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Increased white matter fibre dispersion and lower IQ scores in adults born preterm

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Abstract

Preterm birth has been associated with altered microstructural properties of the white matter and lower cognitive ability in childhood and adulthood. Due to methodological limitations of the diffusion tensor model, it is not clear whether alterations in myelination or variation in fibre orientation are driving these differences. Novel models applied to multi-shell diffusion imaging have been used to disentangle these effects, but to date this has not been used to study the preterm brain in adulthood. This study investigated whether novel advanced diffusion MRI metrics such as microscopic anisotropy and orientation dispersion are altered in adults born preterm, and whether this was associated with cognitive performance. Seventy-two preterm born participants (<37 weeks gestational age) were recruited from a 1982–1984 cohort (33 males, mean age 33.5 ± 1.0 years). Seventy-two term born (>37 weeks gestational age) controls (34 males, mean age 30.9 ± 4.0 years) were recruited from the general population. Tensor FA was calculated with FSL, while microscopic FA and orientation dispersion entropy (ODE) were estimated using the Spherical Mean Technique (SMT). Estimated Full Scale IQ (FSIQ), Verbal Comprehension Index (VCI) and Perceptual Reasoning Index (PRI) were obtained from the WASI-II (abbreviated) IQ test. Voxel-wise comparisons using FSL's tract-based spatial statistics were performed to test between-group differences in diffusion MRI metrics as well as within-group associations of diffusion MRI metrics and IQ outcomes. The preterm group had significantly lower FSIQ, VCI and PRI scores. Preterm subjects demonstrated widespread decreases in ODE reflecting increased fibre dispersion, but no differences in microscopic FA. Tensor FA was increased in a small area in the anterior corona radiata. Lower FA values in the preterm population were associated with lower FSIQ and PRI scores. An increase in fibre dispersion in white matter and lower IQ scores after preterm birth exist in adulthood. Advanced diffusion MRI metrics such as the orientation dispersion entropy can be used to monitor white matter alterations across

the lifespan in preterm born individuals. Although not significantly different between preterm and term groups, tensor FA values in the preterm group were associated with cognitive outcome.

KEYWORDS
cognition, diffusion weighted imaging, magnetic resonance imaging, preterm birth, white matter

1 | INTRODUCTION

Each year approximately 15 million infants are born prematurely, before 37 weeks of completed gestation (Blencowe et al., 2012). In the period from birth to term age, the oligodendrocytes and subplate neurons are particularly susceptible to inflammatory, hypoxic and ischemic injury (Volpe, 2009).

Damage to white matter this early in development results in white matter dysmaturation (Back & Miller, 2014; Dean et al., 2014; Miller & Ferriero, 2009; Volpe, 2009). White matter structural abnormalities are evident using MRI diffusion tensor metrics in preterm infants at term equivalent age, particularly in the corpus callosum (Dibble et al., 2021). A meta-analysis showed that a reduction in FA in preterm born individuals is found in infancy through to adulthood (Allin et al., 2004; Eikenes et al., 2011; Lu, 2015; Meng et al., 2015; Salvan et al., 2014; Vollmer et al., 2017), although it becomes less evident with age (Li et al., 2015). Localised increases in FA in the anterior and posterior corona radiata were reported in a subset of studies in preterm born adolescent and adult populations (Allin et al., 2011; Eikenes et al., 2011; Li et al., 2015; Vangberg et al., 2006). Since tensor metrics are influenced by axonal integrity, density, and orientation dispersion, these studies were not able to disentangle the contribution of each of those factors (Beaulieu, 2002). Frequently the FA decrease is associated with an in increase in radial diffusivity (RD) (Li et al., 2015) in people born preterm, thought to be due to lower axonal integrity, lower axonal packing density, or axonal diameter (Beaulieu, 2013). Higher axial diffusivity in the preterm groups could be attributed to either better fibre organisation or breakdown of long fibres resulting in fewer fibre crossings (Li et al., 2015). Furthermore, FA may be sensitive to different balance of tissue properties in preterm as compared to full term children across different pathways of the brain. Myelin content, as indexed by R1, could drive the differences in white matter between preterm and term born children in some segments of the corpus callosum, and associates with reading abilities in some dorsal and ventral tracts in children born preterm. Axonal diameter and directional coherence, likely contributed to FA differences in the anterior frontal segment of the corpus callosum between preterm and term children and dorsal pathway FA may primarily drive reading abilities in full-term children (Brignoni-Pérez et al., 2022; Travis et al., 2019).

Multi-shell diffusion MRI data in combination with advanced diffusion imaging models can shed more light on the underlying causes of diffusion metric changes. For example, the neurite orientation dispersion and density imaging (NODDI; Zhang et al., 2012) model can estimate the neurite density and orientation dispersion, enabling the analysis of these factors independently. Using NODDI, lower gestational age was found to be associated with altered FA- and neurite density network topology in infants (Batalle et al., 2017). Preterm born children had higher axon dispersion as well as local reductions in FA as compared to term born controls and these diffusion MRI metrics were associated with neonatal brain abnormalities (Kelly et al., 2016; Young et al., 2019). NODDI used in combination with tractography and structural network analysis showed that preterm born adults had a significantly lower FA in the hub sub-network, peripheral sub-network and global connectivity. In a recent study of young adults born preterm, there were no significant differences in axon dispersion or neurite density after multiple comparison corrections using NODDI (Irzan et al., 2021). Using fixel-based analysis, preterm infants showed reduced fibre density, fibre bundle cross-section, and bundle cross-section (FDC) in the corpus callosum, anterior commissure, cortico-spinal tract, optic radiations, and cingulum (Pannek et al., 2018). Fibre density and cross-section were associated with lower gestation and longer ventilation in preterm infants (Pecheva et al., 2019). Further advances in diffusion MRI model fitting have led to the development of the Spherical Mean Technique (SMT) (Kaden, Kruggel, & Alexander, 2016). Similar to NODDI, it aims to separate contributions of neurites and free water (CSF), but it does not assume a single fibre bundle or a fixed diffusion coefficient parallel to the fibres. Thereby it sets out to provide diffusion MRI metrics that are unconfounded by fibre dispersion. This model has not yet been used to examine the differences in white matter microstructure in adults born preterm.

Preterm birth is also associated with lower IQ scores from infancy (Romeo et al., 2010), throughout childhood (Aarnoudse-Moens et al., 2009; Allotey et al., 2018;Bhutta et al., 2002; Kerr-Wilson et al., 2012) until adulthood (Breeman et al., 2015; Eryigit Madzwamuse et al., 2015; Hack et al., 2002) compared to term-born controls. Meta-analyses show the difference is 11–12 IQ points in childhood (Bhutta et al., 2002; Kerr-Wilson et al., 2012)and in adulthood (Eves et al., 2021). White matter microstructural abnormalities might partly explain the lower cognitive performance in preterm individuals. Reductions in FA in major white matter tracts have been associated with lower cognitive performance, particularly the corpus callosum in preterm infants (van Kooij et al., 2012), children (Andrews et al., 2010; Murray et al., 2016), adolescents (Feldman et al., 2012), and adults (Allin et al., 2011; Eikenes et al., 2011; Kontis et al., 2009). Lower FA has also been associated with lower cognitive performance in the longitudinal fasciculus in preterm adolescents (Vollmer

et al., 2017), and adults (Allin et al., 2011; Eikenes et al., 2011), and in the uncinate fasciculus in children (Constable et al., 2008), and adolescents (Feldman et al., 2012; Mullen et al., 2011; Skranes et al., 2007; Vollmer et al., 2017).

Differences in DTI metrics and cognitive performance have consistently been reported across developmental stages between preterm and term-born individuals, but it remains unknown what microstructural white matter properties underlie these differences. This is the first study to use advanced diffusion MRI metrics to investigate if these DTI metrics could be related to increased fibre orientation in adults born preterm, and whether these diffusion MRI metrics are associated with cognitive performance.

2 | METHODS

2.1 | Participants

Seventy-two preterm born participants were recruited from a nutrition intervention trial cohort (Lucas et al., 1984). The original trial included 926 infants with a birthweight below 1850 g who were admitted to the special care baby units in Ipswich, Cambridge, King's Lynn, Norwich, and Sheffield, UK, between 1982 and 1985. Infants with severe congenital abnormality known to affect growth or neurodevelopment were excluded from the original study. Participants who had taken part in previous follow-up studies were approached.

Seventy-two term born (>37 weeks gestational age) controls between the ages 25 and 40 were newly recruited. Inclusion criteria were individuals born after 37 weeks of gestation, fluent in English, with no history of neurological disease, no exclusions to MRI, and no prior experience of cognitive testing. The control cohort consists of family members or friends who met the selection criteria and additional full-term participants were recruited from the community.

Ethics approval was granted by the UCL ethics committee (6235/001). Written informed consent was obtained from participants. The study adhered to the Declaration of Helsinki (World Medical Association, 2013).

2.2 | MRI acquisition and processing

Participants were scanned on a Siemens Prisma 3 T MRI system, using a self-shielding gradient set with maximum gradient strength of 80 mT m^{-1} and a 64 channel head coil. T1-weighted volume scans were acquired with 1 mm isotropic voxels. Repetition time for the T1-weighted images was 2300 ms, and echo time was 2.74 ms. Multi-shell diffusion MRI was acquired with 2 mm isotropic voxels using multi-band echo-planar diffusion-weighted images with an optimized two-shell protocol: two 60-direction shells of $b = 1000$ s mm^{-2} and $b = 2200$ s mm^{-2}, interleaved with 14 T2-weighted ($b = 0$) volumes. The echo time was 60 ms and repetition time was 3050 ms.

T1-weighted images were converted to NIfTI-1 format using the TractoR software package http://www.tractor-mri.org.uk (Clayden et al., 2011). Volumetric data was derived using Freesurfer software (surfer.nmr.mgh.harvard.edu) (Fischl, 2012). The TractoR diffusion pipeline was applied to the multi-shell diffusion data (Clayden et al., 2011). The raw data was corrected for susceptibility-induced distortions using the FSL topup function (Andersson et al., 2003) and for eddy current induced distortions using FSL's eddy function (Andersson & Sotiropoulos, 2016). FSL version 5.0.10 was also used to fit a diffusion tensor and create tensor FA maps (Jbabdi et al., 2012), and SMT was used to create microscopic FA and orientation dispersion entropy maps (Kaden, Kelm, et al., 2016). Microscopic diffusion anisotropy maps reflect diffusion anisotropy without the effects of the neurite orientation distribution within the voxel. SMT maps were adjusted for Rician noise after calculating the median of the voxel-wise estimate of the Rician-distributed noise in the field map (Kaden, Kruggel, & Alexander, 2016). All pre-processed images were checked visually for artefacts. Enlarged ventricles and white matter lesions were classified by a radiologist based on T1.

Tract-based spatial statistics (TBSS) (Smith et al., 2006) was used for voxel-wise analyses. A study-specific template was created by applying nonlinear registration of all individual tensor FA maps to standard space and averaging them. All image registrations were visually inspected. A white matter 'skeleton' is created by applying a threshold of 0.2 (following a visual check of the skeleton) on the mean FA image, consisting of voxels at the core of the white matter tracts common to the group. The warp-fields from the non-linear registration are applied to all other diffusion maps. The subjects' nearest maximum FA values are then projected onto the skeleton, which aims to remove extra spatial variability across subjects. Finally, FA, MD, RD, AD, and microscopic FA and orientation dispersion derived from the same voxel location as the FA, are projected onto the skeleton. If the skeleton encompasses CSF voxels, the participant is excluded from the analysis.

2.3 | Demographic information

Gestational age, birthweight, and maternal education were collected prospectively at birth, for the preterm group. Small for gestational age was defined as a birthweight below the 10th percentile. Maternal education as well as participant's social class was recorded using questionnaires at to the 30-year follow-up visit, for both groups. In case there were two maternal education datapoints available for preterm participants, the prospectively collected information was used. Maternal education was coded: (1) no educational qualifications, (2) up to four passes for the certificate of secondary education (CSE), (3) any general certificate of education (GCE) or ordinary (O) level or more than four CSEs, (4) any GCE at advanced (A) level, (5) degree or higher professional qualification. Participant occupation was coded with the five class self-coded method of the National Statistics Socio-economic classification (NS-SEC). The five classes were: (1) managerial, administrative, and professional occupations, (2) intermediate occupations, (3) small employers and own account workers, (4) lower supervisory and technical occupations, (5) semi-routine and routine occupations (Office for National Statistics, 2010).

2.4 | Cognitive tests

The Wechsler Abbreviated Scale of Intelligence (WASI)-II IQ test (Wechsler, 2011) consists of four subtests; Vocabulary, Similarities, Block Design and Matrix Reasoning. The first two subtests were used to calculate the Verbal Comprehension Index (VCI), the latter two subtests were used to calculate the Perceptual Reasoning Index (PRI) whilst the Full Scale IQ (FSIQ) score was calculated from all four subtests. This abbreviated form provides estimated IQ scores.

2.5 | Statistical analyses

Age, sex, and maternal education were included as covariates in all analyses. Voxel-wise differences between preterm and term groups in diffusion MRI indices and the relationship between IQ scores and diffusion MRI indices in the preterm group were assessed using TBSS. The skeleton maps were entered in a general linear model and analysed using voxel-wise permutation testing in combination with threshold-free cluster enhancement (TFCE) correction (Winkler et al., 2014), adjusting for sex, age, and maternal education. Tracts were identified using the JHU atlas white matter labels. FSL provides the probabilities of a certain cluster being a member of the different labelled tracts in the atlas (Oishi et al., 2010). Statistical analyses were run using the stats package in R version 4.0.3 (R Core Team, 2013). An ANCOVA was used to calculate group difference in cognitive test measures. For significant group differences in the TBSS analyses, mean diffusion values were extracted from the significant voxels of the preterm participants and associations between these mean values and IQ scores were examined using a linear regression adjusted for covariates.

Data can be made available upon request on the condition that a formal data sharing agreement is signed.

3 | RESULTS

3.1 | Study population

Sixty-eight preterm and 70 control participants underwent diffusion-weighted MRI scanning. One preterm participant was excluded from analyses as she had suffered from a severe concussion and reported cognitive problems and fatigue as a result. Diffusion data from three preterm and two control participants was excluded as the FA skeleton contained voxels with partial volume effects of CSF. One preterm participant was excluded due to failing a further step of TBSS processing. Finally, one preterm participant who underwent MRI scanning did not complete the IQ test.

The preterm participants were on average 2.8 years older, and had lower educational attainment (Table 1). Detailed information on differences between the original 1982 cohort and all participants followed up in adulthood (including those who were excluded for MRI analyses) can be found in Table S1.

TABLE 1 Participant characteristics.

	Preterm ($n = 63$)	Control ($n = 68$)
Neonatal		
Sex male, *n* (%)	28 (41%)	30 (44%)
GA (weeks), mean (SD)	30.1 (2.4)	-
Extremely/very preterm (<32 weeks), *n* (%)	43 (68%)	-
Moderately preterm (32 to <34 weeks), *n* (%)	17 (27%)	-
Late preterm (34 to <37 weeks), *n* (%)	3 (5%)	-
Birthweight (g), mean (SD)	1312 (302)	-
Days on ventilation, mean (SD)	4.0 (7.3)	-
Maternal education > A-levels, *n* (%)	38 (62%)	32 (54%)
Adulthood		
Age (years), mean (SD)	33.4 (1.2)	30.6 (3.8)
Height (cm), mean (SD)	169 (9.7)	172 (11.0)
Weight (kg), mean (SD)	78.4 (24.8)	69.4 (13.0)
FSIQ, mean (SD)	107 (15)	115 (12)
PRI, mean (SD)	107 (14)	113 (13)
VCI, mean (SD)	106 (16)	113 (14)
Grey matter volume (mm^3), mean (SD)	528,265 (54,144)	560,313 (59,716)
White matter volume (mm^3), mean (SD)	489,636 (69,581)	498,488 (56,041)
Ventricular volume (mm^3), mean (SD)	15,913 (7127)	12,485 (6081)
Evidence of white matter lesions on T1, *n* (%)	2 (3%)	1 (1%)
Evidence of enlarged ventricles on T1, *n* (%)	2 (3%)	6 (9%)
Highest level of education obtained		
Some secondary school, *n* (%)	3 (5%)	0 (0%)
Finished secondary school, *n* (%)	11 (18%)	11 (17%)
Trade training, *n* (%)	13 (21%)	6 (9%)
University undergraduate, *n* (%)	18 (29%)	20 (31%)
University postgraduate, *n* (%)	17 (27%)	27 (42%)

3.2 | White matter microstructure

In the voxel-wise analysis, preterm subjects demonstrated widespread decreases in ODE corresponding to greater fibre dispersion (Figure 1). Tensor FA was locally increased in a small region in the anterior corona radiata, where the inferior fronto-occiptial fasciculus and the anterior thalamic radiation fibres cross. Tensor AD was higher on the right side where the superior corona radiata and superior longitudinal fasciculus cross (Figure 1). There were no differences in SMT microscopic FA, tensor MD, or tensor RD.

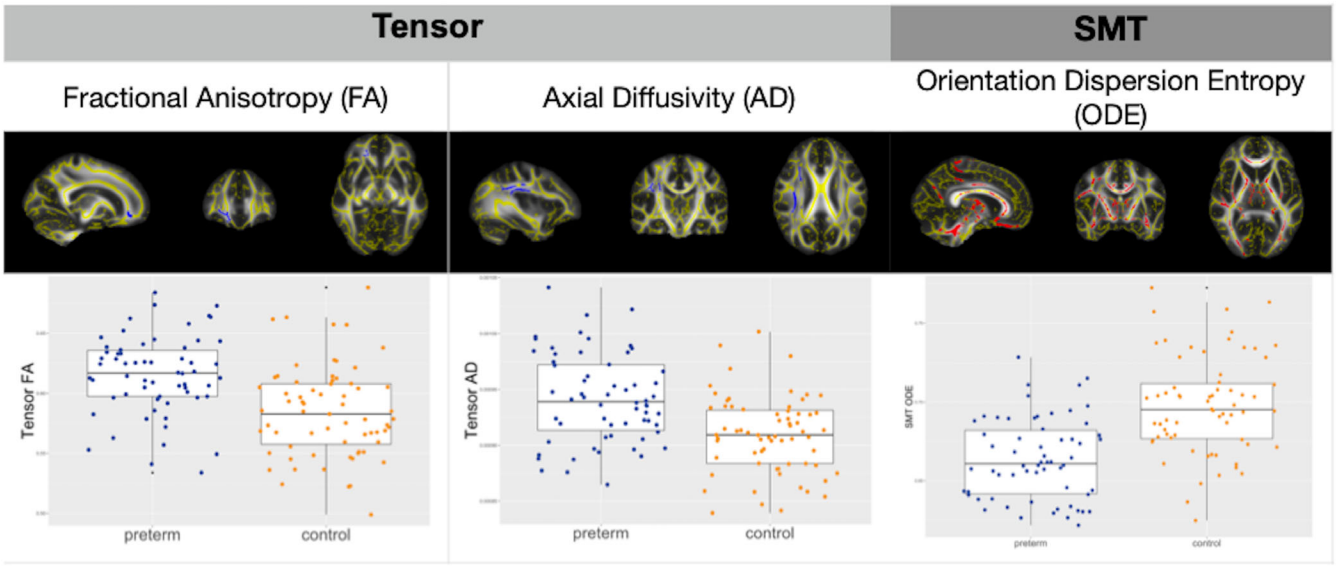

FIGURE 1 Statistical brain maps showing significant differences between preterm and control subjects in diffusion MRI metrics within the white matter skeleton (white) ($p < .05$ TFCE corrected). Red: preterm < control; blue: preterm > control. Boxplots of diffusion MRI metric values averaged across voxels with significant preterm vs term group differences, adjusted for sex, age, and maternal education. A lower ODE reflects higher fibre dispersion.

3.3 | White matter microstructure and cognitive test scores in preterm participants

In the preterm group, TBSS voxel-wise analysis across the entire skeleton showed that higher FA was associated with higher FSIQ a large part of the white matter skeleton, although effect sizes were small in absolute terms (Figure 2). These areas of the white matter skeleton did not overlap with the area where the preterm group showed significantly higher FA as compared to the term group. In the latter region, each FSIQ point was associated with a 0.0008 increase in mean FA ($R^2 = 0.31$, $F(4, 56) = 6.4$, $p < .001$) in the preterm group.

In the preterm group, TBSS voxel-wise analysis across the entire skeleton also showed that higher FA was associated with higher PRI scores (Figure 2). These areas cover half (124/256 voxels) of the area where the preterm group showed significantly higher FA as compared to the term group. Each PRI point was associated with a 0.0003 increase in FA ($R^2 = 0.14$, $F(4, 57) = 2.4$, $p = .02$).

FSIQ and PRI scores were not associated with other tensor or SMT metrics. There were no significant associations VCI scores and white matter microstructure metrics.

4 | DISCUSSION

4.1 | Diffusion MRI

This is the first study to use advanced diffusion imaging techniques and show lower ODE, reflecting higher axon dispersion, in adults born preterm as compared to adults born at term. This study shows that white matter alterations in individuals born preterm exist in adulthood and that differences in the uniformity of the fibre orientations rather than axonal integrity or density remain strongest in adulthood. However, there were no significant associations between ODE and IQ in the preterm group, while there were associations between higher FSIQ and PRI scores and higher FA.

A previous study using SMT in very preterm born children found no associations between ODE and mathematics performance, but they did not compare preterm and term groups, nor did they assess IQ (Collins et al., 2019). In line with this study, preterm born children showed higher axon dispersion as compared to term born controls using NODDI (Kelly et al., 2016; Young et al., 2019). However, the study using NODDI by Irzan et al. (2021), reports no differences in axon dispersion whilst finding lower FA in adults born preterm compared to term born controls. Differences with our results and those of studies by Kelly and Young et al. could be due to methodological differences as well as differences in age of the preterm born subjects, that is, 6–7 years in previous studies and 33 years in the present study. Irzan et al. first created a structural connectivity network based on tractography and then averaged diffusion MRI metrics along the structural network as opposed to the voxel-wise TBSS analysis approach taken here. They did observe associations between lower gestational age and lower FA and higher axon dispersion, but these were not significant after correcting for multiple comparisons (Irzan et al., 2021). The small number of studies that used other advanced diffusion imaging models with multi-shell diffusion MRI data showed lower FA but no difference in axon density in preterm subjects compared to controls (Kelly et al., 2016; Young et al., 2019). Previous findings of reductions in FA in preterm populations could also be in part due to increased fibre dispersion. Future studies should investigate whether fibre dispersion is higher from infancy or whether this

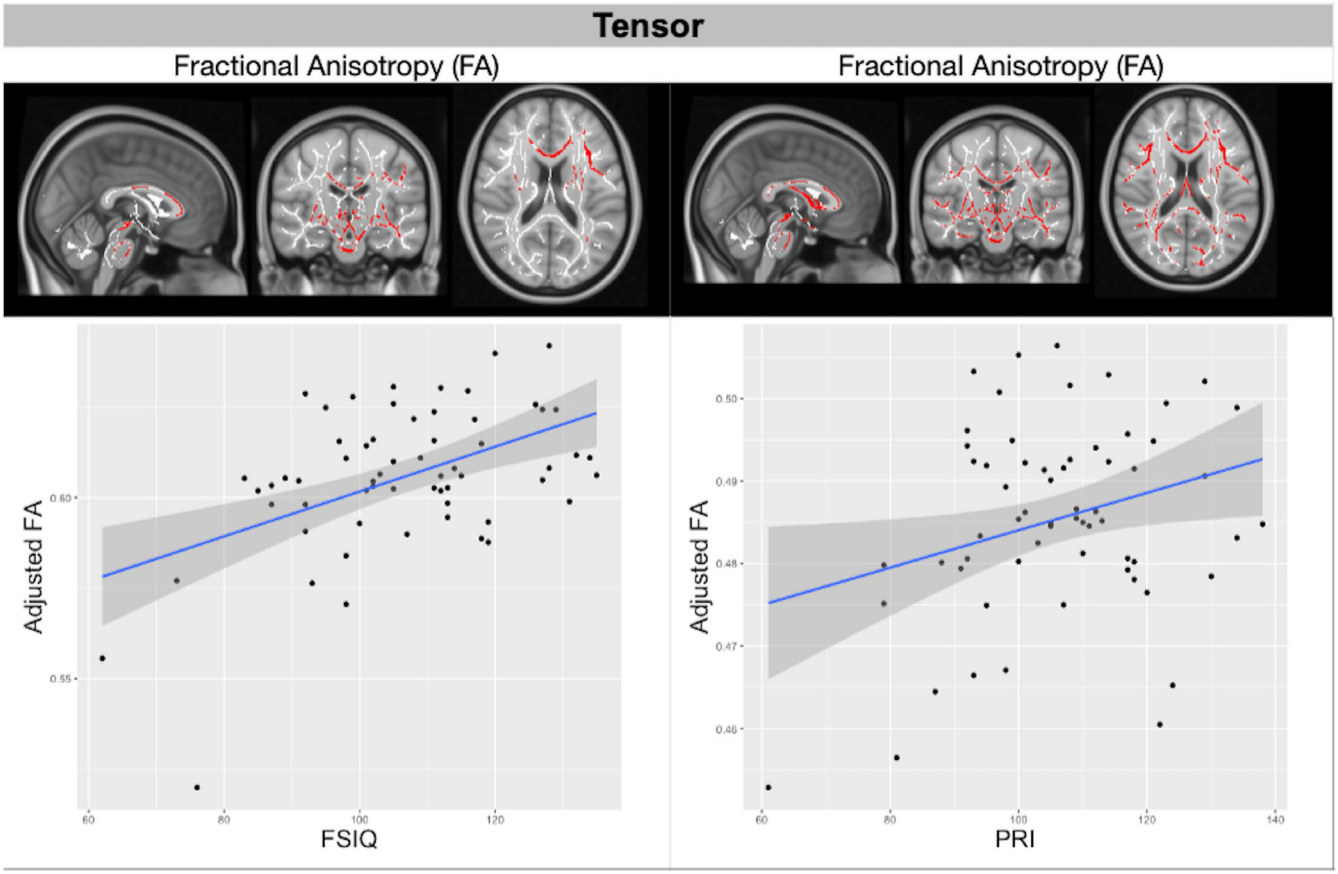

FIGURE 2 Statistical brain maps showing significant associations between FA within the white matter skeleton (white) and IQ scores in preterm subjects ($p < .05$ TFCE corrected). Red: higher FA is associated with higher cognitive score. Scatterplots of diffusion MRI metric values averaged across voxels with significant associations with the IQ scores, adjusted for sex, age, and maternal education.

develops over time and how this associates with cognitive performance at each developmental stage. Studying the contributing characteristics of white matter fibres facilitates a more biologically meaningful interpretation of differences between preterm and term individuals.

However, in this study there were no areas of lower FA in the preterm subjects compared to the term born controls. The apparent contrast with previous reports of lower FA in preterm children (Li et al., 2015) could potentially be attributed to the age differences with the population studied here, differences in methodology or exclusion of participants with significant white matter injury. First, most previous studies have been performed in children, while this study examines the oldest large preterm cohort that has been followed-up with advanced diffusion MRI to date. Second, some studies used tractography to delineate fibre bundles (Groeschel et al., 2014; Salvan et al., 2014), which has a higher statistical power than voxel based analyses of the whole-brain skeleton (Salvan et al., 2014). Third, we excluded subjects with ventriculomegaly from the TBSS analysis because the white matter skeleton overlapped with their ventricles, resulting in partial volume effects. The higher MD and lower FA values in the corpus callosum in adults born preterm and at term reported by Groeschel and colleagues were no longer significant when subjects with significant preterm brain injury were excluded (Groeschel et al., 2014). Similarly, a study by Kontis et al. with a sample of participants who were screened for significant brain injury reported no FA differences in the corpus callosum in adults born preterm compared to people born at term (Kontis et al., 2009). It was suggested that reported differences between people born preterm and term born controls in diffusion parameters in the corpus callosum may be influenced by an increase in partial volume effects with CSF as a result of callosal thinning (Groeschel et al., 2014). Furthermore, the participants in the sample presented in this study are relatively high functioning, as evidenced by their higher childhood IQ than those who were not followed-up, and less likely to have suffered from significant brain injury. This prevented the results from being influenced by a small number of participants with severe injury but consequentially does bias the sample towards preterm subjects with less severe white matter abnormality. Recently, due to improvements in neonatal care, there has been a shift from severe towards milder white matter injury (Moore et al., 2012). Milder cognitive disabilities, learning difficulties and behavioural problems are observed in 25%–50% of school-aged preterm survivors and form a significant public health burden (Hutchinson et al., 2013; Larroque et al., 2008). The population studied here falls within that spectrum. There may have been a selection bias in the control population, given the higher proportion of university education participants relative to the preterm group.

The preterm group had higher FA values at the crossing of the anterior corona radiata, the inferior fronto-occiptial fasciculus, and the anterior thalamic radiations and higher AD where the superior corona radiata and superior longitudinal fasciculus cross. Higher FA and AD are usually interpreted as higher white matter fibre coherence (or in other words lower fibre dispersion) or higher axonal integrity. However, since this is observed in an area with multiple crossing fibre pathways, a higher FA or AD is more likely a result of one pathway being preferentially microstructurally altered than the other (Groeschel et al., 2014). This is also known as the 'unmasking effect'. FA is higher when one crossing fibre bundle is dominant as compared to when two equally large and coherent fibre bundles cross. Higher AD has been reported in preterm populations of different ages (Li et al., 2015). There were no significant differences in microFA, further supporting that there are no differences in anisotropy or axial diffusion in any of the individual fibre populations.

4.2 | Cognition

The preterm group showed lower IQ scores as compared to the term group, and there were strong associations between lower FA across the white matter skeleton and lower FSIQ and PRI scores in the preterm group. These findings are consistent with previous studies that have reported associations between lower FA and lower IQ in children (Constable et al., 2008; Feldman et al., 2012; Skranes et al., 2007; Vollmer et al., 2017) and adults (Allin et al., 2011; Eikenes et al., 2011). However, there were no areas of significantly lower FA in the preterm group as compared to the term group, suggesting that the white matter microstructure properties relating to cognitive performance may not be the same as those underlying differences between preterm and term born populations. The abbreviated form of IQ testing is less reliable than the full IQ test. Furthermore, the four subtests do not cover all subdomains of cognition.

Few studies to date have used SMT alongside cognitive tests, but there is evidence of associations between ODE and language performance in children (Cooper et al., 2019). In this study, no associations were found between ODE and IQ scores in the preterm group in young adulthood. Orientation dispersion changes are a contributory factor to observed changes in FA. ODE could be associated with specific cognitive domains that are not strongly captured by IQ scores and therefore not tested in this study. ODE could be associated with specific cognitive domains that are not strongly captured by IQ scores and therefore not captured in this study. A study using NODDI found that fibre dispersion changes more rapidly than FA after the fourth decade of life (Chang et al., 2015), so it is possible that the effect of ODE on cognition may become more evident with age.

5 | CONCLUSION

This study demonstrates that extensive structural brain alterations in white matter after preterm birth exist in adulthood. In the first study to use SMT in brain diffusion MRI data of adults born preterm, a widespread increase in fibre dispersion was observed. Although we did not observe a relationship with IQ outcome, this study underlines the potential of advanced diffusion MRI metrics such as the ODE used in this study, to monitor white matter alterations across the lifespan in preterm born individuals and sheds light on the biophysical organisation of the white matter in adults born preterm. Such measures may become more important as preterm populations reach middle age. Fractional anisotropy, known to be influenced by both axonal density and dispersion, did however correlate with cognitive measures underlining the importance of white matter microstructure in cognitive outcomes. A better understanding of structural brain alterations and novel techniques to monitor these could help assess whether preterm-born individuals are likely to experience cognitive problems later in life.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest relevant to this article to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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