



Diffusion Weighted and Diffusion Tensor MRI in Pediatric Neuroimaging Including Connectomics: Principles and Applications

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Diffusion weighted MRI (DWI) including diffusion tensor imaging (DTI) are unique imaging techniques that render qualitative and quantitative information of the central nervous system white matter (WM) ultrastructure. It uses the Brownian movement of water molecules to probe tissue microstructure. It is a noninvasive method, with superb sensitivity to the differential mobility of water molecules within various components of the brain without the necessity to inject contrast agents. By sampling the 3 dimensional shape, direction and magnitude of the water diffusion, DWI/DTI generates unique tissue contrasts that can be used to study the axonal WM organization of the central nervous system. Its application allows to study the normal and anomalous brain development including connectivity, as well as a multitude of WM diseases. This article discusses/summarizes the principles of DWI/DTI and its applications in pediatric neuroscience research.

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Introduction

Diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI), are currently the only techniques that provides in-vivo, noninvasive qualitative and quantitative information about the complex brain development, in particular the white matter microarchitecture

DWI/DTI is being used to study a large number of pathologies affecting the pediatric brain including malformations, stroke, tumors, infections, trauma, and neurometabolic/neurodegenerative diseases.^{1–16}

By measuring the three-dimensional directional characteristics of water molecule diffusion/mobility within the brain, DWI/DTI generates unique tissue contrasts that can be used to the study the axonal organization of the central nervous

system (CNS). This article aims to review DWI/DTI principles and its potential qualitative and quantitative applications to study pediatric CNS disorders and highlights the added value of this advanced modality compared to conventional MRI.⁵ In addition, basic principles and applications of DWI/DTI based connectomics are discussed.

Principles of Diffusion Tensor Imaging and Fiber Tractography

DWI generates image contrast based on differences in the mobility of water molecules within tissues.^{17–20} Diffusion in for example cerebrospinal fluid (CSF) is fast and unrestricted, while diffusion in brain tissue is slower, respectively restricted due to the local microstructure (myelin sheaths, neurons). By adding 3 orthogonal arranged diffusion gradients to standard MRI sequences, the degree of water mobility can be studied. Typically, 2D trace of diffusion (DWI) and apparent diffusion coefficient (ADC) maps are calculated. However, classic DWI sequences do not allow to study the 3D shape and direction of diffusion of water molecules within the brain. Depending on the local microstructure, diffusion can be isotropic which means that the magnitude of diffusion is equal in all directions in 3 dimensional space vs

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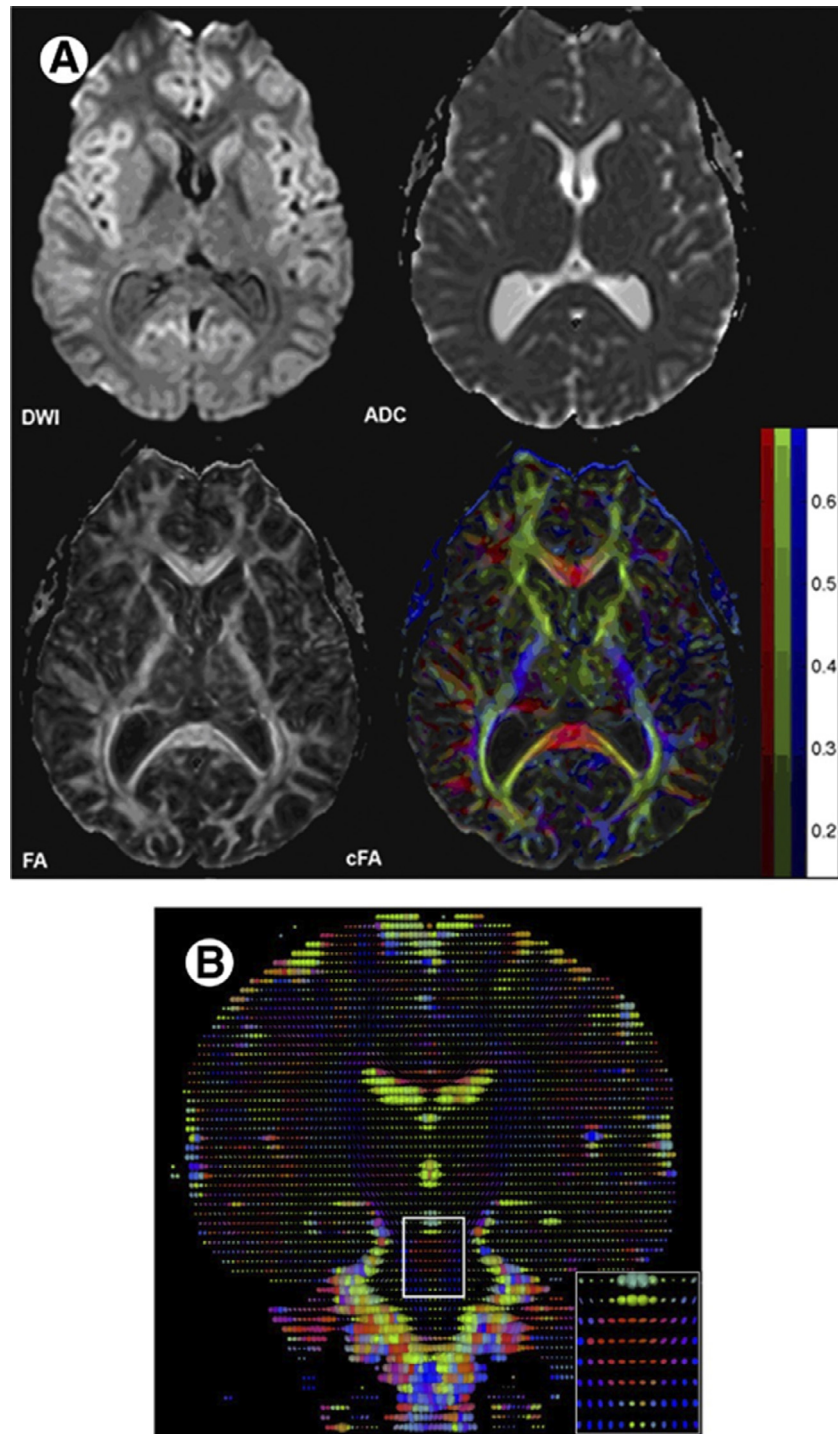


Figure 1 (A) Axial DWI, ADC, FA, and color-coded FA map of a healthy subject at the level of the basal ganglia/thalami. The CSF appears bright on the ADC map, the brain “dark” (low ADC). On the FA map the compact white matter tracts in the area of the corpus callosum and internal capsule are bright (high degree of anisotropic diffusion) while the FA values within the cortex, central gray matter and CSF are dark (low degree of anisotropic diffusion). The matching color-coded FA maps show the principal diffusion direction within the areas of high degree of anisotropic diffusion (white matter tracts and commissures). The corpus callosum is red (left to right diffusion), the internal capsule blue (superior-inferior diffusion), the optic radiation green (anterior-posterior diffusion). The color intensity corresponds to the degree of anisotropic diffusion. (B) Coronal tensor display of a 2-year-old healthy child. In every voxel, the shape and the color of the ellipsoids represent the preferential direction and magnitude of the diffusion tensor. (Modified from Chokshi FH, Poretti A, Meoded A, et al. Normal and abnormal development of the cerebellum and brainstem as depicted by diffusion tensor imaging. *Seminars in ultrasound, CT, and MR* 2011;32:539-554). (Color version of figure is available online.)

Table 1 Frequently Used Indices of Diffusion Anisotropy, their Definition using Eigenvalues, and References. (Modified from Meoded, A., Poretti, A., Mori, S., Zhang, J. Diffusion Tensor Imaging (DTI). In Reference Module in Neuroscience and Biobehavioral Psychology, Elsevier, 2017)

Anisotropy Indices	Definition	Reference
Fractional anisotropy (FA)	$FA = \sqrt{\frac{(\lambda_1 - \lambda_2)^2 + (\lambda_1 - \lambda_3)^2 + (\lambda_2 - \lambda_3)^2}{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$	Basser and Pajevic (2000)
Relative anisotropy (RA)	$RA = \sqrt{\frac{(\lambda_1 - \lambda_2)^2 + (\lambda_1 - \lambda_3)^2 + (\lambda_2 - \lambda_3)^2}{(\lambda_1 + \lambda_2 + \lambda_3)^2}}$	Alexander et al (2000)
Linear, planar, and spherical anisotropy indices (CL, CP, and CS, respectively)	$CL = \frac{\lambda_1 - \lambda_2}{\lambda_1 + \lambda_2 + \lambda_3}, CP = \frac{2(\lambda_2 - \lambda_3)}{\lambda_1 + \lambda_2 + \lambda_3}, CS = \frac{3\lambda_3}{\lambda_1 + \lambda_2 + \lambda_3}$	Westin et al (2002)

anisotropic, which means that the magnitude of diffusion differs along the various directions in space and there is a preponderant direction of diffusion. Diffusion is typically isotropic in CSF and anisotropic along white matter tracts. The myelin sheath along the fiber tracts limits diffusion perpendicular to the main axis of the fiber tract.

In contrast to DWI sequences, DTI allows to study the 3D shape and direction of diffusion by adding at least 3 additional diffusion gradients along multiple collinear directions in space. By measuring the complete tensor of the diffusion, the degree of anisotropic diffusion relative to the overall diffusion can be calculated (fractional anisotropy, FA).^{18,21-24} The degree of anisotropic diffusion can also be represented as a 2D FA-map (Fig. 1).²⁵ Major WM tracts, such as the corpus callosum and corona radiata, have a high degree of anisotropic diffusion and appear as bright structures on the fractional anisotropy image (Fig. 1). The FA values vary between 0 (maximal isotropic diffusion) and 1 (maximal anisotropic diffusion²⁶). High FA values are typically found along fiber tracts (eg, corticospinal tracts, corpus callosum). Measurement of the entire diffusion tensor also gives information about the principal direction and 3D shape of diffusion within the brain. FA maps can be color coded namely, directionally encoded color maps.²⁷ By convention, regions with a predominant left to right diffusion are color coded in red; regions with a superior-inferior diffusion direction are coded in blue while anterior-posterior diffusion is color coded in green. The intensity of the color coding relates to the magnitude of the FA-value. The analysis of the eigenvalues λ_1 , λ_2 , and λ_3 (λ_1 : magnitude of maximal principal diffusion along the long axis and λ_2 , λ_3 , diffusion perpendicular to the long principal axis), allows a more detailed study of the local tissue architecture/integrity by calculating additional diffusion scalars including axial (AD) and radial (RD) diffusivity. AD is defined as the eigenvalue of the primary or principal eigenvector and represents diffusion along the main axis of white matter tracts. RD is defined as the mean of the eigenvalues of the second and third eigenvalues/eigenvectors and represents averaged diffusion perpendicular to main longitudinal axis of white matter tracts.

The simultaneous sampling of the magnitude, direction and shape of the diffusion tensor allows to display and study the complex diffusion of water molecules for each voxel. By increasing the number of diffusion gradients (eg High Angular Resolution Diffusion Imaging, HARDI) the complex white matter architecture with multiple crossing fibers can be

studied. Diffusion can be displayed as complex three dimensional mathematical models per voxel. (Table 1, 2)

Fiber Tractography

In the CNS, WM tracts have a high degree of diffusion anisotropy, and the orientation of fiber trajectory can be extracted/depicted from the orientation of maximal diffusivity (\mathbf{v}_1) from the tensor. By combining the magnitude and directional information of anisotropic diffusion of the measured voxels, white matter tracts can be calculated/reconstructed by fiber tractography (FT).²⁸⁻³² Fibers are reconstructed based upon the assumption that voxel with a similar degree of anisotropic diffusion (FA value) and principal anisotropic diffusion direction are likely belonging to the same white matter tract. Various powerful post-processing mathematical algorithms are available for FT. Based on the used algorithm, FT can be deterministic (eg using the fiber assignment by continuous tracking algorithm) or probabilistic, which allows to track fibers through regions of high uncertainty (regions with multiple crossing fibers).³³⁻³⁶ FT allows us to study the internal neuroarchitecture of the normal and pathological brain non-invasively and may give insights in the development of the various normal and anomalous connections (white matter tracts) between functional systems.^{28,37}

With deterministic tractography, 3D trajectories, for example, 'streamlines', are used to trace putative white-matter paths. The individual streamlines do not represent actual axons; they depict mathematical estimates of the average trajectories of axon bundles, given our assumption that

Table 2 Diffusivities Measures and their Presumed Biological Significance. (Modified from Meoded, A., Poretti, A., Mori, S., Zhang, J. Diffusion Tensor Imaging (DTI). In Reference Module in Neuroscience and Biobehavioral Psychology, Elsevier, 2017)

White Matter Characteristics	Axial Diffusivity	Radial Diffusivity
Definition	λ_1	$(\lambda_2 + \lambda_3)/2$
Increase myelination	High	Low
Dense axonal packing	Unaffected	Low
Large axonal diameter	High	Low
Axonal degeneration	Low	High
Demyelination	Unaffected	High

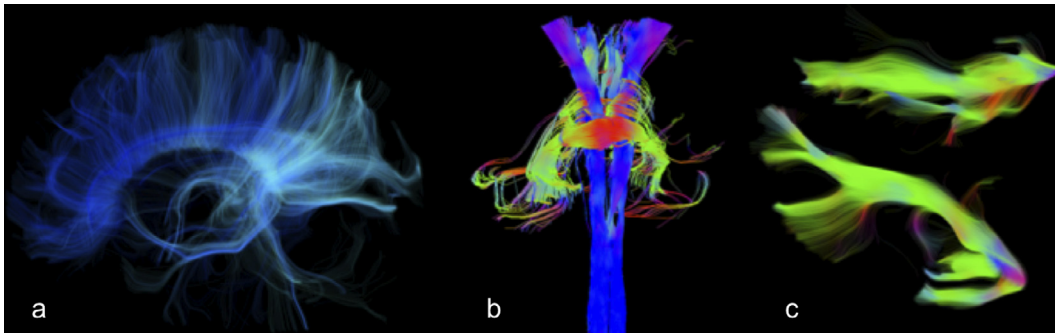


Figure 2 3D fiber tractography performed with deterministic algorithm. Not only pretty pictures - Behind the artistic representation lie the real anatomy. Corpus callosum (A), Corticospinal tracts (B) with brain stem view and uncinate fasciculus (C).

diffusion is least hindered along the principal axis/direction of axons (Fig. 2).

On the other hand, with probabilistic tractography, it is possible to calculate a probability of axonal connection between any pair of gray matter regions on the basis of tractographic analysis of an individual DTI dataset.³⁸

Applications of DWI/DTI to Study CNS Disorders

The advantages of DTI make it an ideal tool to study WM structures. Because DTI is sensitive to the organization and microstructure of WM, it can be used to detect abnormalities

caused by degenerative diseases that affect the WM integrity and consequently allows following disease progression longitudinally for example, for inborn errors of metabolism like adrenoleukodystrophy {Schneider, 2003 #2623}.³⁹ Alternatively, DTI allows to study complex brain malformations with anomalous courses of major white matter tracts like e.g. in Joubert syndrome {Poretti, 2011 #2625}.⁴⁰ DTI may also be used to evaluate tumor progression/extension along white matter tracts or disruption of white matter tracts by tumor infiltration {Wagner, 2016 #2627}.⁴¹ DTI data may be analyzed qualitatively and quantitatively including region of interest (ROI) analysis, atlas-based analysis, voxel-based analysis, and tract-based spatial statistics (TBSS).^{42,43} The decision about which quantitative analysis should be used depends on the hypothesis and research question.

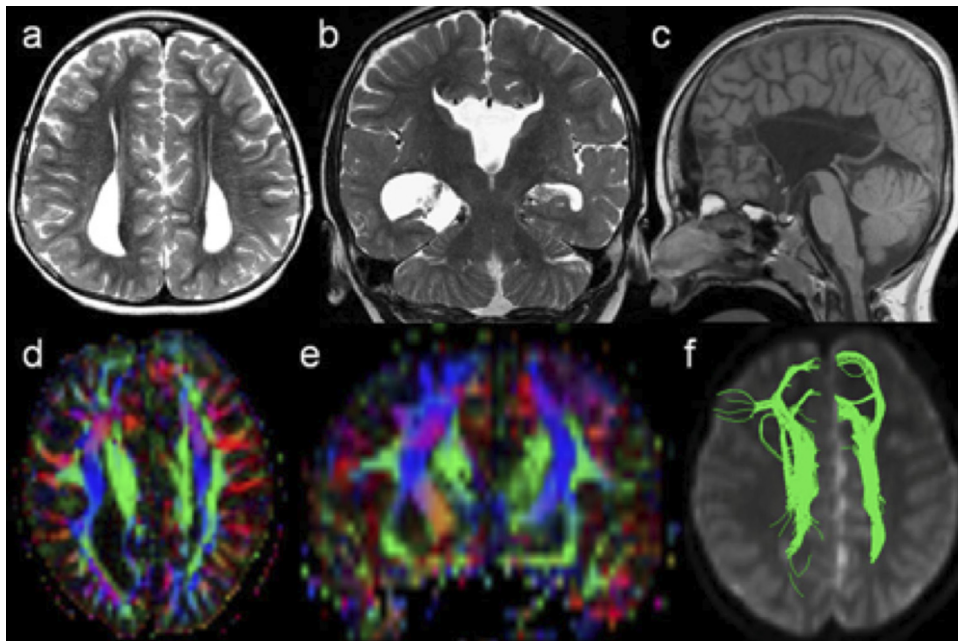


Figure 3 CC agenesis. Images in a child with agenesis of the corpus callosum. (A) Axial T2-weighted image shows parallel lateral ventricles and colpocephaly. (B) Coronal T2-weighted image presents lateral convexity of the frontal horns, absence of the septum pellucidum and malrotation of the hippocampal formations. (C) Midsagittal T1-weighted image demonstrates absence of the corpus callosum. (D) Axial and (E) coronal color-coded FA maps, and (F) FT superimposed on an axial T2-weighted image show the bundles of Probst as large, longitudinally oriented (green on color-coded FA maps) white matter tracts that are running along the medial and superior wall of the lateral ventricles. (Modified from Poretti, A., Meoded, A., Rossi, A. et al *Pediatr Radiol* (2013) 43: 28-54). (Color version of figure is available online.)

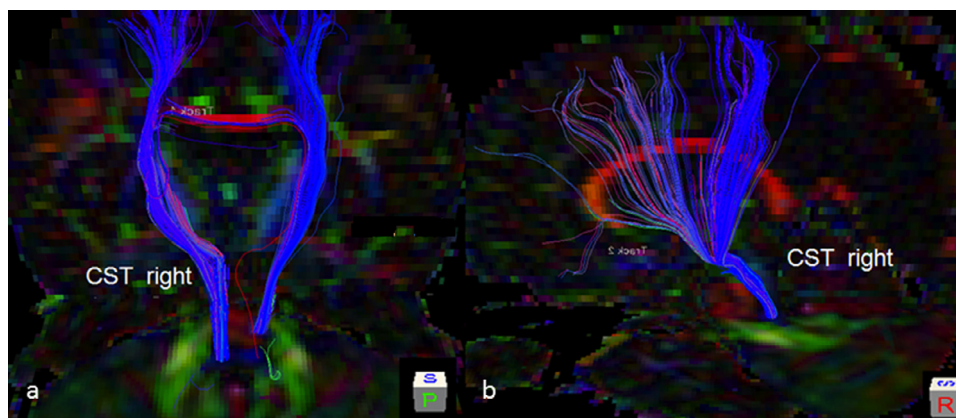


Figure 4 Aberrant cst. FT (A) coronal (B) sagittal fiber tractography superimposed on color-coded FA map display the complete aberrant course of the right CST extending through the dorsal brain stem in the expected location of the ML. The left CST shows a normal course through the ventral brain stem at the level of the pons.

Qualitative evaluation provides morphological information e.g. brain malformations allowing to better understand the pathogenesis/underlying defect (eg, defective non-motile cilia in Joubert syndrome) and the evaluation is based on DEC maps and FT. Knowledge of normal DTI images is mandatory. The neuro-architecture of different congenital malformations can be exquisitely well studied with DTI. Nowadays prenatal DTI has become available, which allows to study the aberrant brain architecture even earlier which enhances differentiation between malformative, disruptive and destructive etiologies of brain pathologies encountered at birth. In addition, in some cases only FT can reveal the abnormal course of white matter tracts. Figures 3 and 4 demonstrate application of qualitative evaluation of different congenital malformations.^{2,44}

On the other hand, different quantitative methods, manual or automated, exist and involve whole brain or region based statistical analysis. Differences between groups, usually patients and controls, can be objectively studied. DTI scalars obtained for each region may serve as biomarkers and can be useful for patient's follow-up, disease progression or even to monitor for treatment response. In addition, longitudinal quantitative assessment of DTI scalars may provide insights into CNS reorganization/plasticity after congenital or acquired injury.⁴⁵ Regions of interest (ROI) drawing approach is the simplest method. However, criteria for ROI placement need to be established a priori. In addition, this method is manual and time consuming. Another quantitative method is atlas-based analysis (ABA) available at <http://www.MriStudio.org/>⁴⁶ (Fig. 5). This method automatically segments the brain into multiple well defined anatomical areas. Main advantage of this method is that analysis can be performed on subject's native space with information obtained for multiple white matter tracts at once. However, the ABA approach may fail if an abnormality does not primarily involve well defined tracts. Alternatively a tract based spatial statistics (TBSS) analysis may be applied (Fig. 6). This is a variation of whole-brain analysis. FA images from multiple subjects are aligned to a common space where tract representation includes only voxels at the center of fiber tracts

common to all. All locations across the brain are tested without a priori hypotheses. The resulting skeleton data for all the subjects are analyzed with a powerful statistical model (FMRIB's Software Library). No distinction between white matter structures is made using the ABA technique. In addition, variations in the periphery of white matter tracts may be missed (not included).

Beyond the Tensor

Diffusion tensor is a simplified model. A major limitation of classical DTI is the inability to detect more than one fiber

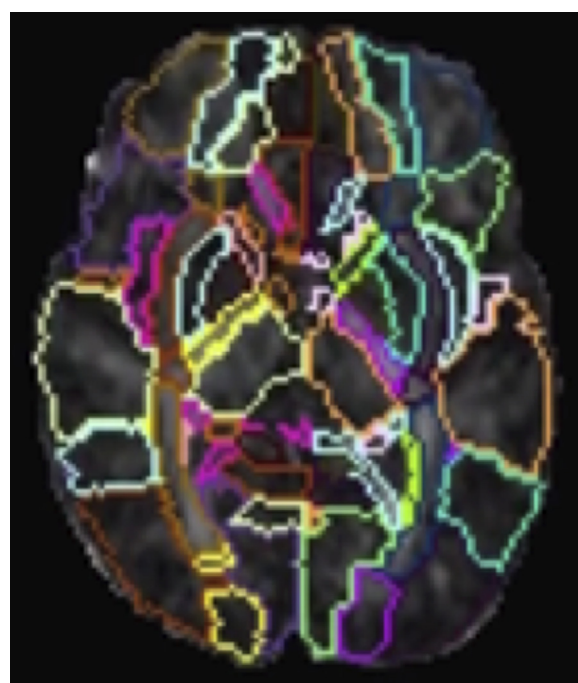


Figure 5 Atlas based analysis. Whole brain automated segmentation. An example of a neonatal brain parcellation according to JHU neonatal atlas.

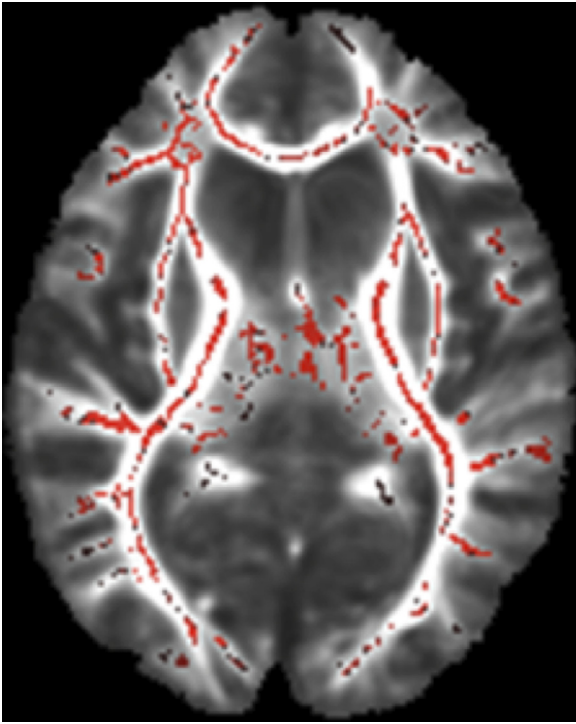


Figure 6 TBSS. FA images from multiple subjects are aligned to a common space. The resulting skeleton data for all subjects are analyzed.

orientation within a single voxel. It assumes that water diffusion is Gaussian. In the case of 2 or more fibers crossing in a pixel, DTI cannot distinguish these fibers. Hence, in regions of complex fiber orientation such as fiber crossing, DTI may fail to depict the complex intravoxel fiber orientation and prevents an accurate reconstruction of the white matter microstructure.⁴⁷

In particular, the diffusion tensor model performs well in regions where there is only one fiber population (ie, fibers

are aligned along a single axis), where it gives a good depiction of the fiber orientation. However, this is not always the case. Fibers are known to disperse (fan), cross, merge and kiss (temporarily run adjacent to one another)—all of which can happen within a single voxel and lead to heterogeneity not accounted for by a simple delta function.

Fiber orientation must be inferred for white-matter voxels individually, before any connectivity analysis can be executed. The goal of diffusion MRI analysis is to infer a probability function for each voxel, which captures the different fiber orientations present and their relative proportions. Estimation of this function—referred to as the fiber orientation density function (fODF)—calculated for each voxel is the first step in estimating structural connectivity (Fig. 7). Complex fODF models better estimate fiber trajectories, particularly when several white-matter tracts intersect and consequently allow recovery of nondominant pathways invisible to DTI. Imaging techniques that provide higher angular resolution are needed (HARDI sequences).

Diffusion spectrum imaging (DSI) and HARDI, and their variations have begun to replace DTI in recent years. Although they differ in their details, DSI and HARDI ultimately work by detecting the complex movement of water along multiple possibly crossing fiber tracts in many more directions within a given voxel.⁴⁸⁻⁵⁰

Diffusion spectrum imaging overcomes the limitation of classical DTI by reconstructing multiple diffusion directions in each voxel.

After estimation of the fODF in each voxel, tractography approaches such as the previously discussed deterministic or probabilistic mathematical models, are used to study the functional/structural connectivity between functional centers also known as connectome nodes (Fig. 8). These high-end diffusion approaches represent an essential component in the structural connectome reconstruction.⁵¹⁻⁵⁴ Estimating the

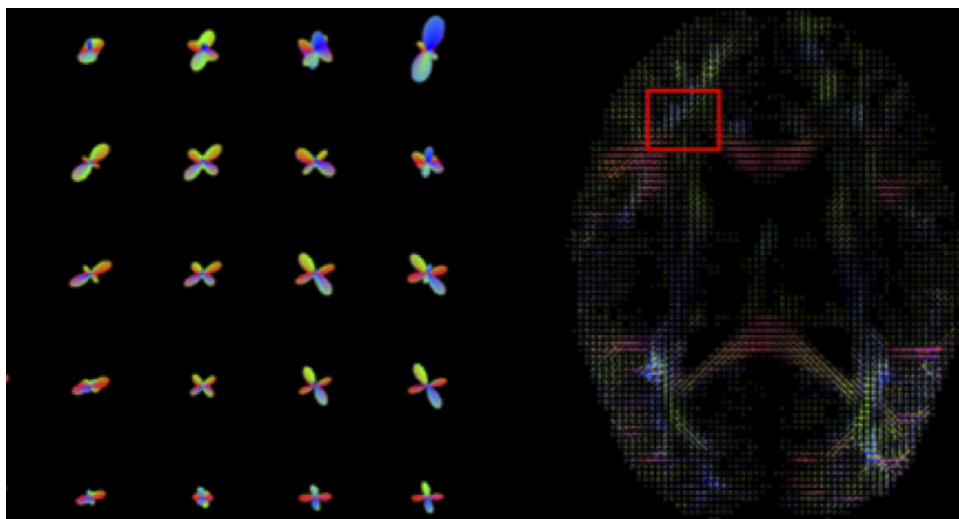


Figure 7 Axial view of DTI fiber orientation estimates. The zoomed area represents the region where corpus callosum, corona radiata and superior longitudinal fasciculus fibers intersect. The fODF estimates fiber trajectories and allow recovery of nondominant pathways invisible to DTI. (Modified from Meoded, A., Poretti, A., Mori, S., Zhang, J. Diffusion Tensor Imaging (DTI). In Reference Module in Neuroscience and Biobehavioral Psychology, Elsevier, 2017).

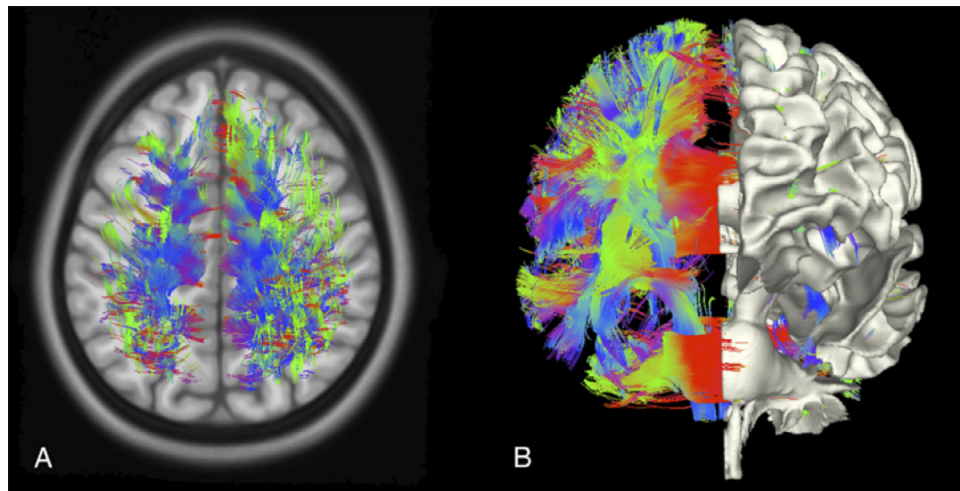


Figure 8 3-D depiction of whole brain tractography obtained with HARDI of a 8 year old healthy subject (A) overlaid on high resolution axial T1WI; (B) coronal view of whole brain tractography with hemi-brain surface. Improved tractography with HARDI is capable of capturing more connections and yield detailed representation of the white mater. (Modified from Meoded, A., et al (2017). “The structural connectome in children: basic concepts, how to build it, and synopsis of challenges for the developing pediatric brain.” *Neuroradiology* 59(5): 445-460).

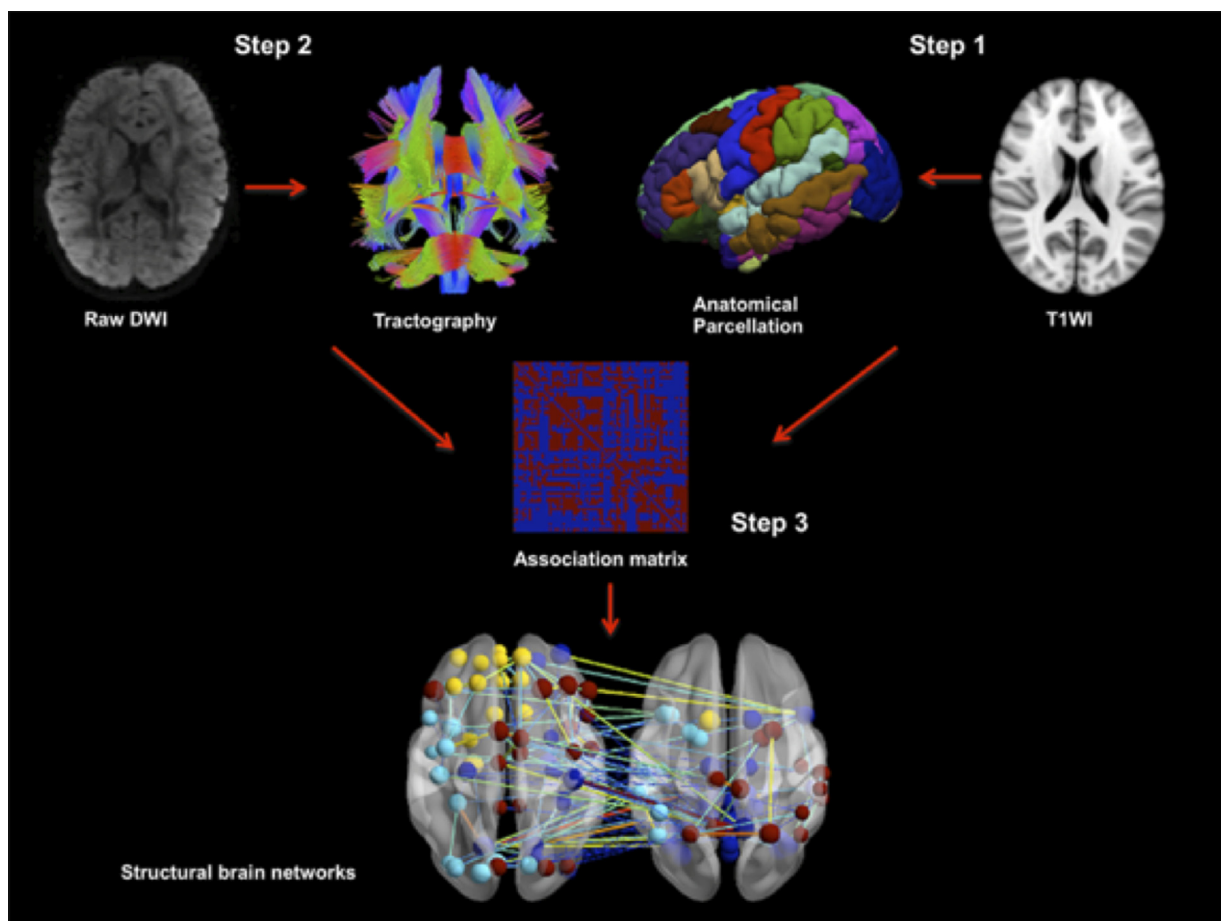


Figure 9 Structural brain connectome was explored using graph theory in a 4-year-old healthy boy through the following steps: (1) *Step 1*: define the network nodes, with anatomical parcellation of high-resolution T1WI, (2) *Step 2*: estimate a continuous measure of association between nodes with structural connectivity, obtained with tractography, and (3) *Step 3*: generate an association matrix by compiling all pairwise associations between nodes. The result of these 3 steps is the structural connectome, a graphical model of a brain network. (Modified from Meoded, A., et al (2017). “The structural connectome in children: basic concepts, how to build it, and synopsis of challenges for the developing pediatric brain.” *Neuroradiology* 59(5): 445-460).

structural connectome enables a comprehensive mapping of structural connectivity within the brain.^{52,55} A global, multi-center project also known as “The Human Connectome Project” aims to build a “network map” that will shed light on the anatomical and functional connectivity within the healthy human brain (Fig. 9). Connectomics – the study of the connectome - has emerged as an ideal tool to study structural networks that are implicated in neurocognitive functions and behavioral disorders including for example, attention deficit and hyperactivity disorder (ADHD) or the autism spectrum disorder (ASD). Connectomics has the potential to enhance our outcome prediction capability which should be seen as a significant step toward realization of precision imaging. Connectomics will transcend anatomy-based imaging toward functional, organizational, networking based imaging.

Conclusion and Future Directions

The various diffusion MR imaging approaches, DWI, DTI, DSI or HARDI, render various categories of in-vivo, noninvasive detailed qualitative and quantitative information about white matter micro-structural integrity. DWI and DTI are widely used advanced MRI sequences that are very helpful to study a wide spectrum of pediatric brain diseases.¹⁷

Currently, FT is the only available tool for identifying and measuring white matter pathways “noninvasively” and “in-vivo”. In addition, the normal and abnormal connectivity between different anatomical centers within the brain can be evaluated with FT.

Moreover, recent advances in neuroimaging technology now allow the construction of comprehensive whole-brain maps of the structural connections of the human cerebrum at the individual level for example, connectome. A significant effort is currently being focused towards the development of novel neuroimaging strategies as encouraged by “The Brain Research through Advancing Innovative Neurotechnologies” (BRAIN) to enable progress in development of new technologies.

In conclusion, diffusion based MRI provides an unparalleled compilation of neural data allowing to study white matter integrity and navigating the brain and exploring brain circuits in a way that was never before possible.

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