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Diffusion Tensor Imaging: Application to the Study of the Developing Brain

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Abstract

Objective: To provide an overview of diffusion tensor imaging (DTI) and its application to the study of white matter in the developing brain, in both healthy and clinical samples. **Method**: The development of DTI and its application to brain imaging of white matter tracts is discussed. 48 studies using DTI to examine diffusion properties of the developing brain are reviewed in the context of the structural magnetic resonance imaging (MRI) literature. Reports of how brain diffusion properties are affected in pediatric clinical samples and how they relate to cognitive and behavioral phenotypes are reviewed. **Results**: DTI has been successfully used to describe white matter development in pediatric samples. Changes in white matter diffusion properties are consistent across studies, with anisotropy increasing and overall diffusion decreasing with age. Diffusion measures in relevant white matter regions correlate with behavioral measures in healthy children and in clinical pediatric samples. **Conclusions**: DTI is an important tool for providing a more detailed picture of developing white matter than can be obtained with conventional MRI alone. **Keywords**: brain, development, white matter, diffusion tensor imaging, magnetic resonance imaging.

Introduction

Since the early 1990's, magnetic resonance imaging (MRI) has been used to characterize brain structure throughout development. Capitalizing on differences in contrast between tissue types, MRI produces exquisite images in which gray matter, white matter, and cerebrospinal fluid (CSF) are cast into sharp relief. These images have been used to quantify the size and describe the shape of whole brain, substructures and cortical areas in humans throughout the developmental lifespan, from premature neonates to elderly adults.

Considerable information about the gross anatomy of the human brain throughout development has been garnered from MRI. Changes in tissue volume, gyri and sulci development, and time courses of the maturation of cortical lobes and subcortical structures have been described (for reviews, see Casey et al., 2000; Durston et al., 2001; Inder and Huppi, 2000). In contrast to gray matter, white matter volume appears to continue to increase throughout childhood and adolescence (Durston et al., 2001; Giedd et al., 1999). However, the relationships between these gross anatomical changes and the changes in behavior and cognition that they are thought to underlie have been difficult to define clearly. In addition, during the first year of life, the contrast of traditional MRI is unable to accurately differentiate the still-myelinating white matter from surrounding gray matter (Paus et al., 2001). The focus of this review is diffusion tensor imaging (DTI), an emerging technique that complements traditional MRI and is able to provide some of this additional information about the developing brain. Built on early work by LeBihan et al. (1985), and extended by Basser and colleagues (1994), DTI is a nascent

application of MRI that has the potential to contribute a much richer understanding of brain white matter structure than conventional MRI alone.

DTI methods

Methods and terminology

DTI relies on modified MRI scanning techniques which render a sensitivity to microscopic, three-dimensional water motion within the tissue. In CSF, this water motion is *isotropic*. This means that the diffusion is roughly equivalent in all directions; i.e. water diffuses freely. In white matter, however, tissue water diffuses in a highly directional, or *anisotropic*, manner (Figure 1). Because of the structure and insulation characteristic of myelinated fiber bundles, water in these bundles is largely restricted to diffusion along the axis of the bundle. DTI can thus be utilized to identify and characterize these white matter pathways, and thereby to inform researchers about properties of connecting pathways in the brain. These pathways are the substrate for functional neural networks: information travels along these pathways from one brain area to another. The ability to measure the integrity of these "information highways" using DTI is an important breakthrough because it provides a link between anatomical and functional neuroimaging.

<figure 1 about here>

Diffusion properties

In general, diffusion tensor data are used to calculate two basic properties: 1) the overall amount of diffusion, and 2) the anisotropy (directionality) of diffusion. Once acquired, MRI images are reconstructed into three-dimensional grids composed of small, box-

shaped units called voxels. The properties of overall diffusion and anisotropy are calculated at each voxel, and can be mapped to illustrate the differences in diffusion in each tissue type (Figure 2). High levels of overall diffusion are characteristic of ventricles, in which CSF flows freely. If high diffusion levels occur in white matter, it is indicative of poorly developed, immature, or structurally compromised white matter. High levels of anisotropy are considered a reflection of very coherently bundled, myelinated fibers oriented along the axis of the greatest diffusion. Local values for diffusion or anisotropy can be computed using a small region of interest (ROI), and brain regions compared by contrasting values in two or more ROIs. In clinical studies, differences between two clinical groups can be calculated by coregistering the images into the same coordinate system, and performing individual t-tests at each voxel, producing a map that displays all voxels for which the groups differ significantly in anisotropy or diffusion. Further detail on how diffusion and anisotropy are calculated and extracted from DTI data is beyond the scope of this review, but we refer interested readers to two excellent reviews by LeBihan et al. (2001) and Taylor et al. (2004).

<figure 2 about here>

DTI applications: Three-dimensional representations of fiber pathways

Anisotropy maps such as Figure 2b are often analyzed by measuring values within a predetermined ROI, giving considerable information about local white matter microstructure, but failing to provide a global representation of white matter tracts. Two methods of visualizing three-dimensional white matter fiber pathways offer a more

complete three-dimensional neuroanatomical picture than anisotropy or diffusion maps alone. The first utilizes color to illustrate anisotropy, with diffusion direction in three-dimensional space represented by hue and the magnitude of the anisotropy represented by the intensity of the color (Figure 3a). The second, known as tractography, computes probable trajectories of white matter fibers between brain regions. This application involves calculation of streamlines between two user-defined brain regions: a "source" and a "target" ROI. The streamlines are calculated through the vector field of largest eigenvectors (the elements of the matrix that define diffusion in three-dimensional space) or through the tensor field itself. These streamlines are then displayed as tube-like "fibers". The result is a virtual representation of fiber tracts (Figure 3b-c), but it is important to note that these are not axons but a local measurement of diffusion properties at the voxel scale. These types of images offer the advantage of a more intuitive representation of white matter than the anisotropy and diffusion maps, but have the disadvantage of being difficult to evaluate quantitatively. This technique also poses difficulty in regions where anisotropy values give ambiguous information, such as regions where two or more tracts intersect, or near terminal regions where tracts splay out to reach their targets.

While not without limitations, tractography has been used to advance our knowledge about white matter neuroanatomy, and has been used to create virtual atlases of fiber tracts in the adult brain (Catani et al, 2002; Wakana et al., 2004). In addition, tractography has the potential to verify and enhance our understanding of the functional anatomy of brain structures. For example, recent studies have produced connectivity-

based subdivisions of the thalamus (Behrens et al., 2003), corpus callosum (Cascio et al., in press), and medial frontal cortex (Johansen-Berg et al., 2004).

<figure 3 about here>

DTI applications: pediatric studies

Because it is a variant of conventional MRI, DTI is safe, noninvasive, and does not require the degree of subject cooperation that functional MRI (fMRI) does. Thus, it can be used to study a variety of populations, including clinical and pediatric populations. In addition, it does not suffer from the same limitations as conventional MRI for differentiating between white and gray matter in the very young brain. Although a relatively new technique, DTI has already been vigorously applied to the study of white matter development in childhood and adolescence. The purpose of this review is to provide an overview of DTI with specific attention to its application to imaging both normal and aberrant white matter development in the developing brain. To the best of our knowledge, these findings have not been comprehensively reviewed elsewhere. We begin with an overview of what has been learned about white matter development through DTI studies of healthy pediatric samples, and then go on to explore how DTI has informed our understanding of white matter properties in clinical pediatric samples. 48 studies are reviewed; all of which are listed in Table 1. Studies were located using the National Center for Biotechnology Information (NCBI) PubMed database with search terms of "diffusion tensor imaging," "DTI," "pediatric," "children," and "tractography." Inclusion criteria were 1) studies published in peer-reviewed journals, 2) studies that used a reasonably well-established application of DTI (regional analysis of diffusion properties

or tractography), and 3) developmentally-oriented studies whose samples included children and/or adolescents. Although a variety of methodologies, design, and approaches to sample selection were used, it is beyond the scope of this paper to provide a critical review of each study. The challenges and limitations of DTI, as well as advanced applications of the technique, are discussed in the context of their applicability to pediatric studies.

DTI studies

Developmental perspective

In 1991, Sakuma and colleagues reported that white matter anisotropy increases with age in a sample ranging from preterm infants to adults. This finding was supported by subsequent demonstrations that anisotropy increases (and overall diffusion decreases) with gestational age in preterm infants (Huppi et al., 1998; Huppi et al., 2001), and that anisotropy is lower and overall diffusion higher in preterm infants than in full term infants (Counsell et al, 2003). Comparing DTI findings with predictions from a theoretical model, Mukherjee and colleagues (2002) demonstrated that these observations at major white matter sites are consistent with decreased water content and increased myelination with age. DTI has also been successfully used in very premature infants to distinguish early patterns of laminar organization in the cerebrum (Maas et al., 2004).

In healthy, full-term neonates, Nomura and colleagues (1994) reported increasing anisotropy, but only up to six months of age. A subsequent study of neonates by Neil et al. (1998) reported a strong negative correlation between overall diffusion and age for a

variety of brain regions, which was corroborated by Forbes and colleagues (2002) for infants up to one year of age. This study made a significant contribution by describing regional differences in the rates of diffusion decreases throughout the first year. Other infant studies have described increased anisotropy with age in specific white matter structures (Boujraf et al., 2002; Gilmore et al., 2004; McGraw et al., 2002). Many have reported strong positive correlations between anisotropy measures in major white matter tracts and age throughout childhood and into adolescence (Barnea-Goraly et al., 2005; Ben Bashat et al., 2005; Mukherjee et al., 2001; Schmithorst et al., 2002; Snook et al., 2005). Likewise, studies focused on older children demonstrate a negative correlation between overall diffusion and age (Mukherjee et al., 2001; Schmithorst et al., 2002; Snook et al., 2005; Zhang et al., 2005). Mukherjee and colleagues measured a very large sample of children, and was able to demonstrate regional differences in the rate of change of diffusion. Although there is some question as to how diffusion properties behave across the entire lifespan (Salat et al., 2005), the literature is remarkably consistent in affirming both the increase of anisotropy and decrease of overall diffusion in white matter structures with increasing age during childhood and adolescence. This provides support for the assumption that increased anisotropy and decreased diffusion are representative of more mature white matter bundles. This maturity is likely the result of a combination of ongoing myelination and axonal pruning that act in concert during development to reduce unrestricted water content in extra-axonal space (Suzuki et al., 2003). These changes increase the efficiency of neuronal communication and provide a substrate for healthy cognitive and behavioral development.

Although there is a clear consensus that anisotropy increases and diffusion decreases with age, there are conflicting data as to what trajectory those changes follow during development. At what time in development do diffusion properties change most dramatically? Do they continue to change into adulthood? While Nomura's early study (1994) found few differences between their child and adult groups, and concluded based on their sample that diffusion properties stabilize by 6 months, Zhang et al. (2005) noted that water diffusion continues to change dramatically throughout the first 2 years of life. A study using a fast DTI sequence on a large sample that ranged from neonates to adolescents described the trajectory of change in diffusion and anisotropy in various white matter structures (Schneider et al., 2004). Their description is consistent with that of Zhang and colleagues, showing the most dramatic changes within the first 24 months of development, and subtle changes beyond that for most white matter areas. However, both Klingberg et al. (1999) and Snook et al. (2005) noted significantly lower regional white matter anisotropy in children compared with adults. An interesting validation of DTI as generating data that are consistent with what is already known about the developmental rate of various white matter tracts was provided in a sample of preterm infants by Partridge et al. (2004). An important step in advancing the clinical utility of DTI for pediatric populations is to establish normative standards, which was the goal of Hermoye and colleagues (2006), in their characterization of DTI data on 30 children. Their study describes three phases of anisotropy evolution, marked by rapid changes in the first 12 months of development, slow changes during the second year, and relative stability after age two. This is consistent with previous studies (Schneider et al., 2004; Zhang et al., 2005).

Cognitive and behavioral correlates of DTI

How are diffusion measures related to behavior and cognitive ability? Two studies have addressed cognitive correlates of diffusion measures in healthy children. Nagy et al. (2004) found that anisotropy in the temporal lobe increased with working memory capacity, while anisotropy in the frontal lobe increased specifically with language ability in children. The following year, Schmithorst and colleagues (2005) reported that anisotropy in frontal and occipitoparietal association areas were related to full-scale IQ in a sample of school-age children and adolescents. Three studies investigated temporoparietal white matter in children with a range of reading abilities (Beaulieu et al., 2005; Deutsch et al., 2005; Niogi and McCandliss, 2006). All found significant positive correlations between anisotropy in temporoparietal white matter and scores on tests of reading ability. The relationship between white matter anisotropy and behavioral ability suggests that one should expect changes in white matter properties in pediatric populations for which cognitive, motor, or other abilities are compromised. It is studies of this nature that we review in the next section.

Studies of pediatric psychopathology

Several studies have investigated white matter integrity using DTI in samples of children with disorders that are characterized or accompanied by a delay in development. In 2003, Nagy and colleagues demonstrated that a group of 11 year-olds with attention deficit associated with preterm birth had lower anisotropy values in the posterior corpus callosum and internal capsule; a study of ADHD children by Ashtari et al. (2005) found

decreased anisotropy in a variety of white matter regions, including several white matter tracts in the motor system. A study of children with generalized developmental delay by Fillipi (2003) and colleagues revealed significantly higher diffusion and lower anisotropy in the corona radiata, corpus callosum, and frontal and parieto-occipital subcortical white matter. Also associated with developmental delay, autism and Fragile X syndrome were the subjects of preliminary studies by Barnea-Goraly and colleagues (2003a, 2004). In autism, reduced anisotropy was seen ubiquitously in cortical white matter as well as in the corpus callosum. In Fragile X, low anisotropy was more limited to frontal-striatal white matter, and parietal sensory tracts. This is consistent with much of the psychopathology of the disorder, particularly motor stereotypies and sensory defensiveness. Another study by this group (Barnea-Goraly et al., 2003b) demonstrated reduced anisotropy in the parietal, frontal and temporal lobes of children with velocardiofacial syndrome (VCFS), a disorder that affects cognition, particularly arithmetic and visuospatial reasoning. In 22q11.2 deletion syndrome, which encompasses VCFS, Simon and colleagues (2005) used DTI in combination with voxel-based morphometry to reveal posterior displacement of the corpus callosum.

Studies of pediatric neuropathology

Tuberous sclerosis (TS) is a disease that affects white matter and is also associated with developmental delay. Lesioned areas in the affected white matter of TS patients have higher ADC and lower anisotropy than contralateral, unaffected white matter within patients, as well as compared to controls (Karadag et al., 2005; Peng et al., 2004). Type 1 neurofibromatosis (NF-1) also affects white matter and can result in cognitive challenges

or learning disorders. Children with NF-1 exhibit higher overall diffusion in white matter, both at the sites of lesions and in white matter that appears unaffected by the disease (Eastwood et al., 2001). Another disease that affects white matter, X-linked adrenoleukodystrophy (X-ALD), was approached with DTI by Eichler et al. (2002). In their sample of adolescents with X-ALD, anisotropy was found to be positively correlated (and overall diffusion negatively correlated) with levels of N-aceytl aspartate, a neuronal marker present in axons, as measured by MR spectroscopy.

Tractography studies

As mentioned above, while tractography provides an excellent qualitative representation of white matter fibers, there is a limited amount of quantitative information available from this application of the technique. Hoon et al. (2002) used tractography in 2 children with periventricular leukomalacia, a disorder that includes deep white matter injury, most likely resulting from perinatal insults. The authors observed a reduced density of fibers in the posterior corpus callosum, internal capsule, and corona radiata in patients qualitatively compared with controls. Current research is underway to determine how best to analyze these fiber representations in a more quantitative manner (Corouge et al., 2004, 2005), and research groups are beginning to apply quantitative analysis to the fiber tracts derived from tractography (Berman et al., 2005). The most informative approach currently is to measure anisotropy values within the fiber tracts themselves. This method was also used in a clinical study by Glenn and colleagues (2003), who measured anisotropy and other diffusion parameters in the pyramidal tracts of children with congenital hemiparesis and compared them to controls. Mori et al. (2002) also compared

anisotropy values within traced white matter bundles in an adolescent boy with X-ALD. Both studies demonstrated reduced anisotropy within white matter tracts in the patient populations. In a similar approach, Beaulieu et al. (2005) identified clusters of temporoparietal white matter whose anisotropy values increased with reading ability, then used tractography overlaid on these clusters to specify which white matter tracts were most important for reading.

Advantages of DTI as a supplement to conventional MRI in pediatric imaging

Diffusion tensor imaging gives a deeper understanding of white matter than conventional MRI alone. While conventional MRI is able to yield information on gray and white matter volume and macrostructure, DTI gives an indication of the microstructure of white matter. This microstructural information provides information about the integrity of the axonal fibers, the coherence with which they are bundled, and thus a closer look at their ability to function as efficient pathways for neural information. The measurement of diffusion offers important insights into the connectivity of the brain. Like conventional MRI, DTI is noninvasive and thus is relatively easily used in pediatric samples, allowing a better characterization of how white matter develops in childhood and adolescence.

Relevance to behavior and cognition

Studies that combined DTI with one or more behavioral or cognitive measures were particularly useful in elucidating the relationships between the integrity of white matter pathways and the development of behaviors they are thought to subserve. For example, Nagy and colleagues correlated anisotropy in the white matter of the left frontal and

temporal lobes with working memory and language abilities. This kind of approach helps to validate the functional relevance of anisotropy measures by confirming that they are associated with behavior in brain regions that are consistent with established findings in neuropsychological, electrophysiological, and functional MRI studies. A similar correlation was also demonstrated by Beaulieu et al. (2005) Deutsch et al., (2005), and Niogi and McCandliss (2006) between reading ability and temporo-parietal white matter.

DTI provides an important complement to functional magnetic resonance imaging (fMRI). fMRI reveals gray matter areas that are metabolically active during performance of a particular behavior or cognitive task. One criticism of this technique is that it can be considered "modern-day phrenology," assigning functional roles to parcels of brain tissue with a limited view of the brain's powerful capacity to function as an interactive network, integrating information across several anatomical sites to produce behavior. The combination of fMRI and DTI will provide important insights into these types of neurobehavioral networks by simultaneously revealing active gray matter areas and the white matter pathways that connect them. This has already been done in adults (Heller et al., 2005; Shinoura et al., 2005). As behavioral training techniques make it increasingly possible to use fMRI to study children (Chappell et al., 2005; Slifer et al., 2002), this two-pronged approach can be used to study how such neurobehavioral networks develop.

Application to clinical pediatric samples

DTI can help to provide a better understanding of pediatric neurological and psychiatric syndromes for which neural tissue, particularly white matter, is affected. Although our

review of clinical pediatric studies above was limited to populations for which cognitive impairment or developmental delay is a hallmark, there are also several studies of neurological syndromes in which white matter development is known to be abnormal. The authors of many of these pediatric studies remarked that DTI revealed differences that were not visible by conventional T1/T2 imaging alone (Engelbrecht et al., 2002; Guo et al., 2001; Khong et al., 2003; Lee et al., 2003; Schneider et al., 2003). Importantly, Guo et al. (2001) noted that DTI revealed differences between treated and non-treated subsets of their clinical group, which has exciting implications for the possibility of using DTI to monitor the brain's response to treatment in both clinical and research settings. This possible application of DTI was also brought out by Als et al. (2004) who used DTI to demonstrate developmental changes in premature neonates in response to a therapeutic intervention program.

In the clinical studies reviewed above, regional differences in white matter anisotropy reflected the relationships between the behavioral and/or cognitive symptoms and the affected areas. For example, in Barnea-Goraly and colleagues' study of children with Fragile X syndrome (2003a), the frontrostriatal and parietal sensory-motor tracts were the regions of greatest anisotropy difference, reflecting the repetitive behaviors and unusual responses to sensory stimuli characteristic of Fragile X. This demonstrates the important role of DTI in solidifying and expanding our understanding of central pathways and their relationship to behavior in both typical and atypical development. In both neurological and psychiatric pediatric disorders, future clinical studies could be improved by

describing the relationship of DTI measures to the severity of behavioral, cognitive or motor symptoms.

Limitations

Like other neuroimaging techniques, DTI is limited by its dependence on the ability of the subject to remain still in the scanner. For clinical studies, this problem can sometimes be circumvented with sedation, but often, acquiring images free from motion artifact remains a challenge, especially in children. One helpful advance in DTI is the development of faster sequences that minimize scan time. One such sequence was employed by Schneider et al. (2004), allowing them to successfully scan a large number of children for their study.

Another limitation of DTI is its susceptibility to artifact. Diffusion images are particularly vulnerable to magnetic susceptibility artifact (Basser and Jones, 2002) and can be noisy and of poor resolution relative to structural MRI images. These limitations are dealt with by acquiring multiple copies of each image, which allows elimination of images which have too much artifact to provide useful data, and improves signal to noise ratio.

Conclusions

In conclusion, this review has reported that DTI can be successfully used to describe white matter development in pediatric samples. White matter tends to increase in anisotropy and decrease in overall diffusion, with age. While these developmental trends

are extraordinarily consistent across all studies that we reviewed, the trajectory of these changes in anisotropy and diffusion in healthy children has yet to be clearly elucidated. Diffusion measures in relevant white matter regions of interest correlate with behavioral measures, including cognitive and motor abilities, both in healthy children and in clinical pediatric samples. This helps to validate DTI and to support previous studies describing relationships between neural networks and behavior. Emerging applications of DTI to pediatric neuroimaging include further integration with behavioral and functional neuroimaging techniques, and the development of quantitative analysis methods for tractography.

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Table 1a. DTI studies of general development, including development of behavior and cognition

Study	(Age) Sample description (n)	General summary of findings
Als et al., 2004	(GA 28-33 wks) preterm infants (30)	↑ anisotropy in internal capsule in group receiving a developmental care program
Barnea-Goraly et al., 2005	(6-19y) healthy (34)	↑ anisotropy with age in various cortical and subcortical areas
Beaulieu et al., 2005	(8-13y) diverse reading ability (32)	Positive correlation of temporoparietal WM anisotropy and reading ability
Ben Bashat et al., 2005	(4 m-23y) healthy (36)	Compared diffusion imaging techniques to detect developmental changes
Berman et al., 2005	(GA 28-43 wks) preterm neonates (27)	Used tractography and examined diffusion properties within sensory and motor tracts; significant correlation with age
Boujraf et al., 2002	(2 days-1y) healthy (22)	Diffusion properties in early development support relationship between WM maturity and anisotropy
Counsell et al., 2003	(GA 25-34 wks) preterm infants (50)	Used diffusion weighted imaging and found higher diffusion values in infants with WM pathology
Deutsch et al., 2005	(7-13y) diverse reading ability (14)	Anisotropy in left temporoparietal WM correlated with reading ability
Forbes et al., 2002	(birth-1y) healthy (40)	↓diffusion with age, different rates depending on region
Gilmore et al., 2004	(neonates) healthy (20)	↑ anisotropy with GA in genu and splenium of corpus callosum
Hermoye et al., 2006	(0-54 mo) healthy brains (30)	3 phases of anisotropy change, rapid in 1st yr, slow in 2nd
Huppi et al., 1998	(GA 25-42 wks) preterm/term neonates (24)	↓ diffusion and ↑ anisotropy toward term in central WM
Klingberg et al., 1999	(8-12y; 20-31y) healthy (12)	↓ anisotropy in frontal WM in children compared to adults
Maas et al., 2004	(GA 25-27 wks) preterm (2)	Used diffusion properties to distinguish early cerebral laminar organization
McGraw et al., 2002	(4 days- 6y) healthy (66)	↑ anisotropy with age, and with ↑ compactness of WM
Mukherjee et al., 2001	(1 day-11y) healthy (153)	Exponential ↓ of diffusion with age, both linear and nonlinear ↑ of anisotropy, depending on region
Mukherjee et al., 2002	(GA 31wks-11y) preterm neonates & healthy (167)	Compared diffusion data to that generated by a theoretical model based on brain water content and myelination.
Nagy et al., 2004	(8-18y) healthy (23)	Correlation of regional anisotropy with cognitive abilities
Neil et al., 1998	(neonates) healthy (22)	↑ diffusion and ↓ anisotropy in neonates compared to adults; diffusion ↓ and anisotropy ↑ with gestational age
Niogi & McCandliss, 2006	(6.5-10.3y) diverse reading ability (31)	Correlation of L temporoparietal anisotropy with reading scores
Nomura et al., 1994	(neonate-adult) healthy (48)	↑ diffusion perpendicular to fibers in frontal and occipital WM for neonates than other age groups
Partridge et al., 2004	(GA 28-39 wks) preterm neonates (50)	↓ diffusion and ↑ anisotropy in earlier maturing than later maturing tracts
Sakuma et al., 1991	(preterm-adult) preterm/healthy (17)	Changes in anisotropy with maturation
Schmithorst et al., 2002	(5-18y) healthy (33)	Negative correlation of diffusion with age throughout WM; positive correlation of anisotropy with age in selected WM regions
Schmithorst et al., 2005	(5-18y) healthy (47)	Positive correlation of anisotropy with IQ in WM association areas
Schneider et al., 2004	(1 day-16y) healthy (52)	Exponential diffusion ↓ and anisotropy ↑ with age; continuous ↑ in anisotropy in deep WM structures
Snook et al., 2005	(8-12y; 21-27y) healthy (60)	↑ anisotropy in various structures with age
Suzuki et al., 2003	(1-10y; 18-34y) healthy (16)	Evaluated which tensor components contribute most to ↑ anisotropy seen with age
Zhang et al., 2005	(1 m-17y) healthy (30)	Negative correlations between age and diffusion in several brain regions

Table 1b. Studies of children with primary psychiatric disorders

Study	(Age) Sample description (n)	General summary of findings
Ashtari et al., 2005	(7-11y) ADHD (33)	↓ anisotropy in frontal cortex, striatum, and cerebellum
Barnea-Goraly et al., 2004	(10-18y) autism (16)	↓ anisotropy in frontal and temporal regions, corpus callosum
Filippi et al., 2003	(2-8y) developmental delay (30)	↑ diffusion and ↓ anisotropy in several WM tracts
Nagy et al., 2003	(11y) attention deficits/born preterm (10)	↓ anisotropy in posterior corpus callosum and internal capsule

Table 1c. Studies of defined genetic or neurological disorders

Eastwood et al., 2001	(6-12y) neurofibromatosis-Type 1 (40)	↑ diffusion in WM, both with and without lesions, significantly higher in lesioned WM
Eichler et al., 2002	(7-30y) X-linked adrenoluekodystrophy (22)	Strong + (anisotropy) and – (diffusion) correlations with spectroscopic measurements of neuronal marker N-acetyl aspartate
Engelbrecht et al., 2002	(1wk-8y) WM diseases (57)	Changes in WM diffusion and anisotropy
Glenn et al., 2003	(10 m-4y) congenital hemiparesis (8)	↓ anisotropy and slightly ↑ diffusion in affected pyramidal tract
Guo et al., 2001	(5 wks-3y) Krabbe disease (16)	↓ anisotropy in several WM regions and basal ganglia; patients treated with stem cell transplantation had levels between untreated patients and controls
Hoon et al., 2002	(6y) periventricular leukomalacia (2)	Qualitative reduction in corpus callosum, corona radiata, and internal capsule fibers, especially where connected to sensory cortex
Huppi et al., 2001	(GA 27-31 wks) preterm/perinatal brain injury (20)	↓ anisotropy in areas of injury
Barnea-Goraly et al., 2003a	(12-23y) fragile X (20)	↓ anisotropy in frontostriatal pathways
Barnea-Goraly et al., 2003b	(7-22y) VCFS (38)	↓ anisotropy in frontal, parietal, and temporal cortex
Karadag et al., 2005	(2-20y) tuberous sclerosis (14)	↑ diffusion in tubers than in corresponding areas in controls; ↑ diffusion and ↓ anisotropy in tubers than in contralateral WM
Khong et al., 2003	(3-19y) medulloblastoma (18)	↓ anisotropy in various WM areas
Lee et al., 2003	(4y) brain injury (2)	DTI revealed microstructural abnormalities that conventional MRI did not
Peng et al., 2004	(5 m-15y) tuberous sclerosis (14)	Different diffusion properties in tubers than in unaffected brain areas and controls
Schneider et al., 2003	(9-13y) adrenoleukodystrophy (10)	↑ diffusion and ↓ anisotropy in all demyelinated areas, as well as in some normal-appearing WM
Simon et al., 2005	(7-14y) DS22q11.2 (36)	Combination of diffusion and volumetric measures indicate morphological abnormality of corpus callosum

Figure 1. a.) Free (isotropic) vs. b.) restricted (anisotropic) diffusion. In a.), water molecules diffuse freely without structural impediment, such as in large fluid-filled spaces like ventricles. In b.), a physical barrier to diffusion forces water molecules along a more circumscribed path. In the brain, bundles of axons encased in myelin form physical barriers that have this effect.

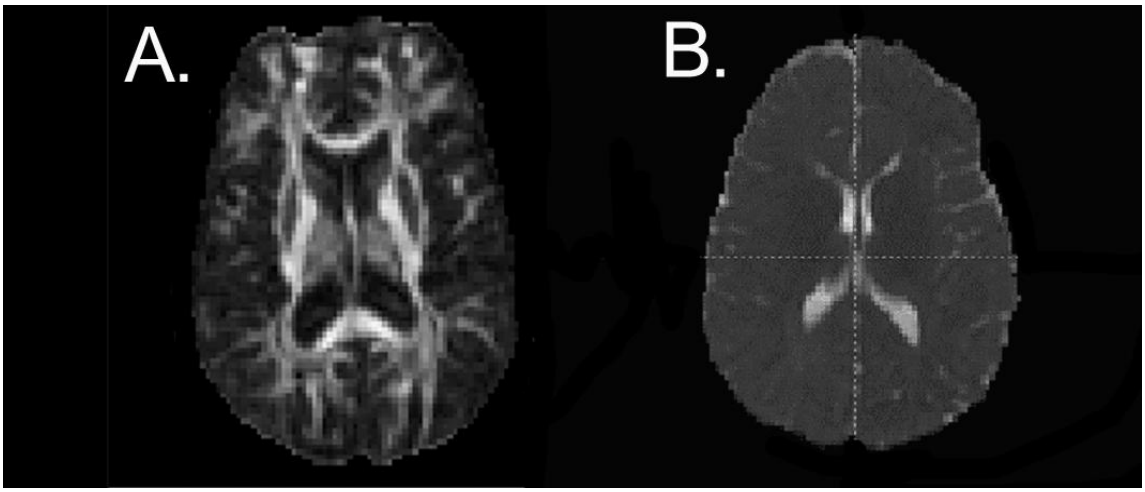

Figure 2. Maps of diffusion anisotropy (a) and overall diffusion (b). Bright voxels indicate higher values, thus in (a) bright voxels indicate high anisotropy characteristic of white matter, and in (b) bright ventricles represent high overall diffusion characteristic of CSF.

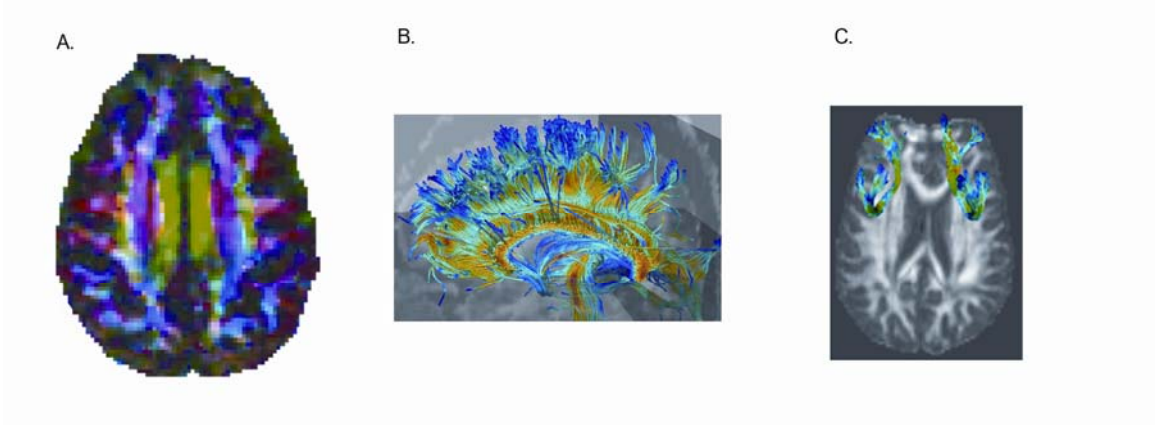

Figure 3. Fiber tract representation by (a) color maps and (b-c) tractography. In (a), the hue (red, green, or blue) represents the direction of the fiber pathways in the three orthogonal directions of anatomical space (x, y, and z), and the brightness of each voxel represents the degree of anisotropy, and thus reflects the coherence of the fiber bundles, which is strongest in the central regions of the tracts, and weaker at the termini. The fibers in (b) are a representation of commissural bundles traveling through the corpus callosum, with anisotropy values illustrated by color. Note the higher anisotropy (reds and yellows) near the center of the bundles, and lower anisotropy (blue) near the terminal regions. Fiber representations for more local, circumscribed tracts can be produced as well, as in the uncinate fasciculi depicted in (c).