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Application of Advanced Neuroimaging Modalities in Pediatric Traumatic Brain Injury

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Abstract

Neuroimaging is commonly used for the assessment of children with traumatic brain injury and has greatly advanced how children are acutely evaluated. More recently, emphasis has focused on how advanced magnetic resonance imaging methods can detect subtler injuries that could relate to the structural underpinnings of the neuropsychological and behavioral alterations that frequently occur. We examine several methods used for the assessment of pediatric brain injury.

Susceptibility-weighted imaging is a sensitive 3-dimensional high-resolution technique in detecting hemorrhagic lesions associated with diffuse axonal injury. Magnetic resonance spectroscopy acquires metabolite information, which serves as a proxy for neuronal (and glial, lipid, etc) structural integrity and provides sensitive assessment of neurochemical alterations. Diffusion-weighted imaging is useful for the early detection of ischemic and shearing injury. Diffusion tensor imaging allows better structural evaluation of white matter tracts. These methods are more sensitive than conventional imaging in demonstrating subtle injury that underlies a child's clinical symptoms. There also is an increasing desire to develop computational methods to fuse imaging data to provide a more integrated analysis of the extent to which components of the neurovascular unit are affected. The future of traumatic brain injury neuroimaging research is promising and will lead to novel approaches to predict and improve outcomes.

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Author Contributions

Each of the authors contributed to the literature review and writing of the manuscript as follows: SA prepared the introductory material and the section on diffusion-weighted imaging; KAT wrote the section on susceptibility-weighted imaging; NG was responsible for the section on computational analysis; BBO prepared the section on diffusion tensor imaging; and BAH wrote the section on magnetic resonance spectroscopy. BAH, BBO, and KAT prepared all figures. All authors reviewed the entire manuscript prior to submission.

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The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This manuscript is a review article and there are no ethical issues of relevance. It is not a report that describes clinical trials. Some of the figures used in this manuscript were from patients enrolled in a NINDS-supported study (Pediatric TBI and DAI: Normal Appearing Brain is not Normal; NINDS—R01 NS054001-01) and Loma Linda University Institutional Review Board consent had been obtained to use any patient images if presented in manuscripts or national meetings. All such patients also had signed informed consent.

Keywords

children; diffusion tensor imaging; diffusion-weighted imaging; infants; magnetic resonance imaging; magnetic resonance spectroscopy; traumatic brain injury

Advances in neuroimaging over the past 2 decades have greatly helped in the clinical care and management of children with traumatic brain injury.^{1–6} Immediately after injury, computed tomography (CT) is important for rapid detection of extra-axial hemorrhage (eg, subdural or epidural hematomas), acute hydrocephalus, fractures, or other intracranial lesions that require acute neurosurgical intervention.⁷ Magnetic resonance imaging (MRI) is very sensitive for intraparenchymal lesion detection but frequently is not acquired acutely.

Newer and more sensitive imaging techniques are now used to better characterize the nature and evolution of injury and the underlying mechanisms that lead to progressive neurodegeneration, recovery or subsequent plasticity. These advanced methods also have begun to demonstrate that “normal appearing” brain as examined with CT or with conventional MRI may not adequately depict brain injury.⁷

This review will describe 3 advanced MRI techniques that are of value in the acute and chronic periods after traumatic brain injury in children. They include (1) susceptibility-weighted imaging; (2) magnetic resonance spectroscopy, particularly magnetic resonance spectroscopic imaging; and (3) diffusion-weighted and diffusion tensor imaging. Several of these methods appear particularly useful for the assessment of diffuse axonal injury that is responsible for a wide range of motor and cognitive impairments. Studies exploring the human *connectome*, examining the brain’s structural and functional interrelationships, are also being used to study brain development as well as genetic and acquired diseases, and in the future should provide important information regarding traumatic brain injury.^{8–10}

Susceptibility-Weighted Imaging

Principles of Susceptibility-Weighted Imaging

Hemorrhage creates a complex signal pattern on MRI, which depends on various factors including the type of blood product (which is associated with the age of the hemorrhage), size and complexity of hematoma, and MRI sequence used to visualize the hemorrhage. Generally, the presence of hemorrhage will disturb the homogeneous magnetic field, particularly if the primary component is deoxyhemoglobin, which has paramagnetic properties. This phenomenon is measured by magnetic susceptibility, and different MRI sequences will be variably affected by susceptibility. Sensitivity to susceptibility effects increase as one progresses from fast-spin echo to routine-spin echo to gradient echo techniques; from T1 to T2 to T2* weighting; from short to long echo times; and from lower to higher field strengths.

Of the standard MRI sequences, T2*-gradient recalled echo methods are more sensitive to hemorrhage. However, susceptibility-weighted imaging is a new, higher spatial resolution, 3-dimensional gradient recalled echo MRI technique that employs an additional phase-subtraction postprocessing step, that accentuates the hypointense signal of paramagnetic

substances. Susceptibility-weighted imaging is therefore extremely sensitive for detecting extravascular blood products.¹¹ These effects are even greater using higher field strengths (3-Tesla vs 1.5-Tesla MRI). In the past decade, the clinical value of susceptibility-weighted imaging in adults and children with various neurologic disorders, including traumatic brain injury, has been described.^{1,12}

Clinical Applications of Susceptibility-Weighted Imaging in Pediatric Traumatic Brain Injury

We and others have shown that susceptibility-weighted imaging performs better than conventional MRI in detecting hemorrhagic diffuse axonal injury lesions after traumatic brain injury (Figure 1). In an early study of children with traumatic brain injury, we demonstrated that the number of hemorrhagic diffuse axonal injury lesions seen on susceptibility-weighted imaging was 6 times greater than on conventional T2*-weighted 2-dimensional gradient recalled echo imaging, and that the volume of hemorrhage was approximately 2-fold greater.¹³ Susceptibility-weighted imaging was particularly helpful in visualizing the smallest of hemorrhages, which were often more numerous. We also have shown that susceptibility-weighted imaging consistently detects more hemorrhages than fluid-attenuated inversion recovery, T2-weighted imaging, and acute CT in pediatric⁷ and adult patients.¹⁴ Beauchamp and colleagues¹⁵ have also confirmed that susceptibility-weighted imaging is more sensitive than CT and conventional MRI in children. They demonstrated that susceptibility-weighted imaging showed more lesions (86% of cases) than CT (68%) or conventional MRI (54%) and that susceptibility-weighted imaging showed additional lesions 30% of the time. In another study of adolescent and adult traumatic brain injury patients (aged 12–76 years), Geurts and colleagues¹⁶ confirmed that susceptibility-weighted imaging at 3.0 Tesla, obtained up to 57.7 weeks postinjury, showed the highest number of lesions, followed by T2*-gradient recalled echo, fluid-attenuated inversion recovery, and T2-weighted imaging. They also reported poor interrater reliability when using T2-weighted imaging or fluid-attenuated inversion recovery to determine lesions, suggesting that susceptibility-weighted imaging is also more reliable in detecting lesions.

Susceptibility-weighted imaging lesions also have shown good correlation with clinical variables and global outcomes. In a study of children and adolescents with mild to severe traumatic brain injury, we found that children with lower Glasgow Coma Scale scores (≤ 8 , $n = 30$) or prolonged coma (>4 days, $n = 20$) had a significantly greater average number and volume of hemorrhagic lesions.¹⁷ In addition, children with normal outcomes or mild neurologic disability at 6 to 12 months after injury, assessed by the Pediatric Cerebral Performance Category Scale (PCPCS) score,¹⁸ had significantly fewer number and volume of hemorrhagic diffuse axonal injury lesions than those who were moderately/severely disabled or in a vegetative state. Regional differences in diffuse axonal injury were also easily demonstrated by susceptibility-weighted imaging. More than 90% of patients had lesions in the parieto-temporal-occipital gray matter, parieto-temporal-occipital white matter, and frontal white matter. Four regions were less commonly affected (ie, $<65\%$ of patients—thalamus, brainstem, cerebellum, and basal ganglia). Only patients with involvement of 7 or more regions had poor outcomes.

Neurocognitive impairment also has been shown to correlate with susceptibility-weighted imaging lesions. In a subset of our pediatric traumatic brain injury patients, we performed neuropsychological assessments in children and adolescents, on average at 2.1 ± 0.5 years postinjury.¹⁹ Exploratory analyses suggested that lesion number and volume in deep brain regions (basal ganglia, thalamus, and brainstem) were strongly associated with poorer neuropsychological performance in almost all domains of intellectual and neuropsychological functioning. Lesions in the corpus callosum and cerebellum were also moderately correlated with cognitive outcomes. Beauchamp and colleagues also confirmed that the number and volume of susceptibility-weighted imaging lesions correlated with the Glasgow Coma Scale score as well as with intellectual functioning in pediatric patients of all traumatic brain injury severities.²⁰ Our recent studies have also shown that susceptibility-weighted imaging can be helpful in mild-to-moderate traumatic brain injury and can show persistent lesions even at 1 year after injury (Figure 2).

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy allows noninvasive analysis of brain metabolites. Proton (¹H) magnetic resonance spectroscopy is the most widely used application of magnetic resonance spectroscopy and has been helpful for the clinical assessment of many pediatric disorders including traumatic brain injury, hypoxic-ischemic injury, brain tumors, epilepsy, and metabolic disorders.

Principles of Magnetic Resonance Spectroscopy

Several brain metabolites are measured using short (ie, 20–40 ms) and intermediate to long (ie, 135–270 ms) echo time magnetic resonance spectroscopy. Each metabolite resonates at a frequency dependent on the structure and strength of interaction between the nucleus and the electron cloud within the particular molecule. The size of the change in frequency is known as the chemical shift (measured in parts per million). After Fourier analysis, the plot of signal amplitude versus frequency in parts per million is known as the MR spectrum. Metabolite levels vary by anatomic region²¹ and change rapidly as the brain develops,²² requiring the use of normal age-matched reference data for interpreting MR spectra from children. In general, metabolite changes associated with brain maturation continue rapidly through the first year of life²³ and continue to a lesser degree through adolescence.^{24,25}

N-Acetylaspartate (NAA; 2.01 ppm), an amino acid synthesized in neuronal mitochondria, is an indicator of neuronal energy metabolism and is considered a neuronal marker that decreases with neuronal loss or dysfunction.²⁶ In white matter, the *N*-acetylaspartate peak includes a greater contribution from *N*-acetylaspartylglutamate than in gray matter. During development, *N*-acetylaspartate reflects active myelination and is expressed early in the thalamus and later in parieto-occipital and periventricular white matter.^{27,28} *N*-Acetylaspartate levels increase dramatically from birth and plateau at 2 to 3 years of age.

Total creatine (3.0 ppm), composed of phosphocreatine and its precursor creatine, are markers for intact brain energy metabolism. The creatine signal has been commonly used as an internal standard for ¹H-magnetic resonance spectroscopy assuming that the creatine-phosphocreatine equilibrium provides a stable concentration of creatine. However, it is

known that creatine concentrations change with age (increasing from birth until 2–3 years of age) as well as with pathologic conditions including traumatic brain injury.²⁹

Total choline (Cho; 3.2 ppm), consisting primarily of phosphoryl and glycerophosphoryl choline is a marker for membrane synthesis or repair, inflammation or demyelination.³⁰ Choline levels are elevated at birth and decrease rapidly with maturation.

Lactate (Lac; 1.33 ppm) accumulates as a result of anaerobic glycolysis and in the setting of traumatic brain injury may be a response to release of glutamate.³¹

Short echo time acquisitions allow for measurement of metabolites with short T2 relaxation times that disappear with long echo time acquisitions. Glutamate and immediately formed glutamine (Glu and Gln; 2.1–2.4 ppm) are excitatory amino acid neurotransmitters released into the extracellular space after brain injury and play a major role in neuronal death.^{31,32} Their overlapping resonances often make it difficult to separate the 2 metabolites so they are often reported together as Glx.

Myoinositol (Ins; 3.56 ppm) is an organic osmolyte located in astrocytes that increases as a result of glial proliferation.³³ Myoinositol also is high at birth and decreases rapidly with brain maturation, leveling off by approximately 2 to 3 years of age.

Acquisition Techniques and Spectral Processing

Several techniques are commonly used to acquire spectroscopic data. Single-voxel spectroscopy (SVS) allows acquisition of a single spectrum from 1 volume element (voxel) typically 8 mL or more, whereas 2- or 3-dimensional magnetic resonance spectroscopic imaging, also called chemical shift imaging, allows simultaneous acquisition of multiple spectra from smaller adjacent voxels through multiple brain sections. Following acquisition, spectral processing identifies metabolites according to their chemical shift resonance, measures the area under each peak corresponding to their concentration and reports the findings as quantitative levels or peak area metabolite ratios such as *N*-acetylaspartate/creatine or choline/creatine. The distribution of metabolite levels or ratios acquired with magnetic resonance spectroscopic imaging displayed as signal intensities are known as metabolite maps or images. Methods to quantitate metabolite levels are used routinely with water as an internal reference³⁴ or phantoms containing known metabolite concentrations to quantify peak areas and report absolute or relative metabolite concentrations rather than ratios.^{35,36}

Metabolite Changes After Traumatic Brain Injury

Although magnetic resonance spectroscopic studies have demonstrated metabolic changes after injury, changes differ depending on several factors, including injury severity, complications after injury, age at injury, and time after injury. As a result, no one spectroscopic pattern is considered “typical” for traumatic brain injury. However, one consistent characteristic reported in magnetic resonance spectra after traumatic brain injury is a reduction of *N*-acetylaspartate and associated ratios (*N*-acetylaspartate/creatine and *N*-acetylaspartate/choline). *N*-Acetylaspartate changes correlate with injury severity in children.^{23,37–40} Reduced *N*-acetylaspartate reflects either neuronal loss from cells beyond

the threshold for recovery or neuronal dysfunction caused by posttraumatic metabolic energy impairment.⁴¹ Severe injury shows a pattern of marked *N*-acetylaspartate reduction reflecting neuronal loss, elevated choline, an indication of cell membrane shearing injury or astrocytosis³³ as well as the presence of lactate, a marker for hypoxic injury and lipids, a marker for cell death.⁴² An example of a severe spectral pattern is shown in Figure 3, taken 2 days after injury from a 13-month-old abused child. Reports of increased lipid signal⁴³ and a higher incidence of lactate^{23,39} in children after nonaccidental traumatic brain injury have been reported compared to accidental traumatic brain injury. This may reflect differences due to age because nonaccidental trauma usually involves younger children or the co-occurrence of hypoxic-ischemic injury. The prognosis of patients with markedly reduced *N*-acetylaspartate and presence of lactate is usually poor regardless of age or type of injury. Spectra from subjects with milder injury showing no structural abnormalities on imaging can also demonstrate abnormalities such as reduced *N*-acetylaspartate^{44–47} or changes in creatine.²⁹ Reduction of *N*-acetylaspartate in acutely and visibly injured brain is likely caused by the primary impact, whereas reduction of *N*-acetylaspartate in normal-appearing brain may reflect diffuse axonal injury or chronic Wallerian degeneration.⁴⁵ More recently, magnetic resonance spectroscopic studies on concussed athletes report altered neuronal function as shown by reduced *N*-acetylaspartate/creatine in frontal white matter up to 15 days postinjury, and longer in subjects who experienced a second concussion.⁴⁸ A reduction of *N*-acetylaspartate and glutamate in the primary motor cortex after sport-related concussion also has been reported.⁴⁹

Several magnetic resonance spectroscopic studies have shown its utility in detecting diffuse axonal injury. Elevated choline detected in white matter may be a breakdown product after shearing of myelin and cellular membranes or astrocytosis, whereas reduced *N*-acetylaspartate likely results from neuronal or axonal injury.^{33,37} Higher choline/creatine ratios have been reported in children with poor long-term outcomes after moderate to severe injury,^{50,51} in patients with subarachnoid hemorrhage⁴⁷ and in individuals with persistent postconcussion headache.⁵²

Quantitation of short echo time magnetic resonance spectroscopy facilitates the measurement of myoinositol and glutamate/glutamine levels. Higher myoinositol levels were found in occipital gray matter of children with poor outcomes after mild to severe traumatic brain injury, attributed to astrogliosis or to a disturbance in osmotic function.⁵³ In addition, glutamate/glutamine from occipital gray matter within 2 weeks of injury was significantly increased in children with traumatic brain injury compared to controls but there was no difference between children with good compared to poor outcomes.⁵⁴ Glutamate/glutamine levels most likely peak early after injury and fall rapidly,⁵⁵ whereas reduction of *N*-acetylaspartate levels may take days to occur.^{42,47} Also, changes in neurometabolites after pediatric traumatic brain injury (particularly *N*-acetylaspartate reductions) correlate with cognitive function.^{19,44,56–59}

Diffusion-Weighted and Diffusion Tensor Imaging

Diffusion-Weighted Imaging

Diffusion-weighted imaging has allowed exploration of the structure and physiology of the brain. Its use in infants and children with neurologic disorders and patients with traumatic brain injury has recently been reviewed.^{60,61} Because diffusion-weighted imaging uses echo-planar imaging technology, imaging times can be shorter than 1 minute.⁶²

Principles of Diffusion-Weighted Imaging

Diffusion represents the random thermal movement of water molecules and is influenced by several variables, including local temperature, molecular nature, and structural architecture of the local tissue environment. Image contrast on diffusion-weighted imaging is related to regional differences in the rate of water diffusion rather than differences in water content. Diffusion is different between gray and white matter, but can also be abnormally restricted, as in the setting of cytotoxic edema, or abnormally increased as in vasogenic edema. Diffusion-weighted imaging has proven to be sensitive to acute infarction due to impaired water diffusion. Similarly, diffusion-weighted imaging can show local pathology from traumatic tissue injury and seems promising in the evaluation of traumatic brain injury. Technical aspects of diffusion-weighted imaging are beyond the scope of this review but have been described by Huisman and by Schaefer and colleagues.^{63,64}

Diffusion-Weighted Imaging and Traumatic Brain Injury

Experimental studies in rodents and piglets and human clinical studies have demonstrated that diffusion-weighted imaging is sensitive in detecting lesions due to traumatic brain injury, although the results are variable. An example of diffusion-weighted imaging in a child with traumatic brain injury and diffuse axonal injury is shown in Figure 4.

Diffusion-weighted imaging can be used to show shearing injuries not visible on spin-echo or fluid-attenuated inversion recovery T2-weighted images but is less sensitive than T2* imaging to detect hemorrhagic lesions.⁶³ In an adult traumatic brain injury study, Hergan and colleagues⁶⁵ previously reported a classification scheme for diffusion-weighted imaging lesions using 3 categories depending on their diffusion-weighted imaging and apparent diffusion coefficient signal characteristics. Type 1 lesions were diffusion-weighted imaging and apparent diffusion coefficient hyperintense, most likely representing lesions with vasogenic edema. Type 2 lesions were diffusion-weighted imaging hyperintense and apparent diffusion coefficient hypointense, likely reflecting cytotoxic edema. Type 3 lesions were central hemorrhagic lesions surrounded by an area of increased diffusion. Lesions also were classified according to their size and extent into 3 groups: group A, focal injury; group B, regional/confluent injury; and group C, extensive/diffuse injury. Another adult traumatic brain injury study, by Huisman and colleagues,⁶⁶ found that the apparent diffusion coefficient values of diffusion-weighted imaging hyperintense lesions were reduced in 64%, elevated in 24%, and normal in 12% of patients. However, these studies did not evaluate time-dependent changes or correlation with outcomes.

Cytotoxic and vasogenic edema have been observed in multiple studies involving experimental and clinical traumatic brain injury although the time course of their evolution may differ.⁶⁵ In addition, associated conditions such as hypoxia/ischemia may worsen development of cytotoxic edema. Restriction of water diffusion associated with cytotoxic edema is likely related to a graded failure of energy metabolism that results in membrane pump failure, leading to a net translocation of water from the extracellular space to the intracellular compartment, where water mobility is relatively restricted.⁶⁵ Cell swelling also results in a reduction of the volume of the extracellular space, and increased tortuosity of the extracellular space is believed to contribute to restricted diffusion.⁶⁷

Some studies have reported that diffusion-weighted imaging identifies the largest number of overall lesions as well as the largest volume of trauma-related signal abnormalities in individuals with diffuse axonal injury compared with conventional MRI sequences that include T2- weighted fast-spin echo, fluid-attenuated inversion recovery and standard T2*-weighted gradient echo sequences⁶⁶; although this was prior to the use of susceptibility-weighted imaging. The total volume of diffusion-weighted imaging signal abnormalities encountered in diffuse axonal injury have been reported to correlate better than other standard imaging variables with the initial Glasgow Coma Scale score and the subacute Rankin score.⁶⁸

Although there is less known about diffusion-weighted imaging in pediatric traumatic brain injury, recent studies have suggested that diffusion-weighted imaging may be a sensitive indicator of traumatic brain injury particularly after nonaccidental trauma. In one study, 89% of children with presumed nonaccidental trauma showed abnormalities on diffusion-weighted imaging and apparent diffusion coefficient maps; and in 81% of the positive cases, diffusion-weighted imaging revealed more extensive injury than conventional MRI or showed injuries when MRI appeared normal.^{69,70} Several studies have now shown that hypoxia and ischemia are common mechanisms of intraparenchymal injury in children with non-accidental trauma and this may be due to reactive vasospasm adjacent to hemorrhagic lesions, strangulation, cervicomedullary injuries, and apnea.^{71,72} All of these mechanisms alone or in combination could cause cerebral ischemic injury manifested by diffusion-weighted imaging changes. Several reports also have demonstrated that diffusion-weighted imaging is more sensitive than conventional MRI and more likely to detect lesions earlier after injury in nonaccidental trauma.^{73,74} These reports also noted large areas of diffusion restriction, supporting the belief that ischemia is a major component of brain injury after nonaccidental trauma, probably more so than diffuse axonal injury.

We previously evaluated the role of diffusion-weighted imaging and apparent diffusion coefficient for outcome prediction after pediatric traumatic brain injury,⁷⁵ using regions of interest manually drawn on apparent diffusion coefficient maps, grouped for analysis into peripheral gray/white matter, deep gray/white matter, and posterior fossa. Apparent diffusion coefficient values in the peripheral white matter were reduced in children with severe traumatic brain injury with poor outcomes compared to those with severe traumatic brain injury and good outcomes. We also found that the average total brain apparent diffusion coefficient value alone had the greatest ability to predict outcome, correctly predicting outcome in 84% of cases. This study showed that assessment of diffusion-

weighted imaging and apparent diffusion coefficient values in pediatric traumatic brain injury was useful in evaluating injury particularly in brain regions that appear normal on conventional imaging.

Diffusion Tensor Imaging

A hallmark of the pathophysiological response to traumatic brain injury is axonal injury; developing over time from focal neurofilament misalignment, impaired axoplasmic transport, focal axonal swelling, and ultimately, axonal disconnection.⁷⁶ In the last 2 decades, diffusion tensor imaging, a technique that measures the magnitude and directionality of water diffusion in tissue, notably of white matter fiber tracts, has been employed in the study of pediatric traumatic brain injury of all severities. Although used primarily as a research tool, mounting evidence suggests that diffusion tensor imaging is a promising approach to assess white matter integrity or microstructural damage, particularly following mild traumatic brain injury and sport-related concussion.⁷⁷

Principles Underlying Diffusion Tensor Imaging

Diffusion-weighted and diffusion tensor imaging incorporate pulsed magnetic field gradients into a standard MRI sequence, resulting in images that are sensitive to the small displacements of water molecules.⁷⁸ Diffusion tensor imaging is a more complex form of diffusion-weighted imaging that makes use of quantitative measures of diffusivity and anisotropy. Diffusion is considered *isotropic* when motion is equal and unconstrained in all directions, such as in the center of a glass of water. However, brain tissue forms physical boundaries that influence diffusion and in white matter tracts, diffusion of water mobility is attenuated across axonal myelin and cellular lipid bilayers and enhanced along the periphery of white matter fiber tracts. This form of diffusion restriction is termed *anisotropic* diffusion.⁷⁹

A diffusion tensor imaging data set includes diffusion-weighted images with the diffusion sensitized in noncollinear directions. A minimum of 6 gradient directions is needed but typically 30 or more directions are collected to increase accuracy. A diffusion tensor matrix is constructed from the collected data and 3 orthogonal eigenvectors are calculated using matrix diagonalization.⁸⁰ The trace (D) of the diffusion tensor is the sum of the scalar values (eigenvalues) of the 3 eigenvectors ($\lambda_1, \lambda_2, \lambda_3$). The largest eigenvalue λ_1 represents diffusivity parallel to the axonal fibers and is referred to as axial diffusivity and the average of λ_2 and λ_3 yield a measure of diffusivity perpendicular to the long axis of the axon referred to as radial diffusivity.⁸¹ As described by Sundgren and colleagues,⁸² diffusivity and anisotropy can be measured in several ways. The mean diffusivity or apparent diffusion coefficient serves for overall diffusivity and is derived from the trace (D) of the diffusion tensor, whereas anisotropy is typically represented by fractional anisotropy and relative anisotropy, or less commonly as a volume ratio. Fractional anisotropy is a measure of the proportion of diffusion anisotropy within a tensor relative to random water motion. The relative anisotropy is derived from a ratio between the anisotropic and isotropic portions of the diffusion tensor. Volume ratio expresses the relation between the diffusion ellipsoid volume and that of a sphere or radius. In fiber tractography or fiber tracking, white-matter tract directions are mapped on the assumption that in each voxel a measure of the local fiber

orientation is obtained using diffusion tensor imaging. Because fiber tractography requires more extensive computer calculations and manpower than diffusion-weighted imaging or diffusion tensor imaging, it remains more of a research tool and so far has limited application.⁸² Technical aspects are beyond the scope of this article and are considered in several key papers.^{77,80,82,83}

Diffusion Tensor Imaging and Traumatic Brain Injury

The pediatric brain is particularly vulnerable to white matter injury owing to differences in brain water content and ongoing myelination.⁸⁴ As diffuse axonal injury most commonly affects white matter, it has been suggested that diffusion tensor imaging could serve as a sensitive marker of white matter injury at both acute and chronic stages. However, there is a considerable amount of discrepancy in the published reports with respect to the direction of fractional anisotropy and diffusivity (apparent diffusion coefficient and/or mean diffusivity) changes (increased or decreased) and is an area of active debate.^{77,85} It is hypothesized that reduced fractional anisotropy and increased apparent diffusion coefficient following traumatic brain injury reflect axonal disconnection or damage to myelin sheaths.^{76,86} Increased fractional anisotropy, which occurs during ongoing myelination, and the presence of reduced apparent diffusion coefficient have been hypothesized to reflect axonal swelling or subtle cytotoxic edema resulting in a reduction of space between axons restricting diffusion in a uniform direction.^{87–89} Numerous factors could contribute to these discrepancies and likely reflect the diversity of the population as related to injury severity, time after injury, differences in injury mechanics (fall, motor vehicle accident, sports-related concussion), location of the injury, and/or differences in the white matter tracts analyzed.⁹⁰

In children and adolescents, early diffusion tensor imaging studies examined moderate-to-severe or mixed populations at chronic time points and reported decreased fractional anisotropy and/or increased apparent diffusion coefficient values in numerous white matter regions including the corpus callosum,^{91–94} inferior and superior frontal and supracallosal white matter,^{81,95} internal capsule, superior longitudinal fasciculus⁹⁶ and orbitofrontal white matter, cingulum bundles, and uncinate fasciculus.^{86,97} Many of these studies also established the value of diffusion tensor imaging as a predictor of long-term neuropsychological outcomes as diffusion tensor imaging changes correlated with cognitive processing, memory, functional (Glasgow Outcome Scale score) and executive function, as well as fine motor and processing speed.^{81,92,94,98–100} An example of diffusion tensor imaging abnormalities following moderate to severe pediatric traumatic brain injury is shown in Figure 4.

More recently, diffusion tensor imaging has been used to study mild traumatic brain injury and sport-related concussion in adolescents at acute and semi-acute time points. In the semi-acute phase following mild traumatic brain injury, Wilde et al reported increased fractional anisotropy and reduced RD in the corpus callosum; changes associated with the severity of post-concussive symptoms.⁸⁷ They also reported an increase in whole brain fractional anisotropy and a reduction in whole brain RD within the first 6 days postinjury that were associated with postconcussive symptoms.¹⁰¹ Similarly, Mayer et al⁸⁸ reported increased fractional anisotropy due to reduced RD, in the corpus callosum and multiple left

hemisphere tracts, with normalization of diffusion tensor imaging in several white matter tracts 3 to 5 months after mild injury. A later study of pediatric mild traumatic brain injury patients by the same group showed increased fractional anisotropy in numerous regions, including the corpus callosum, internal capsule, and anterior and superior corona radiata, with little evidence of recovery over a 4 month period.⁹⁰ In the sport-related concussion population, examples of reported diffusion tensor imaging abnormalities include increased mean diffusivity in several white matter tracts of athletes with symptoms 1 month postinjury¹⁰²; increased fractional anisotropy in the corpus callosum and dorsal regions of corticospinal tracts in varsity-level athletes with concussion injury scanned 1 to 6 months postinjury¹⁰³; increased fractional anisotropy and reduced mean diffusivity in the right corona radiata and inferior longitudinal fasciculus in a cohort of high school athletes,¹⁰⁴ and increased whole brain fractional anisotropy and decreased mean diffusivity in a group of adolescents within 2 months of injury.¹⁰⁵ In contrast, no regional abnormalities in fractional anisotropy, trace, axial diffusivity, or RD were observed in a sport-related concussion group when scanned at 3, 14, or 30 days postinjury.¹⁰⁶

In addition to the inconsistencies in findings between published reports, there is little consensus among studies regarding analysis (region of interest vs whole brain voxel based) methods, which makes comparisons between studies difficult. Although this and other factors pose limitations to the routine clinical use of diffusion tensor imaging at this time, the studies reviewed above suggest emerging patterns over time and injury severity that warrant further study.

Use of Computational Methods in Traumatic Brain Injury Imaging

Increasingly, computational methods are being used to quantify and analyze neuroimaging data. In part, this is because manually derived results from multimodality neuroimaging data often suffer from intra- and interobserver biases, irreproducibility, incomparability, inability to perform complex multimodality fusion, prolonged analysis time, and fatigue-related errors.¹⁰⁷ In contrast, computational methods can provide objective, robust, and efficient processing as well as useful approaches to analyzing and understanding large volumes of neuroimaging data.^{108–110} This is particularly true for analysis of data from diffusion imaging. Computational methods have been used for the analysis of longitudinal maturational diffusion tensor imaging trends in normal pediatric populations,^{111,112} in the development of anatomically correlated imaging atlases¹¹³ or for comparing regional or global normative data to patients with different types of genetic/metabolic disorders or acquired brain injury such as traumatic injury.¹¹⁴

For quantitative comparison of traumatic brain injury patients to controls using diffusion tensor imaging parameters (fractional anisotropy, mean diffusivity, radial diffusivity, axial diffusivity), computation of local statistics from rectangular regions of interest that are manually superimposed on diffusion tensor imaging data can be performed.^{115,116} Large rectangular regions of interest can evaluate small subsets of entire white matter tracts but often lose statistical significance. Manually drawing the entire structure is frequently used but is very time-consuming and suffers from observer bias and irreproducibility.^{91,107} Even automatically extracted regions of interest by aligning diffusion tensor imaging data to

existing age-matched atlases^{88,117} are guided by prior knowledge of the disease and ignore potentially affected structures outside the regions of interest.

Two main methods are now commonly used: (1) voxel-based morphometry analysis or (2) tract-based analysis, also known as tract-based spatial statistics. Voxel-based morphometry allows statistical comparison of multiple points of data within the brain, on a voxel-by-voxel basis. This lends itself well to comparison of subject groups, and can also incorporate atlas-based comparisons to normative data or templates. Tract-based analysis utilizes the anisotropic tensors in diffusion data to create streamlines or “tracts.” Data from each tract can be calculated, such as mean fractional anisotropy values.

Currently, voxel-based analysis methods are used to align 3-dimensional volumes of patient and control diffusion tensor imaging data.¹¹⁸ Standard voxel-based analysis has the potential of exploratory data mining,¹¹⁰ but is severely affected by signal-blurring from intensity normalization and accuracy of different alignment methods, because of the structural variability of individual brains.^{119,120} Semiautomated region-of-interest methods that manually place seed points inside a particular white matter tract, followed by *region-growing* and *boundary following* techniques based on diffusion tensor imaging characteristics of the seed and its neighborhood, also have been reported.¹⁰⁷ Tract-based spatial statistics methods¹²¹ compute the white matter skeleton from fractional anisotropy, summarize the entire white matter information in skeletal voxels, align the skeletons between patients and controls, and simultaneously compares global and local information.^{102,112,122}

Another recent area of diffusion tensor imaging research makes use of analysis of white matter fiber and diffusion directions and tractography to estimate connectivity between different brain regions and the location and density of fiber bundling. These methods can be utilized to detect smaller white matter tract subregions and how they are affected locally and globally by traumatic brain injury.¹²³ Interestingly most of the above computational methods have focused on mild-to-moderate traumatic brain injury and likely would be challenging to perform in individuals with severe traumatic brain injury.

Few studies have attempted fusion of imaging data, for example combining diffusion tensor imaging and magnetic resonance spectroscopy data.¹²⁴ Such methods have enormous potential to better understand disease pathogenesis by evaluating different components of the neurovascular unit and may be more accurate in predicting neurologic outcome.¹¹⁶ Because of the inherent complexity of these various approaches and the explosion of available information, large-scale neuroinformatic systems to share data among groups are being recommended and implemented,¹²⁵ that create petabyte databases to allow collaborative efforts for analysis and web-based queries and content retrieval.^{126,127} Online or downloadable suites of computational frameworks like FreeSurfer,¹²⁸ LONI Pipeline,¹²⁹ FSL,¹³⁰ SPM,¹³¹ and several other application-specific tools¹⁰⁸ are currently freely available for neuroimaging analysis and have tremendously influenced recent traumatic brain injury research. If used correctly, appropriate utilization of computational tools have great potential to facilitate neuroimaging-based traumatic brain injury research.¹³²

Conclusions

We have entered a new era in clinical application of structural neuroimaging techniques to evaluate children with traumatic brain injury. This should provide a better understanding of how the pediatric brain responds to injury across development and also will improve our understanding of the correlation between specific regional injuries and neuropsychological outcomes. Hopefully, this knowledge will translate to developing new treatments to improve outcome and the quality of life for children and adolescents suffering from such devastating injuries.

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Figure 1.

Susceptibility-weighted imaging is extremely sensitive to multifocal hemorrhagic shearing injuries, as illustrated in this 17-year-old girl who was struck by a motorcycle, with an initial Glasgow Coma Scale of 8. Her admission CT (A) was negative, but 2 days later, an MRI showed moderate-sized areas of injury (dashed white arrows) in the left frontal lobe, left thalamus, and left splenium, on T2-weighted imaging (B) and fluid-attenuated inversion recovery (C) images. Small foci of diffusion restriction in the right frontal white matter and splenium, seen on diffusion-weighted imaging (D) are consistent with shearing injuries. However, numerous additional microhemorrhages (small white arrows) are seen throughout the brain on the susceptibility-weighted (E, F) images, including clinically significant hemorrhages in the dorsal midbrain (long white arrow). Her initial course was complicated by posttraumatic seizures and spastic quadriplegia. After 18 months, she has returned to school but with continued cognitive impairment, mild spasticity, and an unsteady gait.

Figure 2.

Susceptibility-weighted imaging (SWI) can be helpful in mild-to-moderate traumatic brain injury, and can show persistent lesions even at 1 year after injury, as illustrated in this 11-year-old boy who was struck by an automobile, with an initial Glasgow Coma Scale of 12. His initial susceptibility-weighted imaging showed more than 100 small lesions, with only a few of the larger ones visible on T2 and fluid-attenuated inversion recovery (FLAIR) images (dashed white arrows). His 12-month IQ, Attention and Memory scores were mildly impaired. His follow-up MRI showed that approximately 60% of susceptibility-weighted imaging lesions had resolved by 1 year, but many others remained (small white arrows).

Figure 3.

Single-voxel magnetic resonance spectrum (stimulated echo acquisition mode [STEAM]; echo time = 20 ms) (A) taken from a 13-month-old healthy child compared to (B) a spectrum taken at 2 days after injury (admission Glasgow Coma Scale score = 3) from a 13-month-old abused child showing markedly reduced *N*-acetylaspartate (NAA) and *N*-acetylaspartate/creatine (Cr) ratio compared to normal, the presence of a large lactate peak consistent with hypoxic-ischemic injury and lipids, a product of cell membrane breakdown. This is an example of a spectrum consistent with severe brain injury and poor prognosis.

Figure 4.

Advanced magnetic resonance imaging (MRI) methods are able to elucidate injuries in different ways and locations, as illustrated in this 12-year-old boy, severely injured in a dirt-bike accident at 40 mph, with an initial Glasgow Coma Scale score of 5. MRI was performed 8 days after injury, on a 3.0-Tesla scanner. Susceptibility-weighted imaging (A) shows numerous tiny hemorrhages throughout the brain (small white arrows), many of which were not visible on computed tomography (CT) or conventional MRI, in addition to larger hemorrhages in the right basal ganglia and ventricles. At the same level of the brain, the apparent diffusion coefficient map from diffusion-weighted imaging (B) shows severely restricted water diffusion suggesting “cytotoxic” changes from cell death in the corpus callosum and right frontal white matter, probably from severe shearing injury. Corresponding color fractional anisotropy map (C) shows accompanying loss of normally symmetric transverse directionality (solid white arrows) of water molecular movement across the corpus callosum (normally red across the genu and splenium). Diffusion tensor imaging tractography (D) depicts the loss of diffusion in the right frontal white matter (dashed white arrow), suggesting impairment or “disruption” of fiber tracts. Multivoxel 3-dimensional magnetic resonance spectroscopy (E) provides information regarding regional metabolite changes and is able to demonstrate additional areas of injury, as highlighted in one (F) of many abnormal voxels within the 3-dimensional volume of tissue studied. Magnetic resonance spectroscopy data also can be displayed using helpful color maps (G) based on the range of metabolite values or ratios, as shown in this color *N*-acetylaspartate (NAA) map, where the lowest values are colored blue and highest values are colored red.