Written Testimony

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Legal Issues Relating to Football Head Injuries

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Mr. Chairman and Members of the Committee:

Thank you for the invitation to testify today on *legal issues relating to football head injuries*. My name is Dr. Randall Benson. I am an assistant professor of Neurology at Wayne State University School of Medicine where I have a neurology clinic, teach students and residents and do research. I am also an attending neurologist at Detroit Receiving and Harper Hospitals ten weeks per year where I admit patients and consult on others. I am the sole fellowship trained behavioral neurologist in the practice so that my clinical, teaching and research are strongly focused on brain function and disorders of brain function.

I received my medical degree in 1987 and am board certified by the American Board of Neurology and Psychiatry. I did my neurology training at Boston University and then at the NMR-Center of Massachusetts General Hospital where I trained in functional neuroimaging and then pioneered the use of a new MRI technique, functional MRI, for mapping language areas in the brain. This technique, I am pleased to report, is now clinically reimbursed by health insurance companies. Following this work, my goal was to combine functional imaging with electromagnetic stimulation of brain to enhance neuroplasticity (neural reorganization underlying functional recovery) in injured brains. I applied this experimental treatment paradigm to stroke patients with language impairment and hand weakness, the latter study a Phase III multi-site, pivotal trial sponsored by Northstar Neurosciences (Seattle, WA).

Since my arrival at Wayne State in 2001 my research emphasis has gradually shifted to the application of “functional” MRI methods to traumatic brain injury. This was in large part driven by cross-campus strengths in TBI at Wayne. Wayne State University has a long and illustrious history of biomechanics head trauma research beginning in the 1940’s with Gurdjian and

Lissner's studies utilizing cadaver brains which led to the Wayne State Concussion Tolerance Curve, which continues to be the foundation for most currently accepted head injury indices. Under Dr. Albert King's leadership for three decades, three dimensional mathematical models of the brain's response to impact and blast forces have resulted in improvements in automobile cabin safety and in football helmet design used in the NFL. On the medical side, hospitals at the Detroit Medical Center are world leaders in the acute and rehabilitation stages of TBI, respectively, and have had continued NIH research support. My clinic is comprised largely of patients with brain disorders, the majority of which are dementia evaluations and traumatic brain injury cases. In a given week I will see as many as 3-4 new patients with TBI and an equal number of memory disorder cases.

I would like share with you some observations from eight years of evaluating traumatic brain injury cases, the vast majority of which I obtain neuropsychological testing and advanced MR imaging: 1) people with TBI are frequently misdiagnosed, often by multiple physicians; 2) the most frequent diagnostic category given is psychiatric—anxiety, depression, conversion disorder; 3) two neuropsychologists studying the same patient may differ considerably regarding existence of TBI; 4) TBI symptoms overlap considerably with those of "primary" psychiatric disorders; 5) without the ability to "see" the brain injury with imaging, there is no completely objective way to determine what is TBI and what is something else, e.g., posttraumatic stress, conversion, malingering; 6) people with brain injury seem to vary considerably in severity of symptoms and recovery in the face of similar falls, crashes, etc. This may speak to population differences in resistance to injury or effectiveness of neural recovery mechanisms and is in agreement with Collins, et al. who found large differences in recovery from single concussion (North American Brain Injury Society Annual Meeting, 2009); 7) advanced MR imaging techniques, including susceptibility-weighted (SWI), diffusion tensor (DTI) and MR spectroscopy (MRSI) are able to reveal brain injuries where CT scans and conventional MRI appear normal.

Sports-related TBI or concussion is not different from non sports-related TBI except that severity is usually mild, but repetitive concussions are the rule in sports which have an increasingly poorer prognosis.

I am involved in several ongoing research studies involving traumatic brain injury, which have in common the application of newer imaging methods but which differ by severity, time frame to imaging, funding status, specifics of scanning sequences and mechanism of injury. Each of these imaging studies is done at the MR Research Center at Wayne State University under the directorship of Mark Haacke, Ph.D., an MR physicist internationally recognized for his achievements in vascular and susceptibility mapping. For example, one study looks at acute mild TBI or concussion while in the ER, a second looks at more severe TBI when medically stabilized, another study has been ongoing for 15 years supported by NIH but has a new imaging component. We have, more recently, studied former NFL players in two capacities. The first, sponsored by the NFL, is an imaging study using imaging methods proscribed by our group with imaging performed at a clinical imaging facility (ProHealth) in New York. Images are then sent by CD-ROM to us for analysis. To date we have received and analyzed 41 scans, sending reports back to Drs. Casson and Viano in New York. My role is as a consultant on both image quality and data analysis and reporting. This study projected to scan more than twice this number and thus is incomplete at this juncture. The second study is a pilot imaging study of former NFL players with scanning and analysis performed in Detroit. To date, we have enrolled eight subjects.

I would like to now review some of the imaging methods we have developed and applied to TBI. The unabashed emphasis of our work is to image traumatic axonal injury (TAI) also known as diffuse axonal injury (DAI) which is responsible for the bulk of the chronic cognitive deficit following TBI. In addition, the most devastating consequence of repetitive TBI, chronic

traumatic encephalopathy (CTE) (McKee, et al. 2008) is thought to be the result of diffuse axonal injury, possibly caused by a series of concussions before full recovery occurs from the prior concussion (Dr. Ann McKee, personal communication). This hypothesis is supported by the existence of phosphorylated Tau protein within damaged axons which is known to be toxic to neurons. Electrophysiologic data from event related potentials (ERP) (Broglio, et al. 2009) indicate that even after symptoms have abated from sports concussion, the brain has not normalized. This suggests that clinical symptoms are not a reliable indicator of recovery and that to rely on symptoms exclusively to guide return to sport is to put the athlete at risk for permanent neurologic impairment. In summary, head injury including mild TBI causes varying amounts of axonal injury which a) recovers slower than clinical symptoms; b) underlies the more important and longstanding functional impairments; c) gives rise to phosphorylated Tau in damaged axons and d) likely leads to CTE with repetitive concussions (possibly in genetically predisposed individuals (Teasdale, Lancet, 1997).

Most of our work has used victims of transportation related injuries and falls, however our principle research focus has always been closed head injury, under which concussion falls and is otherwise known as mild head injury. I will also include some examples of former players scans. The focus of my testimony will be susceptibility-weighted imaging (SWI) and diffusion tensor imaging (DTI). An equally important imaging method for addressing concussion is MR Spectroscopic Imaging (MRSI) a technique which is measures metabolic and biochemical processes. We (WSU) have been collaborating on TBI research with Loma Linda University School of Medicine (Drs. B. Holshouser and K. Tong) who have demonstrated the sensitivity and predictive ability of MRSI in TBI. Space and time prevent me from saying more on MRSI but an imaging study of concussion on current and former NFL players should contain SWI, DTI and MRSI at minimum.

Susceptibility-Weighted Imaging (SWI)

Imaging research of TBI began at WSU in 2004 when an eleven year old boy (C.G.) survived after his family's ATV skidded off a mountain road in Colorado plunging 200 ft. He was still in coma two months later when we scanned him at WSU. His CT and standard MRI revealed a skull fracture and atrophy but not much more. **Figure 1** compares a standard, clinically available T1-weighted image with a *susceptibility-weighted image* (SWI) through the temporal lobes and brainstem for C.G. sixty days after injury. Note the many "black holes" present in the SWI image which are small ("micro") hemorrhages indicating severe diffuse axonal injury (DAI) from TBI.

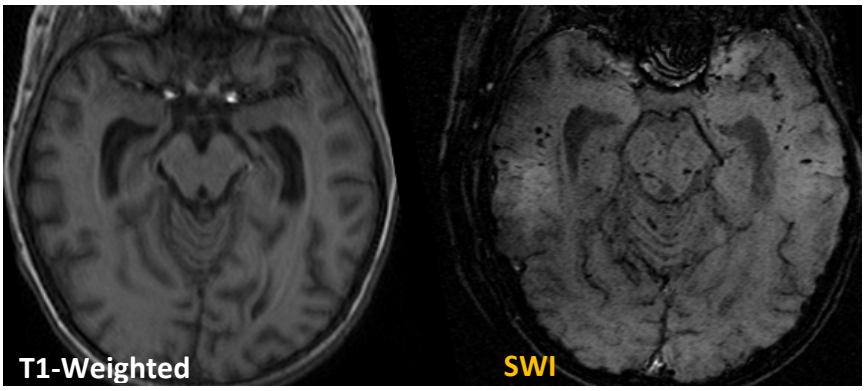


Figure 1. Comparison of T1 and SWI images for C.G. Note the many dark "holes" in the SWI image that are not present on the T1 weighted image. These "black holes" are caused by signal loss induced by paramagnetic hemoglobin or other iron containing blood products.

Developed by Mark Haacke, SWI is extremely sensitive to iron and blood products and detects microhemorrhages where conventional MRI fails. SWI detects hemorrhage at all stages, since iron remains even after the fluid from blood is reabsorbed. Prior work by Dr. Haacke with Loma Linda University (Karen Tong, M.D.) had demonstrated the value of SWI for detecting DAI in children with "shaken baby syndrome" where it was five times more sensitive than gradient echo imaging. In a series of 20 TBI patients (transportation related and falls) varying in severity and elapsed time since injury, we found an excellent correlation (P=0.54) between total hemorrhage volume and the number of days in post-traumatic amnesia which is known to be a good

predictor of one-year neurological outcome (*JMRI, 2009*). We have, since 2004, scanned over 100 TBI patients with SWI at WSU alone and a similar number at Loma Linda. In addition to TBI, it is being used in stroke, cerebral amyloid angiopathy (CAA) (**Figure 2**), Alzheimer's disease and disorders of iron metabolism. SWI is now clinically available on GE and Siemens MRI scanners.

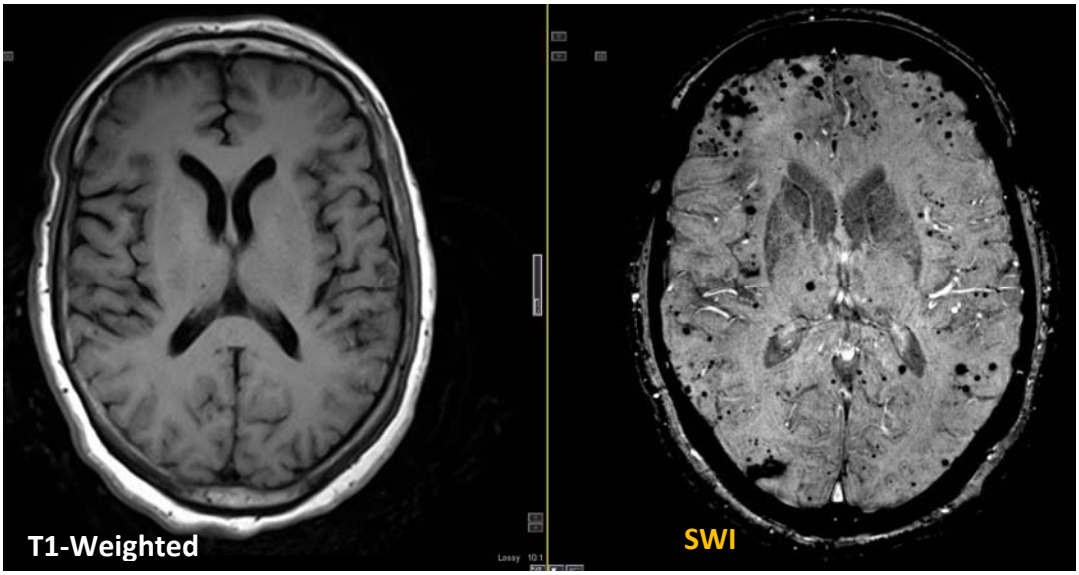


Figure 2. Comparison of T1-weighted and SWI images for cerebral amyloid angiopathy, another disorder involving multiple small brain hemorrhages in the elderly.

In our experience with **mild TBI/concussion**, hemorrhaging within the brain substance is more often caused by the direct blow (contusion) than diffuse axonal injury. More severe blows *will* cause microhemorrhages from diffuse axonal injury, which is the result of nonelastic deformation of brain white matter and vessels (shear injury) (**see Figure 3**).

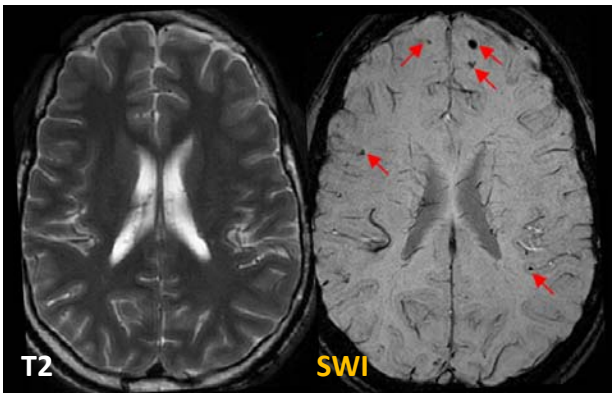


Figure 3. 41 year old female (N.D.) scanned eight days after motor vehicle accident with LOC and 3 days of post-traumatic amnesia (GCS=13). Red arrows indicate microhemorrhages revealed in the SWI image but not the conventional T2 image or the other standard clinical images.

Figure 4 is an example of a cortical contusion in a 63 year-old woman with persistent mild cognitive impairment following a fall.

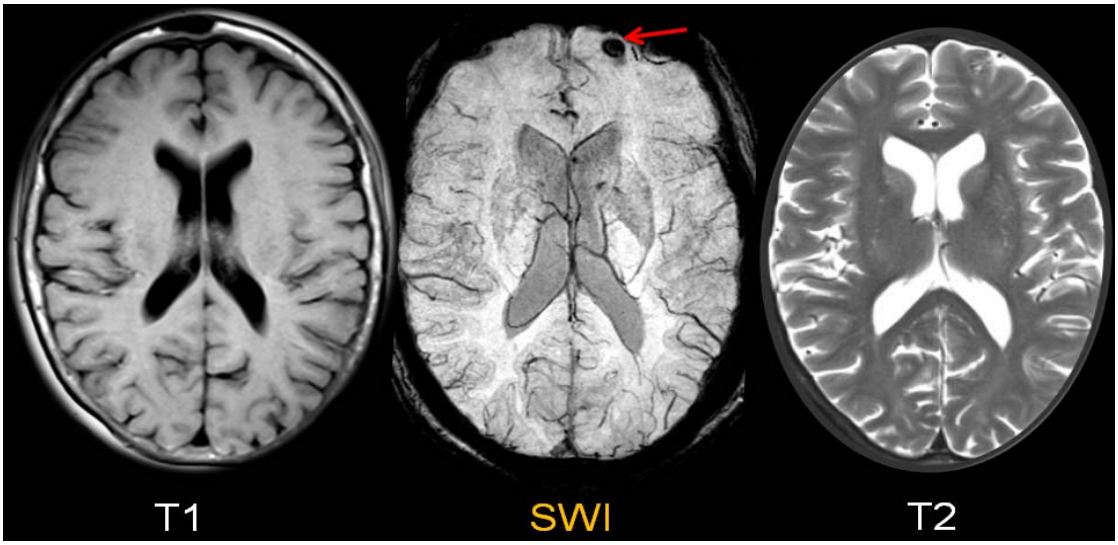


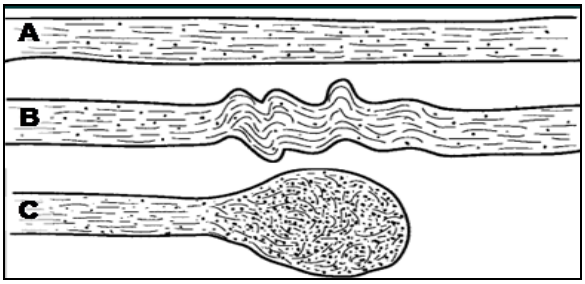
Figure 4. Only SWI clearly reveals a superficial hemorrhage in the left frontal lobe in a 63 year-old woman who tripped and hit her head on an iron bar. No loss of consciousness but mild confusion and persistent mild cognitive deficit.

In summary, SWI reveals large and small hemorrhages occurring as a consequence of trauma and detects acute as well as chronic hemorrhage, although systematic study of the evolution of hemorrhage in SWI has not been performed to date. In addition, measurement of total brain hemorrhage on SWI images using automated methods is predictive of neurological outcome at one year post injury. The hemorrhages, it should be noted, probably do not, in and of themselves, cause neurological impairment but are a marker of significant diffuse axonal injury.

Diffusion Tensor Imaging

Developed in the mid-1990's, diffusion tensor imaging (DTI) is sensitive to the 3D flow of water inside and outside of white matter fibers (the long extensions from nerve cell bodies which connect nearby or distant cells). Closed head injuries (non-penetrating) including concussion are caused by sudden acceleration or deceleration of the head which causes local deformations of the brain within the cranium. The anatomical and biomechanical properties of the brain are such that white matter fibers are stretched and damaged, resulting in diffuse axonal injury (DAI) which is the hallmark pathology and accounts for most of the neurological disability in TBI. The typical cognitive deficits in TBI, i.e., slowed information processing, decreased attention and memory, and psychiatric symptoms are caused by damage to the "cables" which allow for efficient transmission of information between neurons. TBI reduces brain network efficiency resulting in decreased capacity and global functional impairment. Concussive injury such as occurs in football with high speed collisions also causes deformation of brain substance and is felt to account for many of the immediate and delayed symptoms including the post-concussive syndrome. ERP studies of sports related concussion suggest that symptomatic recovery may occur while neurologic and brain metabolic functioning continues to be impaired from weeks to months after injury. Incurring a second concussion before neurologic recovery has been shown to worsen outcome and may begin a downward spiral culminating in chronic traumatic encephalopathy (CTE) but this is not known. Diffusion tensor imaging (DTI) is able to detect damaged white matter fibers (axons) which have altered flow of water molecules compared with healthy axons (**see Figure 5**). DTI, like SWI can be performed on a standard clinical scanner (1.5-3 Tesla) and is available on virtually all clinical scanners.

Figure 5. Schematic of healthy and injured axons. A. depicts an uninjured axon which is long and thin; B. Early after injury fiber becomes shows undulations; C. Late stage of degeneration "retraction bulbs" are seen scattered throughout the white matter. Water flow is altered as fiber geometry is changes and is detectable with DTI.



Our initial investigation of DTI in 20 TBI cases found that (similar to SWI and hemorrhage) an index of DTI, fractional anisotropy (FA), is decreased uniformly in TBI compared with 14 controls (**see Figure 6**), and that the magnitude of the decrease in average FA for global white matter is highly correlated with TBI severity (**Figure 7**). Even the 6 mild TBI cases (GCS 13-15) had decreased FA compared with the controls. The separation of the milds from the controls is especially relevant to sports concussions where the great majority of injuries are mild. **Figure 6a** shows the non-overlapping FA distributions between the TBI and control subjects.

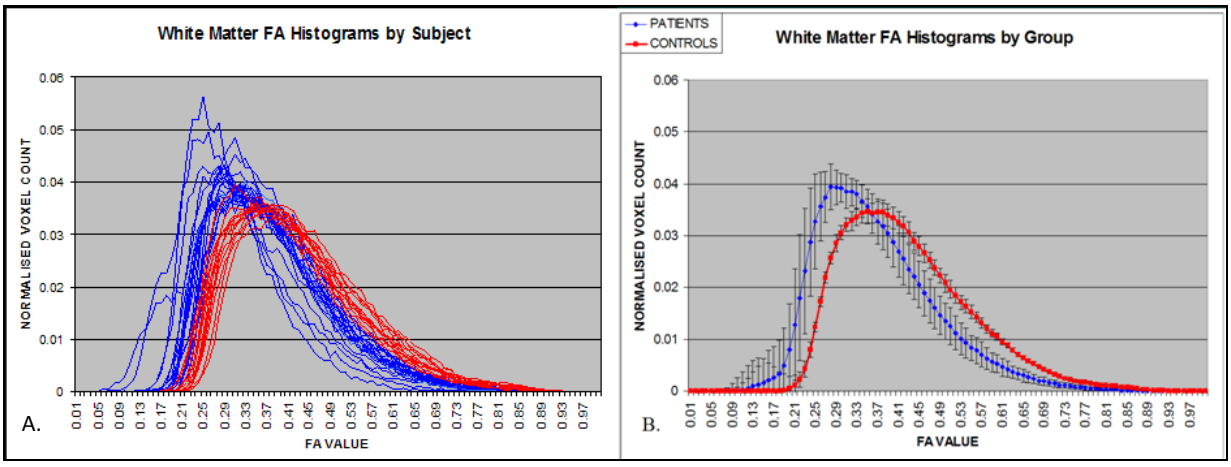


Figure 6. Comparison between 20 TBI cases (blue) and 14 healthy controls (red) on distribution of FA (0-1). **A**. All subjects' FA distributions given; **B**. Group average distributions shown with standard error of the mean plotted for error bars. Note the leftward shift, higher peak and greater variance for the TBI cases compared with the control group.

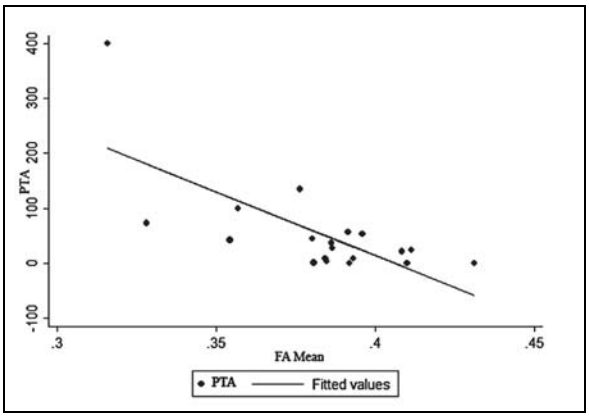


Figure 7. Plot of mean FA and length of post-traumatic amnesia for 20 TBI cases. Each dot represents a single case. Note that lower FA values are associated with longer period of post-traumatic amnesia during which patients cannot learn new information. Correlation is (-) 0.64 (Spearman).

To increase the sensitivity of DTI to axonal injury in mild TBI we have employed two regional analysis methods. Both of these methods require "normalizing" the images into a standard brain space and then comparing regional FA values of a single TBI patient *statistically* with those of 50 healthy control subjects taking into account normal variation. The first of these methods, ("regional" analysis), divides the total white matter into atlas-defined white matter regions (**see Figure 8**), while the second method ("voxel-based" analysis) compares the FA value of each voxel location (i.e., three-dimensional pixel) with the corresponding voxel from the 50 controls and displays abnormally low FA voxels in color (**see Figure 9**).

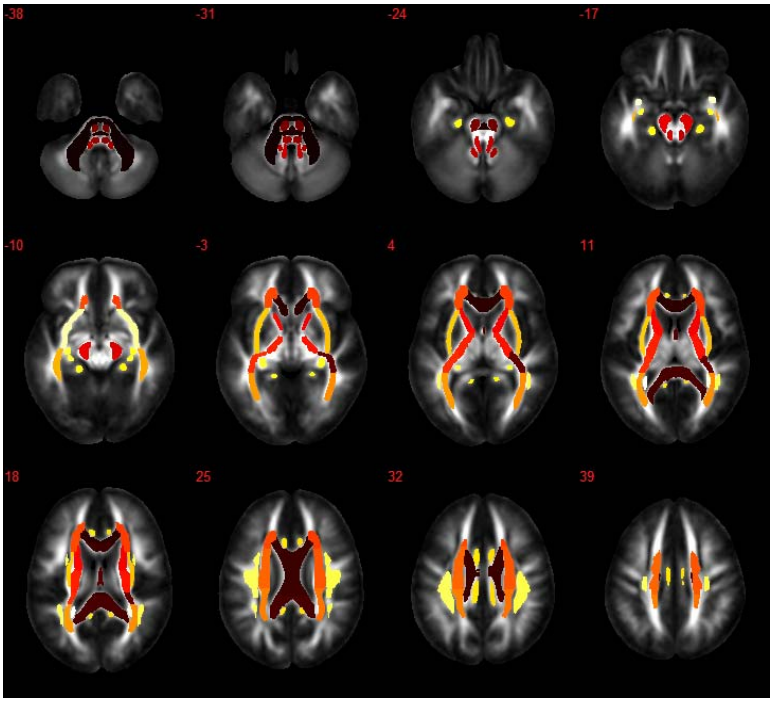


Figure 8. Atlas used for regional analysis. Regions are indicated using color masks. Subject's FA map is spatially normalized to fit reference anatomy. After transformation into standard space, region masks are applied automatically to obtain regional FA means. Key advantages over the global approach is to increase sensitivity (in mild TBI) and to localize axonal injury to specific regions which may correlate with neurocognitive impairments.

Computer programs such as Statistical Parametric Mapping (University College, London) and DTI Studio (Johns Hopkins University) allow for near automation of these processing steps. These two methods have improved our ability to detect axonal injury in the milder cases which have less extensive damage.

Figure 9 is the voxel-based analysis for a 43 y/o previously healthy woman who was in a parked car when her car was struck hard by a van. She was dazed at the scene but did not lose consciousness. She was extremely fatigued for a month and found to have cognitive slowing, speech difficulties, mood lability and loss of motor coordination. SWI did not reveal hemorrhage but DTI showed abnormalities in motor pathways and deep temporal lobe.

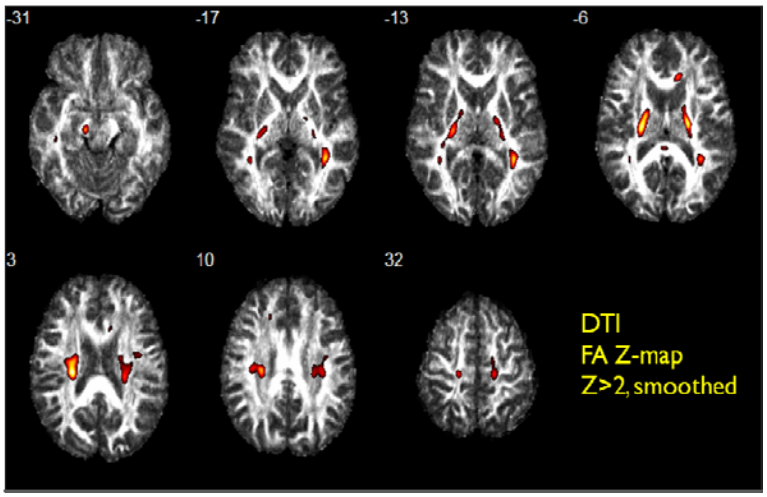


Figure 9. Voxel Based Statistical Map
- 43 year old woman, scan 21 months post
- Unrestrained and parked when struck hard by a semi-truck to rear of car.
- No LOC but was dazed and speaking slowly.
- She suffered whiplash, herniated disk at C3-4, cognitive slowing, stuttering, irritability, loss of fine motor dexterity.
- Dx'd with depression and/or anxiety.
- Colorized voxels had significantly decreased FA compared with controls

In an effort to optimize the image quality at ProHealth in New York with our own image quality we scanned the same subject at both ProHealth and at WSU within a 4 month period. He was a 37 y/o former linebacker who played seven years in the NFL and reported multiple concussions throughout his collegiate and pro career. He reported mild forgetfulness. **Figure 10** shows the strikingly similar findings in the left hemisphere (right of image) with results indicating axonal injury in his corticospinal tract and corona radiate. No other regions obtained significance. The average of the two scans revealed the same findings, despite the scans being acquired on two different scanners months apart. The reproducibility, although in a single subject, is encouraging and suggests that a multi-site study may be feasible with proper image quality.

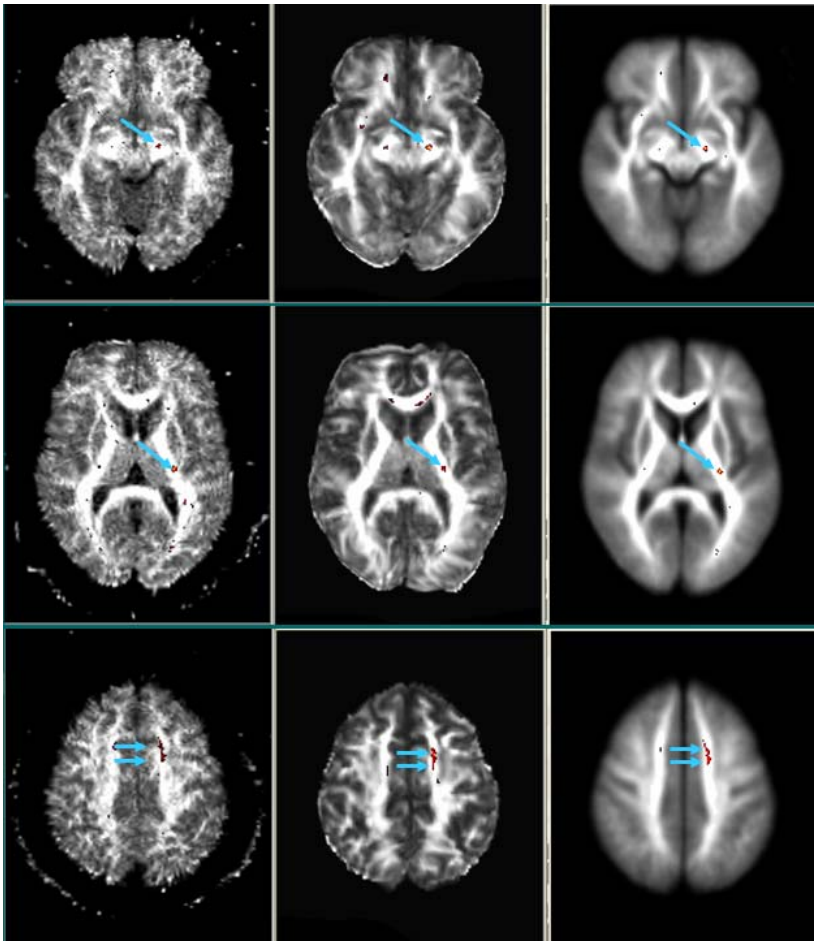


Figure 10. Retired NFL player. Reproducibility across two imaging sites. Column on left contains images acquired at WSU. Middle column images acquired at ProHealth (N.Y.). Right column is average of both WSU and ProHealth statistical maps overlaid on an anatomical image which is itself our average of 50 controls. Three slices of 181 are displayed. Actual native DTI dimensions are 2 x2x3 mm but resampled to 1mm isotropic. Left of image is right hemisphere and vice versa.

Another former NFL player was scanned at WSU in 2009. He was 36 y/o and was a fullback playing for 11 years as a starter for most (1995-2006). He suffered "over 50" episodes of vision loss after hits lasting a minute or so and several episodes of being "dazed" and needing help to get to the huddle. He did not report these symptoms which became more frequent as he "became older". **Figure 11** shows the most prominent abnormality which is located in the splenium of the corpus callosum, a white matter bundle which carries visual information between the hemispheres. In fact, this white matter tract has been shown in autopsy studies to be one of the most common locations of traumatic axonal injury. Interestingly, he reports no ongoing visual impairment despite the multiple transient episodes and the imaging findings.

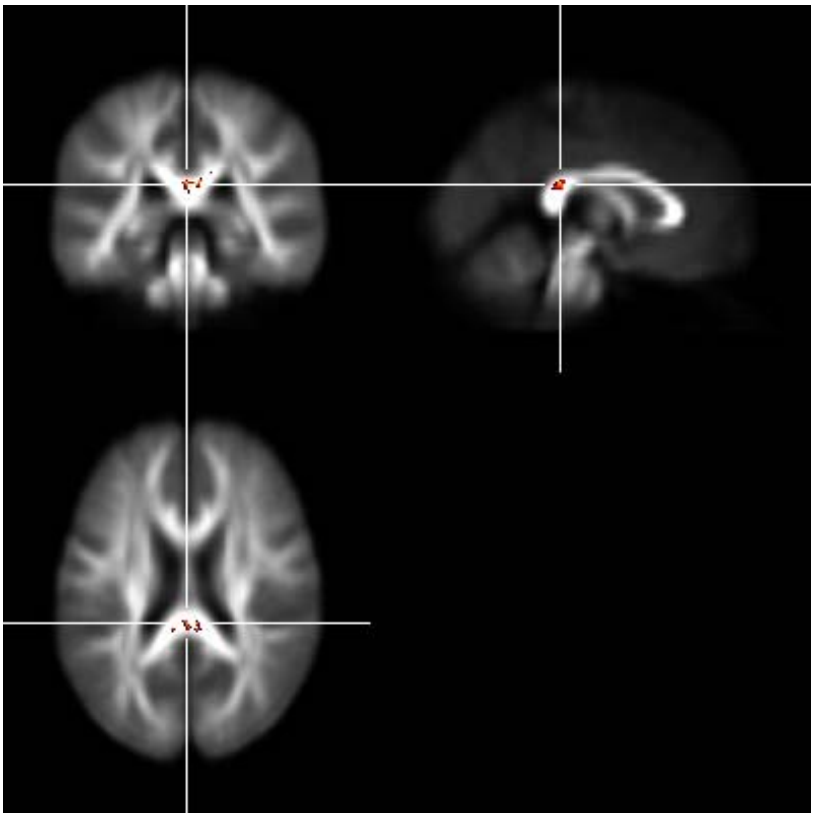


Figure 11. Voxel-based statistical map for a 36 y/o eleven year veteran of the NFL who retired three years prior to scanning. Crosshairs are on a large region of low FA (Z<2) in the splenium which contains visual fibers.

In summary, DTI is able to "visualize" diffuse axonal injury from TBI. In some cases location of lesions appears to correlate with specific symptoms but generally the severity of DAI as indicated by DTI is strongly predictive of general neurocognitive disability. Since concussion produces axonal injury, particularly repetitive concussion, imaging with DTI would appear to be ideal to study NFL players. Certainly, a large scale cross-sectional study wherein head injury history, position, age, genetic risk (ApoE genotype), neuropsychological testing (focused) and possibly electrophysiological testing with EEG (ERP, qEEG) and PET are factors. In addition, a prospective study with serial scans over a player's career, tracking concussions or hits and relating imaging to neurocognitive performance (IMPACT or similar) and other factors as in cross-sectional study. Imaging would also facilitate the evaluation of helmet and neck support designs in animal models and in the field.

My strong recommendation is that these studies are initiated soon since TBI is epidemic and is not solely an urban problem and occurs at all levels of football and other sports such as hockey and soccer. The brain begins losing cells in the second decade of life and TBI does not enhance intellectual functioning in the maturing brain. The answer is to more thoroughly investigate the issues and attempt to minimize brain injury at any cost. Certainly improving recognition of TBI and identifying the imaging predictors of adverse outcomes would be an important beginning.

I thank this committee for allowing me to testify on this important issue.