NeuroImage: Clinical 32 (2021) 102843

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

White matter alterations and cognitive outcomes in children born very low birth weight

Julie Sato [a,b,c,*], Marlee M. Vandewouw [a,c,d,e], Nicole Bando [f], Helen M. Branson [a,g], Deborah L. O'Connor [f,h,j], Sharon L. Unger [h,i,j,k], Margot J. Taylor [a,b,c,g,i]

[a] Diagnostic Imaging, Hospital for Sick Children, Toronto, Ontario, Canada
[b] Psychology, University of Toronto, Toronto, Ontario, Canada
[c] Neurosciences & Mental Health, Hospital for Sick Children, Toronto, Ontario, Canada
[d] Autism Research Centre, Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital, Toronto, ON, Canada
[e] Institute of Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada
[f] Translational Medicine, SickKids Research Institute, Toronto, Ontario, Canada
[g] Medical Imaging, University of Toronto, Ontario, Canada
[h] Nutritional Sciences, University of Toronto, Toronto, Ontario, Canada
[i] Paediatrics, University of Toronto, Toronto, Ontario, Canada
[j] Paediatrics, Mount Sinai Health, Toronto, Ontario, Canada
[k] Division of Neonatology, The Hospital for Sick Children, Toronto, Ontario, Canada

ARTICLE INFO

Keywords:
Very low birth weight
White matter
Diffusion tensor imaging
Cognition
Children

ABSTRACT

Background: Very low birth weight (VLBW) infants are at risk for disrupted white matter maturation, yet little is known about the contributing factors, particularly at preschool-age when cognitive difficulties begin to emerge. We examined white matter microstructure in five-year-old VLBW and full-term (FT) children, and its association with cognitive outcomes and birth weight.

Methods: Multi-shell diffusion and MR images were obtained for 41 VLBW (mean birth weight: 1028.6 ± 256.8 g) and 26 FT (3295.4 ± 493.9 g) children. Fractional anisotropy (FA), radial diffusivity (RD), neurite orientation dispersion index (ODI) and density index (NDI) were estimated using diffusion tensor and neurite orientation dispersion and density imaging models. Between-group analyses used a general linear model with group and sex as explanatory variables. Within-group associations between white matter microstructure, cognitive outcomes and birth weight were also investigated.

Results: VLBW compared to FT children showed lower FA and NDI across widespread white matter regions. Smaller clusters of atypical ODI were also found in VLBW children. Within-group analyses in FT children revealed that lower RD and higher NDI were associated with vocabulary acquisition and working memory. In VLBW children, higher FA and NDI, and lower RD and ODI, were associated with improved processing speed. In both groups, FA was positively associated with birth weight.

Conclusions: Our findings demonstrate white matter alterations in young VLBW children, including widespread reductions in axon density that may reflect sustained myelination disruptions. The associations with cognitive outcomes may also highlight which of the VLBW children are at higher risk for later cognitive difficulties.

1. Introduction

Infants born preterm (<37 weeks gestational age (GA)) comprise approximately 10% of all live births worldwide, with global estimates showing an increasing trend of preterm births over the past 20 years (Blencowe et al., 2012; Chawanpaiboon et al., 2019). Advancements in neonatal care have led to the increased survival of infants born preterm and very low birth weight (VLBW; <1500 g), as well as reductions in serious medical morbidities and brain injury (Ancel et al., 2015; Costeloe et al., 2012; Hart et al., 2008). The risk of long-term cognitive impairments, however, remains high in this population (Burnett et al., 2018; Pierrat et al., 2017). These difficulties have been reported as early

* Corresponding author at: Diagnostic Imaging, Hospital for Sick Children, 555 University Ave., Toronto, ON M5G 1X8, Canada.
E-mail address: julie.sato@sickkids.ca (J. Sato).

https://doi.org/10.1016/j.nicl.2021.102843
Received 29 March 2021; Received in revised form 23 September 2021; Accepted 24 September 2021
Available online 28 September 2021
2213-1582/© 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

as two years of age (Pierrat et al., 2017; Adams-Chapman et al., 2018) and remain stable through early childhood and adolescence (Mangin et al., 2017). A recent *meta*-analysis, including children born very preterm (VPT; <32 weeks GA) or VLBW, found that intelligence scores were 0.86 standard deviations (12.9 IQ points) lower in VPT compared to full-term (FT) children (Twilhaar et al., 2018). While considerable heterogeneity exists across and within studies, convergent findings support overall lower IQ scores in preterm compared to full-term children (Bhutta et al., 2002; Kerr-Wilson et al., 2012). Further, deficits are evident in multiple cognitive domains including language, attention, memory, and perceptual-motor function (Foster-Cohen et al., 2007; Woodward et al., 2009). While these difficulties range in severity, they can have long-term implications for academic achievement and behavioural development. However, despite evidence of these wide-ranging cognitive impairments, the underlying contributions from possible atypical brain structural development are not well understood.

Previous studies suggested that white matter is particularly vulnerable due to the disrupted maturation of oligodendroctyes and myelination processes during the preterm period (Dubois et al., 2014; Ferriero and Miller, 2010). Even in the absence of neonatal white matter injury, infants born preterm are still vulnerable to white matter alterations, with one study reporting lower white but not grey matter volumes in preterm compared to full-term infants (Pavaine et al., 2016). These alterations are present at the microstructural level, with studies showing lower fractional anisotropy (FA) in preterm populations from infancy to early adulthood (Allin et al., 2011; Anjari et al., 2007; Constable et al., 2008; Duerden et al., 2013), reflecting sustained changes in white matter microstructure. Although some studies have reported atypical white matter metrics in young children born VPT that were associated with cognitive outcomes (Barnes-Davis et al., 2020; Dodson et al., 2017), few studies have investigated white matter microstructure using multi-shell diffusion imaging at preschool-age, which is typically when cognitive difficulties become more apparent (Neubauer et al., 2008). Thus, there is a critical gap in the literature regarding if and what type of white matter alterations may be present in preschool-age children born preterm and especially those born VLBW.

Diffusion tensor imaging (DTI) is invaluable to study white matter microstructure, by measuring the diffusion properties of water within brain tissues to estimate fibre structures (Jones et al., 2013). DTI metrics including FA and radial diffusivity (RD), reflect the degree to which diffusion is directionally restricted and the diffusion of water perpendicular to fibre bundles, respectively (Jones et al., 2013). These measures show distinct and marked maturational trends in white matter, with increases in FA and decreases in RD with age in both typical and preterm brain development (Dubois et al., 2014; Pecheva et al., 2018). At term-equivalent age, infants born preterm show lower FA and increased RD within various white matter tracts compared to FT controls (Anjari et al., 2007), which are associated with later cognitive outcomes (Counsell et al., 2008). However, despite the sensitivity of diffusion metrics to detect group and age-related differences, they lack the specificity as to which structural factors are contributing to these changes. The more recent neurite orientation dispersion and density imaging (NODDI; Zhang et al., 2012) model quantifies two key factors that contribute to changes in FA, including the orientation dispersion and the density of neurites (axons or dendrites). The orientation dispersion index (ODI) reflects the organization of neurite orientations and the neurite density index (NDI) reflects the density of axons within a voxel and is thought to be a useful marker for myelination (Jespersen et al., 2010; Zhang et al., 2012).

A recent review (Lebel and Deoni, 2018) found that NDI is more strongly correlated with age than ODI or FA across childhood and adolescence, suggesting that axon density may be a more sensitive marker of white matter development and underlie the associated maturation of cognitive functions. In line with this, two previous studies reported significant associations between FA and NDI with IQ scores in school-age children born VPT (Kelly et al., 2016; Young et al., 2019). The authors also found lower FA and higher ODI within widespread white matter tracts compared to FT controls, suggesting that lower FA found in preterm children could be partially explained by increases in axon dispersion (Kelly et al., 2016; Young et al., 2019). Although these group differences in ODI were not found to be associated with cognitive outcome in children born preterm, they provide contributing explanatory factors of the impacts of preterm birth on white matter maturation. Thus, the aim of our study is to extend these findings to a younger sample of preterm children born VLBW, using both DTI and NODDI metrics, to evaluate white matter microstructure before school-age.

Using multi-shell diffusion imaging, we assessed differences in white matter microstructure between VLBW and FT children at five years of age. We also tested associations between DTI and NODDI metrics with neonatal predictors and cognitive outcomes. Consistent with reports in older preterm children, we hypothesized that VLBW children would show reductions in FA and NDI and increases in RD and ODI in widespread white matter regions. We also hypothesized higher FA and NDI would be positively associated with cognitive scores. Lastly, we expected improved measures of white matter microstructure (i.e., higher FA and NDI and lower RD and ODI) to be associated with higher birth weight status.

2. Materials and methods

2.1. Participants

At five years of age, a cohort of 56 VLBW and 28 FT children were recruited for this study between August 2016 and July 2018 at the Hospital for Sick Children (SickKids), Toronto, Canada. VLBW participants were recruited as part of a five-year follow-up (NCT02759809) to the randomised clinical trial, Donor Milk for Improved Neurodevelopmental Outcomes (ISRCTN35317141) that enrolled infants between October 2010 and December 2012. Details of the feeding protocol of the trial (Unger et al., 2014) and this VLBW sample have been previously published (Sato et al., 2021). FT controls were recruited via in-hospital advertisements and word-of-mouth. Exclusion criteria for both groups included any known chromosomal or major congenital abnormalities. For the FT group, exclusion criteria also included a history of preterm birth (<37 weeks GA), as well as any learning, language or developmental disabilities. Participants were screened and approved for MRI compatibility. All children provided verbal assent and parents gave written informed consent in accordance with the Declaration of Helsinki. The SickKids Research Ethics board approved the study protocol.

2.2. Clinical and demographic information

Perinatal clinical data, including demographics and presence of neonatal morbidities, were collected during primary hospitalization in the neonatal intensive care unit. Neonatal morbidities included the presence of patent ductus arteriosus (diagnosis confirmed by echocardiography or indomethacin treatment), chronic lung disease (oxygen support at 36 weeks gestational age), late-onset sepsis (positive blood or cerebrospinal fluid culture at $\geq$ 5 postnatal days), and necrotizing enterocolitis (Modified Bell Staging Criteria $\geq$ II). Two neonatologist and one radiologist assessed each child's cranial ultrasound scans for the presence of brain injury (defined as the presence of at least one of the following findings: echodense intraparenchymal lesions, white matter lesions, periventricular leukomalacia, porencephalic cysts and ventriculomegaly with or without intraventricular hemorrhage).

2.3. Cognitive assessment

Cognitive assessments were completed for all participants using the Wechsler Preschool and Primary Scale of Intelligence-IV (WPPSI-IV), using Canadian norms (Wechsler, 2012). Full scale IQ (FSIQ) was obtained, as well as six other cognitive measures: Verbal Comprehension,

Vocabulary Acquisition, Visual Spatial, Fluid Reasoning, Processing Speed and Working Memory Indexes. Composite scores were converted into standardized scores with a population mean of 100 and a standard deviation of 15, with 'low average' scores defined as those < 90 (Wechsler, 2012).

2.4. MRI data acquisition

Multi-shell diffusion and T1-weighted anatomical images were acquired for each participant while awake on a 3T MAGNETOM Siemens PrismaFIT with a 20-channel head and neck coil. The multi-shell diffusion protocol was acquired based on the echo planar imaging diffusion pulse sequence (TR/TE = 3800/73 ms, FA = 90°, FOV = 244x244, # slices = 70, resolution = 2.0 mm isotropic, b = 1000/1600/2600 s/mm^2 (30/40/60 directions); 15 interleaved b = 0 s/mm^2 volumes). Distortions in the diffusion data were corrected by estimating a B0 map of the main magnetic field using a double-echo gradient-recalled echo sequence (TR/TE1/TE2 = 600/7.65/5.19 ms, FA = 60°, FOV = 252x252mm, # slices = 50, resolution = 3.0 mm isotropic). Anatomical T1-weighted images were acquired with 3D magnetization prepared rapid acquisition gradient echo sequence (TR/TE = 1870/3.14 ms, FA = 9°, FOV = 240x256mm, # slices = 192, resolution = 0.8 mm isotropic).

2.5. Diffusion processing

Multi-shell diffusion data were denoised (Veraart et al., 2016) and corrected for Gibbs ringing (Kellner et al., 2016) using MRtrix3. The FMRIB Software Library (FSL) was used to correct for motion-induced distortion and eddy currents using estimated fieldmaps prepared by FSL's FUGUE (Andersson and Sotiropoulos, 2016). The eddy toolbox was also used to identify slices with motion-induced signal dropout via an outlier replacement procedure, which were then replaced with Gaussian Process predictions (Andersson and Sotiropoulos, 2016). Multi-shell diffusion data were also corrected for bias field inhomogeneities using the N4 algorithm (Tustison et al., 2010). Both the DTI and NODDI models were used to obtain maps of FA, RD, ODI and NDI using all three b-values. The NODDI measures were estimated using the NODDI MATLAB toolbox version 1.0.1 (Zhang et al., 2012).

2.6. Tract-based spatial statistics

We employed a whole-brain approach using FSL's tract-based spatial statistics (TBSS) to analyse group differences in white matter microstructure (Smith et al., 2006). Non-linear co-registration was performed between each child's FA image and every other child's FA image to identify the most representative image as the cohort-specific target FA image. This target image was then registered to MNI152 standard space. Then each child's FA image underwent linear registration to standard space via the target image. A mean FA skeleton, representing the centre of major white matter tracts, was generated and thresholded at the recommended 0.2 FA threshold. The same registration was applied to each child's FA, RD, NDI and ODI data, and these images were then projected onto the skeleton.

2.7. Statistical analyses

2.7.1. Participant characteristics

To determine whether VLBW and FT groups were matched on age and sex ratio, a *t*-test and Chi-square test were used, respectively. A nonparametric Mann-Whitney *U* Test was used to assess differences in maternal education levels between groups. Differences in cognitive scores between VLBW and FT children were assessed using an independent *t*-test. Statistical analyses were performed using Statistica (version 7.0; Statsoft Inc., Tulsa, OK, USA). Hypothesis tests were two-sided with a significance level of $p < 0.05$.

2.7.2. TBSS analyses

Using FSL's randomise (Anderson and Robinson, 2001), between- and within-group voxel-wise analyses were performed using 5000 permutations and threshold-free cluster enhancement (Smith and Nichols, 2009), holding significance at $p_{corr} < 0.05$, family-wise error corrected. Between-group analyses were conducted using a general linear model (GLM) with group and sex as explanatory variables. Then group-by-sex interactions were tested. GA was not included as a covariate in the between-group analyses as one of the exclusion criteria for the FT group was a history of preterm birth and all FT children were within normal limits for GA and birth weight. Using GA as a covariate would remove the shared variance with group status since all VLBW children were born preterm; thus, GA and the effect of group were not independent, and the group effect would be obscured if GA was included as a covariate. Within each group, regression analyses were performed between DTI and NODDI metrics with cognitive outcomes, adjusting for sex and birth weight. Finally, within each group, we also investigated associations between DTI and NODDI metrics with birth weight, adjusting for sex.

Additionally, three sensitivity analyses were also performed to examine whether history of neonatal brain injury, FSIQ or maternal education influenced our between-group findings: 1) excluding five VLBW children with a history of neonatal brain injury, resulting in a sub-sample of 36 VLBW and 26 FT children, 2) matching a sub-sample of 34 VLBW children and 26 FT children on FSIQ, 3) matching a sub-sample of 28 VLBW and 24 FT children on maternal education level. Significant regions along the white matter skeleton were identified using the John Hopkins University (JHU) white matter tractography atlas (Mori et al., 2005) and thickened to help visualize results.

3. Results

3.1. Participant characteristics

Of the 56 VLBW children, 41 participants (mean birth GA: 28.1 ± 2.4 weeks; mean birth weight: 1028.6 ± 256.8 g) had MRIs that passed quality control and were included in the final analyses. In the FT group, 26 out of 28 participants (mean birth GA: 39.1 ± 1.7 weeks; mean birth weight: 3295.4 ± 493.9) were included in the final analyses. Demographic and clinical characteristics for the final sample of VLBW and FT children are summarized in Table 1. The VLBW and FT groups had a similar proportion of males and did not differ by age at scan. Maternal education level was significantly lower in the VLBW group. Five VLBW children (12.2%) had incidences of brain injury during initial hospitalization, 13 (31.7%) had patent ductus arteriosus, six (14.6%) had

Table 1
Demographic and clinical characteristics in VLBW and FT children.

	VLBW group (n = 41)	FT group (n = 26)	*p*-value [1]
Scan age (years)	5.8 (0.2)	5.8 (0.5)	0.40
Sex (Males)	21 (50%)	13 (50%)	0.92
Birth GA (weeks)	28.1 (2.4)	39.1 (1.7)	7x10^-29
Birth weight (grams)	1028.6 (256.8)	3295.4 (493.9)	2x10^-16
Maternal education level			
High School	12/41 (29.3%)	0/26 (0%)	0.01
University or College	23/41 (56.1%)	12/26 (46.2%)	
Post-graduate training	6/41 (14.6%)	14/26 (53.8%)	
Clinical characteristics for children born VLBW			
Brain injury	5/41 (12.2%)	–	–
Patent ductus arteriosus	13/41 (31.7%)	–	–
Chronic Lung Disease	6/41 (14.6%)	–	–
Late-onset sepsis	11/41 (26.8%)	–	–
Necrotizing enterocolitis (>=2)	0/41 (0%)	–	–

Categorical variables are presented as frequency (percentage) and continuous variables as mean (standard deviation).
[1] Comparisons by two-sample *t*-test.

chronic lung disease, and 11 (26.8%) had late-onset sepsis. No children born VLBW had any incidence of NEC stage II or greater. Mean cognitive scores for each group indicated average levels of ability on most measures, except for working memory and verbal comprehension indices that were in the above average range for the FT group (Table 2). VLBW children performed comparably to FT children on visual spatial and fluid reasoning ability but had significantly lower scores of FSIQ, verbal comprehension, working memory, processing speed and vocabulary acquisition. Low average scores were not statistically different between groups.

3.2. Between-group DTI and NODDI results

Group differences were present between VLBW and FT children in FA, NDI and ODI metrics. VLBW children exhibited lower FA and NDI than FT children within the white matter regions, including the corpus callosum (body) and posterior limb of the internal capsule (Fig. 1A) (see Supplemental Table S1 for the number of significant voxels per subregion). VLBW children also displayed lower NDI within widespread fibre tracts, including the corpus callosum, retrolenticular part of the internal capsule, corona radiata, posterior thalamic radiation and superior longitudinal fasciculus (Fig. 1B). In addition, VLBW children showed reductions in ODI within many of the same regions that had lower FA, as well as regions where ODI was higher compared to controls (Fig. 1C; Supplemental Table S2). For instance, we found higher ODI in VLBW children in regions including the retrolenticular part of the internal capsule, superior and posterior corona radiata and superior longitudinal fasciculus while there was a cluster of voxels in the anterior and posterior limbs of the internal capsule where ODI values were lower in VLBW children than controls. There were no areas where RD differed between VLBW and FT children.

To investigate the effect of VLBW independent of children with a history of brain injury, we excluded five VLBW children with brain injuries and repeated the between-group contrast. The results were similar, albeit less widespread for decreases in FA and NDI in VLBW compared to FT children (Fig. 2). Secondly, to ensure that FSIQ differences were not driving between-group effects, seven VLBW children who were not FSIQ-matched with FT controls were excluded and the analyses re-run. The results again were similar to the original between-group analyses, with slightly less widespread FA and ODI (FT > VLBW) differences and more widespread ODI (VLBW > FT) differences between groups (Fig. 3). Finally, in a separate sensitivity analysis, VLBW and FT groups were also matched on maternal education levels. Similar to the aforementioned results, the between-group contrast yielded similar results to the original analyses, with the exception of increased RD in VLBW compared to FT children (Fig. 4).

Table 2
Cognitive performance in VLBW and FT children.

WPPSI-IV indices	VLBW group (n = 41)	FT group (n = 26)	*p*-value [1]
Full-Scale IQ	102.56 (12.97)	109.8 (9.8)	0.02
Verbal Compre hension Index	101.78 (16.31)	110.7 (7.7)	0.03
Visual Spatial Index	101.80 (12.64)	107.3 (9.6)	0.10
Fluid Reasoning Index	101.24 (13.80)	101.8 (17.8)	0.89
Working Memory Index	103.0 (15.26)	117.3 (12.3)	$9.13x10^{-4}$
Processing Speed Index	102.34 (11.18)	108.3 (8.4)	0.05
Vocabulary Acquisition Index	99.33 (15.80)	108.3 (10.9)	0.03
FSIQ scores < 90, no./total (%)			
Full-Scale IQ	7/41 (17.1%)	1/26 (3.8%)	0.14 [2]

Means and standard deviations are reported.
[1] Comparisons by two-sample *t*-test.
[2] Comparisons by Fisher's exact test.

3.3. Associations between DTI and NODDI metrics with cognitive outcomes

Within the FT group, associations were found between lower RD and higher NDI (Fig. 5A) with improved vocabulary acquisition scores (Supplemental Table S2). Additionally, lower RD was associated with higher working memory scores (Fig. 5B). No other significant associations were found between DTI and NODDI metrics with cognitive measures in FT controls. Within the VLBW group, associations were found between higher FA and NDI (Fig. 5C), but lower RD (Fig. 5D), with higher processing speed scores. Importantly, there were many overlapping areas of white matter with significant associations between higher FA and NDI and lower RD with processing speed, including the corpus callosum, superior and posterior corona radiata, cerebral peduncle and posterior thalamic radiation. Lower ODI was also associated with higher processing speed scores in a cluster in the corpus callosum (body, splenium). No significant associations were found between DTI and NODDI metrics with other cognitive measures in children born VLBW.

3.4. Associations between DTI and NODDI metrics with birth weight

There were positive associations between FA and NDI with birth weight in VLBW children (Fig. 6A; Supplemental Table S3), seen within central and posterior white matter tracts including splenium of corpus callosum, posterior corona radiata, posterior thalamic radiation and external capsule. RD values were negatively associated with birth weight in many areas of the white matter skeleton. In the FT group, we also found areas of white matter where birth weight was positively associated with FA (Fig. 6B; Supplemental Table S3). In contrast to the VLBW group, these significant clusters of positive associations between FA and birth weight in the FT children were present within more central and anterior white matter tracts, including the corpus callosum (genu, body, and splenium), cerebral peduncles, anterior and posterior limbs of the internal capsule and corona radiata. RD was also negatively associated with birth weight in FT children. In neither group were significant associations found between ODI and birth weight.

4. Discussion

In our study, we found significant alterations in white matter microstructure in children born VLBW compared to age- and sex-matched FT controls. VLBW children had lower FA within major white matter regions including the corpus callosum compared to FT children, a consistent finding among very preterm children from infancy to adolescence (Anjari et al., 2007; Duerden et al., 2013; Mullen et al., 2011; Young et al., 2018). Importantly, our study extends previous DTI findings by applying NODDI to multi-shell diffusion images to assess the structural properties of axons and dendrites (Zhang et al., 2012). We found widespread reductions in NDI in our cohort of VLBW children, suggesting disrupted white matter maturation. NDI estimates the density of axons within a voxel, or degree of axonal packing, and is thought to be closely associated with the degree of myelinated axons in the cortex (Carper et al., 2017). Thus, lower NDI in the VLBW compared to the FT group may point to early disturbances of myelination processes during the preterm period in the VLBW infants. Given the extensive maturation and early stages of myelination that occur during the third trimester, infants born preterm are vulnerable to white matter injury and other neonatal disturbances that can disrupt the maturation of pre-oligodendrocyte glial cells occurring during this time, and in turn, the myelination of axons (Ferriero and Miller, 2010; Volpe, 2009). We also found less widespread differences in FA and NDI when removing VLBW children with a history of brain injury, consistent with neonatal brain injury interfering with the early myelination of axons and subsequent cortical maturation in VLBW children (Ferriero and Miller, 2010). This is supported by studies that have linked neonatal brain injury with DTI

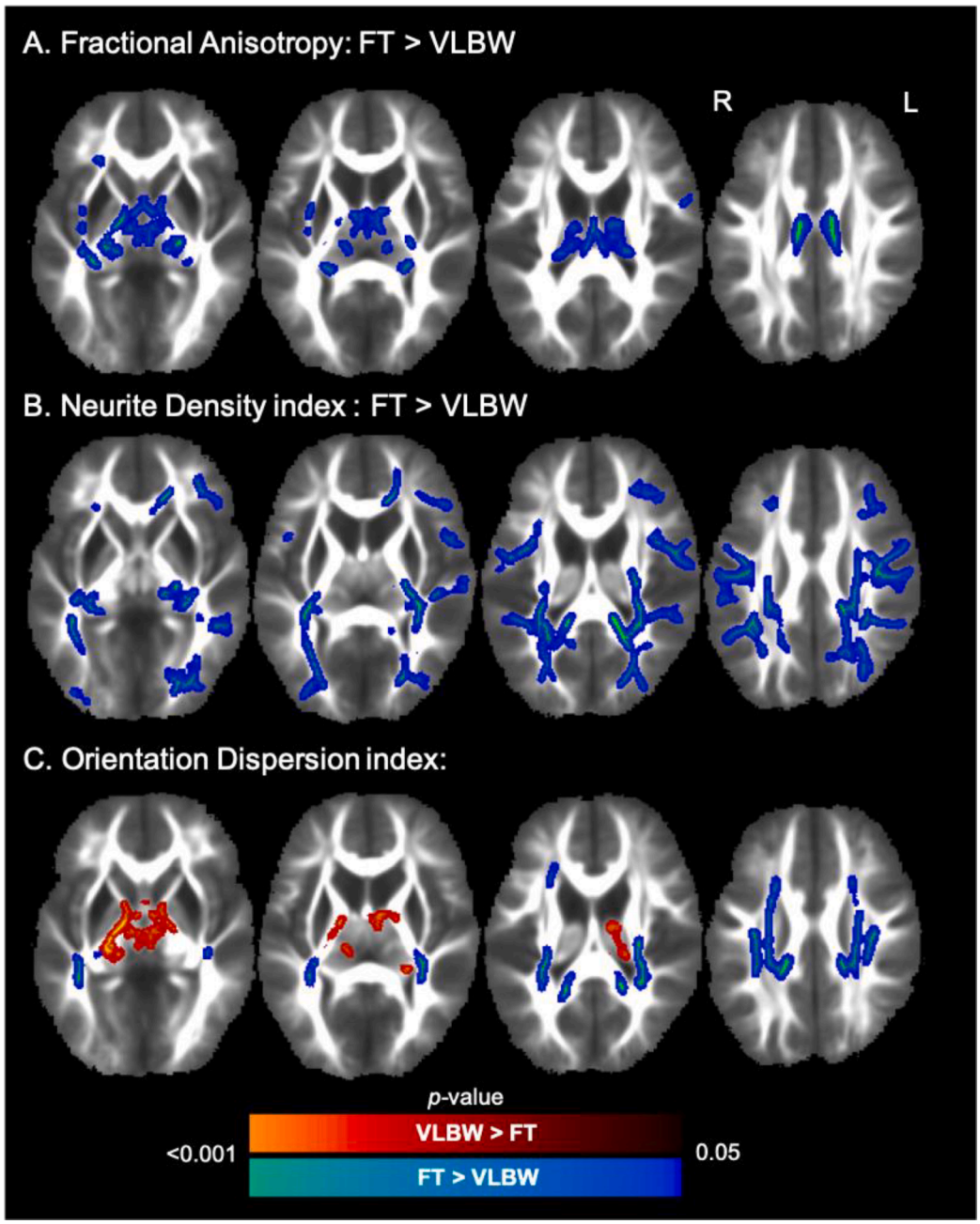

Fig. 1. FA and NODDI between-group results. A. Blue areas represent regions in which FA was significantly lower in VLBW compared to FT children. Significant regions included the body of the corpus callosum and posterior limb of the internal capsule. B. Voxels with significantly lower NDI in VLBW children are indicated in blue. Significant regions included the corpus callosum (genu, splenium), retrolenticular part of the internal capsule, corona radiata, posterior thalamic radiation and superior longitudinal fasciculus. C. Voxels in red depict regions with increased ODI in VLBW children including the corpus callosum and posterior limb of the internal capsule. Blue areas are regions with reduced ODI in VLBW children including the superior and posterior corona radiata and the superior longitudinal fasciculus. Significance was held at $p_{corr} < 0.05$. Colour bars indicate p-values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

measures in school-aged children and adolescents born preterm (Feldman et al., 2012; Kelly et al., 2016). However, as our study included only a small number with a history of brain injury (n = 5), direct associations with DTI and NODDI measures could not be performed.

Lower NDI in VLBW children was found notably in the corpus callosum (splenium), superior and posterior corona radiata and superior longitudinal fasciculus. The corona radiata is a projection fibre tract that contains ascending and descending axons to and from the cerebral cortex and is associated with cognitive functions such as processing speed (Bendlin et al., 2010). The superior longitudinal fasciculus is an association fibre tract connecting the frontal and parietal cortices and has been linked with verbal abilities (Tamnes et al., 2010). Thus, alterations in axon density in these fibre tracts may partially explain the lower scores in these cognitive domains in our VLBW cohort, as well as deficits in language skills commonly reported in preterm children (Foster-Cohen et al., 2007; Putnick et al., 2017). Only two other studies have used NODDI metrics to investigate white matter in very preterm children; however, both identified increases in ODI in very preterm children but no group effects in NDI (Kelly et al., 2016; Young et al., 2019). These differences in axon density are likely due to the younger preterm cohort in our study, scanned at five years of age. Developmental studies have reported rapid increases in NDI during early childhood (Chang et al., 2015; Genc et al., 2017), suggesting that alterations in axon density are more pronounced at preschool-age and may reflect sustained myelination disruptions in this cohort of VLBW children (Carper et al., 2017).

We also found smaller clusters of higher ODI in VLBW compared to FT children, notably in the corpus callosum and the posterior limb of the internal capsule. Higher ODI within white matter regions reflects greater bending and fanning of axons or areas of crossing fibres (Zhang et al., 2012), and thus suggests less coherently organized axons within fibre tracts in VLBW children. However, there were also clusters where higher ODI was found in FT compared to VLBW children, which may reflect areas of crossing fibres in FT children (Zhang et al., 2012). These

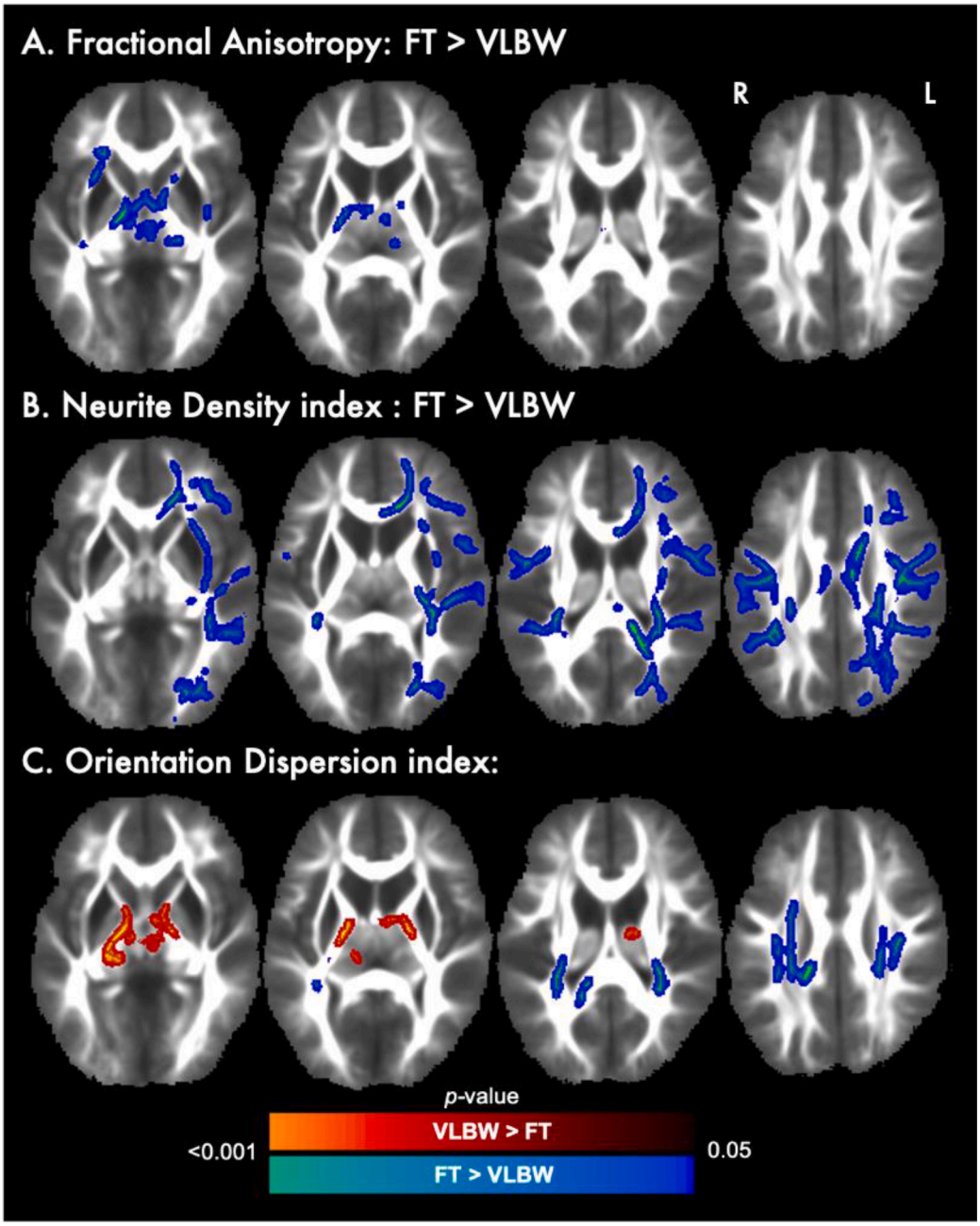

Fig. 2. Sensitivity analysis for between-group contrast: excluding VLBW children with a history of brain injury (n = 5). A. Blue areas represent regions along the white matter skeleton in which FA was reduced in VLBW compared to FT children B. Voxels with reduced NDI in VLBW children are indicated in blue. C. Voxels in red depict regions with increased ODI in VLBW children, whereas blue areas are regions with reduced ODI in VLBW compared to FT children. Significance was held at $p_{corr} < 0.05$. Colour bars indicate p-values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

findings need to be further investigated in longitudinal studies over a wider age range. Our results showed that group differences in FA and ODI were similar, such that VLBW children showed higher ODI within many of the same regions that had lower FA. This suggests that at preschool-age, lower FA in VLBW children may be partly due to increases in axon dispersion. Our results are concordant with previous studies showing a close association between FA and ODI, reinforcing that FA is more sensitive to changes in axon dispersion compared to axon density (Kelly et al., 2016; Zhang et al., 2012). In addition, we found our results remained similar when matching a sub-sample of VLBW and FT children on FSIQ, suggesting that IQ does not need to be analysed as a covariate in this population. For maternal education levels, the results were largely similar with and without matching, although there was the addition of a significant group difference in RD (higher in VLBW compared to FT) when groups were matched for maternal education. In contrast with IQ, this highlights the importance of controlling for socioeconomic confounders in analyses with these children.

Most importantly, within each group, associations between DTI and NODDI metrics with cognitive performance were investigated. In FT children, significant clusters of positive associations between NDI and working memory scores were present within areas of the corpus callosum, internal capsule and corona radiata. These results complement previous findings in both children and adults, which find associations between FA in several white matter regions including the corpus callosum and working memory performance (Olesen et al., 2003; Darki and Klingberg, 2015; Schulze et al., 2011). In addition, lower RD and higher NDI were associated with improved vocabulary acquisition scores. These associations are consistent with the maturational trends of these metrics, which show general increases in NDI and decreases in RD with development (Dubois et al., 2008; Jones et al., 2013), and this structural maturation influences cognitive development. Associations between NDI and vocabulary acquisition were found within regions such as the corpus callosum (body, splenium), left anterior limb of the internal capsule, left anterior corona radiata and right superior longitudinal

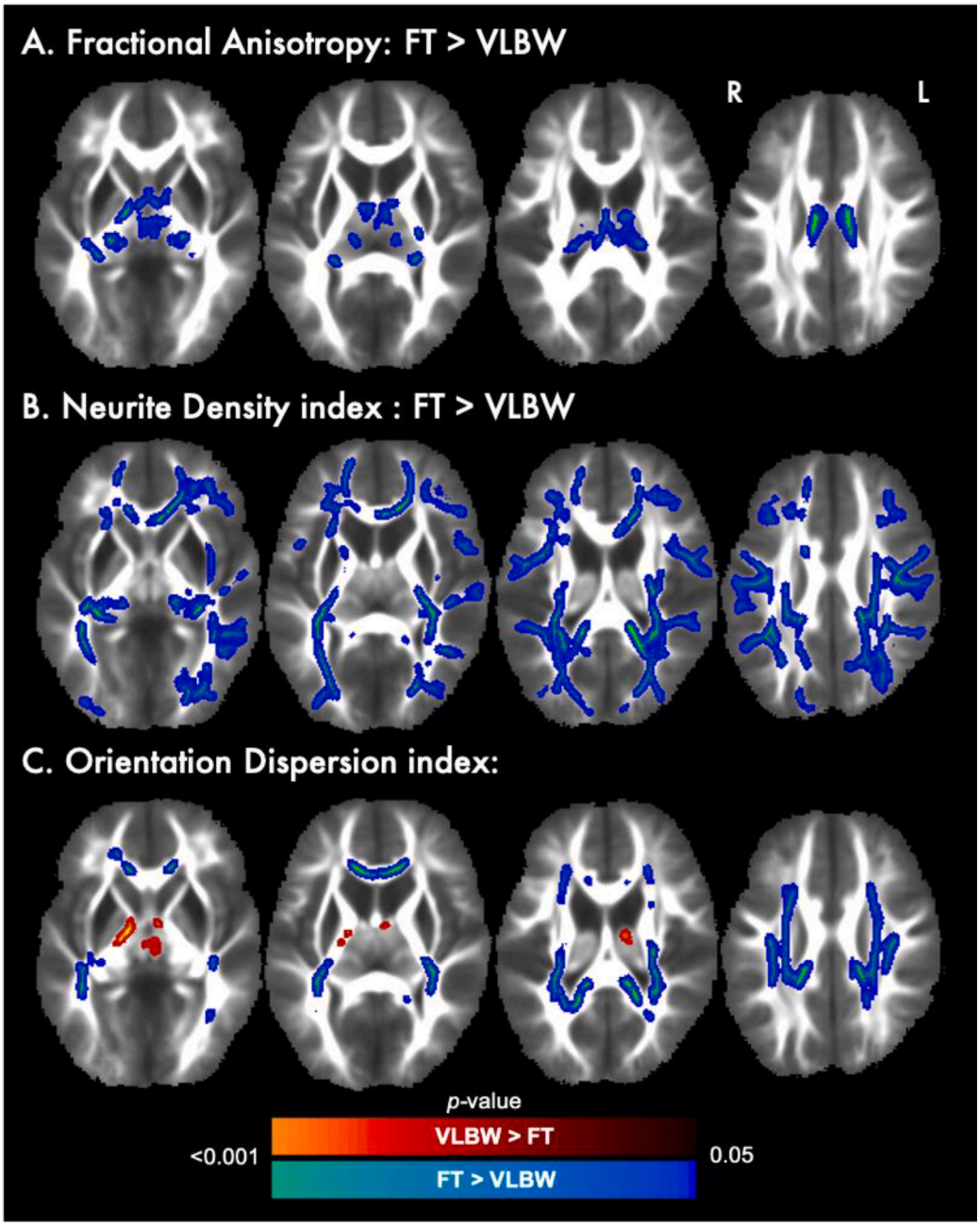

Fig. 3. Sensitivity analysis for between-group contrast: excluding VLBW children who were not IQ-matched to FT controls (n = 7). A. Blue areas represent regions along the white matter skeleton in which FA was reduced in VLBW compared to FT children B. Voxels with reduced neurite density in VLBW children are indicated in blue. C. Voxels in red depict regions with increased ODI in VLBW children, whereas blue areas are regions with reduced ODI in VLBW compared to FT children. Significance was held at $p_{corr} < 0.05$. Colour bars indicate p-values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

fasciculus. The corpus callosum is thought to play a crucial role in the development of language functions and the transfer of information across brain hemispheres (Bartha-Doering et al., 2021), while the superior longitudinal fasciculus has been previously associated with language abilities in normative samples and is thought to be part of core language pathways (Tamnes et al., 2010; Middlebrooks et al., 2017). Our findings extend these results to a young cohort of typically developing children and is consistent with the ongoing maturation of language abilities at preschool-age.

VLBW children showed associations between higher FA and NDI with processing speed scores, and consistent with their maturational pattern of decreasing with age, lower ODI and RD were also associated with improved processing speed. In particular, FA, NDI and RD showed widespread associations with processing speed in various white matter regions such as corpus callosum and posterior tracts including the corona radiata and thalamic radiation. These widespread associations are consistent with a previous study that found that global white matter volume was associated with processing speed performance in healthy adults (Magistro et al., 2015). Thus, our results suggest that slower processing speed in this relatively high-functioning cohort of VLBW children, may be partly due to alterations in white matter microstructure. Prior studies have linked white matter microstructure with processing speed, which in turn is related to fluid reasoning abilities (Ferrer et al., 2013; Kail, 2007). Early difficulties with processing speed may therefore be an important risk factor for broader cognitive deficits observed in very preterm and VLBW children. While we did not find a significant association with fluid reasoning in our study, it is possible that this association may emerge later, as these higher-order cognitive skills continue to mature throughout childhood. Our lack of significant findings may thus be related to maturational differences, as the study that previously reported this association had a much wider age range (6-18yrs) (Ferrer et al., 2013).

Finally, we also investigated the association between white matter microstructure and birth weight within each group. Not surprisingly, we

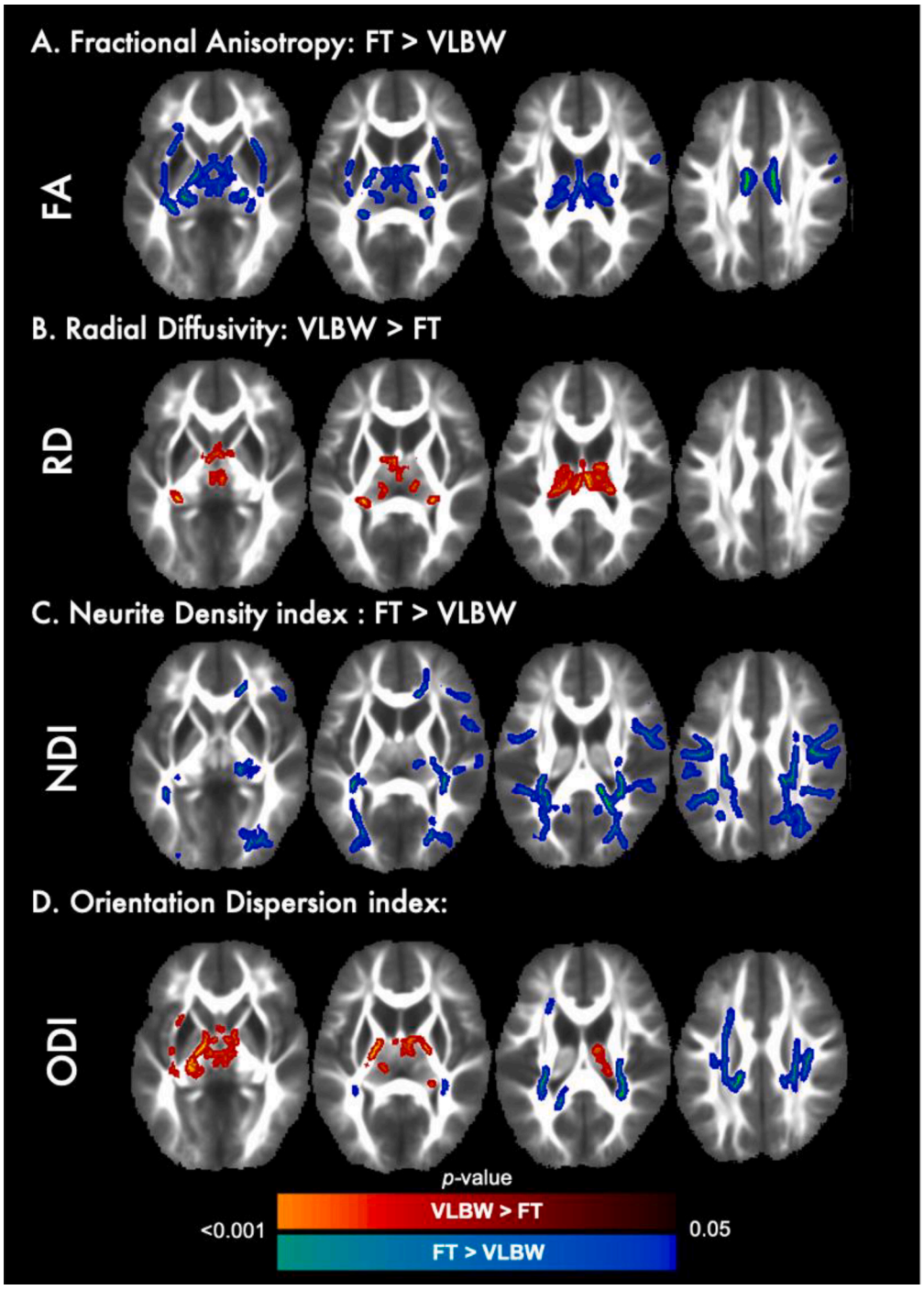

Fig. 4. Sensitivity analysis for between-group contrast: matching a sub-sample of VLBW (n = 28) and FT children (n = 24) on maternal education levels. A. Blue areas represent regions along the white matter skeleton in which FA was reduced in VLBW compared to FT children B. Red areas represent voxels with higher RD values in VLBW children. C. Voxels with reduced NDI in VLBW children are indicated in blue. D. Voxels in red depict regions with increased ODI in VLBW children, whereas blue areas are regions with reduced ODI in VLBW compared to FT children. Significance was held at $p_{corr} < 0.05$. Colour bars indicate p-values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

found that greater birth weight was positively associated with FA and negatively associated with RD in both VLBW and FT children. The distribution of the association, however, differed markedly between groups such that higher birth weight was associated with increases in FA within more anterior fibre tracts in the FT group, whereas this was found posteriorly in the VLBW group. These results support a posterior-to-anterior gradient of white matter maturation and expand upon previous findings showing that between preterm birth and term-equivalent age posterior tracts develop more quickly than anterior tracts (Young et al., 2017). This striking contrast seen here at five years of age is important evidence for a maturational delay in white matter development in the VLBW cohort.

While a significant strength of our study was the use of multi-shell diffusion imaging to assess the microstructural properties of white matter in this young cohort of VLBW children and the associations with cognitive outcomes, there are some limitations to consider. Firstly, unlike the VLBW children who were initially recruited through a randomised clinical trial, the FT children were recruited through in-hospital advertisements and word-of-mouth. This led to a selection bias whereby the FT group had higher levels of maternal education, which may not be representative of the larger community. Despite this being a common issue in developmental studies, especially in those that are more time-intensive and demanding on family's schedules, we acknowledge this as a potential limitation of our study. To address this, we performed a sensitivity analysis with matched groups, and found that group results were similar albeit more widespread differences in RD in the VLBW

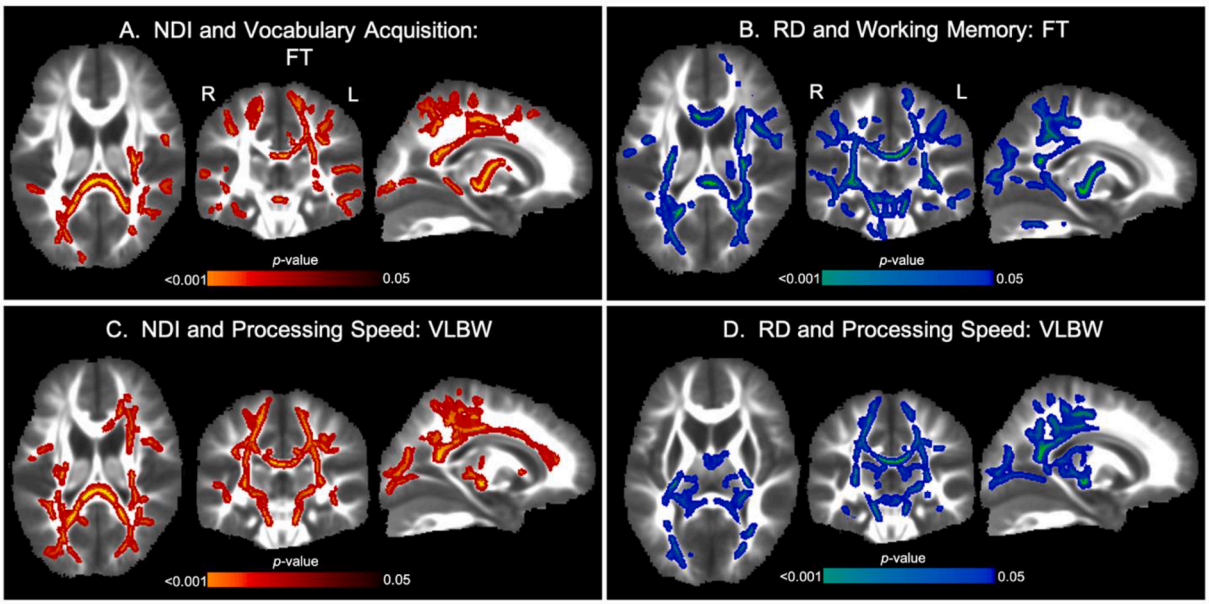

Fig. 5. Within-group associations between DTI and NODDI metrics with cognitive outcomes. A. The red areas represent regions in which a significant positive association between NDI and vocabulary acquisition scores was found in FT children. B. Blue areas represent regions with a negative association between RD and working memory in FT children. C. Significant positive associations between NDI and processing speed in VLBW children are represented by red areas. D. Significant negative associations between RD and processing speed in VLBW children are shown in blue. Significance was held at $p_{corr} < 0.05$. Colour bars indicate p-values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

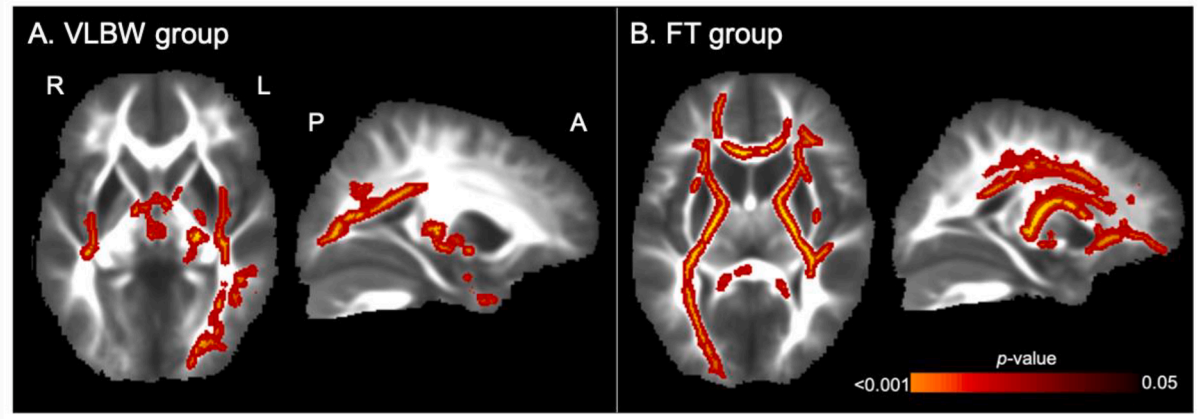

Fig. 6. Within-group associations between FA and birth weight. Significant positive association was found between birth weight and FA in VLBW (left side; 3A) and FT groups (right side; 3B). Significance was held at $p_{corr} < 0.05$ and significant voxels are displayed in red. Colour bars indicate p-values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

compared to FT children. Secondly, we also acknowledge that being small for gestational age (SGA) may affect developmental outcomes and white matter microstructure in VLBW infants. In our study, only 7 of the 41 (17%) VLBW children were SGA, while none of the FT children were SGA. While a small portion of our VLBW cohort were SGA, future studies with larger samples should investigate the effect of SGA as an independent risk factor of outcomes. Thirdly, we also acknowledge that TBSS is not the most sensitive technique to investigate white matter differences as it confines the analyses to the FA skeleton and is thus not representative of the entire white matter tract. Despite these limitations, however, TBSS is a robust and widely implemented approach, allowing for more direct comparisons with the extensive literature that also used TBSS. Future studies, however, could extend these results comparing TBSS with other techniques to confirm these findings.

5. Conclusions

In conclusion, we demonstrate widespread alterations in white matter microstructure in VLBW compared to FT children at five years of age. Compared with matched FT controls, VLBW children show reductions in FA and NDI, indicative of disrupted white matter maturation. Group differences were also found in ODI, reflecting less coherently organized fibre tracts in regions such as the corona radiata. Our study is significant in extending DTI findings to a young preschool cohort of VLBW children and in applying NODDI measures to multi-shell diffusion images. Our results of lower FA in VLBW compared to FT children confirm earlier studies, however, we also found group differences in NDI that have not previously been reported. These novel findings reflect the ongoing microstructural changes occurring at preschool-age in VLBW children, which NODDI measures may be more sensitive to detect. Further, we found significant associations between white matter

microstructure with cognitive outcomes and birth weight within VLBW and FT groups. Together, these results improve our understanding of the factors contributing to white matter alterations and developmental outcomes in VLBW and preterm children. Importantly, our findings demonstrate that these microstructural differences are present as early as preschool age and emphasize the need to follow these children to understand the maturational trajectory of white matter and its role in cognitive development. Future studies with larger numbers of participants in both VLBW and FT groups, ideally in a longitudinal design, would provide more power and allow a fuller determination of the relations between white matter metrics and cognitive outcomes with age.

6. Data availability statement

The clinical and demographic data of this study cannot be made available in order to protect the privacy and confidentiality of our participants. However, the neuroimaging data are available upon reasonable request to the senior author (margot.taylor@sickkids.ca).

Funding

This study was supported by the Canadian Institutes of Health Research (grant numbers: FHG 129919, FDN 143233). JS is partially funded by a Restracomp award from the SickKids Research Institute.

CRediT authorship contribution statement

Julie Sato: Conceptualization, Writing – original draft, Investigation, Methodology, Formal analysis, Visualization. **Marlee M. Vandewouw:** Methodology, Software, Data curation, Formal analysis, Writing – review & editing. **Nicole Bando:** Project administration, Investigation, Writing – review & editing. **Helen M. Branson:** Investigation, Writing – review & editing. **Deborah L. O'Connor:** Conceptualization, Supervision, Funding acquisition, Writing – review & editing. **Sharon L. Unger:** Conceptualization, Supervision, Funding acquisition, Writing – review & editing. **Margot J. Taylor:** Conceptualization, Supervision, Funding acquisition, Resources, Data curation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank the GTA-DoMINO families for their participation and ongoing support of this work. We would also like to thank Michael Jory for setting up our database (The Hospital for Sick Children). The authors also thank Meghan McGee and Aisling Conway for assisting with study visits, and Tammy Rayner and Ruth Weiss for all their support in MRI data acquisition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102843.

References

Adams-Chapman, I., Heyne, R.J., DeMauro, S.B., Duncan, A.F., Hintz, S.R., Pappas, A., Vohr, B.R., McDonald, S.A., Das, A., Newman, J.E., Higgins, R.D., 2018. Neurodevelopmental impairment among extremely preterm infants in the neonatal research network. Pediatrics 141 (5), e20173091. https://doi.org/10.1542/peds.2017-3091.

Allin, M.P., Kontis, D., Walshe, M., Wyatt, J., Barker, G.J., Kanaan, R.A., McGuire, P., Rifkin, L., Murray, R.M., Nosarti, C., 2011. White matter and cognition in adults who were born preterm. PloS One 6 (10). https://doi.org/10.1371/journal.pone.0024525.

Ancel, P.Y., Goffinet, F., Kuhn, P., Langer, B., Matis, J., Hernandorena, X., Kaminski, M., 2015. Survival and morbidity of preterm children born at 22 through 34weeks' gestation in france in 2011 results of the EPIPAGE-2 cohort study. JAMA Pediatrics.

Anderson, M.J., Robinson, J., 2001. Permutation tests for linear models. Aust. N. Z. J. Stat. 43 (1), 75–88. https://doi.org/10.1111/anzs.2001.43.issue-110.1111/1467-842X.00156.

Andersson, J., Sotiropoulos, S.N., 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.

Anjari, M., Srinivasan, L., Allsop, J.M., Hajnal, J.V., Rutherford, M.A., Edwards, A.D., Counsell, S.J., 2007. Diffusion tensor imaging with tract-based spatial statistics reveals local white matter abnormalities in preterm infants. NeuroImage 35 (3), 1021–1027. https://doi.org/10.1016/j.neuroimage.2007.01.035.

Barnes-Davis, M.E., Williamson, B.J., Merhar, S.L., Holland, S.K., Kadis, D.S., 2020. Rewiring the extremely preterm brain: Altered structural connectivity relates to language function. NeuroImage. Clinical 25, 102194. https://doi.org/10.1016/j.nicl.2020.102194.

Bartha-Doering, L., Schwartz, E., Kollndorfer, K., Fischmeister, F., Novak, A., Langs, G., Werneck, H., Prayer, D., Seidl, R., Kasprian, G., 2021. Effect of corpus callosum agenesis on the language network in children and adolescents. Brain Struct. Funct. 226 (3), 701–713. https://doi.org/10.1007/s00429-020-02203-6.

Bendlin, B.B., Fitzgerald, M.E., Ries, M.L., Xu, G., Kastman, E.K., Thiel, B.W., Rowley, H. A., Lazar, M., Alexander, A.L., Johnson, S.C., 2010. White matter in aging and cognition: a cross-sectional study of microstructure in adults aged eighteen to eighty-three. Dev. Neuropsychol. 35 (3), 257–277. https://doi.org/10.1080/87565641003696775.

Bhutta, A.T., Cleves, M.A., Casey, P.H., Cradock, M.M., Anand, K.J., 2002. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA 288 (6), 728–737. https://doi.org/10.1001/jama.288.6.728.

Blencowe, H., Cousens, S., Oestergaard, M.Z., Chou, D., Moller, A.B., Narwal, R., Adler, A., Vera Garcia, C., Rohde, S., Say, L., Lawn, J.E., 2012. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet (London, England) 379 (9832), 2162–2172. https://doi.org/10.1016/S0140-6736(12)60820-4.

Burnett, A.C., Anderson, P.J., Lee, K.J., Roberts, G., Doyle, L.W., Cheong, J.L.Y., 2018. Trends in Executive Functioning in Extremely Preterm Children Across 3 Birth Eras. Pediatrics 141 (1), e20171958. https://doi.org/10.1542/peds.2017-1958.

Carper, R.A., Treiber, J.M., White, N.S., Kohli, J.S., Müller, R.A., 2017. Restriction spectrum imaging as a potential measure of cortical neurite density in autism. Front. Neurosci. 10, 610. https://doi.org/10.3389/fnins.2016.00610.

Chang, Y.S., Owen, J.P., Pojman, N.J., Thieu, T., Bukshpun, P., Wakahiro, M.L.J., Berman, J.I., Roberts, T.P.L., Nagarajan, S.S., Sherr, E.H., Mukherjee, P., Gong, G., 2015. White Matter Changes of Neurite Density and Fiber Orientation Dispersion during Human Brain Maturation. PLoS ONE 10 (6), e0123656. https://doi.org/10.1371/journal.pone.0123656.

Chawanpaiboon, S., Vogel, J.P., Moller, A.B., Lumbiganon, P., Petzold, M., et al., 2019. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. The Lancet 7 (1), e37–e46. https://doi.org/10.1016/S2214-109X(18)30451-0.

Constable, R.T., Ment, L.R., Vohr, B.R., Kesler, S.R., Fulbright, R.K., Lacadie, C., Delancy, S., Katz, K.H., Schneider, K.C., Schafer, R.J., Makuch, R.W., Reiss, A.R., 2008. Prematurely born children demonstrate white matter microstructural differences at 12 years of age, relative to term control subjects: an investigation of group and gender effects. Pediatrics 121 (2), 306–316. https://doi.org/10.1542/peds.2007-0414.

Costeloe, K.L., Hennessy, E.M., Haider, S., Stacey, F., Marlow, N., Draper, E.S., 2012. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ (Clinical research ed.) 345 (dec04 3), e7976. https://doi.org/10.1136/bmj.e7976.

Counsell, S.J., Edwards, A.D., Chew, A.T., Anjari, M., Dyet, L.E., Srinivasan, L., Boardman, J.P., Allsop, J.M., Hajnal, J.V., Rutherford, M.A., Cowan, F.M., 2008. Specific relations between neurodevelopmental abilities and white matter microstructure in children born preterm. Brain : A J. Neurol. 131 (Pt 12), 3201–3208. https://doi.org/10.1093/brain/awn268.

Darki, F., & Klingberg, T. (2015). The role of fronto-parietal and fronto-striatal networks in the development of working memory: a longitudinal study. Cerebral cortex (New York, N.Y. : 1991), 25(6), 1587–1595. https://doi.org/10.1093/cercor/bht352.

Dodson, C.K., Travis, K.E., Ben-Shachar, M., Feldman, H.M., 2017. White matter microstructure of 6-year old children born preterm and full term. NeuroImage. Clinical 16, 268–275. https://doi.org/10.1016/j.nicl.2017.08.005.

Dubois, J., Dehaene-Lambertz, G., Kulikova, S., Poupon, C., Hüppi, P.S., 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., Dehaene-Lambertz, G., Perrin, M., Mangin, J.-F., 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/(ISSN)1097-019310.1002/hbm.v29:110.1002/hbm.20363.

Duerden, E.G., Card, D., Lax, I.D., Donner, E.J., Taylor, M.J., 2013. Alterations in frontostriatal pathways in children born very preterm. Dev. Med. Child Neurol. 55 (10), 952–958. https://doi.org/10.1111/dmcn.12198.

Feldman, H.M., Lee, E.S., Loe, I.M., Yeom, K.W., Grill-Spector, K., Luna, B., 2012. White matter microstructure on diffusion tensor imaging is associated with conventional magnetic resonance imaging findings and cognitive function in adolescents born preterm. Dev. Med. Child Neurol. 54 (9), 809–814. https://doi.org/10.1111/j.1469-8749.2012.04378.x.

Ferrer, E., Whitaker, K.J., Steele, J.S., Green, C.T., Wendelken, C., Bunge, S.A., 2013. White matter maturation supports the development of reasoning ability through its influence on processing speed. Dev. Sci. 16 (6), 941–951. https://doi.org/10.1111/desc.12088.

Ferriero, D.M., Miller, S.P., 2010. Imaging selective vulnerability in the developing nervous system. J. Anat. 217 (4), 429–435. https://doi.org/10.1111/j.1469-7580.2010.01226.x.

Foster-Cohen, S., Edgin, J.O., Champion, P.R., Woodward, L.J., 2007. Early delayed language development in very preterm infants: evidence from the MacArthur-Bates CDI. J. Child Lang. 34 (3), 655–675. https://doi.org/10.1017/s0305000907008070.

Genc, S., Malpas, C.B., Holland, S.K., Beare, R., Silk, T.J., 2017. Neurite density index is sensitive to age related differences in the developing brain. NeuroImage 148, 373–380. https://doi.org/10.1016/j.neuroimage.2017.01.023.

Hart, A.R., Whitby, E.W., Griffiths, P.D., Smith, M.F., 2008. Magnetic resonance imaging and developmental outcome following preterm birth: review of current evidence. Dev. Med. Child Neurol. 50 (9), 655–663. https://doi.org/10.1111/j.1469-8749.2008.03050.x.

Jespersen, S.N., Bjarkam, C.R., Nyengaard, J.R., Chakravarty, M.M., Hansen, B., Vosegaard, T., Østergaard, L., Yablonskiy, D., Nielsen, N.C., Vestergaard-Poulsen, P., 2010. Neurite density from magnetic resonance diffusion measurements at ultrahigh field: comparison with light microscopy and electron microscopy. NeuroImage 49 (1), 205–216. https://doi.org/10.1016/j.neuroimage.2009.08.053.

Jones, D.K., Knösche, T.R., Turner, R., 2013. White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. NeuroImage 73, 239–254. https://doi.org/10.1016/j.neuroimage.2012.06.081.

Kail, R.V., 2007. Longitudinal evidence that increases in processing speed and working memory enhance children's reasoning. Psychol. Sci. 18 (4), 312–313. https://doi.org/10.1111/j.1467-9280.2007.01895.x.

Kellner, E., Dhital, B., Kiselev, V.G., 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.v76.510.1002/mrm.26054.

Kelly, C.E., Thompson, D.K., Chen, J., Leemans, A., Adamson, C.L., Inder, T.E., Cheong, J. L.Y., Doyle, L.W., Anderson, P.J., 2016. Axon density and axon orientation dispersion in children born preterm. Hum. Brain Mapp. 37 (9), 3080–3102. https://doi.org/10.1002/hbm.v37.910.1002/hbm.23227.

Kerr-Wilson, C.O., Mackay, D.F., Smith, G.C., Pell, J.P., 2012. Meta-analysis of the association between preterm delivery and intelligence. J. Public Health (Oxford, England) 34 (2), 209–216. https://doi.org/10.1093/pubmed/fdr024.

Lebel, C., Deoni, S., 2018. The development of brain white matter microstructure. NeuroImage 182, 207–218. https://doi.org/10.1016/j.neuroimage.2017.12.097.

Magistro, D., Takeuchi, H., Nejad, K.K., Taki, Y., Sekiguchi, A., Nouchi, R., Kotozaki, Y., Nakagawa, S., Miyauchi, C.M., Iizuka, K., Yokoyama, R., Shinada, T., Yamamoto, Y., Hanawa, S., Araki, T., Hashizume, H., Sassa, Y., Kawashima, R., Chen, K., 2015. The Relationship between Processing Speed and Regional White Matter Volume in Healthy Young People. PLoS ONE 10 (9), e0136386. https://doi.org/10.1371/journal.pone.0136386.

Mangin, K.S., Horwood, L.J., Woodward, L.J., 2017. Cognitive development trajectories of very preterm and typically developing children. Child Dev. 88 (1), 282–298. https://doi.org/10.1111/cdev.2017.88.issue-110.1111/cdev.12585.

Middlebrooks, E.H., Yagmurlu, K., Szaflarski, J.P., Rahman, M., Bozkurt, B., 2017. A contemporary framework of language processing in the human brain in the context of preoperative and intraoperative language mapping. Neuroradiology 59 (1), 69–87. https://doi.org/10.1007/s00234-016-1772-0.

Mori, S., Wakana, S., Van Zijl, P.C.M., Nagai-Poetscher, L.M., 2005. MRI Atlas of Human White Matter. Elsevier, Amsterdam, The Netherlands.

Mullen, K.M., Vohr, B.R., Katz, K.H., Schneider, K.C., Lacadie, C., Hampson, M., Makuch, R.W., Reiss, A.L., Constable, R.T., Ment, L.R., 2011. Preterm birth results in alterations in neural connectivity at age 16 years. NeuroImage 54 (4), 2563–2570. https://doi.org/10.1016/j.neuroimage.2010.11.019.

Neubauer, A.P., Voss, W., Kattner, E., 2008. Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment. Eur. J. Pediatr. 167 (1), 87–95. https://doi.org/10.1007/s00431-007-0435-x.

Olesen, P.J., Nagy, Z., Westerberg, H., Klingberg, T., 2003. Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network. Brain Res. Cogn. Brain Res. 18 (1), 48–57. https://doi.org/10.1016/j.cogbrainres.2003.09.003.

Pavaine, J., Young, J.M., Morgan, B.R., Shroff, M., Raybaud, C., Taylor, M.J., 2016. Diffusion tensor imaging-based assessment of white matter tracts and visual-motor outcomes in very preterm neonates. Neuroradiology 58 (3), 301–310. https://doi.org/10.1007/s00234-015-1625-2.

Pecheva, D., Kelly, C., Kimpton, J., Bonthrone, A., Batalle, D., Zhang, H., & Counsell, S. J. (2018). Recent advances in diffusion neuroimaging: applications in the developing preterm brain. F1000Research, 7, F1000 Faculty Rev-1326. https://doi.org/10.12688/f1000research.15073.1.

Pierrat, V., Marchand-Martin, L., Arnaud, C., Kaminski, M., Resche-Rigon, M., Lebeaux, C., Bodeau-Livinec, F., Morgan, A.S., Goffinet, F., Marret, S., Ancel, P.Y., 2017. EPIPAGE-2 writing group, Neurodevelopmental outcome at 2 years for preterm children born at 22 to 34 weeks' gestation in France in 2011: EPIPAGE-2 cohort study. BMJ (Clinical research ed.) 358, j3448. https://doi.org/10.1136/bmj.j3448.

Putnick, D.L., Bornstein, M.H., Eryigit-Madzwamuse, S., Wolke, D., 2017. Long-term stability of language performance in very preterm, moderate-late preterm, and term children. J. Pediatr. 181, 74–79.e3. https://doi.org/10.1016/j.jpeds.2016.09.006.

Sato, J., Vandewouw, M.M., Bando, N., Ng, D., Branson, H.M., O'Connor, D.L., Unger, S. L., & Taylor, M.J. (2021). Early nutrition and white matter microstructure in children born very low birth weight. Brain Communications, 3(2), fcab066. https://doi.org/10.1093/braincomms/fcab066.

Schulze, E.T., Geary, E.K., Susmaras, T.M., Paliga, J.T., Maki, P.M., Little, D.M., 2011. Anatomical correlates of age-related working memory declines. J. Aging Res. 2011, 1–9. https://doi.org/10.4061/2011/606871.

Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., Behrens, T.E., 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.

Smith, S.M., Nichols, T.E., 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.

Tamnes, C.K., Østby, Y., Walhovd, K.B., Westlye, L.T., Due-Tønnessen, P., Fjell, A.M., 2010. Intellectual abilities and white matter microstructure in development: a diffusion tensor imaging study. Hum. Brain Mapp. 31 (10), 1609–1625. https://doi.org/10.1002/hbm.v31:1010.1002/hbm.20962.

Tustison, N.J., Avants, B.B., Cook, P.A., Zheng, Y., Egan, A., Yushkevich, P.A., Gee, J.C., 2010. N4ITK: improved N3 bias correction. IEEE Trans. Med. Imaging 29 (6), 1310–1320. https://doi.org/10.1109/TMI.2010.2046908.

Twilhaar, E.S., Wade, R.M., de Kieviet, J.F., van Goudoever, J.B., van Elburg, R.M., Oosterlaan, J., 2018. Cognitive Outcomes of Children Born Extremely or Very Preterm Since the 1990s and Associated Risk Factors: A Meta-analysis and Meta-regression. JAMA pediatrics 172 (4), 361–367. https://doi.org/10.1001/jamapediatrics.2017.5323.

Unger, S., Gibbins, S., Zupancic, J., O'Connor, D.L., 2014. DoMINO: Donor milk for improved neurodevelopmental outcomes. BMC Pediatrics 14, 123. https://doi.org/10.1186/1471-2431-14-123.

Veraart, J., Fieremans, E., Jelescu, I.O., Knoll, F., Novikov, D.S., 2016. Gibbs ringing in diffusion MRI. Magn. Reson. Med. 76 (1), 301–314. https://doi.org/10.1002/mrm.v76.110.1002/mrm.25866.

Volpe, J.J., 2009. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. The Lancet. Neurol. 8 (1), 110–124. https://doi.org/10.1016/S1474-4422(08)70294-1.

Wechsler, D., 2012. Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition. The Psychological Corporation, San Antonio, Texas.

Woodward, L.J., Moor, S., Hood, K.M., Champion, P.R., Foster-Cohen, S., Inder, T.E., Austin, N.C., 2009. Very preterm children show impairments across multiple neurodevelopmental domains by age 4 years. Arch. Dis. Child. Fetal Neonatal Ed. 94 (5), F339–F344. https://doi.org/10.1136/adc.2008.146282.

Young, J.M., Morgan, B.R., Whyte, H., Lee, W., Smith, M.L., Raybaud, C., Shroff, M.M., Sled, J.G., & Taylor, M.J. (2017). Longitudinal Study of White Matter Development and Outcomes in Children Born Very Preterm. Cerebral cortex (New York, N.Y. : 1991), 27(8), 4094–4105. https://doi.org/10.1093/cercor/bhw221.

Young, J.M., Vandewouw, M.M., Morgan, B.R., Smith, M.L., Sled, J.G., Taylor, M.J., 2018. Altered white matter development in children born very preterm. Brain Struct. Funct. 223 (5), 2129–2141. https://doi.org/10.1007/s00429-018-1614-4.

Young, J.M., Vandewouw, M.M., Mossad, S.I., Morgan, B.R., Lee, W., Smith, M.L., Sled, J. G., Taylor, M.J., 2019. White matter microstructural differences identified using multi-shell diffusion imaging in six-year-old children born very preterm. NeuroImage. Clinical 23, 101855. https://doi.org/10.1016/j.nicl.2019.101855.

Zhang, H., Schneider, T., Wheeler-Kingshott, C.A., Alexander, D.C., 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.