Decreases in FA may be due to lower axial diffusivity that results from alterations in axonal structure or to the increased radial diffusivity that results from differences in myelin, or to some combination of both [3-5]. FA is therefore a nonspecific indicator of changes in white matter composition. In particular, in voxels containing more than one fiber, the FA calculation is inherently inaccurate, and this can lead to misinterpretation of changes.

Unlike routine MR imaging in which white matter tracts are visually indistinguishable, DTI allows the larger individual white matter tracts to be visualized as discreet anatomic structures that can be identified on directionally encoded color maps [6-8]. By definition, white matter tracts oriented left-right are seen as red, those oriented cephalocaudad are seen as blue and those oriented anterior-posterior are seen as green.  

White matter tracts readily visualized by DTI include (Figures 1a and 1b):
• brainstem
• projection
• association
• limbic fibers
• commissural fibers.

Fiber tract reconstruction may be done using probabilistic tractography, which estimates the probability of fiber connections, or the continuous fiber tracking method, which traces pixels within a certain area based on anisotropy.
In clinical practice, tractography that utilizes the FACT (fiber association by continuous tracking method) algorithm is more widely used. Examples of larger white matter tracts as seen by FT in normal children are shown in (Figures 2a to 2e).

Tractography is a mathematical estimation of white matter tracts rather than a precise anatomical depiction and fibers may appear disproportionately large due to higher FA. In addition, transections or thinning of tracts may be caused either by crossing/kissing fibers, or by artifacts in the underlying data, for example, a hemorrhage.

The images derived from diffusion tensor imaging reflect the averaged water diffusion within a pixel and not the actual axonal structures. Examples of the limitations of tractography are seen in the optic pathways where the chiasm is not visible (Figure 3) as two fibers with a crossing trajectory are seen as “kissing” (><) rather than “crossing” (><) [7, 8, 9].

The mathematical tensor calculations are biased by the dominant axonal component; smaller tracts oriented obliquely or even perpendicular to large white matter projections may be missed by DTI. The minimum spatial voxel resolution in DTI data provided by current MR technology is in the order of a millimeter or more [8, 9].

In order to reconstruct multiple crossing fiber orientations within regions of complex white matter architecture, dozens or even hundreds of uniformly distributed diffusion directions in 3D space must be acquired to resolve intra voxel fibers orientated in different directions. At present, these large data sets are cumbersome to
include development of axolemmal membranes and early wrapping of axons by oligodendroglial processes with increases in fiber diameter and cell packing density [10, 11]. The net result of these macromolecular changes is impedance of physiologic movement of water perpendicular to the axon and accelerated diffusion parallel to the axons.

During normal early childhood, FA within white matter increases because of either disproportionate decreases in the three eigenvalues, or increases in axial diffusivity along with decreases in radial diffusivity [10, 11]. Age-related increases in FA are most pronounced during the first two years of life and continue to lesser degrees in regions of the brain involved in cognition and higher-order functioning [11, 12]. Different white matter tracts mature at different rates and the fronto-temporal white matter appears to develop more slowly than other regions.

As cerebral white matter matures, changes are visible on the anisotropy maps as well as directionally encoded color maps. Examples of anisotropy and color maps for infants and children of increasing ages are shown in (Figures 4a and 4b; compare with Figure 1b). Certain white matter tracts are identifiable on the color maps at in very young children, although the white matter tracts are thinner and have lower anisotropy than in older children.

These tracts include the internal capsules, corpus callosum, fornix and cingulum, inferior fronto-occipital and inferior longitudinal fasciculus. At birth, the anisotropy of peripheral white matter is close to that of cortex; by three months the anisotropy of the U-fibers has matured sufficiently that subcortical white matter is identifiable on the color maps.

The most accurate and precise means of quantifying the diffusion tensor data, which is most often the FA, is controversial. Different methodologies include voxel-based analysis, tractography, region of interest (ROI) analysis, and tract-based spatial statistics (TBSS) [9, 13, 14]. TBSS is an automated observer-independent method of aligning fractional anisotropy images from multiple subjects to allow group wise comparisons of DTI data [13].

Voxel-based morphometry is observer independent and allows whole brain comparison of groups of subject [14]. However, the image data must be spatially normalized and smoothed, which can blur differences between subjects or groups. Tractography takes bulk-averaged tissue properties in each voxel and through
mathematical modeling infers the dominant fiber orientation within each voxel [9].

Problems using tractography include insensitivity to crossing fibers, limited spatial resolution during image acquisition, and the inherent mathematical uncertainty [1, 2, 9]. ROI analysis is tedious, subject to sampling error, imprecise, and insensitive to changes occurring outside the region of interest but manual measures may show additional important variances.

FA decreases in most disease states that affect white matter; changes in FA values are therefore not specific for any disease entity. Alterations in white matter anisotropy are nonetheless being studied in many conditions some of which are unique to children [16, 17, 18].

**Applications of DTI in acquired white matter diseases**

DTI has potential application in children with strokes, brain tumors, trauma, and metabolic and storage disorders. In the acute setting, DTI usually lacks the sensitivity to restrict diffusion of diffusion-weighted imaging and it is therefore not used as a diagnostic tool. In hyper acute strokes in neonates, the acutely infarcted brain may show increased anisotropy rather than lower FA in addition to restricted diffusion (Figure 5).

In the subacute setting, DTI may show loss of integrity of the regional projection and association fibers that may be more extensive than the actual infarCTION as well as early Wallerian degeneration. Before the age of five years, the pediatric brain retains a sufficient degree of plasticity. Considerable function may be regained after a stroke; significantly more than is usually seen after a cerebrovascular accident occurs in an adult.

In combination with functional MR imaging which can be used to identify secondary somatosensory cortex recruited after a stroke, DTI may provide insight as to how the regional white matter “rewires” to connect the uninjured brain. Children with closed head injury are being studied using fMRI and DTI to evaluate the severity of injury, the implications for cognitive performance, and brain plasticity.

An important potential application of DTI is in children with tumors in whom operative morbidity may be lessened by the avoidance of intact white matter tracts, especially in deep hemispheric and brainstem tumors (Figure 6a and 6b) [20]. DTI has limited application in
extra-axial tumors and those arising from within the ventricles, as tumors in these locations as a rule, do not affect the regional white matter.

**Application of DTI to congenital brain malformations**

DTI can be used in the study of congenital brain malformations associated with abnormalities of larger white matter tracts. There are scattered reports of cerebral malformations studied with DTI including callosal agenesis, cortical dysplasia, holoprosencephaly, lissencephaly, and the Chiari II malformation [20-23] (Figures 7 to 13). DTI and FT may provide detail of white matter tracts not possible with pathologic dissection as dissection by its nature disrupts fibers and cannot distinguish adjacent white matter tracts.

**Callosal agenesis/dysgenesis**

Congenital anomalies of the corpus callosum include complete agenesis, partial agenesis with preservation of the rostral corpus callosum, and variable dysgenesis ranging from hypoplasia to gross thickening. In callosal agenesis, the bundles of Probst when present are seen as longitudinally oriented fibers coursing along the medial wall of the lateral ventricles (Figure 7a) [20]. The fornices are dysplastic, often deficient, and widely separated; the Probst bundles are fused with the rudimentary cingulum and the dysplastic fornices (Figure 7b).

In partial callosal agenesis, the preserved callosal fibers may appear by fiber tractography to connect both neocortex and archicortex (Figures 8a and 8b) suggesting disordered axonal migration. DTI also suggests that in some patients, gross thickening of a dysplastic corpus callosum may be due to anomalous course of supracallosal fibers (Figures 9a and 9b).

**Cortical dysplasia**

Areas of cortical dysplasia (Figures 10a and 10b) may be difficult to identify by DTI given the relatively poor spatial resolution of DTI, and the low fractional anisotropy of subcortical white matter even in the fully myelinated brain. Identification of cortical dysplasia using DTI is even more problematic in the brain of the infant and young child in whom myelination of peripheral white matter is incomplete.

In the fully myelinated brain, DTI may show areas of reduced anisotropy and increased diffusivity within the region of dysplastic brain. Some patients also have abnormalities of diffusion metrics in cerebral parenchyma that appears normal on conventional T1-
T2-weighted images. Performing a voxel-by-voxel comparison of brains with cortical dysplasia to those of normal controls requires normalization of all brains into a common space in order to minimize the overall variability in size and shape between brains. As in functional MR imaging, the brains are normalized to Talairach space using one of many software programs available in the public and private domain.

**Holoprosencephaly**

Holoprosencephaly is a complex malformation of the brain and face characterized with respect to the degree of formation of the ventricular system as alobar, semilobar, lobar, or of the middle-hemisphere variant. Holoprosencephaly is due to failure of induction or abnormal fusion of normally paired and separate neocortex, caudates, and claustrum [21].
In an example of semilobar holoprosencephaly, tractography (Figure 11) shows large white matter tracts within the cerebrum not apparent on routine MR imaging. With large symmetric fiber bundles having the expected course of the frontooccipital fasciculus connected across the midline in the subfrontal region and dysplastic fornix-like structures embedded in the basal ganglia (Figures 11a and 11b) [21]. As seen by DTI, hypoplasia of the middle cerebellar peduncles correlates with the severity of frontal lobe underdevelopment and increasing severity of the prosencephalic malformation.

**Lissencephaly**

Lissencephaly is an uncommon cerebral malformation characterized by thickened and undersulcated cortex and layers of gray matter embedded within deep white matter. The cerebral cortex is normally composed of six horizontal cell layers while the lissencephalic cortex has four cell layers. The two most superficial layers of cortex in the lissencephalic brain are formed by the neurons that migrated normally early in gestation, while the deeper layers are composed of neurons in migratory arrest.

The third cell layer contains astrocytes, oligodendroglial cells, and dysplastic neurons, and the thickest, densely cellular fourth layer shows radial orientation, limited cellular differentiation, and no lamination. DTI in lissencephaly shows peripheral subcortical brush-like fibers corresponding to the densely cellular fourth layer. The parallel organization of glial fibers in the cerebral cortex that normally involutes when intra-cortical connectivity is established later in gestation in the normal brain persists in lissencephaly. (Figures 12a and 12b) [22]. As in many other severe cerebral malformations, the limbic system in lissencephaly is dysplastic.
hindbrain abnormalities [24]. There are reports of diffusion tensor abnormalities of brainstem tracts in patients with Joubert syndrome. The variability of DTI abnormalities may parallel the severity of the malformation and ranges from normal to absence of the transverse pontine fibers such that the corticospinal tracts and medial lemniscus are juxtaposed (Figures 15a and 15b).

By DTI, the fibers of the superior cerebellar peduncles did not decussate in the mesencephalon and the corticospinal tracts do not cross in the caudal medulla

Brainstem abnormalities may be identifiable in patients with the Chiari II malformation and appear to be related to the extent of brainstem and cerebellar hypoplasia. More severe cerebellar hypoplasia seems to be associated with hypoplasia of the transverse pontine fibers while the medial lemniscus and corticospinal tracts are preserved (Figures 14a and 14b). The superior and inferior cerebellar peduncles are often underdeveloped.

**Chiari II malformation**

The Chiari II malformation is a relatively common CNS malformation almost invariably associated with a myelomeningocele [22]. The hallmark of the Chiari II malformation is a constricted posterior fossa, wide foramen magnum, and variable caudal displacement of dysplastic brainstem and cerebellar vermis into the upper cervical canal [23]. DTI suggests some patients with the Chiari II malformation have dysplastic supracallosal fibers (Figures 13a and 13b).

**Joubert syndrome**

Joubert syndrome was initially described as a clinical diagnosis; the “molar tooth sign” is the radiologic hallmark of Joubert syndrome although there is considerable variability in the hindbrain abnormalities [24]. There are reports of diffusion tensor abnormalities of brainstem tracts in patients with Joubert syndrome. The variability of DTI abnormalities may parallel the severity of the malformation and ranges from normal to absence of the transverse pontine fibers such that the corticospinal tracts and medial lemniscus are juxtaposed (Figures 15a and 15b).

By DTI, the fibers of the superior cerebellar peduncles did not decussate in the mesencephalon and the corticospinal tracts do not cross in the caudal medulla

**Conclusion**

In conclusion, DTI has numerous potential applications in the pediatric brain both in the normal and disease states. Further technical refinements are needed to improve the spatial resolution of diffusion tensor imaging, in addition to increasing the sensitivity of DTI to crossing fibers without making DTI too time-consuming for clinical use.
References


