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ORIGINAL ARTICLE

Gray matter based spatial statistics framework in the 1-month brain: insights into gray matter microstructure in infancy

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Abstract
The neurodevelopmental epoch from fetal stages to early life embodies a critical window of peak growth and plasticity in which differences believed to be associated with many neurodevelopmental and psychiatric disorders first emerge. Obtaining a detailed understanding of the developmental trajectories of the cortical gray matter microstructure is necessary to characterize differential patterns of neurodevelopment that may subserve future intellectual, behavioral, and psychiatric challenges. The neurite orientation dispersion density imaging (NODDI) Gray-Matter Based Spatial Statistics (GBSS) framework leverages information from the NODDI model to enable sensitive characterization of the gray matter microstructure while limiting partial volume contamination and misregistration errors between images collected in different spaces. However, limited contrast of the underdeveloped brain poses challenges for implementing this framework with infant diffusion MRI (dMRI) data. In this work, we aim to examine the development of cortical microstructure in infants. We utilize the NODDI GBSS framework and propose refinements to the original framework that aim to improve the delineation and characterization of gray matter in the infant brain. Taking this approach, we cross-sectionally investigate age relationships in the developing gray matter microstructural organization in infants within the first month of life and reveal widespread relationships with the gray matter architecture.

Keywords GBSS · Diffusion MRI · Microstructure · Neurodevelopment · Infant

Introduction

From early fetal stages to the first years of life, the brain undergoes immense morphological change that shapes its underlying structural and functional framework (Thompson et al. 2001; Douet et al. 2014; Teeuw et al. 2019; Gao et al. 2014), providing the foundation for the development of future cognition and behavioral skills (Ouyang et al. 2019a; Steinberg 2005). This period of peak growth and neural plasticity encompasses a window of vulnerability in which alterations believed to be associated with many neurodevelopmental and psychiatric conditions first emerge(Rees and Inder 2005; Bale et al. 2010; De Asis-Cruz et al. 2022; Al-Haddad et al. 2019; Oskvig et al. 2012; Smith and Pollak 2020; Hazlett et al. 2017; Marín 2016). In particular, gray matter structures and associated cytoarchitecture help govern key neuronal processes supporting motor abilities, sensory integration, and cognitive functioning(Arsalidou et al. 2013; Herrero et al. 2002; Catani et al. 2013) and are believed to play a critical role in various developmental

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conditions(DiPiero et al. 2022a, 2023; Rogers et al. 2014; Batty et al. 2010; Nakao et al. 2011). Therefore, understanding the early patterns of the brain's cortical development and organization, which is the goal of the current study, is important to characterize normative development and detect diverging patterns of neurodevelopment that may be central to future intellectual, behavioral, and psychiatric challenges.

Quantitative magnetic resonance imaging (MRI) techniques such as diffusion MRI (dMRI) allow for in vivo characterization of the microstructural organization of the brain. dMRI probes tissue microstructure by quantitatively describing the random motion of water molecules in restricted tissue environments(Afzali et al. 2021; Basser and Ozarslan 2009). Diffusion tensor imaging (DTI) is the most widely used dMRI technique, enabling quantitative examination of the brain's microstructure through the estimation of four scalar indices(Alexander et al. 2007): fractional anisotropy (FA), and mean (MD), radial (RD), and axial (AD) diffusivity. DTI metrics have been widely utilized in studies of neonatal white matter maturation(Qiu et al. 2015; Gao et al. 2009; Geng et al. 2012; Stephens et al. 2020; Cancelliere et al. 2013; Dubois et al. 2008), however, DTI studies of infant gray matter have been largely limited and mostly studied in premature infants(Lean et al. 2019; Bouyssi-Kobar et al. 2018; Ball et al. 2013; Kelly et al. 2019). Moreover, several limitations of the DTI model make it difficult to analyze and interpret DTI metrics in gray matter, including the assumption of a Gaussian diffusion distribution within the complex microstructure of the cortical gray matter(Wheeler-Kingshott and Cercignani 2009) and bias from partial volume effects of the cerebrospinal fluid (CSF)(Alexander et al. 2001). As such, considerable efforts toward developing alternative dMRI signal models have been made(Alexander et al. 2019; Novikov et al. 2019) including the development of biophysical models such as the neurite orientation dispersion and density imaging (NODDI)(Zhang et al. 2012) model. Biophysical models aim to improve the interpretation of the acquired dMRI signal by incorporating characteristics of the brain's cytoarchitecture in the signal modeling to quantify characteristics of the brain's microstructure with enhanced biological specificity compared to traditional methods. NODDI metrics provide a quantitative estimation of neurite and axonal densities (FICVF), describe the extent of orientational dispersion of axonal projections (ODI), and estimate the fraction of free water CSF within a voxel (fISO) (Zhang et al. 2012).

As early neurodevelopmental processes of the cortex, including synaptogenesis, axon growth, and synaptic pruning, begin to lay the foundation for the brain's neural circuitry and shape the functional architecture of the brain (Ouyang et al. 2019a), it is critical to characterize the morphology of the emerging cytoarchitecture and define the developmental timing of these cortical processes. Despite the importance of understanding this microstructural development, few studies have applied advanced dMRI methods to assess cortical microstructural changes occurring in early brain development. This gap in literature is due to challenges posed by incomplete white matter myelination and poor gray-white matter contrast in the underdeveloped brain (Dubois et al. 2014, 2021; Wang et al. 2015) as well as the inherent difficulties of scanning infants and young children (Hendrix and Thomason 2022; Raschle et al. 2012; Dean et al. 2014; Spann et al. 2022).

Nonetheless, NODDI metrics have been used in studies of early brain development to describe the organization of both white and gray matter regions (Dean et al. 2017, 2018a, b; Kimpton et al. 2021; Stoye et al. 2020; Fenchel et al. 2020; Kunz et al. 2014; Dowe et al. 2020) and have reported widespread non-linear increases in FICVF (Batalle et al. 2019; Dimitrova et al. 2021; Wang et al. 2023) and ODI (Dimitrova et al. 2021) across development. However, much of the extant work focuses on infants born preterm and utilizes region-of-interest-based approaches that are unable to assess developmental variations across the whole brain. For a comprehensive review of applications of advanced dMRI in studies of brain development, see DiPiero et al. 2022 (DiPiero et al. 2022a).

NODDI gray matter based spatial statistics (GBSS) (Nazeri et al. 2017; Nazeri et al. 2015) is a recent framework that utilizes information gleaned from the NODDI model to perform statistical analysis across a skeletonized representation of the gray matter microstructure, analogous to the white matter tract based spatial statistics approach (Smith et al. 2006). Methods described in Nazeri et al. 2015 and 2017 build on original GBSS methods proposed by Ball and colleagues in 2013 (Ball et al. 2013) and use information directly from the NODDI dMRI model. In this framework, brain tissues are classified directly from the diffusion data, reducing partial volume contamination effects and improving sensitivity (Nazeri et al. 2017). The NODDI GBSS framework (which we will refer to as the conventional GBSS framework) has been used in conjunction with NODDI in studies of autism (DiPiero et al. 2022b, 2023), schizophrenia and bipolar disorder (Nazeri et al. 2017), mild cognitive impairment and Alzheimer's Disease (Vogt et al. 2020) and healthy aging (Nazeri et al. 2015). Three previous studies have additionally utilized GBSS to assess cortical microstructure in the infant brain (Kelly et al. 2019; Ball et al. 2013; Wang et al. 2023), describing dysmaturation of the cortex within cohorts of preterm infants (Ball et al. 2013; Wang et al. 2023) and infants with congenital heart disease (Kelly et al. 2019). However, a key step of GBSS analysis surrounds accurate tissue class segmentation, which can be challenging in the developing brain due to reduced tissue contrast and rapid development during the first years of life. These previous studies relied on segmenting a separate structural MRI, thus requiring accurate spatial registration between the anatomical and dMRI images. Moreover, it is unclear whether the conventional GBSS framework proposed by Nazeri et al. may be directly adopted to studies in the infant brain or if modifications would be necessary to improve segmentation directly from the diffusion imaging data.

The aim of the current work was to investigate early age relationships in cortical gray matter microstructure using GBSS. To accomplish this, we adopted and modified the conventional GBSS framework proposed by Nazeri et al. for the 1-month infant brain such that tissue segmentation is performed directly from the diffusion imaging data. Taking this approach, we quantify DTI and NODDI measures across the cortical gray matter and assess associations of these measures with infant age. Although sex differences in white matter microstructure are minimally detected in neonates (Dean et al. 2017; Liu et al. 2011; Gilmore et al. 2018), we additionally investigated potential sex differences in gray matter organization. Following previous literature of full-term infants in the first month of life, we hypothesize that the organization of the gray matter will increase with age across much of the cortex and will not show differences between male and female infants in this early developmental period. We believe this modified GBSS framework enables improved dMRI measurements and characterization of the developing cortical microstructure and will forge opportunities for large-scale investigations of the gray matter microstructure across the lifespan.

Methods

Participants

Recruitment for this study was conducted as part of a longitudinal study conducted at the University of Wisconsin–Madison investigating the brain and emotion development over the first two years of life. Extensive inclusion and exclusion criteria are described elsewhere (Dean et al. 2017, 2018a, b, 2021; Planalp et al. 2023; Birn et al. 2022; Dowe et al. 2020). Briefly, 149 pregnant women were enrolled during the second trimester of pregnancy (<28 weeks' gestation). Inclusion criteria required mothers to be between 18 and 40 years of age, expecting a singleton birth, have no previous diagnosis of major psychiatric conditions or major head trauma, no pre-existing neurological conditions, no autoimmune disorders or infections during pregnancy, and had an uncomplicated childbirth. Infants were excluded postnatally if they were admitted into the neonatal intensive care unit (NICU) for medical care and/or if the infant was not discharged with the mother. All inclusionary criteria were confirmed with mothers prior to enrollment and were confirmed by study team via medical history questionnaires across the longitudinal study visits. Infants (77 female; 72 male) underwent an MRI scan at one month of age (mean = 34.1 days ± 7.7 days [corrected to a 40-week gestational period]). Of these infants, dMRI data was not collected from 33 infants, 14 infants woke up during the exam and did not have enough dMRI volumes collected for processing, and an additional 11 infants were excluded for motion artifacts that could not be corrected during preprocessing steps.

The current study utilizes dMRI from the remaining 91 infants (48 female; 43 male; mean age = 32.86 ± 6.08 days [corrected to a 40-week gestation]). Additional demographic information can be found in Table 1. Parental consent was obtained from each participating family upon enrollment. All study procedures were approved by the Institutional Review Board at the University of Wisconsin – Madison.

Table 1 Participant demographics

Sample Demographics	
N	91
Sex (F; M)	48:43
Infant Age at Scan (days, corrected to 40-week gestation length); Mean (SD) [Range]	32.86 (6.08) [18–50]
Mother Age at Birth (years); Mean (SD) [Range]	32.92 (3.78) [20.12–41.06]
Infant Race	
White	82
Black	1
Asian	5
Native American	2
Missing/Not Reported	1

MRI data acquisition

MRI visits were scheduled to align with the infant's sleep schedule. Upon arrival, infants were fed and swaddled, and data were acquired during natural non-sedated sleep (Dean et al. 2014; Spann et al. 2022). After infants were asleep, they were fit with ear protection, including ear plugs, MiniMuff® (Natus Medical Incorporated) neonatal noise attenuating ear covers, and white noise played through electrodynamic headphones (MR Confon, Germany) to limit the acoustic noise of the scan. To further limit the acoustic sound during the MRI and increase the likelihood of the infant remaining asleep, an acoustically optimized imaging protocol was designed that limited the peak gradient slew rates of the MRI pulse sequences to approximately 67% of their nominal value.

MRI data were acquired on a 3 Tesla General Electric MR750 Discovery scanner using a 32 channel receive-only head RF array coil (Nova Medical, Wakefield, MA). A three-shell diffusion weighted imaging (DWI) protocol was acquired using a single shot spin-echo echo-planar imaging pulse sequence. Parallel acquisition with a geometric reduction factor of two was used to reduce image acquisition time and distortions from magnetic field inhomogeneities. A total of 69 DWIs were acquired, 6 directions acquired with no diffusion weighting ($b = 0$ s/mm^2), and diffusion weighting of $b = 350$ s/mm^2 in 9 directions, $b = 800$ s/mm^2 in 18 directions, and $b = 1500$ s/mm^2 in 36 directions. Other DWI acquisition parameters included a repetition time [TR] = 8400 ms; echo time [TE] = 94 ms; bandwidth = 3906 Hz/pixel; field of view [FOV] of 25.6 cm × 25.6 cm and an acquisition matrix of 128 × 128, providing a 2 mm × 2 mm in-plane resolution. Coverage across the cerebrum and cerebellum was achieved by acquiring 60 sagittal-oriented contiguous slices with a slice thickness of 2.0 mm. The total time for the multiple *b*-value DTI acquisition while using strategies to reduce the acoustic noise was approximately 10 min.

Structural T1- and T2-weighted images were obtained using GE's 3D BRAVO (BRAin VOlume) and CUBE imaging pulse sequences, respectively. Images were acquired in a sagittal orientation with a 1.0 mm isotropic spatial resolution. Additional BRAVO imaging parameters included: TR = 8.7 ms; TE = 3.4 ms; inversion time (TI) = 450 ms; flip angle = 12 degrees; FOV = 25.6 cm × 25.6 cm × 17.0 cm; and an acquisition time of 8 min 10 s. CUBE T2-weighted imaging parameters were: TR = 2500 ms; FOV = 25.6 cm × 25.6 cm × 16.0 cm; echo train length = 65; and an acquisition time of 5 min and 36 s.

Image processing

All DWI and structural T1- and T2- weighted images were manually assessed for motion and other image artifacts and confirmed by a trained researcher (MD). DWI volumes containing motion artifacts were manually removed prior to processing. Data processing was conducted with an in-house processing pipeline. Briefly, DWIs were denoised (Tournier et al. 2019) and corrected for Gibbs ringing artifact (Kellner et al. 2016) using tools from MRtrix3 (Tournier et al. 2019). Eddy current and motion correction was performed using *FSL*'s *eddy* tool (Jenkinson et al. 2002; Andersson et al. 2016, 2017; Andersson and Sotiropoulos 2016), while gradient directions were further corrected for rotations (Leemans and Jones 2009). Non-parenchyma signal was removed using the *hd-bet* (Isensee et al. 2019). DWIs were then up-sampled to 1mm^3 isotropic resolution and linearly co-registered to the individuals' T2-weighted image using the Advanced Normalization Tools (ANTs) software (Avants et al. 2009) to enhance apparent resolution and improve tissue delineation in accordance to the TiDi-Fused workflow (Guerrero-Gonzalez et al. 2022). Diffusion tensors were estimated at each voxel from the final pre-processed DWI image using a weighted-least squares algorithm via the Diffusion Imaging in Python (DIPY) package (Garyfallidis et al. 2014). DTI metrics (Basser 1995; Basser and Pierpaoli 1996) including fractional anisotropy, and mean, radial, and axial diffusivities, (FA, MD, RD, AD) were computed. DWIs were also fit to the multi-compartment NODDI tissue model (Zhang et al. 2012) with a Watson distribution using DMIPY (Fick et al. 2019) to estimate NODDI metrics of intracellular volume fraction (FICVF) or neurite density, orientation dispersion index (ODI), and isotropic volume fraction (FISO).

A study-specific template was constructed from the infant FA maps using the ANTs software package and associated "antsMultivariateTemplateConstruction" script (Avants et al. 2011a). The resulting infant FA template was then coregistered to the MNI template using ANTs. The resulting infant FA template was used as the study-specific template for the GBSS framework. As the study specific template was aligned with the MNI template, we utilized the Harvard Oxford cortical atlas for identifying brain regions observed to have significant statistical associations in our subsequent analyses.

Adapting the GBSS framework for the infant brain

GBSS adopts the tract-based spatial statistics (TBSS) (Smith et al. 2006) framework to allow for analysis of diffusion MRI measures in the cortical gray matter. Processing steps for the conventional GBSS framework have been previously described (Nazeri et al. 2015, 2017). Briefly, the GBSS framework leverages the gray-white matter contrast of a DTI FA map to perform a two-tissue type segmentation and estimation of the white matter fraction using Atropos (Avants et al. 2011b). A gray matter fraction map is then estimated by subtracting the white matter fraction and CSF fraction (NODDI FISO parameter) maps from 1. Gray matter fraction maps are then aligned to a template and averaged to create a representative gray matter fraction map. This map is then skeletonized using the *tbss_skeleton* tool in FSL (Jenkinson et al. 2012; Smith et al. 2006) and thresholded to include only voxels with an average gray matter fraction > 0.65 (Nazeri et al. 2017) (Fig. 1A). NODDI and DTI metrics are projected onto the gray matter skeleton from local voxels with the greatest gray matter fraction.

However, applying this framework directly to infant diffusion imaging data may pose several challenges given the differing diffusion characteristics of the infant brain. For example, we observe the contrast in FA maps from the infants is not sufficient for accurate gray and white matter

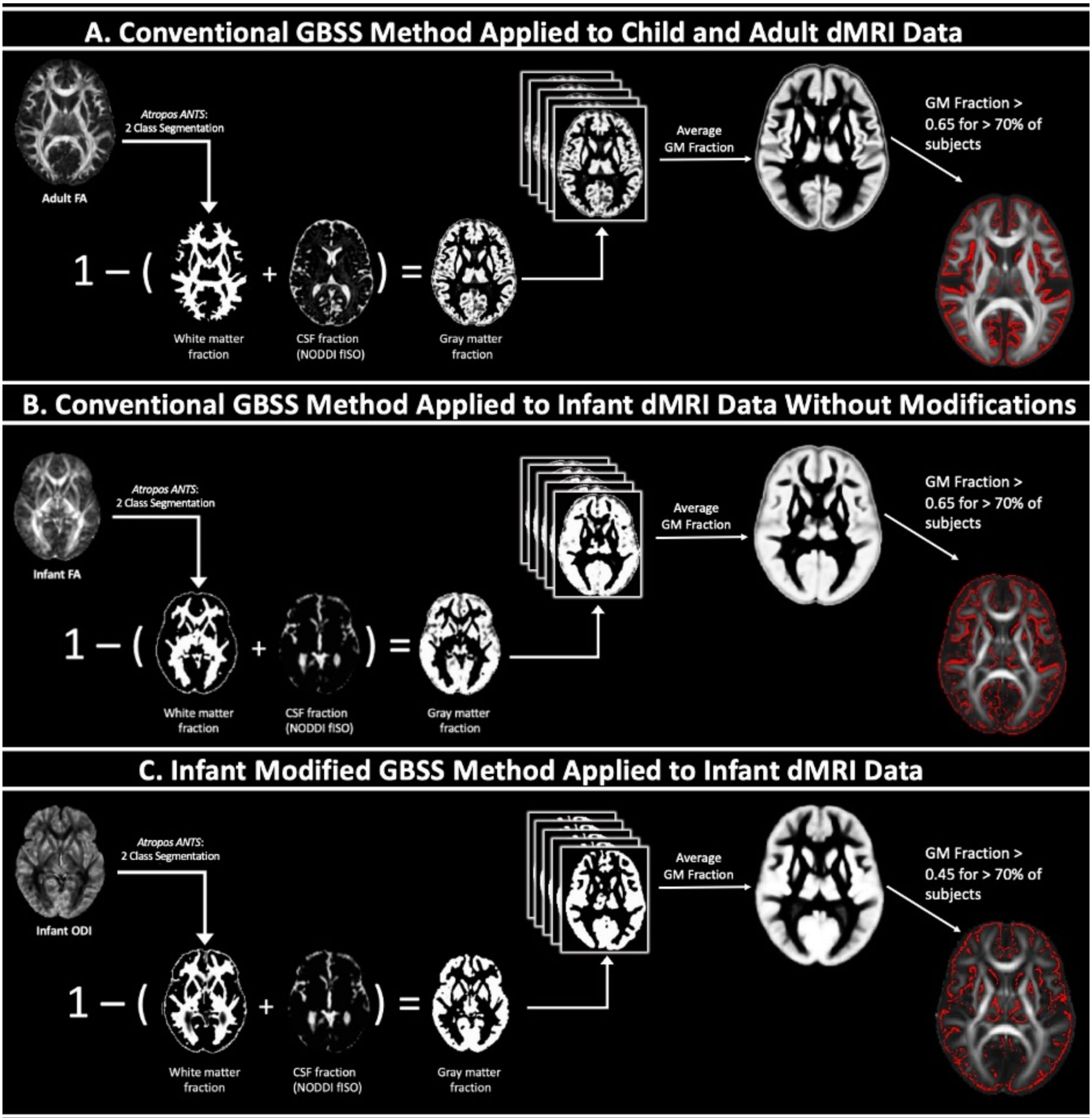

Fig. 1 **The GBSS Processing Steps Adapted for the Infant Brain**. **(A) Conventional GBSS method applied to data from children and adults.** For each subject, a white matter fraction map is estimated via Atropos from the DTI FA map. A gray matter fraction map is then generated by subtracting the white matter fraction and the CSF fraction (NODDI fISO) from 1. A mean gray matter fraction map is generated by averaging the gray matter fraction maps for each participant and is skeletonized. The dMRI parameter maps (from DTI and NODDI) are then projected onto the GM skeleton from the local gray matter fraction maxima. The final skeleton was generated by keeping only voxels with a GM fraction > 0.65 in > 75% of the subjects. **(B) Conventional GBSS method applied directly to infant data without modification**. The FA map was used to derive the white matter fraction estimate. The final skeleton was generated by keeping only voxels with a gray matter fraction > 0.65 in > 75% of the subjects leads to inaccuracies in gray matter fraction estimation and poor skeleton generation. **(C) Infant Modified GBSS method applied to infant data.** For each subject, the NODDI ODI map was fed into Atropos for white matter fraction estimation. The final skeleton was generated by keeping only voxels with a gray matter fraction > 0.45 in > 75% of the subjects leads an improvement in gray matter fraction estimation and skeleton generation compared to the conventional method in infants

segmentation and can result in erroneous estimates of the white matter fraction and, subsequently, the gray matter fraction (Fig. 1B). This erroneous gray matter fraction estimation can result in subsequent issues with the skeletonization of the gray matter as seen in Fig. 2B.

To combat this suboptimal segmentation of the infant FA map, we propose using the NODDI-based ODI map for the two-tissue class segmentation and white matter fraction estimation due to its improved gray-white matter contrast in the underdeveloped brain (Fig. 1C). The gray matter fraction map is then estimated by subtracting the white matter fraction and CSF fraction (NODDI FISO parameter) maps from 1. Gray matter fraction maps are aligned to our study-specific template using ANTs, averaged to create a mean gray matter fraction map, and skeletonized using the *tbss_skeleton* tool in FSL (Jenkinson et al. 2012; Smith et al. 2006). Due to the reduced gray matter fraction values in the 1-month brain, an adjusted gray matter fraction threshold of 0.45 was used to construct the infant gray matter skeleton (Fig. 2C), which was used in subsequent statistical analyses. NODDI and DTI metrics were projected onto the gray matter skeleton from local voxels with the greatest gray matter fraction. To evaluate the performance of the conventional and our infant modified methods in the infant brain, we examined the level of agreement between the two methods by calculating the percentage of overlapping voxels of both methods relative to the total number of skeletonized voxels in the infant modified method.

Statistical analyses

Relationships with age, sex, and cortical microstructure

FSL was used to build General Linear Models (GLMs) to investigate age relationships across the cortical microstructure. Infant age at scan was corrected for gestational length. Models controlled for infant sex. Covariates in all analyses were centered. Non-parametric permutation testing with tail approximation ($n = 500$) was carried out using Permutation Analysis of Linear Models (PALM) (Smith et al. 2006; Winkler et al. 2014). Tail approximation was used to fit the tail of the permutation distribution to a generalized Pareto distribution (James 1975) and reduce the overall total number of permutations necessary to estimate p-values. A multivariate analysis was run for all gray matter metrics (FICVF, ODI, FA, MD, RD, AD). Joint inference of age was assessed with the non-parametric combination (NPC) and Fisher's combining function across five dMRI metrics: FICVF, FA, MD, AD, and RD, while differences in individual metrics were also evaluated. Threshold free cluster

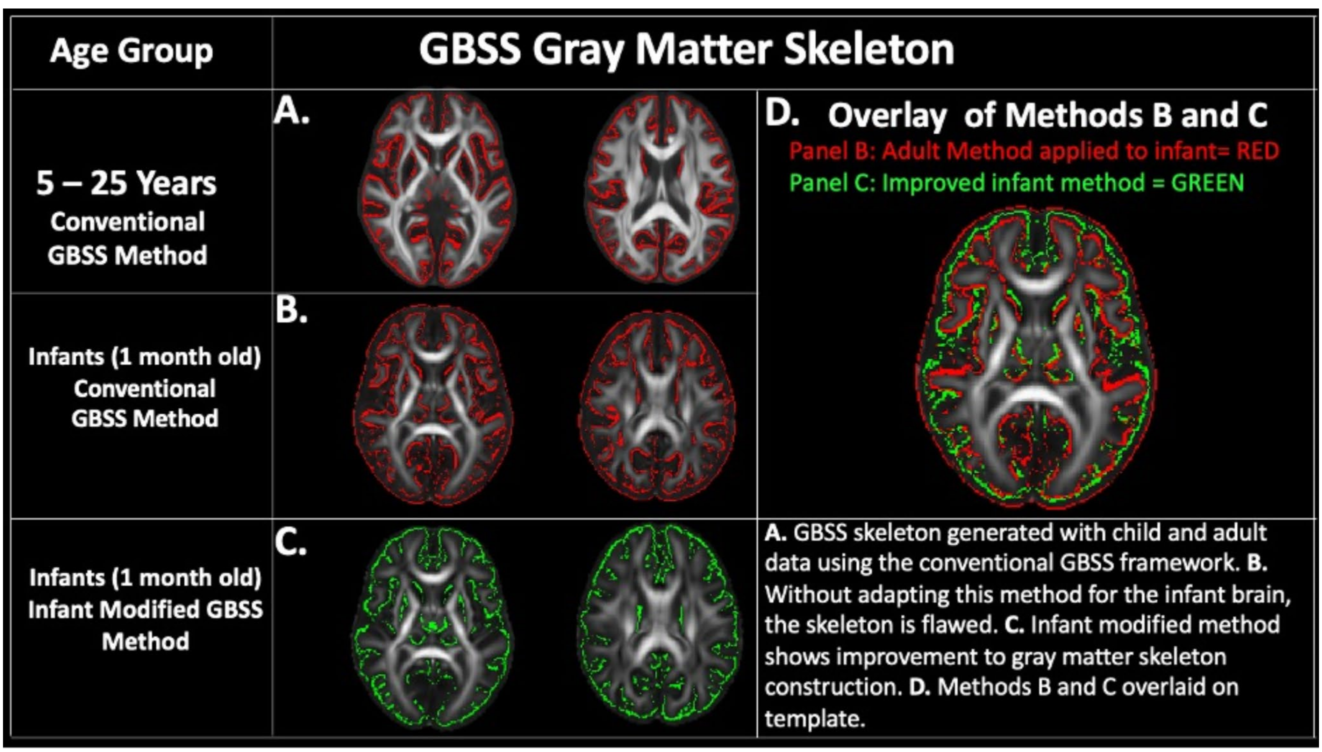

Fig. 2 GBSS Skeleton Construction and Improvement for the Infant Brain. (**A**) Conventional GBSS method applied to data from children and adults. (**B**) Conventional GBSS method applied to infant brain without modification. (**C**) Improved infant GBSS skeleton with infant modified GBSS method. (**D**) Conventional GBSS method applied to infants without modification and infant GBSS method overlaid on top of one another

enhancement (TFCE) (Smith and Nichols 2009) was used to identify significant regions at $p < 0.05$, FWER-corrected across modality and contrast. Statistical maps were overlaid on the Harvard-Oxford cortical atlas (Desikan et al. 2006) to identify regions with a significant age relationship.

Age by sex interactions on cortical microstructure

Age by sex interaction GLMs were also generated to separately examine sex related differences in the relationship between age and cortical organization. GLMs included mean-centered infant age (gestation corrected) and sex in addition to the interaction term. Non-parametric permutation testing with tail approximation ($n = 500$) was carried out using Permutation Analysis of Linear Models (PALM) (Smith et al. 2006; Winkler et al. 2014). Tail approximation was used to fit the tail of the permutation distribution to a generalized Pareto distribution (James 1975) and reduce the overall total number of permutations necessary to estimate p-values. A multivariate analysis was run for all gray matter metrics (FICVF, ODI, FA, MD, RD, AD). Joint inference of age was assessed with the non-parametric combination (NPC) and Fisher's combining function across five dMRI metrics: FICVF, FA, MD, AD and RD, while differences in individual metrics were also evaluated. Threshold free cluster enhancement (TFCE) (Smith and Nichols 2009) was used to identify significant regions at $p < 0.05$, FWER-corrected across modality and contrast.

Results

GBSS skeleton construction for the infant brain

Improved skeletonization of the gray matter microstructure in the infant brain is observed with our adapted GBSS framework. Our modifications to the conventional GBSS framework, including utilization of the NODDI ODI map for improved gray matter fraction estimate and adjusted threshold for generation of the gray matter skeleton (Fig. 1C) contribute to an improved gray matter skeleton for infants (Fig. 2C). When applying the conventional GBSS framework directly to infants without these modifications, the resulting gray matter skeleton is centered at the gray-white matter boundary rather than within the cortical gray matter (Fig. 2B). Moreover, we observe that erroneous segmentation of the DTI FA map results in inaccurate delineation of gray and white matter around the brain's edges (Fig. 2B). The GBSS skeleton constructed via our infant modified framework provides a more robust estimate of the gray matter fraction (Fig. 2C) and generates a skeleton that is more centered within the gray matter compared to the conventional GBSS framework without modifications for infant contrasts (Fig. 2B). Further, the gray matter skeletons generated from both the conventional and infant modified GBSS methods overlaid on one another highlight discrete regions of the brain (Fig. 2D) with very few overlapping voxels in the cortex (Fig. 3). Between the two GBSS approaches, only a 9.7% agreement was found between skeletonized voxels. Additionally, to further compare these different approaches, we computed the average gray matter fraction across the skeletons produced by each method. The infant modified

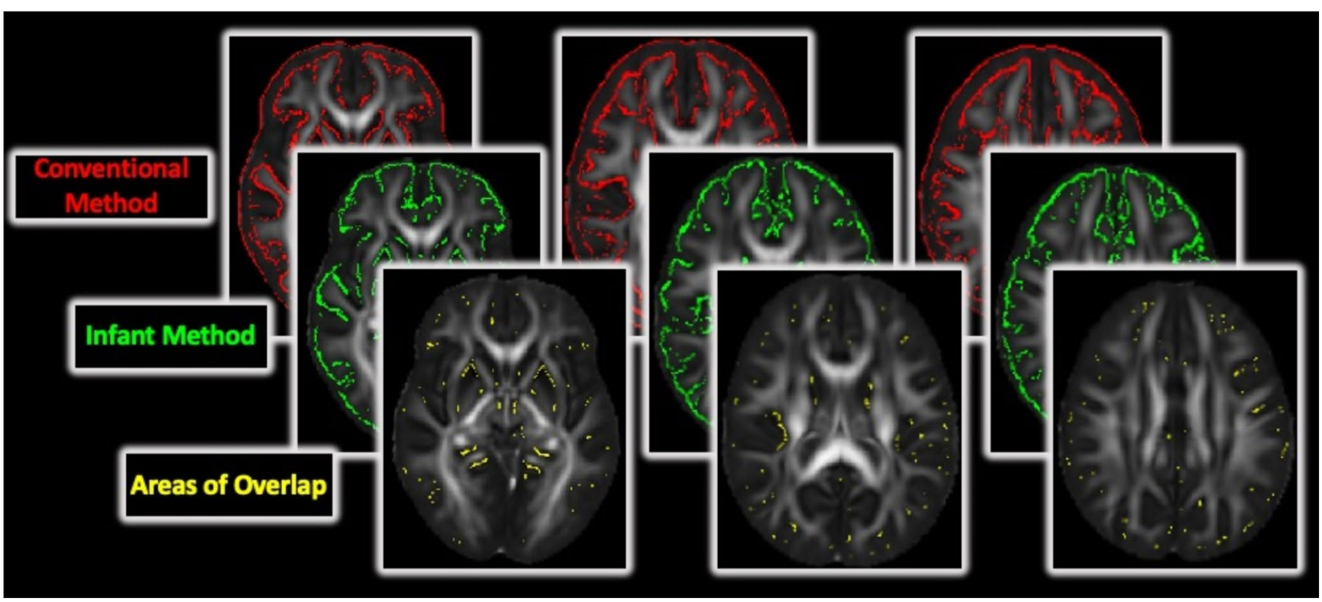

Fig. 3 **GBSS Skeleton Agreement Between Conventional and Infant Modified GBSS Methods Applied to Infant Data.** Yellow voxels represent voxels identified as gray matter across both the conventional (Red) and infant modified (Green) methods

GBSS method (Fig. 1C) yielded an average gray matter fraction of 0.92, while the average gray matter fraction from the conventional GBSS method applied to the infant data (Fig. 1B) was 0.60. Compared to the conventional GBSS method, this higher average gray matter fraction with the infant modified GBSS method indicates that the skeleton provides improved overlap with voxels of high gray matter fraction.

Cortical microstructure associations with age and sex

A significant main effect of sex was not detected with cortical microstructure, however, age analyses controlled for the effects of sex. Significant voxelwise relationships with age and gray matter microstructure were observed in measures of FICVF, MD, RD, and AD ($p < 0.05$, FWER-corrected) (Fig. 4). FICVF was observed to increase with age, whereas MD, RD and AD decreased with age. A summary of brain regions observed to have significant age relationships can be found in Table 2. Across significant dMRI metrics, age associations were observed in the cuneal cortex, lateral occipital cortex, occipital pole, paracingulate gyrus, cingulate gyrus, and the superior frontal gyrus. Across measures of FICVF, MD, and RD, significant age associations were also noted in the following regions: Angular gyrus, central opercular gyrus, inferior frontal gyrus, supplemental motor cortex, frontal pole, middle frontal gyrus, post central gyrus, precentral gyrus, supramarginal gyrus, and inferior temporal gyrus. While a majority of age relationships were found in bilateral hemispheres for FICVF, the majority of significant age relationships with the DTI metrics of MD and RD were found in the right hemisphere. Significant relationships between age and ODI were not detected across the cortical skeleton.

Across dMRI measures, we did not detect a significant main effect of sex or age-by-sex interactions in the cortical microstructure.

Discussion

The early organization of the cortical gray matter plays a critical role in the formation of the neural circuitry that is foundational for future behavioral health and well-being. Despite the importance of this early organization, limited work has applied advanced dMRI methods to investigate the highly complex and rapidly changing architecture of neurites in the cortex. This study attempts to address aspects of this gap in knowledge regarding gray matter organization in early life. To accomplish this, we employ GBSS (Nazeri et al. 2015, 2017) for characterizing the cortical microstructure and propose refinements to the original framework that aim to improve the delineation and characterization of gray

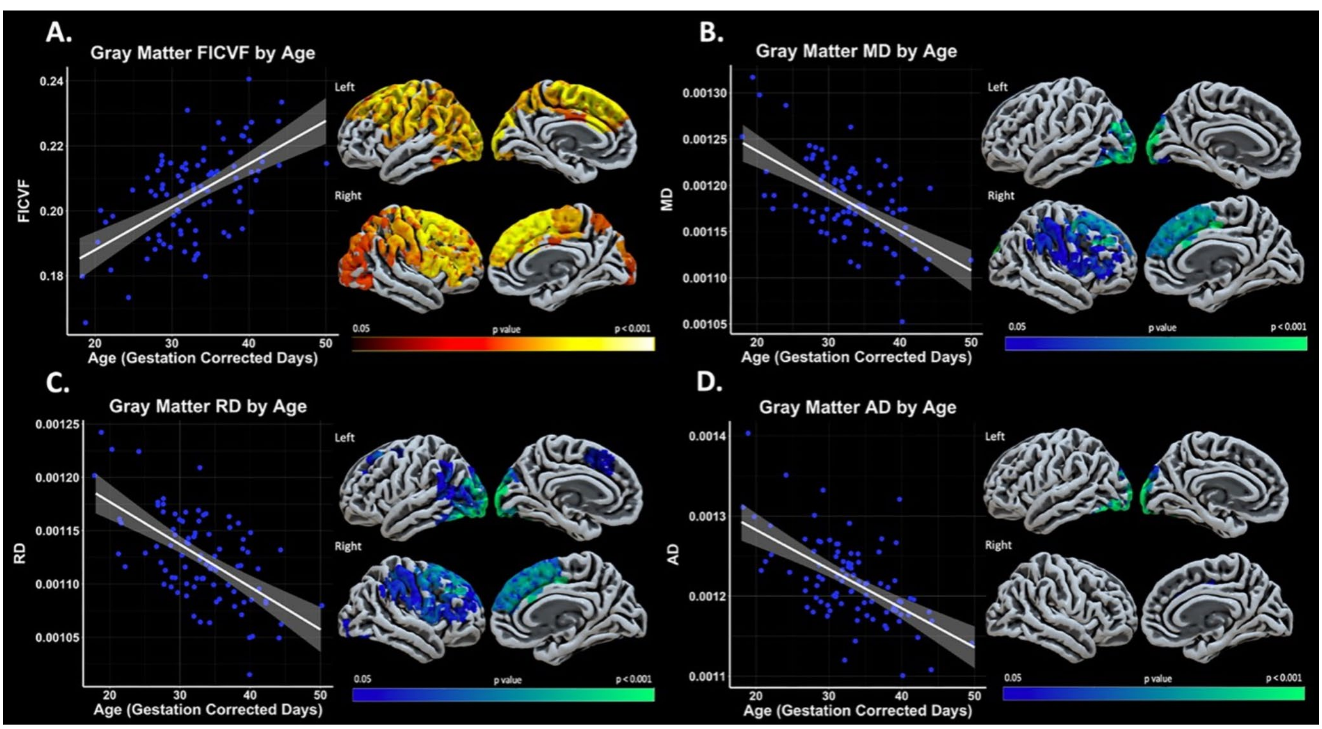

Fig. 4 **Age Relationships in Cortical Microstructure.** Neuroanatomical maps show regions with a significant age relationship. Color indicates level of significance. Red/Yellow scale indicates a significant positive relationship. Blue/Green scale indicates a significant negative relationship. Scatter points represent the average dMRI measure across significant voxels for each measure

Table 2 Neuroanatomical locations of significant Age relationships

Hemisphere	DWI Measures					
	FICVF	ODI	FA	MD	RD	AD
Bilateral	Angular gyrus Central opercular cortex Cingulate gyrus, anterior division Cingulate gyrus, posterior division Cuneal cortex Frontal operculum cortex Frontal pole Inferior frontal gyrus, pars opercularis Juxtapositional lobule cortex (formerly supplementary motor cortex) Lateral occipital cortex, inferior division Lateral occipital cortex, superior division Middle frontal gyrus Occipital pole Paracingulate gyrus Postcentral gyrus Precentral gyrus Precuneous cortex Superior frontal gyrus Superior parietal lobule Supramarginal gyrus, anterior division Supramarginal gyrus, posterior division	-	-	-	Angular gyrus Juxtapositional lobule cortex (formerly supplementary motor cortex) Lateral occipital cortex, inferior division Middle frontal gyrus Occipital pole Paracingulate gyrus Superior frontal gyrus Supramarginal gyrus, posterior division	-
Left	Inferior temporal gyrus, pars triangularis Lingual Gyrus Middle temporal gyrus, temporooccipital part	-	-	Cuneal cortex Inferior temporal gyrus, temporooccipital part Lateral occipital cortex, inferior division Lateral occipital cortex, superior division Occipital pole	Cuneal cortex Inferior temporal gyrus, temporo-occipital part Lateral occipital cortex, superior division Middle temporal gyrus, temporoccipital part	Cuneal cortex Lateral occipital cortex, inferior division Occipital pole
Right	Inferior frontal gyrus, pars triangularis Superior parietal lobule	-	-	Angular gyrus Central opercular cortex Cingulate gyrus, anterior division Frontal pole Inferior frontal gyrus, pars opercularis Inferior frontal gyrus, pars triangularis Juxtapositional lobule cortex (formerly supplementary motor cortex) Middle frontal gyrus Paracingulate gyrus Parietal lobule Postcentral gyrus Precentral gyrus Superior frontal gyrus Supramarginal gyrus, anterior division Supramarginal gyrus, posterior division	Central opercular cortex Cingulate gyrus, anterior division Frontal pole Inferior frontal gyrus, pars opercularis Inferior frontal gyrus, pars triangularis Postcentral gyrus Precentral gyrus Superior parietal lobule Supramarginal gyrus, anterior division	Cingulate gyrus, anterior division Paracingulate gyrus Superior frontal gyrus

matter in the infant brain. DTI and NODDI based measures of cortical microstructure were estimated in the cortical gray matter and varied across much of the cortex, signaling rapid development and organization within the first month of life. These results complement the extant literature on the development of cortical microstructure and provide new insights into gray matter organization in the neonatal brain.

Studies utilizing NODDI to examine the cortical organization of infants at 37 to 44 weeks post-menstrual age (PMA) show FICVF and ODI measured in the gray matter to increase with age (Dimitrova et al. 2021; Wang et al. 2023), potentially capturing gray matter processes of dendritic arborization, glial proliferation, and synapse formation. A study with a small sample size including pre-term infants born $\leq$28 gestational weeks and scanned before term equivalent age (between 29 and 34 weeks) reported increases in ODI but not FICVF in the cortex (Eaton-Rosen et al. 2015). Other work including older infants suggests a developmental plateau in gray matter organization around 38 weeks PMA (Ouyang et al. 2019b; Batalle et al. 2019). For example, in a whole-brain gray matter analysis of preterm infants scanned between 25 and 47 weeks PMA, Batalle et al. reported a developmental plateau in ODI accompanied by an increase in FICVF after 38 PMW (Batalle et al. 2019), suggesting the completion of basal dendritic branching and ongoing apical branching at this developmental stage (Mrzljak et al. 1988; Batalle et al. 2019). However, dynamic cytoarchitectural changes continue into the neonatal period and within the first weeks of life and include processes of neuronal aggregation in the formation of neural circuitry expanding both tangentially and radially (Kostović et al. 2019). These cytoarchitectural events may explain increases in FICVF and ODI in the gray matter of infants scanned between 37- and 44-weeks PMA (Dimitrova et al. 2021; Wang et al. 2023). In line with findings from Batalle et al. 2019, our observations of a rise in neurite density with age without a corresponding increase in neurite dispersion may be attributed to the ongoing apical dendritic development of pyramidal neurons at term age (Kostović et al. 2019; Becker et al. 1984; Huttenlocher 1990).

Across the infant modified GBSS skeleton, we detected significant relationships with age and gray matter microstructure measures of FICVF, MD, RD, and AD in brain regions including the cuneal cortex, lateral occipital cortex, occipital pole, paracingulate gyrus, cingulate gyrus, and the superior frontal gyrus. Within these regions, neurite density was positively associated with age, whereas the diffusivity metrics were negatively related to infant age. While the cuneal cortex, lateral occipital cortex, and occipital pole are located in the occipital lobe and play a major role in visual processes including interpreting visual stimuli (Uysal 2023), the paracingulate gyrus, cingulate gyrus, and the superior frontal gyrus are involved in cognitive and emotional processing (Rolls 2019; Boisgueheneuc et al. 2006).

Early postnatal visual experiences influence the structural and functional maturation of the infant visual system (Li et al. 2022). Our observations of microstructural development, characterized by increased neurite density and decreased diffusivity metrics in these brain regions, conform to the expected developmental timeline and are consistent with white matter findings described in studies utilizing NODDI (Kimpton et al. 2021; Dean et al. 2017). Moreover, our results complement cortical findings from Batalle et al. 2019 (Batalle et al. 2019) of increased neurite density visual brain areas after 38 weeks PMA and are further supported by post-mortem histology findings of increased branching and spine densities at 1 month of age (Takashima et al. 1980). Additional studies are needed to specifically link developing cortical microstructure to histology across developmental epochs.

The development of cognitive and emotional brain areas begins in infancy, with studies linking infant white matter microstructure of tracts supporting cognitive and emotional processes with future attentional (Dowe et al. 2020) and fear (Planalp et al. 2023) behaviors. Neurite density of infant white matter tracts in frontal brain areas has also been shown to increase with age (Dean et al. 2017; Kimpton et al. 2021). However, less work has specifically investigated these relationships in gray matter regions. Dimitrova et al. 2021 reported positive associations in FICVF with age in some regions of the frontal lobe of term-born neonates scanned between 37- and 44-weeks PMA (Dimitrova et al. 2021). This work supports our findings of increased neurite density in the superior frontal gyrus and limbic brain structures. While other work also observed increased neurite density in the insula in infancy (Wang et al. 2023; Dimitrova et al. 2021), these studies included younger infants than represented in our sample (mean = 44.68 ± 0.86 weeks PMA) which may account for the lack of findings in this region within our cohort.

Occurring in tandem with development in cognitive and emotional brain areas is the ongoing development of auditory and language centers. The development of hearing begins at the onset of the third trimester of pregnancy (Granier-Deferre et al. 2011). Studies have shown that within the first postnatal months of life, infants already possess the ability to distinguish between different phonemes (Dehaene-Lambertz and Pena 2001; Cheour-Luhtanen et al. 1995). Work utilizing NODDI to probe white matter organization in early infancy describe a positive association between gestational age and neurite density within white matter tracts supporting language processing (Dean et al. 2017). Moreover, studies have linked infant brain structure to later language abilities (Deniz Can et al. 2013;

Ortiz-Mantilla et al. 2010), reporting relationships between subcortical gray matter densities and volumes and later language skills. The current work supports the early emergence of this protracted developmental process, with findings of increased neurite density and decreased mean and radial diffusivities observed within brain regions supporting phonetic and semantic language processes, including the middle frontal gyrus, inferior frontal gyrus, supramarginal gyrus, and angular gyrus.

In addition to language areas, we also observed an increase in structural organization in motor and sensory regions including the central opercular gyrus, supplemental motor regions, and the pre-and post-central gyri. Findings from Fenchel et al. 2020 utilizing NODDI metrics and morphometric similarity networks highlighted sensory, limbic, and parietal brain areas to have the largest maturational change over the neonatal period compared to cognitive brain regions (Fenchel et al. 2020). These findings are consistent with histological findings of increased neurite density in this developmental period within primary motor and sensory cortices (Huttenlocher 1990) and are further supported by diffusion MRI studies showing increased neurite density in the corticospinal tract (Kimpton et al. 2021) and sensory cortices (Dimitrova et al. 2021) and decreased diffusion anisotropy in sensorimotor cortices (Ball et al. 2013; deIpolyi et al. 2005).

In conclusion, our work is amongst the first to employ the GBSS framework in conjunction with NODDI metrics to investigate the microstructural organization of the cortex in infants. With this framework adapted for the neonatal brain, we forge opportunities to explore this maturation in expanded developmental epochs. Interpretation of our current work is limited by the cross-sectional design, limited sample diversity, and narrow age range of included infants. We encourage future work to utilize our current methods for exploring developmental patterns in more diverse samples of infants and across age ranges. Further, alternative approaches for applying the conventional GBSS framework to infant datasets with single shell DWI acquisitions must be explored, including improved segmentation strategies leveraging information from infant brain atlases, as such applications of GBSS in legacy data have major potential for both replication and expansion of the current work and application into clinical cohorts. While outside the scope of the current study, future work should also apply the current methods to pediatric and adult dMRI data to investigate if this method improves cortical skeletonization across developmental periods after early infancy. Subsequent work should also apply these tools in conjunction with NODDI and TBSS to probe the developmental interplay between gray and white matter maturation in infancy. Large-scale studies are currently underway that will provide opportunities for these explorations including the "Developing Human Connectome Project (Edwards et al. 2022)", "Baby Connectome Project (Howell et al. 2019)", and the "Healthy Brain and Child Development (Volkow et al. 2021)" study, building the potential for innovation in the understanding of human brain development from its earliest stages. Applying the methods outlined in the current paper to large and more diverse samples in conjunction with histological analysis for ground truth comparisons of gray matter microstructure will allow for a thorough evaluation of method accuracy, stability, and reproducibility across various cohorts. Nonetheless, the development and modification of advanced tools for probing cytoarchitectural maturation in the cortex in infancy, such as the current infant modified GBSS framework, paves the way for insights into the emergence of individual developmental differences that may underly future behavioral outcomes and creates room for the development of targeted interventions that promote the long-term health and well-being of children across the lifespan.

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Author contributions Author contributions: M.A.D.: conceptualization, data curation, methodology, software, formal analysis, investigation, writing – original draft, Writing – review & editing, visualization, project administration; P.G.R.: Data curation, investigation, writing – original draft, Writing – review & editing, visualization; M.J.: Data curation, investigation, writing – original draft, Writing – review & editing, visualization; S.R.: Data curation, investigation, writing – original draft, Writing – review & editing, visualization; E.B.: Data curation, investigation, writing – original draft, Writing – review & editing, visualization; J.G.G.: methodology, software, data curation, resources, writing – review & editing; R.J.D.: data curation, resources, writing – review & editing, funding acquisition, project administration; E.M.P.: data curation, resources, writing – review & editing; D.C.D. III.: conceptualization, methodology, software, resources, data curation, resources, writing – review & editing, supervision, funding acquisition, project administration.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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References

Afzali M, Pieciak T, Newman S, Garyfallidis E, Ozarslan E, Cheng H, Jones DK (2021) The sensitivity of diffusion MRI to microstructural properties and experimental factors. J Neurosci Methods 347:108951. https://doi.org/10.1016/j.jneumeth.2020.108951

Al-Haddad BJS, Oler E, Armistead B, Elsayed NA, Weinberger DR, Bernier R, Burd I, Kapur R, Jacobsson B, Wang C, Mysorekar I, Rajagopal L, Adams Waldorf KM (2019) The fetal origins of mental illness. Am J Obstet Gynecol 221(6):549–562. https://doi.org/10.1016/j.ajog.2019.06.013

Alexander AL, Hasan KM, Lazar M, Tsuruda JS, Parker DL (2001) Analysis of partial volume effects in diffusion-tensor MRI. Magn Reson Med 45(5):770–780. https://doi.org/10.1002/mrm.1105

Alexander AL, Lee JE, Lazar M, Field AS (2007) Diffusion tensor imaging of the brain. Neurotherapeutics 4(3):316–329. https://doi.org/10.1016/j.nurt.2007.05.011

Alexander DC, Dyrby TB, Nilsson M, Zhang H (2019) Imaging brain microstructure with diffusion MRI: practicality and applications. NMR Biomed 32(4):e3841. https://doi.org/10.1002/nbm.3841

Andersson JLR, Sotiropoulos SN (2016) An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. NeuroImage 125:1063–1078. https://doi.org/10.1016/j.neuroimage.2015.10.019

Andersson JLR, Graham MS, Zsoldos E, Sotiropoulos SN (2016) Incorporating outlier detection and replacement into a non-parametric framework for movement and distortion correction of diffusion MR images. NeuroImage 141:556–572. https://doi.org/10.1016/j.neuroimage.2016.06.058

Andersson JLR, Graham MS, Drobnjak I, Zhang H, Filippini N, Bastiani M (2017) Towards a comprehensive framework for movement and distortion correction of diffusion MR images: within volume movement. NeuroImage 152:450–466. https://doi.org/10.1016/j.neuroimage.2017.02.085

Arsalidou M, Duerden EG, Taylor MJ (2013) The centre of the brain: topographical model of motor, cognitive, affective, and somatosensory functions of the basal ganglia. Hum Brain Mapp 34(11):3031–3054. https://doi.org/10.1002/hbm.22124

Avants BB, Tustison N, Song G (2009) Advanced normalization tools (ANTS). Insight j 2(365):1–35

Avants BB, Tustison NJ, Song G, Cook PA, Klein A, Gee JC (2011a) A reproducible evaluation of ANTs similarity metric performance in brain image registration. NeuroImage 54(3):2033–2044. https://doi.org/10.1016/j.neuroimage.2010.09.025

Avants BB, Tustison NJ, Wu J, Cook PA, Gee JC (2011b) An open source multivariate framework for n-tissue segmentation with evaluation on public data. Neuroinformatics 9(4):381–400. https://doi.org/10.1007/s12021-011-9109-y

Bale TL, Baram TZ, Brown AS, Goldstein JM, Insel TR, McCarthy MM, Nemeroff CB, Reyes TM, Simerly RB, Susser ES, Nestler EJ (2010) Early life programming and neurodevelopmental disorders. Biol Psychiatry 68(4):314–319. https://doi.org/10.1016/j.biopsych.2010.05.028

Ball G, Srinivasan L, Aljabar P, Counsell SJ, Durighel G, Hajnal JV, Rutherford MA, Edwards AD (2013) Development of cortical microstructure in the preterm human brain. Proc Natl Acad Sci U S A 110(23):9541–9546. https://doi.org/10.1073/pnas.1301652110

Basser PJ (1995) Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. NMR Biomed 8(7–8):333–344. https://doi.org/10.1002/nbm.1940080707

Basser PJ, Ozarslan E (2009) Introduction to Diffusion MR. Diffusion Mri: From Quantitative Measurement to in Vivo Neuroanatomy:3–10

Basser PJ, Pierpaoli C (1996) Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B 111(3):209–219. https://doi.org/10.1006/jmrb.1996.0086

Batalle D, O'Muircheartaigh J, Makropoulos A, Kelly CJ, Dimitrova R, Hughes EJ, Hajnal JV, Zhang H, Alexander DC, Edwards AD, Counsell SJ (2019) Different patterns of cortical maturation before and after 38 weeks gestational age demonstrated by diffusion MRI in vivo. NeuroImage 185:764–775. https://doi.org/10.1016/j.neuroimage.2018.05.046

Batty MJ, Liddle EB, Pitiot A, Toro R, Groom MJ, Scerif G, Liotti M, Liddle PF, Paus T, Hollis C (2010) Cortical gray matter in attention-deficit/hyperactivity disorder: a structural magnetic resonance imaging study. J Am Acad Child Adolesc Psychiatry 49(3):229–238. https://doi.org/10.1016/j.jaac.2009.11.008

Becker LE, Armstrong DL, Chan F, Wood MM (1984) Dendritic development in human occipital cortical neurons. Dev Brain Res 13(1):117–124. https://doi.org/10.1016/0165-3806(84)90083-X

Birn RM, Dean DC, Wooten W, Planalp EM, Kecskemeti S, Alexander AL, Goldsmith HH, Davidson RJ (2022) Reduction of motion artifacts in functional connectivity resulting from Infrequent large motion. Brain Connect 12(8):740–753. https://doi.org/10.1089/brain.2021.0133

Boisgueheneuc Fd, Levy R, Volle E, Seassau M, Duffau H, Kinkingnehun S, Samson Y, Zhang S, Dubois B (2006) Functions of the left superior frontal gyrus in humans: a lesion study. Brain 129(12):3315–3328. https://doi.org/10.1093/brain/awl244

Bouyssi-Kobar M, Brossard-Racine M, Jacobs M, Murnick J, Chang T, Limperopoulos C (2018) Regional microstructural organization of the cerebral cortex is affected by preterm birth. Neuroimage Clin 18:871–880. https://doi.org/10.1016/j.nicl.2018.03.020

Cancelliere A, Mangano FT, Air EL, Jones BV, Altaye M, Rajagopal A, Holland SK, Hertzler DA, Yuan W (2013) DTI values in Key White Matter tracts from Infancy through Adolescence. Am J Neuroradiol 34(7):1443. https://doi.org/10.3174/ajnr.A3350

Catani M, Dell'Acqua F, De Schotten MT (2013) A revised limbic system model for memory, emotion and behaviour. Neurosci Biobehavioral Reviews 37(8):1724–1737

Cheour-Luhtanen M, Alho K, Kujala T, Sainio K, Reinikainen K, Renlund M, Aaltonen O, Eerola O, Näätänen R (1995) Mismatch negativity indicates vowel discrimination in newborns. Hear Res 82(1):53–58

De Asis-Cruz J, Andescavage N, Limperopoulos C (2022) Adverse prenatal exposures and fetal Brain Development: insights from advanced fetal magnetic resonance imaging. Biol Psychiatry: Cogn Neurosci Neuroimaging 7(5):480–490. https://doi.org/10.1016/j.bpsc.2021.11.009

Dean DC 3rd, Dirks H, O'Muircheartaigh J, Walker L, Jerskey BA, Lehman K, Han M, Waskiewicz N, Deoni SC (2014) Pediatric neuroimaging using magnetic resonance imaging during non-sedated sleep. Pediatr Radiol 44(1):64–72. https://doi.org/10.1007/s00247-013-2752-8

Dean DC 3rd, Planalp EM, Wooten W, Adluru N, Kecskemeti SR, Frye C, Schmidt CK, Schmidt NL, Styner MA, Goldsmith HH, Davidson RJ, Alexander AL (2017) Mapping White Matter Microstructure in the one Month Human Brain. Sci Rep 7(1):9759. https://doi.org/10.1038/s41598-017-09915-6

Dean DC 3rd, Planalp EM, Wooten W, Kecskemeti SR, Adluru N, Schmidt CK, Frye C, Birn RM, Burghy CA, Schmidt NL, Styner MA, Short SJ, Kalin NH, Goldsmith HH, Alexander AL, Davidson RJ (2018a) Association of Prenatal Maternal Depression and anxiety symptoms with infant White Matter Microstructure.

JAMA Pediatr 172(10):973–981. https://doi.org/10.1001/jamapediatrics.2018.2132

Dean DC 3rd, Planalp EM, Wooten W, Schmidt CK, Kecskemeti SR, Frye C, Schmidt NL, Goldsmith HH, Alexander AL, Davidson RJ (2018b) Investigation of brain structure in the 1-month infant. Brain Struct Funct 223(4):1953–1970. https://doi.org/10.1007/s00429-017-1600-2

Dean DC 3rd, Madrid A, Planalp EM, Moody JF, Papale LA, Knobel KM, Wood EK, McAdams RM, Coe CL, Hill Goldsmith H, Davidson RJ, Alisch RS, Kling PJ (2021) Cord blood DNA methylation modifications in infants are associated with white matter microstructure in the context of prenatal maternal depression and anxiety. Sci Rep 11(1):12181. https://doi.org/10.1038/s41598-021-91642-0

Dehaene-Lambertz G, Pena M (2001) Electrophysiological evidence for automatic phonetic processing in neonates. NeuroReport 12(14):3155–3158

deIpolyi AR, Mukherjee P, Gill K, Henry RG, Partridge SC, Veeraraghavan S, Jin H, Lu Y, Miller SP, Ferriero DM, Vigneron DB, Barkovich AJ (2005) Comparing microstructural and macrostructural development of the cerebral cortex in premature newborns: diffusion tensor imaging versus cortical gyration. NeuroImage 27(3):579–586. https://doi.org/10.1016/j.neuroimage.2005.04.027

Deniz Can D, Richards T, Kuhl PK (2013) Early gray-matter and white-matter concentration in infancy predict later language skills: a whole brain voxel-based morphometry study. Brain Lang 124(1):34–44. https://doi.org/10.1016/j.bandl.2012.10.007

Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage 31(3):968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Dimitrova R, Pietsch M, Ciarrusta J, Fitzgibbon SP, Williams LZJ, Christiaens D, Cordero-Grande L, Batalle D, Makropoulos A, Schuh A, Price AN, Hutter J, Teixeira RP, Hughes E, Chew A, Falconer S, Carney O, Egloff A, Tournier JD, McAlonan G, Rutherford MA, Counsell SJ, Robinson EC, Hajnal JV, Rueckert D, Edwards AD, O'Muircheartaigh J (2021) Preterm birth alters the development of cortical microstructure and morphology at term-equivalent age. NeuroImage 243:118488. https://doi.org/10.1016/j.neuroimage.2021.118488

DiPiero M, Rodrigues PG, Gromala A, Dean DC (2022a) Applications of advanced diffusion MRI in early brain development: a comprehensive review. Brain Struct Function. https://doi.org/10.1007/s00429-022-02605-8

DiPiero MA, Surgent OJ, Travers BG, Alexander AL, Lainhart JE, Dean Iii DC (2022b) Gray Matter microstructure differences in autistic males: a gray matter based spatial statistics study. Neuroimage Clin 37:103306. https://doi.org/10.1016/j.nicl.2022.103306

DiPiero M, Cordash H, Prigge MB, King CK, Morgan J, Guerrero-Gonzalez J, Adluru N, King JB, Lange N, Bigler ED, Zielinski BA, Alexander AL, Lainhart JE, Dean DC (2023) Tract- and gray matter- based spatial statistics show white matter and gray matter microstructural differences in autistic males. Front NeuroSci 17. https://doi.org/10.3389/fnins.2023.1231719

Douet V, Chang L, Cloak C, Ernst T (2014) Genetic influences on brain developmental trajectories on neuroimaging studies: from infancy to young adulthood. Brain Imaging Behav 8(2):234–250. https://doi.org/10.1007/s11682-013-9260-1

Dowe KN, Planalp EM, Dean DC 3rd, Alexander AL, Davidson RJ, Goldsmith HH (2020) Early microstructure of white matter associated with infant attention. Dev Cogn Neurosci 45:100815. https://doi.org/10.1016/j.dcn.2020.100815

Dubois J, Dehaene-Lambertz G, Perrin M, Mangin JF, Cointepas Y, Duchesnay E, Le Bihan D, Hertz-Pannier L (2008) Asynchrony of the early maturation of white matter bundles in healthy infants: quantitative landmarks revealed noninvasively by diffusion tensor imaging. Hum Brain Mapp 29(1):14–27. https://doi.org/10.1002/hbm.20363

Dubois J, Dehaene-Lambertz G, Kulikova S, Poupon C, Huppi PS, Hertz-Pannier L (2014) The early development of brain white matter: a review of imaging studies in fetuses, newborns and infants. Neuroscience 276:48–71. https://doi.org/10.1016/j.neuroscience.2013.12.044

Dubois J, Alison M, Counsell SJ, Hertz-Pannier L, Huppi PS, Benders M (2021) MRI of the neonatal brain: a review of Methodological challenges and neuroscientific advances. J Magn Reson Imaging 53(5):1318–1343. https://doi.org/10.1002/jmri.27192

Eaton-Rosen Z, Melbourne A, Orasanu E, Cardoso MJ, Modat M, Bainbridge A, Kendall GS, Robertson NJ, Marlow N, Ourselin S (2015) Longitudinal measurement of the developing grey matter in preterm subjects using multi-modal MRI. NeuroImage 111:580–589. https://doi.org/10.1016/j.neuroimage.2015.02.010

Edwards AD, Rueckert D, Smith SM, Abo Seada S, Alansary A, Almalbis J, Allsop J, Andersson J, Arichi T, Arulkumaran S, Bastiani M, Batalle D, Baxter L, Bozek J, Braithwaite E, Brandon J, Carney O, Chew A, Christiaens D, Chung R, Colford K, Cordero-Grande L, Counsell SJ, Cullen H, Cupitt J, Curtis C, Davidson A, Deprez M, Dillon L, Dimitrakopoulou K, Dimitrova R, Duff E, Falconer S, Farahibozorg SR, Fitzgibbon SP, Gao J, Gaspar A, Harper N, Harrison SJ, Hughes EJ, Hutter J, Jenkinson M, Jbabdi S, Jones E, Karolis V, Kyriakopoulou V, Lenz G, Makropoulos A, Malik S, Mason L, Mortari F, Nosarti C, Nunes RG, O'Keeffe C, O'Muircheartaigh J, Patel H, Passerat-Palmbach J, Pietsch M, Price AN, Robinson EC, Rutherford MA, Schuh A, Sotiropoulos S, Steinweg J, Teixeira R, Tenev T, Tournier JD, Tusor N, Uus A, Vecchiato K, Williams LZJ, Wright R, Wurie J, Hajnal JV (2022) The developing human connectome project neonatal data release. Front Neurosci 16:886772. https://doi.org/10.3389/fnins.2022.886772

Fenchel D, Dimitrova R, Seidlitz J, Robinson EC, Batalle D, Hutter J, Christiaens D, Pietsch M, Brandon J, Hughes EJ, Allsop J, O'Keeffe C, Price AN, Cordero-Grande L, Schuh A, Makropoulos A, Passerat-Palmbach J, Bozek J, Rueckert D, Hajnal JV, Raznahan A, McAlonan G, Edwards AD, O'Muircheartaigh J (2020) Development of Microstructural and Morphological cortical profiles in the neonatal brain. Cereb Cortex 30(11):5767–5779. https://doi.org/10.1093/cercor/bhaa150

Fick RHJ, Wassermann D, Deriche R (2019) The Dmipy Toolbox: Diffusion MRI Multi-compartment modeling and microstructure recovery made Easy. Front Neuroinformatics 13. https://doi.org/10.3389/fninf.2019.00064

Gao W, Lin W, Chen Y, Gerig G, Smith JK, Jewells V, Gilmore JH (2009) Temporal and spatial development of axonal maturation and myelination of white matter in the developing brain. AJNR Am J Neuroradiol 30(2):290–296. https://doi.org/10.3174/ajnr.A1363

Gao W, Elton A, Zhu H, Alcauter S, Smith JK, Gilmore JH, Lin W (2014) Intersubject variability of and genetic effects on the brain's functional connectivity during infancy. J Neurosci 34(34):11288–11296. https://doi.org/10.1523/jneurosci.5072-13.2014

Garyfallidis E, Brett M, Amirbekian B, Rokem A, van der Walt S, Descoteaux M, Nimmo-Smith I, Dipy C (2014) Dipy, a library for the analysis of diffusion MRI data. Front Neuroinform 8:8. https://doi.org/10.3389/fninf.2014.00008

Geng X, Gouttard S, Sharma A, Gu H, Styner M, Lin W, Gerig G, Gilmore JH (2012) Quantitative tract-based white matter development from birth to age 2years. NeuroImage 61(3):542–557. https://doi.org/10.1016/j.neuroimage.2012.03.057

Gilmore JH, Knickmeyer RC, Gao W (2018) Imaging structural and functional brain development in early childhood. Nat Rev Neurosci 19(3):123–137. https://doi.org/10.1038/nrn.2018.1
Granier-Deferre C, Ribeiro A, Jacquet AY, Bassereau S (2011) Near-term fetuses process temporal features of speech. Dev Sci 14(2):336–352
Guerrero-Gonzalez J, Surgent O, Adluru N, Kirk GR, Dean DC III, Kecskemeti SR, Alexander AL, Travers BG (2022) Improving imaging of the Brainstem and Cerebellum in Autistic children: Transformation-Based High-Resolution Diffusion MRI (TiDi-Fused) in the human brainstem. Front Integr Nuerosci 16. https://doi.org/10.3389/fnint.2022.804743
Hazlett HC, Gu H, Munsell BC, Kim SH, Styner M, Wolff JJ, Elison JT, Swanson MR, Zhu H, Botteron KN, Collins DL, Constantino JN, Dager SR, Estes AM, Evans AC, Fonov VS, Gerig G, Kostopoulos P, McKinstry RC, Pandey J, Paterson S, Pruett JR, Schultz RT, Shaw DW, Zwaigenbaum L, Piven J (2017) Early brain development in infants at high risk for autism spectrum disorder. Nature 542(7641):348–351. https://doi.org/10.1038/nature21369
Hendrix CL, Thomason ME (2022) A survey of protocols from 54 infant and toddler neuroimaging research labs. Dev Cogn Neurosci 54:101060. https://doi.org/10.1016/j.dcn.2022.101060
Herrero MT, Barcia C, Navarro JM (2002) Functional anatomy of thalamus and basal ganglia. Childs Nerv Syst 18(8):386–404. https://doi.org/10.1007/s00381-002-0604-1
Howell BR, Styner MA, Gao W, Yap PT, Wang L, Baluyot K, Yacoub E, Chen G, Potts T, Salzwedel A, Li G, Gilmore JH, Piven J, Smith JK, Shen D, Ugurbil K, Zhu H, Lin W, Elison JT (2019) The UNC/UMN Baby Connectome Project (BCP): an overview of the study design and protocol development. NeuroImage 185:891–905. https://doi.org/10.1016/j.neuroimage.2018.03.049
Huttenlocher PR (1990) Morphometric study of human cerebral cortex development. Neuropsychologia 28(6):517–527. https://doi.org/10.1016/0028-3932(90)90031-I
Isensee F, Schell M, Pflueger I, Brugnara G, Bonekamp D, Neuberger U, Wick A, Schlemmer H-P, Heiland S, Wick W, Bendszus M, Maier-Hein KH, Kickingereder P (2019) Automated brain extraction of multisequence MRI using artificial neural networks. Hum Brain Mapp 40(17):4952–4964. https://doi.org/10.1002/hbm.24750
James P, III (1975) Statistical inference using Extreme Order statistics. Annals Stat 3(1):119–131. https://doi.org/10.1214/aos/1176343003
Jenkinson M, Bannister P, Brady M, Smith S (2002) Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage 17(2):825–841. https://doi.org/10.1016/s1053-8119(02)91132-8
Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM (2012) Fsl Neuroimage 62(2):782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015
Kellner E, Dhital B, Kiselev VG, Reisert M (2016) Gibbs-ringing artifact removal based on local subvoxel-shifts. Magn Reson Med 76(5):1574–1581. https://doi.org/10.1002/mrm.26054
Kelly CJ, Christiaens D, Batalle D, Makropoulos A, Cordero-Grande L, Steinweg JK, O'Muircheartaigh J, Khan H, Lee G, Victor S, Alexander DC, Zhang H, Simpson J, Hajnal JV, Edwards AD, Rutherford MA, Counsell SJ (2019) Abnormal Microstructural Development of the cerebral cortex in neonates with congenital heart disease is Associated with impaired cerebral oxygen delivery. J Am Heart Assoc 8(5):e009893. https://doi.org/10.1161/JAHA.118.009893
Kimpton JA, Batalle D, Barnett ML, Hughes EJ, Chew ATM, Falconer S, Tournier JD, Alexander D, Zhang H, Edwards AD, Counsell SJ (2021) Diffusion magnetic resonance imaging assessment of regional white matter maturation in preterm neonates. Neuroradiology 63(4):573–583. https://doi.org/10.1007/s00234-020-02584-9
Kostović I, Sedmak G, Judaš M (2019) Neural histology and neurogenesis of the human fetal and infant brain. NeuroImage 188:743–773. https://doi.org/10.1016/j.neuroimage.2018.12.043
Kunz N, Zhang H, Vasung L, O'Brien KR, Assaf Y, Lazeyras F, Alexander DC, Huppi PS (2014) Assessing white matter microstructure of the newborn with multi-shell diffusion MRI and biophysical compartment models. NeuroImage 96:288–299. https://doi.org/10.1016/j.neuroimage.2014.03.057
Lean RE, Han RH, Smyser TA, Kenley JK, Shimony JS, Rogers CE, Limbrick DD Jr., Smyser CD (2019) Altered neonatal white and gray matter microstructure is associated with neurodevelopmental impairments in very preterm infants with high-grade brain injury. Pediatr Res 86(3):365–374. https://doi.org/10.1038/s41390-019-0461-1
Leemans A, Jones DK (2009) The B-matrix must be rotated when correcting for subject motion in DTI data. Magn Reson Med 61(6):1336–1349. https://doi.org/10.1002/mrm.21890
Li M, Liu T, Xu X, Wen Q, Zhao Z, Dang X, Zhang Y, Wu D (2022) Development of visual cortex in human neonates is selectively modified by postnatal experience. eLife 11:e78733. https://doi.org/10.7554/eLife.78733
Liu Y, Metens T, Absil J, De Maertelaer V, Balériaux D, David P, Denolin V, Van Overmeire B, Avni F, Van Bogaert P (2011) Gender differences in language and motor-related fibers in a population of healthy preterm neonates at term-equivalent age: a diffusion tensor and probabilistic tractography study. Am J Neuroradiol 32 (11)
Marín O (2016) Developmental timing and critical windows for the treatment of psychiatric disorders. Nat Med 22(11):1229–1238. https://doi.org/10.1038/nm.4225
Mrzljak L, Uylings HBM, Kostovic I, van Eden CG (1988) Prenatal development of neurons in the human prefrontal cortex: I. A qualitative golgi study. J Comp Neurol 271(3):355–386. https://doi.org/10.1002/cne.902710306
Nakao T, Radua J, Rubia K, Mataix-Cols D (2011) Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. Am J Psychiatry 168(11):1154–1163. https://doi.org/10.1176/appi.ajp.2011.11020281
Nazeri A, Chakravarty MM, Rotenberg DJ, Rajji TK, Rathi Y, Michailovich OV, Voineskos AN (2015) Functional consequences of neurite orientation dispersion and density in humans across the adult lifespan. J Neurosci 35(4):1753–1762. https://doi.org/10.1523/JNEUROSCI.3979-14.2015
Nazeri A, Mulsant BH, Rajji TK, Levesque ML, Pipitone J, Stefanik L, Shahab S, Roostaei T, Wheeler AL, Chavez S, Voineskos AN (2017) Gray Matter Neuritic Microstructure Deficits in Schizophrenia and Bipolar Disorder. Biol Psychiatry 82(10):726–736. https://doi.org/10.1016/j.biopsych.2016.12.005
Novikov DS, Fieremans E, Jespersen SN, Kiselev VG (2019) Quantifying brain microstructure with diffusion MRI: theory and parameter estimation. NMR Biomed 32(4):e3998. https://doi.org/10.1002/nbm.3998
Ortiz-Mantilla S, Choe M-s, Flax J, Grant PE, Benasich AA (2010) Associations between the size of the amygdala in infancy and language abilities during the preschool years in normally developing children. NeuroImage 49(3):2791–2799
Oskvig DB, Elkahloun AG, Johnson KR, Phillips TM, Herkenham M (2012) Maternal immune activation by LPS selectively alters specific gene expression profiles of interneuron migration and oxidative stress in the fetus without triggering a fetal immune response. Brain Behav Immun 26(4):623–634. https://doi.org/10.1016/j.bbi.2012.01.015

Ouyang M, Dubois J, Yu Q, Mukherjee P, Huang H (2019a) Delineation of early brain development from fetuses to infants with diffusion MRI and beyond. NeuroImage 185:836–850. https://doi.org/10.1016/j.neuroimage.2018.04.017
Ouyang M, Jeon T, Sotiras A, Peng Q, Mishra V, Halovanic C, Chen M, Chalak L, Rollins N, Roberts TPL, Davatzikos C, Huang H (2019b) Differential cortical microstructural maturation in the preterm human brain with diffusion kurtosis and tensor imaging. Proc Natl Acad Sci U S A 116(10):4681–4688. https://doi.org/10.1073/pnas.1812156116
Planalp EM, Dowe KN, Alexander AL, Goldsmith HH, Davidson RJ, Dean DC III (2023) White matter microstructure predicts individual differences in infant fear (but not anger and sadness). Dev Sci 26(3):e13340. https://doi.org/10.1111/desc.13340
Qiu A, Mori S, Miller MI (2015) Diffusion tensor imaging for understanding brain development in early life. Annu Rev Psychol 66:853–876. https://doi.org/10.1146/annurev-psych-010814-015340
Raschle N, Zuk J, Ortiz-Mantilla S, Sliva DD, Franceschi A, Grant PE, Benasich AA, Gaab N (2012) Pediatric neuroimaging in early childhood and infancy: challenges and practical guidelines. Ann N Y Acad Sci 1252:43–50. https://doi.org/10.1111/j.1749-6632.2012.06457.x
Rees S, Inder T (2005) Fetal and neonatal origins of altered brain development. Early Hum Dev 81(9):753–761. https://doi.org/10.1016/j.earlhumdev.2005.07.004
Rogers CE, Barch DM, Sylvester CM, Pagliaccio D, Harms MP, Botteron KN, Luby JL (2014) Altered gray matter volume and school age anxiety in children born late preterm. J Pediatr 165(5):928–935. https://doi.org/10.1016/j.jpeds.2014.06.063
Rolls ET (2019) The cingulate cortex and limbic systems for emotion, action, and memory. Brain Struct Funct 224(9):3001–3018. https://doi.org/10.1007/s00429-019-01945-2
Smith SM, Nichols TE (2009) Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. NeuroImage 44(1):83–98. https://doi.org/10.1016/j.neuroimage.2008.03.061
Smith KE, Pollak SD (2020) Early life stress and development: potential mechanisms for adverse outcomes. J Neurodevelopmental Disorders 12(1):34. https://doi.org/10.1186/s11689-020-09337-y
Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE (2006) Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. NeuroImage 31(4):1487–1505. https://doi.org/10.1016/j.neuroimage.2006.02.024
Spann MN, Wisnowski JL, Smyser CD, Howell B, Dean DC 3rd (2022) The art, Science, and secrets of scanning Young Children. Biol Psychiatry. https://doi.org/10.1016/j.biopsych.2022.09.025
Steinberg L (2005) Cognitive and affective development in adolescence. Trends Cogn Sci 9(2):69–74. https://doi.org/10.1016/j.tics.2004.12.005
Stephens RL, Langworthy BW, Short SJ, Girault JB, Styner MA, Gilmore JH (2020) White Matter Development from Birth to 6 years of age: a longitudinal study. Cereb Cortex 30(12):6152–6168. https://doi.org/10.1093/cercor/bhaa170
Stoye DQ, Blesa M, Sullivan G, Galdi P, Lamb GJ, Black GS, Quigley AJ, Thrippleton MJ, Bastin ME, Reynolds RM, Boardman JP (2020) Maternal cortisol is associated with neonatal amygdala microstructure and connectivity in a sexually dimorphic manner. Elife 9. https://doi.org/10.7554/eLife.60729
Takashima S, Chan F, Becker LE, Armstrong DL (1980) Morphology of the developing visual cortex of the human infant: a quantitative and qualitative golgi study. J Neuropathology Experimental Neurol 39(4):487–501. https://doi.org/10.1097/00005072-198007000-00007
Teeuw J, Brouwer RM, Guimarães JPOFT, Brandner P, Koenis MMG, Swagerman SC, Verwoert M, Boomsma DI, Hulshoff Pol HE (2019) Genetic and environmental influences on functional connectivity within and between canonical cortical resting-state networks throughout adolescent development in boys and girls. NeuroImage 202:116073. https://doi.org/10.1016/j.neuroimage.2019.116073
Thompson PM, Cannon TD, Narr KL, van Erp T, Poutanen V-P, Huttunen M, Lönnqvist J, Standertskjöld-Nordenstam C-G, Kaprio J, Khaledy M, Dail R, Zoumalan CI, Toga AW (2001) Genetic influences on brain structure. Nat Neurosci 4(12):1253–1258. https://doi.org/10.1038/nn758
Tournier JD, Smith R, Raffelt D, Tabbara R, Dhollander T, Pietsch M, Christiaens D, Jeurissen B, Yeh CH, Connelly A (2019) MRtrix3: a fast, flexible and open software framework for medical image processing and visualisation. NeuroImage 202:116137. https://doi.org/10.1016/j.neuroimage.2019.116137
Uysal S (2023) The Occipital lobes and Visual Processing. Functional neuroanatomy and clinical neuroscience: foundations for understanding disorders of Cognition and Behavior. Oxford University Press. https://doi.org/10.1093/oso/9780190943608.003.0014
Vogt NM, Hunt JF, Adluru N, Dean DC, Johnson SC, Asthana S, Yu JJ, Alexander AL, Bendlin BB (2020) Cortical microstructural alterations in mild cognitive impairment and Alzheimer's Disease Dementia. Cereb Cortex 30(5):2948–2960. https://doi.org/10.1093/cercor/bhz286
Volkow ND, Gordon JA, Freund MP (2021) The healthy brain and child development study—shedding light on opioid exposure, COVID-19, and Health disparities. JAMA Psychiatry 78(5):471–472. https://doi.org/10.1001/jamapsychiatry.2020.3803
Wang L, Gao Y, Shi F, Li G, Gilmore JH, Lin W, Shen D (2015) LINKS: learning-based multi-source IntegratioN frameworK for segmentation of infant brain images. NeuroImage 108:160–172
Wang W, Yu Q, Liang W, Xu F, Li Z, Tang Y, Liu S (2023) Altered cortical microstructure in preterm infants at term-equivalent age relative to term-born neonates. Cereb Cortex 33(3):651–662. https://doi.org/10.1093/cercor/bhac091
Wheeler-Kingshott CA, Cercignani M (2009) About axial and radial diffusivities. Magn Reson Med 61(5):1255–1260. https://doi.org/10.1002/mrm.21965
Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE (2014) Permutation inference for the general linear model. NeuroImage 92:381–397. https://doi.org/10.1016/j.neuroimage.2014.01.060
Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC (2012) NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. NeuroImage 61(4):1000–1016. https://doi.org/10.1016/j.neuroimage.2012.03.072