



Applications of advanced diffusion MRI in early brain development: a comprehensive review

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Abstract

Brain development follows a protracted developmental timeline with foundational processes of neurodevelopment occurring from the third trimester of gestation into the first decade of life. Defining structural maturational patterns of early brain development is a critical step in detecting divergent developmental trajectories associated with neurodevelopmental and psychiatric disorders that arise later in life. While considerable advancements have already been made in diffusion magnetic resonance imaging (dMRI) for pediatric research over the past three decades, the field of neurodevelopment is still in its infancy with remarkable scientific and clinical potential. This comprehensive review evaluates the application, findings, and limitations of advanced dMRI methods beyond diffusion tensor imaging, including diffusion kurtosis imaging (DKI), constrained spherical deconvolution (CSD), neurite orientation dispersion and density imaging (NODDI) and composite hindered and restricted model of diffusion (CHARMED) to quantify the rapid and dynamic changes supporting the underlying microstructural architectural foundations of the brain in early life.

Keywords Brain development · Microstructure · Advanced diffusion MRI · NODDI · DKI · CHARMED · CSD

Introduction

The first decade of life is widely recognized as a critical and sensitive period of brain development (Mah and Ford-Jones 2012; Dubois et al. 2014; DeGiudice 2018). Across this period, foundational neurodevelopmental processes (e.g., neurogenesis, pruning, synaptogenesis, myelination) operate under the direction of genetic and environmental forces to establish and shape the brain's structural and functional architecture (Thompson et al. 2001; Douet et al. 2014; Gao et al. 2014, Teeuw, Brouwer et al. 2019) and provide the foundation for nearly all cognitive and behavioral skills (Steinberg 2005; Ouyang et al. 2019a, b). This period of

peak growth and plasticity is also a time in which the brain is vulnerable to adverse experiences and insults (Miguel et al. 2019; Tooley et al. 2021) and is a time in which alterations believed to be associated with many neurodevelopmental and psychiatric disorders first emerge (Rees and Inder 2005; Bale et al. 2010; Oskvig et al. 2012; Al-Haddad et al. 2019; Smith and Pollak 2020; De Asis-Cruz et al. 2022). As such, there has been significant interest and substantial efforts to characterize the dynamic patterns of early brain development, elucidate brain–behavior associations, and to help understand the etiology of neurodevelopmental disorders.

Magnetic resonance imaging (MRI) has emerged as an incredibly powerful tool that can be used to non-invasively investigate the brain's anatomical structure and function in vivo and provide unprecedented opportunities to study brain maturation (Giedd et al. 1999; Knickmeyer et al. 2008; Lebel et al. 2012; Ball et al. 2013; Dennis and Thompson 2013; Eaton-Rosen et al. 2015; Krogsrud et al. 2016; Batalle et al. 2017; Levman et al. 2017; Lebel and Deoni 2018; Tamnes et al. 2018; Andrews et al. 2019; Ouyang et al. 2019a, b). Many early and influential papers on infant and early childhood neurodevelopment have examined the dynamic changes of brain volume and morphometry that

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occur during this period (Pfefferbaum et al. 1994; Giedd et al. 1999; Gogtay et al. 2004; Knickmeyer et al. 2008). However, underlying these macrostructural growth changes is maturation of the brain's microstructure. The use of diffusion MRI (dMRI), which is sensitive to the mobility of water molecules in biological tissues and modulated by the density, spacing, and orientational organization of tissue membranes (e.g., axons, dendrites, myelin), have provided additional opportunities to measure changes associated with brain development and characterize the maturation of the brain's microstructure in vivo (Zhang et al. 2012; Lebel and Deoni 2018; Tamnes et al. 2018; Alexander, Dyrby et al. 2019; Ouyang et al. 2019a, b, Lynch, Cabeen et al. 2020; Neil and Smyser 2021).

The most widely used dMRI technique to study brain development has been diffusion tensor imaging (DTI) (Basser et al. 1994; Basser 1995; Alexander et al. 2007), which assumes the diffusion of water in the underlying tissue can be described by a multivariate Gaussian probability distribution and represented by the diffusion tensor (Basser et al. 1994; Basser 1995; Alexander et al. 2007). Several quantitative metrics, including fractional anisotropy (FA), mean, axial, and radial diffusivity (MD, AD, RD, respectively), can be estimated from DTI and used to examine neurodevelopmental changes (Barnea-Goraly et al. 2005; Dubois et al. 2008; Lebel et al. 2008; Schmithorst et al. 2008; Asato et al. 2010). Indeed, the use of DTI to study patterns of infant and child brain development has been the topic of several reviews (Feldman et al. 2010; Yoshida et al. 2013; Qiu et al. 2015; Dibble et al. 2021). However, while informative, DTI-derived parameters are exquisitely sensitive to a host of mechanisms, and therefore are unable to resolve changes that may correspond to specific features of tissue microstructure (Jones and Cercignani 2010; Soares et al. 2013). Moreover, as the complexity and heterogeneity of tissue microenvironments increases, such as in the cerebral cortex and within areas of high-density crossing or diverging fibers, the behavior of water diffusion in tissue deviates from the assumed Gaussian behavior, making the interpretation of DTI-derived parameter estimates difficult (Wheeler-Kingshott and Cercignani 2009).

Recent years have seen the development of an abundance of dMRI methods aimed to overcome the limitations of DTI and provide improved modeling of the white matter microstructure and measures greater specificity (Assaf et al. 2004; Assaf and Basser 2005; Jensen et al. 2005; Zhang et al. 2012). These dMRI approaches can generally be grouped as signal representations (also referred as statistical models) and biophysical models. Signal representations, such as DTI, diffusion kurtosis imaging (DKI) (Jensen et al. 2005) and constrained spherical deconvolution (CSD) (Tournier et al. 2004, 2007; Jeurissen et al. 2014; Dhollander and Connelly 2016), aim to describe the diffusion imaging signal without

assumptions about the tissue composition or organization (Pierpaoli et al. 1996; Jelescu, Palombo et al. 2020). Biophysical models, on the other hand, model the geometry of the underlying tissue microstructure and attempt to provide more biologically relevant and interpretable metrics (Jelescu and Budde 2017; Jelescu, Palombo et al. 2020). Such dMRI methods beyond DTI (e.g., DKI, CSD, and advanced dMRI biophysical models) have been increasingly utilized to examine changes in white matter and cortical microstructure (Li et al. 2012; Geeraert et al. 2019; Shi, Yang et al. 2019; Dimond, Heo et al. 2020a, b; Geeraert, Chamberland et al. 2020), including growing adoption of these techniques in infants and young children to characterize brain development with improved specificity (Kunz et al. 2014; Paydar et al. 2014; Pannek et al. 2018; Bataille et al. 2019; Ouyang et al. 2019a, b; Pecheva, Tournier et al. 2019; Pannek, George et al. 2020; Chandwani, Kline et al. 2021; Chandwani, Harpster et al. 2022).

Here, we aimed to review recent applications, findings, and limitations of dMRI methods beyond DTI in studies of the developing brain. Specifically, we focus on studies utilizing advanced dMRI techniques, including DKI, CSD (Raffelt et al. 2015, 2017), and recent dMRI biophysical models, such as neurite orientation dispersion and density imaging (NODDI) (Zhang et al. 2012) and composite hindered and restricted model of diffusion (CHARMED) (Assaf and Basser 2005), to characterize the dynamic patterns of microstructural maturation that occur during the first years of life. We focus on the period of infancy to 10 years of age due to the dynamic and rapid neurodevelopment that occurs over this period. Given that the World Health Organization's definition of adolescence spans 10–19 years of age, studies with a population age range surpassing our upper-age limit by no more than 8 years were included if majority of participants fell within our age range of interest. Included studies are listed in Table 1.

Overview of early brain development

Human brain development comprises a series of highly regulated and synchronized processes that follow a protracted timeline beginning in the third gestational week and extend across the life span. Developmental processes including neurogenesis, neuronal migration, synaptogenesis, dendritic formation and arborization, and axonal growth and pruning occur within the earliest stages of fetal neurodevelopment and continue into early postnatal life, establishing the foundations for future developmental processes (Tierney and Nelson 2009; Ouyang et al. 2019a, b). Postnatally, the brain continues to undergo substantial growth and synaptic pruning, while myelination of axons begins to facilitate neuronal activity and rapid axonal communication. Brain

Table 1 Reviewed papers

Citation	Sample age	Conditions	Sample size
(A) Diffusion kurtosis imaging			
Chinnadurai et al. (2016)	2 months–17 years	Cochlear nerve deficiency	25 patients; 25 controls
Gao et al. (2012)	5–9.4 years old	Temporal lobe epilepsy	8 patients; 8 controls
Li et al. (2012)	1–6 years	Typical development	10 participants
Li et al. (2022)	37.4–43.6 PMA	Term birth	50 term infants
Ouyang et al. (2019a, b)	31–42 PMA	Preterm birth	59 participants
Paydar et al. (2014)	Birth–4.6 years	Typical development	35 preterm, 10 term
Shi et al. (2016)	Preterm: PMA < 37 weeks Preterm: PMA > = 37 weeks Full term: mean PMA = 40.5	Preterm and term birth	
Shi et al. (2019)	2 days to 14 years old	Typical development	218 participants
Zhang et al. (2013)	Epilepsy: 3–11.9 years Controls: 4.1–9.3 years old	Epilepsy	15 patients; 18 controls
Zhang et al. (2016)	3.3–12.6 years	Epilepsy	18 children with epilepsy (9 in each the left and right hemispheres); 18 controls
Zhang et al. (2017)	3–8 days	Bilirubin encephalopathy	17 patients; 21 controls
Zheng et al. (2017)	1–8 years	Sensorineural hearing loss	72 patients; 38 controls
Zheng et al. (2021)	1–28 days	Bilirubin encephalopathy	76 patients; 40 controls
Citation	Sample age	Conditions	Sample size
(B) Constrained spherical deconvolution			
Barendse et al. (2020)	8.5–10 years	Typical development	120 participants
Bleker et al. (2019)	3.9–7.1 years	Prenatal maternal depression	16 participants
Bleker et al. (2020)	5 years	Prenatal maternal depression	16 participants
Blommaert et al. (2020)	9 years	Cancer-complicated pregnancies	84 total participants, 42 controls
Chandwani et al. (2021)	≤ 32 weeks GA; Average PMA at scan 42.8 weeks	Very preterm infants; cerebral palsy (CP)	223 total infants; 14 early CP, 209 low risk CP
Chandwani et al. (2022)	≤ 32 weeks GA; Average PMA at scan 42.8 weeks	Very preterm infants	191 preterm infants
Collins et al. (2021)	7–13 years	Very preterm infants	176 preterm, 60 term-born
Dimond et al. (2020a, b)	4–7 years	Typical development	73 participants
Jeong et al. (2022)	Average of 39.2 weeks GA; average postconceptional age at scan 40.7 weeks	Neonatal encephalopathy	15 neonates
Kelly et al. (2020a, b)	7–13 years	Very preterm infants	103 preterm, 21 term-born
Lautarescu et al. (2022)	32.1–42.3 weeks GA Average PMA at scan 41.3 weeks	Prenatal maternal depression	413 participants

Table 1 (continued)

Citation	Sample age	Conditions	Sample size
Liu et al. (2021)	25.3–36.6 weeks GA; Average PMA at scan 48 weeks	Preterm infants	65 participants
Liu et al. (2022)	28.1–36.4 weeks GA	Preterm infants	89 participants
Pannek et al. (2018)	Average PMA at scan 47.3 weeks 23–41 weeks GA;	Preterm infants	55 preterm, 20 term-born
Pannek et al. (2020)	PMA at scan 38–44 weeks <31 weeks GA	Preterm infants	80 participants
Pecheva et al. (2019)	Scan at term equivalent age 24–32.9 weeks GA	Preterm infants	50 participants
Pietsch et al. (2019)	PMA at scan 38.6–47.1 weeks 32.9–44.1 weeks GA	Preterm and term-born infants	113 participants
Pretzel et al. (2022)	PMA at scan 33–44 weeks 7 years	Neonatal stroke	32 patients, 31 controls
Citation	Sample age	Conditions	Sample size
(C) Composite hindered and restricted model of diffusion			
Kunz et al. (2014)	Born 30–40 weeks gestation scanned at 40 weeks	Typical development	13 neonates
Kunz et al. (2013)	Born 29–40 weeks gestation scanned at 40 weeks	Typical development	6 neonates
Kunz et al. (2011)	Born and scanned at 40 weeks gestation	Typical development	3 neonates
Citation	Participant age	Conditions	Sample size
(D) Neurite orientation and dispersion density imaging			
Bataille et al. (2017)	Preterm: 24–41 weeks GA at birth Full term: 25–45 PMA at scan	Preterm and term birth	65 neonates
Bataille et al. (2019)	25 and 37 weeks GA at birth	Preterm birth	99 infants
Blesa et al. (2020)	25 and 47 weeks PMA at scan Preterm: 23.4–32 weeks GA Full term: 36.4–42 weeks GA	Preterm and term birth	76 preterm, and 59 term
Borghesani et al. (2021)	Children with dyslexia: average age = 10.4 ± 2.0 years Typically developing children: average age = 10.4 ± 1.6 years	Dyslexia	26 patients, 14 controls
Caverzasi et al. (2018)	7–15 years	Dyslexia	26 patients, 21 controls
Dean et al. (2018a, b)	8–50 days	Typical development	101 full term infants
Dean et al. (2021)	32 weeks GA at scan	Typical development	52 full-term infants
Dean et al. (2016)	3 months–7.5 years	Typical development	18 participants

Table 1 (continued)

Citation	Participant age	Conditions	Sample size
Dimitrova et al. (2021)	Preterm infants: average PMA at scan 40.93 (range = 37–45.14) Term infants: average PMA at scan 40.86 (range = 37.43–44.71) 4.1–7.3 years	Preterm and term birth	259 term infants; 76 preterm infants
Dimond et al. (2020a, b)	1 month at scan; follow up at 6, 12, and 18 months Infants born at ≤ 28 weeks of gestational age at two time points: once when stable after birth, and again at term-equivalent age Infants born 37–42 weeks scanned at PMA 40.92 ± 1.58 weeks	Typical development	139 participants; 55 participants returned for a second scan 12 months after first scan 97 infants 12 very preterm infants
Dowe et al. (2020)	Infants born at ≤ 28 weeks of gestational age at two time points: once when stable after birth, and again at term-equivalent age	Typical development	241 infants
Eaton-Rosen et al. (2015)	Infants born at ≤ 28 weeks of gestational age at two time points: once when stable after birth, and again at term-equivalent age	Very preterm birth	30 infants born preterm; 65 infants born at term
Fenchel et al. (2020)	Infants born 37–42 weeks scanned at PMA 40.92 ± 1.58 weeks	Typical development	50 participants; 23 participants returned for a second scan 2 years after their first scan
Galdi et al. (2018)	Preterm infants scanned at term-equivalent age (PMA at scan range 38–45 weeks; born before 32 weeks GA) Term infants (PMA at scan range 37–44 weeks; born after 36 weeks GA)	Preterm birth	46 participants 72 participants 104 ADHD; 94 controls 55 participants 55 participants
Geeraert et al. (2019)	6–15 years	Typical development	12 infants scanned within first week of life; 13 were imaged at 6 months of life
Geeraert et al. (2020)	6–16 years	Typical development	19 patients; 16 controls
Genc et al. (2017)	4–9 years	Typical development	145 children born very preterm; 33 term-born children
Hare et al. (2022)	Mean age = 5.45 years	ADHD and typical development	48 patients; 48 controls
Huber et al. (2019)	7–12 years	Typical development	43 children born very preterm
Jelescu et al. (2015)	1 day–2.8 years	Typical development	144 children born very preterm; 33 children born full term
Kansagra et al. (2016)	Term infants scanned at 1 week old and 6 months old	Infants with moderate to severe encephalopathy	
Karmacharya et al. (2018)	Infants with congenital heart disease (mean age: 39.54 ± 1.08 weeks) Controls (mean age: 42.03 ± 2.28 weeks)	Congenital heart disease	
Kelly et al. (2016)	Infants born very preterm (< 30 weeks' GA and/or < 1250 g) scanned at 7 years Controls (> = 37 weeks' GA); scanned at 7 years	Preterm and term birth at childhood	
Kelly et al. (2019)	Infants born and scanned at 38.6–39.7 gestational weeks	Congenital heart disease	
Kelly and Thompson et al. (2019)	Infants born < 28 weeks GA or < 1000 g; scanned at 7 years old	Very preterm birth	
Kelly et al. (2021)	7 years	Very preterm birth and term birth	

Table 1 (continued)

Citation	Participant age	Conditions	Sample size
Kimpton et al. (2021)	Infants born < 37 weeks GA and scanned before > 46 weeks PMA	Preterm birth	31 infants
Kunz et al. (2014)	Infants born 30–40 weeks gestation scanned at 40 weeks	Typical development	13 neonates
Kunz et al. (2015)	Preterm infants scanned: T1: 28–32 weeks T2 at 34 weeks (31–36 weeks) T3 at 40 weeks (39–43 weeks) corresponding to term equivalent age	Preterm birth	T1; $n = 9$, T2; $n = 8$, T3; $n = 14$
Kunz et al. (2013)	Infants born 29–40 weeks GA; scanned at 40 weeks	Typical development	6 neonates
Lynch et al. (2020)	6 months–18 years	Typical development	104 participants
Mah et al. (2017)	8–13 years	Typical development	27 participants
Murner-Lavanchy et al. (2018)	Very preterm (GA < 30 weeks) and 33 term-born (37 to 42 weeks' GA) children; follow-up at 2, 5, and 7 years	Children born preterm and full term	145 children born very preterm; 33 term-born children
Sato et al. (2021a, b)	Mean scan age = 5.75 years	Very low birth weight	41 children
Sato et al. (2021a, b)	Mean scan age = 5.8 years	Very preterm birth and term birth	41 children born very low birth weight; 26 children born full term
Shao et al. (2021)	Mean \pm SD age, 5.1 ± 6.2 years	Tuberous sclerosis	27 patients
Stoye et al. (2020)	24.0–42.0 GA; scanned at term-equivalent age	Preterm and term birth	36 preterm; 42 full term
Sullivan et al. (2020)	Mean GA at birth = 29 weeks Scanned at mean GA 29 ± 4 weeks	Preterm birth; scanned at term age	102 preterm infants
Vaher et al. (2022)	Preterm = 40.78 weeks mean GA Full term = 42 weeks mean GA	Preterm and term birth	141 preterm; 76 full term
Wang et al. (2022)	Preterm: born at ± 32.4 weeks GA; scanned at term age (40.3 ± 1.73) Full term = born at 40.06 ± 1.18 weeks GA; scanned at 41.11 ± 1.54 weeks GA	Preterm and term birth	73 preterm; 69 full term
Wheater et al. (2022)	Preterm: range = 23.28–34.84 weeks GA; scanned at mean 40 weeks GA Full term: range = 36.42–42.14 weeks GA; scanned at mean 42 weeks GA	Preterm and term birth	155 preterm; 103 full term
Young et al. (2019)	Preterm: born at < 32 weeks GA; scanned at 6.57 ± 0.34 years Full-term: born at > 37 weeks GA; scanned at 6.62 ± 0.37 years	Preterm and term birth	23 preterm; 24 full term
Zhao et al. (2021)	1 day to 14 years	Typical development	214 participants

***GA gestational age, PMA post-menstrual age, preterm = < 36 weeks GA, very preterm = < 28 weeks GA*

developmental processes generally proceed in a posterior-to-anterior and inferior-to-superior fashion, establishing the structural and functional architecture of the developing brain, and laying the foundation for future cognitive and behavioral development (Giedd et al. 1999; Diamond 2002).

Rapid brain development occurring during the first years of life positions the brain at approximately 90% of adult volume by 2 years of age (Pfefferbaum et al. 1994; Courchesne et al. 2000; Lenroot and Giedd 2006). Remarkable macro- and microscopic remodeling of the brain continues with age including reductions in gray matter volume and increases of white matter volume (Giedd et al. 2012), and rapid increases in neurite density, accompanied by slower increases in fiber orientation dispersion in childhood and adolescence (Chang, Owen et al. 2015). As these structural neurodevelopmental changes coincide with ongoing emergence and refinement of brain function and behavior, it is critical to understand how the developmental time course of the brain's microstructure and organization in early life occurs. Advanced dMRI techniques of infants and young children provide the ability to probe and study these processes.

Dysmaturation of the brain in preterm birth

Infants born preterm have a particular vulnerability to disruption of early neurodevelopmental processes (Ment and Vohr 2008), placing them at high risk for motor, cognitive, and behavioral deficits which become more apparent in later childhood (Saigal and Doyle 2008). Preterm birth is also associated with an increase in risk for psychiatric disorders in adulthood (Nosarti et al. 2012). Much of the dMRI work conducted in early infancy and childhood has been conducted in preterm infants to learn about early injury and outcomes associated with being early and therefore we review this work here. In particular, we will refer to infants born at 32–37 weeks of gestation as preterm, and infants born between 28 and 32 weeks of gestation as very preterm. Gestational age (GA) refers to the total number of weeks of gestation, whereas post-menstrual age (PMA) refers to the number of weeks of gestation plus the postnatal age.

Advanced diffusion MRI techniques in studies of brain development

Diffusion MRI has been widely used to characterize changes in brain microstructure across the life span (Lebel et al. 2012; Dean et al. 2018a, b; Beck, de Lange et al. 2021; Zhao, Shi et al. 2021); however, comparatively less work has focused on the critical period of development occurring in infants and young children. This is in part due to the challenges of acquiring and analyzing dMRI data in this population (see “Challenges of acquiring dMRI data in Infants

and Young Children”). Together with the inherent limitations of the DTI model (Soares et al. 2013), the application of dMRI techniques beyond DTI (which we refer as ‘advanced dMRI’) is necessary to obtain a more comprehensive depiction of the microstructural components of the developing cerebral cortex.

Diffusion kurtosis imaging (DKI)

Patterns of anisotropic diffusion arise in complex biological systems where the diffusion of water is constrained by the presence of crossing myelinated and unmyelinated fibrous axons, resulting in the diffusion distribution to deviate from a Gaussian distribution. Diffusion kurtosis imaging (DKI) aims to extend the DTI model and attempts to estimate the degree to which water diffusion deviates from a single Gaussian model (Jensen et al. 2005; Lu et al. 2006; Steven et al. 2014; Arab et al. 2018). As such, DKI is sensitive to the restricted and non-Gaussian diffusion effects in evaluating brain tissue microstructural complexity (Hui et al. 2008; Kelm et al. 2016). Analogous to DTI, DKI defines several rotationally invariant measures from the kurtosis tensor to quantify tissue microstructure: kurtosis anisotropy (KA), mean kurtosis (MK), axial kurtosis (AK), and radial kurtosis (RK) (Jensen and Helpert 2010). Moreover, since DKI is an extension of the diffusion tensor model, DKI allows for the estimation of all DTI metrics.

Given that the DKI model is not restricted to anisotropic environments, additional information can be gleaned from kurtosis metrics regarding the microstructural organization of the cortex in both gray and white matter compared to DTI (Lu et al. 2006). However, study protocols of DKI require diffusion weighted images (DWI) to be collected with at least 2 non-zero *b*-values in at least 15 independent diffusion gradient directions, whereas DTI requires a single *b*-value collected in at least six independent diffusion gradient directions (De Santis et al. 2011; Veraart et al. 2011). Although the DKI protocols necessitates a slightly more complex DWI data acquisition compared to DTI, the multi-shell DWI acquisition allows for increased sensitivity to diffusion properties in isotropic and anisotropic environments (Jensen and Helpert 2010). As such, DKI approaches may offer increased sensitivity to the rapid and ongoing neurodevelopmental processes occurring in early developmental periods, including neuronal and dendritic organization and myelination of white matter tracts. In “Applications of DKI in studies of brain development”, we review studies of brain development utilizing DKI.

Applications of DKI in studies of brain development

Recent interest has been placed on incorporating DKI analysis into studies of human brain development for improved

characterization of the tissue microstructure, with a particular interest in extending the application of dMRI to quantify diffusion features of isotropic tissue environments. While work utilizing DKI in children 0–10 years is limited, studies have adopted the framework for describing microstructural maturation in cohorts of healthy infants and children (Li et al. 2012; Paydar et al. 2014; Shi, Yang et al. 2019), pre-term infants (Shi, Chang et al. 2016; Ouyang et al. 2019a, b), and infants and children with neurological and/or developmental disorders (Gao et al. 2012; Zhang et al. 2013; Chinnadurai et al. 2016; Zhang et al. 2016; Zhang, Li et al. 2017; Zheng et al. 2017, Chen et al. 2020; Zheng, Lin et al. 2021).

To complement and build on existing knowledge regarding the rapidly changing microstructural features of brain development from birth to 4.5 years with improved accuracy, a study utilizing DTI and DKI reported differential time to plateau between FA and MK in white matter regions of the corpus callosum, frontal and parietal white matter, and anterior and posterior limbs of the internal capsule (Paydar et al. 2014). Specifically, study findings show that around 2 years of age, MK continues to rise while FA during this period reaches a plateau (Paydar et al. 2014). Results provide evidence for the improved sensitivity of DKI to further resolve isotropic diffusion barriers occurring in typical developmental processes and capture aspects of white matter maturation beyond the peak of myelination and axonal packing during the first 4 years of life. This same developmental pattern was replicated in a larger sample and across a wider age range from birth to 14 years (Shi, Yang et al. 2019) further implicating MK as an improved measurement for describing features of microstructural brain development. Moreover, DKI measures changed more rapidly than DTI measures across the first 14 years of life in both gray and white matter (Shi, Yang et al. 2019) thereby suggesting an advantage of kurtosis in quantitatively describing microstructural properties of infant to adolescent brain development over DTI. While both studies implemented a cross-sectional and region of interest (ROI) study design, longitudinal work is needed to resolve these changing microstructural features within individuals across the whole brain.

In addition to regional analyses of the brain's microstructure, whole brain analysis of DKI parameters were performed using tract-based spatial statistics (TBSS) in white matter. Microstructural differences have been reported across major white matter pathways between groups of children 1–6 years old (Li et al. 2012). Though the sample size used in this analysis does not provide sufficient power for whole brain analysis ($n = 10$), preliminary findings implicate TBSS as a potential method to yield higher sensitivity with DKI. However, more work with larger samples of individuals in this age range are necessary to better define microstructural brain changes occurring during this developmental period.

Studies have also focused on utilizing DKI to characterize the brain's microstructural characteristics in infants born preterm. For example, differential cortical microstructural profiles and maturational patterns were observed across the entire cortex using DKI-derived MK and FA measurements (Ouyang et al. 2019a, b). While MK was observed to decrease most rapidly with age in occipital lobes, the area where FA showed the most rapid decreases was the prefrontal cortex. The differential cytoarchitectural profile of diffusion between DTI and DKI and emphasizes the improved ability of DKI to measure the rapid and dynamically changing microstructural features of neurodevelopment. In infants of the same gestational age, another study found that MK was more positively correlated with age in within deep gray matter regions compared to FA (Shi, Chang et al. 2016). Taken together, these studies further suggest greater specificity of DKI for identifying key characteristics of early developmental processes that DTI may be less sensitive to.

Outlining the cytoarchitecture of developmental trajectories not only awards us a deeper understanding of the emerging structural supports of cognitive and behavioral development, but also provides critical information regarding the structural development of aberrant trajectories foundational to various sensory and neurodevelopmental disorders in early childhood. Using voxel-based morphometry, MK and MD differentially revealed microstructural differences in gray and white matter between children 3–11 years old with and without epilepsy (Zhang et al. 2013). In a broader age range of children 4–13 years, Zhang et al. 2016 reported differential microstructural abnormalities between children with epileptic with waveforms originating in the left or right hemispheres, further revealing the heightened sensitivity of DKI to quantitatively describe structural abnormalities associated with epilepsy (Zhang et al. 2016). A small study ($n = 8$ per group) preliminarily applied DKI to understand the structural brain differences in children 5–7 years old with and without temporal lobe epilepsy (Gao et al. 2012), finding higher MK in both temporal white and gray matter in the patient group compared to the control group, whereas only MD in gray matter was significantly different in the DTI analysis. Overall, these studies suggest that DKI is more sensitive than DTI for detection of microstructural abnormalities of epilepsy. Future work employing longitudinal study designs with larger patient samples will improve the currently lacking understanding of structural brain changes associated with the development of epilepsy and other neurodevelopmental disorders arising in childhood.

DKI has also been shown to improve the understanding of the structural brain changes associated with sensorineural disorders in children (Chinnadurai et al. 2016; Zheng et al. 2017). Preoperative microstructural changes have been detected with DKI in the white and gray matter of 1-to 7-year-old children with sensorineural hearing loss

(SNHL) (Zheng et al. 2017). SNHL patients 1–3 years old exhibited significant widespread changes in FA accompanied by a lack of change in MK in any region. Based on these findings, this paper argues that DKI analysis may play an essential role in gaining a more comprehensive understanding of developmental delays effecting auditory, speech, and emotional responses in SNHL and will serve to inform better and earlier treatment plans for affected children.

In the more extreme case of pediatric hearing loss, cochlear nerve deficiency (CND), treatment plans are limited compared to SNHL as children are ineligible to receive cochlear implants due to the degeneration of the cochlear nerve. Focused on auditory and language centers, DKI measures of MK and RK showed significant age-related increases in the control group and were absent in children with CND (Chinadurai et al. 2016). Although this study was conducted over a wide age range (2 months – 17 years) and small sample size per group ($n=25$), it highlights the ability of DKI to provide important information regarding disruption of auditory tract maturation in CND which will aid in improved detection and earlier diagnosis of CND over the diffusion tensor method. Additionally, DKI has also been shown to detect differential microstructural profiles of newborns with bilirubin encephalopathy (Zhang, Li et al. 2017; Zheng, Lin et al. 2021) consistent with known patterns of neurological damage associated with the disorder, with MK shown to be a sensitive indicator of the severity of brain damage.

Collectively, these studies suggest DKI may provide more sensitive measures over those from DTI for resolving the brain's microstructure during development. However, the method is not without limitations. First, DKI modeling requires multi-shell data acquisition. Hence, it cannot be used to analyze existing DTI data acquired with a simpler protocol utilizing a single non-zero b-value. Multi-shell acquisitions are also often longer and therefore more challenging to acquire in pediatric populations because of concerns of motion artifact and non-compliance. Moreover, the need to acquire images with increased diffusion weightings can cause the acquisitions repetition and echo times to be longer which, consequently, can result in reduced signal-to-noise ratio (SNR). This reduced SNR in acquired images, combined with the fact that DKI is a more complex model with 21 independent parameters (compared to DTI's 6), can result in model fits that are noisier, more prone to artifact, and less precise (Henriques, Correia et al. 2021). Finally, while DKI (and DTI) is a signal representation model that does not explicitly make assumptions regarding the underlying tissue composition or microstructure, further work validating and examining the sensitivity and *specificity* of the DKI-derived measures is needed to improve the interpretation of DKI metrics, particularly during early developmental ages.

White matter tract integrity with DKI

Studies discussed in “Applications of DKI in studies of brain development” used DKI parameters directly to inform about microstructural brain development, however, additional microstructural models using the diffusion and kurtosis tensor framework have been developed to provide measures specific to tissue microstructure (Zhou, Tong et al. 2020). One such model is the white matter tract integrity (WMTI) model, which characterizes diffusion in white matter within two non-exchanging compartments, the intra- and extra-axonal compartments (Fieremans et al. 2011). Metrics derived from WMTI include axonal water fraction and the compartment specific diffusivities including intra-axonal, axial, and radial diffusivities. It is thought that axial diffusivity from WMTI is related to structural changes along the axonal bundle in both the intra- and extra-axonal spaces (Fieremans et al. 2013), whereas the radial component is reflective of myelination (Jelescu et al. 2016).

One recent study has used WMTI to interpret DKI metrics with more specificity in neonates (Li et al. 2022). WMTI was able to demonstrate age-related changes in microstructure in agreement with maturational sequences past what the diffusion tensor metrics were sensitive to. Further, this study computed Mahalanobis distance based on DTI ($D_{M,DT}$) and WMTI ($D_{M,DT-KT}$) metrics to compare correlations with age and a generalized neurobehavioral score. Study findings show that $D_{M,DT-KT}$ demonstrated a stronger negative correlation with age and the neurobehavioral score compared to $D_{M,DT}$ and in agreement with known maturational patterns. Overall, findings from Li 2021 et al. 2022 demonstrate the benefits of multiparametric analysis with DKI in further understanding white matter maturational processes in neonates and highlight the potential for biophysical models to advance our knowledge of human brain development.

Constrained spherical deconvolution (CSD)

White matter is comprised of tightly packed fiber bundles of axons that introduces a directional preference of water diffusion along the fibers. dMRI images acquired across multiple non-collinear encoding directions can be used to infer the directionality and orientations of the fibers, providing an indirect measure of underlying tissue density (Jeurissen et al. 2014). Fiber tractography methods then can be applied to constrict local and long-range white matter pathways across the brain. While DTI based tractography methods have been most widely used (Basser et al. 1994), issues with model validity arise, especially in areas of densely crossing fibers, causing inaccuracies in white matter tract estimation that propagate through analysis (Pierpaoli et al. 2001; Behrens, Berg et al. 2007). Constrained spherical deconvolution (CSD) (Tournier et al.

2004, 2007; Jeurissen et al. 2014; Dhollander and Connelly 2016), on the other hand, assumes the dMRI signal of a single white matter voxel can be represented as the spherical convolution of the white matter response function (RF) and the fiber orientation distribution (fOD). Leveraging high angular resolution diffusion imaging with at least one non-zero b-value, CSD can overcome the crossing fiber limitation of the DTI model in white matter. As such, CSD has become one of the most widely used methods to estimate white matter fiber orientation information from dMRI data.

CSD has been extensively used in pediatric research to generate improved white matter tractograms for analysis of white matter connectivity (Thompson et al. 2016; Pascoe et al. 2019; Craig et al. 2020; Ní Bhroin, Abo Seada et al. 2020; Sa de Almeida, Meskaldji et al. 2021), morphology (Liégeois et al. 2013a, b; Liégeois et al. 2013a, b; Kelly, Cheong et al. 2014; Kelly, Chan et al. 2015; Fiori et al. 2016, Murray et al. 2016, Hyde et al. 2021), and microstructure (Liégeois et al. 2013a, b; Liégeois et al. 2013a, b; Kelly, Cheong et al. 2014, Thompson et al. 2014; Kelly, Chan et al. 2015, Fiori et al. 2016; Murray et al. 2016; Batalle et al. 2017; Salvan et al. 2017; Murner-Lavanchy et al. 2018; Banfi et al. 2019; Polspoel et al. 2019; Hyde et al. 2021; Toescu et al. 2021), with more recent work focusing on deriving quantitative metrics from CSD to describe white matter organization. For example, the amplitude of the fOD, also known as the apparent fiber density (AFD), has been proposed as a fiber bundle specific measure providing information about location and orientation of fiber bundles (Raffelt et al. 2012). Statistical methods, such as fixel-based analyses (FBA) methods (Raffelt et al. 2015, 2017), can also be utilized in conjunction with CSD fODs to delineate multiple fiber bundle populations within a voxel, enabling derivation of fixel-wise metrics sensitive to axonal density/packing Fiber Density (FD), fiber bundle cross-sectional size Fiber Cross-section (FC), and a combined measure of both micro- and macro-structure fiber density and cross-section (FDC). While voxels contain information from multiple distinct fiber populations, information contained in fixels relate directly to the underlying white matter anatomy, thereby awarding increased specificity to white matter fiber pathways compared to diffusion tensor tractography (Jeurissen et al. 2011; Reijmer, Leemans et al. 2012). Further, FBA offers two major advantages over alternative dMRI analysis techniques including sensitization to microstructure-specific properties independent of local fiber geometry, and specificity of the analysis and results with respect to individual fiber-specific effects (Dhollander, Clemente et al. 2021). As such, application of CSD techniques, particularly FBA, is of major interest to the study of early brain microstructural development.

CSD applications of fixel-based analysis in studies of brain development

A large body of the work utilizing CSD and FBA to study white matter development focuses on populations of infants born preterm (Pannek et al. 2018; Pecheva, Tournier et al. 2019; Pannek, George et al. 2020; Chandwani, Kline et al. 2021; Liu, Gao et al. 2021; Chandwani, Harpster et al. 2022; Liu, Wu et al. 2022). Non-linear positive relationships with age have been reported with FD, FC, and FDC throughout white matter in infants (Pannek et al. 2018, Pecheva, Tournier et al. 2019; Liu, Gao et al. 2021; Liu, Wu et al. 2022), female children 4–7 years old (Dimond, Rohr et al. 2020a, b), and children 8–10 years old (Barendse, Simmons et al. 2020) highlighting infancy and early childhood as a period of ongoing dynamic white matter maturation. Large-scale studies leveraging data from the developing Human Connectome Project (dHCP) also report that non-linear age-related increases in FD have similar developmental patterns between infants born preterm and full term scanned (Liu, Gao et al. 2021; Liu, Wu et al. 2022).

Preterm infants scanned at term-equivalent age have also been shown to have reduced FD, FC, and FDC across white matter, including regions of the corpus callosum, anterior commissure, corticospinal tract, optic radiations, and cingulum (Pannek et al. 2018). Interestingly, within the very preterm infants, improved neurodevelopmental outcomes at 1 year were associated with higher FC, FC, and FDC at term-equivalent age (Pannek, George et al. 2020). This suggests that these improved outcomes may be related to increased number of neurons, increased myelination, thicker bundles, and/or combinations thereof. Using FBA, higher FD, FC and FDC, predominantly in visual, sensorimotor and corticothalamic/thalamic–cortical tracts, were associated with better math computation ability in 7- and 13-year-old children, irrespective of their gestational age at birth (very preterm vs. full term) (Collins, Thompson et al. 2021). Children born very preterm have also been reported to have lower FD, FC, and FDC across major white matter tracts at 7 and 13 years compared to their term-born peers, and demonstrate slower FDC development in the corpus callosum and corticospinal tract (Kelly et al. 2020a, b).

CSD has also been an important tool for delineating white matter organization and differences that may arise with early injury. A recent study of infants with hypoxic–ischemic encephalopathy (HIE) reports reduced FD in widespread white matter tracts in HIE infants compared to controls (Jeong et al. 2022). Pretzel et al. 2022 applied CSD-derived FBA to investigate the long-term effects of neonatal arterial ischemic stroke in 7-year-old children (Pretzel, Dhollander et al. 2022); reporting reduced FD and FDC within the parietal and temporal white matter of the affected hemisphere, as well as within interhemispheric connecting

tracts. CSD-derived fixel-based measures of white matter in major sensorimotor tracts have been shown to be independently associated with early diagnosis of cerebral palsy in infants born very preterm scanned at term-equivalent age (Chandwani, Kline et al. 2021). Another study used FBA to investigate the white matter contribution to visual-behavioral problems in infants born very preterm (Chandwani, Harpster et al. 2022); they report higher FD, FC, and FDC of the left posterior thalamic radiations, left inferior longitudinal fasciculus, right superior longitudinal fasciculus, with left inferior fronto-occipital fasciculus significantly associated with better early visual attention and visual communication abilities. These findings highlight the potential of CSD-derived FBA metrics for identifying early white matter markers of neurodevelopmental impairments associated with early birth.

Recent work has further investigated the relationship between maternal cancer and treatments during pregnancy on child brain morphology at 9 years of age (Blommaert, Radwan et al. 2020); finding both cancer and chemotherapy in pregnancy are related to FD, FC, and FDC differences in the posterior corpus callosum and its tapetal fibers compared to controls, however, these differences did not relate to collected psycho-behavioral parameters. CSD-derived fixel-based measures have also been used to understand the associations between maternal depression and white matter organization in infants (Lautarescu et al. 2020) and children (Bleker, Milgrom et al. 2019; Bleker et al. 2020). Maternal depressive symptoms were positively associated with infant FD in the left and right uncinate fasciculus, with left uncinate fasciculus FD positively associated with social-emotional abilities in toddlerhood (Lautarescu et al. 2020); however, as this study only included male infants, more work is needed to investigate potential sex differences. Preliminary studies conducted in children between 5 and 7 years also suggest cognitive therapies for mothers during pregnancy may mitigate negative neurodevelopmental outcomes in children; however, small sample sizes and attrition limit interpretation of this work (Bleker, Milgrom et al. 2019; Bleker et al. 2020). Further work with FBA is needed to investigate the relationship between intrauterine environments and early white matter development.

Overall, these studies highlight the importance of CSD and FBA metrics for studying the developing white matter micro- and macrostructure. FBA addresses two major limitations of voxel-based analysis regarding the sensitization to multiple fiber orientations independent of local fiber geometry and increased specificity for detecting axonal changes along a fiber tract across voxels (Raffelt et al. 2015). However, challenges exist within this framework that must be acknowledged. For example, direct comparison between voxel- and fixel-based analyses is complex as it is difficult to relate the nature of effects of voxel-wise diffusion metrics to

a given fiber-specific effect without making strong assumptions (Dhollander, Clemente et al. 2021). CSD requires complex dMRI protocols as it relies on high angular resolution diffusion imaging data containing at least one non-zero b -value. Based on work from Tournier et al. 2013, the ideal b -value used should be between 2500 and 3000 s/mm² acquired in at least 45 diffusion gradient directions (Tournier et al. 2013). Such acquisitions can result in longer scan times and reduced SNR. Another limitation of CSD-derived FBA is in the interpretation of the apparent fiber density metric, particularly at low b -values. As reviewed in Dhollander et al. 2021, at b -values used in DTI analysis (e.g., 1000 s/m²), signals from the extracellular space will contribute to and bias the apparent fiber density metric, and thus challenging biological interpretation (Dhollander, Clemente et al. 2021). However, when sampled at higher b -values (~3000 s/m²), more accurate measures of apparent fiber density can be estimated that are approximately proportional to the total amount of intracellular volume of axons due to the increased specificity to the intra-axonal water signal at higher b -values (Raffelt et al. 2012; Genc et al. 2020).

Biophysical models of dMRI in studies of brain development

Advancements in dMRI data acquisition methods and imaging gradient hardware have allowed for development of stronger diffusion weighting with b -values up to 3000 s/mm² and beyond. Such innovations have paved the way for development of novel biophysical models of the diffusion weighted signal to enhance our understanding of emerging microstructural organization supporting neurodevelopment and its disorders (Clark and Le Bihan 2000; Tuch et al. 2002; Assaf and Basser 2005). Biophysical models aim to improve the specificity of dMRI measures and characterize underlying tissue composition by parametrizing the dMRI signal as a function of biophysical tissue properties, such as neurite density.

There has been great interest in the use of dMRI biophysical models, such as CHARMED and NODDI, for investigating brain microstructure and changes with development and disease across the lifespan (Kunz, Zhang et al. 2011; Kunz, Zhang et al. 2013; Kunz et al. 2014; Chang, Owen et al. 2015; Dean et al. 2017; Collorone et al. 2020; Dimond, Heo et al. 2020a, b; Matsuoka et al. 2020; Andica et al. 2021; Dean et al. 2021). Such quantitative neuroimaging allows for computation of *in vivo* virtual histology and provides insight into the cellular architecture supporting various developmental trajectories of the brain. This has certainly been observed in studies of infant brain development. In the subsequent sections, we review and comprehensively discuss applications of CHARMED (“Composite hindered

and restricted model of diffusion (CHARMED)”) and NODDI (“Neurite orientation dispersion and density imaging (NODDI)”) models to elucidate key features of brain development in early life.

Composite hindered and restricted model of diffusion (CHARMED)

One such model, composite hindered and restricted model of diffusion (CHARMED), was developed to express the signal decay observed in terms of hindered and restricted diffusion contributions (Assaf et al. 2004). Specifically, the CHARMED framework models the dMRI signal as contributions from a hindered and restricted compartment. The CHARMED model assumes cylinders that have radii following a gamma distribution (Assaf et al. 2008), forming bundles with distinct orientations. CHARMED allows for tissue modeling of intracellular and extracellular tissue compartments, offering the opportunity to probe axonal changes associated with development in white matter. In particular, the CHARMED model also assumes that the extra-axonal volume to be represented by the hindered contribution follows Gaussian decay, whereas the intra-axonal volume is represented by the restricted contribution that follows a non-Gaussian decay (Assaf and Basser 2005). With CHARMED, estimates of various microstructural white matter parameters can be obtained including fiber orientation, the T2-weighted fractions of extra and intra-axonal spaces, and intra-axonal diffusivity, as well as the net displacement distribution produced by water diffusing in both compartments. Despite these estimates enabling new and important insights into the microstructural composition of the maturing brain, few studies have utilized the CHARMED model in the study of early brain development.

Applications of CHARMED in studies of brain development

To date, only one peer-reviewed study has applied CHARMED to assess white matter microstructure in newborns (Kunz et al. 2014), differentiating white matter intra-axonal water fraction and axonal dispersion in alignment with expected patterns of maturation (Kunz et al. 2014). Additionally, intra-axonal water fractions were lower in late-maturing white matter regions, highlighting CHARMED’s sensitivity to contribute insights into the cellular architectures of the developing brain. These findings are further supported by a preliminary study of infants ($n = 6$) that reported lower values of intra-axonal volume from CHARMED in the posterior limb of the internal capsule compared to the corpus callosum (Kunz, Zhang et al. 2013). Another earlier preliminary study in infants ($n = 3$) shows that the intra-axonal volume fraction from CHARMED was significantly higher in the corpus

callosum than in the corticospinal tract, and lower than previously reported in adults (Kunz, Zhang et al. 2011) suggesting feasibility of CHARMED in the newborn brain.

While these studies using demonstrate the potential of the CHARMED framework to differentiate between microstructural features of developing white matter, a significant limitation has been the dearth of studies utilizing CHARMED to investigate early brain development. The white matter nature of the CHARMED model also limits the application of CHARMED to studies of gray matter microstructure as it may bias estimates of dendritic density (Alexander, Dyrby et al. 2019). Further, the intra-axonal signal arising from the restricted diffusion compartment is determined by the cylinder radius and the intrinsic diffusivities parallel and perpendicular to the cylinder. However, parallel cylinders assumed by CHARMED do not account for complex axonal configurations, such as bending and fanning fibers, that therefore may not fully capture the complexity of white matter fiber orientation. As such, it is critical to take a multimodal neuroimaging approach with biophysical modeling of dMRI to isolate key features of neurodevelopment where other models are limited.

Neurite orientation dispersion and density imaging (NODDI)

In addition to CHARMED, another multicompartment biophysical dMRI modeling technique that has gained much interest and use has been the neurite orientation dispersion and density imaging (NODDI) (Zhang et al. 2012) model. NODDI aims to improve the microstructural specificity by modeling diffusion within three distinct biological tissue microenvironments: the intracellular compartment including axons and dendrites, the extracellular compartment including glial cells, and the extracellular CSF free-water compartment. This multicompartment system allows for estimation of free, hindered, and restricted diffusion compared to CHARMED, which allows for only hindered and restricted diffusion.

Like CHARMED, NODDI requires a multi-shell acquisition, with at least two non-zero shells and typically a larger number of diffusion gradient directions (Zhang et al. 2012; Nazeri et al. 2020). While this slightly more complex data acquisition can result in longer scan times compared to DTI and DKI, these modifications allow for increased sensitivity of dMRI to diffusion barriers. The NODDI model provides quantitative metrics sensitive to neurite and axonal densities (NDI), characterizes the extent of orientational dispersion of axonal projections (ODI), and quantifies the isotropic signal fraction (fISO), while these parameters can additionally be utilized to describe diffusion properties in both gray and white matter.

Applications of NODDI in studies of brain development

NODDI has been applied in developmental research to describe the dynamically changing structural properties of the brain occurring from infancy to adolescence, and their role in supporting various behavioral outcomes. NDI and ODI have been shown change across the lifespan following consistent trajectories as other diffusion metrics (Lebel et al. 2012; Dean et al. 2017; Dimond, Heo et al. 2020a, b). Given the ability of NODDI to capture neurodevelopmental processes of myelination and axonal organization (Kunz et al. 2014; Jelescu et al. 2015; Dean et al. 2016; Dean et al. 2018a, b), NODDI has been of particular interest in the study of brain development in infants and children. Additionally, NODDI allows for increased biological specificity in gray matter compared to single-compartment models of diffusion (Nazeri et al. 2020). As such, NODDI is viewed a powerful tool for delineating microstructural changes that support child well-being and potentiates the early identification of aberrant developmental processes foundational to behavioral disorders arising in early childhood.

Complementary to information provided by DTI, information gleaned from NODDI demonstrates that infants at 1-month display hemispheric and regional variations in white matter microstructure (Dean et al. 2017) suggesting the central-to-peripheral and posterior-to-anterior developmental gradient of white matter is already apparent at 1 month. Comparable patterns of neurodevelopment were also observed in infants scanned across the first 8 weeks of life (Fenchel et al. 2020). When used to study white matter maturation in the developing brain of newborns, NODDI metrics differentiated between the spatiotemporal dynamics of myelinated white matter fibers (posterior limb of the internal capsule) versus fibers that have not yet been myelinated (anterior limb of the internal capsule) in terms of intra-axonal water fraction (fISO) and axon dispersion (ODI) (Kunz et al. 2014). Dowe et al. 2020 investigated the relationship between white matter microstructure of attention networks at 1-month and attention indices at 6 months reporting a positive association of NDI and FA with attention scores at 6 months of age (Dowe, Planalp et al. 2020). Findings suggest that increased white matter microstructure in this network plays a key role in early attentional development, with the structural groundworks of emerging behavior already established at 1 month.

NODDI has further been used to investigate associations between early environmental influences and measures of brain development. For example, investigation into the link between maternal prenatal depression and anxiety on infant brain development at 1-month of age revealed lower NDI in white matter of full-term infants born to mothers with heightened, albeit sub-clinical, depression and anxiety symptoms (Dean et al. 2018a, b). Interestingly, this study

reported a significant sex-by-symptom interaction; higher levels of maternal depression and anxiety were associated with higher white matter FA and NDI in males compared to females. However, in the left amygdala, higher maternal cortisol was associated with higher FA and lower ODI in females compared to males (Stoye, Blesa et al. 2020) providing mechanistic insights by which maternal psychological state may modulate infant brain development in gray matter regions. Expanding on these findings, Dean et al. 2021 identified a latent mechanism by which maternal depression and anxiety negatively regulate white matter microstructural development through epigenetic alterations in fetal and placental DNA methylation patterns (Dean et al. 2021). Specifically, differentially methylated genomic positions were associated with decreased NDI in the left hemisphere sagittal striatum. Overall findings suggest an important association between prenatal maternal psychological state and microstructural brain development in a sex-specific manner and warrants further longitudinal investigations in larger samples of infants across a wider age range.

Collectively, these NODDI studies contribute new knowledge and understanding of normative microstructural brain development. The overarching findings of these studies strongly emphasize the dependence of structural brain organization on biological and environmental processes occurring in utero prior to major influence by postnatal experience.

Applications of NODDI in the preterm brain

NODDI studies have also reported an association between prematurity reduced NDI in white matter related to the degree of prematurity at birth (Batalle et al. 2017). However, across approximately 30–40 gestational weeks, NDI increases rapidly in white matter of the primary motor and somatosensory tracts and slower in association tracts (Kunz et al. 2014; Kimpton et al. 2021). When compared to their term peers, preterm infants between 37 and 45 weeks PMA demonstrated decreased NDI in occipital, parietal, temporal, and somatosensory cortices (Dimitrova, Pietsch et al. 2021) indicating a less mature pattern of tissue organization in the preterm brain even at the age of term equivalence. Consistent with less coherent white matter organization in preterm vs. term-born infants, infants born preterm and scanned at term-equivalent age also show higher variability in water content (toward higher values) and intra-axonal volume (toward lower values) which is further implicated by an overall higher ODI across white matter tracts compared to term-born infants (Blesa et al. 2020). Elevated immune marker of IL-8, a characteristic feature of intrauterine and postnatal systemic inflammation, collected within the first week of life, was associated with white matter dysmaturation at term-equivalent age, thereby implicating the role of generalized inflammation

in the etiology of deviant developmental trajectories associated with preterm birth (Sullivan et al. 2020). Furthermore, associations between differential DNA methylation patterns and variations in white matter NDI have been reported in preterm infants (Wheater, Galdi et al. 2022), which may serve as potential mechanism for white matter dysconnectivity in developing neural networks in preterm infants.

Patterns of dysmaturation associated with preterm birth have also been explored using predictive modeling for computing relative brain maturation; infants scanned at term-equivalent age showed consistently lower brain maturation values than infants born at term, suggesting an overall delay in brain maturation (Galdi, Blesa et al. 2018). More recently, logistic regression and structural equation modeling was used to evaluate the predictive performance of PCA derived single-metric dMRI versus multi-modal information from DTI and NODDI (Vaher, Galdi et al. 2022), suggesting each dMRI metric provides additive aspects of the underlying microstructure that differ in preterm compared to term subjects. This work suggests a principled analytical approach may be favorable in future investigations of the upstream determinants and neurocognitive consequences of altered white matter maturation (Vaher, Galdi et al. 2022).

Beyond white matter, NODDI is also increasingly being utilized to study the gray matter microstructure. A study of premature infants scanned between 25 and 47 weeks PMA reported increases in ODI in gray matter up to 38 weeks followed by a plateau, whereas NDI increased after 38 weeks (Batalle et al. 2019). This increase in NDI is also observed in cortical gray matter of very preterm infants from 35 to 50 weeks (Eaton-Rosen et al. 2015). These studies emphasize the developmental interplay between gray and white matter growth, where cortical organization prior to approximately 38 weeks PMA is predominantly governed by dendritic arborization and growth, while the period after 38 weeks is governed by increasing cellular and organelle density. Complementing these findings, a study of preterm neonates scanned at term age observed FA increases were strongly correlated with NDI, but not ODI (Kimpton et al. 2021), suggesting axonal growth density/packing or premyelination/myelination increases are mainly attributed during the preterm-to-term period, rather than changes in axon coherence or geometry. Moreover, a recent study utilizing the NODDI gray matter based spatial statistics framework (NODDI-GBSS) reported widespread decreases in NDI in both primary and higher-order association cortices in infants born preterm and scanned at term-age versus term-born infants (Wang et al. 2022). Future work is needed utilizing the NODDI-GBSS framework in longitudinal samples of infants, both preterm and term age, to better understand gray matter organizational patterns and their relationships to future cognitive outcomes.

Researchers have also used NODDI to understand the downstream developmental consequences of very preterm birth on white matter microstructure at 5 (Sato, Vandewouw et al. 2021a; b), 6 (Young, Vandewouw et al. 2019), and 7 (Kelly et al. 2016, 2021; Murner-Lavanchy et al. 2018; Kelly et al. 2020a, b) years of age. Increases in NDI were noted across a 5- to 7-week period in 7-year-old children born very preterm or with extremely low birth weight (Kelly et al. 2020a, b) consistent with trends reported in Dean et al. 2016 in children born full term (Dean et al. 2016). Compared with children who were born at term age, children born very preterm displayed lower FA and higher ODI values within many major white matter fiber tracts (Kelly et al. 2016; Young, Vandewouw et al. 2019). Children born very preterm also have been shown to demonstrate higher AD, RD, MD, and ODI and lower NDI within the fornix, along with higher ODI in the medial forebrain bundle at 7 years of age (Kelly et al. 2021).

In children born very preterm, lower NDI correlated with lower IQ (Kelly et al. 2016; Young, Vandewouw et al. 2019) and worse semantic performance (Murner-Lavanchy et al. 2018) in widespread white matter tracts. Interestingly, Young et al. 2019 reported that children in the full-term group followed an opposite trajectory with IQ, where high NDI and ODI across white matter tracts were negatively correlated with IQ (Young, Vandewouw et al. 2019), potentially highlighting a differential or compensatory developmental trajectory supporting cognitive processes in children born very preterm. Five-year-old children born very preterm and with very low birth weight < 1500 g, showed reductions in FA and NDI across widespread white matter regions compared to their term-born peers (Sato, Vandewouw et al. 2021a) indicating disrupted white matter maturation. Within group analyses reveal higher FA and NDI and lower RD and ODI are related to faster processing speed in children born very preterm and low birth weight, whereas children born full term showed decreased RD and NDI to be associated with better vocabulary acquisition and working memory (Sato, Vandewouw et al. 2021b). Using the TBSS framework to investigate white matter microstructure in 5-year-old children born very preterm and with low birth weight, another study reports significant positive relationships between FA and NDI and higher processing speed scores, and lower RD and ODI and improved processing speed (Sato, Vandewouw et al. 2021a; b). This work collectively provides a call to action for further research into the biological mechanisms supporting differential neurodevelopmental and cognitive outcomes in children born very preterm and with very low birth weight.

Throughout infancy and early childhood, widespread non-linear increases in NDI are observed across the first 3 years of life (Jelescu et al. 2015; Dean et al. 2016; Fenchel et al. 2020) continues to non-linearly increase to 7.5 years of age

(Dean et al. 2016; Dimond, Heo et al. 2020a, b), and plateaus at adolescence (Geeraert et al. 2019; Lynch, Cabeen et al. 2020). These increases in NDI from infancy to adolescence are more rapid in white matter than in gray matter (Zhao, Shi et al. 2021), are thought to reflect myelination and axonal packing (Genc et al. 2017) and constitutes prominent features of white matter development during early life. From infancy to adolescence, cross-sectional studies show that NDI exhibits stronger age-related changes in gray and white matter compared to DTI measures (Kunz et al. 2014; Genc et al. 2017; Mah, Geeraert et al. 2017). Age-related increases in NDI were also longitudinally detected in children 6–13 years scanned 2 years apart (Geeraert et al. 2019). ODI was also reported to increase with age cross-sectionally from 0 to 14 years with both NDI and ODI showing rapid increases in early childhood that slowed in adolescence (Zhao, Shi et al. 2021). Further longitudinal investigations are needed to better define individual rates of change occurring in early stages of brain development, and their relationship to behavioral development.

Applications of NODDI in clinical research and developmental disorders

Taking a multi-modal approach to understanding white matter microstructural maturation in children 6–16 years scanned two years apart, Geeraert et al. 2020 applied principal component analysis across DTI, NODDI, and inhomogeneous magnetization transfer (ihMT) (Varma et al. 2015a, b; Varma et al. 2015a, b; Manning et al. 2017) and multicomponent driven equilibrium single-pulse observation of T1/T2 (mcDESPOT) (Deoni et al. 2008) in white matter regions in the reading network (Geeraert, Chamberland et al. 2020). While study findings report age-related increases in tissue complexity in the left arcuate fasciculus and increases in myelin and axonal packing the bilateral arcuate, inferior longitudinal, inferior fronto-occipital fasciculi, and splenium, these morphological changes were not related to reading abilities in this cohort. However, contradictory to these findings, Huber et al. 2019 reports that an increase in NDI in the splenium correlate with reading skill in children 7–12 years of age (Huber, Henriques et al. 2019), although unlike Geeraert et al. 2020, this sample included children with dyslexia which may contribute to these differential findings.

In children with dyslexia, ODI and NDI in cortical regions responsible for language were found to be differentially correlated with measures of local gyrification compared to typically developing children suggesting that changes in cortical folding in dyslexia may be related to abnormal neurite organization (Caverzasi et al. 2018). Another study of children with dyslexia utilizing NODDI showed that compared to typical readers of the same age, children with dyslexia showed higher ODI in gray matter of

the left ventral occipitotemporal cortex (Borghesani et al. 2021). No differences in NDI were observed between groups in this cohort indicating a disorganization of neurite architecture in dyslexia, rather than myelination. More work is needed to clarify conflicting and varying findings across age groups and brain regions in dyslexia.

The dynamic neural events occurring during early-life position this developmental stage as both a critical period of neurodevelopment and a period of substantial vulnerability to suboptimal environmental conditions and adverse experiences that may alter developmental outcomes in childhood. A recent study applied NODDI to investigate the effects of heightened risk factors for adverse childhood experiences on brain development in children with and without attention deficit hyperactivity disorder (ADHD) (Hare, Dick et al. 2022). They report a significant group by risk interaction in children with ADHD such that a greater cumulative risk was associated with increased NDI in corpus callosum. This work highlights the role of early adverse childhood experiences in brain development between children with and without ADHD and demonstrates the sensitivity of NODDI to these neurodevelopmental differences and may serve as a foundation for the development of targeted interventions for children at high risk for adverse childhood experiences.

Recent work has highlighted the potential clinical utility of NODDI; see Kamiya et al. 2020 for a recent review of NODDI in clinical research (Kamiya, Hori et al. 2020). NODDI has been used in pediatric clinical research to understand the altered structural brain dynamics occurring early-life disorders. For example, in the case of perinatal clinical encephalopathy, NODDI metrics provided a more detailed characterization of microstructural maturation compared to FA (Kansagra et al. 2016), highlighting the clinical value of NODDI in detecting microstructural injury or insult related to perinatal encephalopathy. NODDI has also been used to detect structural brain alterations in neonates with congenital heart disease (Karmacharya et al. 2018; Kelly, Christiaens et al. 2019). Compared to controls, infants with congenital heart disease showed decreased ODI and increased NDI in major white matter tracts (Karmacharya et al. 2018), and decreases in ODI in cortical gray matter (Kelly, Christiaens et al. 2019). Findings are suggestive of an altered trajectory of brain development, potentially related to reduced brain oxygenation in this disorder, with NODDI metrics providing added sensitivity to tissue changes compared to historical methods such as DTI. NODDI has also been shown to be a valuable clinical tool in for assessment of structural brain abnormalities associated with tubers sclerosis complex (Shao et al. 2021), a rare genetic disorder that affects the central nervous system. Studies suggest promise for the application of NODDI in clinical pediatrics.

Taken together, this collection of studies provide evidence of the increased sensitivity of NODDI to microstructural

brain changes occurring in development across health and disordered states; however, there are important limitations to NODDI. While biophysical modeling relies on simplified assumptions of tissue properties, these assumptions must be extensively explored. For example, Guerrero et al. 2019 demonstrated that the default intrinsic parallel diffusivity of NODDI ($1.7 \mu\text{m}^2\cdot\text{ms}^{-1}$) is suboptimal for parameterizing the microstructural properties of the brain of 1-month-old infants and adult gray matter (Guerrero, Adluru et al. 2019) and suggest that optimal values for infants fall approximately between 1.4 and $1.5 \mu\text{m}^2\cdot\text{ms}^{-1}$ for white matter and 1.2 and $1.3 \mu\text{m}^2\cdot\text{ms}^{-1}$ for gray matter; however, no consensus has been reached on the optimal values. Additional work examining the influence of the intrinsic parallel diffusivity on infant NODDI parameter metrics is critical. Further, the competency of NODDI metrics to detect developmental changes is limited given by intrinsic model assumptions of fixed parallel intrinsic diffusivity and equality between parallel intrinsic diffusivity of the extra- and intracellular compartments (Zhang et al. 2012; Jelescu et al. 2015). To address this limitation, studies have utilized WMTI derived from DKI which provides estimates of intra-axonal axial diffusivities, axonal water fractions, fiber dispersion, extra-axonal axial and radial diffusivities, and tortuosity (Li et al. 2022). It is suggested that combining dMRI techniques with other imaging modalities can further enhance the sensitivity of dMRI to the variability of neurodevelopmental and pathological processes (Nazeri et al. 2020; Li et al. 2022).

Challenges of acquiring dMRI data in infants and young children

As previously discussed, dMRI is an incredibly powerful tool for studying the brain's microstructure. However, neuroimaging conducted in neonates and pediatric populations poses several unique challenges. First, advanced diffusion imaging acquisitions, such as high angular resolution diffusion imaging (HARDI) or multi-shell protocols, requires longer scan times and poses major challenges for obtaining motion-free data. dMRI data is highly susceptible to patient motion as it causes image blurring, ghosting, drop out, and other artifacts that ultimately degrade image quality. However, some of these motion artifacts can be corrected using post-processing techniques (Taylor et al. 2016); and alternative retrospective (Holdsworth et al. 2012; Kreilkamp et al. 2016) and prospective correction (Herbst et al. 2017; Berglund, van Niekerk et al. 2021) techniques is an active area of research that have great potential for mitigating dMRI motion artifacts in pediatric populations. Current clinical MRI protocols routinely utilize general anesthetics minimize motion (Arlachov and Ganatra 2012); however, the use of anesthesia for research purposes is not feasible

due to the health risks of sedation (DiMaggio et al. 2011). Alternative strategies of scanning during natural, non-sedated sleep have been employed in research settings to help reduce motion while scanning infants and young children (Raschle et al. 2012; Dean et al. 2014; Howell, Styner et al. 2018); however, these strategies have both significant advantages and limitations (Spann et al. 2022). For older children, typically around 4 years and older, strategies to acclimate the child to the MRI environment, such as playing scanner acquisition sounds, using 0-Tesla MRI simulator or mock scanner to practice remaining still during a scan (de Bie et al. 2010), and having children watch a movie or TV show during the scan have all been effective strategies for successfully acquiring dMRI data from children. Other training-based or visual feedback methods in which motion triggers a pause or reminder for the child to remain still have also been used (Woods-Frohlich et al. 2010). However, these training-based methods do not fully eliminate motion artifacts, especially for younger children, or children unable to follow verbal instructions. Preparation and behavioral based methods have also been proposed to include young autistic children in MRI studies (Nordahl et al. 2008) taking into consideration specific sensitivities and sensory needs of children. As with all of these pediatric neuroimaging strategies, it is critical to adopt and tune attitudes, attention, and efforts to these children, their families, and their broader communities (Spann et al. 2022).

In addition to motion, loud acoustic sounds, and long scan times, the small size of brain size of neonates to young children can additionally cause challenges in obtaining adequate SNR and requires increased resolution to avoid effects of partial volume artifact, which in turn increases scan times (Afacan et al. 2016). Additionally, signal inhomogeneities and variability in tissue characteristics are observed in early developmental stages originating from asynchronous temporal development of myelination across brain regions. The underdeveloped infant brain consisting of high-water content and low myelin, is accompanied by differential diffusion characteristics including longer relaxation times and differential diffusivity patterns and signal inhomogeneities (Dubois et al. 2014, 2021) in infants compared to adults. These challenges causes poor gray-white-matter contrast and can complicate brain segmentation methods (Wang et al. 2015). The emergence of large-scale studies, such as the “Developing Human Connectome Project” including fetuses and newborns between 20 and 44 weeks PMA and “Baby Connectome Project”, including children between birth to 5 years of age, have begun to pave the way for the development of advanced imaging protocols, motion correction methods, and improved neonatal atlases (Hughes et al. 2017; Cordero-Grande et al. 2018; Hutter et al. 2018; Howell et al. 2019; Chen et al. 2022). Furthermore, as diffusion characteristics in brain tissue continue to non-linearly change

with development with high variability, complications the application and interpretation across large age ranges arise. These large-scale studies, in addition to the recently announced Healthy Brain and Child Development (HBCD) study including newborns to 10 years (Volkow et al. 2021) will continue to help address these challenges of pediatric neuroimaging across data collection, processing, analysis, and interpretation.

Limitations of advanced dMRI and future directions

dMRI is the gold-standard for non-invasively obtaining information of the brain's microstructure *in vivo*; however, a challenge of dMRI research lies in the interpretation of the biological contributions to the measured diffusion weighted signal. As reviewed in Jelescu et al. 2020, biophysical models are built upon a simplified assumption of tissue properties, with model interpretations often referring specifically to axons or dendrites, while ignoring other cell types such as glial cells with similar geometry that may contribute to compartment signals (Jelescu, Palombo et al. 2020). For example, glial cells play a fundamental role in brain development and highly influence nervous system development from processes of neurogenesis and cell migration to the formation and fine-tuning of neural circuitry and synapse formation modeling contributions from microglial and astrocytes (Garcia-Hernandez, Cerdán Cerdá et al. 2022), the majority of biophysical dMRI models disregard the ensemble of cellular types contributing to brain development (and the dMRI signal). While it is of utmost interest to develop advanced biophysical models that can distinguish cellular features, validation and development of phantoms that can be used to evaluate such biophysical models is critically important. As discussed regarding the NODDI model, it has been suggested that model assumptions of tissue diffusion properties may also vary across age ranges and with pathology (Guerrero, Adluru et al. 2019), and therefore underlying assumptions of biophysical models are important to consider, while changing these assumptions could change estimated parameters and potentially contribute to false detected effects and biased interpretations. Indeed, recent work has further demonstrated uncertainty surrounding the interpretation of dMRI results detect neurodevelopmental differences in adolescents with 22q11.2 deletion syndrome (Raven et al. 2022). As dMRI measures are highly variable in neonatal and infant stages, the findings of reviewed studies are limited by uncertainty in the biological contributions to the detected patterns; more work is needed to improve specificity of biophysical models and their interpretation across early brain development in both normative samples and in developmental conditions, particularly in rare conditions conducive to

small sample sizes. Lastly, while biopsychical models do indeed demonstrate improved biological specificity compared to signal compartment models, DTI and DKI remain important in future dMRI studies as a 'baseline' comparison with no assumptions, constraints, or model fitting strategies. We encourage researchers to remain cautious in interpreting the biological contributions to the dMRI signal described by biophysical models.

Conclusions

In summary, technical and methodological challenges of pediatric neuroimaging in conjunction with inherent limitations of the DTI model warrant the investigation of the developing cortical and white matter microstructure with advanced modeling of the dMRI signal to obtain a more comprehensive depiction of the microstructural components of the developing brain. Advancements of technologies and techniques of dMRI over the past two decades have paved the way for momentous progress in our understanding of brain maturation in health and disease. The studies discussed suggest remarkable potential for advanced and multi-shell dMRI in describing the cellular architecture of early brain maturation and detecting structural abnormalities in various disordered states central to pathophysiology. The magnitude to which non-invasive neuroimaging with dMRI informs future child health positions it well for adoption into clinical practice. The neurobiologically informed nature of current biophysical models CHARMED and NODDI as well as their enhanced performance when coupled will undoubtedly continue to propel the field of neurodevelopment forward. Furthermore, statistical methods of dMRI such as fixel-based analyses have allowed for fiber-specific metrics to quantify white matter properties with improved specificity over voxel-based methods. With a deeper understanding of the developmental patterns occurring in early brain development detected by advanced and biophysical models of dMRI comes novel opportunities for early detection, diagnosis, and treatment of conditions during the earliest phases of establishment of neural foundations.

Author contributions MD conceptualized the review, reviewed literature, supervised team, drafted manuscript, revised and approved the final version. PGR and AG assisted with reviewing literature and creating table, and reviewed and approved the final versions. DCD conceptualized the review, drafted sections of manuscript, supervised team, and revised and approved the final version.

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Declarations

Conflict of interest The authors declare no competing interests, financial or non-financial, that relate to the current work.

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