ENHANCING PERSONAL INJURY DAMAGES

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CHRONIC PAIN

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1. INTRODUCTION.

Pain is one of the body's most important self-protection mechanisms. It acts as a warning to indicate that we are exposed to danger. When we touch a flame we react by removing our hand. Reacting to the pain prevents us from serious injury.

Pain is also the body's way of communicating that it has sustained an injury. When we are injured, e.g. – a herniated disc, we experience pain from that injury every time the disc impinges on a nerve. The nerve sends a pain signal through the spinal cord to the brain. The brain then senses pain. Because of the pain we know that we need to seek medical care to treat the cause of the pain. When pain persists we know that the injury has not been adequately treated.

Chronic pain is pain that persists beyond the usual recovery time. This pain is not protective. Chronic pain is not just pain related to the underlying injury. It is pathological pain because chronic pain, itself, causes damage to the body. In essence, chronic pain is a separate injury from the original condition that caused the pain.

There are two types of damage caused by chronic pain. Those are: structural damage to the brain; and neurochemical changes within the brain. This brain damage results in cognitive and psychological impairment, similar to the deficits caused by a traumatic head injury.

2. STRUCTURAL BRAIN DAMAGE.

Chronic pain damages brain tissue. Radiological studies show atrophy in the structure of the brain in chronic pain patients.[1] The brain contains both gray matter and white matter. Anatomically, gray matter contains most of the brain's neuronal cell bodies. It is where the synapses occur. Gray matter includes the regions of the brain involved in muscle control, eyesight, hearing, memory, emotions, speech, decision making, and self-control. White matter consists of axons that connect the different parts of the gray matter to each other. Both gray and white matter in the brain show damage from chronic pain. Even the inter-relationship

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between gray and white matter is abnormal.[2] Brain structural abnormalities were first described in patients with chronic back pain.[3] Since that initial research, more than fifty chronic pain studies have documented decreases in the size of multiple regions of the brain. These include decreases in gray matter density, volume, and thickness.[4] Other literature shows that, in the face of chronic pain, these brain cells do not regenerate as normal.[5]

There is no question that the changes in the brain are the direct consequence of chronic pain. Numerous studies have shown that the decrease in gray matter density is at least partially reversible when the underlying pain is properly treated.[6] [7] [8]

Damage to the brain has been observed in patients with chronic back pain[9] [10], frequent headaches[11] [12] [13], fibromyalgia[14] [15] [16], osteoarthritis of the hip[17], and Complex Regional Pain Syndrome.[18]

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Chronic pain in our clients equates to brain damage.

3. NEUROCHEMICAL CHANGES IN THE BRAIN.

Chronic pain also alters the human brain chemistry.[19] Tests of neurochemicals in the brain of chronic pain patients show that there are increases in chemicals that sense pain and decreases in chemicals that reduce pain sensation.[20] These chemicals change the primary sensory neurons and lead to abnormal responsiveness to the somatosensory system.[21] There is then an increase in excitability (sensitivity to feeling pain) and a decrease in inhibition (protection from feeling pain).[22] As a result of these chemical changes, each time we feel pain, there are changes that occur in the brain that amplify the experience of pain.[23] The patient with chronic pain becomes hypersensitive to pain.[24]

The neurochemical changes in chronic pain patients have also been shown to lead to neuronal loss and degeneration.[25] This may, in part, explain the damage to brain cells.

As a result of these neurochemical changes caused by chronic pain, our clients are more susceptible to sensing pain and the pain they experience is more severe.

4. COGNITIVE IMPAIRMENT.

Testing shows that chronic pain patients have impaired cognition, with attention and mental flexibility most significantly affected.[26] [27] Numerous studies have demonstrated cognitive impairment on neuropsychological testing, particularly pronounced in attention, processing

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speed, and psychological equilibrium.[28] Impaired cognitive functioning is independent of the intensity of the pain.[29] It is theorized that the cognitive deficits in chronic pain patients is caused by the damage to brain cells.

Our brain is equipped with the capacity to think while we are at rest and not focusing on a specific task. This is a network of regions in the brain called the "default network." This network is used for introspection, creativity, attention and executive functioning. It is the default network we use for daydreaming, contemplating complex issues, and problem solving. When we begin to focus on a task the default network is deactivated. We can then concentrate on the task at hand without the mind wandering.

The second area of cognitive impairment relates to chronic pain's harm to this default network. The inability to deactivate the default network is a common symptom of Alzheimer's disease, autism, schizophrenia, and other pathological neurological/psychological diseases of the brain. Chronic pain also disrupts the default network. The brain of a chronic pain patient is altered by the persistent pain in a manner consistent with these other neurological conditions that cause cognitive impairment.[30] [31] The patient experiencing chronic pain is unable to shut off the default network and is unable to focus and attend to the task at hand. The effect is like watching two television shows at once and not being able to focus on either one.

The impact of chronic pain on cognition is similar to that of someone who has suffered a mild to moderate traumatic brain injury. The attorney for a chronic pain client should ask about any changes in attention, concentration, memory, or decision-making. A head injury check list is a valuable tool for evaluating whether chronic pain has caused cognitive deficits in our clients. Where the cognitive changes are pronounced, neuropsychological testing is beneficial for proving these deficits.

5. PSYCHOLOGICAL DAMAGE.

When the brain of a chronic pain patient is imaged with functional MRI, the area that lights up is the prefrontal cortex of the brain. This is the area of the brain that controls negative

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emotions, response conflict, and detection of unfavorable outcomes.[32] [33] In addition, the neurochemical changes caused by chronic pain cause dysfunction of the hypothalamo-pituitary-adrenal organ in the body.[34] [35] These organs play an integral role in our emotions and psychological health.

As would be expected, there is a direct link between chronic pain and depression and/or anxiety. And studies have consistently found that there is a statistical relationship between chronic pain and depression.[36]

As attorneys for chronic pain clients, we need to ask whether there have been changes in the personality and emotions of the plaintiff. The client may be able to answer your questions satisfactorily but family members, friends, co-workers can also provide powerful insight into the emotional status of our client. A good psychologist can also provide valuable evidence of personality and emotional changes in the client.

6. TREATING PHYSICIANS.

The vast majority of primary care physicians have little understanding of the harmful effects of chronic pain. They assume that if there has been proper treatment that the patient should not have on-going pain. Many physicians associated chronic pain with drug-seeking behavior. Chronic pain patients change doctors frequently hoping to find a physician that can relieve their pain.

Those physicians who have knowledge of chronic pain include: Physical Medicine and Rehabilitation physicians; Pain Management specialists; and neurologists. If your client has chronic pain they should be encouraged to seek treatment from a physician who is familiar with the pathology of chronic pain and is knowledgeable of the proper treatment of chronic pain.

7. TREATMENT OF CHRONIC PAIN.

The only effective treatment of chronic pain is treatment of the underlying condition causing the pain. However, where the cause of the pain is unknown or treatment of the cause

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has not been effective, the pain itself needs to be treated. Chronic pain syndrome must be treated differently than acute pain. To persist in treating chronic pain syndrome as an acute problem very often leads to unsuccessful treatment results.[37]

Pain management physicians agree that the most effect treatment of chronic pain is a multi-faceted approach. This approach combines analgesic medications and injections, physical therapy, psychological support, biophysical feedback, and alternative forms of treatment (mediation, yoga, massage, etc.). There is no cure for chronic pain. The longer the pain has persisted the greater the likelihood that it will continue into the forseeable future.

A physician who is familiar with effective treatment of chronic pain can assist in putting together a Life Care Plan to insure that compensation can be obtained to reduce or eliminate the patient's pain. Effectively treating chronic pain is expensive and should be an essential part of the damages presented for our clients.

8. IMPACT OF CHRONIC PAIN ON LIVING.

Every facet of life of the person experiencing chronic pain is harmed.

Experiencing severe pain prevents the chronic pain patient from enjoying pleasurable activities. They no longer pursue hobbies or other activities they once relished performing.

Chronic pain is associated with sleep disturbance and fatigue. They are constantly tired, their patience wears thin, and everything annoys them. Fatigue, depression, cognitive deficits, lack of attention and focus, and the inability to perform routine physical activities leads to reduced performance on the job and, eventually, termination of employment.

Chronic pain causes depression, anxiety and irritability. These conditions prevent participation in children's activities and family functions. The marital relationship and the family are harmed.

The chronic pain our client's experience is the basis for substantial noneconomic damages. Lay witnesses are crucial to demonstrating the harmful effect of chronic pain on the plaintiff.

9. CONCLUSION.

Chronic pain is more than on-going pain. It is a separate injury that needs to be compensated for. It causes brain damage and significant impairment of the client's ability to lead a normal life. Adequate compensation is possible only when the client's attorney is familiar with

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[37] Addison, R.G., Chronic Pain Syndrom

the consequences of chronic pain and can demonstrate the damage from chronic pain to the insurance adjuster and/or jury.

EEG / ERP

ERP for Diagnosis and Prognosis of Traumatic Brain Injury

Marco Cecchi, PhD

OVERVIEW

The Centers for Disease Control and Prevention defines a traumatic brain injury (TBI) as *"a disruption in the normal function of the brain that can be caused by a bump, blow, or jolt to the head, or penetrating head injury."*

The severity of a TBI may range from "mild" (i.e., a brief change in mental status or consciousness) to "severe" (i.e., an extended period of unconsciousness or memory loss after the injury). Mild TBIs (mTBI) are the most common[1], and the most challenging for clinicians to evaluate. Only a small minority of patients with mTBI present with intracranial CT scan abnormalities, and there is little evidence that traditional cognitive testing can provide a reliable and sensitive assessment of cognitive dysfunction after mTBI[2]. A recent systematic review of peer-reviewed published literature found that *"diagnostic accuracy for mTBI is currently insufficient for discriminating between the disease and co-occurring mental health conditions for both acute and historic mTBI."*[3].

Event related potentials (ERPs) are an objective measure of cortical synaptic dysfunction associated with mTBI and are sensitive to cognitive deficits even with the milder injuries. Thus, ERP testing can improve patient management by providing clinicians with a more accurate assessment of patients' cognitive status after a traumatic event, especially in hard to evaluate mild cases.

EVENT RELATED POTENTIALS

ERPs are part of the EEG generated by sensory and cognitive processing of external stimuli, and reflect the summed synaptic activity produced when similarly oriented neurons fire in synchrony in response to the stimuli[4].

The stimuli of the ERP test are grouped into sequences of repeating sounds or visual cues. The type, timing, and sequence of stimuli (often called an "ERP paradigm") are organized to target specific cognitive processes such as selective attention, memory encoding, executive function, etc. While the brain subconsciously analyzes the incoming stimuli, EEG time-locked to each stimulus is recorded. At the end of the test, the time-locked EEG recordings are averaged according to stimulus type, and all brain activity not related to the specific stimulus group is "filtered out". What is left are the ERP waves that represent the physiological responses evoked by each stimulus type played during the test (Figure 1).

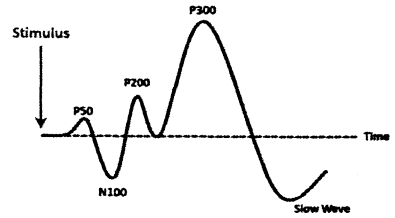

Figure 1: Example of an ERP wave

These ERP waves contain a sequence of positive and negative peaks, or "ERP Features", that have been extensively characterized in the scientific literature (for an overview see [5]). The early peaks are primarily "sensory" responses that depend largely on the physical parameters of the stimulus. The sensory features are followed by later "cognitive" peaks which reflect information processing, and can be used to detect and quantify cognitive deficits associated with mTBI[6].

ERP MEASURES FOR TBI

ERPs have been used to elucidate and characterize sensory and cognitive deficits that may follow brain injury since the early 1980s[7]. A large scientific literature on the usefulness of these biomarkers for diagnosis and prognosis of TBI has followed.

Recent reviews of published literature on electro-physiological methods for diagnosis of TBI have found that ERPs offer significant utility in TBI detection[8–11]. Indeed, **the American College of Occupational and Environmental Medicine (ACOEM) guidelines for TBI now recommend Cognitive Event-Related Potentials as a diagnostic measure for TBI**[12].

ERPs contribution to TBI diagnosis seems especially important to detect subtle deficits in information processing in patients that present with otherwise normal clinical findings[9–11,13].

There is good evidence for the use of ERPs as biomarkers to also support TBI prognosis. In a recent review Duncan et al. summarize the peer-reviewed published data as: *"The consensus would appear to be that the use of N100, MMN, P300, and perhaps P3a in various combinations, has great prognostic value for both awakening and cognitive recovery. The particular choice of components differs among investigators, but the use of ERPs in assessing coma would appear to be an essential, if not mandatory, aspect of medical practice."*[9].

ERP testing provides flexibility in protocol design. ERP paradigms can be designed to produce measures that correlate with different sensory and cognitive domains (for an overview see [4]). Several ERP paradigms have been

shown to detect deficits associated with TBI. An ERP test that is especially sensitive to those deficits is the Active Auditory Oddball Paradigm.

ACTIVE AUDITORY ODDBALL PARADIGM

In this ERP protocol, an infrequent (target) tone is played occasionally during a stimulus sequence of frequent (standard) stimuli. A third unexpected (distractor) tone can also be present. The test subject is instructed to respond when the infrequent target tone is heard[9].

The active oddball paradigm generates ERP features such as P3b, P3a and N200 that reflect aspects of information processing involved in stimulus discrimination, evaluation, and categorization[5], and are sensitive to cognitive deficits associated with TBI.

The P3b, or classic P300, is a positive-going component that that is elicited by rare, attended (target) stimuli. It is of maximal amplitude at the centro-parietal electrodes and reflects an update in working memory (for review of the neuropsychological origins of the P3b, please see [14]). P3b amplitude is determined by the amount of attentional resources allocated when working memory is updated[15]. The peak latency reflects stimulus evaluation and classification speed[16,17].

P3b is a highly sensitive ERP measure for deficits in cortical synaptic function that follow TBI. In a study aimed at investigating neuropsychological and neurophysiological changes after sport concussion in children, adolescents and adults, Baillargeon et al. found that *"all concussed athletes had significantly lower amplitude for the P3b component compared to their non-injured teammates"*[18]. In another study to measure P3b components from patients with TBI, Doi and colleagues reported a significant decrease in the peak amplitude compared to healthy individuals[19].

P3b can show significant changes even in mild cases of the disease. A study that looked at ERP changes in college students after mild TBI reported a *"striking"* decreased in P3b amplitude. Moreover, the change in P3b amplitude was strongly related to the severity of post-concussion symptoms[20]. Similarly, a study that looked at the effects of a minor head injury on P3b found significant abnormalities in both peak amplitude and latency[21]. A study of neurophysiological anomalies in symptomatic and asymptomatic concussed athletes showed as significant reduction in P3b amplitude in both groups of subjects compared to controls[22], and another study that compared the performance of 10 well-functioning university students who had experienced a mild head injury an average of 6.4 years previously, and 12 controls on a series of standard psychometric tests and ERP measures also found a significant decrease in P3b amplitude in the mild head injury group[23].

The P3a is a positive-going peak that in an active two-deviant oddball paradigms is generated in response to the distractor stimulus and is of maximal amplitude at the centro-parietal electrodes[24]. The P3a is associated with engagement of attention and processing of novel information[14]. The peak amplitude is a measure of focal attention, and has been shown to positively correlate with executive function[25]. Its latency reflects orientation to a non-target deviant stimulus[26].

Several studies have shown P3a changes after mTBI. A study in asymptomatic multiple concussed college football players reported significantly decreased P3a (and P3b) amplitude in study subjects that sustained their last concussion within a year of the ERP recording. The deficit was no longer present in athletes who sustained their concussions more than 2 years prior to testing[27]. Moore et al. have recently reported similar results in soccer players with a history of concussion[28]. In a study on moderate to severe TBI survivors, Solbakk et al. found that P3a amplitude was reduced compared to healthy controls when frontal or fronto-temporal brain regions were injured. In addition, TBI survivors also exhibited a trend towards prolonged peak latency[29]. Interestingly, in a study that correlated ERP to malingered executive function Hoover et al. reported that malingerers were unable to produce a significant change in P3a response[30]. The study findings are consistent with the ACOEM guidelines for TBI that include ERPs as a recommended test under "Memory/Malingering Tests"[12], and suggest that ERP measures could help differentiate between malingerers and patients with genuine TBI.

Finally, the N200 is a component of negative polarity that in an active oddball paradigm is elicited by rare, attended (target) stimuli. The N200 precedes the P3b and is linked to the cognitive processes of stimulus identification and distinction[31]. The peak is maximal over fronto-central brain regions[24] and its latency has been shown to correlate with measures of executive function and attention[32].

N200 measures seem to be mostly affected in patients with a history of moderate or severe TBI. Sarno et al. have shown prolonged N200 latency in survivors of severe TBI[33]. In two similar studies, Duncan et al. reported smaller amplitude and prolonged latency for N200 in of survivors of moderate and severe TBI[34,35]. In one of the studies significant correlations were also found between severity of head injury, as measured by length of unconsciousness, and N200 latency and amplitude[34].

ARE ERP NECESSARY FOR THE EVALUATION OF TBI?

When head trauma requires medical attention, clinicians will often request structural neuroimaging data provided by CT or MRI scans. However, these two neuroimaging techniques seem to underestimated brain injury and are poorly correlated with outcome (see for example [36–40]). The main reason for this seems to be that neither CT nor conventional MRI sequences detect diffuse axonal injuries, the most common form of TBI[41–46].

In their review on the potential usefulness of electrophysiological markers for cognitive deficits in TBI, Dockree and Robertson conclude that *"Cognitive testing and electrophysiological analysis provides sensitivity to impairments which are otherwise undetectable by general neuropsychological evaluation and standard MRI. It is noteworthy that studies which have restricted their analysis to mild TBI where cognitive sequelae are difficult to measure routinely have nevertheless identified ERP markers of more subtle deficits of visual processing speed[47] attention deployment[48–50] and error monitoring[51]. A World Health Organization investigation has reported that 70–90% of all treated for TBI were classified as mild severity[52]. Although it is important that electro-physiological markers are utilized across all severities of brain injury to understand the diversity of processing deficits, their use in conjunction with cognitive paradigms may be more sensitive to persistent cognitive dysfunction resulting from mild TBI where signs of damage may elude routine assessment."*[10].

In the latest revision of their guidelines for TBI, the American College of Occupational and Environmental Medicine now recommends cognitive ERPs for *"Post-TBI patients who either have symptoms of cognitive deficits and/or have sustained a TBI sufficient to cause same."*[12].

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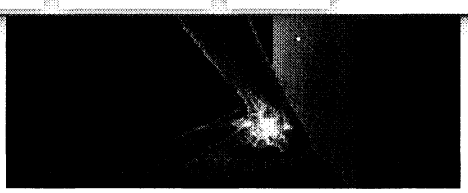
DIGITAL MOTION X-RAY

Digital Motion X-ray (DMX)

DMX: See an X-ray of your body in motion!

Digital Motion X-ray (DMX) is an amazing tool for visualizing why you have pain, and more importantly, help you and your provider determine the best treatment plan.

- **DMX is ideal for anyone who has suffered a whiplash, concussion, or other neck injury and has developed chronic symptoms.**
- **DMX provides a unique look at the structures causing your pain and other joint instability symptoms.**
- **DMX can be especially helpful when MRI and static X-ray showed "nothing" but you still have chronic symptoms!**



peripheral joint instability from ligament damage. Pain typically occurs with motion. By being able to see the bones in motion, DMX picks up the abnormal or excessive motion whereas MRI, CT scan and static x-rays do not. You could think about it this way: Static MRI is like a formal family portrait whereas DMX is the video of how your family really acts.

DMX is an ideal way to document underlying instability in chronic joint pain

When a person has joint instability, the increased motion between two adjacent bones causes excessive tension on the supporting structures and the nerve endings within those structures (which are not stretchable really) causing severe chronic pain. Most of the time the injury or weakness is in the ligamentous support of the joint. It is the primary responsibility of the ligaments to connect adjacent bones. When ligaments are injured, torn and weakened the adjacent bones move excessive and the body to limit this motion does one of the three things: 1. swells the joint; 2. causes muscle spasms around the joint; 3. bone spurs to form over the long-term. (See Figure) All of which limit motion. Cortisone shots to limit swelling, massages to relax muscles and surgeries to remove bone spurs often have only temporary effects because they don't address the underlying cause of the issue which is joint instability. Prolotherapy, on the other hand, is the only treatment that addresses the instability in a non-surgical manner, thereby offering long-term pain relief.

More DMX Case Studies and Success Stories

How is a Digital Motion X-ray performed?

person holding a weight, by the person doing a specific exercise, or by the radiology technician or physician putting passive pressure in a certain direction to help document the instability.

If I already had x-rays and MRI, how is Digital Motion X-ray helpful?

Stationary x-rays and MRIs don't typically show the cause of most chronic pain: joint instability from a ligament injury. The ligaments are the connectors of the joint, connecting one bone to another. When the connectors are not tight, the bones move too much. Ligament damage from car accidents, exercise, and routine twisting and bending are often not seen on routine x-rays and MRIs. However, can be more easily seen using Digital Motion X-ray while the person is moving, or while there is pressure on the joint. MRI and DMX are complementary, as the MRI is designed to show disc problems well, just as DMX is designed to show other soft tissue injuries.

How quickly will I know my results?

You will receive a link to see and download your actual scan on it immediately. An official report will follow. For patients of Caring Medical, the Prolotherapist will go over the DMX at your appointment. For patients who have Prolotherapy treatment scheduled for the same day as their DMX, the treatment will be done after the DMX exam.

The report will be a comprehensive analysis of what was found during the exam, providing you and your healthcare team the information you need to make informed decisions on diagnoses and future medical care. Check out Ross Hauser's DMX Report, taken after he had been suffering from cervical radiculopathy. The report clearly shows cervical instability,

Is DMX good for my case?

Caring Medical has been ordering DMX scans on individuals for many years to document the extent of the joint instability/injury, set an objective baseline, and develop an effective treatment plan. We find it beneficial as an advanced diagnostic tool for certain conditions that can have severe consequences if not properly diagnosed. These cases can include:

- Upper **cervical instability** including C1-C2 instability
- Spinal instability that involves severe neurologic symptoms including vertigo, drop attacks and certain types of radiculopathy
- Peripheral joint instabilities where a person's occupation is at risk, including professional athletes, musicians or manual laborers.
- Conditions where Prolotherapy may be an option instead of surgery. A high percentage of the cases that come to Caring Medical have been told that surgery is their only option. If a person doesn't want surgery, then obtaining a DMX could point them to a more conservative option such as Prolotherapy.

How much radiation exposure is there with DMX?

The annual occupational dose limits recommended by the Code of Federal Regulations in the United States for adults to be exposed to are 5000 mrem for the whole body.[10]

Common Radiation Doses in mrem.

Source	Amount of Exposure (mrem)[1-10]
MRI or ultrasound	0
X-ray inspect at airport	.002
Airplane travel/per hour	0.5
One static Cervical image with DMX	7
½ pack of cigarettes smoked	18
Standard chest x-ray	20

(90 seconds of continuous exposure)	
CT of spine	1000
High dose Fluoroscopy (non-DMX machine)	1500
(90 seconds of exposure)	

*Approximately 550 mrem....the actual DMX machine measures total radiation exposure with each scan. Some scans at 90 seconds are more and some less than this depending on the collimation of the beam (filtering and amount of site exposure). Scans that are less than 90 seconds will typically have less than 550 mrem and those that are more than 90 seconds more than this number.

[1]Radiation Dose Chart. American Nuclear Society. http://ww.ans.org/pi/resources/dosechart/ 5/28/2014

[4]Tuohy CJ, Weikert DR, Watson JT. Hand and body radiation exposure with the use of mini C-arm fluoroscopy. J Hand Surg Am. 2011;36:632-8.

[5]Kim TW, Jung JH, Jeon HJ. Radiation exposure to physicians during interventional pain procedures. Korean J Pain. 2010;23:24-27.

[6]Actual measurements on radiation exposure from DMX. The total dosage of radiation is measured by the DMX.

[7]Fact sheet on biological effects of radiation. United States Nuclear Regulatory Commission. May 28, 2014 http://www.nrc.gov/reading-rm/doc-collections/fact-sheets/bio-effects-radiation.html

[8]Manchikanti L, Cash KA, Moss TL, Pampati V. Radiation exposure to the physician in interventional pain management. Pain Physician 2002;5:385-93.

[9]Cho JH, Kim JY, Kang JE. A study to compare the radiation absorbed dose of the c-arm fluoroscopic modes. Korean J Pain. 2011; 24:199-204.

[10]Singer G. Radiation exposure to the hands from mini C-arm fluoroscopy. J Hand Surg Am 2005;30:795-7.

Where can I learn more about DMX?

The below-referenced articles address the cervical spine uses with DMX.

Cervical Spine

Yoshimoto H, Abumi K, Ito M, Kanayama M, Kaneda K. Kinematic evaluation of atlantoaxial joint instability: in vivo cineradiographic

instability in Down's syndrome for Special Olympics. Chiropractic Sports Medicine 1994; 8 (4):144

Betge, G. The value of cineradiographic motion studies in diagnosis of dysfunctions of the cervical spine. Journal of Chiropractic 1979; 2(6):40-44

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Shippel, A. Radiological and Magnetic Resonance Imaging of cervical spine instability: A case report. Journal of Manipulative and Physiological Therapeutics 1987; 10 (6)

Howe, J. Preliminary observations from cineroentgenological studies of the spinal column. ACA Journal of Chiropractic 1970; IV

Robinson, G.K. Cinefluoroscopic joint motion study of the post traumatic cervical spine. Digest of Chiropractic Economics 1984; Nov/Dec:156-157

Freeman M, et al. Diagnostic accuracy of videofluoroscopy for symptomatic cervical spine injury following whiplash trauma. *Int. J. Environ. Res. Public Health* **2020**, *17*(5), 1693; https://doi.org/10.3390/ijerph17051693

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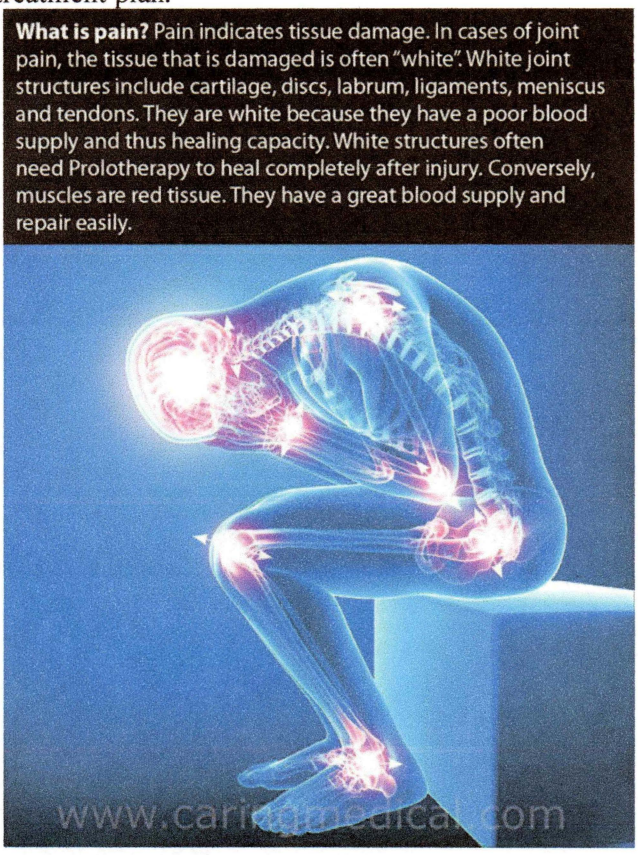
We are an out-of-network provider. Treatments discussed on this site may or may not work for your specific condition.

Digital Motion X-ray (DMX)

DMX: See an X-ray of your body in motion!

Digital Motion X-ray (DMX) is an amazing tool for visualizing why you have pain, and more importantly, help you and your provider determine the best treatment plan.



- **DMX is ideal for anyone who has suffered a whiplash, concussion, or other neck injury and has**
- **developed chronic symptoms. DMX provides a unique look at the structures causing your pain and other joint instability symptoms.**
- **DMX can be especially helpful when MRI and static X-ray showed "nothing" but you still have chronic symptoms!**

DMX is a motion picture of the bones while a person is moving. It is a dynamic diagnostic tool, versus a static one, and can be used for all joints of the body. The scan is produced in real time, while the person is moving. Other terms for Digital Motion X-ray used in the medical literature or cineradiography or video fluoroscopy. DMX can show spinal and peripheral joint instability from ligament damage. Pain typically occurs with motion. By being able to see the bones in motion, DMX picks up the abnormal or excessive motion whereas MRI, CT scan and static x-rays do not. You could think about it this way: Static MRI is like a formal family portrait whereas DMX is the video of how your family really acts.

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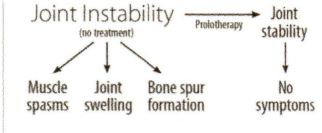

When a person has joint instability, the increased motion between two adjacent bones causes excessive tension on the supporting structures and the nerve endings within those structures (which are not stretchable really) causing severe chronic pain. Most of the time the injury or weakness is in the ligamentous support of the joint. It is the primary responsibility of the ligaments to connect adjacent bones. When ligaments are injured, torn and weakened the adjacent bones move excessive and the body to limit this motion does one of the three things: 1. swells the joint; 2. causes muscle spasms around the joint; 3. bone spurs to form over the long-term. (See Figure) All of which limit motion. Cortisone shots to limit swelling, massages to relax muscles and surgeries to remove bone spurs often have only temporary effects because they don't address the underlying cause of the issue which is joint instability. Prolotherapy, on the other hand, is the only treatment that addresses the instability in a non-surgical

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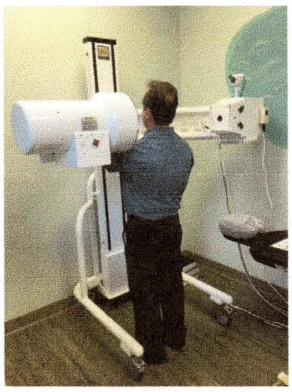
More DMX Case Studies and Success Stories

How is a Digital Motion X-ray performed?



Once in position, the person puts his or her neck, spine or peripheral joint through a series of motions while the DMX is videotaping the bone movement. Digital Motion X-ray is similar to a movie camera. The camera takes 30 individual x-ray frames per second to create the motion x-ray. The successive x-rays are digitized and sequenced to create a video representation of the movement of the bones. Sometimes, additional views are done where the joint is put under stress: by the person holding a weight, by the person doing a specific exercise, or by the radiology technician or physician putting passive pressure in a certain direction to help document the instability.

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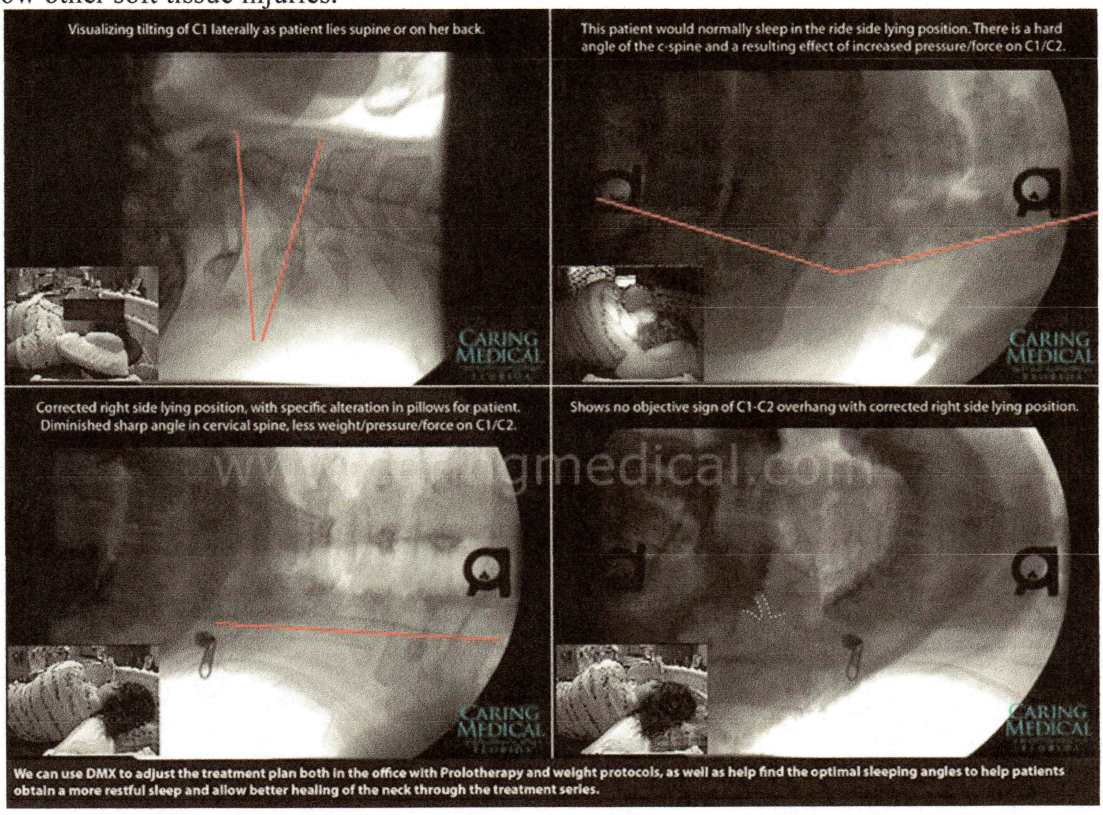

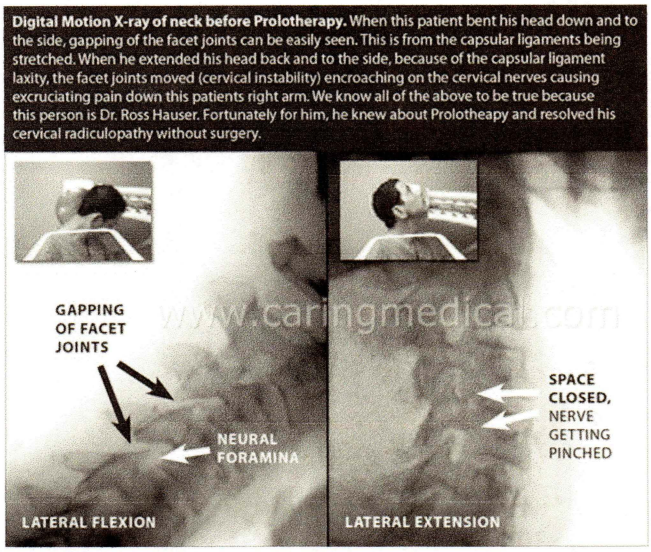

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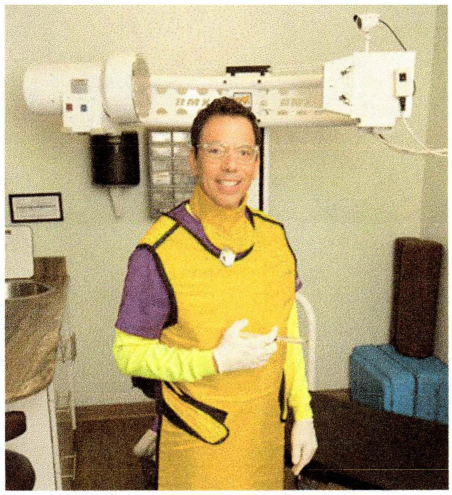
The report will be a comprehensive analysis of what was found during the exam, providing you and your healthcare team the information you need to make informed decisions on diagnoses and future medical care. Check out Ross Hauser's DMX Report, taken after he had been suffering from cervical radiculopathy. The report clearly shows cervical instability, which was then treated with Prolotherapy to stabilize the cervical vertebrae and stop the radiculopathy.

Is DMX good for my case?

Caring Medical has been ordering DMX scans on individuals for many years to document the extent of the joint instability/injury, set an objective baseline, and develop an effective treatment plan. We find it beneficial as an advanced diagnostic tool for certain conditions that can have severe consequences if not properly diagnosed. These cases can include:



- Upper **cervical instability** including C1-C2 instability
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- Conditions where Prolotherapy may be an option instead of surgery. A high percentage of the cases that come to Caring Medical have been told that surgery is their only option. If a person doesn't want surgery, then obtaining a DMX could point them to a more conservative option such as Prolotherapy.
- Injury cases. Some people are involved in litigation or insurance appeals and need documentation of the injury to help with a settlement or to get their medical care covered. Health care insurance coverage. Sometimes guided injections are preferred by insurers and may help treatment cost reimbursement for the patient.

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The annual occupational dose limits recommended by the Code of Federal Regulations in the United States for adults to be exposed to are 5000 mrem for the whole body.[10]

Common Radiation Doses in mrem.

Source	Amount of Exposure (mrem)[1-10]
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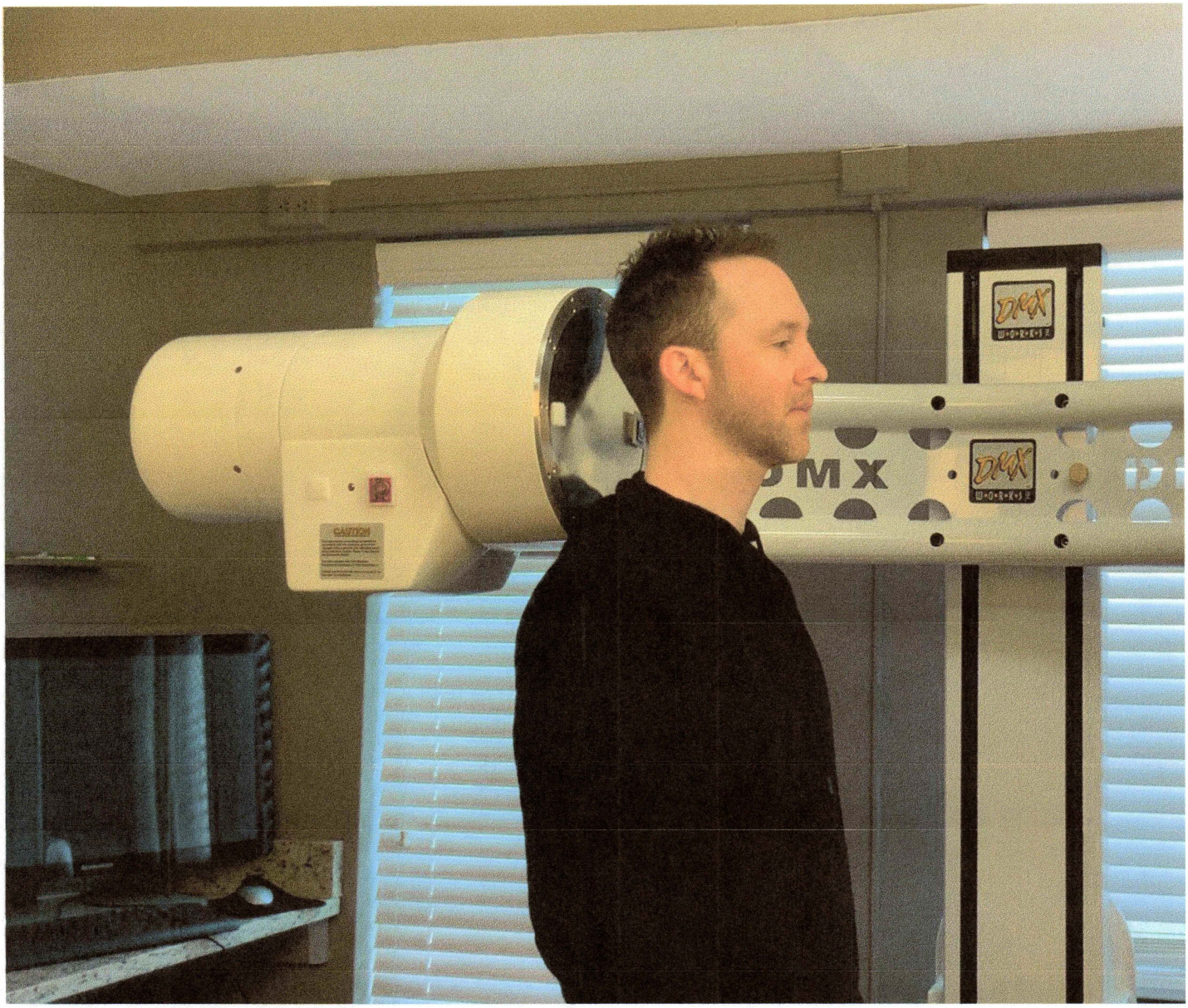
Airplane travel/per hour	0.5
One static Cervical image with DMX	7
½ pack of cigarettes smoked	18
Standard chest x-ray	20
One standard static hip x-ray	70-120
One standard static X-ray of cervical spine	70-120
DMX full exam of peripheral joint	150-350
Complete lumbar/cervical standard x-ray series 600-800 Average annual exposure in US	620
Complete DMX neck exam (90 seconds)	550
* Normal Fluoroscopy (non-DMX machine) (90 seconds of continuous exposure)	750
CT of spine	1000
High dose Fluoroscopy (non-DMX machine) (90 seconds of exposure)	1500

*Approximately 550 mrem.... the actual DMX machine measures total radiation exposure with each scan. Some scans at 90 seconds are more and some less than this depending on the collimation of the beam (filtering and amount of site exposure). Scans that are less than 90 seconds will typically have less than 550 mrem and those that are more than 90 seconds more than this number.



[1]Radiation Dose Chart. American Nuclear Society. http://ww.ans.org/pi/resources/dosechart/ 5/28/2014

[2]Crawley MT, Rogers AT. Dose area product measurements in a range of common orthopaedic procedures and their possible use in establishing local reference levels. Br J Radiol. 2000; 73:740-744.

[3]Mahesh M. Fluoroscopy: patient radiation exposure issues. The AAPM/RSNA Physics Tutorial for Residents. Presented at December 1999 Radiological Society of North America scientific assembly, Chicago IL. From The Russell H. Morgan Department of Radiology and Radiological Science, John Hopkins University of Medicine, Baltimore MD.

[4]Tuohy CJ, Weikert DR, Watson JT. Hand and body radiation exposure with the use of mini C-arm fluoroscopy. J Hand Surg Am. 2011;36:632-8.

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Cervical Spine

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DIFFUSION TENSOR IMAGING

(DTI)

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Diffusion Tensor Imaging of TBI: Potentials and Challenges

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Abstract

Neuroimaging plays a critical role in the setting in traumatic brain injury (TBI). Diffusion tensor imaging (DTI) is an advanced magnetic resonance imaging technique that is capable of providing rich information on the brain's neuroanatomic connectome. The purpose of this article is to systematically review the role of DTI and advanced diffusion techniques in the setting of TBI, including diffusion kurtosis imaging (DKI), neurite orientation dispersion and density imaging, diffusion spectrum imaging, and q-ball imaging. We discuss clinical applications of DTI and review the DTI literature as it pertains to TBI. Despite the continued advancements in DTI and related diffusion techniques over the past 20 years, DTI techniques are sensitive for TBI at the group level only and there is insufficient evidence that DTI plays a role at the individual level. We conclude by discussing future directions in DTI research in TBI including the role of machine learning in the pattern classification of TBI.

Keywords

diffusion tensor imaging; tractography; traumatic brain injury

Traumatic brain injury(TBI) is a common problem that affects 1.7 million people and results in 275,000 hospitalizations and 52,000 deaths in the United States annually. The incidence in emergency room visits related to TBI has been increasing over the past decade.[1–3] Adults older than 75 years of age have higher rates of hospitalization and death.[1] The most common causes of TBI are motor vehicle accidents, falls, sports-related injury, and assault,[1–3] with falls being the most common overall while motor vehicle accidents are the most common cause of TBI-related deaths.[1] In the military population, TBI is common in soldiers who have been exposed to an explosion.[4] According to the Veterans Health Administration, the cost of treating a patient with TBI for the first year averages $11,700, whereas the cost of

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treating a non-TBI patient is $2400.[4] The clinical symptoms from TBI range from mild cognitive impairment to severe disability.

Neuroimaging plays a critical role in the acute setting to guide appropriate management by detecting injuries that require intervention or further monitoring. For example, in the setting of severe TBI, the detection of an epidural hematoma may require emergent neuro-surgical management. However, in the setting of a concussion, conventional magnetic resonance imaging (MRI) is typically normal.[5] Many advanced neuroimaging techniques are actively being researched in an attempt to better diagnose concussions.

In contrast, diffusion tensor imaging (DTI) is an advanced MRI technique that came into existence in the mid-1980s and is capable of providing rich information on the brain's neuroanatomic connectome.[6,7] DTI metrics are thought to reflect the integrity of microstructural properties of white matter and have been applied extensively as neuroimaging biomarkers to study a range of clinical conditions.[8]

This article will review the potential benefits and challenges of using DTI in TBI. First, we briefly introduce the fundamental principles that subtend DTI. We then present an overview of DTI, and image acquisition techniques and processing methods for techniques beyond DTI. Next, we review clinical applications of DTI, with a focus on its use in imaging TBI. We then conclude with a discussion on future directions of DTI research.

FUNDAMENTALS OF DTI IMAGING

The white matter of the human brain is composed of axons. These axons travel from gray matter wherein the cell bodies of the neurons are located to other areas of the brain or spinal cord. Axon bundles traveling together constitute white matter tracts, which putatively connect functionally specialized yet segregated regions of the brain.

Conventional MRI is unable to visualize many of these white matter tracts. This is because conventional MRI contrast resolution is based solely on T1 and T2 relaxation times and white matter tracts have similar T1 and T2 relaxation times irrespective of the direction of the tracts.

DTI allows for visualization of these white matter tracts by imaging the anisotropy of water diffusion[9–13] (Fig. 1). Many excellent books and review articles have been published discussing DTI imaging methodology in detail.[11–16]

Mori[15] explains the concept of water diffusion by providing the analogy of an ink drop falling onto a piece of paper, with the subsequent diffusion (or spread) of the ink on the paper. As the ink spot grows over time, the rate of growth correlates to the rate of diffusion. If we extend this heuristic, isotropic diffusion occurs when the ink drop grows equally in all directions. Anisotropic diffusion occurs if the ink drop grows preferentially in 1 direction, such as would be seen if the ink drop fell onto a piece of fabric made up of woven fibers that were more tightly packed in 1 direction. In white matter tracts, water tends to have preferential diffusion along the axons and the shape of the ink spot would be more elliptical.

Cell membranes, axons, and myelin sheaths contribute to white matter tract anisotropy, with axons thought to be the major component.[17]

The pulse sequence for any DTI imaging technique is a spin-echo diffusion-weighted pulse sequence. DTI is able to image the anisotropy of white matter tracts by applying diffusion weighting in multiple different spatial directions using diffusion-sensitizing gradients. For example, the same white matter tract has different diffusivity constants depending on the direction of the diffusion-sensitizing gradient applied (Fig. 2). For each diffusion-sensitizing gradient, there is a 4D data set with x, y, z spatial locations with a diffusion constant that is proportional to the magnitude or rate of water diffusion. This process needs to be repeated with a minimum of 6 diffusion-sensitizing gradients and will ultimately yield a set of vectors that can be used to generate a structural connectivity map of the brain.

KEY CONSIDERATIONS IN PERFORMING TRACTOGRAPHY

The first key consideration in performing tractography is determining the diffusion model and whether to choose a model-based or model-free technique. The second key consideration is how to deal with the uncertainty in the tractography whether to perform deterministic or probabilistic tractography.

Model-Based Versus Model-Free Techniques

The most commonly used model-based technique is DTI. Other model-based approaches include diffusion kurtosis imaging (DKI) and neurite orientation dispersion and density imaging (NODDI).[18] The model-based approaches are based on an assumption of the fiber orientation within each voxel. For example, a single tensor model is based on the assumption that the voxel is composed of a single fiber orientation, whereas a 2-tensor model assumes that voxels are composed of 2-fiber orientations. DTI uses a Gaussian approximation for diffusion. DKI is based on a Kurtosis model, which characterizes the non-Gaussianity of the diffusion. In order to recover the brain's complex neuroanatomic connectome, sampling must be performed along with many different diffusion-sensitizing orientations, called high angular sampling. We will therefore discuss high angular resolution diffusion imaging (HARDI) acquisition technique. We will also discuss multi-band acquisitions, a method to speed up acquisition.

In contrast to the assumptions used in the model-based diffusion techniques, the model-free approaches estimate the fiber orientation with a 3D measurement of the water diffusion in the voxel of interest.

The 3D data acquired for these approaches are called q-space signal.[19] These model-free methods have the potential for more accurate characterization of the structural and orientation of the white matter tracts. The most commonly used model-free technique is diffusion spectrum imaging (DSI).

Deterministic Versus Probabilistic Tractography

Deterministic tractography assumes a single orientation at each voxel, such that a single tract is determined at each voxel. All of the clinical applications are based on deterministic

tractography. Probabilistic tractography is based on a distribution of multiple possible orientations at each voxel with each orientation having an associated probability.

IMAGE ACQUISITION

DTI Imaging Acquisition

The simplest form of DTI is the single tensor (or single ellipsoid) model. This form requires at least 2 B-values: 1 B = 0 mm/s^2 reference image and 1 additional B-value (eg, B ¼ 1000 mm/s^2) upon which the diffusion-sensitizing gradients are applied. Two B-values are required in order to perform a Gaussian model for the diffusion process. Another requirement for this single tensor DTI is the use of a minimum of 6 diffusion-sensitizing gradients, which is also referred to as directions; this obtains enough information to reconstruct the orientation and anisotropy information. The field of view for DTI imaging has no overlap and no skip between successive slices. Slice thickness and matrix size are variably set, but a standard protocol typically consists of a thickness of 2.0 mm and a matrix of 128 × 128.[20,21]Techniques that use few directions (such as the single tensor model using 6 directions) are unable to resolve crossing fibers. Accurate measurement of parameters such as fractional anisotropy (FA) requires approximately 25 to 30 diffusion directions depending on signal to noise ratio (SNR) of the individual diffusion-weighted images.[22]

The total number of volumes in a DTI series can be defined as *of volumes in a DTI series = References volumes + of diffusionen-coding volumes.*

The total number of images in a DTI series can be defined as *of images in a DWI series = slices in B0 reference image + additional B values × of directions × of slicesinthe brain.*

For example, the number of images in a DTI series for acquisition with 40 directions, 63 slices in the brain, and a B0 reference image of 63 images would equal 63 + 1 × 40 × 63 a total of 2583 images. This sequence takes approximately 8 minutes on a 3-Tesla scanner. Each image in a DTI series is referred to as a diffusion constant map, which represents the raw data for a particular gradient direction and a particular B-value. Thus, after repeating acquisition for all directions and all B-values, each pixel will have a magnitude associated with each gradient direction.

SNR and Tradeoffs

As with any MRI sequence, the goal of DTI is to provide the optimum SNR. For a single magnetic resonance (MR) image, the SNR is defined by the equation[23]:

$$SNR\ for\ a\ single\ MR\ image = \frac{S}{\sigma}$$

where: S represents the mean signal intensity within a region of interest

σ represents the standard deviation within that region of interest

SNR is most commonly measured in the B = 0 reference image. Repetition of acquisition with the same diffusion-sensitizing gradient can be performed with data averaging on the MRI scanner to improve SNR. The addition of more encoding directions can also improve the SNR in addition to the ability to resolve crossing fibers. These SNR improving techniques come with the penalty of longer scan acquisition. Longer sequences have their own potential undesirable consequences such as motion artifact. There is still debate regarding the tradeoff between repeat acquisition and more encoding directions, with some studies suggesting that more encoding directions are better at improving SNR (eg,[24,25]); however, there is evidence to the contrary (eg,[26]).

Acquisition Issues

DTI relies on echo planar imaging (EPI) pulse sequences, which can take several minutes to acquire, when whole brain coverage is desired. Parallel imaging can reduce distortion,[27] with a reduction in echo time that can balance the loss in SNR as a result of g-factor noise. Multi-band sequences have revolutionized DTI by parallelizing slice excitation[28] and acquiring several slices simultaneously.[29] The total scan time can be reduced by 3- to 5-fold depending on coil sensitivity and by acquiring multiple slices simultaneously and separating the simultaneous acquisitions mathematically, with very little penalty on SNR.[29] This accelerated scan protocol also reduces the time during which subject movement can occur during a scan. Movement artifacts can bias both FA and mean diffusivity (MD) DTI metrics, [28] which are discussed further below, leading to spurious conclusions, particularly at the group level.[30] Recently, multiband imaging has been shown to reduce the biased effects of subject motion.[31]

Diffusion Kurtosis Imaging Acquisition

DKI is similar to DTI, but provides further characterization of the water diffusion by estimating the kurtosis of the distribution. Kurtosis is a dimensionless higher-order statistic that quantifies the non-Gaussianity of a distribution. Two distributions with the same mean and variance may have different kurtosis values. For example, a positive kurtosis measurement means that the distribution is more strongly peaked.[32] In addition to the standard diffusion tensor in DTI, DKI also requires an additional tensor called the diffusional kurtosis tensor. Thus, a minimum of 3 B-values are required[33] and a minimum of 15 different diffusion gradient directions are also required.[34,35]

The key advantages of DKI are the improved ability to resolve intravoxel crossing fibers resulting in an overall improvement of white matter tractography[36] and the added specificity and sensitivity of DKI metrics such as mean kurtosis or radial kurtosis.[37] DKI acquisition can typically be performed on conventional MRI scanners. A limitation of DKI is its longer scan time than DTI, typically requiring 10 to 20 minutes per acquisition.

HARDI Acquisition

HARDI is an acquisition technique used in DTI that uses high number of directions (eg, 40 or more). HARDI are typically acquired with higher diffusion sensitization than DTI. HARDI acquisitions are most often followed by spherical deconvolution-based processing methods such as constrained spherical deconvolution (CSD). CSD is able to resolve multiple

fiber orientations within a single voxel.[38] The limitation of HARDI acquisition is the longer scan time. Each additional direction requires another diffusion sensitizing gradient.

Q-Space Acquisition

As is true with any DTI sequence, the pulse sequence for the acquisition of Q-space is a spin-echo diffusion-weighted pulse sequence. Q-space acquisition uniquely uses a series of 2 short, but very strong diffusion gradients applied to "label" the molecule during the diffusion process. Then, a displacement distribution function (or probability density function) is derived to calculate the 3D diffusion-driven displacement measurement of MR signal at each point (q_x, q_y, q_{xz}) within the Q-space. A diffusion-weighted image is acquired for each diffusion-encoding step (q-value). Thus, a total of $N_{qx} \times N_{qy} \times N_{qz}$ diffusion-weighted images are required to sample Q-space of size N_{qx}, N_{qy}, N_q.[39] The large number of images required to obtain Q-space information is a limitation of bringing this technology to clinical application. There are several Q-space based techniques, most notably DSI and q-ball imaging (QBI). Q-space sampling schemes are displayed in Fig. 3.[40]

DSI Acquisition

DSI is a Q-space based technique that uses HARDI acquisition with a 3D Cartesian sampling scheme of each voxel.[39] This method of processing was developed in attempt to resolve multiple intravoxel fiber crossings by imaging the spectra of water diffusion.[41] DSI uses the probability density function to describe the diffusion process within each voxel, and it requires a sufficient signal sample to resolve this diffusion probability density function. In order to achieve the sufficient signal, repeated diffusion gradients[42] and high spectral bandwidth[41] are required. DSI acquisition involves up to 5 to 10 times more data. DSI with 515 diffusion-encoding gradients takes approximately 1 hour, whereas reducing the number of diffusion-encoding gradients to 203 reduces the time to approximately 30 minutes.[43] These longer scan times allow for increased motion artifact. Despite these high requirements and long image acquisition times, DSI is now clinically available.[44]

Q-Ball Acquisition

QBI is a model-free Q-space based technique that uses HARDI acquisition with a spherical sampling scheme of each voxel involving only a single-shell B-value.[39] QBI also requires repeated gradients and high bandwidth; however, these are 2 to 3 times lower than that of DSI. In addition, QBI does not require as great a demand for the gradient performance as compared with DSI. Consequently, QBI is more efficient, but is not as accurate as DSI; however, QBI is more feasible for clinical applications.[43]

Neurite Orientation Dispersion and Density Imaging Acquisition

Projections from a cell body of a neuron are referred to as neurites and may take the form of either axons or dendrites. Neurite density and orientation dispersion estimates are 2 key contributing factors to FA. NODDI acquisition is a technique that uses a 2-shell HARDI acquisition and a 3-compartment model [including the intracellular volume (ICV), extracellular volume (ECV), and cerebrospinal fluid] in an attempt to separate out neurite

density from orientation dispersion estimates in an attempt to improve the map, dendrites, and axons in the brain.[18]

IMAGE PROCESSING

DTI Processing

DTI, the most common and simplest method of diffusion imaging, processes the diffusion anisotropy data with a Gaussian model and a mathematical process referred to as diagonalization of the tensor.[45,46] For each voxel, a set of directions and magnitudes forming a 3D ellipsoid can be generated, which represents the local cytoarchitecture. The 3D ellipsoid is characterized with 3 eigenvectors defining the axes with 3 associated eigenvalues (l) defining the lengths. MD is a scalar metric representing total amount of diffusion at a voxel and is calculated as the average of the 3 eigenvalues.[47] FA is a scalar metric representing the relative anisotropy at a voxel and is a scalar metric between 0 and 1. FA is calculated as the square root of the sum of squares of the diffusivity differences divided by the square root sum of squares of the diffusivities.[47] FA can characterize the 3D ellipsoid as linear, planar, or spherical. An FA value of 0 would represent perfectly isotropic diffusion, which is equal diffusion in all directions. An FA of 1 would represent an infinite cylinder (Fig. 4).

The diffusion tensor model assumes that there is a single ellipsoid with all axons traveling in the same direction within each imaging voxel. This model requires 7 measurements including 1 B0 and 6 gradient directions to determine the 3D ellipsoid and is therefore time efficient; however, the key limitation is the ability to assess fiber tracts crossing within a voxel. For many of the voxels in the human brain, this assumption is not true.[48,49] In fact, it has recently been suggested that over 90% of voxels contain crossing fibers[50] and resolving these intravoxel crossing fibers is particularly important for visualization of smaller tracts.[51] DTI and advanced techniques are summarized in Table 1.

DKI Processing

Although DTI uses a Gaussian water diffusion probability function, DKI uses a non-Gaussian probability function. In addition to the DTI metrics of FA and MD, DKI processing provides an additional set of metrics including the mean, axial, and radial kurtosis.[32] These additional metrics help characterize the non-Gaussianity of the water diffusion distribution.[32] A positive kurtosis value would mean that the curve is more strongly peaked than a Gaussian distribution with the same variance. DKI processing helps resolve crossing fiber tracks, which are within a voxel[36] (Fig. 5).

Constrained Spherical Deconvolution processing

Recovering the single or multiple-fiber orientations in each voxel is done on the basis of the diffusion properties of a single fiber. These single-fiber properties can be derived from the diffusion tensor or obtained directly from the data in regions with 1-fiber orientation, such as the posterior limb of the internal capsule or corpus callosum. With this knowledge, the measured diffusion signals are mathematically deconvolved to obtain a fiber orientation distribution that contains the orientations of all fibers within that voxel. CSD works

optimally with high b-values (eg, 2500–3000 s/mm^2) but can still resolve crossing fibers at regular clinical b-values.

DSI Processing

Recall that DSI is a model-free approach. The signal at each voxel within the diffusion-weighted spin echo images is reconstructed into a 3D probability density function of spin displacements using the 3D Fourier transform of the signal. DSI is able to resolve multiple intravoxel fiber crossings by imaging the spectra of water diffusion.[41] On a 3T scanner, it was found that if the bmax (diffusion sensitivity) is optimized, DSI can achieve similar angular precision for both higher and lower number of diffusion gradients. Thus, the DSI scan with 515 gradients with bmax of 6500 s/mm^2 and DSI scan with 203 gradients and bmax of 4000 s/mm^2 can achieve similar angular precision of 8 degrees for single fibers and 30 degrees for crossing fibers.[43]

QBI Processing

Recall that QBI is also a model-free approach. Vector math called the Funk Radon Transform is used and geometric tomography and probability distributions to describe the diffusion process within each voxel are determined (Fig. 6). This probability distribution is similar in concept to the fiber orientation distribution from CSD. This process helps to resolve intravoxel fiber crossings, and ultimately, a fiber orientation distribution function (fODF) is obtained. Optimizing the bmax for QBI has found similar angular precision as DSI for single and crossing fibers for QBI when using both high number of diffusion gradients (493 diffusion gradients with bmax of 3000 s/mm^2) and lower number of diffusion gradients (253 diffusion gradients with bmax of 2500 s/mm^2).[43]

Neurite Orientation Dispersion and Density Imaging processing

NODDI's 3-compartmental tissue requires a unique model for each compartment. The white matter ICV is composed of the volume bounded by the membranes of the neurites and the ODF is modeled with the Watson distribution. The white matter ECV is composed of the space between the neuritis. The ECV is not restricted by the membranes of the neurites and an anisotropic Gaussian model is used. The CSF compartment is modeled by an isotropic diffusion model. A NODDI sequence can be performed in 10 minutes[18] (Fig. 7).

CLINICAL PRACTICE OF DTI

There are multiple workstations available to the radiologist, which allow the selection of a tract by drawing a region of interest (ROI) to "seed" or select the fiber tracts of interest entering through this ROI (Fig. 8). Additional "include" and "exclude" boundaries can be set to isolate the tract of interest. The typical parameters are as follows: FA threshold of 0.2, maximum angle between current major eigenvector and previous major eigenvector of 37 degrees, minimum fiber length of 50 mm, and number of starting points per voxel of 8.[52] DTI is typically used in clinical applications such as mapping a tract before a neurosurgical procedure.

One of the limitations that the radiologist commonly experiences is that a high fraction of fibers in the ROI does not travel the full distance. One reason for this is that a fiber tract of interest crosses several other tracts before reaching its final destination. These locations of crossing fibers have a reduced FA. A voxel may contain 2 white matter tracts coursing in different directions. This would result in loss of anisotropy. Such a voxel will have low diffusion signal intensity and will appear dark. Fiber crossing causes a problem in clinical DTI, as some tracts simply cannot be visualized throughout their course (Fig. 9). In clinical practice, this can be a major limitation for performing tractography, and this is the problem that more advanced methods are currently trying to solve.

DTI CLINICAL APPLICATIONS

The majority of clinical applications of tractography involve preoperative neurosurgical planning to identify a specific white matter tract coursing in the vicinity of the lesion. This can help the neurosurgeon determine the amount of tissue he can take before reaching the white matter tract of interest (Fig. 10).

DTI TBI APPLICATIONS

There have been numerous studies involving DTI in the TBI population. We will review the current literature and provide a discussion on future DTI research.

Review of Current Literature of DTI Studies in TBI

There are many DTI studies in the literature for TBI. Many studies have found decreased FA and increased MD in the TBI population as compared with the control group.[53–70] The mechanism of decreased FA is thought to be as a result of demyelination or disruption of the microstructure of the tissue.

For example, 1 study by Hart et al[70] studied 26 retired NFL players, of whom 39% were cognitively impaired and 59% were cognitively normal. DTI analysis revealed statistically significant reduced FA in the bilateral frontal, bilateral parietal, corpus callosum, and left temporal lobe in the cognitively impaired group, but no statistically significant difference between the cognitively unimpaired group and the controls.[70]

Another study by Wilde et al[53] imaged 43 children with moderate to severe TBI and compared them with controls who had sustained orthopedic injury. Statistically significant decreased FA was found in the cingulum bundle in the TBI group.[53]

Miles et al[57] imaged 17 patients with mild TBI and 29 age-matched controls and found decreased FA in the centrum semiovale, corpus callosum, and posterior limb of the internal capsule.

Newcombe et al imaged 33 patients with moderate to severe TBI and compared them with 28 age-matched controls. This study analyzed whole brain white matter injury by assessing the proportion of voxels falling below a critical FA threshold. A statistically significant reduced FA was found in the TBI group.

Many studies, including those mentioned, demonstrate the common finding of decreased FA at the group level; however, the specific locations of decreased FA are variable. This variability may be as a result of the heterogeneity of the cohorts involved in these studies, such as severity and locations of TBIs, variability of the timing of imaging, and variability of imaging parameters.[71] DTI has been found to be sensitive for detection of acute and chronic TBI changes within the brain at the group level.[72]

Despite the sensitivity of decreased FA at the group level of TBI, the finding of decreased FA lacks specificity. Alterations in FA can be seen in a variety of other neurological conditions, particularly those that affect the white matter.

In conclusion, DTI techniques are sensitive for TBI at the group level only for population-based research. There remains insufficient evidence at the present time to suggest that DTI plays a clinical role in patients with TBI at the individual level.[72,73]

FUTURE DTI RESEARCH IN TBI

As a result of the fact that conventional MRI can be normal in mild TBI, there is a strong need for bringing advanced neuroimaging including DTI to clinical practice at the individual level. In addition to advances in acquisition and processing of DTI, there are continued improvements in clinical scanner performance. These improvements are helping advanced DTI techniques become a part of routine clinical protocols.

Despite all of these advances, DTI has limited application to TBI at the individual patient level. One barrier is a current lack of reference imaging data across an age-stratified normal population. A solution is to have a normative database with variations. Then, it will be possible to perform advanced computational analysis of the patient's scan and compare the results with the normative database in assessment for injury. At the Joint ASNR-ACR-HII-ASFNR TBI workshop on May 23, 2014 in Montreal, Canada, these issues were discussed including the formation of a consensus of the ideal database, normal control subject, and standardizing clinical and research neuroimaging protocols. With a normative database, future DTI research with computer-aided diagnosis and machine learning (ML) could be performed and has the potential for a more refined diagnosis.

Pattern Classification in TBI

The heterogeneity of TBI is considerable, and this variability represents a major obstacle in finding effective treatments at the individual level.[74] Pattern classification, synonymous with ML, has become a core tool for studying neuroimaging data during the past decade. As a result of their inherent multivariate nature, pattern classifiers may be capable of revealing effects that may otherwise be invisible with conventional univariate statistics.[75–77] In this sense, ML tools may reveal *patterns* of brain signal data consistent with etiological, symptom-based, prognostic, and pathoanatomic classifications of TBI.[74]

Pattern classification refers to the process of training a computer algorithm to "learn" from past experience. Classifiers operate on "features," or descriptive variable categories (eg, DTI FA values) for the purpose of either prediction or description. When applied in a

predictive capacity, classification takes place within a supervised framework and each set of features is paired with an outcome label.[78] Together, these can be used to predict a binary diagnosis (eg, microbleed or normal) or multilevel outcome (eg, 1–15 on the Glasgow Coma Scale). For example, ML applied to DTI data was able to discriminate between patients with microbleeds and age-matched controls with a high degree of accuracy.[79] Combining DTI with additional MRI metrics has also been successful in classifying patients with mild TBI from controls with up to 86% accuracy.[80]

Ideally, however, ML algorithms could be applied for the dual purpose of classification and interpretation of the informative MRI features that are used for prediction. Great care should be taken when attempting this, as data features are typically assigned weights in order to collaboratively optimize discrimination using a multidimenstional hyperplane. Therefore, data features that absorb noise with little information on their own may be assigned a strong weight.[81] When the data features are statistically independent, as would be the case for independent component features, this issue is less problematic.[82,83] However, in most applications, data features should be back projected into their native space before interpretation.[81]

In supervised learning, each data feature must be assigned a label (eg, TBI or healthy control). In many instances, however, the number of labels may be unknown. For example, one may wish to understand the number of underlying symptom clusters that exist under the broad definition of TBI. In this case, unsupervised learning may be appropriate. For example, nonnegative matrix factorization has recently been applied to ADHD data to uncover both the number of archetypal patient ''clusters'' in this population, as well as the phenotypic and neuroimaging linkages that are associated with each group.[84] Unsupervised analysis applied to DTI data has recently revealed a linkage between induction of MCP-1 following TBI and a predisposition for development of Alzheimer disease.[85]

Structure-Function Integration

As discussed above, development of a canonical DTI reference atlas across the lifespan is imperative. Nonetheless, in isolation, DTI may prove insufficient to fully understand the neural and cellular underpinnings of TBI, and a multimodal fusion approach may be more effective. In addition to clustering and pattern classification methods, structural connectivity measures derived from DTI data have been used as priors in estimating effective connectivity measures from functional MRI data within the context of dynamic causal modeling analysis.[86] An integrated structure-function approach that combines clinical information may yield insights into the phenomenology of TBI and future directions for treatment pathways.

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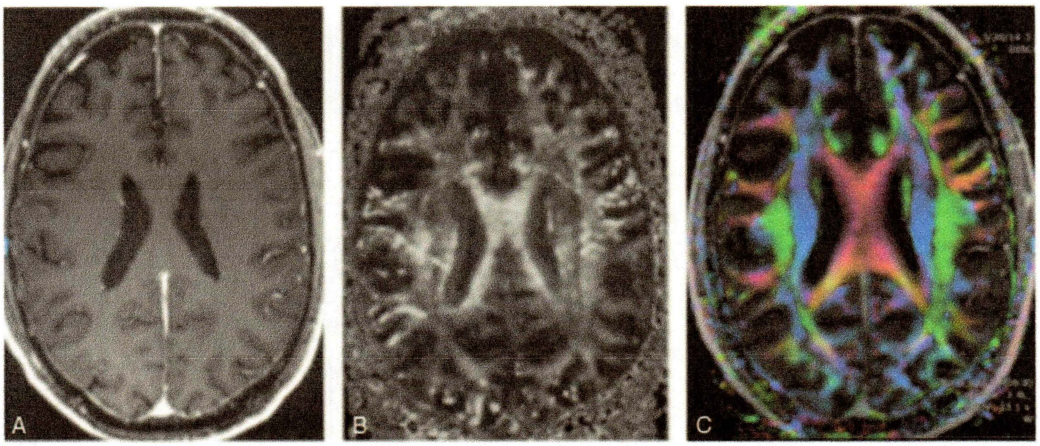


FIGURE 1.

(A) T1-weighted inversion recovery prepared fast spoiled gradient-recalled (IR-FSPGR) postcontrast image. There is no ability to distinguish the different fiber tracts. For example, all of the white matter tracts within the centrum semiovale and the same intensity and directional information cannot be obtained. (B) DTI fractional anisotropy gray scale image. There is varying signal intensities within the white matter tracts within the centrum semiovale and fiber tracts are visualized separately. (C) DTI color-coded fractional anisotropy. The colors correspond to the direction of the fiber tracts with red, blue, and green tracts denoting transverse, superior-inferior, and anterior-posterior directions, respectively. Different components of white matter fascicles can be much more clearly delineated.

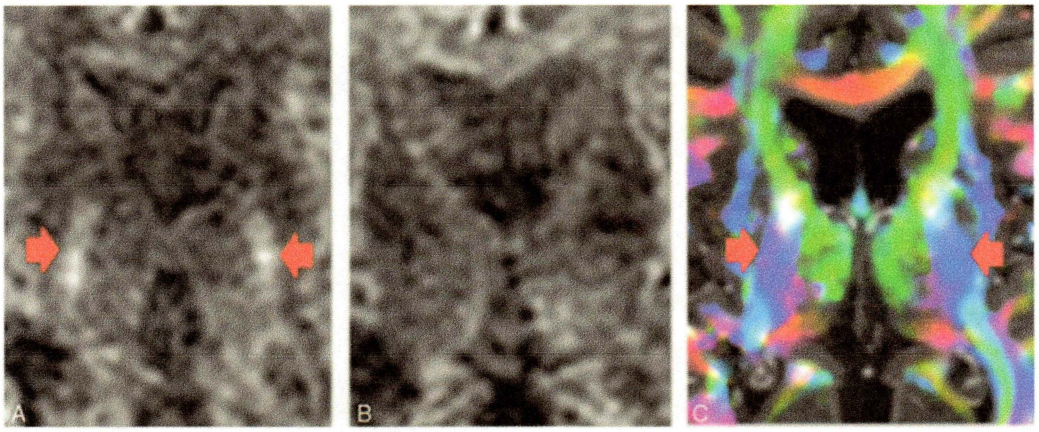


FIGURE 2.

(A) Diffusion-weighted image. The corticospinal tracts (CSTs) coursing through the posterior limb of the internal capsule (denoted by the arrows) are hyperintense. (B) Diffusion-weighted image with different gradient direction. Note that the CST coursing through the posterior limb of the internal capsule have lost their signal. The diffusion signal goes down if the gradient is applied along the axis of diffusion. Therefore, if the diffusion-encoding gradient is directed superior–inferior, then the CST will decrease in signal intensity on the diffusion-weighted image. Similarly, if the diffusion-encoding gradient is directed anterior–posterior, then the superior longitudinal fasciculus will decrease in signal intensity. Finally, if the diffusion-encoding gradient is directed transversely, then the portions of the corpus callosum will decrease in signal intensity. (C) DTI color-coded fractional anisotropy map. The CSTs running through the posterior limb of the internal capsule are denoted by the blue color, which indicates the tracts are coursing in the superior–inferior direction.

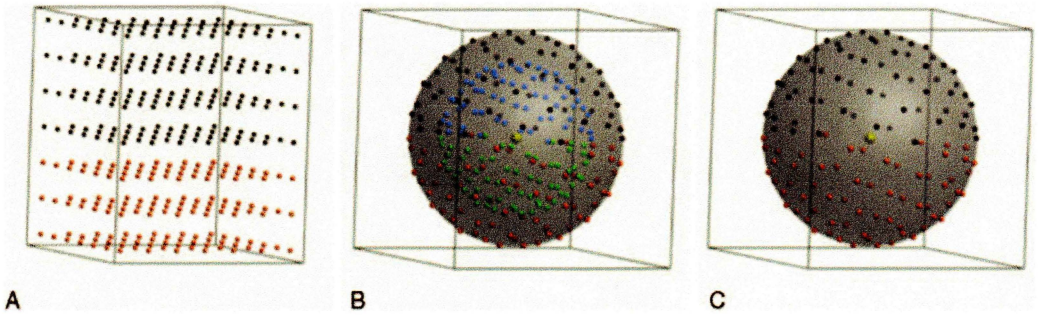
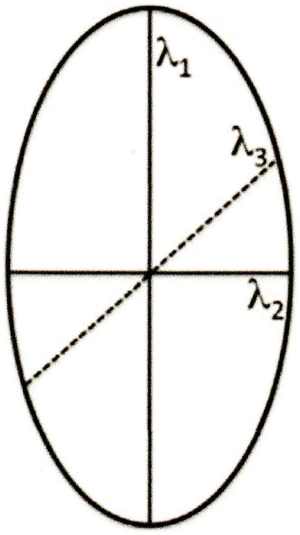


FIGURE 3.

Representation of q-space sampling schemes: single-shell (A), multi-shell (B), and Cartesian (C). The black dots in the left and middle panel indicate 64 gradient directions, optimized on the half-sphere, the red dots those same gradient directions mirrored on the other side of the sphere. The blue and green dots in the middle panel represent a similar sampling on a shell with a lower b-value (or q-value). The Cartesian sampling is shown for a $7 \times 7 \times 7$ cubic grid for visualization purposes (DSI default is $11 \times 11 \times 11$). The black dots again represent points in q-space with $qz \geq 0$ and the red dots indicate $qz < 0$.



$$\text{Mean Diffusivity (MD)} = \frac{(\lambda_1 + \lambda_2 + \lambda_3)}{3} = \lambda$$

$$\text{Fractional Anisotropy (FA)} = \frac{\sqrt{3}}{\sqrt{2}} \frac{\sqrt{(\lambda_1 - \lambda)^2 + (\lambda_2 - \lambda)^2 + (\lambda_3 - \lambda)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

FIGURE 4.
3D ellipsoid with MD and FA.

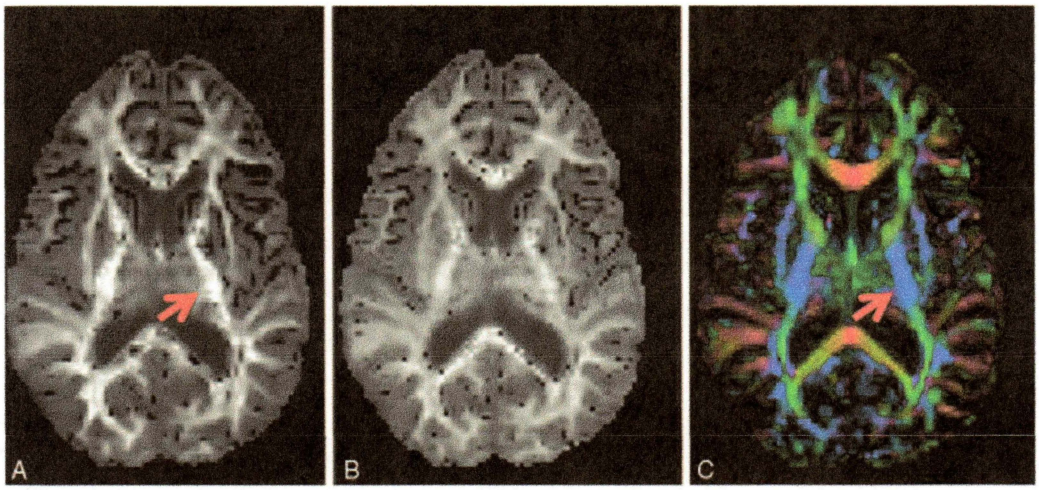


FIGURE 5.

DKI images showing diffusion-encoded color DEC-map (A), and mean and radial kurtosis (B and C, respectively). Nonzero Kurtosis means non-Gaussian diffusion, with positive kurtosis indicating that the distribution is more peaked. In terms of neuronal tissue, this is often caused by restricted diffusion, as for instance is the case inside axons. Arrows indicate the posterior limb of the internal capsule (similar to Fig. 2), wherein the high radial kurtosis is an indication of restricted diffusion perpendicular to the main fiber orientation (CST). Acquisition: 112 × 112 matrix with 22.4 × 22.4 cm field-of-view, 70 axial slices of 2 mm thickness. 6 b = 0 images, 60 gradient directions at b ¼ 1200 s/mm^2 and 60 gradient directions at b = 2500 s/mm^2. TE/TR = 107 ms/10.3 s, acquisition time 21m33.

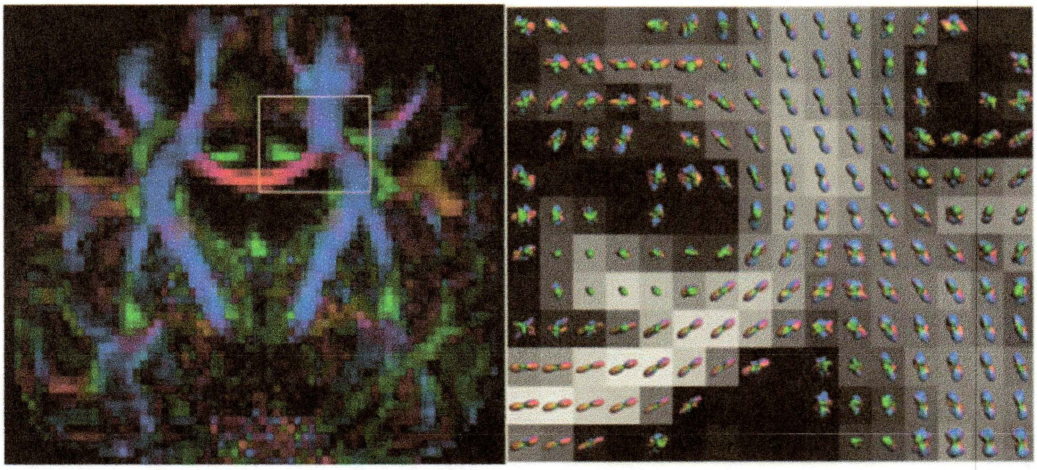


FIGURE 6.

Example output from a Q-ball Imaging scan. On the left, a conventional diffusion-encoded color map. On the right, a zoomed region—as indicated—with the probability distributions in each voxel shown over an FA map. Clear single-fiber areas (corpus callosum) and crossing fiber areas (more laterally) can be observed in these voxel-wise distributions, with QBI being able to resolve these fiber crossings. QBI acquisition: 112 × 112 matrix with 22.4 × 22.4cm field-of-view, 70 axial slices of 2 mm thickness. 6 b = 0 images, 60 gradient directions at b = 2500s/mm^2. SENSE acceleration factor 2, TE/TR = 107ms/10.3 s, acquisition time 11m20s.

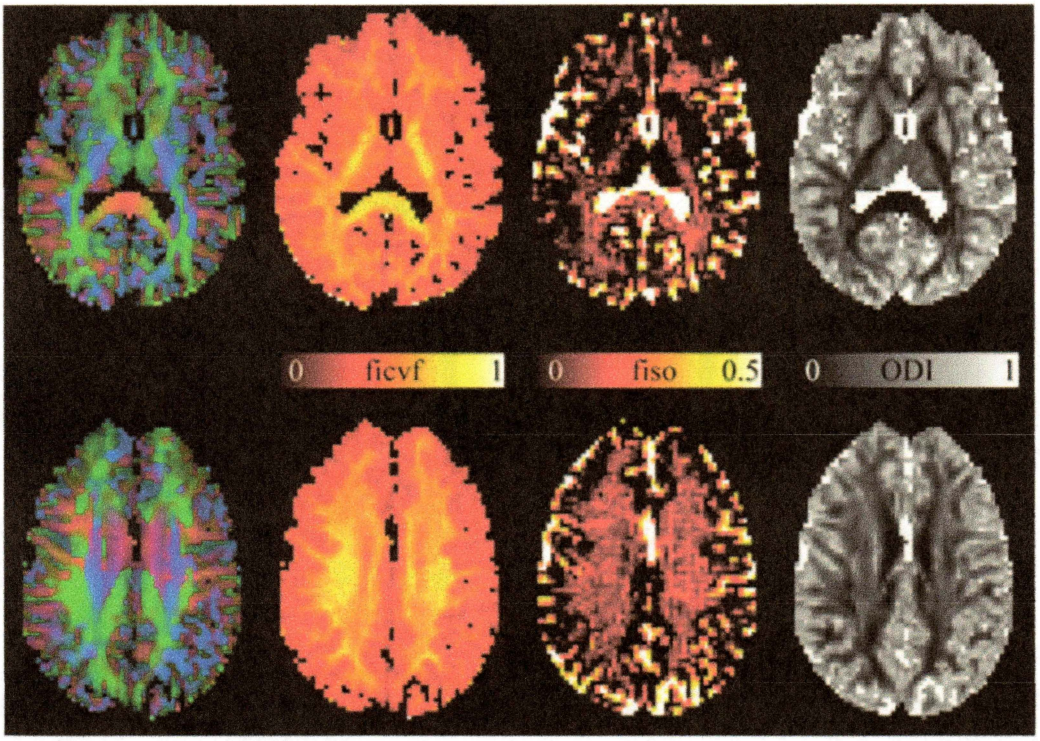


FIGURE 7.

Example images from model parameters from NODDI, the intracellular volume fraction (ficvf), isotropic volume fraction (fiso), and orientation dispersion index (ODI). The color-encoded DEC map is shown on the left to indicate location within the brain. Values of ficvf are high in neurite-rich areas such as white matter, as can most clearly be seen in the internal capsule and the splenium of the corpus callosum. The fiso maps accurately highlight the ventricles and surrounding CSF that have a very high isotropic diffusivisity. The orientation dispersion index (ODI) maps the dispersion of neurites around the principal diffusion direction. In single-fiber regions in the white matter, this can be regarded as an indication of the coherence of the axons in that voxel. This can most clearly be seen in the posterior limb of the internal capsule, wherein the ODI is low indicating high axonal coherence. NODDI scan parameters: 96 × 96 matrix, 240 × 240 mm FOV, 50 slices of 2.5 mm thickness, 11 b = 0 images, and 8, 32, and 64 DWIs at b-values of 300, 700, and 2500 s/mm^2, respectively. SENSE acceleration factor 2, TE/TR *71.7*/5200 ms, acquisition time 9m58 s.

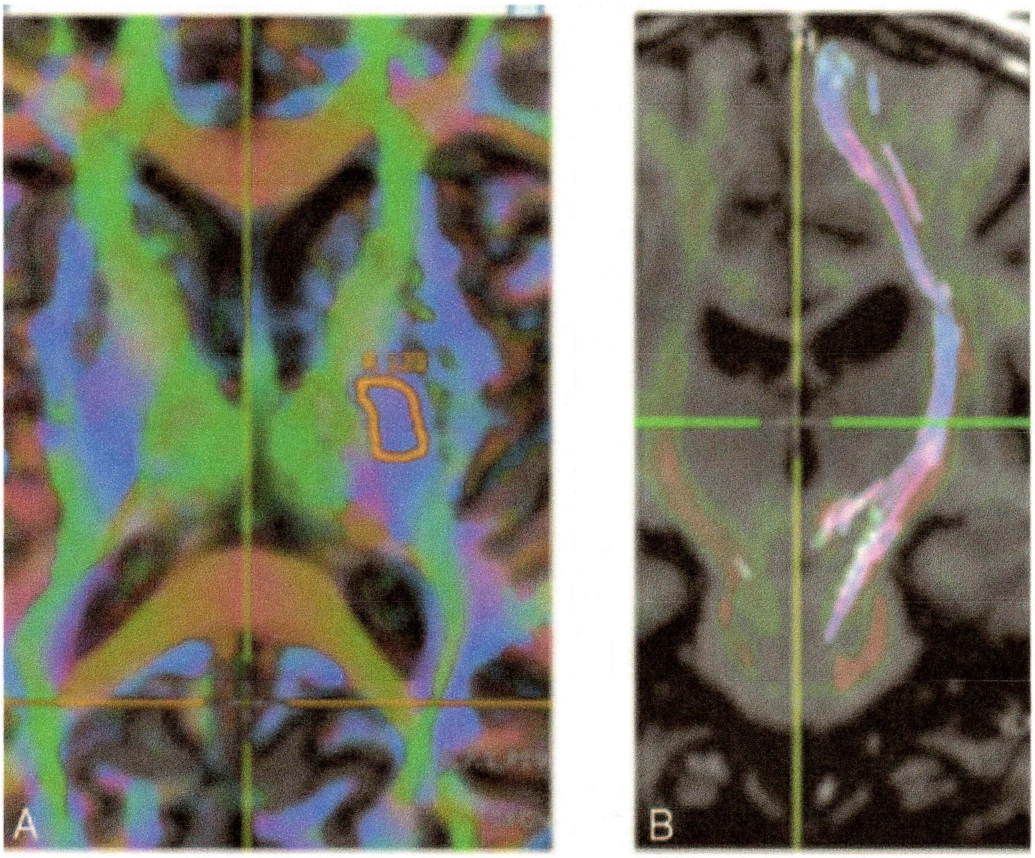


FIGURE 8.

(A) Axial DTI Anisotropy map overlaid on a T1 IR-FSPGR image demonstrates a ''seed'' site at the left CST at the left posterior limb of the internal capsule. (B) Coronal T1 IR-FSPGR image with the left CST colored and coursing superior-inferior.

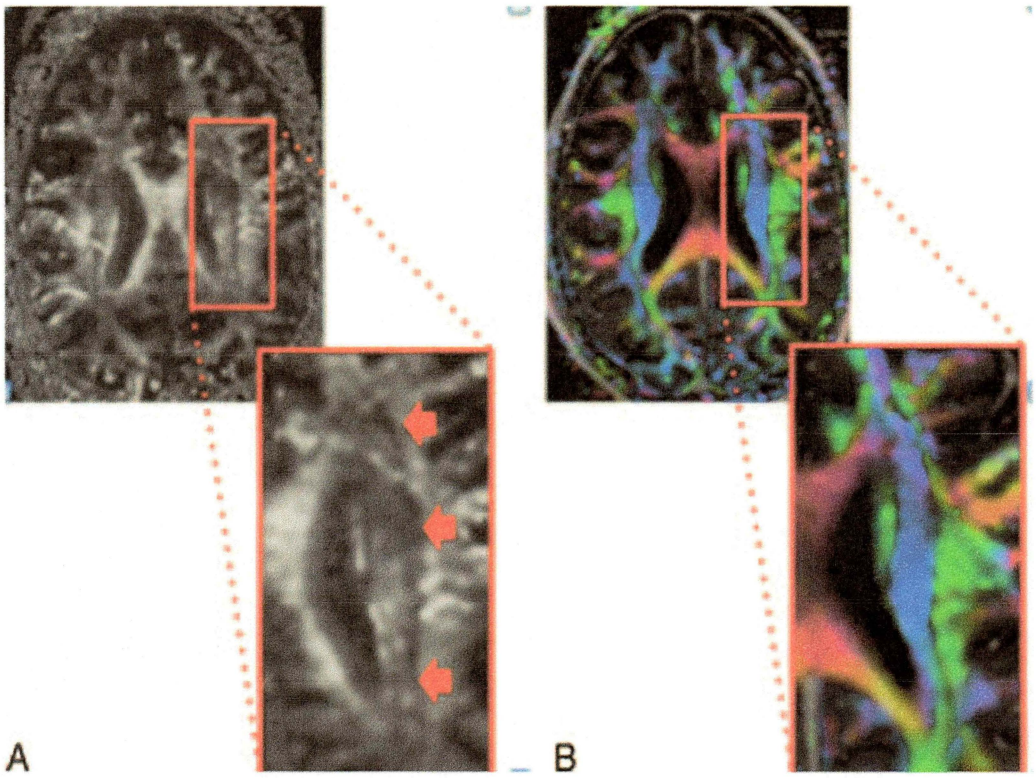


FIGURE 9.

Figure illustrating fiber tract crossing. (A) The image on the left is a DTI fractional anisotropy gray scale image. The dark band denoted by the arrows in the corona radiata white matter represents the intersection between the superior-inferior oriented corticospinal tract located medially and the anterior-posterior oriented superior longitudinal fasciculus. The dark pixels at the interface between these 2 perpendicularly oriented tracts occur because the tensor model cannot distinguish between low anisotropy as a result of a weak primary bundle and low anisotropy as a result of crossing fibers. (B) The image on the right is a DTI anisotropy color map, which shows the blue corticospinal tract and the green superior longitudinal fasciculus with a thin black line at the interface.

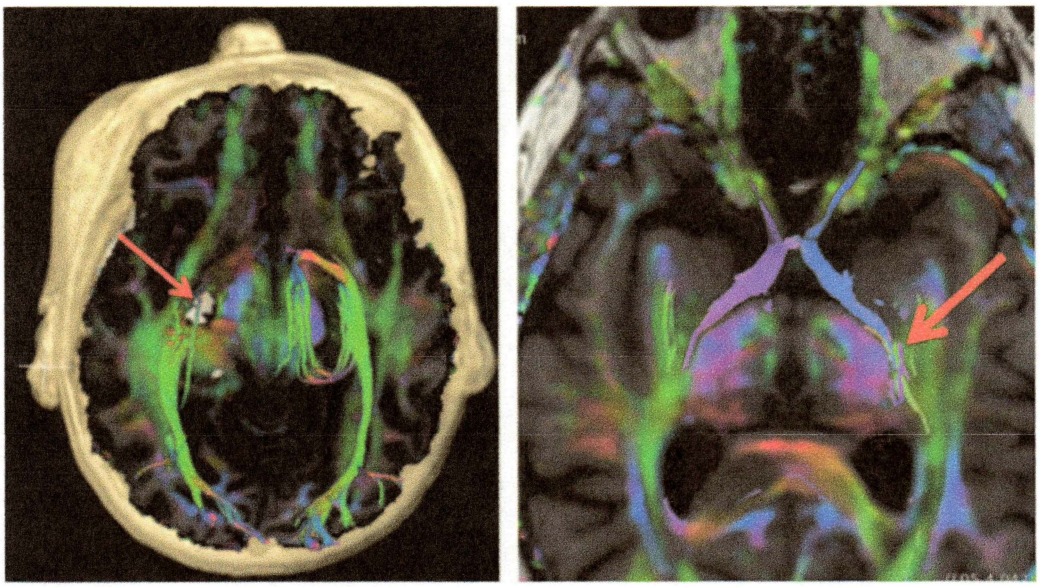


FIGURE 10.

Example of clinical DTI imaging. Axial-fused T1 IR-FSPGR and color FA map with volume rendering (left image) was performed for preoperative planning in a patient with a presumed cavernous malformation (red arrow) in close proximity to the lateral geniculate nucleus with selective tractography of the optic radiations (predominantly green tracts bilaterally). Axial-fused T1 IR-FSPGR and color FA map with selective tractography of the bilateral optic tracts (left side is blue and right side is purple) extending toward the lateral geniculate nucleus (red arrow). Note that the chiasm and the optic nerves can also be seen further anteriorly.

TABLE 1.

Summary of Diffusion Techniques

	Technique	Information Acquired at Each Voxel	Advantages	Disadvantages
Model-based techniques	DTI	3D diffusion tensor	Short acquisition time; validated metrics; reproducible; hardware readily available	Hypothesis driven and the assumption may not be accurate for voxels containing multiple fiber orientations
	DKI	3D diffusion and 3D kurtosis tensors	Better at resolving intravoxel crossing fibers; Hardware readily available	Longer scan times; Hypothesis driven and the assumption may not be accurate for voxels containing multiple fiber orientations
	NODDI	Orientation dispersion, intracellular volume fraction, free water component	Intracellular volume fraction should be like FA except should not go down as much in regions of fiber crossings. Only a few parameters are fitted.	Longer scan times to acquire 2 b-shells. Long processing time.
	CSD	3D fiber orientation distribution	Can resolve fiber crossings; Tolerable acquisition times	No validated metrics
Model-free techniques	DSI	3D diffusion displacement distribution	Can resolve fiber crossings	Long acquisition time; no validated metrics; hardware demands
	QBI	3D fiber orientation distribution	Can resolve fiber crossings; tolerable acquisition times	No validated metrics; hardware demands

CSD, constrained spherical deconvolution; DKI, diffusion kurtosis imaging; DSI, diffusion spectrum imaging; DTI, diffusion tensor imaging; NODDI, neurite orientation dispersion and density imaging; QBI, Q-ball.