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Sex differences, asymmetry, and age-related white matter development in infants and 5-year-olds as assessed with tract-based spatial statistics

Venla Kumpulainen¹  | Harri Merisaari^{1,2}  | Eero Silver¹ | Anni Copeland¹ | Elmo P. Pulli¹  | John D. Lewis³ | Ekaterina Saukko² | Satu J. Shulist¹ | Jani Saunavaara⁴ | Riitta Parkkola^{1,2} | Tuire Lähdesmäki^{1,5} | Linnea Karlsson^{1,6,7,8} | Hasse Karlsson^{1,7,8} | Jetro J. Tuulari^{1,7,8,9,10}

¹FinnBrain Birth Cohort Study, Turku Brain and Mind Center, Department of Clinical Medicine, University of Turku, Turku, Finland

²Department of Radiology, Turku University Hospital, Turku, Finland

³Montreal Neurological Institute, McGill University, Montreal, Canada

⁴Department of Medical Physics, Turku University Hospital and University of Turku, Turku, Finland

⁵Department of Pediatric Neurology, Turku University Hospital, University of Turku, Turku, Finland

⁶Department of Paediatrics and Adolescent Medicine, Turku University Hospital and University of Turku, Turku, Finland

⁷Department of Psychiatry, Turku University Hospital & University of Turku, Turku, Finland

⁸Centre for Population Health Research, Turku University Hospital and University of Turku, Turku, Finland

⁹Turku Collegium for Science, Medicine and Technology, University of Turku, Turku, Finland

¹⁰Department of Psychiatry, University of Oxford, Oxford, UK

Correspondence

Venla Kumpulainen, FinnBrain Birth Cohort Study, Turku Brain and Mind Center, Department of Clinical Medicine, University of Turku, Kiinamyllynkatu 10, FinnBrain study, Medisiina A Building, 20520, Turku, Finland. Email: veviku@utu.fi

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Abstract

The rapid white matter (WM) maturation of first years of life is followed by slower yet long-lasting development, accompanied by learning of more elaborate skills. By the age of 5 years, behavioural and cognitive differences between females and males, and functions associated with brain lateralization such as language skills are appearing. Diffusion tensor imaging (DTI) can be used to quantify fractional anisotropy (FA) within the WM and increasing values correspond to advancing brain development. To investigate the normal features of WM development during early childhood, we gathered a DTI data set of 166 healthy infants (mean 3.8 wk, range 2–5 wk; 89 males; born on gestational week 36 or later) and 144 healthy children (mean 5.4 years, range 5.1–5.8 years; 76 males). The sex differences, lateralization patterns and age-dependent changes were examined using tract-based spatial statistics (TBSS). In 5-year-olds, females showed higher FA in wide-spread regions in the posterior and the temporal WM and more so in the right hemisphere, while sex differences were not detected in infants. Gestational age showed stronger association with FA

Eero Silver, Anni Copeland, and Elmo P. Pulli shared contribution equally.

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values compared to age after birth in infants. Additionally, child age at scan associated positively with FA around the age of 5 years in the body of corpus callosum, the connections of which are important especially for sensory and motor functions. Lastly, asymmetry of WM microstructure was detected already in infants, yet significant changes in lateralization pattern seem to occur during early childhood, and in 5-year-olds the pattern already resembles adult-like WM asymmetry.

KEYWORDS

asymmetry, development, DTI, sex differences, TBSS, white matter

1 | INTRODUCTION

White matter (WM) microstructural development is linear during prenatal period (Wilson et al., 2021) and continues throughout the childhood with widespread increase in fractional anisotropy (FA) and corresponding decrease in mean diffusivity (MD) (Hermoye et al., 2006; Krogsrud et al., 2016; Lebel et al., 2016; Lebel & Deoni, 2017; Löbel et al., 2009; McGraw et al., 2002; Muftuler et al., 2012; Qiu et al., 2008; Reynolds et al., 2019; Rollins et al., 2010; Taki et al., 2013; Tamnes et al., 2010; Uda et al., 2015). The remodelling follows specific trajectories with both regional and temporal variation reflecting the concomitant maturation of motor, behavioural, and cognitive skills.

Generally, postnatal brain development advances with posterior-to-anterior and central-to-peripheral, non-linear patterns (Krogsrud et al., 2016) and continues from the second trimester into adulthood. Especially rapid developmental period occurs during the first 2 years of life, when myelination and pruning of axonal connections are driving the increase in WM integrity (Dubois et al., 2014; Hermoye et al., 2006; Huang et al., 2006). The myelination mainly limits the diffusion perpendicular to the axon axis, which is detected as decreasing radial diffusivity (Song et al., 2002) and concomitantly increasing FA values during the development (Barnea-Goraly et al., 2005; Bonekamp et al., 2007; Chen et al., 2016; Clayden et al., 2012; Colby et al., 2011; Dubois et al., 2014; Gao, Lin, et al., 2009; Genc et al., 2020; Hermoye et al., 2006; Huang et al., 2015; Krogsrud et al., 2016; Lebel & Deoni, 2017; Lebel et al., 2008, 2016; Moon et al., 2011; Moura et al., 2016; Muftuler et al., 2012; Qiu et al., 2008; Reynolds et al., 2019; Rollins et al., 2010; Snook et al., 2005; Stephens et al., 2020; Tamnes et al., 2010; Uda et al., 2015). Commissural and projection fibres, including corpus callosum and pyramidal tracts, are first to reach the adult-like integrity before school-age (Asato et al., 2010; Lebel et al., 2008; Reynolds et al., 2019; Tamnes et al., 2010). These tracts are related to improvement of both gross and fine motor skills, which are prerequisites for further learning of more elaborate skills like writing (Grohs et al., 2018; Johansen-Berg et al., 2007; Sigurdsson et al., 2002). Subsequently, the connections from occipital and limbic areas, associated with, for example, the development of language skills, mature between ages 5 and 8 years (Broce et al., 2018; Catani et al., 2007; Yeatman et al., 2012), followed by the maturation of fronto-temporal association tracts, related to higher-order functions

(Gao, Zhu, & Lin, 2009; Hutton et al., 2017; Oishi et al., 2013; Poussaint & Moeller, 2002; Salman et al., 2017; Simmonds et al., 2014), with prolonged development continuing to early adulthood (Reynolds et al., 2019). However, the exact timing of changes especially in young children is still partly elusive and warrants further study.

The developmental patterns of WM show sexual dimorphism with earlier maturation detected in females (Asato et al., 2010; Bava et al., 2011; Seunarine et al., 2016; Simmonds et al., 2014; Wang et al., 2012), yet more rapid and longer-lasting age-dependent increases in FA in males contributes to levelling off the differences by the age between 10 and 14 years (Seunarine et al., 2016). The studies have provided varying results on the divergence of the trajectories, both in the timing and tract-specific features (Table 1). In two studies, sex differences were already detected during neonatal age (Geng et al., 2012; Saadani-Makki et al., 2019), even though the differences were limited to few areas. In a sample of 25 infants, males had lower FA in right corticospinal tract (Saadani-Makki et al., 2019), and in another study of age range 0–2 years (Moura et al., 2016), females showed higher FA in the right sensory and the right uncinate tracts and lower FA in the arcuate and motor tracts. Differences in WM development between females and males were detected in multiple study populations of older children and adolescents (Asato et al., 2010; Bava et al., 2011; Clayden et al., 2012; Lewis et al., 2022; Wang et al., 2012), and more specifically between the ages of 2 and 8 years (Reynolds et al., 2019). On the other hand, no developmental sex differences were detected in some studies with wide age ranges (Eluvathingal et al., 2007; Lebel et al., 2008; Muetzel et al., 2008; Uda et al., 2015). Furthermore, part of the studies have shown FA values in specific tracts (e.g., in the corticospinal tract [CST] [Asato et al., 2010; Clayden et al., 2012; Reynolds et al., 2019; Wang et al., 2012]) to be higher in males during childhood, in contrast to generally lower FA values detected in males. Additionally, the lateralization of WM microstructure is well acknowledged both during the brain development (Bonekamp et al., 2007; Eluvathingal et al., 2007; Lebel & Beaulieu, 2009; Snook et al., 2005; Stephens et al., 2020) and adulthood (Cao et al., 2003; Catani et al., 2007; Takao, Abe, et al., 2011; Vernooij et al., 2007; Westerhausen et al., 2007). Asymmetry of WM tract diffusion properties has been shown to emerge as early as during neonatal age (Song et al., 2015), and is associated with later development of, for

TABLE 1 Literature review of white matter sex differences in age groups close to our study.

Author Year Journal	Age (years)	Sample size	Method	Main finding
Seunarine et al., 2016 Brain Connectivity	8–16	53	TBSS	<ul style="list-style-type: none"> Females: ↑FA in females Males: ↑ MD in males in majority of tracts (e.g., bilateral CST, IC, EC, thalamic radiation, SLF, left cingulum)
Asato et al., 2010 Cerebral Cortex	8–28	114	TBSS	<ul style="list-style-type: none"> Earlier maturation in females (RD) Females: only right frontal SLF continued to mature after adolescence Males: most tracts continued to develop into adulthood (exception: right SLF and IFOF)
Bava et al., 2011 Brain Research	12–14	58	TBSS	<ul style="list-style-type: none"> Females: ↑FA in right SCR and bilateral CST + ↓MD in right ILF and left forceps major Males: ↑AD in right SLF, ILF and forceps minor
Herting et al., 2012 Cerebral Cortex	10–16	77	TBSS	<ul style="list-style-type: none"> Males: ↑FA in all regions analysed (SCP, PLIC, IFOF, midbrain, cingulum)
Geng et al., 2012 NeuroImage	0–2	211	Tractography TBA	<ul style="list-style-type: none"> Females: ↑FA in right sensory tract + ↑AD in right UNC Males: ↑AD in right AF and right motor tracts
Reynolds et al., 2019 NeuroImage	2–8	120	Tractography	<ul style="list-style-type: none"> Earlier development in females, faster and greater development in males Females: ↓ global MD and ↓MD in BCC, fornix, ILF and SLF + faster ↑ FA in CST Males: ↑FA in GCC and CST + faster ↓ MD in fornix, ILF and SLF
Lebel et al. 2011 The Journal of Neuroscience	5–32	103	Tractography	<ul style="list-style-type: none"> Females: ↑FA in SCC Males: ↑FA in cingulum, bilateral CST, SLF, UNC
Eluvathingal et al., 2007 Cerebral Cortex	6–17	31	Tractography	<ul style="list-style-type: none"> Females: ↓RD in bilateral ILF and right IFOF
Clayden et al., 2012 Cerebral Cortex	8–16	59	Tractography	<ul style="list-style-type: none"> Males: faster decrease of MD (higher initial values, cross during development)
Schmithorst et al., 2008 Human Brain Mapping	5–18	106	ROI	<ul style="list-style-type: none"> Females: ↑FA in SCC + ↑MD in right occipito-parietal and superior part of CST <ul style="list-style-type: none"> Positive correlation between age and right frontal/occipito-temporal FA Negative correlation between age and left frontal FA Males: ↑ FA in frontal regions, in right AF and in left parietal and occipito-parietal WM + ↑MD in right CST and frontal WM <ul style="list-style-type: none"> Positive correlation between age and frontal FA Negative correlation between age and right AF FA
Muetzel et al., 2008 NeuroImage	9–24	92	ROI	<ul style="list-style-type: none"> No sex difference in FA or MD values detected in corpus callosum

Abbreviations: AD, axial diffusivity; AF, arcuate fasciculus; BCC, body of corpus callosum; CST, corticospinal tract; FA, fractional anisotropy; GCC, genu of corpus callosum; IC, internal capsule; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; MD, mean diffusivity; PLIC, posterior limb of internal capsule; RD, radial diffusivity; ROI, region of interest; SCC, splenium of corpus callosum; SCP, superior cerebral peduncle; SLF, superior longitudinal fasciculus; TBA, tract-based analysis; TBSS, tract-based spatial statistics; UNC, uncinate fasciculus.

example, language skills (Banfi et al., 2019) but is a relatively understudied topic.

Sex differences in emotional processing (Christov-moore et al., 2014; Else-Quest et al., 2012), personality features (Schmitt et al., 2017; Weinstein & Dannon, 2015), temperament (De & Spiering, 2009; Else-quest et al., 2006; Olino et al., 2014) and behaviour (Coe et al., 2021; Hines, 2010) are widely reported during childhood and adolescence. Additionally, prevalence of certain diseases is related to sex, for example, females show more internalizing symptoms and associated disorders such as anxiety (Alloy et al., 2017; Li & Graham, 2017) while incidence of antisocial behaviour (Holthausen & Habel,

2018) and diagnosis of attention deficit hyperactivity disorder (ADHD) (Mowlem et al., 2019; Rucklidge, 2010) are overrepresented in males. Unravelling sex-associated features of brain structure and function provide important knowledge on the factors inducing these sex-specific cognitive patterns. Furthermore, alterations in WM lateralization have been associated with conditions such as autism (Carper et al., 2016) and ADHD (Silk et al., 2016). Distinguishing normal variability of WM lateralization might open up new venues for characterizing also disease-associated changes.

Here, we describe sex differences, lateralization patterns, and developmental changes of the brain WM microstructure in

populations of infants and 5-year-olds. We hypothesized to find higher FA values in females, positive association between FA values and age, and leftward asymmetry in both age groups based on prior literature.

2 | MATERIALS AND METHODS

This study was reviewed and approved by the Ethics Committee of the Hospital District of Southwest Finland ([07.08.2018] §330, ETMK: 31/180/2011), and performed in accordance with the Declaration of Helsinki.

2.1 | Participants

The study included two subpopulations of families recruited as a part of FinnBrain Birth Cohort (Karlsson et al., 2017) to brain magnetic resonance imaging (MRI). Twenty-two subjects were included in both subpopulations (10 males). The exclusion criteria of both subpopulations were set to screen healthy participants with no acknowledged developmental problems. The first subpopulation of 190 infants (age of 11–54 days from birth at scan, mean 27, SD 7.9; 103 males and 87 females) participated in brain MR scanning between December 2012 and January 2016. The exclusion criteria for infants were: (1) Birth before gestational week (gwk) 36, (2) birth weight of less than 2500 g, (3) Apgar score <5 at 5 min after birth, (4) previously diagnosed central nervous system anomaly, an abnormal MRI finding in any previous MRI scan or severe perinatal complication with neurological consequences.

The MR scans of 203 5-year-olds were performed between October 2017 and March 2021. The participants were healthy, normally developing children aged from 5.1 to 5.8 years (mean 5.4, SD 0.11, 111 males, 92 females, 182 right-handed, 14 left-handed, 7 with no preference). The exclusion criteria, in addition to general MRI contraindications, were the following: (1) Birth before gwk 35 (before gwk 32 for separate nested cohort with exposure to synthetic glucocorticoids during pregnancy), (2) major developmental disorder, (3) other types of long-term diagnosis that requires constant contact to hospital, (4) sensory abnormalities (e.g. blindness or deafness), (5) use of daily, regular medication (asthma inhalers during infections was not an exclusion criterium; and desmopressin [®Minirin] medication was allowed), (6) head trauma requiring inpatient care (reported by parents). The informed consent was collected from both parents.

2.2 | MR imaging

Data acquisition was conducted in Turku University Hospital with a Siemens Magnetom Verio 3T scanner (12-element head/neck matrix coil) for infants and with a Siemens Magnetom Skyra fit 3T scanner (20-element head/neck matrix coil) for 5-year-olds. The scanner was upgraded in between the two data collections. The Generalized

Autocalibrating Partially Parallel Acquisition (GRAPPA) technique was used to accelerate imaging. Diffusion weighted imaging protocol was applied with a standard twice-refocused Spin Echo-Echo Planar Imaging (SE-EPI): TR (time of repetition)/TE (time of echo) = 8500/90.0 ms (for infants) and 9300/87.0 ms (for 5-year-olds), FOV (field of view) = 208 mm, isotropic voxels with $2.0 \times 2.0 \times 2.0$ mm resolution, *b* value 1000 s/mm, 96 noncollinear diffusion gradient directions divided into three scanning sets (31, 32, and 33 directions) with 9 *b*₀ images (3 *b*₀ = 0 s/mm volumes scattered at the beginning, middle and the end of the set). The scan visits included also structural and functional MRI scans (Copeland et al., 2021), but the current study uses only the structural diffusion data.

The infants were imaged during natural sleep after being fed by (breast) milk. A vacuum mattress was used to reduce movement during the imaging. Soft mouldable silicone ear plugs and hearing muffs were used for hearing protection. Infant MR images included 12 subjects with incidental findings (mainly small subdural hemorrhages), which were handled according to the procedure described in our earlier work (Kumpulainen et al., 2020) and were regarded not to affect the results.

The imaging visit of 5-year-olds was preceded by a home visit to provide detailed information on the study and a home practice period. The imaging session was also simulated before scanning, including practices of lying still and learning how to communicate during imaging. All children were imaged awake or during natural sleep. For more detailed description of the whole image set, the practice period and the imaging visit, see the previous published studies (Copeland et al., 2021; Kumpulainen et al., 2022; Pulli et al., 2022).

2.3 | Data analysis

DTI data acquisition was successful with 169 infants and with 163 5-year-olds. We used default settings in DTIprep denoising, slice-wise intensity checking, interlace-wise venetian blind artefact setting, and baseline averaging prior to porting the denoised and cleaned data for tensor fitting with FSL tools (<https://nitrc.org/projects/dtiprep/> [Oguz et al., 2014]). As the applied settings were detected to pass volumes with motion-related artifacts, all volumes were manually inspected and the ones with residual artifacts were excluded. For subsequent analysis, 30 directions were chosen per subject by maximizing the angular resolution, and subjects with insufficient number of directions after quality control steps were excluded (Merisaari et al., 2019). We chose to use 30 directions, as in our previous study (Kumpulainen et al., 2022) we observed that increasing the number of diffusion-encoding directions over 18 provided no additional advantage in repeatability of results. Further, inclusion of more directions would have led to a decrease in the sample size. With this choice, the final number of subjects was 166 infants (89 males, 77 females) and 144 5-year-olds (76 males, 68 females).

Pre-processing of quality-controlled data was conducted with FSL 6.0 (FMRIB software library, University of Oxford, UK). *b*₀ images, including at least one image per imaging set, were co-

registered and averaged (FLIRT, FMRIB's Linear Image Registration Tool), and the brain mask was created with Brain Extraction Tool (BET version 1.0.0) (Smith, 2002) with settings -R -f 0.3. Motion and eddy current correction were performed with FSL tools with concurrent rotation of the b vector matrix. The scalar maps were computed with FSL's dtifit. Tract-based spatial statistics (TBSS) pipeline of FSL (Smith et al., 2006) was used to estimate WM tract skeletons with the following settings (5-year-olds/infants): "tbss_2_reg" flag -T/-t (target being a study-specific template), "tbss_3_postreg" flag -S, FA threshold 0.2/0.15. Relative residual rotational and translational framewise displacements were measured to quantify the intrascanner head motion. The used pipelines have been thoroughly validated, please see more detailed description of data analysis pipeline, test-retest reliability, and assessment of optimal number of diffusion-encoding directions to DTI scalars in our previously published articles (Kumpulainen et al., 2022; Merisaari et al., 2019; Nolvi et al., 2020).

General linear model (GLM) with FSL's randomise tool was used for voxel-wise analysis of inter-subject variation. In the infant group, sex, age from birth and gestational age, rotational and translational mean framewise displacement measures (to control intrascanner head motion), maternal pre-pregnancy body mass index (BMI), birth weight, maternal smoking during pregnancy, and maternal socio-economic status (SES; evaluated by educational level and categorized into two classes: (1) low [elementary school] and medium [high school or occupational education], (2) high [examination from university or university for applied sciences]) were explored as independent contributors. For 5-year-olds, sex, age at scan, handedness, rotational and translational mean framewise displacement measures, maternal pre-pregnancy BMI, ponderal index, maternal smoking during pregnancy and maternal SES were explored as independent contributors. The analyses were conducted with 5000 permutations and multiple comparison correction with threshold-free cluster enhancement (TFCE; corrected $p < .05$ regarded as statistically significant). As the age and sex showed statistically significant correlations with FA, further analyses were performed with age and sex as main variables and other variables as covariates.

Sensitivity analyses with gestational age (birth before gestational week 35 for 5-year-olds), maternal pre-pregnancy BMI, maternal age at birth, maternal SES, smoking during pregnancy, prenatal exposure to corticosteroids or selective serotonin/serotonin-noradrenaline reuptake inhibitors (SSRI/SNRI) during pregnancy, and maternal perinatal depressive/anxiety symptoms (Edinburgh Postnatal Depressive Scale [EPDS] [Cox et al., 1987] and Symptom Checklist [SCL-90] [Holi et al., 1998]) at second trimester and 3 months postpartum (for 5-year-olds) were conducted. See the supplementary material for demographical information and regression analysis workflow (Tables S1 and S2).

Additionally, we examined the lateralization patterns of FA by FSL's "tbss_sym" both over all participants and separately in females and males. Lateralization was estimated by subtracting the right-sided FA values from the left-side ones, followed by a "one-sample t test" randomise analysis (5000 permutations, TFCE correction) to detect areas with significant variation. The mean image and standard

deviation (SD) of lateralized values was calculated with fslmaths. Tract-wise mean FA values were extracted with coregistration of JHU Neonate atlas (Oishi et al., 2011) for infants and JHU-ICBM-DTI atlas (Mori et al., 2008) for 5-year-olds to the TBSS skeleton images.

Statistical analyses for tract-wise extracted mean FA values were performed with SPSS version 27.0 (IBM Corp. 2020, Armonk, NY, USA). Tract-wise sex differences were estimated with independent samples t test (two-tailed), and asymmetric differences with one-sample t test, with Bonferroni corrected p value thresholded at 0.001 (0.05/36 tracts). Effect sizes for group differences were estimated with Cohen's d . Comparison between asymmetries in a subcohort of 22 infants and 5-year-olds was conducted with paired t test with Bonferroni corrected p value threshold at 0.002 (0.05/22).

3 | RESULTS

3.1 | Sex differences

3.1.1 | Infants

Sex showed no statistically significant correlation with FA values in the infants after controlling for age at scan and gestational age, intrascanner head motion, birth weight, maternal BMI, SES, and smoking.

3.1.2 | Five-year-olds

A significant effect of sex on FA values was detected in widespread regions at the age of 5 years, and was statistically strongest in posterior and temporal parts, and in the right hemisphere (Figure 1). Females had higher FA values in all regions with significant difference, that is, no regions with higher FA in males were detected. The results remained significant after controlling for gestational age, handedness, ponderal index, intrascanner head motion, smoking during pregnancy, pre-pregnancy BMI, and SES. In sensitivity analyses, the pattern of results in TBSS remained similar and statistically significant (data not shown). Group differences of whole WM tract mean FA values between females and males are provided in Table S3.

3.2 | Age effects

3.2.1 | Infants

The gestational age showed wide statistically significant positive correlations ($p < .01$) with FA values after controlling for age from birth and sex (Figure 2; results with $p < .05$ in Figure S1). Additionally, age from birth showed positive correlations with FA values ($p < .05$) after controlling for the gestational age and sex. The effect of gestational age on FA values was greater compared to the effects detected after birth. The results remain significant after controlling for intrascanner head motion, prenatal exposure to smoking, maternal age, pre-

FIGURE 1 Sex-differences with tract-based spatial statistics (TBSS) at the age of 5 years. Higher fractional anisotropy (FA) values detected in females are present in widely distributed areas, especially in posterior and right hemisphere regions. Regions with statistically significant difference showed in 3D (top left corner) and in axial plane (bottom left), threshold-free cluster enhancement (TFCE) correction applied, regression with 5000 permutations, $p < .05$ (red colour bar showing p values), age as a covariate. Additionally, on the right, group-differences in mean FA across whole tract between females (F) and males (M) showed in splenium of corpus callosum (SCC; Cohen's d 0.48), right retrothenticular internal capsule (r1 IC; Cohen's d 0.58), left inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (ILF/IFOF; Cohen's d 0.58) and left posterior thalamic radiation and optic tract (PTR/OR; Cohen's d 0.66). * $p < .005$, ** $p < .001$. R, right; L, left.

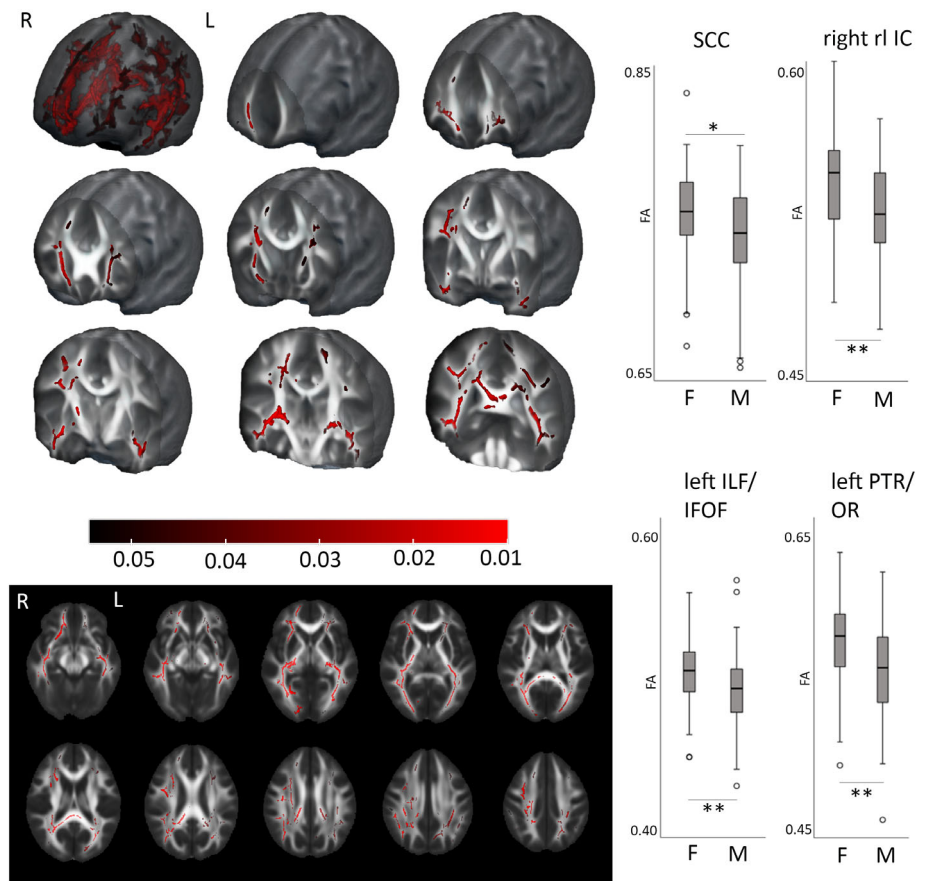
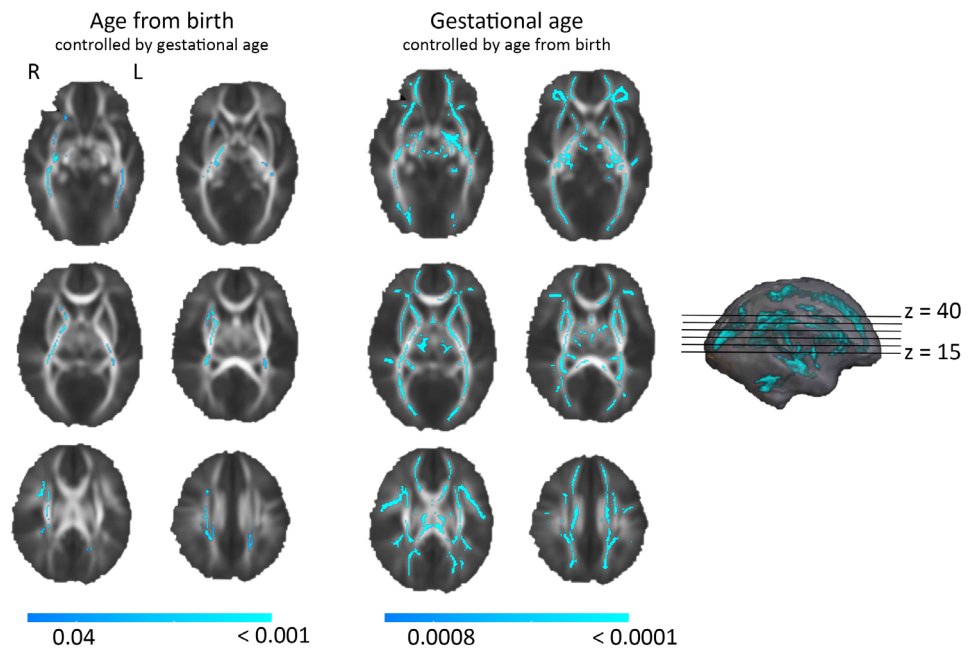


FIGURE 2 Effect of the age (controlled with gestational age) and the gestational age (controlled with age after birth) on fractional anisotropy (FA) with tract-based spatial statistics (TBSS) in infants. Positive correlation between both ages and FA are detected, with stronger and wider correlation between gestational age and FA. TFCE (threshold-free cluster enhancement) correction applied, 5000 permutations, $p < .05$ (for age from birth) and $p < .001$ (for gestational age), blue colour bar showing p value. R, right; L, left.



pregnancy BMI and SES. The covariates included in the sensitivity analyses did not affect the results. We inspected the age effects also separately in females and males and observed no difference in association between gestational age and FA after controlling for age after

birth or other covariates between males and females. When inspected separately, the age after birth and FA showed positive association in males ($p < .05$ after controlling for covariates), but the result did not remain statistically significant in females.

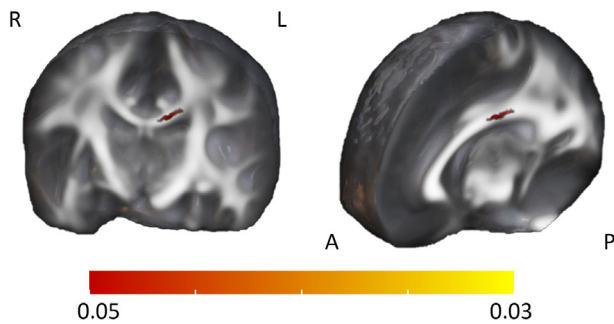


FIGURE 3 Effect of the age on fractional anisotropy (FA) with tract-based spatial statistics (TBSS) around the age of 5 years. Positive correlation between age and FA of corpus callosum is detected. TFCE (threshold-free cluster enhancement) correction applied, 5000 permutations, $p < .05$ (red-yellow colour bar showing p value), age as a covariate. P, posterior; A, anterior; R, right; L, left.

3.2.2 | Five-year-olds

Within our age range of 5.1–5.8 years, the age was positively correlated with FA values in the body of corpus callosum (BCC) (Figure 3). After controlling for maternal pre-pregnancy BMI, maternal age, SES, and exposure to tobacco smoking during pregnancy, the result did not remain significant (TFCE corrected $p < .06$, with which also an additional cluster in left frontal area was observed; See Figure S2). When examined separately, no significant age-effects were found in males, and in females the effect in BCC did not reach statistical significance ($p = .08$).

3.3 | Lateralization

3.3.1 | Infants

Lateralization of brain WM was detected in infants in multiple tracts. Leftward lateralized WM regions are depicted in Figure 4 (TFCE corrected $p < .01$; results with $p < .05$ in Figure S3). Sex was not observed to affect the lateralization pattern.

3.3.2 | Five-year-olds

The WM structure was highly lateralized at the age of 5 years (Figure 5). Statistically significantly higher FA values in left-sided tracts were detected in multiple areas (e.g. frontal and temporal areas and in mid-brain; TFCE corrected $p < .001$ in Figure 5 and with $p < .05$ in Figure S4). The mean image of lateralization pattern (Figures S5 and S6) indicating the magnitude and direction (left/rightward) of the hemispheric asymmetry of FA values also shows rightward lateralized regions, for example, in the anterior limb of internal capsule (ALIC) and antero-lateral corpus callosum. Leftward asymmetry was detected, for example, in cingulate, inferior fronto-occipital fasciculus, posterior corpus callosum, fronto-parietal region, and midbrain. In

most of the WM tracts, both leftward and rightward lateralized subregions were observed. Inter-subject variation of FA asymmetry was detected to be emphasized to peripheral WM tract regions (Figure S7 shows the SD of lateralization pattern). Tract-wise lateralized FA (left–right) and effect sizes for the differences between whole tract mean FA values are provided in Table S4. Statistically significant differences in the asymmetry pattern were not observed between females and males (Figure S8 shows sex-specific left–right lateralization patterns).

Differences in left–right lateralization of WM tracts between infants and 5-year-olds was compared in subset of 22 subjects included in both age groups (Figure 6). The detected asymmetries were more distinct in 5-year-olds, and the direction of asymmetry did not remain similar in all tracts from birth to the age of 5 years. Leftward asymmetries were detected in both age groups in superior longitudinal fasciculus (SLF), cingulum (CING), and cingulate (CG) and rightward asymmetry, for example, in the ALIC. However, the initial rightward asymmetry of posterior limb of internal capsule (PLIC), corticospinal tracts (CST), and inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (ILF/IFOF), was revealed to shift to leftward laterality. A similar pattern was detected when repeating the comparison with entire subpopulations of infants ($N = 166$) and 5-year-olds ($N = 144$). In the group of 22 that were included in both the infant cohort and the 5-year-olds, the difference between lateralized FA in infants and 5-year-olds were statistically significant ($p < .002$) for CST, PLIC, anterior corona radiata and CG. Mean FA values of each tract in infants and in 5-year-olds are provided in Table S5.

4 | DISCUSSION

We found widespread sex differences in white matter FA values in our sample of healthy, typically developing ca. 5-year-olds. Females had higher FA in all areas with significant differences, which were widely scattered throughout WM tracts. Sex differences were not detected in infants. Additionally, significant hemispheric asymmetries of FA values were observed in multiple WM tracts both in infants and at the age of 5 years. Hemispheric lateralization pattern was detected not to stay stable from birth to the age of 5 years. Lastly, age was positively associated with FA values during 6th year of life in mid-posterior part of the corpus callosum.

Sex differences in WM tract structure were expected based on prior studies (Table 1). The previous literature on sex difference during development is, however, inconclusive, as the age ranges, methods and results vary widely between studies. In part of prior studies, no sex differences were observed (Eluvathingal et al., 2007; Muetzel et al., 2008; Uda et al., 2015), and in longitudinal developmental studies the observed sex differences have argued to be minor (Bonekamp et al., 2007; Lebel et al., 2008). In the current study, the differences were significantly wider than previously described, and higher FA in females was observed in all regions with differences. The result highlights the sexual dimorphism in brain structure during development with significant detectable differences in multiple regions at the age

FIGURE 4 Lateralization pattern of white matter tract fractional anisotropy (FA) with tract-based spatial statistics (TBSS) in infants. Significant regions with leftward asymmetry in blue. Threshold-free cluster enhancement (TFCE) correction applied, 5000 permutations, $p < .01$ (blue colour bar showing p value). Tracts are marked with white circles. Additionally, left–right difference (left minus right, negative values denote rightward asymmetry) of FA in uncinate (UNC), anterior limb of internal capsule (ALIC), posterior limb of internal capsule (PLIC), thalamic radiation/optic tract (PTR/OR), posterior and superior corona radiata (PCR and SCR), and the statistical significance with one-sample t test and effect sizes. R, right; L, left; A, anterior; P, posterior.

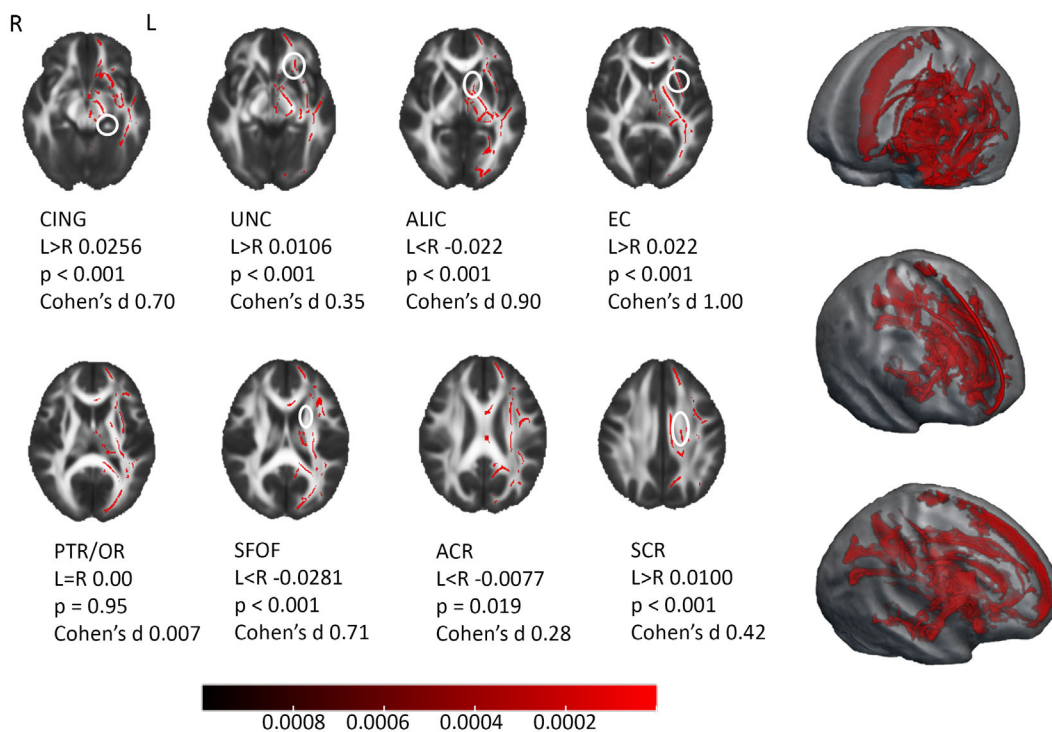
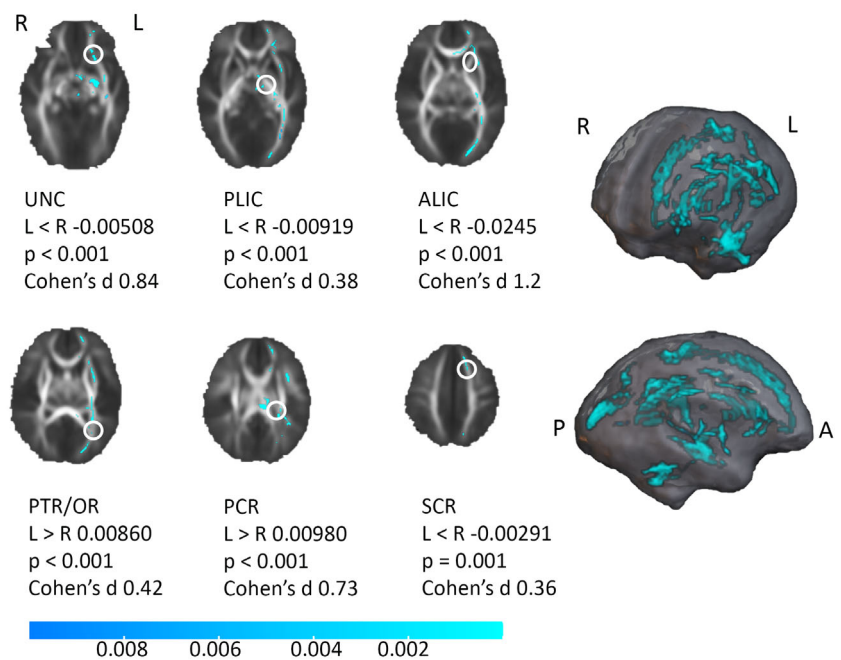


FIGURE 5 Lateralization pattern of white matter (WM) tract fractional anisotropy (FA) with tract-based spatial statistics (TBSS) around the age of 5 years. Significant regions with leftward asymmetry in red, threshold-free cluster enhancement (TFCE) correction applied, 5000 permutations, $p < .001$ (red colour bar showing p value). Specified tracts are marked with white circles. Additionally, left–right difference (left minus right, negative values denote rightward asymmetry) of FA in cingulum (CING), uncinate (UNC), anterior limb of internal capsule (ALIC), external capsule (EC), posterior thalamic radiation/optic tract (PTR/OR), superior fronto-occipital fasciculus (SFOF), anterior and superior corona radiata (ACR and SCR), and the statistical significance with one-sample t test and effect sizes. R, right; L, left.

of 5 years. Instead of tract-specific differences detected in a part of previous studies, we detected FA values to be higher in females across all brain regions. One possible explanation for varying results in

prior literature may be the transient dynamics of sex differences. In studies reporting higher FA values in specified tracts in males (Asato et al., 2010; Clayden et al., 2012; Wang et al., 2012) the age ranges

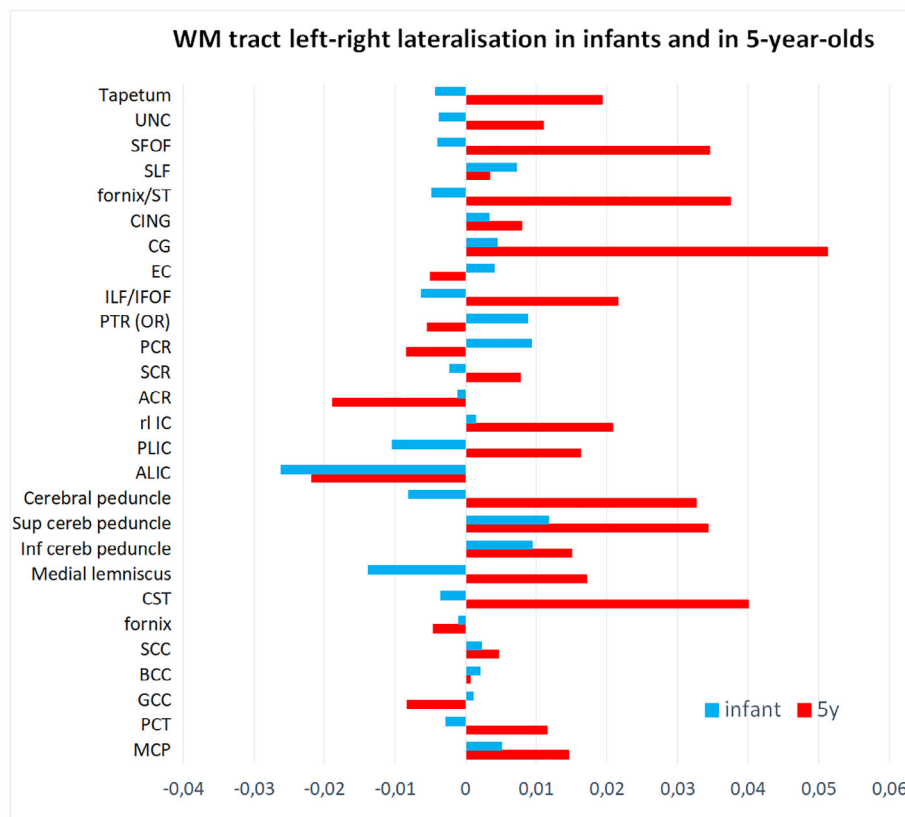


FIGURE 6 Left-right asymmetries of white matter (WM) tract fractional anisotropy (FA) values in infants and in 5-year-olds, measured from left–right tract-based spatial statistics (TBSS) skeleton by extracting with JHU-ICBM Atlas. Subpopulation of 22 subjects with MR scanning both at 2–5 weeks after birth and at age of 5 years. Positive values denote for leftward and negative values for rightward asymmetry. UNC, uncinata; SFOF, superior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; ST, stria terminalis; CING, cingulum; CG, cingulate; EC, external capsule; ILF/IFOF, inferior longitudinal fasciculus/inferior fronto-occipital fasciculus; PTR (OR), posterior thalamic radiation (optic tract); PCR, posterior corona radiata; SCR, superior corona radiata; ACR, anterior corona radiata; rl IC, retrolenticular internal capsule; PLIC, posterior limb of internal capsule; ALIC, anterior limb of internal capsule; sup, superior; inf, inferior; cereb, cerebellar; CST, corticospinal tract; SCC, splenium of corpus callosum; BCC, body of corpus callosum; GCC, genu of corpus callosum; PCT, pontine crossing tract; MCP, middle cerebellar peduncle.

are also higher (from 8 years onwards). The WM development of males has been shown to proceed later but also with steeper rates achieving and, in part of tracts, outpacing females (Reynolds et al., 2019). A large cohort of 9–65-year-old subjects also showed sex differences to diminish with age (Seitz et al., 2021), further explaining why differences might not have been observed in older samples. Widespread sex differences observed in our 5-year-old population were emphasized to the posterior and temporal parts of the brain and were statistically more significant in the right hemisphere. These results agree with the prior studies showing both earlier brain development in females (Asato et al., 2010; Barnea-Goraly et al., 2005; Bava et al., 2011; Seunarine et al., 2016; Simmonds et al., 2014; Wang et al., 2012) and developmental pattern of maturation progressing in posterior-to-anterior direction. Our result of higher FA in females in widespread regions provides new insight into the timing of sex-dependent WM development trajectories and implies that at the age of 5 years the WM integrity is higher in females.

Hemispheric asymmetries of WM microstructure appear early (Song et al., 2015) and are also suggested to remain stable throughout the brain development (Stephens et al., 2020; Takao, Hayashi, & Ohtomo, 2011). However, asymmetries in WM of healthy, normally

developing children are not inspected carefully across whole WM, even though alterations of asymmetry is associated with different conditions such as dyslexia (Banfi et al., 2019). Knowledge of normal variation in asymmetric WM features is an important prerequisite for making conclusions from alterations in asymmetry. One recent study by Stephens et al. has shown significant asymmetry in all WM regions inspected (arcuate, cingulum, uncinata, IFOF, ILF, SLF and SCC) during the first 6 years of life (Stephens et al., 2020). Other studies on WM asymmetries in pediatric populations have mainly focused on age groups over 5 years of age, the sample sizes have remained quite modest and mainly leftward laterality in limited WM tracts has been observed (Bonekamp et al., 2007; Eluvathingal et al., 2007; Snook et al., 2005; Verhoeven et al., 2010; Wilde et al., 2009). Our findings further consolidate the emergence of hemispheric asymmetries during WM development. Lateralization patterns were detected already during neonatal ages, but also changes in asymmetric WM structure were detected between birth and the age of 5 years. The pattern of 5-year-olds resembled considerably the WM asymmetry detected in adult population. We compared our results with two prior adult-population studies (Figure S9), a TBSS study by Takao, Hayashi, & Ohtomo (2011) and a Fixel-Based Analysis (FBA) study by Honnedevassthana

Arun et al. (2020). However, according to our results, some alterations in asymmetric pattern seem to occur between neonatal period and the age of 5 years. In comparison to prior longitudinal study of 0–6-year-olds (Stephens et al., 2020), in which the lateralization was measured based on mean DTI indices of each tract, we also detected variation in asymmetry within the tracts. Mainly leftward lateralization of CG was repeated in our population, however, the asymmetries of certain WM tracts varied between infants and 5-year-olds suggesting further development of the lateralization pattern during first years of life. Similarly, as in prior adult-studies (Honnedeavasthana Arun et al., 2020; Takao, Abe, et al., 2011), we did not find association between the lateralization pattern and sex. Taken together, these findings highlight the role of asymmetry in fundamental structure of WM and underline the importance of early childhood as an essential period in the appearance of diverging lateralization patterns that may contribute to variation in cognitive measures and executive functions (Yin et al., 2013), language development (O'Muircheartaigh et al., 2013) and to predisposition to diseases such as ADHD (Yin et al., 2013) and autism (Carper et al., 2016; Liu et al., 2019).

Age from birth and gestational age were expectedly detected to correlate positively with FA values. Gestational age showed stronger correlation with FA after controlling for the age from birth, which is plausible given the extensive WM development and partial myelination already in utero. When inspected separately, age after birth showed significant positive association with FA in males but not in females. The result may partly stem from different sample sizes (89 males vs. 77 females) and is addressed for future longitudinal studies with more optimal data for observing developmental changes. Also, significant positive correlation between the age and FA of BCC was detected even in a narrow age range between 5.1 and 5.8 years. The posterior BCC and the isthmus of CC contain the primary somatosensory and motor fibres (Fabri et al., 2014), and the finding of rapid increase in the integrity in this area at the age of 5 years may be related to, e.g. the concurrent development of motor skills and bimanual movements (Grohs et al., 2018; Johansen-Berg et al., 2007). Previously, higher initial FA values of callosal fibres have been associated with lower increase rates after the age of 2 years compared to for example association tracts (Reynolds et al., 2019). One explanatory factor for detecting distinct age-effect in our data specifically in the CC might be the highly uniform organization of callosal fibres rendering the area susceptible for finding group differences if they exist.

The current study has also some limitations. The sample size is acknowledged to be modest, and the results need to be repeated in larger population and in other ethnic groups. As there were only 22 subjects included in both subpopulations, and the MR scanner was updated between imaging, the study setting is not technically longitudinal, but the subpopulations are considered as separate groups.

5 | CONCLUSIONS

Rapid increase of the WM integrity, that is, increase in FA values, occurs during the first 5 years of life. At that developmental timing, broad sex differences in WM structure are observed: higher FA and thus

presumably more advanced development is detected in multiple regions in females compared to males. Additionally, the WM structure is widely lateralized during early development, and at the age of 5 years the lateralization pattern resembles considerably the ones previously described in adult studies, which has clear differences to those observed in infants.

AUTHOR CONTRIBUTIONS

Venla Kumpulainen: data collection (5-year-olds), data pre-processing, formal analyses, writing the manuscript draft. **Harri Merisaari:** designing data processing pipeline, writing the manuscript. **Elmo P. Pulli, Anni Copeland, Eero Silver:** data collection (5-year-olds), writing the manuscript. **John D. Lewis and Jani Saunavaara:** designing the MR acquisition protocol, writing the manuscript. **Satu J. Shulist:** data collection (infants), writing the manuscript. **Riitta Parkkola:** radiological evaluation of the MR images, writing the manuscript. **Tuire Lähdesmäki:** neurological evaluation of the infants, writing the manuscript. **Linnea Karlsson and Hasse Karlsson:** establishing the cohort, building infrastructure for carrying out the study, writing the manuscript. **Jetro J. Tuulari:** study conception, funding acquisition, supervision of **Venla Kumpulainen**, building the pre-processing pipelines.

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DATA AVAILABILITY STATEMENT

The Finnish law and ethical permissions do not allow open sharing of the data used in this study, but data access is possible via formal material transfer agreements (MTA). Investigators that wish to access the data are encouraged to contact Principal Investigator of the Finn-Brain Birth Cohort study Hasse Karlsson (hasse.karlsson@utu.fi).

ETHICS STATEMENT

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland ([07.08.2018] §330, ETMK: 31/180/2011), and performed in accordance with the Declaration of Helsinki.

INFORMED CONSENT

Both parents of the participating child signed a written informed consent form. The child assent was assured prior to neuroimaging visits.

DECLARATIONS OF INTEREST

None.

ORCID

Venla Kumpulainen  <https://orcid.org/0000-0003-3375-5445>Harri Merisaari  <https://orcid.org/0000-0002-8515-5399>Elmo P. Pulli  <https://orcid.org/0000-0003-3871-8563>

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