease in CT usage in an ER situation
- Stable usage of MR, with an increase in sedation/anesthesia usage in an outpatient pediatric population

The benefits that MRI offers over CT, which include the avoidance of ionizing radiation, and the detection of additional pathologies, signify the importance of utilizing MRI when dealing with pediatric brain injuries.
Sports Injuries

Structural MRI

Much recent attention has been focused on concussions, or mild traumatic brain injuries, and how they affect athletes in various sports. Are there long-term effects that are not being taken into account? Are athletes returning to the playing field too early? Structural MRI, as well as DTI and fMRI, are leading the way in finding answers to the questions concerning head injuries in sports.

Professional football has probably received the most attention as far as long-term effects of multiple concussions. One study examined 28 former professional football players, ranging in age from 36 to 79. When compared to imaging performed on a control group of similar age and education, the imaging on the retired NFL players showed smaller hippocampal volumes. More specifically, those with a history of concussion and loss of consciousness had smaller hippocampal volumes and lower memory test scores when compared to those who had a history of concussion but no loss of consciousness. Some players also met the criteria for mild cognitive impairment, which typically affects memory and may lead to dementia. These results were more pronounced among those who experienced more severe concussions. The researchers concluded that a history of concussions and mild cognitive impairment appear to have a cumulative effect on hippocampal size and function.

MRI and a computer model of the brain have been used to show that concussions can be caused by brain and skull rotation. Helmet-testing equipment and conventional detection techniques may not be adequately evaluating all potential causes of concussions. The standard test for football helmets used in college and professional ranks involves a device that drops a helmet-clad dummy head from multiple heights to approximate various impact magnitudes. Data from sports-related head impacts was collected for many years from Stanford University football players who wore mouthguards fitted with accelerometers. These devices showed that players frequently experienced head oscillations in the 20-Hz range. MRI and a computerized brain model showed that the brain’s relative motion is amplified when the head oscillates at 15Hz to 20 Hz, completing a single back-and-forth motion in about 50 msec. High rotational velocities, which are thought to induce brain strain and have been predictive of concussions, were observed in the field impacts, but not the drop tests. Helmet evaluation is in need of standardization and improvement in testing.
MRI was used to connect concussions sustained by young ice hockey players with subtle changes in the outer layer of the brain that controls higher-level reasoning and behavior. As the severity of the concussion symptoms increased, the cortex became thinner than what is considered normal at that age. This is troublesome, as thinning of the cortex occurred in areas associated with attention control, memory, and emotions. Concussions account for 15% to 22% of all reported injuries in young male hockey players. This study included preparatory school and collegiate ice hockey players, aged 14 to 23. Almost half of the subjects reported having one to four concussions, and all athletes were at least 3 months removed from their most recent concussion. For cognitive testing purposes, Immediate Postconcussion Assessment and Cognitive Testing (ImPact) was used to assess verbal and visual memory, processing speed, reaction time, and impulse control. This test includes a scale of 22 commonly reported concussion symptoms, which are rated for severity using a seven-point Likert scale, resulting in a total symptom score (TSS). After reviewing structural MRI images and the ImPACT results, researchers found an inverse association between TSS and cortical thickness (Figure 14). The cortex was thinner in the frontal, parietal, and temporal regions of the brain in subjects with greater self-reported post-concussion symptoms. However, concussion history was not associated with cortical thickness. It is speculated that the reduced cortical thickness in the specified areas may be tied to more subtle, repetitive blows to the head, as opposed to discrete concussive episodes. It is also possible that the hockey players were incorrectly recalling their concussion history. The long-term effects of the thinning cortex are unclear, but it is feared that the condition may be a harbinger of future brain damage, and that this type of injury to a young still-developing brain could have more severe consequences than a similar injury to an adult brain.

![Image](image.png)

Figure 14 Example of the inverse relationship between post-concussive symptoms and cortical thickness; blue regions indicate where this relationship was statistically significant (Image courtesy of the University of Vermont)

A follow-up study suggests that a greater volume of hyperintensities is associated with decreased thickness in the cortex. Previous studies have linked hyperintensities with cognitive impairment and Alzheimer’s disease. People generally accumulate one hyperintensity for every 10 years of life. However, one college-age athlete in the study had 18 such hyperintensities. This is a clinically concerning finding, but long term effects are still unclear.
Young Canadian hockey players (aged 18-36) were included in a study where researchers were looking at the dynamic effects of acute MTBI on myelin in the human brain. Myelin is the insulating sheath that protects the nerve fibers in the brain. It is critical to brain function, and damage or disruption of myelin can lead to a disability. The most common disease associated with myelin damage is multiple sclerosis. For this study, MRI scans were performed both before the hockey season and at the end of the season. If the athletes suffered a concussion during the season, they received follow-up MR scans three days, two weeks, and two months after their injuries. Researchers analyzed myelin water fraction changes, comparing the concussed athlete’s baseline MR images to subsequent MR scans. There were no significant differences in myelin water fraction between baseline MRI scans of non-concussed athletes and players who later suffered MTBI. Among the concussed athletes, the myelin water maps showed clusters of voxels with significantly reduced myelin water fraction (a reduction of 6% ± 1.2%) two weeks after the injury, compared to baseline results (Figure 15). These changes were most evident in the splenium of the corpus callosum, right posterior thalamic radiation, left superior corona radiata, left superior longitudinal fasciculus, and left posterior limb of the internal capsule. A decline in myelin water fraction was seen in the scans performed 72 hours post-concussion, but the results did not achieve statistical significance. This may have been due to the reduced sample size, as the subjects were acutely concussed and enduring the worst phase of their symptoms at this point, so only 72% of the subjects participated. There were no significant myelin water fraction changes between the baseline scans and those performed two months post-concussion.

From this study, the authors felt they could strongly infer that the changes in myelin water fraction are indicative of true changes in myelination within the brain. However, even though the changes appear to become less severe after two weeks, the athletes’ conditions will not magically change back to normal on the 15th day. There may be some residual myelin change after even three weeks, and this change may not be visible or detectable by cognitive tests. The lack of significant myelin water fraction changes two months after a concussion suggests that the myelin has recovered during that length of time.

Figure 15 Myelin water fraction maps show a concussed athlete at baseline (left) and two weeks after the injury (right); a region of the corpus callosum had a visible reduction in myelin water fraction post-injury (red arrow); (Image courtesy of PLOS One)
DTI

DTI is being used to show that even one season of play in a contact sport (typically including soccer, football, and ice hockey) can result in brain changes, even in the absence of concussion. A multi-year study called the Einstein Soccer Study has been asking athletes to report their concussion symptoms from a variety of causes, ranging from the subconcussive impact from heading the ball, to hard impact collisions with other players or a goalpost, which are more likely to result in a concussion. Players are scanned prior to play, giving researchers a before-and-after look at the brains of athletes who have concussions. It was thought that soccer’s continuous low-level impacts to the head were not clinically significant. However, repeated impacts to the head can add up to potentially more than the sum of the parts. Researchers are gaining a better understanding of the sport’s cumulative effects on the brain, and any additional risks from an especially large number of repeated impacts.

A 2013 study by this group found that soccer players who headed the ball six to twelve times per game performed poorly on memory tests, and had brain abnormalities similar to those found in patients with traumatic brain injury. These results were based on DTI studies that showed areas of abnormally low fractional anisotropy that correlates with nerve fiber damage and cognitive impairment. MRI with DTI allows us to see changes in the brain before there are overt symptoms or brain dysfunction, which is important when planning preventive strategies in sports.

A recently published study by this group involved 222 adult soccer players who completed a total of 470 questionnaires about their soccer activity during two-week periods over the course of nine months. The players were asked to tally the number of times they experienced concussion symptoms, ranging from none to mild, moderate, and severe. Mild symptoms included persistent headache and dizziness, while moderate symptoms included disorientation to the point of having to stop playing, at least temporarily. Severe symptoms included being knocked unconscious.

The median number of headings over a two-week period was 40.5. Thirty five percent of players reported one unintentional head impact during a two-week period, while sixteen percent reported more than one such impact. Twenty percent of players experienced moderate to very severe concussion symptoms. Twenty percent of the total questionnaires reported concussion symptoms. Players who headed the most were 3.17 times more likely to have central nervous system symptoms. Athletes who headed the ball less were only 1.5 times more likely to have concussion symptoms. The moderate to severe concussion symptoms were more strongly connected with the unintentional head impacts. Researchers found heading to be an independent risk factor for concussion symptoms, as those players who headed the most times were the most susceptible to concussion. Participants in this study have undergone additional MRI scans to determine if certain brain regions are more susceptible to injury. This data is being analyzed, and will be helpful in reaching the goal of this study- to determine the long-term effects of heading and other head impacts on soccer players.

DTI scans have shown significant brain changes in young football players after one season of games and practice, even when they appear concussion-free. This study involved 25 male football players between the ages of 8 and 13 years, and took place over 2 seasons of play. Head impacts were recorded using a Head Impact Telemetry System, and all games and practices were video recorded. In one season, concussions were reported when a player, parent, and coach suspected the injury. During the next season, a certified athletic trainer was present for all games and practices to evaluate players suspected of having a concussion. Study participants underwent pre- and post-season evaluations that included
DTI of the brain. The researchers were particularly interested in seasonal fractional anisotropy changes in three white matter tracts - the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus, and the superior longitudinal fasciculus. These specific fiber tracts are of interest in MTBI, and will assist in detecting the location of traumatic axonal injury as it relates to sub-concussive head impact exposure.

In 88% of the cases, there was a statistically significant relationship between the head impact telemetry results and decreased fractional anisotropy values in the whole inferior fronto-occipital fasciculus as well as the left inferior fronto-occipital fasciculus. This relationship suggests that an increase in sub-concussive head impact exposure may have an effect on white matter integrity in youth athletes, even in the absence of a clinically diagnosed concussion. This same statistically significant trend was seen in the right superior longitudinal fasciculus, but not in the inferior longitudinal fasciculus. These results suggest that sub-concussive impacts can result in changes in the white matter microstructure of areas of the brain that are of interest in MTBI. This study adds to the growing body of evidence that a season of play in a contact sport can result in brain changes on MR imaging, even in the absence of concussion, as none of the players showed any signs or symptoms of concussion from two seasons of games and practices (Figure 16). These changes in the brain may resolve with little consequence, but more research is needed to understand the meaning of these changes to the long-term health of our youngest athletes.

Figure 16 MRI shows the left inferior fronto-occipital fasciculus before (top) and after (middle) the playing season; in an overlay of the two images (bottom), the red region illustrates the brain after the season, while the blue region represents the brain before the season (Image courtesy of Radiology)
The majority of studies on concussions and their possible long-term effects look at only a single measure at one time—e.g. volumetrics or blood flow. Canadian researchers were interested in the convergence across three measures, which included cerebral blood flow, gray matter volume, and white matter microstructure. They studied these different metrics within a single cohort made up of 43 active college athletes, ages 18-23, from seven varsity sports (volleyball, hockey, soccer, football, rugby, basketball, and lacrosse). Their university mandated baseline testing for concussion prior to the start of each season. Twenty-two of the athletes had no previously documented concussions, while twenty-one of the subjects had a prior history of concussion. A median of 2 head injuries was reported for the concussed athletes, with a median time of 26 months since their last concussion. The time from their most recent head injury until receiving medical clearance to return to play was an average of 18 days.

DTI sequences were performed to calculate cerebral blood flow, gray matter volume, white matter microstructure through fractional anisotropy, and mean diffusivity (Figure 17). Athletes with prior concussions showed a 10%-20% decrease in gray matter volume compared with athletes with no concussions. Much of the shrinkage was in the frontal lobes, which are vulnerable to injury due to their location. Another finding primarily in the frontal lobes was 25%-35% less blood flow. The frontal lobe is a critical area of the brain for different processes, including decision-making, planning, and impulse control. Reduced gray matter volume was also found in the temporal lobes, supplementary motor area, and the anterior cingulate. These deficiencies were associated with a longer recovery time among concussed athletes.

![Figure 17 Brain MR images plot the average cerebral blood flow (left panel) and gray matter volume fraction (right panel) for athletes with and without a history of concussion; red arrows denote areas where concussed athletes showed significantly lower blood flow and gray matter volume (Images courtesy of Nathan Churchill, PhD, and St. Michael's Hospital)]
Although the causal relationship among changes in gray matter volume, cerebral blood flow, and white matter microstructures is not a simple one-to-one corollary, common characteristics were shared among the three variables. For example, decreases in frontal cortical volume were found in the same areas where there were decreases in blood flow. This speaks to the “crosstalk” between structure and function in the brain. Unique changes were also seen—e.g., athletes who took longer to recover from their last hit had lower blood flow throughout the brain, but the cortical volume itself was not affected.

While the MR images on the athletes with no previous concussions showed no alterations, the MR scans acquired 9 months to as long as 10 years after injury demonstrated less gray matter, decreased blood flow in the frontal lobe, and microstructural changes in white matter. Speculation remains concerning the potentially long-term adverse effects of concussions, which may range from chronic traumatic encephalopathy and neurodegeneration, to loss of cognition and motor skills due to long-term changes in brain structures. Researchers plan to acquire more data, which may involve following subjects at multiple time points to see if brain abnormalities have resolved, as well as looking at subjective outcomes.

**DTI and DKI**

DTI has been performed in combination with DKI in order to better measure changes in the brain’s white matter integrity (Figure 18). One study in which both DTI and DKI were performed suggested that playing just one season of high school football caused brain alterations seen on both structural and functional imaging. This study included twenty four high school football players who received MRI scans (including DTI and DKI) before and after their season. They also underwent magnetoencephalography scans, which record and analyze the magnetic fields produced by brain waves. This is another method of assessing changes in brain function. These athletes wore helmets fitted with the Head Impact Telemetry System (mentioned previously) during all practices and games. Their helmets were lined with six accelerometers that measure the magnitude, location, and direction of impacts. Data from the helmets was then uploaded to a computer for analysis. The researchers calculated the change in imaging metrics between the pre- and post-season imaging exams, and combined the imaging results with player-specific impact data from their helmets. None of the 24 players were diagnosed with a concussion during the study.
Players with greater head impact exposure had the greatest change in diffusion imaging and magnetoencephalography metrics. The study demonstrated that even subconcussive impacts can result in physical damage to nerve fiber tracts in the white matter of the brain. The magnetoencephalography showed the generation of delta waves, which may be an indicator of impaired brain function. Researchers are hoping that future studies will involve a larger population and a longitudinal study method to determine if the brain’s developmental trajectory is truly altered, or if the off-season time allows for the brain to return to normal. It is also important to determine if the physical changes in the brain subsequently lead to changes in memory, thinking, and reasoning capabilities, which are traditionally assessed with specialized neuropsychiatric examinations.

![Figure 18 Example of a white matter rendering from DTI and DKI scans (Image courtesy of RSNA)](image)

**DTI and fMRI**

DTI and fMRI were both performed on former collegiate and professional football players in a study that compared brain injuries in relation to the number of concussions athletes incurred while playing, as well as which areas of the brain were affected, based on the player’s position. The study enrolled 32 former college players with a mean age of 58.2 years. Those who had one concussion or less and those who had three concussions or more played for a mean of approximately eight years, including participation before college. The 31 professional players in the study had a mean age of 58.5 years, and those with one concussion or less or three concussions or more were active for a mean of approximately 17.6 years. The number of contact hours was also tallied, based on the former athletes’ practice and game time. Mean totals for college players with one concussion or less were about 1,062 contact hours, and 1,332 contact hours for those with three concussions or more. However, amongst the retired NFL players, those with one concussion or less had more mean contact hours at 3,284, compared to those with three concussions or less at 3,041. The researchers were also taking into account whether the players had a speed position or non-speed position. Speed position players took impacts at higher rates, and had more closing distance between them and the people they were impacting. Speed position players included quarterbacks, running backs, wide receivers, linebackers, and defensive backs. Non-speed position players experienced an impact on every play with the person who was lined up one foot...
away, so they were experiencing more repetitive hits to the head. Non-speed players included offensive and defensive linemen.

DTI revealed consistently lower fractional anisotropy in the forceps minor and genu of the corpus callosum near the frontal cortex in non-speed players with 3 or more concussions, compared with players with one or no concussions (Figure 19). The forceps minor and genu of the corpus callosum cross over the two hemispheres of the brain and are closely connected to the frontal cortex, which is associated with cognition and higher-level functioning. The lower the fractional anisotropy value, the more likely there is a microstructural white matter abnormality. Researchers felt that these results may be due in part to the types of impacts that players are exposed to, especially those in non-speed positions. They may not receive as many high-magnitude impacts in the front of their helmets, but they are receiving many lower impacts, which may have an effect.

Figure 19 The statistical heat map for the concussion-position interaction is shown in red-orange; the major clusters were within the frontal white matter, specifically within the forceps minor (blue); this result suggests there may be a modifying effect of sub-concussive impact exposure on damage to white matter structures caused by recurrent concussions; this modifying effect appears most prominently in the frontal white matter structures; implications of such white matter structural changes on late-life cognitive function are unknown (Images courtesy of Allen Champagne and Michael Clark)
All players were given a series of neuropsychological tests, and were considered cognitively normal. Their fMRI test was an n-back cognitive test, which evaluates subjects’ working memory by asking them to recall a sequence of letters and numbers and press a button each time they see the image again. fMRI preliminary results suggested that the subjects appeared cognitively normal, regardless of concussion history or player position. However, fMRI also allows researchers to determine how much of the players’ cognitive resources they needed to recruit to complete their task. The amount of “additional processing” appears to be related to concussion history, although head impact exposure also has a role. Researchers summarized that both the nature of the players’ exposure to head impacts, and their concussion history play a major role with regard to differences in white matter integrity.

Research indicates that those who have had concussions, particularly in sports, who return to play too early are at increased risk of negative outcomes, such as a second concussion, or possibly worse symptoms. Researchers hypothesize that there may be some ongoing process, be it recovery or reorganization in the brain, that goes on for quite some time after the initial injury. Recent investigations are trying to determine the best time for athletes to return to sports activities, and the consequences of returning too early. Twenty four concussed athletes and 27 age- and gender-matched control athletes took part in the study. The athletes were from various sports, including volleyball, hockey, soccer, football, rugby, basketball, and lacrosse. The concussed athletes were scanned on two occasions- once within one to seven days of their injury (median, four days), and again after receiving medical clearance to return to action (median, seven days after clearance). On average, the athletes were playing again in eighteen days. Based on structural MRI, no abnormalities, such as clinically significant white-matter hyperintensities, contusions, or microhemorrhages, were identified among the concussed athletes.
DTI was performed to detect changes in the microstructure of brain tissue, using fractional anisotropy to measure the directionality of water diffusion and mean diffusivity to quantify total water diffusion in the brain’s white matter (Figure 20). Decreased fractional anisotropy values and elevated mean diffusivity are potential indications of an abnormality. DTI analyses showed concussed athletes’ fractional anisotropy (FA) was significantly less than the control subjects’ value for the scan right after injury. FA was also less for the concussed athletes at the second MRI scan, after medical clearance. Concussed athletes exhibited statistically significant increases in average mean diffusivity at both the first MRI scan and upon clearance to return to play. The decrease in FA and the increase in mean diffusivity were interpreted as likely signs of cellular swelling and potential inflammatory processes.

![Figure 20](image1.png)

Figure 20 MR images show mean fractional anisotropy in white matter in top row, and mean global functional connectivity in gray matter in bottom row; control subjects were compared with concussed athletes after their injury (acute) and when they were clinically cleared to return to play (RTP); red circles indicate areas of significant concussion effects (Images courtesy of Nathan Churchill, PhD)

fMRI was used in this study to assess brain function based on regional blood oxygenation levels. Through resting-state fMRI, the researchers sought to assess global functional connectivity across the brain, looking for evidence of changes in how brain regions communicate with each other. The average global function connectivity value for concussed athletes was significantly greater than for the controls, both immediately after their injuries and at the time of medical clearance to return to play. The difference between the first and second scans was not statistically significant, leading researchers to the conclusion that adverse changes in the brain were still present at the latter time point. Results showed widespread adverse effects in white matter tracts, which included clusters located predominantly within the right corona radiata, and bilaterally in posterior limbs of the internal capsule. At the time of acute injury,
these brain regions showed evidence of being hyperconnected, which included the areas involved in vision, planning certain tasks, and motor activities. This hyperconnection has been seen in studies done on stroke patients and more severe brain injury patients, where it may be a protective mechanism in which the brain is increasing redundancy communication. Future injury would then be less devastating. Researchers did not necessarily expect to find that the microstructural change seen early in the injury, an average of three days post-concussion, was still present at the time of medical clearance.

Once medically cleared, all athletes returned to their normal level of performance. However, researchers are interested in following these athletes in the coming months and years to evaluate previously injured areas of the brain that might become vulnerable if another concussion or repeated head injuries are experienced. Possible areas of risk include their ability to switch between tasks and their ability to maintain visual tracking. Researchers are interested in determining if the athletes’ brain structure and executive function return to baseline levels, or if their condition is their “new normal”.

**Summary**

Structural MRI has been used in research studies on both football and hockey players to highlight effects of these sports. Former professional football players with a history of concussions and mild cognitive impairment have shown a cumulative effect from these injuries on both the size and function of the hippocampus. A different type of helmet testing has shown high rotational velocities, which are predictive of concussion. Research on hockey players has shown a decrease in frontal cortical thickness and an increase in hyperintensities that might not be attributed to concussion, but rather to repetitive blows to the head. Decreases in myelination have also been seen, but recovery may be occurring within two months of a concussion.

DTI studies of concussed athletes in a variety of sports have also brought to light the problems of subconcussive impacts. Soccer players that head the ball often may show a decrease in fractional anisotropy, indicating possible nerve fiber damage, which could lead to cognitive impairment. Young football players, wearing head impact telemetry units in their helmets, suffered from changes in the microstructure of their white matter. Research on groups from a variety of sports that had had prior concussions showed decreases in their gray matter volume, as well as a decrease in blood flow in their frontal areas. When combined with DKI, DTI results from studies on football players reaffirmed the physical damage to nerve fiber tracts in white matter, even from subconcussive impacts. DTI combined with fMRI in football players showed the decrease in fractional anisotropy, as well as the issue that “additional processing” was necessary in functional testing. Concussed athletes from multiple sports showed lower fractional anisotropy and increased mean diffusivity, indicating abnormalities, and maintained their decreased fractional anisotropy even after medical clearance to return to their sports. fMRI results stayed the same after medical clearance, indicating that the athlete’s brains had stayed “hyperconnected”, in order to protect themselves. Many researchers plan to continue with their studies to gain further understanding of the effects of contact sports on athletes of all ages.
Chronic Traumatic Encephalopathy

CTE is a neurodegenerative disease thought to be caused, at least in part, by repetitive brain trauma that can occur during contact sports, as well as military combat participation. This trauma can include MTBI, or concussions, as well as sub-concussive injuries. Sub-concussive injuries are mild brain traumas that do not result in the readily observable signs and symptoms of a concussion. CTE cannot be confused with a prolonged post-concussive syndrome, as its symptoms typically do not present until years after the trauma-producing activity, when the symptoms of initial injury have ended. CTE has been found to be pathologically distinct from other neurodegenerative diseases, such as Alzheimer’s disease.

It has been known for almost a century that repeated blows to the head are associated with cognitive and behavioral impairments later in life. One of the first publications was a 1928 paper by Martland who called the condition he observed in boxers “punch drunk”. His hypothesis was that the symptoms he observed resulted from the repeated blows to the head taken by boxers during their careers. In 1937, Millspaugh outlined a disease marked by motor deficits and cognitive dysfunction under the name “dementia pugilistica” (boxer’s dementia), as he too had primarily observed the disorder in boxers. A 15-case series in 1973 neuropathologically distinguished dementia pugilistica from other neurodegenerative disorders. Literature in the 1960’s was using the term CTE, but it wasn’t until more recently (2005-2009) that it was recognized that this disease affected more than just boxers. CTE has been found in others with a history of repetitive concussions from sports, such as professional football players, professional wrestlers, professional hockey players, as well as other activities or situations, such as members of the military, a victim of physical abuse, an epileptic, a self-injurer, and even a circus clown who was repeatedly shot from a cannon. Repetitive sub-concussive trauma may also lead to the development of this neurodegenerative disease, as it has been neuropathologically confirmed in football players with no history of diagnosed or reported concussions, but who played positions with the greatest exposure to repetitive hits to the head.

The cognitive and behavioral symptoms associated with CTE are reflective of the regions that have been pathologically determined to be most affected by CTE. The regions of the brain most severely damaged by CTE include the cerebral cortex, and the medial structures of the limbic system (amygdala, mammillary bodies, hippocampus, etc.). The severity of the clinical manifestation progresses through the course of the disease, as the neurodegeneration increases. Neuropsychological and neuropsychiatric changes associated with CTE can be classified into the categories of cognition, mood, and behavior. Symptoms generally begin years or decades after repeated brain trauma, when the neurodegeneration is severe enough to manifest clinical symptoms. Early cognitive symptoms primarily include learning and memory impairment, as well as executive dysfunction. This is consistent with the deterioration of the hippocampus and other medial temporal structures seen in cases of CTE. Mood changes typically include depression, apathy, and irritability, as well as suicidality. Behavioral changes primarily include poor impulse control, with individuals described as having a “short fuse” or being “out of control”. Aggression and increased violence are often experienced. Disinhibition and problems with substance and other forms of abuse also occur. Mood and behavior changes are consistent with the neuropathologic changes in the medial temporal lobe, especially the amygdala, and the orbitofrontal regions, including atrophy of the frontal lobes. Later in the disease, these cognitive, mood, and behavioral impairments worsen, with dementia evident in all older cases (65 years or greater) with advanced stage CTE.

CTE has typically been only definitively diagnosed neuropathologically, during autopsy. Advanced stages of CTE are accompanied by generalized atrophy of the brain with reduced brain weight, as well as
atrophy of the frontal and temporal cortices and medial temporal lobe. There is often pronounced atrophy of the thalamus, hypothalamus, and mammillary bodies. Thinning of the corpus callosum and generalized atrophy of the cerebral subcortical white matter is common. Pallor of the substantia nigra, and locus coeruleus is a typical feature of advanced CTE. Dilation of the lateral and third ventricles, anterior cavum septum pellucidum, and posterior septal fenestrations are also frequent findings. A cavum septum pellucidum occurs when the leaflets of the septum pellucidum are separated and the space is filled with cerebrospinal fluid. Repetitive concussive and sub-concussive brain trauma likely produces a fluid wave within the ventricles that damages the septum pellucidum.

**Structural MRI**

There are many neuroimaging techniques involving MRI that may be found to be appropriate for CTE diagnostic purposes. Volumetric MRI can detect whole brain atrophy, as well as atrophy of specific areas of interest. These areas may include the hippocampus, amygdala, thalamus, hypothalamus, mammillary bodies, as well as more pronounced atrophy of the frontal and temporal lobes. Generalized cortical atrophy may also be present. MRI can also be used to diagnose a cavum septum pellucidum, with or without fenestrations. In 2016, MRI was utilized in a single case study, thought to be the first time that CTE was identified in a living person, rather than through autopsy. This case involved a 51-year-old male who had played three years of high school football, often on the field for much of the entire game. He had also participated in summer training camps in college, but did not play in any college football games. During his high school career, he sustained hundreds of blows to the head, with multiple confirmed concussions and at least one experience of being knocked unconscious. As he aged, he had six years of cognitive decline and depressed mood, as well as increasing memory loss, difficulty in maintaining attention, and mood swings. He was diagnosed with attention deficit hyperactivity disorder and bipolar disorder. An MRI of the brain was performed on this subject in 2012. In 2016, he sought medical help at the UCLA Psychiatry Cognitive Health Clinic and Research Program, where neuropsychological testing confirmed his impairments in attention, impulse control and other measures of executive function, but indicated that his memory was normal. An MRI brain scan at this time showed no evidence of Alzheimer’s, stroke, or dementia, but did reveal a few small lesions consistent with the subject’s history of brain trauma. Volumetric analyses were conducted with a new FDA-cleared MRI software tool called Neuroreader, which measures the volumes of 45 different regions of the patient’s brain, and benchmarks the results against an FDA database of healthy brain tissue. In comparing the two MRI brain scans performed 4 years apart, the researchers noticed areas of T1 hypointense and T2 hyperintense foci of encephalomalacia in the midbrain of the brainstem. This is a cerebral softening due to degenerative changes, which is consistent with atrophy. In addition, total gray matter volume decreased by 14%, which is the volume taken up by brain cells, not nerve fibers. The largest volume shrinkage was in the ventral diencephalon, followed by the frontal lobes, and the brainstem. The specific brain areas that were abnormally low in volume led the researchers to believe that the patient’s cognitive symptoms were likely due to his history of traumatic brain injury. Volume loss happens in the midbrain because the forces of football impacts are triangulated into that region. The frontal lobes are affected because they are right behind the skull when the person is hitting their head. The ventral diencephalon sits on top of the brainstem, so this region is affected as well. There has been conjecture that CTE is an early indication of Alzheimer’s disease in football players, usually accompanied by hippocampal atrophy. Interestingly, this subject’s hippocampus volume increased over four years. In addition, he had no volume loss in the temporal or parietal lobes, suggesting that he does not suffer from frontotemporal dementia. This subject “jumpstarted” his brain when neurological issues began to surface by making lifestyle changes that included changing to a diet high in fatty omega-3 acids,
increasing his physical activity, and playing chess online. Even though he had sustained a good deal of head trauma, he was able to improve his brain, seen in the results as an improvement in his hippocampal volume. Although this was a single case report, the longitudinal component (atrophy being identified over four years) makes researchers optimistic that their data may help identify a potential signature of CTE on MRI. An MR-based technique for detecting this pattern of brain changes could be used to diagnose CTE and related conditions in living people, giving them the opportunity for earlier diagnosis (Figure 21).

![Figure 21 PET scan of NFL player’s brain (on left) compared to MRI of former high school football player’s brain (on right) show similar suspected CTE pathology in the midbrain](image)

**Susceptibility-Weighted Imaging**

Susceptibility-Weighted Imaging can be performed on the Hitachi Oasis and Echelon Oval MR systems using an option called BSI, or Blood Sensitive Imaging. This technique could be useful for a differential diagnosis of CTE. Proposed mechanisms in the development of CTE are a disruption in the blood brain barrier and changes in the cerebral vasculature. Susceptibility-weighted imaging has been found to detect microhemorrhages resulting from neurotrauma. It has found some success when utilized to predict long-term outcomes following traumatic brain injury in children. Additional research is required to determine the clinical utility of susceptibility-weighted imaging for understanding the long-term effects of repeated brain trauma, including CTE, in adults.
Diffusion Tensor Imaging

DTI is sensitive to diffuse axonal injury, which is thought to be one of the causal mechanisms involved in CTE. It has supported the link between executive dysfunction and axonal injuries in humans, and has shown to be predictive of long-term outcomes following traumatic brain injury in experimental models in rats. DTI was utilized in a pilot study involving five former professional athletes that showed an association between overall exposure to repetitive brain trauma and degradation of callosal white matter nerve fiber bundles (Figure 22).

![Figure 22 DTI images analyzed with streamline tractography; control brain on left, former professional boxer’s brain on right; top two images are sagittal views with callosal fiber tracts delineated, showing that boxer’s fiber tracts are markedly shorter than the control; bottom images are coronal views showing athlete’s corpus callosum (red structure in middle of the brain) is thinner than the control](image)

Functional MRI

fMRI has been useful in understanding brain-behavior relationships in numerous neurologic diseases. Recent studies of high school football players have utilized fMRI and found significant changes from pre-season to post-season in those athletes with repetitive subconcussive hits, as determined by helmet accelerometer data. It is possible that fMRI will be helpful in determining brain-behavior associations in CTE as well as differentiating CTE from other neurodegenerative disorders. The use of blood oxygen level dependent (BOLD) fMRI has already been able to differentiate between various types of neurodegeneration, including Alzheimer’s disease, frontotemporal dementia, and dementia with Lewy bodies.
Magnetic Resonance Spectroscopy

MRS uses MR scanners to non-invasively measure in vivo brain biochemical metabolites. Significant chemical changes in the brains of individuals with various levels of brain trauma have been found, but most of these studies have been conducted in the acute, rather than the long-term, time frame. One pilot study did examine the utility of MRS for determining the long-term effects of repetitive brain trauma and possible CTE. This small-scale study of former athletes with a history of repetitive brain trauma found significant increases in Cho (Choline) and Glx (Glutamate-glutamine peak) when compared to age-matched controls. Choline is a cell membrane marker, and glutamate-glutamine are neurotransmitters.

Summary

Research related to CTE is in its infancy. There is a definite need to understand the mechanism behind this disease, its incidence and prevalence, and how to diagnose, treat, and prevent the disease during life. The type, number, and severity of concussive and/or subconcussive hits necessary to trigger the neurodegenerative cascade leading to CTE has yet to be determined. Studies must be performed to ascertain what additional factors, such as duration of exposure to head trauma, age at first exposure, gender, age, race, and genetic predisposition, play a role in the development of CTE. Researchers are working to create valid diagnostic criteria through the combination of clinical symptoms, history, and objective biomarkers. Neuroimaging techniques, including various MRI-based tests, could lead to non-invasive methods of diagnosing CTE in the living, rather than having to wait for post-mortem diagnoses, as is currently the case. CTE may come to represent an important issue in public health, due to the large population that could potentially be affected.

Conclusion

This concludes the MR Imaging for Brain Injuries module. You must complete the post-test for this activity with a score of 75% or better in order to receive Continuing Education credits.
Appendix A: References for MR Imaging for Brain Injuries Module


Appendix B: References for Pictures for MR Imaging for Brain Injuries Module

- Figure 1 – http://www.auntminnie.com/index.aspx?sec=sup&sub=mri&pag=dis&ItemID=111216
- Figure 2 – http://www.auntminnie.com/index.aspx?sec=sup&sub=mri&pag=dis&ItemID=107124
- Figure 3 – http://www.auntminnie.com/index.aspx?sec=sup&sub=mri&pag=dis&ItemID=114396
- Figure 4 – http://www.ajronline.org/doi/full/10.2214/AJR.13.11365
- Figure 5 – http://www.auntminnie.com/index.aspx?sec=sup&sub=mri&pag=dis&ItemID=100430
- Figure 6 – http://www.auntminnie.com/index.aspx?sec=sup&sub=mri&pag=dis&ItemID=110831
- Figure 7 – http://www.auntminnie.com/index.aspx?sec=sup&sub=mri&pag=dis&ItemID=112034
- Figure 8 – https://www.sciencedaily.com/releases/2015/12/151215091344.htm
- Figure 9 – https://spectrum.ieee.org/the-human-os/biomedical/diagnostics/brain-scans-to-distinguish-between-brain-injury-and-ptsd
- Figure 10 – http://www.auntminnie.com/index.aspx?sec=sup&sub=mri&pag=dis&ItemID=113817
- Figure 11 – https://en.wikipedia.org/wiki/Glasgow_Coma_Scale
- Figure 14 – http://www.auntminnie.com/index.aspx?sec=sup&sub=mri&pag=dis&ItemID=110070
- Figure 15 – http://www.auntminnie.com/index.aspx?sec=sup&sub=mri&pag=dis&ItemID=113838
- Figure 16 – http://www.auntminnie.com/index.aspx?sec=sup&sub=mri&pag=dis&ItemID=115414
- Figure 17 – http://www.auntminnie.com/index.aspx?sec=sup&sub=mri&pag=dis&ItemID=114718
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- Figure 19 – http://www.auntminnie.com/index.aspx?sec=rca&sub=rsna_2015&pag=dis&ItemID=112813
- Figure 20 – http://www.auntminnie.com/index.aspx?sec=sup&sub=mri&pag=dis&ItemID=118111
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• Figure 22 – http://www.bu.edu/cte/files/2012/05/Baugh_Chronic-Traumatic-Encephalopathy_2012.pdf