Diffusion Tensor Imaging in Very Preterm, Moderate-Late Preterm and Term-Born Neonates: A Systematic Review

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Objective To examine white matter abnormalities, measured by diffusion tensor imaging, in very preterm (<32 weeks) and moderate-late preterm neonates (32-37 weeks) at term-equivalent age, compared with healthy full-term controls (≥37 weeks).

Study design A search of Medline (PubMed) was conducted to identify studies with diffusion data collected on very preterm, moderate-late preterm and full-term neonates, using the guidelines from the Meta-analysis of Observational Studies in Epidemiology and PRISMA statements.

Results Eleven studies were included with diffusion tensor imaging data from 554 very preterm, 575 moderate-late preterm, and 318 full-term neonates. Widespread statistically significant diffusion measures were found in all preterm subgroups at term-equivalent age compared with full-term neonates, and this difference was more marked for the very preterm group. These abnormalities are suggestive of changes in the white matter microstructure in the preterm groups. The corpus callosum was a region of interest in both early and moderate-late preterm groups, which showed statistically significant diffusion measures in all 11 studies.

Conclusions Microstructural white matter changes may underpin the increased risk of neurodevelopmental disability seen in preterm infants in later life. diffusion tensor imaging may therefore be a useful prognostic tool for neuro-disability in preterm neonates. *(J Pediatr 2021;232:48-58)*.

Prenatally, there is accelerated brain development, involving the growth and elaboration of cortical and subcortical features.[1] There is a relative slowing in development after birth. Cognitive development is coupled to the structural and functional maturation of the brain.[2] Preterm birth perturbs this developmental trajectory of the brain and so poses a considerable risk to cognitive development.[3] Preterm birth is the leading cause of death in children under the age of 5 years, and accounts for 3.1% of all disability-adjusted life-years in the Global Burden of Disease.[4-6] Preterm neonates who survive are at greater risk of a range neurodevelopmental sequalae, including cognitive dysfunction, cerebral palsy, impaired vision and hearing, and behavioral and emotional problems.[7]

The standard of care for preterm neonates at present is sequential cranial ultrasound examination, which is used to assess white matter injury such as cystic periventricular leukomalacia, intraventricular hemorrhage, and ventricular enlargement in the brain at term-equivalent age.[8,9] However, magnetic resonance imaging (MRI) has been shown to be superior to cranial ultrasound assessments in its sensitivity and prognostic ability.[9-11] Diffusion-weighted imaging is an advanced MRI technique to measure the diffusion of water in the brain, which differs depending on the type of tissue, and provides information from which one may infer the cellular structure of a region. In the cerebrospinal fluid, water is unrestricted and free to diffuse in any direction, and so is isotropic. However, in the white matter, which mostly consists of axonal fibers pointing in a specific direction, diffusion is restricted and occurs along the same direction as the fibers, and so is anisotropic. In the grey matter, which mostly consists of dendrites with a randomly oriented microstructure, diffusion may seem to be isotropic, although it is in fact anisotropic; this appearance of isotropy is due to limitations in the diffusion-weighted imaging sequences. The three-dimensional shape of this diffusion is modelled through diffusion tensor imaging (DTI). With the DTI model, it is possible to infer, in each voxel, properties such as the molecular diffusion rate (mean diffusivity), the directional preference of diffusion (fractional anisotropy), the axial (diffusion rate along the main axis of diffusion), and radial (rate of diffusion in the transverse direction) diffusivity.

Preterm neonates are at significant risk of acute ischemic and/or hemorrhagic brain injury, most notably periventricular leukomalacia, a distinctive variant of cerebral white matter injury.[12,13] However, evidence suggests that, when studied

DTI	Diffusion tensor imaging
JHU-ICBM DTI-81	Johns Hopkins University-International Consortium of Brain Mapping-Diffusion Tensor Imaging-81
MRI	magnetic resonance imaging

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at term-equivalent age, preterm neonates show markedly different diffusion values compared with term neonates even in the absence of abnormalities on their clinical evaluation or cranial ultrasound.[14] The purpose of this systematic review was to examine current DTI findings in very preterm (<32 weeks) and moderate-late preterm (32-37 weeks) neonates at term-equivalent age, as compared with healthy, full-term neonates (≥37 weeks). This process would allow for the identification of white matter microstructural alterations present in preterm neonates at term-equivalent age, which may contribute to later neurodevelopmental sequelae.

Methods

A systematic review of the literature was carried out using the guidelines from the Meta-analysis of Observational Studies in Epidemiology[15] and PRISMA[16] statements. Medline (PubMed) was searched using combinations of the terms (preterm), (term), (white matter), and (diffusion tensor imaging). We selected the relevant papers using the PRISMA flowchart (Figure 1). This search of the literature was conducted over a period of 10 weeks.

Studies were included based on the following inclusion criteria: (1) neonates were grouped by gestational age at birth, (2) at least 1 of these groups was very preterm or moderate-late preterm, (3) a control group of full-term neonates was present or a comparison of the 2 preterm groups was made, (4) neonates were scanned at term-equivalent age, and (5) diffusion-weighted images were obtained and analyzed. We also included studies with preterm neonates born with extremely low birth weight and very low birthweight. Cross-sectional, cohort, and case-control study designs were included in the search. Studies were excluded if there was insufficient data on the gestational age of the neonates, neonates were not scanned at term-equivalent age, there was no comparison between groups based on gestational age, animal models were used, grey matter alone was studied, or studies were not published in the English

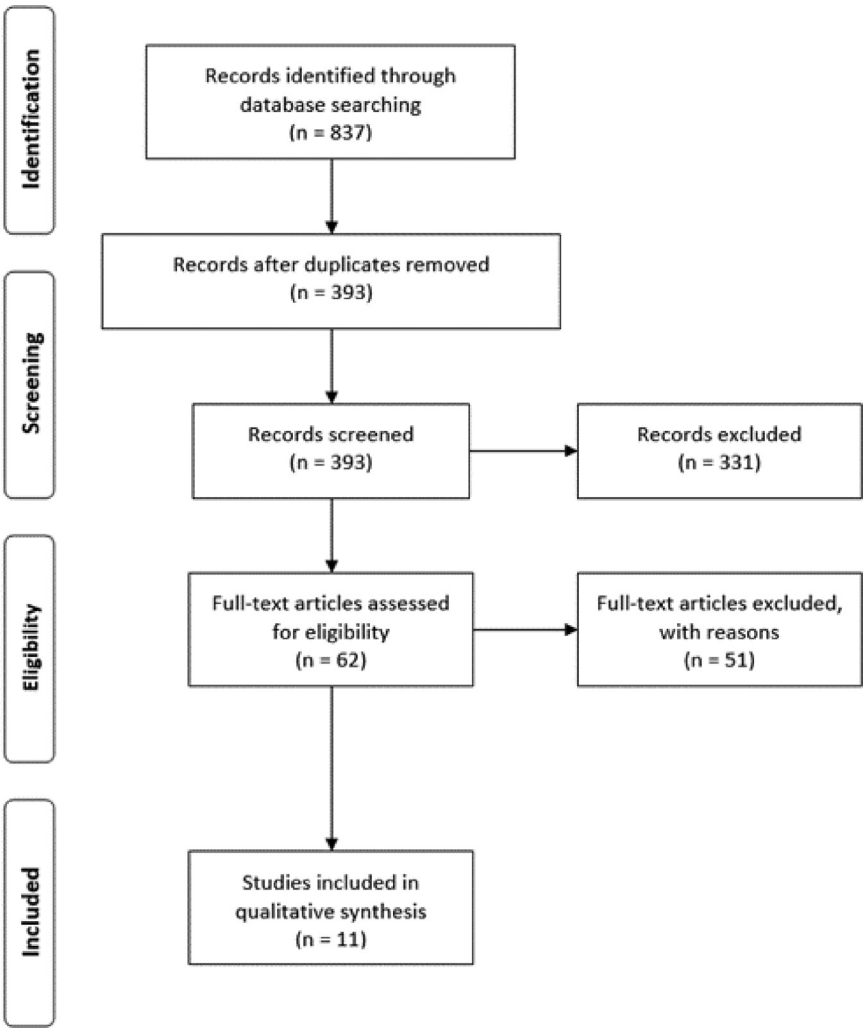

Figure 1. PRISMA flowchart of the search and selection process.

Table I. Data extracted from the literature for the main variables of interest

Authors	Year	Definition/criteria	Neonates with diffusion-weighted imaging scan	Metrics	Whole brain/ROIs	Findings
Brossard-Racine et al[18]	2017	Very low birth weight: ≤32 weeks gestational age, ≤1500 g. FT: ≥37 weeks gestational age. Exclusion: multiple pregnancies, fetal cranial ultrasound/ neonatal MRI abnormalities, congenital infection, chromosomal abnormalities, and/or multiorgan dysmorphic conditions.	73 very low birth weight 73 term	3T MRI 8-channel head coil 27 gradient directions b = 1000 s/mm^2 1.56 × 1.56 × 3 mm^3 DTI measures: FA, MD	ROI - 7 cerebellar regions (anterior vermis, right/ left SCP, MCP, and dentate nuclei) and the genu and splenium of CC	No significant difference between left and right side of bilateral ROIs measured, except MD in the MCP of FT infants where the left MCP shows significantly lower MD compared with the right MCP. Preterm infants at TEA presented with higher FA in the dentate nuclei and middle cerebellar peduncle, and significant lower MD in the vermis compared with controls. Conversely, preterm infants showed reduced FA and increased MD in both the genu and splenium of the CC.
Thompson et al[19]	2011	Very low birth weight: <30 weeks gestational age, <1250 g. Exclusion: congenital anomalies. FT: ≥37 weeks gestational age. Exclusion: antenatal, perinatal, or neonatal complications and congenital or chromosomal abnormalities.	106 very low birth weight 22 term	1.5 T MRI 6 gradient directions b = 700 s/mm^2 DTI measures: FA, MD, RD, AD	ROI - CC (genu, rostral body, anterior midbody, posterior midbody, isthmus and splenium)	FA was lower and MD, RD were higher in CC of VPT, especially at the anterior and posterior ends. Volume of tracts originating from the CC reduced in VPT, particularly for anterior midbody and isthmus tracts. Reductions in CC area in VPT at TEA. Cross-sectional area: absolute difference in CC size of 8.5% between FT and VPT. Reductions in cross-sectional area of the VPT rostral body, anterior and posterior midbody, isthmus, and splenium compared with FT. VPT CC more circular. Mean FA within the CC lower in VPT, while mean MD and RD higher in VPT CC compared with FT. No difference in AD between VPT and FT. FA and AD highest in the splenium, followed by the genu, and lowest in the midbody, for both VPT and FT. Both MD and RD values were highest in the midbody, and lowest in the genu and splenium of the CC. Diffusion within CC subregions FA was lower in VPT compared with FT within the genu, rostral body, isthmus and splenium of the CC. Significant increase in MD and RD values in the genu, posterior midbody and isthmus of the VPT CC compared with FT, as well as significantly increased AD values in the genu. No significant difference in gender between FT and VPT infants.

(*continued*)

Table I. Continued

Authors	Year	Definition/criteria	Neonates with diffusion-weighted imaging scan	Metrics	Whole brain/ROIs	Findings
Pannek et al[20]	2018	VPT: <31 weeks gestational age. Exclusion: genetic or chromosomal abnormality, non-English speaking caregivers, lived >200 km from the hospital. FT: 38-41 weeks gestational age. Exclusion: pregnancy or delivery complications, birth weight below 10th percentile, admission to NICU, abnormal neurological examination at the time of the MRI.	55 VPT 20 term	3T MRI 8-channel head coil 64 gradient directions b = 2000 s/mm^2 1.75 x 1.75 × 2 mm^3 HARDI measures: FD, fiber cross-section FC, FDC	Whole brain – fixel-based analysis	Reduced FD, FC and FDC in VPT without brain abnormalities compared with FT. FD reduced in the anterior commissure, genu, midbody, and splenium of the CC, and a small area of the right fornix bilaterally to occipital and temporal lobe. FDC reduced within the same structures as FD except the anterior midbody of CC and anterior commissure. FC was reduced in the: (1) CC (genu and splenium); (2) Optic radiations (left hemisphere - more extensive), CG bundle, cerebral and cerebellar peduncles bilaterally; (3) WM of the right postcentral gyrus, left SLF. No significant differences between VPT with no and with minimal brain abnormality in FDC and FC when compared to term born babies. Reduction of FD more spatially extensive in VPT with minimal brain abnormalities than VPT without brain abnormalities when compared with FT. FD reduced in the anterior commissure extending to the temporal lobes and a small area within the splenium of the CC that showed statistically significant differences in FD between the 2 groups. Correlation between FC and FDC, and ICV statistically significant throughout the WM after correction for PMA, while correlation between FD and ICV significant only in the left PLIC, cerebral and cerebellar peduncles, and anterior commissure.
Pogribna et al[21]	2013	VPT: ≤29 weeks gestational age and/or extremely low birth weight: <1000 g. Exclusion: congenital anomalies, mechanically ventilated. FT: 37-42 weeks gestational age. Exclusion: history of perinatal distress or complications.	75 VPT 15 term	3T MRI 8-channel head coil 15 gradient directions b = 800 s/mm^2 1.6 × 1.6 × 2 mm^3 DTI measures: FA, MD	7 WM ROIs: ALIC, PLIC, FPVZ, OPVZ, centrum semiovale, subventricular zone, genu and splenium of CC	Compared with FT, VPT infants with significantly lower FA in 3 of 7 (PLIC, occipital periventricular zone, CC) and higher MD in 6 of 7 WM study regions (PLIC, FPVZ, OPVZ, CC, centrum semiovale, subventricular zone).

(*continued*)

Table I. Continued

Authors	Year	Definition/criteria	Neonates with diffusion-weighted imaging scan	Metrics	Whole brain/ROIs	Findings
Rose et al[22]	2008	VPT: 25-29 weeks gestational age. Preterm: 29-32 weeks gestational age. FT: 37-42 weeks gestational age.	12 VPT 11 preterm 10 term	1.5 T MRI 44 gradient directions b = 1100 s/mm^2 0.9 × 0.9 × 2.5 mm^3 DTI measures: FA	Whole brain and ROI – TBSS and sagittal striatum, frontal WM, CC genu, external capsule, cerebral peduncle, CC splenium, corona radiata, centrum semiovale	Reduced FA within the frontal lobe, and a number of anterior and posterior commissural pathways in VPT compared with FT (indicating reduced WM maturity). VPT show significant increased FA in corticospinal pathway within cerebellar peduncle compared with FT. Increased FA within the sagittal striatum, frontal lobe WM, genu of the CC, external capsule, and WM at the level of the centrum semiovale within the preterm compared with the VPT group.
Kaur et al[23]	2014	Extremely low birth weight: <1000 g. Exclusion: severe WM injury, major congenital anomalies. FT: 37-41 weeks gestational age Exclusion: history of perinatal distress or complications.	29 extremely low birth weight 15 term	3T MRI 8-channel head coil 15 gradient directions b = 800 s/mm^2 1.6 × 1.6 × 2 mm^3 DTI measures: FA, MD, RD, AD	ROI - CC, CST, ILF, IFO, UNC, CG, fornix, optic radiations, MCP, SCP	Most tracts displayed a lower FA, higher MD, AD, and RD, and fewer fiber numbers and voxels in extremely low birth weight than FT. FA significantly reduced in the CC, CG UNC and IFO tracts and significantly elevated MD in the CC, CG, CST, ILF and fornix in extremely low birth weight compared with FT.
Kelly et al[24]	2016	MLPT: 32-26 weeks gestational age. Exclusion: conditions known to affect development. FT: ≥37 weeks gestational age, ≥2500 g. Exclusion: resuscitation at birth, clinically unwell, admitted to the newborn nursery.	193 MLPT 83 term	3T MRI 45 gradient directions b = 100-1200 s/mm^2 (increments of 50) 1.2 × 1.2 × 1.2 mm^3 DTI measures: FA, MD, RD, AD	Whole brain - TBSS	Many voxels had lower FA in MLPT infants vs FT, encompassing approximately 59% of the WM skeleton. No regions in which FA was higher in MLPT infants than FT. Many voxels with higher MD in MLPT infants, generally co-located on same tracts as FA differences, encompassing approximately 64% of the WM skeleton. Many voxels had higher RD in MLPT than FTs, overall encompassed approximately 69% of the WM skeleton. Voxels with higher AD in MLPT infants found in many of the same tracts as FA group differences, less continuous in length, encompassed approximately 41% of the WM skeleton. AD, RD, and MD all higher in the superior cerebellar region in MLPT vs FT, no difference in FA between groups in this region. Only a small region where gestational age at birth correlated positively with FA and negatively with RD in MLPT infants.

(*continued*)

Table I. Continued

Authors	Year	Definition/criteria	Neonates with diffusion-weighted imaging scan	Metrics	Whole brain/ROIs	Findings
Knight et al[25]	2018	VPT: <32 weeks gestational age (singletons). LPT: 33-36 weeks gestational age (twins).	11 VPT 20 LPT	30 gradient directions DTI measures: FA, MD, RD, AD	Whole brain - TBSS	FA lower, RD higher in VPT group compared with LPT group, with a bias toward early myelinating regions. VPT group appears to show myelogenesis which is lacking behind the LPT group at TEA, with early myelinating regions suffering the greatest adverse effects. Late-myelinating regions appear to follow a more similar myelogenesis pathway, being less affected by premature birth.
Thompson et al[26]	2019	VPT: <32 weeks gestational age. MPT: 32-33 weeks gestational age. LPT: 34-36 weeks gestational age. FT: ≥37 weeks gestational age. Exclusion: congenital abnormalities likely to affect brain growth or development.	92 VPT 69 MPT 120 LPT 80 term	3T MRI 45 gradient directions b = 100-1200 s/mm^2 (increments of 50) 1.2 × 1.2 × 1.2 mm^3 DTI measures: FA, MD, AD, RD	Whole brain – TBSS	Gestational age group associated with FA, MD, AD, and RD in 45%-67% of the mean FA skeleton. The regions in which gestational age group was associated with FA, MD, AD, and RD overlapped with some of the regions in which gestational age group was associated with WM volume (CC, fornix, occipital WM, temporal WM). Overall voxels that differed (lower FA, higher MD) between MPT and FT were approximately 10%-20% fewer than in the VPT-FT. Overall voxels that differed (lower FA, higher MD) between LPT and FT were approximately 10%-20% fewer than in the MPT-FT. Small number of voxels with higher FA and lower MD in each preterm group vs FT group. Mostly in approx. location of cerebellar and brainstem WM, cerebral peduncle, internal capsule, corona radiata. Relatively stable number of voxels with this opposite pattern was relatively stable between VPT-FT, MPT-FT, and LPT-FT. Differences in FA and MD between each preterm group and FT group mostly driven by RD rather than AD.
Kelly et al[27]	2019	VPT: 24-29 weeks gestational age. MLPT: 32-36 weeks gestational age.	90 VPT 173 moderate to LPT	3T MRI 45 gradient directions b = 100-1200 s/mm^2 1.2 × 1.2 × 1.2 mm^3 DTI measures: FA, RD, MD, AD	Whole brain – TBSS	Some evidence that alterations in WM microstructure of various tracts at TEA were related to atypical performance on some neurological and behavioral domains of the NNNS and HNNE in preterm infants at TEA. Relationships between brain structure and neurological and behavioral performances relatively similar between VPT and MLPT groups. Association generally in the direction of suboptimal scores associated with lower FA and higher AD/RD/MD. Except for suboptimal NNNS tonicity, which was associated with lower AD and MD.

(*continued*)

Table I. Continued

Authors	Year	Definition/criteria	Neonates with diffusion-weighted imaging scan	Metrics	Whole brain/ROIs	Findings
Thompson et al[28]	2019	VPT: <32 weeks gestational age. MPT: 32-33 weeks gestational age. LPT: 34-36 weeks gestational age. FT: ≥37 weeks gestational age. Exclusion: congenital abnormalities likely to affect brain growth or development.	92 VPT 69 MPT 120 LPT 80 term	3T MRI 45 gradient directions B = 100-1200 s/mm^2 1.2 × 1.2 × 1.2 mm^3 DTI measures: FA, MD, AD, RD	Whole brain - TBSS	Male sex associated with lower FA and higher AD, RD, MD in optic radiation, external and internal capsules, and corona radiata. These associations were generally similar between gestational age groups. Postnatal growth not associated with brain volumes or diffusion values. Higher BWSDS associated with higher FA and lower RD, MD consistently in CC, sagittal striatum, posterior thalamic radiation, internal and external capsules, and corona radiata in MPT and LPT groups. With higher BWSDS, FA increased in approximately 33% of the WM skeleton, covering many of the major WM tracts. Mainly driven by MPT group and also by LPT group to lesser extent.

AD, axial diffusivity; *AUC*, anterior limb of the internal capsule; *BWSDS*, birth weight standard deviation score; *CC*, corpus callosum; *CG*, cingulum; *CST*, corticospinal tract; DTI, diffusion tensor imaging; *FA*, fractional anisotropy; *FC*, fiber cross-section; *FD*, fiber density; *FDC*, fiber density and bundle cross-section; *FPIZ*, frontal periventricular zone; *FT*, full term; *HNNE*, Hammersmith Neonatal Neurological Examination; *ICV*, intracranial volume; *IFO*, inferior-fronto occipital fasciculus; *ILF*, inferior longitudinal fasciculus; *LPT*, late preterm; *MCP*, middle cerebellar peduncle; *MD*, mean diffusivity; *MLPT*, moderate to late preterm; *MPT*, moderate preterm; *NICU*, neonatal intensive care unit; *NNNS*, Neonatal Intensive Care Unit Network Neurobehavioral Scale; *OPVZ*, occipital periventricular zone; *PLIC*, posterior limb of the internal capsule; *PLK*;, *PMA*, postmenstrual age; *RD*, radial diffusivity; *SCP*, superior cerebellar peduncle; *SLF*, superior longitudinal fasciculus; *TEA*, term-equivalent age; *UNC*, uncinate fasciculus; *VPT*, very preterm; *WM*, white matter.

language. We selected articles in which neonates did not present with any illness or disease for any of the groups (very preterm, moderate-late preterm, and full-term). However, we did not exclude the articles that also included infants with minor abnormalities if the inclusion criteria were met. Studies were also assessed for quality and bias with the application of the Strengthening the Reporting of Observational Studies in Epidemiology statement[17] to selected articles.

Data extracted from the studies included population characteristics, criteria for determining groups based on gestational age, diffusion metrics for white matter, and specific white matter tracts, or regions of interest, that showed statistically significant diffusion measures in preterm neonates compared with full-term neonates. These variables were then compiled into **Table I**.

We aimed to define and quantify the specific white matter tracts, or regions of interest, that seem to be implicated in preterm birth. By using the Johns Hopkins University-International Consortium of Brain Mapping-Diffusion Tensor Imaging-81 (JHU-ICBM DTI-81) white matter labels.[29] As a starting point, we calculated the number of times each region of interest was mentioned in the results section of these studies as having statistically significant diffusion measures. We then visualized the results by creating a greyscale image using FSLeyes (www.fmrib.ox.ac.uk/fsl). Using FSL's FMRIB58 fractional anisotropy image as a template, we placed the JHU-ICBM DTI-81 white matter labels atlas as an overlay, selecting the relevant tracts and removing the tracts that were not part of the results in the literature review. The relative weighting of the tracts was a function of the number of times it appeared in the literature review.

Study selection, data extraction and analysis, and quality assessment were conducted by three authors independently, 1 author for the early preterm group, 1 author for the moderate-late preterm group, and 1 author for the 2 groups combined.

Results

The search yielded 837 articles, which after the removal of duplicates, left 393 individual studies. The full texts of 62 studies were examined, and 11 studies were included in our final list for review. These 11 studies included DTI data from 554 very preterm, 575 moderate-late preterm, and 318 full-term neonates (2 studies used the same cohort of infants).[18-28] These studies all met the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology statement regarding quality and bias (**Table II**; available at www.jpeds.com).[17] Overall, all preterm subgroups showed atypical brain microstructure at term-equivalent age when compared with a full-term group. Most white matter tracts in preterm subgroups scanned at term-equivalent age presented with lower fractional anisotropy; higher mean diffusivity, radial diffusivity, and axial diffusivity; and less fiber count compared with full-term controls. Furthermore, moderate-late preterm neonates were shown to have higher fractional

anisotropy and lower axial diffusivity, radial diffusivity, and mean diffusivity when compared with very preterm infants, with 1 study demonstrating an approximately 10%-20% difference in overall percentage of voxels between successive gestational age groups.[26]

We also calculated the frequency of regions of interest implicated in both very and moderate-late preterm birth (**Table III**). Although widespread diffusion abnormalities were observed, 1 particular region of interest was identified, namely, the corpus callosum, which had statistically significant diffusion measures in all 11 studies reviewed. The frequencies of these regions of interest were then converted to a greyscale image, in which the tracts with the most mentions (such as the corpus callosum), are shown as the brightest (white), and the tracts with the least mentions are shown as the darkest (black), with various levels of grey in between (**Figure 2**). Three studies provided sufficient data to calculate the effect size of differences in diffusion measures in these regions of interest between groups (**Table IV**; available at www.jpeds.com). Notably, Cohen *d* and Hedges *g* values for various regions of the corpus callosum were found to exceed the convention for a large effect size (≥0.80).

When considering very preterm neonates, data from 5 studies suggested that this group presents with a decreased fractional anisotropy and increased mean diffusivity in the genu and splenium of the corpus callosum when compared with full-term controls.[18,19,21-23] This finding indicates a decreased white matter maturity in this region in the very preterm groups. In contrast, very preterm infants present with higher fractional anisotropy and lower mean diffusivity in the corticospinal tract within the cerebellar peduncles compared with the controls; however, this finding may be due to the presence of crossing fibers in this region, which can affect DTI measures.[18,22] A study measuring the fiber density, fiber cross-section, and fiber density and bundle cross-section found that early preterm infants compared with term-born controls show a reduced fiber density, fiber cross-section, and fiber density and bundle cross-section in many regions of the brain, including the corpus callosum, anterior commissure, corticospinal tract, optic radiations, and cingulum.[18] This finding is consistent with another study that found the callosal area to be decreased by 8.5% in very preterm infants compared with full-term controls.[19]

Each of the studies looking at moderate-late preterm neonates took a whole brain approach using tract-based spatial statistics. Diffusion abnormalities encompassed up to 70% of the white matter skeleton, and the voxels were located bilaterally within several major fiber tracts, including the corpus callosum, cerebral peduncle, sagittal stratum, inferior fronto-occipital fasciculus, posterior thalamic (optic) radiation, uncinate fasciculus, forceps minor and major, cingulum, stria terminalis, external capsule, internal capsule (anterior limb, posterior limb, and retrolenticular part), fornix, superior longitudinal fasciculus, and corona radiata (anterior, superior, and posterior sections).[24] The estimates of the percentage of the white matter skeleton with a lowered fractional anisotropy ranged between one-third, approximately 59%,and approximately 45%-67%.[24,26,27]

The very preterm group seems to show myelogenesis, which is lagging behind the moderate-late preterm group at term-equivalent age, with early myelinating regions suffering the greatest adverse effects. This finding is demonstrated by lower fractional anisotropy and higher radial diffusivity in the very preterm group compared with the moderate-late preterm group.[25] Late myelinating regions seem to follow a more similar myelogenesis pathway, being less affected by premature birth.

Discussion

All preterm subgroups show widespread white matter abnormalities when scanned at term-equivalent age compared with full-term neonates. This result is demonstrated by statistically significant diffusion measures in most white matter tracts throughout the brain. This difference is more marked for the very preterm group compared with the moderate-late preterm group, with fractional anisotropy increasing and mean diffusivity, axial diffusivity, and radial diffusivity decreasing as gestational age at birth advances.

DTI is increasingly being applied in studies of the developing brain, because these measures seem to be sensitive to maturational processes that alter the microstructure of the infant brain. Cellular substrates for diffusion changes seen during development may include decreases in axon packing density, number of oligodendroglia, degree of myelination or membrane integrity, and/or increases in tissue water content or extracellular space.[30-33] DTI measures have in fact been linked to myelination, the process in which the axons of neurons are surrounded in an insulating fatty sheath called myelin in order to facilitate neural connectivity and communication.[1,30] Myelination is a major developmental process that begins during the second trimester and continues through to adulthood, with its most rapid development occurring during the first year of life.[34] Myelination occurs in several predictable neuroanatomical sequences: from

Table III. Summary of ROIs implicated in preterm neonates from the literature and how often they were mentioned

ROIs	No. of ROIs mentioned in results
CC	11
OR, CG, PLIC, Cerebellar WM	6
SS, EC, CR, IFO	5
Fornix, CP, SLF, ALIC	4
CST, UNC	3
CS, ILF	2
AC, OPVZ, FPVZ, SVZ, Forceps minor and major	1

ROIs were chosen based on the JHU-ICBM DTI-81 white matter atlas.
AC, anterior commissure; *CP*, cerebral peduncle; *CR*, corona radiata; *CS*, centrum semiovale; *EC*, external capsule; *OR*, optic radiations; *ROI*, region of interest; *SS*, sagittal striatum; *SVZ*, subventricular zone.

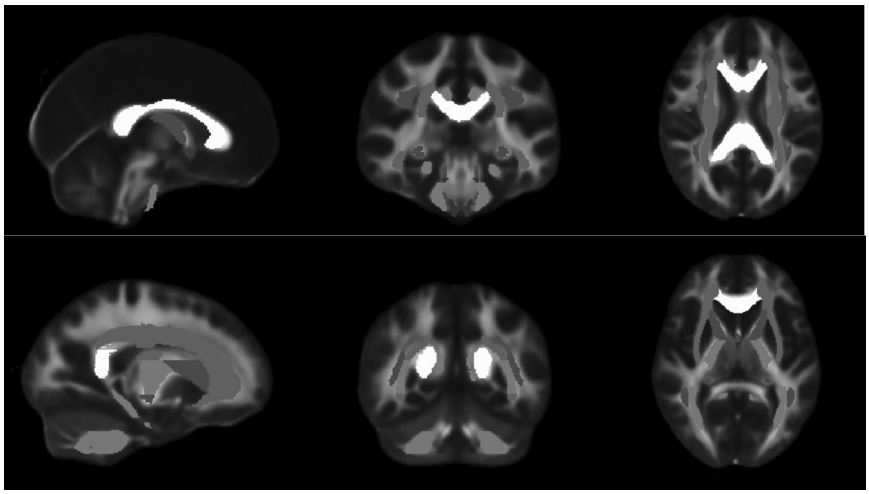

Figure 2. Tract regions of interest as defined by JHU-ICBM DTI-81 white matter atlas, shown on the FMRIB58 fractional anisotropy template, in sagittal (*left*), coronal (*center*), and axial (*right*) views. Tracts shown are those that arose as areas of interest in the literature search, with color representing the relative amount of times that region of interest was mentioned; regions of interest in white being the most mentioned and regions of interest in black being the least.

central to peripheral, from posterior to anterior, and from caudal to rostral.[35] For this reason, premature birth may interrupt the normal scheme of myelination differently, depending on gestational age.

Preterm infants often present with neurodevelopmental deficits later in life, such as lower performance IQ, learning difficulties, and developmental coordination disorder.[36] Our identification of the corpus callosum as a region of interest in preterm neonates is consistent with this finding—the corpus callosum is a large commissural fiber tract connecting the left and right hemispheres and is thought to play a key role in cognitive and even motor functioning.[37,38] It has in fact been found that abnormal corpus callosum integrity is associated with poorer neurodevelopmental outcomes in preterm infants, with callosal shape alterations associated with later cognitive impairment, and microstructural abnormalities within the tract associated with motor impairment at 2 years of age.[39] Another study found that, at term-equivalent age, extremely preterm infants (<26 weeks gestational age) had significantly lower fractional anisotropy in the splenium of the corpus callosum compared with preterm infants (>26 weeks gestational age). However, after 1 year of corrected age, there were no longer any significant between-group differences, suggesting that the white matter of younger gestational age infants may mature more quickly and eventually catch up with the older gestational age infants.[40]

It should be considered that, although this review focused solely on diffusion changes in the white matter tracts of the brain, DTI has also been used to demonstrate detectable changes in deep grey matter regions during the preterm period. It has been found that fractional anisotropy and mean diffusivity both decreases significantly in the thalamus during the preterm period, as well as an increase in the intraneurite volume fraction. This measure represents how much of the remaining space is occupied by the neurites and suggests that the thalamus is also sensitive to myelination status in preterm infants.[41] Thalamic abnormalities are often a feature of brain injury in preterm neonates and have been associated with the neurodevelopmental sequelae seen in these infants later in life.

Several studies have found a relationship between diffusion measures at term-equivalent age and outcomes at 18-24 months corrected age; notably, associations between cognitive outcomes and fractional anisotropy values in the corpus callosum, as well as motor outcomes and fractional anisotropy values in the corpus callosum, fornix, cingulum, and internal and external capsules.[42-44]

Preterm neonates display alterations in the white matter microstructure when compared with full-term controls, including a decrease in fractional anisotropy and an increase in axial diffusivity, radial diffusivity, and mean diffusivity. This difference is more marked for very preterm than moderate-late preterm neonates, potentially owing to a disruption in the myelination process. Cellular substrates for these changes may include changes in water content and axon packing density, and are suggestive of altered brain development. This process may underpin the increased risk of neurodevelopmental disability seen in preterm infants in later life. DTI may be used, alongside other complimentary MRI measures such as absolute T_1 and T_2 relaxation times, to assess white matter maturity in preterm neonates, and may therefore be a useful prognostic tool for neurodisability in these infants. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Dissecting Down Microform Cleft Lip

Pomerance HH. Congenital prolabial-maxillary scar: A possible minor expression of cleft lip. J Pediatr 1971;78:868-70.

Three cases of infants (2 female) born with a linear scar located at the right prolabial-maxillary junction and flattening of the right nares were reported by Pomerance in 1971. In 1 of the 3 cases, notching of the upper lip was observed. A family history of a first-degree relative with clefting was noted in 2 cases with an older sibling in 1 case having a unilateral cleft lip and the mother of a different affected infant having a repaired cleft lip and palate. The presence of an affected first-degree family member in 2 of the 3 cases and notching of the upper lip in the third case provided strong evidence that the prolabial maxillary scar observed in the 3 cases represented a form fruste of a cleft lip.

Facial development begins during the fourth week of embryologic development and is mediated by migrating neural crest cells which form the facial prominences. Isolated cleft lip falls within the spectrum of nonsyndromic cleft lip with or without cleft palate. A cleft lip usually represents a failure of fusion between the maxillary and medial nasal processes and its occurrence may be mediated by a number of genes such as *IRF6*, *VAX1*, and *PAX7*.[1]

Based on a retrospective chart review of 393 cases with unilateral cleft lip, Yuzeriha and Mullikan stratified the "lesser forms of unilateral cleft lip" into 3 groupings on the basis of extent of disruption at the vermilion-cutaneous junction: minor-form clefts, which are defects extending 3 mm or above the normal Cupid's bow peak; microform clefts, defined as a vermilioncutaneous notch less than 3 mm above the normal peak; and mini-microform clefts, which represent disrupted vermilion-cutaneous junction without elevation of the bow peak.[2] All 3 forms were associated with different surgical correction procedures and all forms had some degree of nasal deformity, with the minimicroform cleft having a variable nasal deformity referred to as a depressed nasal sill.

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Table II. STROBE reporting for each study

Characteristics	Item no,		Brossard-Racine et al[18] 2017	Thompson et al[19] 2011	Pannek et al[20] 2018	Pogribna et al[21] 2013	Rose et al[22] 2008	Kaur et al[23] 2014	Kelly et al[24] 2016	Knight et al[25] 2018	Thompson et al[26] 2019	Kelly et al[27] 2019	Thompson et al[28] 2019
Title and abstract	1	a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		b	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Introduction													
Background/ rationale	2		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Objectives	3		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Methods													
Study design	4		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Setting	5		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Participants	6	a	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I
		b	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Variables	7		Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I
Data sources/ measurement	8		Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I
Bias	9		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Study size	10		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Quantitative variables	11		Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I
Statistical methods	12	a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		b	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		c	N/A	N/A	N/A	N/A	N/A	Y	N/A	N/A	N/A	N/A	N/A
		d	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		e	N/A	N/A	N/A	N/A	N/A	Y	N/A	N/A	N/A	N/A	N/A
Results													
Participants	13	a	Y	Y	Y	Y	Y	Y	Y	Final nos. only	Y	Y	Y
		b	Y	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y
		c	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Y	N/A	N/A
Descriptive data	14	a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		b	N/A	N/A	N/A	N/A	N/A	Y	N/A	N/A	N/A	N/A	N/A
		c	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Outcome data	15		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Main results	16	a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
		b	N/A	N/A	N/A	N/A	Y	N/A	N/A	Y	Y	Y	Y
		c	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Other analyses	17		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Discussion													
Key results	18		Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I	Y – see Table I
Limitations	19		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Interpretation	20		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Generalizability	21		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Other information													
Funding	22		Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y

N/A, not applicable.
See **STROBE_checklist** for superscript alphabets a-e.

Table IV. Effect sizes (Cohen d and Hedges' g) calculated for the studies that provided sufficient data

Brocard-Racine et al[18] 2017	Very preterm (mean (SD))	Term (mean (SD))	*P* value	Cohen d	*(MD = ×10−3)*
CC genu	FA: 0.574 (0.076) MD: 1.372 (0.162)	FA: 0.669 (0.070) MD: 1.351 (0.117)	FA: <.001 MD: .754	FA: 1.300272 MD: 0.148617	
CC splenium	FA: 0.639 (0.101) MD: 1.271 (0.200)	FA: 0.756 (0.073) MD: 1.106 (0.138)	FA: <.001 MD: <.001	FA: 1.327746 MD: 1.096497	
Pontine corticospinal tract	FA: 0.374 (0.083) MD: 0.811 (0.120)	FA: 0.393 (0.079) MD: 0.797 (0.113)	FA: .445 MD: .435	FA: 0.234496 MD: 0.120117	
Superior cerebellar peduncle	FA: 0.379 (0.050) MD: 1.036 (0.159)	FA: 0.373 (0.064) MD: 1.074 (0.154)	FA: .664 MD: .587	FA: 0.104478 MD: 0.242781	
Middle cerebellar peduncle	FA: 0.614 (0.071) MD: 0.827 (0.115) MD: (l) 0.807 (0.120)	FA: 0.610 (0.065) MD: 0.848 (0.122) MD: (l) 0.805 (0.132)	FA: .028 MD: .063 MD: (l) .148	FA: 0.058766 MD: 0.177138 MD: (l) 0.015855	
Dentate nuclei	FA: 0.172 (0.027) MD: 0.807 (0.120)	FA: 0.158 (0.024) MD: 0.805 (0.132)	FA: <.001 MD: .148	FA: 0.548072 MD: 0.015855	
Vermis	FA: 0.207 (0.044) MD: 0.761 (0.061)	FA: 0.206 (0.042) MD: 0.777 (0.060)	FA: .234 MD: .023	FA: 0.0232 MD: 0.264454	

Thompson et al[19] 2011	Very Preterm	Term	*P* value	Hedges' g
CC whole	FA: 0.29 (0.06) MD: 1.61 (0.13) AD: 2.13 (0.16) RD: 1.35 (0.15)	FA: 0.33 (0.05) MD: 1.53 (0.08) AD: 2.10 (0.14) RD: 1.24 (0.09)	FA: .007 MD: .006 AD: .5 RD: .001	FA: 0.684319 MD: 0.7312 AD: 0.191273 RD: 0.77588
CC genu	FA: 0.32 (0.07) MD: 1.63 (0.14) AD: 2.20 (0.20) RD: 1.35 (0.17)	FA: 0.35 (0.08) MD: 1.49 (0.12) AD: 2.10 (0.20) RD: 1.19 (0.13)	FA: .04 MD: <.0005 AD: .03 RD: <.0005	FA: 0.41804 MD: 1.02287 AD: 0.5 RD: 0.975537
CC RB	FA: 0.20 (0.06) MD: 1.72 (0.24) AD:2.06 (0.29) RD: 1.55 (0.24)	FA: 0.24 (0.08) MD: 1.67 (0.18) AD: 2.09 (0.24) RD: 1.47 (0.19)	FA: .005 MD: .4 AD: .7 RD: .1	FA: 0.62725 MD: 0.216371 AD: 0.106277 RD: 0.344212
CC AMB	FA: 0.23 (0.06) MD: 1.59 (0.18) AD: 1.95 (0.24) RD: 1.41 (0.17)	FA: 0.25 (0.05) MD: 1.56 (0.15) AD: 1.95 (0.19) RD: 1.36 (0.15)	FA: .2 MD: .4 AD: .9 RD: .3	FA: 0.34216 MD: 0.17108 AD: 0 RD: 0.2997
CC PMB	FA: 0.21 (0.06) MD: 1.61 (0.17) AD: 1.96 (0.24) RD: 1.44 (0.16)	FA: 0.23 (0.04) MD: 1.51 (0.09) AD: 1.87 (0.14) RD: 1.34 (0.08)	FA: .3 MD: .009 AD: .1 RD: .003	FA: 0.349927 MD: 0.627044 AD: 0.397489 RD: 0.668153
CC isthmus	FA: 0.20 (0.06) MD: 1.74 (0.18) AD: 2.08 (0.22) RD: 1.57 (0.18)	FA: 0.24 (0.06) MD: 1.58 (0.18) AD: 1.99 (0.19) RD: 1.37 (0.19)	FA: .001 MD: <.0005 AD: .06 RD: <.0005	FA: 0.666667 MD: 0.888889 AD: 0.41804 RD: 1.100686
CC splenium	FA: 0.40 (0.10) MD: 1.53 (0.23) AD: 2.24 (0.22) RD: 1.17 (0.27)	FA: 0.45 (0.08) MD: 1.49 (0.12) AD: 2.30 (0.20) RD: 1.08 (0.14)	FA: .04 MD: .4 AD: .2 RD: .1	FA: 0.515711 MD: 0.185529 AD: 0.276759 RD: 0.35571

(*continued*)

Table IV. Continued

Brocard-Racine et al[18] 2017	Very preterm (mean (SD))	Term (mean (SD))	*P* value	Cohen d		*(MD = ×10−3)*
Rose et al[22] 2008	**Extremely Preterm**	**Very Preterm**	**Term**	**Hedges's g: EPT-VPT**	**Hedges's g: EPT-VPT**	**Hedges' g: VPT-FT**
Sagittal striatum	FA: 0.26 (0.03)	FA: 0.33 (0.03)*	FA: .30 (.02)†	FA: 2.277979	FA: 1.539601	FA: 1.164965
Frontal WM	FA: 0.23 (0.03)	FA: 0.31 (0.04)*	FA: .30 (.04)†	FA: 2.333333	FA: 2.008214	FA: 0.25
CC genu	FA: 0.40 (0.04)	FA: 0.46 (0.01)*	FA: .44 (.06)†	FA: 2.016065	FA: 0.8	FA: 0.477017
External capsule	FA: 0.25 (0.02)	FA: 0.29 (0.02)*	FA: .30 (.03)†	FA: 2	FA: 2	FA: 0.396264
Cerebral peduncle	FA: 0.42 (0.02)	FA: 0.44 (0.03)	FA: .38 (.02)†,‡	FA: 0.791748	FA: 2	FA: 2.329929
CC splenium	FA: 0.52 (0.07)	FA: 0.52 (0.05)	FA: .58 (.05)†,‡	FA: 0	FA: 0.970777	FA: 1.2
Corona radiata	FA: 0.20 (0.02)	FA: 0.22 (0.02)	FA: .33 (.04)†,‡	FA: 1	FA: 4.240132	FA: 3.534765
Centrum semiovale	FA: 0.25 (0.03)	FA: 0.31 (0.03)*	FA: .29 (.04)†	FA: 2	FA: 1.147551	FA: 0.5699

*$P < .001$ for very preterm and preterm.
†$P < .001$ for very preterm and normal term.
‡$P < .001$ for preterm and normal term.