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Lassi Björnholm

EARLY PREDICTORS OF WHITE MATTER MICROSTRUCTURE IN THE ADULT BRAIN

UNIVERSITY OF OULU GRADUATE SCHOOL;
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FACULTY OF MEDICINE;
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Abstract

The foundations for the brain's structural organisation are laid already during prenatal life. External and internal signals interact to guide brain development in axonal growth, myelination and pruning, but also seem to programme long-term epigenetic effects which may only appear later in life. Altered neurodevelopment has been linked with psychiatric conditions and other states of compromised health. This work focuses on white matter, a brain structure that has received relatively little attention in research on typical and altered neurodevelopment. White matter constitutes about half of the human brain's volume, and its axonal pathways provide conduction and modulation of signals across brain regions. The variation in the structural features of white matter in association with early-life factors is, however, far from resolved.

This work studies associations between prenatal factors and brain white matter structural features from childhood to early adulthood. White matter structural correlates of sex, prenatal maternal BMI and cigarette smoking are studied in five cohort samples from different countries. Statistical models are adjusted for important prenatal and later-life covariates. The structural features of main white matter tracts, including the corpus callosum (CC), are studied using mutually complementary metrics of multimodal brain magnetic resonance imaging (MRI).

The findings in the CC showed, first, a correlation between MRI relaxometry measures and small-calibre axons and second, sexual dimorphism in microstructural features in the midsagittal CC. Prenatal maternal BMI and cigarette smoking were observed to be associated with structural alterations of white matter tracts in adolescence and early adulthood, but with inconclusive replication across cohorts at different ages. These findings indicate that early-life factors are associated with alterations of white matter structure in offspring during the first decades of life, and thus pinpoint the importance of health support during pregnancy. The findings also emphasise the importance of considering participant age as well as prenatal and later-life covariates when planning research. Future research would benefit from longitudinal and genetically informed study designs.

Keywords: adolescent, birth cohort, corpus callosum, diffusion tensor imaging, microstructure, myelin, white matter, young adult

Björnholm, Lassi, Aikuisen aivojen valkoisen aineen mikrorakenteen ennustavat tekijät.

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Tiivistelmä

Aivojen rakenteen kehityskulut alkavat hahmottua jo ennen syntymää. Ulkoisten ja sisäisten tekijöiden vuorovaikutus ohjaa hermosyiden kasvua, myelinisaatiota ja hermoyhteyksien karsiutumista, mutta näyttöä on myös pitkäaikaisista vaikutuksista perimän luentaan, jolloin vaikutukset saattavat olla havaittavissa vasta myöhemmin elämässä. Hermoston kehityksellisten poikkeavuuksien on havaittu liittyvän psykiatrisiin sairauksiin ja muihin epäedullisiin terveydentiloihin. Tämän työn kohteena on aivojen valkoinen aine, jonka poikkeavan ja normaalin kehityksen piirteisiin on aiemmin kohdistunut verrattain niukasti tutkimusta. Valkoinen aine kattaa noin puolet ihmisen aivojen tilavuudesta, ja sen aksoniyhteydet välittävät ja muokkaavat aivoalueiden välisiä viestejä. Valkoisen aineen rakenteen yhteydet varhaisiin ennustaviin tekijöihin vaativat kuitenkin lisää tutkimusta.

Työssä tutkitaan raskaudenaikaisten tekijöiden yhteyksiä aivojen valkoisen aineen rakenteeseen lapsuudesta nuoreen aikuisuuteen. Valkoisen aineen ominaisuuksia suhteessa sukupuoleen sekä äidin raskaudenaikaiseen painoindeksiin ja tupakointiin tutkitaan hyödyntäen viittä erimaalaista kohorttia. Tilastollisissa malleissa huomioidaan useita raskaudenaikaisia ja myöhempiä sekoittavia muuttujia. Valkoisen aineen ratojen, mukaan lukien aivokurkiaisen (*corpus callosum*), rakenteellisia piirteitä tutkitaan toisiaan täydentävillä magneettikuvantamisen menetelmillä.

Tutkimuksessa havaittiin, että tutkitussa osassa aivokurkiaista magneettikuvantamisen relaksaatioajat ovat yhteydessä ohuiden hermosyiden tiheyteen ja että miesten ja naisten välillä on huomattavia eroja aivokurkiaisen valkoisen aineen mikrorakenteessa. Äidin raskaudenaikaisen painoindeksin ja tupakoinnin osoitettiin olevan yhteydessä lapsen valkoisen aineen ratojen rakenteen poikkeavuuksiin nuoruusiässä ja varhaisessa aikuisuudessa, mutta tulos ei ollut täysin toistettavissa eri-ikäisillä henkilöillä. Tulokset osoittavat, että varhaiset tekijät ovat yhteydessä valkoisen aineen rakenteen ominaisuuksiin elämän ensimmäisten vuosikymmenten aikana, ja tukevat näin raskaudenaikaisen terveystyön merkitystä. Tulokset myös korostavat tutkittavien iän sekä raskaudenaikaisten ja myöhempien tekijöiden huomioinnin tärkeyttä tutkimusta suunniteltaessa. Tulevat tutkimukset hyötyisivät pitkittäisestä sekä yksilöiden sukulaisuusuhteita hyödyntävästä tutkimusasetelmasta.

Asiasanat: aivokurkiainen, diffuusiotensorikuvantaminen, mikrorakenne, myeliini, nuoret, nuoret aikuiset, syntymäkohortti, valkoinen aine

To my family

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Oulu, March 2022 Lassi Björnholm

Abbreviations

ADC	Apparent diffusion coefficient
ADHD	Attention deficit hyperactivity disorder
ALSPAC	Avon Longitudinal Study of Parents and Children
B1	Radiofrequency field in magnetic resonance imaging
BEDPOSTX	Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques including modelling Crossing Fibres
BMI	Body mass index
CC	Corpus callosum
DTI	Diffusion tensor imaging
dwMRI	Diffusion-weighted magnetic resonance imaging
EPI	Echo-planar imaging
FA	Fractional anisotropy
FSL	Functional magnetic resonance imaging of the brain Software Library
GM	Grey matter
IQ	Intelligence quotient
LME	Linear mixed effects
mcDESPOT	Multicomponent-driven equilibrium steady-state observation of T1 and T2
MD	Mean diffusivity
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
MToff	MRI image without magnetisation saturation pulse
MTon	MRI image with magnetisation saturation pulse
MTR	Magnetisation transfer ratio
MWF	Myelin water fraction
NFBC	Northern Finland Birth Cohort
NMR	Nuclear magnetic resonance
PEMCS	Prenatal exposure to maternal cigarette smoking
PVE	Partial volume effect
PREOBE	Role of nutrition and maternal genetics on the programming of development of foetal adipose tissue
R1	Relaxation rate 1
R2	Relaxation rate 2
RD	Radial diffusivity

REKINDLE	Robust extraction of kurtosis indices with linear estimation
RF	Radio frequency
SRY	Sex-determining region Y
SYS	Saguenay Youth Study
T1	Longitudinal relaxation time
T2	Transverse relaxation time
TE	Time of echo
TR	Time of repetition
WM	White matter

List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals I-III:

I Björnholm, L., Nikkinen, J., Kiviniemi, V., Nordström, T., Niemelä, S., Drakesmith, M., Evans, J. C., Pike, G. B., Veijola, J., & Paus, T. (2017). Structural properties of the human corpus callosum: Multimodal assessment and sex differences. *NeuroImage, 152*, 108–118. https://doi.org/10.1016/j.neuroimage.2017.02.056

II Björnholm, L., Nikkinen, J., Kiviniemi, V., T., Niemelä, S., Drakesmith, M., Evans, J. C., Pike, G. B., Richer, L., Pausova, Z., Veijola, J., & Paus, T. (2020). Prenatal exposure to maternal cigarette smoking and structural properties of the human corpus callosum. *NeuroImage, 209*, 116477. https://doi.org/10.1016/j.neuroimage.2019.116477

III Verdejo-Román, J.*, Björnholm, L.*, Muetzel, R. L., Torres-Espínola, F. J., Lieslehto, J., Jaddoe, V., Campos, D., Veijola, J., White, T., Catena, A., Nikkinen, J., Kiviniemi, V., Järvelin, M. R., Tiemeier, H., Campoy, C., Sebert., S., & El Marroun, H. (2019). Maternal prepregnancy body mass index and offspring white matter microstructure: results from three birth cohorts. *International Journal of Obesity, 43*(10), 1995-2006. https://doi.org/10.1038/s41366-018-0268-x

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Contents

1 Introduction

Early-life environment lays the foundations for later health and well-being. The human brain shows a vast potential for plasticity but also great demands for stimulation and support, especially during the vulnerable early phases of brain organisation (Purves et al., 2018). Structural development is guided by numerous intrinsic and extrinsic stimuli; Genomic and environmental factors interact via *developmental cascades* i.e., directed transactions over time and space (Cicchetti, 2016). The biological intermediaries of these cascades are reflected in brain imaging findings in adolescence and early adulthood. The study of early predictors of white matter (WM) structure, including sex and maternal prenatal cigarette smoking and BMI, offers valuable insights into the relationships of different factors and associated structural features in the human brain.

Sex is a most profound predictor of brain structure throughout development, as noted in brain size and microstructural composition, as well as sex-specific developmental timelines (Giedd et al., 2012; Lenroot et al., 2007; Schmithorst et al., 2008). Males and females also differ in their vulnerability to the quality and time of emergence of psychiatric morbidities (Grant & Weissman, 2007). Understanding the sexual dimorphism of the brain is essential for the study of altered and typical brain development, and further research is needed.

The prevalence of smoking during pregnancy remains high at 15% in Finland, and even higher in some other European countries (Euro-Peristat project with SCPE and Eurocat, 2013). Besides the numerous harmful outcomes reported, including reduced birth weight and lower cognitive results of the offspring (D'Onofrio et al., 2003; Ramsay et al., 2016), prenatal exposure to maternal cigarette smoking exposes the foetus to nicotine and other teratogenic substances which have the potential to modulate the development of the nervous system across youth (Slotkin, 1998). Neuroimaging is in a position to study the long-term neural correlates of the exposure, but reports to date remain scarce.

Overweight is a growing health problem, with disadvantageous lifestyles commonly transferred to offspring (Gissler & Kiuru, 2019; Whitaker, 2004). Acting as an inflammatory factor in pregnancy, suboptimal maternal weight may alter child neurodevelopment and affect health in later life. Associations between suboptimal maternal pre-pregnancy weight and offspring's cognitive and motor abilities have been reported (Adane et al., 2016), but alterations in brain structure are poorly understood.

Imaging the structural properties of white matter enables the estimation of the integration of information processing across brain regions. Information is transferred and modulated in axonal processes in white matter, which accounts for about half of brain volume. The corpus callosum (CC) is a major white matter tract connecting the two brain hemispheres. The type of information conveyed between the hemispheres is reflected in the profile of the callosal fibre composition. Extensive earlier literature and histological information enable the correlation of callosal imaging findings with known microstructural features, and thus aid their interpretation in relation to early predictors.

Magnetic resonance imaging (MRI) is a non-invasive method of studying brain structure *in vivo*. It is scalable to large cohorts and, together with genomic, behavioural, and other biological information, can be used to study neural correlates of various factors, as done in the field of *population neuroscience* (Paus, 2013b). Studying brain structure by imaging is challenging because of numerous uncontrolled factors, technical challenges, and the substantial intra- and interindividual variation and indirect nature (or lack of specificity) of imaging measures. The reliability of findings can be enhanced by using large samples, replication, biological models, and hypothesis based on earlier literature. This work describes the analysis and outcomes of three important early predictors of white matter structure in childhood, adolescence, and early adulthood. To answer the study questions, this work focuses on the Northern Finland Birth Cohort 1986 (NFBC1986) and diffusion tensor imaging of the corpus callosum. Further, four large prospective cohort samples with mutually complementary brain imaging data enable the comparison and interpretation of the findings.

2 Early predictors of white matter structure

2.1 Typical development of white matter

At its fastest, 250,000 new neurons are born each minute in the developing nervous system and, apart from a few exceptions, no new neurons emerge after birth. The structure and timeline for this development are orchestrated by the complex interplay of genes and cell-to-cell signalling factors. Cellular origin and neighbouring cells further guide the morphogenesis of cells in the nascent nervous system, which eventually results in the approximately 86 billion neurons and equal amount of glia in the adult brain (Purves et al., 2018).

Early patterns of neuronal connectivity are established during the second trimester by growth cones of pioneering axons, as they probe their way to target cells, guided by extracellular matrix molecules and gradients of attraction and repulsion signals. This process is followed by axonal growth and bundling during the third trimester, giving rise to the early topography of brain connectivity. External stimulus, along with several neurotrophic factors, is necessary for the survival of neurons during critical developmental periods. The loss of redundant synapses and axons, i.e. pruning, works as a major brain morphogenic factor before and, most notably, after birth (Huttenlocher & Bonnier, 1991; Purves et al., 2018).

Selective myelination of WM tracts begins during the second trimester and gradually increases the volume and maturity of the microstructural composition of white matter (Benes, 1989; Poduslo & Jang, 1984; Yakovlev & Lecours, 1967). During the *pre-myelination stage*, oligodendrocyte precursor cells, a species of glia, proliferate and target axons with longitudinal processes that start to wrap around axons. During the following *myelination stage*, an increasing number of layers of myelin spiral around the axon and mature in molecular composition to gradually form the so-called myelin sheath (Baumann & Pham-Dinh, 2001; Poduslo & Jang, 1984).

Earlier postmortem studies have shown that myelination of white matter continues from childhood into adolescence (Benes, 1989; Yakovlev & Lecours, 1967) and further into early adulthood, especially in associative regions (Benes et al., 1994). The process of myelination is asynchronous and advances in the direction from the inferior to superior and posterior to anterior brain regions. More specifically, proximal regions myelinate earlier than distal ones, sensory

earlier than motor, projection earlier than associative and occipital earlier than other cortical regions (Baumann & Pham-Dinh, 2001; Kinney et al., 1988). Because of the low correlation between the sequence of myelination and the corresponding behavioural function, it is possible that myelination provides compensation for signal conduction velocity as the distance between regions increases with brain growth (Salami et al., 2003). It is also hypothesised that the maturational sequence relates to the order of stabilisation of activity first in lower-level regions, which then stimulate higher regions (Guillery, 2005).

The brain weight of a 5-year-old is already 90% of that of an adult (Dekaban, 1978). Modifications in axonal features from childhood to adulthood are, however, poorly characterised. It is suggested that the growth of axon diameter and myelination both continue into early adulthood (Aboitiz et al., 1996; Lassek, 1942; Verhaart, 1950). Information about the trajectories of white matter development during this period has been largely obtained using indirect brain imaging methodology.

2.2 Imaging the development of white matter

The developmental phenomena observed in animal and post-mortem studies have been largely confirmed and elaborated by *in vivo* human imaging studies during the last three decades (Dubois et al., 2014; Lenroot & Giedd, 2006; Paus, 2010a). As a general pattern of maturation from the foetal period to adolescence, a decrease in the absolute T1-weighted and T2-weighted contrasts (i.e. shortening of the relaxation times T1 and T2, respectively) is observed due to a reduction in the proportion of water in the brain tissue (Barkovich et al., 1988; Gilmore et al., 2007; Hassink et al., 1992; Kucharczyk et al., 1994; Steen et al., 1997). The relation of white vs. grey matter intensity, however, changes during the first year of life; first, an *infantile pattern* as a lower intensity of WM relative to GM in T1 contrast is observed until 6 months of age (and *vice versa* for T2). During the *isointense pattern* at 8-12 months, GM and WM are poorly separable, and from approximately 12 months onwards, the *early adult pattern* of higher WM relative to GM intensity in T1 can be observed (Paus et al., 2001).

The shifts in relaxation times are accounted for in part by the myelination, which is highly asynchronous between brain regions, as observed in postmortem (Yakovlev & Lecours, 1967) and MRI studies (Barkovich et al., 1988). The sequence of myelination has been further described as starting from the pons at birth and advancing from the posterior limb of the internal capsule, optic radiation

and splenium of the corpus callosum at 1-3 months to the callosal genu and the anterior limb of the internal capsule at approximately 6 months and finally to the frontal, parietal and occipital lobes at 8-12 months (Paus et al., 2001). Obtained from T1-weighted contrast, the "density" of white matter was observed to correlate with age in the internal capsule and the arcuate fasciculus in participants 4-17 years of age, possibly reflecting variations in iron content, axon diameter or myelination in these fibres (Paus et al., 1999). More specific information about myelination has been obtained using MRI measures of tissue water compartmentalisation, showing patterns comparable to those in postmortem studies (Deoni et al., 2012; O'Muircheartaigh et al., 2014).

The developmental trajectories of brain GM and WM volume have been detailed using structural MRI (Giedd & Rapoport, 2010). The total cerebral volume peaks at 10.5 years in females and 14.5 years in males, with 95% of this volume reached already at age 6 years (Lenroot et al., 2007). The absolute volume of white matter shows a linear increase from childhood to adulthood (Pfefferbaum et al., 1994; Steen et al., 1997), with a 12.4% total increase between 4 and 22 years and little variation across brain lobes (Giedd, Blumenthal, Jeffries, Castellanos et al., 1999). A gradual increase in white matter volume, with large inter-regional variation, has been reported to continue until 40-60 years of age, followed by a decrease into older age (Westlye et al., 2010).

Grey matter (GM) volume peaks at age four years (Pfefferbaum et al., 1994; Steen et al., 1997), followed by a gradual decline until it shows an increase in pre-adolescence and again decrease after adolescence, peaking at different times in different lobes (Giedd et al., 1999; Matsui et al., 2016). The volume of grey matter relative to white matter (GM/WM) is at its highest at the neonatal period and shows a decrease subsequently, reflecting the regionally specific pattern of synaptic pruning (Bourgeois et al., 1994; Dubois et al., 2014; Gilmore et al., 2007; Gogtay et al., 2004; Huttenlocher & Dabholkar, 1997; Steen et al., 1997). Interestingly, the variation in regional grey matter volume does not seem to correspond with the variation of volume or microstructure of the adjacent white matter during adolescence (Giedd et al., 1999; Tamnes et al., 2010), although local associations have been reported (Giorgio et al., 2008).

The rapid developmental changes of white matter microstructure in infancy can be further characterised using diffusion-weighted MRI (Dubois et al., 2006; Dubois et al., 2014; Mukherjee et al., 2001). The decrease in mean diffusivity (MD) and increase in fractional anisotropy (FA) throughout maturation is accounted for by the reduction in tissue water content, increased tissue packing

and reduced permeability of membranes (Hüppi et al., 1998), but also more intricate features such as the appearance of the early oligodendroglial processes (Nossin-Manor et al., 2013). These changes result primarily in a decrease in transverse, or "radial", diffusivity (RD) and a corresponding increase in FA (Dubois et al., 2008), even in the absence of myelin (Beaulieu, 2002). Later studies of early development have utilised advanced tractography methodology in the postmortem foetal brain, investigating the early patterns of cellular migration in WM (Kolasinski et al., 2013; Xu et al., 2012) and the developmental timeline of the emergence of the early axonal bundles during the second and third trimester (Huang et al., 2009; Takahashi et al., 2011).

Diffusion measures have also been used to characterise the development of WM microstructure in childhood and adolescence and, especially, its prolonged development into adulthood (Geeraert et al., 2019; Hüppi & Dubois, 2006). The timeline and magnitude of the overall maturational pattern, including the increase in FA and decrease in mean, radial and parallel diffusivity, have been reported to be specific for each white matter tract. Longitudinal and cross-sectional studies in wide age ranges have shown associations between age and diffusion measures in the cerebrospinal tract, the internal capsule, the superior and inferior longitudinal fasciculus, the arcuate fasciculus, the body of the corpus callosum and the cingulum, the order of which agrees with the sequence of myelination observed in postmortem studies (Faria et al., 2010; Giorgio et al., 2008; Lebel et al., 2008; Lebel & Beaulieu, 2011; Schmithorst et al., 2002). The same amount of increase in FA can be observed during 3-19 weeks after birth as between 5 and 30 years of age (Geeraert et al., 2019). A relative plateau in the FA of white matter tracts is reached around 24 to 33 years of age (Westlye et al., 2010), with the associative and limbic regions peaking last (Lebel et al., 2008; Lebel & Beaulieu, 2011). While the underlying changes in tissue microstructure are largely unspecified, modern diffusion measures suggest a widespread increase in fibre diameter and a regional increase in fibre density in early adolescence (Genc, Smith et al., 2018).

Changes in white matter volume are poorly reflected in markers of microstructure, for example myelination in infancy (Dai et al., 2018), adolescence (Lebel et al., 2008; Lebel & Beaulieu, 2011), and adulthood (Westlye et al., 2010). Furthermore, the age-dependent microstructural changes observed in diffusion measures were not accounted for by the magnetisation transfer ratio (MTR), a putative marker of myelin, during childhood and adolescence (Moura et al., 2016). In addition, the relationship between behavioural development and brain structural markers is generally weak (Dubois et al., 2014). Variation in

different microstructural measures is dependent on numerous factors, including brain region, age and sex, with differing contributions of tissue characteristics, for example, myelin, axon diameter and density (Paus, 2010a; Perrin et al., 2008; Perrin et al., 2009). Increasing the specificity of imaging measures and the use of a longitudinal study design can progress the interpretation of neuroimaging findings and have been shown to support and particulate earlier views (Genc et al., 2018).

2.3 Development of corpus callosum

Theories of callosal development have been of great interest from the early anatomists to modern neuroscience (Caminiti et al., 2013; Giedd, Rumsey et al., 1996; Innocenti, 1986; Rakic & Yakovlev, 1968). Pioneering callosal axons cross the interhemispheric junction during the early second trimester of pregnancy (Judaš et al., 2005; Radoš et al., 2006), guided by the glial wedge (Shu & Richards, 2001; Silver et al., 1982) and migratory neurons (Niquille et al., 2009; Shu et al., 2003). Axonal growth in the callosum occurs in the cranio-caudal direction between 11-20-weeks' post-conception (Griffiths et al., 2009). The following axonal bundling, or "fasciculation", is guided by axon-axon interaction via cell adhesion molecules (Purves et al., 2018; Zhou et al., 2013).

The number of callosal axons is believed to be at a maximum near birth, preceding a gradual pruning during the first two postnatal months (Innocenti & Price, 2005; Kostović & Jovanov-Milošević, 2006). In the monkey, a total of 70% of callosal axons are lost during the first four postnatal months (LaMantia & Rakic, 1990). Regardless of axonal pruning, a growth spurt in volume occurs in the genu during the second and in the splenium between the fourth and sixth postnatal months in humans (Barkovich & Kjos, 1988). Most overall callosal growth takes place before two to three years of age (Garel et al., 2011; Tanaka-Arakawa et al., 2015). During this period, myelination of callosal axons follows a posterior-to-anterior profile, in that the myelination of the splenium and body at four months precedes that of the genu and rostrum at six months postnatally (Barkovich & Kjos, 1988; Kinney et al., 1988). Fractional anisotropy and T2-weighted signal intensity reach relative stability during the first three years of life in the callosum (Hermoye et al., 2006). The adult-like pattern of higher FA, higher T1-weighted and lower T2-weighted signal intensity in the splenium compared to other callosal regions is already present in neonates (Gilmore et al., 2007) and children (Hasan et al., 2008).

Following infancy, mainly an increase in the proportion of large, myelinated axons is believed to take place until adulthood, as noted in post-mortem histology (Aboitiz et al., 1996). During childhood and adolescence, regions of the posterior corpus callosum have been shown to exhibit the most prominent growth in imaging studies (Giedd et al., 1996; Giedd, Blumenthal, Jeffries, Rajapakse et al., 1999), although the finding was not confirmed using different methodology (Garel et al., 2011; Thompson et al., 2000). Advanced diffusion measures suggest an increase in fibre density throughout the corpus callosum and especially in the posterior body (Genc, Malpas et al., 2018). While noting the regional variation, the overall callosal growth has been shown to be nonlinear and follow a gradual increase until the mid-20s (Allen et al., 1991; Hasan et al., 2008; Pujol et al., 1993). Studies in adults have shown an inverted U-shaped profile of callosal FA and volume, similar to that of total white matter volume, peaking at approximately 40 years of age (Allen et al., 1991; Hasan et al., 2008).

2.4 Sex differences in white matter structure

The masculinising transcription factor *sex-determining region Y* (SRY) determines an individual's genetic sex on conception. Consequently, a surge of testosterone during the second trimester of pregnancy masculinises the male brain, influencing neurotransmitter function in a region-specific manner. Hypothalamic nuclei are a key area for sexual dimorphism, most likely because of their supportive role in reproductive behaviours (Byne et al., 2000; Purves et al., 2018). Gonadal steroid hormones regulate neuron survival through apoptosis but also impact neuron morphology and activity (Grön et al., 2000). During adolescence, sex hormones further guide the sex specific morphogenesis of white matter, including myelination (Juraska et al., 2013). The sex hormone function, together with genetic and environmental modulators, guides the differential development of white matter volume and microstructure in males and females (Clark et al., 1988; Giedd et al., 1999; Paus et al., 2001; Paus et al., 2010; Paus, 2010b).

The brain regions with strongest structural sexual dimorphism have been shown to overlap with sex hormone receptor density (Goldstein et al., 2001). This is reflected, for instance, in the high density of androgen and oestrogen receptors in the amygdala and hippocampus, respectively, and the congruent sex-specific increase in the volumes of these structures during adolescence (Clark et al., 1988; Giedd, Vaituzis et al., 1996; Morse et al., 1986). The modulating effect of

androgen receptor phenotype on the association of testosterone level and white matter volume was evaluated in a large cross-sectional study of adolescents of 13-18 years. A functional polymorphism in the androgen receptor gene, modulating the effect of testosterone, was associated with WM volume in males: Blood testosterone level explained 26% and 8% of the variance in WM volume in the high and low transcriptional activity groups, respectively (Perrin et al., 2008).

Larger axonal diameter in the developing male WM was suggested to account for the observed decrease in T1w and MTR intensities and increase in WM volume. Increase in T1w and MTR contrasts in females, with little change in WM volume, was inferred to account for myelination in female WM during adolescence (Hervé et al., 2009; Pangelinan et al., 2016; Perrin et al., 2008; Perrin et al., 2009). Based on these findings, it was suggested that the fast growth of axon diameter, induced by testosterone, outpaces the rate of myelination in adolescence in males (Paus & Toro, 2009; Paus, 2010a).

Grey matter and white matter volumes are already larger in males compared to females at birth (Gilmore et al., 2007) and the difference increases throughout childhood and adolescence (Giedd et al., 1999; Lenroot et al., 2007). While GM volume follows an inverted U-shaped profile, peaking one to two years earlier in females, the profile of WM volume shows an increase from childhood to early adulthood in both sexes. It has also been reported that GM and WM volumes and the callosal midsagittal area increase more steeply in males during adolescence (De Bellis et al., 2001; Giedd et al., 1999; Lenroot et al., 2007). In adulthood, females show higher GM volume relative to total brain volume (Lenroot et al., 2007; Lüders et al., 2002). The adult male brain, again, is approximately 8–10% larger (Goldstein et al., 2001), contains more WM relative to GM, and exhibits a larger callosal midsagittal area (Westerhausen et al., 2004).

The schedule of maturation of individual white matter tracts is different for males and females across youth. Maturation takes place in most main tracts by adolescence in females and by early adulthood in males, as reflected in the decrease in radial diffusivity (Asato et al., 2010). In adolescence, higher FA has been reported in males in the frontal lobes, while higher MD was reported bilaterally in the corticospinal tract. In females, higher MD was reported in multiple regions of the right hemisphere. The finding is, however, likely transient, because of the decreasing MD and increasing FA in these regions between 5–18 years in females. Correspondingly, FA seems to increase in males in the left inferior frontal gyrus during adolescence (Schmithorst et al., 2008). In young adulthood, sex differences have been observed in various white matter regions

(Chou et al., 2011) of which only some have been replicated, including the higher FA in males in the cingulum (Huster et al., 2009; Menzler et al., 2011).

Findings of sex differences in the corpus callosum are conflicting and seem to vary by age. Although higher FA was observed in the splenium in females at 5–18 years, the values of FA in the splenium in males were shown to increase faster during this age, possibly indicating later organisation of the posterior callosum in males (Schmithorst et al., 2008). In young adulthood, higher FA was observed in the genu in males (Westerhausen et al., 2011), whereas a contrary finding of higher FA in this region in females was reported in another study (Kanaan et al., 2014). Conflicting findings have also been reported in the callosal body, with higher FA in males compared to females (Menzler et al., 2011) and in females compared to males (Chou et al., 2011). Higher FA was also reported in all callosal segments in males (Shin et al., 2005). Similarly, a study using diffusion tractography reported higher callosal mean FA in males, while some fibres in the genu, isthmus, and splenium showed higher FA in females (Oh et al., 2007).

Earlier studies provide conflicting results likely due to limited sample sizes, variation in methodology, variation in region of interest (e.g., parasagittal vs. midsagittal CC), and wide distribution of age of participants in each study. The findings, however, suggest that callosal sex differences exist and that they vary by age, as demonstrated by the finding of higher FA in the splenium in females compared to males, observable only after adding older individuals to the study sample (Kanaan et al., 2014). Findings of sex differences are also easily confounded by the partial volume effect due to differences in brain size. The male brain contains a larger volume of WM and 16% more axonal length (Marner et al., 2003), suggesting that the volume occupied by crossing tracts is relatively smaller, which likely manifests as higher mean FA in males (Takao et al., 2013).

2.5 Prenatal exposure to maternal cigarette smoking and white matter structure

External and internal disruptions to inductive signalling alter the timing and location of early developmental events. Among the most notable, insufficiency of folic acid and excess of retinoic acid are known to lead to neural tube defects. Besides these relatively well-known factors, a multitude of early external exposures can modify developmental trajectories well into adult life and senescence (Slotkin, 1998). Cigarette smoking is one of the most prevalent harmful prenatal factors in industrialised countries (Lange et al., 2018). In

Finland, about 15% of pregnant women smoke cigarettes, while the prevalence in some European countries has been reported to be over 30% (Euro-Peristat project with SCPE and Eurocat, 2013).

Prenatal exposure to maternal cigarette smoking (PEMCS) predisposes the developing offspring to numerous teratogenic substances, including nicotine (Dempsey & Benowitz, 2001; Jauniaux et al., 1999; Luck et al., 1985). The ill-effects of PEMCS have been characterised as pertaining to hypoxia, induced by altered placental morphology and circulation (Albuquerque et al., 2004; Bush et al., 2000) and disrupted neurodevelopment (Slotkin, Orband-Miller et al., 1987; Slotkin, 1998). The effects of nicotine on the developing nervous system are particularly momentous because of the early emergence of nicotinic receptors in the developing nervous system (Atluri et al., 2001; Falk et al., 2005). The actions of nicotine are analogous to acetylcholine, a major neuromodulator during development, but with improper timing and scale (Slotkin, 1998). Nicotine has been shown to alter cell proliferation and differentiation (McFarland et al., 1991; Slotkin et al., 1986; Slotkin et al., 1987) and disrupt axonal pathfinding (Pugh & Berg, 1994; Zheng et al., 1994), development of cholinergic and catecholaminergic systems (Navarro, Seidler, Eylers et al., 1989; Oliff & Gallardo, 1999; Slotkin, Cho et al., 1987), and the developmental functions of sex hormones (Lichtensteiger & Schlumpf, 1985; Sarasin et al., 2003). The effects also seem to persist after birth (Ajarem & Ahmad, 1998; Roy & Sabherwal, 1994; Slotkin et al., 1986) or only emerge later in development, possibly due to altered genetic programming (Cao et al., 2013; Yochum et al., 2014).

Maternal cigarette smoking during pregnancy has been associated with various foetal and postnatal outcomes in offspring, including reduced birth weight (D'Onofrio et al., 2003) and head circumference (Källén, 2000). Associations with later outcomes in offspring include overweight (Albers et al., 2018), lower cognitive scores (Fried, 1995; Ramsay et al., 2016), and many psychiatric disorders, e.g. criminality (Räsänen et al., 1999), schizophrenia (Niemelä et al., 2016), and conduct disorder (Fergusson et al., 1998; Weissman et al., 1999). Outcomes are, however, difficult to attribute specifically to PEMCS because of the various unmeasured genetic and environmental factors that have been shown to better explain some of the observations (D'Onofrio et al., 2003; Quinn et al., 2017). For instance, inherited and family factors, rather than direct effects of PEMCS, have been shown to account for the emergence of attention deficit hyperactivity disorder (ADHD) in exposed individuals (D'Onofrio et al., 2008; Gustavson et al., 2017). Overall, the moderation of smoking-related findings by

socio-economic factors is a substantial confound which should be controlled in a study design by matching or controlling for relevant covariates, for example, using extensive birth cohort data (Heikura et al., 2008), or by applying genetically informed designs (D'Onofrio et al., 2008; Quinn et al., 2017).

Studies of the association between PEMCS and offspring brain outcomes are scarce and centre on childhood and adolescence. Earlier work associates the exposure to reduced head growth during the foetal period (Roza et al., 2007), lower cerebellar and frontal lobe volumes in preterm new-borns (Ekblad et al., 2010), smaller cortical grey-matter and total brain volumes in school-aged children (El Marroun et al., 2014), a thinner orbitofrontal cortex (Toro et al., 2008), and a smaller cross-sectional area of the corpus callosum in adolescence (Paus et al., 2008). Associations have also been reported in microstructural measures as higher (Jacobsen et al., 2007) and lower (Liu et al., 2011) fractional anisotropy in the corpus callosum in adolescence, albeit the two studies were restricted by small sample size.

2.6 Maternal prenatal BMI and offspring white matter structure

Average maternal prepregnancy weight has increased during the last decade in Finland, with over one-third of women being overweight preceding pregnancy (Gissler & Kiuru, 2019). Maternal overweight negatively impacts infant outcomes for example, by increasing the risk of macrosomia and caesarean delivery (Ruager-Martin et al., 2010). In childhood, associations have been reported, among others, with increased risk of diabetes (Chu et al., 2007), epilepsy (Razaz et al., 2017), and obesity (Whitaker, 2004). Neurodevelopment may also be compromised due to excess weight in pregnancy, as indicated in a decline in children's cognitive and motor abilities (Adane et al., 2016) and increased risk of mental health disorders in childhood (Deardorff et al., 2017; Rodriguez, 2010) and adulthood (Edlow, 2017).

The few existing studies of maternal obesity and offspring brain structural and functional features suggest alterations in brain connectivity in infancy. Lower global and regional fractional anisotropy were observed in the white matter tracts of exposed offspring after adjusting for several factors. Reported tracts included the association, projection, callosal, and limbic fibres (Ou et al., 2015). Another study reported weaker functional connectivity of the dorsal anterior cingulate cortex to the prefrontal network in the offspring of obese, compared to normal weight, mothers. Maternal fat mass percentage was also shown to correlate with

functional connectivity strength in this region (Li et al., 2016). These two studies were, however, limited by their small sample size (less than 40 individuals) and only included two-week-old infants, apparently from the same sample (same study site and authors).

3 Structure and multimodal imaging of white matter

3.1 Anatomy of white matter

The term “white matter” derives from the white appearance of the lipid-rich tissue. Although largely covered by the cortical mantle, white matter constitutes about half of the total brain volume in adults. The cortical and deep grey matter regions exchange information via axonal pathways that, together with the supporting and modulatory glial cells, make up the primary composites of white matter. Axons form a large topography of networks for local and global information processing. Laid out in series, the length of myelinated axons in the adult brain would circle the Earth more than three times (Marner et al., 2003; Udin & Fawcett, 1988).

Axonal bundles or *fascicles* are aggregates of somewhat coherently oriented axons that combine to form so-called white matter *tracts*, albeit these two terms are often used interchangeably. White matter tracts can be named and structurally identified by their location and the type of information processed by the connected grey matter regions. *Commissural tracts* connect mostly regions of the same function (“homotopic” regions) between the two cerebral hemispheres; *projection tracts* convey signals between the cerebral cortex and thalamus, brainstem and spinal cord; *limbic tracts* connect the deep grey matter regions of limbic functions; and *association tracts* are intra-hemispheric cortico-cortical fibres connecting higher-function associative grey matter regions. The most superficial fibres connecting adjacent cortical grey matter regions, termed “U-fibres” due to their shape, are also part of the associative tracts (Wakana et al., 2004).

Whereas the bodies (i.e., *somata*) and dendrites of neurons form the main part of grey matter, white matter contains the longitudinal processes of neurons, termed *axons*, which synapse with the dendrites of other neurons. Besides this simplified view, axons also constitute a significant proportion of cortical grey matter and commonly exhibit branching into multiple axonal arborisations inside white matter. Axonal diameter also varies not only across axons, but also along the length of a single axon (Tomasi et al., 2012).

Other constituents of white matter include different glial cells that hold a supportive and modulatory role for signal conduction, metabolism, and

immunology and which, taken together, account for about 90% of cells in the human brain (He & Sun, 2007). Oligodendrocytes have longitudinal processes that form myelin sheets around axons, thus forming the so-called *fibre*. While a single oligodendrocyte may myelinate multiple axons, the effects of axon-oligodendrocyte interaction, for example, the adjustment of myelin thickness, are specific to each axon (Friede, 1972; Kinney et al., 1988). The thickness of the myelin sheet and the distance between the nodes of Ranvier also vary along the length of each fibre and across fibres (Tomassy et al., 2014). Other types of glial cells include astrocytes that, among other things, maintain synaptic transmission, microglia with immunologic function and oligodendrocyte progenitor cells (OPC) that give birth to oligodendrocytes during development but the role of which is unknown in the adult brain (Purves et al., 2018).

Current knowledge of white matter anatomy is largely founded on former post-mortem (Dejerine & Dejerine-Klumpke, 1895; Williams et al., 1999), histological (Rakic & Yakovlev, 1968), lesion (De Lacoste et al., 1985), and electron-microscopic studies (Liewald et al., 2014) in humans and animals and, more recently, on *in vivo* magnetic resonance imaging. The development of imaging technology enables advances in the field, as shown by the discovery of a novel fibre tract in the human brain (David et al., 2019).

A longstanding challenge in research on brain anatomy and function is posed by the difficulty and lack of knowledge in combining findings on the micro (~ 1 µm) and macro (~ 1 mm) scales. Indeed, a single voxel at a neuroimaging resolution of 1x1 mm has been estimated to contain up to 5 million axons and large numbers of glia (Walhovd et al., 2014). Novel approaches gather scalable histological, genetic, and MRI-derived information to create detailed atlases of brain anatomy, function, and development (Toga et al., 2006), for example the Allen Brain Atlases (Ding et al., 2016), the BigBrain Project (Amunts et al., 2013) and the Human Connectome Project (Van Essen et al., 2013).

3.2 Structure of the corpus callosum

The corpus callosum is the largest white matter tract in the human brain, connecting the cortices of the two cerebral hemispheres. With around 200 million fibres (Aboitiz et al., 1992), it is substantially larger than the other two commissural fibre tracts, the anterior and hippocampal commissures. Found only in placental animals, the corpus callosum has a phylogenetically novel role in the

interhemispheric integration of different modes of cortical information processing (Innocenti, 1986; Raybaud, 2010).

The composition of callosal fibres across the anterior-posterior axis differs by the connected, mostly homotopic, cortical areas (Aboitiz et al., 1992; Caminiti et al., 2013; De Lacoste et al., 1985). The *rostrum* (or *lamina rostralis*) is the anterior "beak" of the corpus callosum, connecting most likely fronto-basal cortical regions. The *genu* (or knee) is the sharply bending anterior callosal segment that connects the whole anterior frontal lobes including prefrontal and anterior cingulate areas. Fibres traversing the genu, collectively known as the *forceps minor*, are mainly associative fibres of generally small diameter with thin or missing myelin sheets. Located posterior to the genu, the callosal *body* constitutes a horizontal callosal segment that interconnects the precentral cortices and the adjacent portions of the insulae and the overlying cingulate gyri. Next, the *isthmus* is a local callosal narrowing and is situated at the union of the underlying fornix tracts and the corpus callosum. It carries fibres of relatively large diameter and a thick myelin sheet from the motor, somatosensory, and primary auditory areas. The *splenium* ("spleen") is the thickest and most posterior callosal segment with a more intermediate fibre diameter and myelination profile. It includes fibres from the posterior parietal, medial occipital, and medial temporal cortices. The fibres of the splenium make up the *forceps major* fibre tract (Aboitiz & Montiel, 2003; Hofer & Frahm, 2006; Velut et al., 1998).

The name of the corpus callosum follows the compact packing of its fibre structure (Raybaud, 2010). Callosal fibres are vertically organised such that homotopic fibres originating from medial (or dorsal) cortical regions occupy the superior and fibres from lateral cortical sites the inferior part of the corpus callosum (Niquille et al., 2009). Questioning the earlier view of their coherent parallel orientation, recent research indicates the relatively strong dispersion of fibres' orientation in the callosal midline, possibly accounted for by developmental aspects or the formation of heterotopic callosal connections (Mollink et al., 2017). During development, axonal organisation in the CC seems to determine the later topography of axonal cortical projections (Zhou et al., 2013).

Of anatomical and methodological interest, callosal fibres cross with other fibre populations in two locations. The CC is perforated near the sagittal midline by fibres of the *septum pellucidum* which form the ipsilateral *septocingulate pathway* (Dejerine & Dejerine-Klumpke, 1895; Shu et al., 2001). In the central white matter, called "periventricular crossroads", callosal fibres are crossed by

associative fibres (in the sagittal direction) and thalamo-cortical/cortico-fugal fibres (in the radial direction), of which the latter include the superior longitudinal fasciculus and the cerebrospinal tract (Wakana et al., 2004; Williams et al., 1999).

3.3 Diffusion-weighted MRI

Diffusion-weighted MRI (dwMRI) characterises tissue structural features indirectly using water diffusion *in vivo*. The effect of water self-diffusion in the MR signal was reported as early as in 1950 (Hahn, 1950). Diffusion terms were soon introduced to the nuclear magnetic resonance (NMR) formalism (Torrey, 1956), which later enabled the diffusion effect to be quantised (Stejskal & Tanner, 1965). Stejskal and Tanner also introduced pulsed diffusion gradients and described restricted diffusion in plant cells in NMR (Tanner & Stejskal, 1968), inventions that turned out to be crucial for modern diffusion imaging.

The development of magnetic resonance imaging in the 1970s (Lauterbur, 1973; Mansfield, 1977) allowed diffusion properties in the voxels of live tissue to be probed non-invasively. Magnetic properties of hydrogen nuclei i.e., protons, commonly used in MRI, can be simplified as spinning magnet dipoles. The magnets are aligned in a strong magnetic field in the imaging scanner. Pulsed magnetic fields, or "gradients", modulate the phase and frequency of the magnets, specific to the location. The state of the magnets can be manipulated using radio frequency (RF) pulses to locate voxels and generate tissue contrast. Relaxation from such states, again, produces a measurable RF signal.

Diffusion is based on the Brownian motion of molecules in tissue fluids. To detect diffusion, the magnets' phases are set to vary linearly along a chosen dimension (by transiently altering their frequency). Rephasing the magnets using an opposite gradient pulse fails if the magnets have moved in the gradient direction between the two gradients. The RF signal produced by the final relaxation is weaker if the magnets are out of phase due to this movement. The measured signal attenuation in a voxel thus reflects the magnitude of diffusion in the given direction (Mori & Zhang, 2006; Mori & Barker, 1999).

Diffusion is restricted perpendicular to numerous brain structures in each voxel which imposes a rotationally variant profile of diffusion magnitude. A common diffusion parameter, the A*pparent diffusion coefficient* (ADC), estimates the magnitude, but only in the gradient direction as explained above (Le Bihan et al., 1986). The introduction of *diffusion tensor imaging* (DTI) enabled the practical approximation of the main diffusion properties in a voxel. The DTI

model of diffusion is an ellipsoid with three orthogonal eigenvectors, the lengths (or eigenvalues) of which correspond to diffusivity in the three directions (λ_1, λ_2 and λ_3), Figure 1.

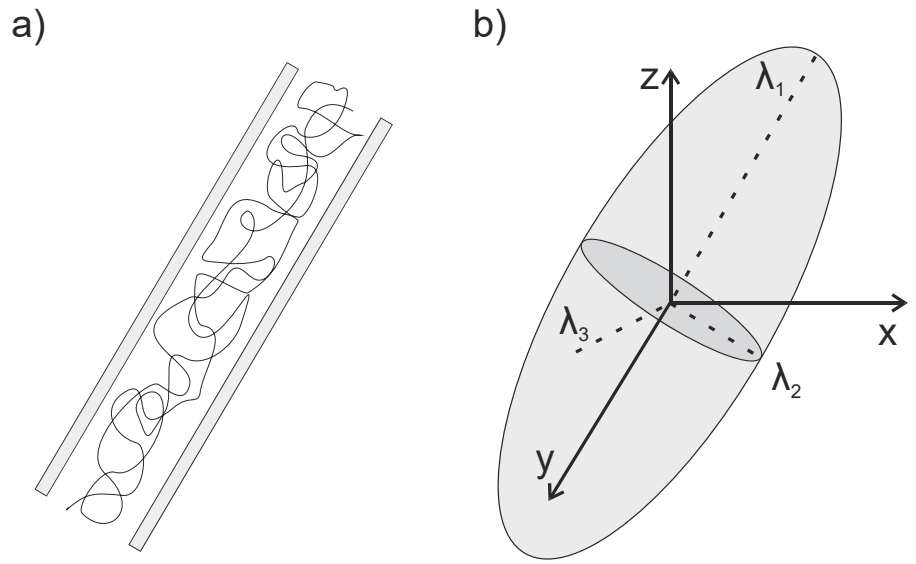

Fig. 1. The diffusion model. a) The path moved in by a single intra-axonal water molecule. b) The diffusion tensor can be viewed as an ellipsoid with three orthogonal eigenvectors, here pictured in the Cartesian coordinate system.

Useful rotationally invariant indices, non-specific to microstructural features, are commonly calculated based on the diffusion model in each voxel. The two indices used in this work are the *fractional anisotropy*, which estimates the magnitude of diffusion in the primary diffusion direction (λ_1) relative to the other two directions (λ_2 and λ_3), Equation 1, and the *mean diffusivity*, which estimates the average diffusion magnitude in the three directions (Pierpaoli & Basser, 1996).

$$FA = \sqrt{\frac{1}{2}}\frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_3-\lambda_1)^2}}{\sqrt{\lambda_1^2+\lambda_2^2+\lambda_3^2}} \quad (1)$$

Calculating the diffusion model requires diffusion-weighted scans in at least six noncollinear directions and a scan with no diffusion-weighting (Basser et al.,

1994). Due to its simplified view of diffusion, the DTI model inherently lacks sensitivity to common structural features such as crossing, kissing, and bending of fibres (Pierpaoli & Basser, 1996; Vos et al., 2012). Increasing methodological complexity in DTI data processing allows different indices to be estimated, but also increases sources of bias (Jones & Cercignani, 2010).

3.3.1 Tractography

Tractography methods aim to model brain white matter trajectories as lines of voxels that show a continuum in the diffusion orientation (Jeurissen et al., 2019). From early on, diffusion imaging was used for mapping fibre orientations using the rotationally variant quality of dwMRI data (Douek et al., 1991). Models of white matter tracts were later reconstructed in 3D in live human and animal data (Conturo et al., 1999; Xue et al., 1999). Notable correspondence was reported between tractography and postmortem anatomical atlases (Wakana et al., 2004). Image registration methods soon enabled automated tractography tracings in larger samples of MR images (Zhang et al., 2008).

Methodology in tractography algorithms is versatile but commonly diffusion trajectories are traced using a seed, possibly a target region, and other criteria based on existing anatomical information (Wakana et al., 2007). First, the orientation of fibres is modelled in each voxel using either a single-fibre model for example, the classic DTI, or a multi-fibre model, for example, the BEDPOSTX (Behrens et al., 2007). Second, a diffusion path or *streamline* is traced through the WM data field. The decision of propagation from one voxel to another can be deterministic, i.e. a fixed direction is chosen, or probabilistic, i.e. the direction is chosen by probability (Behrens et al., 2007); for a review see (Sarwar et al., 2019). The probabilistic tractography of 27 major white matter tracts can be automated for dwMRI data using the autoPTX pipeline; see Figure 2 for an example. The process includes automatically starting and stopping the propagation of streamlines in specific brain regions to produce each tract of interest (de Groot et al., 2015).

3.4 Magnetisation transfer imaging

Magnetisation transfer imaging is an MRI contrast sensitive to tissue macromolecular content and is dominated by myelin in brain white matter (Schmierer et al., 2004; Sled, 2018). While the method is rarely used in the

clinical setting, it has been widely adapted to research on brain development (Nossin-Manor et al., 2013; Paus et al., 2001) and decease (Filippi & Rocca, 2004).

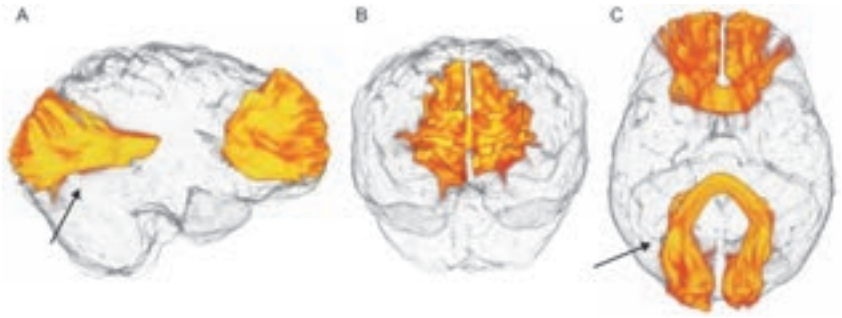

Fig. 2. Probabilistic tractography of callosal tracts of an NFBC1986 participant as traced using autoPTX. *Forceps minor* and *forceps major* (arrow) are shown in the sagittal (A), coronal frontal (B) and axial (C) orientation. The density of streamlines is visualised as a gradient from yellow (high density) to red (low density).

Transfer of magnetisation between protons was first reported in 1989 (Wolff & Balaban, 1989). Protons bound to tissue macromolecules are tightly coupled together, which gives rise to a wide spectrum of resonant states. The protons can be saturated with a broad off-resonance radio frequency pulse which has relatively little effect on free-water protons. Magnetisation then transfers from the bound to nearby free water protons via dipolar coupling and chemical exchange. Longitudinal magnetisation of the free pool decreases due to this transfer, resulting in a measurable decrease in signal. A simple application is the *magnetisation transfer ratio* (MTR), calculated as the percentage decrease in signal intensity due to magnetisation transfer (Henkelman et al., 2001). Image with (MT_{on}) and without (MT_{off}) saturation pulses are used to calculate MTR, Equation 2.

$$MTR = \frac{MT_{off} - MT_{on}}{MT_{off}} \quad (2)$$

3.5 Relaxometry MRI

Relaxometry in MRI aims to separate and quantise the different nuclear relaxation phenomena in tissue. The method is sensitive but unspecific to various tissue characteristics and has been used for research on normal brain development

(Deoni et al., 2012; Dvorak et al., 2021) and decease (Deoni et al., 2015; Laule et al., 2006), with also some interest in clinical imaging (Margaret Cheng et al., 2012). Key challenges include finding suitable models of tissue characteristics for signal interpretation and the more demanding image acquisition techniques (Does, 2018).

Contrast in structural MRI is largely set by the longitudinal (T1) and transverse (T2) relaxation times of water proton spins. While the resulting image intensities are usually *weighted* by T1 or T2 and influenced by numerous other parameters, the methods in *quantitative relaxometry* aim to yield voxel intensities as absolute values of T1 and T2. Interpretation of the measures is more informative because the spectra of T1 and T2 in tissue have been extensively studied and the values, being quantitative, are comparable across imaging hardware (Deoni, 2010). Short T2 has been shown to correspond with water coupled with myelin bilayers (Dyakin et al., 2010; Mackay et al., 1994), making it possible to formulate parameters such as *myelin water fraction* (MWF). The instrument for modelling the relaxation times in this work is the mcDESPOT algorithm (Deoni et al., 2008).

4 Aims and hypothesis

The purpose of this work was to examine associations between early-life factors and brain white matter structure in childhood, adolescence, and early adulthood. Earlier histological information was used to interpret structural imaging findings in the corpus callosum. The aims and hypotheses of the original publications were as follows.

1. The aim was to examine the microstructural composition of the corpus callosum in MRI in relation to earlier histological information and to study sex differences in callosal microstructural measures. We hypothesised that FA would be higher and MTR lower in the corpus callosum of males compared to females.
2. The aim was to study the association between prenatal exposure to maternal cigarette smoking and microstructural MRI measures in the corpus callosum in adolescence and early adulthood. Our hypothesis, based on earlier literature, was that PEMCS would be associated with alterations in callosal white matter structure.
3. The aim was to study the association between maternal prepregnancy BMI and white matter microstructure in major white matter tracts in childhood, adolescence, and early adulthood. Based on prior work, we hypothesised that maternal prepregnancy BMI would be associated with widespread alterations in white matter.

5 Materials and methods

The samples used in this work were based on existing cohorts and collected at different ages and on multiple sites. To improve the comparability of outcomes, information on early predictors and the processing of brain scans were harmonised in each publication. Early predictors and later brain MRI measures were studied using statistical association methods.

5.1 Participants

Participants in this work include children, adolescents, and young adults from five cohorts in Finland, Canada, the United Kingdom, Spain, and the Netherlands. Each cohort has a unique focus and only participant data relevant to this work was used in each publication. The number of participants with usable MRI measures in each cohort varied by publication due to the use of different brain measures and differences in image processing.

5.1.1 The Northern Finland Birth Cohort 1986 (I, II, III)

The Northern Finland Birth Cohort 1986 (NFBC1986) is a prospective birth cohort study in the two most northern provinces of Finland, Oulu and Lapland, originally aimed to study the prevention of child morbidity and mortality. Children with an expected date between 01 July 1985 and 30 June 1986 were included and 99% of deliveries during the period were recorded, resulting in the inclusion of 9,432 live-born children (Järvelin et al., 1993). Data collection started at the tenth gestational week and later follow-ups were recorded at birth, 1 y, 7-8 y, 15-16 y and 33-35 y (https://www.oulu.fi/nfbc). Parts of the data collected at pregnancy, birth, and at 20-25 years (Oulu Brain and Mind Study II) were used in this dissertation.

The Oulu Brain and Mind Study II

The Oulu Brain and Mind Study II, a subsample of the NFBC1986, was collected during 2011-2013 when participants were 25-28 y. The aim was to study maternal cigarette smoking during pregnancy and offspring health, addictions, and brain MRI. In brief, the sample inclusion was based on the availability of data from a previous 16-year follow-up of 6,985 individuals (74% of NFBC1986). Of these,

698 individuals were exposed to maternal cigarette smoking during pregnancy and eligible after exclusion (Lotfipour et al., 2014). A non-exposed control group of 698 individuals were matched to the exposed individuals by maternal education (5 levels) and place of birth (urban/rural) (Lotfipour et al., 2014; Ramsay et al., 2016).

Of the invited 1,396 individuals, 471 (34%) participated in the study. Scanning was completed successfully in 451 individuals. Common contraindications included pregnancy, metal or electronic implants, and severe claustrophobia. For scanner characteristics, see Publication I Materials and Methods: Image Acquisition. The study was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District in Finland and written informed consent was provided by the participants and their parents. Partly missing or corrupt data and extreme outliers were excluded, leaving a final number of 433, 446 and 437 participants in the NFBC1986 in Publications I, II and III, respectively.

5.1.2 The Avon Longitudinal Study of Parents and Children (I, II)

Based in the UK, The Avon Longitudinal Study of Parents and Children (ALSPAC) cohort aims to study environmental and genetic predictors of health and development. Pregnant women residing in the former Avon Health Authority with expected date of delivery between 01 April 1991 and 31 December 1992 were invited to participate in the study (http://www.bristol.ac.uk/alspac). The study included 14,541 pregnancies and 13,988 children alive at 12 months of age (Boyd et al., 2013; Fraser et al., 2013). Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees.

In the present subsample of the ALSPAC, only male participants were scanned in MRI owing to the focus of a funding grant. Individuals living within a three-hour one-way journey from the study site and with adequate prior blood samples were invited (Khairullah et al., 2014). Of 507 participants, 456 completed the scanning protocol. For scanner characteristics, see Publication II Table 1. After exclusion of missing data and outliers (±4 SD), the final number of participants in the ALSPAC sample was 402 and 367 in Publications I and II, respectively.

5.1.3 The Saguenay Youth Study (I, II)

The Saguenay Youth Study (The SYS) is a two-generational study of adolescents and their parents aimed at investigating gene-environment interactions in brain and cardiometabolic health (http://saguenay-youth-study.org/). The study is based in Canada in the Saguenay Lac Saint-Jean region in a geographically isolated population with a known founder-effect: French-Canadian adolescents and their siblings, N=1,029 aged 12-18 years, were recruited from high schools with half prenatally exposed to maternal cigarette smoking and the other half non-exposed and matched to the exposed by maternal education and school attended. Exclusion criteria included amongst other matters prematurity (<35 weeks) and alcohol abuse during gestation, see Publication 2 for details. For MRI scanner characteristics, see Publication II Table 1. Written assent and consent were given by the adolescents and their parents, respectively. Ethical approval for the study was given by the Research Ethics Committee of the Chicoutimi Hospital (Pausova et al., 2007; Pausova et al., 2017). Partly missing or corrupt data was excluded in the SYS, leaving 934 participants available in Publication 2.

5.1.4 The Generation R (III)

The Generation R is a prospective cohort in urban Rotterdam in the Netherlands aimed at studying genetic and environmental determinants of development and health from foetal life to early adulthood (https://generationr.nl/). Mothers with a date of delivery between April 2002 and January 2006 were enrolled to the study, resulting in 9,778 mothers and a participation rate of 61% (Kooijman et al., 2016). Brain scans were acquired approximately at the age of 10 years on 3,992 children of which 3,063 had usable data. For MRI scanner characteristics, see Publication III Table 1. Information on maternal prepregnancy BMI was missing for 587 participants, and 10 participants had incidental findings that could potentially influence analysis, leaving 2,466 participants with data eligible for the study (White et al., 2018).

5.1.5 The PREOBE Study (III)

The PREOBE (Study of maternal nutrition and genetic on foetal adiposity programming) is a prospective cohort study aimed to investigate the influence of peri- and post-natal factors on offspring programming of adiposity with a focus

on maternal nutrition, weight, and genetics. Women aged 18 to 42 years with singleton pregnancies were enrolled at 12 weeks of pregnancy at the Clinical University Hospital San Cecilio and Mother-Infant Hospital in the city of Granada, Spain. For MRI scanner characteristics, see Publication III Table 1. The study was approved by the Ethical Committees of the Clinical University Hospital San Cecilio and the Medical faculty of the University of Granada (Campoy et al., 2008). Of 350 participants, 331 were included in the study and 135 gave consent for the neuroimaging of the child at 6 years of age. After exclusion of 19 individuals due to motion or scanner-related artefacts, 116 individuals were included for the final analysis.

5.2 Callosal histological measures

Callosal histological densities of four classes of fibre diameters were kindly provided by Dr Aboitiz (personal communication 31 August 2015). The two extremes of fibre diameters (small: $d > 0.4$ μm and large: $d > 5$ μm) were chosen for the analysis and the mean and standard deviation were calculated.

5.3 Processing of callosal MRI measures

To separate the region of interest, ten segments of the corpus callosum were drawn on the mid-sagittal slice and identically on the adjacent left and right slices (altogether three slices) in the MNI152 1 mm template brain. The segmentation scheme was based on earlier histological information on the human corpus callosum (Aboitiz et al., 1992; Witelson, 1989), Figure 3. First, the long axis of the corpus callosum was rotated in the horizontal anterior-posterior direction. Next, the structure was divided into three equal parts in the long axis and the division was repeated for the anterior (genu) and middle (body) thirds. The posterior fifth of the structure was marked splenium and divided into three equal parts perpendicular to the long axis of the splenium. The remaining part anterior to the splenium was marked isthmus. Finally, the segments were eroded in the sagittal plane by approximately one voxel from the edges to limit the partial volume effect.

The ten callosal segments were used to extract parametric measures for statistical analysis. Slightly different processing was used in Publications I and II due to differences in the used samples and measures chosen. Processing of each callosal MRI measure is described below and in more detail in the original

publications. Exclusion of erroneous data in each MRI modality and individual is described in more detail in the original publications.

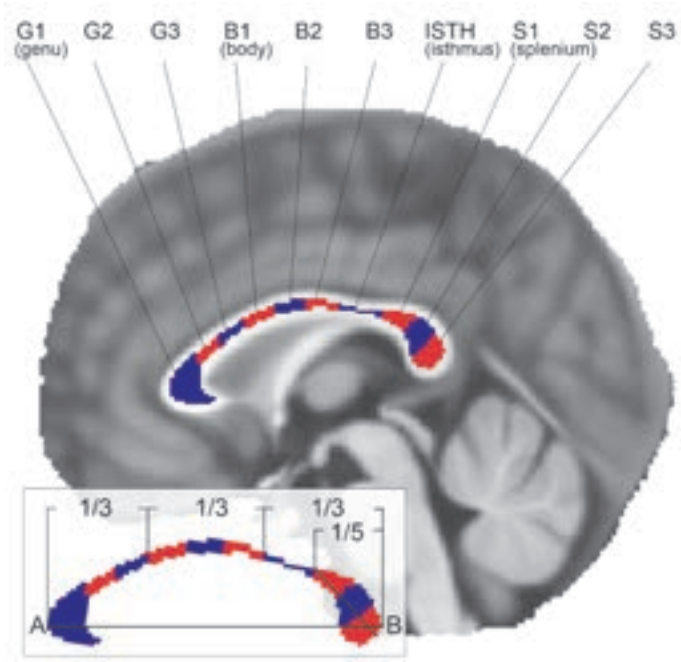

Fig. 3. Segmentation of the midsagittal corpus callosum overlaid on the MNI152 template brain. Modified from Publication I.

5.3.1 Callosal volume

A separate segmentation scheme was used for extracting the callosal volume. The corpus callosum was divided into ten segments identically in two adjacent mid-sagittal slices in the MNI152 template and the segmentation was expanded to the outermost edges of the callosal structure. The expanded segments were transformed from the MNI152 template to native high-resolution T1w images using nonlinear registration. In the SYS sample, segments in the MNI152 were first registered to a study-specific SYS808 template, to which native T1w images were also registered. The segments were then transformed in one interpolation step from the MNI152 to the SYS808 template and then to native T1w images to account for anatomical variability in this sample of adolescents (13-18 y). In all

MRI samples, the callosal segments were finally masked with tissue classified as white matter with 95% probability by the FSL FAST algorithm. The resulting segments were visually inspected and volumetric values were extracted.

5.3.2 Diffusion-weighted measures

Images without diffusion weighting (b0 images) were stripped of non-brain tissue using the FSL BET algorithm. The handling of artefacts and calculating of FA and MD maps differed slightly between Publications I and II. In Publication I, diffusion-weighted volumes were corrected for eddy currents and head motion using the ExploreDTI (Leemans et al., 2009), after which b-vectors were rotated and FA and MD values were calculated based on the REKINDLE model. EPI artefacts were minimised by registering the FA maps nonlinearly to the native T1w volumes in the anterior-posterior phase encoding direction. In Publication II, diffusion-weighted volumes were corrected for head motion, eddy currents, slice-wise outliers, and within-volume motion using FSL eddy cuda 8.0 (Andersson & Sotiropoulos, 2016). After rotating b-vectors, FA and MD maps were calculated using FSL DTIFIT. Finally, FA maps were registered nonlinearly to the native T1w images to minimise EPI distortions. In both publications, EPI distortions in MD maps were minimised using transforms from the FA-to-T1w registrations. The images were visually inspected and mean values of the ten callosal segments were extracted in the native T1w space.

5.3.3 Magnetisation transfer ratio

The magnetisation transfer ratio was calculated using images with (MT_{on}) and without (MT_{off}) a saturation pulse. First, the images were stripped of non-brain tissue using FSL BET. Next, the MT_{on} image was registered linearly to the MT_{off} image. The magnetisation transfer ratio was calculated as a percentage decrease in signal intensity using Equation 2. In the ALSPAC sample, MTR maps were corrected for bias field inhomogeneities using the N3 algorithm (Sled et al., 1998). In all samples, the MTR maps were registered linearly and transformed into the native T1w volumes where images were visually inspected and callosal segment mean values were extracted.

5.3.4 Relaxometry measures

Calculating relaxometry parameters (T1, T2 and myelin-water fraction [MWF]) was conducted using the mcDESPOT algorithm (Deoni et al., 2008) at the Cardiff University Brain Research Imaging Centre, please refer to original publications for details. The parametric maps were registered nonlinearly to the native T1w images to account for distortions in the 3T scanner in ALSPAC. The images were visually inspected and callosal segment mean values were extracted.

5.3.5 Statistical analysis

Histological and MRI measures of the corpus callosum were compared in Publication I using quantitative measures as explained below. In Publications I and II, associations between early predictors and callosal MRI measures were studied using linear mixed effects (LME) analyses, also explained in detail below. The model allows the relatedness of values of the 10 callosal segments in each individual and across individuals to be taken into account and reduces the number of tests.

In the ALSPAC sample, relaxation rates were calculated as $R_1=1/T_1$ and $R_2=1/T_2$. In the SYS sample, MTR data for two different acquisition schemes were separately cleaned of outliers (± 4 SD) and normalised as z-scores. Finally, all data were normalised (z-score) by each cohort, sex, and imaging measure. In Publication II, data were also normalised by callosal segment to remove unwanted by-segment variation.

Comparison of histological and MRI measures

Three separate analyses were used to quantitatively compare the literature-based histological and our measures of MRI parameters in the ten callosal segments. First, the anterior-posterior trajectories of normalised histological vs. MRI values were compared using slopes: The difference in a histological measure between two adjacent segments i.e., the slope, was subtracted from the corresponding slope of an MRI measure, after which the result was turned to absolute value and summed over the nine segment interval pairs. Second, correlation between each histological and MRI measure was calculated using Spearman correlation coefficients. Third, similarities across the normalised histological and MRI

measures were studied using hierarchical clustering. Please refer to Publication I for further details.

Linear mixed effects model

Associations between early predictors and callosal measures were studied using linear mixed effects models (LME) in R software (R Core Team, 2018) in Publication I (PI) and Publication II (PII). The ten callosal segments were placed in a single LME separately in each cohort, sex, and modality. The main effect of a predictor (Sex in PI and PEMCS in PII), as well as interactions of predictor*Segment (PI and PII) and Sex*PEMCS (PII) were estimated based on the model. Random effects included, in PI, Individual and Segment and, in PII, Individual (nested in sibship in the SYS). Note that in PII data were normalised by Segment and no random effects term was needed in the model. Confounding fixed effects included in PII model 1 participant Age at imaging and in model 2 additionally Maternal education, Maternal alcohol use during pregnancy, Family income and Maternal drug use during pregnancy (the latter two only in ALSPAC and SYS). In PII, a mega-analysis of the three cohorts was also conducted by including all data in each modality in a single LME with a random effects term for cohort.

Statistical significance was estimated by comparing models with and without the predictor using likelihood ratio tests because LME does not provide a straightforward p-value. Multiple comparisons were controlled using False Discovery Rate (FDR) in each MRI measure (PI) and sex and MRI measure (PII). As a post-hoc analysis, t-tests (PI) or multivariate linear model (controlling for the same confounders as in model 2, in PII) were fitted in segments that showed a main effect of predictor (PI) or predictor*Segment interaction (PI and PII).

5.4 Processing of tractography measures

Tractography for 27 white matter tracts was automatically traced using the *autoPTX* algorithm (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/AutoPtx). The pipeline runs probabilistic tractography to produce streamline count and mean values of diffusion measures (FA and MD) for each tract. Pre-processing included correction for eddy-currents and head motion artefacts using linear transformation of diffusion-weighted volumes into non-diffusion-weighted (b0) volume in each individual. Orientations of diffusion-weightings (b-vectors) were rotated

according to the corrected volumes and brain masks were extracted in b0 volumes using the *bet* algorithm.

The pre-processing stage in *autoPTX* was given the brain-extracted b0 and corrected diffusion volumes to estimate probabilistic diffusion models per voxel using the *bedpostx* algorithm. The pipeline calculated parametric (FA and MD) maps and the native FA maps were registered to the FMRIB58 high-resolution FA template. The registrations were visually inspected, after which seed, target, stop, and exclusion masks were back-projected from the template into individual native space. The second stage of *autoPTX* executed probabilistic tractography using the above masks in the native space; each voxel in a given tract was given a scalar value based on the number of streamlines traversing the voxel. These tract images were then normalised by the total number of successful streamline tracings in a given individual and, finally, thresholded according to de Groot et al. (de Groot et al., 2015). Tracts were visually inspected for erroneous tracings.

Mean FA and MD were extracted using the resulting tract masks automatically in each individual. Tracts that appeared in the left and right hemisphere were averaged together by tract in each individual. Also, the three tracts in the thalamic radiation (anterior, posterior, and superior) were averaged together by individual, resulting in 13 tract mean values per individual in FA and MD.

5.4.1 Statistical analysis of tractography measures

Maternal BMI values were normalised (z-score) for comparability across birth cohort samples (PREOBE, Generation R, and NFBC1986) in Publication II. Associations between maternal BMI and MRI measures (FA and MD) were studied using multiple linear regression models separately in the 13 white matter tracts in each sample. In Model 1, no confounders were included. In Model 2, the same confounders were used in all samples, including maternal age, ethnicity, education level, and cigarette and alcohol use during pregnancy, as well as child sex, birth weight, and age at imaging. Multiple comparisons were adjusted for using False Discovery Rate in the 13 tracts in FA and MD in each sample and an adjusted p-value below 0.05 was considered significant.

6 Ethical considerations and personal involvement

The study plan of the Northern Finland birth Cohort 1986 was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District. The plan for the Oulu Brain and Mind 2 study was approved by the same ethical committee in 2011. The collection of other cohorts used in this work were approved by local ethics committees as detailed in Section 4.1.

The personal involvement of the PhD student included taking part in formulating the study questions and choosing approaches for analyses. The PhD student was solely responsible for all analyses of MRI data, besides running the mcDESPOT algorithm. All statistical analysis were planned and executed by the PhD student with help from a statistician when needed. All tables and figures were prepared and publications drafted by the PhD student. The PhD student wrote the first and final versions of all the three publications, and the summary part of the thesis.

7 Results

7.1 White matter multimodal assessment and sex differences (I)

7.1.1 Histological correlates of microstructural MRI measures

Sample demographics are detailed in Publication I Table 1. The comparison of callosal anterior-posterior profiles between MRI measures and histological measures revealed similarities in quantitative comparison (slope difference, sld), correlation coefficients between the measures, and multivariate hierarchical clustering. In the ASLPAC sample, the highest similarity in anterior-posterior callosal profiles was observed between small diameter fibres ($d > 0.4$ μm) and the myelin-water fraction (MWF), showing the smallest value in slope difference (sld = 0.7) and strong correlation across segments ($\rho = 0.84$, p-value = 0.007). The other mcDESPOT metrics also showed consistent similarity with the small fibre profile (R1: sld = 1.1, $\rho = 0.97$, p-value = 0.006 and R2: sld = 1.6, $\rho = 0.88$, p-value = 0.005). Less similarity was observed between the small fibre profile and FA (sld = 2.4, $\rho = 0.73$, p-value = 0.073) and MD (sld = 3.1, $\rho = -0.71$, p-value = 0.04).

As expected based on the inverse relation between the small and large fibre profiles (sld = 4.1), considerable differences were observed between the large fibres ($d < 5$ μm) and the profiles of R1 (sld=3.8, $\rho=-0.88$, p-value=0.005), MWF (sld=3.7, $\rho=-0.88$, p-value=0.005), FA (sld=3.7, $\rho=-0.66$, p-value=0.054) and R2 (sld=3.5, $\rho=-0.92$, p-value<0.001) but less so with that of MD (sld=2.8, $\rho=0.65$, p-value=0.054). A further pair-wise comparison of each MRI measure–fibre diameter correlation coefficient was indicative of differences between the coefficients of MD and small and large fibres and all other correlation coefficients (all p-values < 0.00167). See Figure 4 and Publication I Figure 2 and 3 for further details.

Hierarchical clustering of all individuals' callosal MRI measures produced two clusters, the first consisting of R1, R2, MWF and FA and the second of MD alone, with high reproducibility for each. Sub-clusters included only one of each MRI measure except for MWF and R2, which were clustered together. Anatomically adjacent callosal segments were clustered next to each other in 29 of the 45 segment intervals, see Publication I Figure 4.

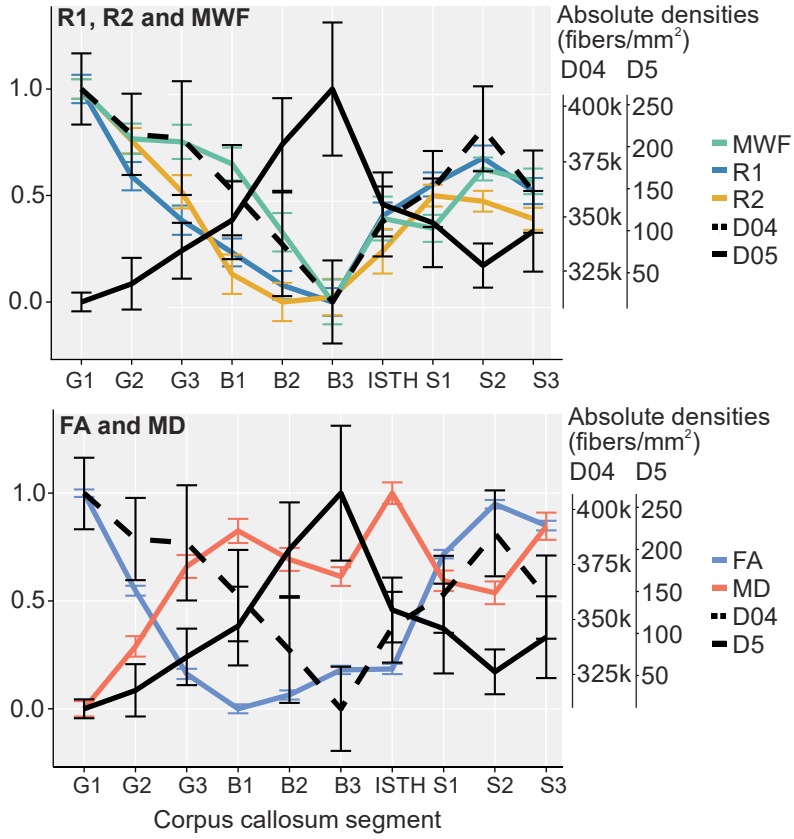

Fig. 4. Anterior-posterior profiles of callosal MRI measures and axon diameter (histological data). Relative MRI intensity and density of fibres is shown on the vertical axis and corpus callosum segment on the horizontal axis, modified from Publication I.

Profile of MTR in the ALSPAC sample

In the ALSPAC sample, MTR values increased linearly from the anterior to the posterior CC. This is contradictory to the V-shaped callosal anterior-posterior profile of MTR observed earlier in (Paus et al., 2008) and in the NFBC1986 sample in this work (7.1.2 Sex differences in white matter microstructure), raising the possibility that the MTR signal in this work is affected by scanner field inhomogeneity. A magnetic field of 3 T, as used in this work, introduces stronger

bias than lower field strength, for example 1.5 T used in above reported studies. A possible explanation is that while B1 receive-field biases cancel out in the calculation of MTR, B1 transmit-field biases do not. Furthermore, a non-uniformity correction tool N3 was run on the ALSPAC MTR data, but the results were not considered reliable. For these reasons, all ALSPAC sample MTR data was removed from further analysis.

7.1.2 Sex differences in white matter microstructure

In the NFBC1986 sample, linear mixed effects analysis showed a main effect of Sex only for MTR ($\chi^2(1) = 15.411$, $p = 0.00009$). Different anterior-posterior profiles were observed in males and females in a Sex*Segment interaction for FA ($\chi^2(9) = 29.274$, $p = 0.0006$). Sex differences were observed in *post hoc* by-segment t-tests for FA and MTR, se Publication I Figure 5. Hierarchical clustering grouped FA and MTR in one and MD alone in another cluster with high reproducibility. Anatomically adjacent callosal segments were located next to each other in 20 of the 27 segment intervals.

7.2 Prenatal exposure to maternal cigarette smoking and structure of the corpus callosum (II)

7.2.1 Sample characteristics

In each cohort, individuals exposed to maternal cigarette smoking during pregnancy differed from the non-exposed in several measures. Birth weight in those exposed was lower in SYS males (3365.39 ± 475.12 g vs. 3540.79 ± 471.96 g, $p < 0.001$) and females (3210.44 ± 473.45 g vs. 3490.77 ± 459.21 g, $p < 0.001$) and in NFBC1986 females (3417.43 ± 451.95 g vs. 3576.69 ± 450.62 g, $p = 0.006$). The difference in birth weight was not statistically significant in NFBC1986 males (3602.15 ± 491.92 g vs. 3717.26 ± 461.12 g, $p = 0.100$), nor in the ALSPAC (3477.94 ± 471.58 g vs. 3555.76 ± 513.84 g, $p = 0.369$).

Of other measures, IQ was lower in the exposed (vs. non-exposed) males in the NFBC1986 and Maternal education in exposed females in the SYS and ALSPAC. Maternal alcohol use during pregnancy was more prevalent amongst males and females in the SYS and females in the NFBC1986, whereas Family income was lower in males in the SYS and ALSPAC. One exposed individual in

the ALSPAC was also positive for Maternal drug use during pregnancy. In all cohorts, the exposed and non-exposed groups were similar concerning participant age, see Publication II Table 2 for details.

7.2.2 PEMCS and callosal structural MRI measures

A main effect of PEMCS was observed in specific MRI measures in males in the ALSPAC and NFBC1986 samples when controlling for covariates (Model 2: Age, Maternal education, Maternal alcohol use during pregnancy, Family income and Maternal drug use). Callosal R2 was higher (r = 0.37 ± 0.15 SE, $\chi^2(1) = 6.31$, p = 0.012) and MD lower (r = -0.39 ± 0.13 SE, $\chi^2(1) = 8.51$, p = 0.004) in ALSPAC, whereas exposed males in the NFBC1986 showed higher FA (r = 0.20 ± 0.08 SE, $\chi^2(1) = 5.47$, p = 0.019) and lower segment volume (r = -0.18 ± 0.08 SE, $\chi^2(1) = 5.70$, p = 0.017).

An Exposure-by-Sex interaction revealed a differential effect of PEMCS in NFBC1986 males and females for FA (males r = 0.20 and females r = -0.12; $\chi^2(1) = 6.93$, p = 0.008) and segment volume (males r = -0.18 and females r = 0.08; $\chi^2(1) = 6.99$, p = 0.008) and a trend for MD (males: r=-0.12, females: r=0.06; $\chi^2(1) = 3.49$, p = 0.062). An Exposure-by-Segment interaction was observed for all MRI measures in NFBC1986 males: segment volume (r = -0.16 ± 0.15 SE, $\chi^2(9) = 39.95$, p < 0.001), FA (r = 0.07 ± 0.15 SE, $\chi^2(9) = 38.55$, p < 0.001), MD (r = -0.09 ± 0.15 SE, $\chi^2(9) = 38.7$, p < 0.001) and MTR (r = 0.20 ± 0.15 SE, $\chi^2(9) = 28.42$, p < 0.001. The interaction terms for diffusion MRI measures in NFBC1986 females, while of the opposite sign to those in males, did not survive correction for multiple testing: FA (r = -0.18 ± 0.13 SE, $\chi^2(9) = 18.31$, p = 0.032) and MD (r = 0.11 ± 0.13 SE, $\chi^2(9) = 18.18$, p = 0.033). No main or interaction effects with PEMCS were observed in other measures nor in the SYS, the youngest cohort. Due to the observed Exposure-by-Segment interactions, a *post hoc* analysis of the by-segment effect of PEMCS was conducted in NFBC1986 males. The analysis in individual callosal segments showed associations between PEMCS and segment volume (in G3: r = -0.55, B1: r = -0.57 and B2: r = -0.38), FA (in G3: r = 0.46, B1: r = 0.36, B2: r = 0.50, B3: r = 0.56 and S2: r = -0.32) and MD (in G3: r = -0.45, B2: r = -0.46 and B3: r = -0.47). No significant by-segment association were found for MTR, see Publication II Figure 1.

7.3 Maternal prepregnancy BMI and offspring white matter microstructure (III)

7.3.1 Sample characteristics

Demographic and anthropometric characteristics of the three cohorts are presented in Publication III Table 2. In all cohorts, the majority of maternal prepregnancy BMI scores were categorised as normal. In the PREOBE cohort, the percentages of overweight and obese BMI scores were 22.4% and 16.4%, respectively (mean BMI 25.1). In Generation R, the corresponding percentages were 24.5% and 9.8% (mean BMI 24.4) and in the NFBC1986 11.4% and 5.7% (mean BMI 22.5). Underweight maternal BMI scores were reported in Generation R (1.8%) and the NFBC1986 (8.2%).

Maternal education in the PREOBE and Generation R was mostly categorised as Higher or Secondary, whereas in the NFBC1986, mothers had mostly Secondary or Primary education. While most of the mothers never drank in pregnancy or only drank until pregnancy was known, continued drinking of more than 1-2 glasses of alcohol was reported for 5.4% of mothers in the PREOBE, 10.3% in Generation R and 14.5% in the NFBC1986. Maternal smoking during pregnancy was reported for 15.3% of mothers in the PREOBE, 13.2% in Generation R and 45.5% in the NFBC1986 (variable of interest in the study design). No statistical comparison across cohorts could be performed due to data-sharing policies.

7.3.2 Maternal prepregnancy BMI and offspring white matter diffusion measures

Several associations were observed between maternal prepregnancy BMI and microstructural measures of offspring white matter tracts at 10 years (Generation R) and at 26 years (NFBC1986), but not at 6 years (PREOBE), see Publication III Figures 1 and 2 and Tables 3 and 4. None of the associated tracts, however, overlapped between the cohorts. In Generation R, lower FA was associated with higher maternal BMI in the medial lemniscus and the forceps minor, whereas a relation with higher FA was discovered in the middle cerebellar peduncle, the limbic system and some of the association and projection fibres. In the NFBC1986, higher FA was associated with higher maternal BMI in the superior longitudinal fasciculus and the corticospinal tract. Lower MD was associated with

higher maternal BMI in the parahippocampal part of the cingulum in Generation R. In the NFBC1986, relations with lower MD were present in individual brainstem, association and projection fibre tracts.

8 Discussion

8.1 Main findings

The main findings of the study were:

1. In Publication I Part 1, we compared the anterior-posterior profiles of microstructural MRI measures in the mid-sagittal corpus callosum in young men with earlier histological information on axon diameter. In Part 2, we studied sex differences in the profiles of callosal MRI measures in young men and women. We observed that the two relaxation rates and myelin-water fraction co-vary with the density of small-diameter axons. Sex differences appeared as higher MTR in males throughout the callosum, while those in FA varied by callosal region. We suggest that MRI relaxometry measures are driven by the high surface area of myelin in regions of small-diameter axons. Males may show more myelin in the mid-sagittal corpus callosum, whereas the fibre milieu may be more dense in the splenium in females.
2. In Publication II, we studied the association between prenatal exposure to maternal cigarette smoking (PEMCS) and structural measures of the corpus callosum in three community-based samples. We observed, in a mega-analysis of all samples lower MD in the mid-sagittal corpus callosum in males. We speculate that PEMCS disrupts callosal development and increases the proportion of small-diameter axons.
3. In Publication III, we studied the association between maternal prepregnancy BMI and microstructural measures of 13 white matter tracts in children, adolescents, and young adults from three birth cohorts. We observed higher FA and lower MD in multiple white matter tracts in adolescence and adulthood, but none of the findings were consistent between the samples. These alterations may indicate the possible role of prenatal inflammation on early white matter programming.

8.2 White matter multimodal assessment and sex differences (I)

This work aimed to quantitatively compare multiple microstructural MRI measures with earlier histological information. The work focused on the mid-sagittal corpus callosum, which has a reasonably unidirection fibre composition, running perpendicular to the studied MRI slices. The callosal microstructure

reflects properties of interhemispheric information transfer and has been extensively studied. In this work, we reported histological correlates of microstructural MRI measures and implemented those to interpret sex differences in a population-based sample of youth.

8.2.1 Histological correlates of microstructural MRI measures

We observed highly similar anterior-posterior profiles of MRI relaxometry measures and small-diameter fibres in the mid-sagittal corpus callosum. The profile of FA was somewhat similar to that of small fibres, especially in the genu and splenium. The profile of MD to some degree resembled that of large fibres, which was mostly inverse in relation to that of small fibres.

A higher density of small relative to large fibres increases the surface area of fibres in a unit volume of tissue, see Publication I. Lower g-ratios have also been reported in smaller fibres, indicating relatively thicker myelin sheets (Paus & Toro, 2009). These factors increase the amount of water between and adjacent to the lipid bilayers of axonal myelin sheets, which has been proposed to impose a short T2 relaxation time signal (Mackay et al., 1994). Short T2 pertains to the myelin-water fraction, the profile of which most strongly resembled that of small-diameter fibres. Higher relaxometry (i.e., short T1 and T2) measures have also been associated with small-fibre regions in an earlier study (Harkins et al., 2016). The higher relaxometry measures in the genu may, furthermore, relate to a smaller median fibre diameter (Aboitiz et al., 1992) and higher fraction of non-water tissue content (Mezer et al., 2013) in the genu compared to other callosal regions. This work underlines the importance of considering fibre diameter (and surface area) when interpreting MRI relaxometry findings.

The diffusion measures FA and MD had more intermediate profiles in comparison to the histology. The low values of FA (and high MD) in relation to relaxometry measures in the genu and body may indicate a stronger influence of lower fibre density on diffusion measures in these segments. The hypothesis is supported by the relatively low relaxation rate of T1, possibly relating to higher water content in these segments (Fatouros et al., 1991). Furthermore, the overall density of fibres seems to decrease by 25% from the anterior to the mid CC, imposing a less dense fibre milieu (Aboitiz et al., 1992). Another possible explanation for the relatively high FA and low MD in the anterior CC is the presence of unmyelinated fibres (16% in the genu in reference histology), which would likely have a lesser influence on relaxometry measures. The presence of

both small and large diameter fibres in the splenium may account for the relatively high FA and MD in this region. While fibre diameter seems to be an important factor for diffusion measures, other contrast-generating mechanisms including water content should be also considered.

8.2.2 Sex differences in white matter microstructure

In this work, we observed higher MTR in males vs. females throughout the anterior-posterior profile of the mid-sagittal corpus callosum. Males also showed higher FA in the callosal body, while lower values were observed in the splenium. The findings suggest sex differences in microstructural features of the corpus callosum.

The magnetisation transfer ratio is weighted to capture the signal from macromolecular water and seems to correlate with myelin content (Schmierer et al., 2004). Possible explanations for our finding of higher MTR in males thus include denser packing of myelinated axons, smaller axon calibre (relating to a lower g-ratio and relatively thicker myelin sheet), or overall stronger myelination of fibres. The profile of MTR is highly similar to those of the relaxometry measures and small-diameter fibres in Part 1, suggesting myelin may in part account for the differences. Interestingly, the finding is in contrast with an earlier report of higher callosal MTR in females in adolescence (Perrin et al., 2009). One explanation for the discrepancy is the later myelination of the male vs. female brain, noting the difference in age in these samples.

The factor accounting for sex differences in MTR is not, however, reflected in differences in FA or MD, of which the later shows no effect of sex. Differences in FA may thus be accounted for by some factor other than myelin, including higher fibre density in males in the callosal body and females in the splenium. The possible role of unmyelinated axons in generating the contrast also cannot be disregarded. While keeping in mind the somewhat conflicting earlier reports, our findings are in line with those on sexual dimorphism in callosal FA at different ages (Menzler et al., 2011; Schmithorst et al., 2008), suggesting a reasonably stable microstructural characteristic with possible analogues in interhemispheric information processing.

The partial volume effect (PVE) is a considerable source of error in our study of the corpus callosum, especially in the craniocaudal direction, which holds voxel dimensions of 1 mm (mcDESPOT), 2.4 mm (ALSPAC: DTI), 2.3 mm (NFBC1986: DTI) and 3 mm (NFBC1986: MTR). Inclusion of non-callosal tissue

was minimised by eroding the callosal mask in the sagittal plane, see Publication I. This resulted in a callosal mid-sagittal area of 345 mm^2, which is less than half the earlier histological (981.3 mm^2) and MRI based (764.5 mm^2) mean values (Aboitiz et al., 1992; Hasan et al., 2008). Furthermore, PVE would likely most strongly influence MTR in NFBC1986 due to the 3 mm slice thickness, but the profile of MTR, or any other profile in this work, does not show larger error margins at the most narrow CC segments of the body or isthmus.

8.3 Prenatal exposure to maternal cigarette smoking and structure of the corpus callosum (II)

In this work, we observed higher FA and lower volume in the corpora callosa of males exposed prenatally to maternal cigarette smoking. The findings were observed in the discovery cohort, the NFBC1986 but not in the younger replication cohorts, the ALSPAC or SYS. A mega-analysis of the callosal data of the NFBC1986 and ALSPAC showed lower MD in exposed males. Together the findings may suggest a higher density of small fibres in the corpus callosum in exposed males in early adulthood.

Our finding of smaller callosal volume could be explained by fewer callosal axons, smaller axon diameter, or a thinner myelin sheet of the axons in exposed males. Lower density of axons is an unlikely explanation because density seems to be invariant of callosal size (Aboitiz et al., 1992). Of the aforementioned alternatives, the presence of thinner axons could also relate to higher FA and lower MD (mega-analysis) in exposed males, a contrast mechanism also proposed in Publication I. In the present work, a higher R2 relaxation rate was associated with exposure in males in a supplementary analysis of data available only in the replication cohort, the ALSPAC (Table S2). The intensity of R2 correlated with small-diameter fibres in Publication I Part 1, which further suggests that a higher number of small-diameter fibres in exposed males could account for our findings.

No associations were observed in MTR in this work, which suggests that axonal alterations, rather than myelination, could explain our findings. In Publication I, significantly higher callosal MTR was observed in males vs. females in the same sample (NFBC1986), which implies that tissue features accountable for by sex differences in MTR seem to be different from those of PEMCS. It should, however, be kept in mind when comparing the two studies that the magnitude of the expected effect of PEMCS on brain measures is notably

smaller and the many confounding factors of greater impact as compared to those of Sex.

Lower birth weight is a commonly reported outcome of PECMS, especially in female new-borns (Voigt et al., 2006). In this work, birth weight seemed to be smaller in males and females in all samples, but the association was significant only in females in the NFBC1986 and males and females in the SYS. These groups are the largest by the number of exposed individuals which may, in part, render the associations detectable. Contrary to those on birth weight, outcomes of exposure on brain measures were observed in males in the NFBC1986 and ALSPAC (mega-analysis). It should be, however, kept in mind that the neurodevelopmental consequences of nicotine in rodents have been reported already on lower than growth-impairing levels (Navarro, Seidler, Schwartz et al., 1989; Ribary & Lichtensteiger, 1989).

The observed Exposure-by-Sex interaction in the NFBC1986 indicates a differential effect of exposure in the sexes, even though no main effect was observed in females. The opposite sign of correlation in the sexes between PEMCS and callosal volume (males: $r = -0.18$ and females: $r = 0.08$) and FA (males: $r = 0.20$ and females: $r = -0.12$) suggests different, and potentially opposite, effects of exposure in males and females, with possible correlates in the prenatal and adolescence programming of brain sexual dimorphism. Another possible explanation for the lack of associations in females is that the female brain may be more vulnerable to insults during the postnatal vs. prenatal period (Fitch et al., 1991a; Fitch et al., 1991b).

Males in the NFBC1986 also showed an Exposure-by-Segment interaction in all measures, namely segment volume, FA, MD, and MTR, suggesting a differential effect of the exposure across the anterior-posterior profile of the corpus callosum. As a *post hoc* analysis, the effect of the exposure was modelled in individual callosal segments; Associations between PEMCS and callosal volume, FA, and MD, but not MTR, were observed mostly in the genu and body segments (G3, B1, B2 and B3). The median fibre diameter in these regions is below 1 μm, which is intermediate of the genu and splenium. Gigantic fibres of more than 3 μm in diameter with interhemispheric conduction delays of a few milliseconds are also characteristic of the region (Aboitiz et al., 1992). Fibres in these regions seem to connect the somatosensory and auditory areas in macaques and humans, with a possible function in the timing of cellular responses between the two body representations and auditory fields (Aboitiz et al., 1992; Alexander & Warren, 1988; Lamantia & Rakic, 1990).

The samples used in this work were of considerably different ages; NFBC1986: 25-27 y, SYS: 12-18 y and ALSPAC: 18-21 y. Correlations between Age and callosal MRI measures were calculated to aid interpreting the findings at different ages: The observed correlations were weak ($r < 0.1$) and did not differ considerably across callosal segments. This may be due to the narrow age ranges in the NFBC1986 and ALSPAC and also because age-related variation may be too subtle to detect in the used measures of the corpus callosum. We decided, however, to adjust our models for Age to account for the minor associations and any differential effect on exposed and unexposed individuals. White matter shows a protracted developmental trajectory until the 30s (Westlye et al., 2010), and it is reasonable to expect some alterations due to PEMCS (or other factors) to emerge not only postnatally, but during the adolescence phase of brain developmental reprogramming (Andersen, 2003; Paus, 2013a). Such postponed effects may partly explain the findings of associations only in the two older samples in this work. It should, however, be kept in mind that the possible age effects cannot be distinguished from cohort effects due to lack of longitudinal data.

Unlike their usual mode of action in the adult brain, neurotransmitters in the developing nervous system modify gene expression and guide the programming of cell morphology, differentiation, and survival (Slotkin, 1998). Nicotine regulates neurodevelopment through premature cellular differentiation and brain-specific deficits in cell numbers (Slotkin et al., 1987). The reported functional and behavioural consequences are largely sex-specific and vary by maturational phase (Ribary & Lichtensteiger, 1989). Numerous interactions of prenatal nicotine exposure on typical testosterone-induced development have been described in animal literature, including suppression of the characteristic plasma testosterone rise during gestation (Lichtensteiger & Schlumpf, 1985) and reduced testosterone production in the testis of young adult rats (Sarasin et al., 2003). The effect is possibly conveyed by stimulation of corticosterone by prenatal nicotine and the following suppression of testosterone (Sarasin et al., 2003). In humans, PEMCS has been associated with the programming of foetal testis function and gene expression (Fowler et al., 2009), factors that may modulate the various ill effects of the exposure on male reproductive and pubertal development in adolescence and early adulthood (Jensen et al., 2004).

The impact of foetal testosterone seems to be essential for the masculinization of the rat corpus callosum in adulthood (Fitch et al., 1991a; Mack et al., 1996). In humans, foetal testosterone has been associated with grey (Lombardo et al., 2012) and white matter (Chura et al., 2010) structure. White matter volume increases

more steeply in adolescence in males compared to females (Giedd et al., 1999). In males, the increase of white matter volume has been associated with plasma testosterone level, which is mediated by the transcriptional activity of the testosterone receptor (Perrin et al., 2008). Reflecting the simultaneous variation in the T1w and MTR measures, the increase in WM volume in males may be accounted for by the increase in axonal volume rather than myelination (Paus & Toro, 2009). Noting this evidence, it is possible that PEMCS modulates the programming of the foetal brain, resulting in alterations in the androgen activity-mediated emergence of large axons in adolescence and early adulthood. Caution should, however, be taken in interpreting the findings, because earlier literature on the actions of prenatal nicotine on the human brain is extremely scarce and because no developmental models could be tested in this work.

8.4 Maternal prenatal body mass index and offspring white matter microstructure (III)

In this work, we studied the relation between maternal prepregnancy BMI and white matter microstructural measures in offspring in three prospective birth cohorts: in the PREOBE at 6 years, in Generation R at 10 years and in the NFBC1986 at 26 years. Tractography tracings of 13 major white matter tracts were studied using means of diffusion measures. Maternal prepregnancy BMI was associated with higher FA and lower MD in multiple tracts at ages 10 and 26 years, but none of the associations were in the same tracts across the two cohorts. No associations were observed at 6 years.

One prior case-control study examined the relation between maternal body composition in early pregnancy and child white matter FA at two weeks of age. The study reported that maternal fat mass percentage is negatively associated with child FA mostly in the frontal white matter regions and, further, that methylation of neurodevelopment-related genes in umbilical cord tissue is altered in obese vs. normal-weight mothers (Ou et al., 2015). Negative and relatively large, while still statistically insignificant, beta estimates of the relation of maternal BMI and child FA were also observed in our work at six years. Our findings between the measures at ten years, again, show negative association in some e.g., the *forceps minor*, and positive in other tracts e.g., the *inferior fronto-occipital fasciculus*. It is unclear whether the field of view in Ou et al. (2015) included the *medial lemniscus* or *middle cerebellar peduncle*, which showed negative and positive associations, respectively, between maternal BMI and child FA at ten years in our

work. Opposite to the earlier report in infants, we observed positive associations in the *superior longitudinal fasciculus* and *corticospinal tract* (part of the *corona radiata*) at 26 years.

The discrepancy between the findings and Ou et al. (2015) may be explained by differences in study design or methodology, but, noting the large age difference, also by the extensive changes due to the maturation of white matter from birth to adulthood. The development of white matter at two weeks of age, as in Ou et al. (2015), concerns the beginning of regionally asynchronous axonal pruning and myelination, while FA is strongly influenced by large extra cellular space, low axonal packing, and high permeability of axonal membranes. Contrast-generating features for FA are different at 10 and 26 years, when maturation takes place mostly in myelination and axonal growth. The mechanisms underlying the observed variation in FA in Ou et al. (2015) and the present work may thus be considerably different, but possibly intertwined, for example, by the reported maternal obesity-induced epigenetic alterations that may influence white matter maturation across youth.

A recent work by Alves et al. (2021) failed to find an association between maternal prepregnancy BMI and offspring FA in a sample of 100 children but, instead, reported an interaction with child physical activity: Higher global and regional FA, partly overlapping with the findings of our work, were observed in physically active vs. inactive children of obese mothers, while no associations were observed in children of lean mothers (Alves et al., 2021). Numerous factors, including maternal diet and offspring physical activity, may modify the effects of maternal prepregnancy BMI on offspring white matter outcomes from childhood to adulthood, and should be considered in future studies.

Our observations of associations between higher maternal prepregnancy BMI and FA in the *cingulum tract* in children aged ten years may relate to earlier findings in functional MRI (fMRI) in the *dorsal anterior cingulate cortex* (dACC), a region linking motivational outcomes and behaviour (Hayden & Platt, 2010). Maternal prepregnancy fat mass percentage was associated with weaker connectivity of the dACC to the prefrontal network in resting-state fMRI in two-week-old infants (Li et al., 2016). Even earlier, alterations associated with maternal BMI seem to exist already in the foetal brain (Norr et al., 2021). Two studies in older children and adolescents, however, report associations between maternal current, but not early-pregnancy, BMI and offspring food cue reactivity in the dACC (Carnell et al., 2017; Luo et al., 2021). Earlier studies suggest maternal current BMI should be taken into account in future studies of exposure

and offspring neurodevelopment. Further, despite some regional correspondence, the findings in fMRI should be considered with caution due to the different methodologies and models of signal origin.

The observed associations between maternal prepregnancy BMI and white matter microstructural measures at ages 10 and 26 years and lack of associations at 6 years may be explained by differences in cohorts, including scanner effects, or various uncontrolled factors e.g., breast feeding, maternal diet, child BMI and physical activity. Further, data on maternal BMI in the three cohorts were gathered in different decades and nationalities, which may modulate associations between the exposure, outcome, and confounders.

Earlier preclinical studies have shown mechanistic causal findings in offspring neurodevelopment and white matter alterations due to maternal BMI before and during pregnancy (Kim et al., 2016; Wang et al., 2006). The lack of causal evidence in humans, however, emphasises that a wider framework of *early adversity* should be considered when interpreting findings in the present and other observational studies (Nelson & Gabard-Durnam, 2020). The hypothesis of the *developmental origins* of effects of maternal obesity on offspring health incorporates various pathways, including placental, inflammatory, epigenetic, metabolic, and mechanisms via circulatory substances (Patel et al., 2015). For example, maternal inflammation seems to mediate the effects of different early adversities, including non-optimal maternal BMI, on offspring neurodevelopment (Girchenko et al., 2020). Further, maternal BMI and inflammation seem to be coupled through different markers (Madan et al., 2009). Maternal inflammation has been shown to cause convergent neurodevelopmental alterations in preclinical studies (Graf et al., 2014; Gumusoglu & Stevens, 2019; Wang et al., 2006), whereas clinical studies show associations with neurodevelopmental disorders and brain alterations (Han et al., 2021; Nazzari & Frigerio, 2020).

One explanation for our finding of associations at 10 and 26 but not 6 years is that maternal prepregnancy BMI, or a related unknown factor, may programme long-term white matter development, for example, via epigenetic alterations (Edlow et al., 2016). Indeed, transcriptional changes concerning neural development and signalling in adulthood were observed to depend on offspring's current age and time of prenatal immune activation (Richetto et al., 2017). Noting that FA, a sensitive marker of human white matter microstructure, markedly increases during development and plateaus only between 24 and 33 years (Westlye et al., 2010), it is possible that our finding of higher FA in exposed individuals in childhood and early adulthood may partly arise from shifts in

developmental timing. The hypothesis of earlier maturation agrees with the finding of earlier menarche in females of mothers with obesity (Keim et al., 2009; Rubin et al., 2009), whereas early adversity in general may also alter the timing of maturation (Rickard et al., 2014).

8.5 Strengths of the study

A major strength of this work is the prospective cohort samples available in each publication. All samples were based on birth cohorts, notwithstanding the SYS, which was collected in childhood. While different exclusion criteria were used, the cohorts in general were aimed to represent the general population, which offers some degree of generalisability of results. Collection of parents' and offsprings' demographic and clinical data started before or during pregnancy in all samples, which reduces recall bias for these variables. Owing to the prospective birth cohort design, a comprehensive set of covariates were able to be recorded during initial data collection and utilised for adjusting statistical models.

All publications also benefited from the relatively large sample sizes of participants with neuroimaging data, multiple mutually complementary imaging modalities, and harmonised methodology across the used samples. This reduced variation in results due to methodological discrepancies and aided testing for replication across samples and interpretation of the findings. The young age of participants (from 6 to 26 years) and limited variation in age in each cohort allowed the study of brain outcomes at intermediate points of maturation and prevented confounding due to brain alterations of senescence.

Albeit the research setting was explorative due to limited earlier information, all publications benefited from focusing analysis on distinct regions. Publications I and II were targeted on the midsagittal corpus callosum, where histology had been earlier described. Publication III was focused on analysing individual tracts. Each white matter tract is associated with a set of actions and is coarsely distinguishable from other tracts, for example, using prior anatomical knowledge and tractography in native space, which make tracts feasible targets of study. Using callosal segments or white matter tracts also alleviates the problem of multiple comparisons as compared to voxel-wise analysis and reduces the appearance of spurious or artefactual effects. Although brain imaging measures are technically limited and interpretation of findings is generally challenging, the measures capture sensitive information on underlying biology and are not subject to biases or unwanted variation of behavioural or questionnaire data.

8.6 Limitations of the study

A major limitation of this work is the lack of longitudinal data, which would allow changes in brain outcomes at different ages to be studied and the effects of time-dependent covariates to be separated. While data processing across samples was harmonised in each publication, the use of replication analysis was limited by the variation in participant age, MRI scan settings, and quality of covariate information across samples. Pertaining to Publication III, first, covariate data for breast feeding was partly missing and was not used and, second, pre-pregnancy maternal weight was self-reported at the beginning of pregnancy, although a clinical measure would have been more accurate. The exposures of interest in Publications II and III i.e., maternal smoking and BMI, respectively, may be partly heritable and the participant's own smoking or BMI may account for similar or different brain outcomes, but these effects were not studied.

The work would have benefited from larger sample sizes and more comprehensive records of covariates at the time of pregnancy, although these limitations are alleviated by the use of the birth cohort setting. Attrition limits considerably the representativeness of the imaging samples, including the used subsample of the NFBC1986 with a 34% participation rate. Common to many neuroimaging studies, the non-specificity of imaging measures impedes making definitive interpretations of underlying anatomical features. Using a model structure with known anatomical features, such as the corpus callosum, or complementing findings with other imaging modalities can, however, endorse hypotheses on more specific anatomical variation.

9 Conclusions

9.1 Main conclusions

Based on our findings, early-life factors, including sex, maternal cigarette smoking during pregnancy, and maternal pre-pregnancy BMI, are associated with alterations in the white matter structure of offspring in humans. The use of multiple prospective cohort samples and various covariates strengthens this conclusion and, together with earlier preclinical and human histological findings, enables possible pathways and mechanisms to be discussed. The hypothesis of the developmental origins of our findings, however, cannot be confirmed using the present observational cross-sectional study design, and mechanisms underlying white matter alterations remain elusive.

The different samples, imaging measures, and study questions pertaining to each publication offer complementary information on the role of early predictors of white matter structure. The imaging measures used in Publication I were observed to be sensitive to different tissue features in the corpus callosum, which emphasises the need to consider, whenever possible, local histological information in interpreting imaging measures. Reflecting these findings, males and females in early adulthood seem to differ in fibre density and myelination in parts of the mid-sagittal callosum, a finding that is partly consistent with earlier work.

This is the first work to investigate maternal prenatal cigarette smoking and BMI using multimodal measures of white matter structure in different cohorts of children and young adults. As shown in Publication II, maternal cigarette smoking during pregnancy is associated with variation in callosal microstructural measures in male offspring, possibly relating to higher density of small-diameter fibres. In Publication III, maternal pre-pregnancy BMI is associated with microstructural variation in multiple non-overlapping white matter tracts in offspring at different ages. As one possible hypothesis, maternal inflammation may programme the myelination, density, or thickness of fibres in these tracts, possibly via altered maturational timing.

As demonstrated in preclinical studies, prenatal factors may modulate typical developmental programming and thus give rise to the emergence of white matter alterations only in adolescence or adulthood. While preclinical studies offer causal evidence, findings in animals cannot be generalised to humans due to the

complex interplay of intrinsic and environmental factors across human development. The findings of this work should, instead, be interpreted in a wider context of clusters and pathways of factors pertaining to the exposure; for example, maternal smoking may be related to factors in the family environment and other early adversities, which may interact with an individual's health and development across youth, ultimately bringing about the measured variation in white matter structure. The directionality of effects also remains unknown; a white matter alteration associated with an early exposure may already exist in the parents and act through reverse causality. Despite the limitations, the studied early factors seem to be associated with offspring white matter alterations that require further research.

9.2 Clinical implications

In this work, prenatal maternal cigarette smoking and BMI are associated with white matter alterations, which may relate to earlier reports linking the exposures to neurodevelopmental and psychiatric disorders. In association with increasing rates of maternal prenatal obesity, indicators of compromised brain health in mothers and children are becoming more prevalent. The reported neuroimaging findings show long-term associations with the exposures and emphasise the need for care and intervention in reducing maternal smoking during pregnancy and, overall, in compromised health.

9.3 Implications for future research

The findings of this work need replication in a longitudinal study design to better elucidate the roles of predictors and covariates in relation to the brain findings. Factors affecting the development of white matter and especially the corpus callosum need more research. Standardised image processing methods and data-sharing policies are needed to better compare results across individual studies and cohorts.

The findings of early predictors and white matter structural alterations are valid for stimulating discussion on possible important covariates and underlying mechanisms in future studies. The observed associations in large human samples are, as such, also important for preventative work and aid in discussing known, possibly harmful, effects of exposures. Further, the birth cohort study design is important for directing future observational, preclinical, and case-control studies

to relevant topics. Future studies of early-life exposures and brain outcomes would benefit from a Mendelian randomisation approach and consideration of genetic, metabolic, and somatic variables. Finally, future studies on the NFBC1986 should include the study of paternal factors, in conjunction with corresponding maternal exposures, to aid separating *in utero* effects from familial or genetic effects.

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Original publications

I Björnholm, L., Nikkinen, J., Kiviniemi, V., Nordström, T., Niemelä, S., Drakesmith, M., Evans, J. C., Pike, G. B., Veijola, J., & Paus, T. (2017). Structural properties of the human corpus callosum: Multimodal assessment and sex differences. *NeuroImage, 152*, 108–118. https://doi.org/10.1016/j.neuroimage.2017.02.056

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III Verdejo-Román, J.*, Björnholm, L.*, Muetzel, R. L., Torres-Espínola, F. J., Lieslehto, J., Jaddoe, V., Campos, D., Veijola, J., White, T., Catena, A., Nikkinen, J., Kiviniemi, V., Järvelin, M. R., Tiemeier, H., Campoy, C., Sebert., S., & El Marroun, H. (2019). Maternal prepregnancy body mass index and offspring white matter microstructure: results from three birth cohorts. *International Journal of Obesity, 43*(10), 1995-2006. https://doi.org/10.1038/s41366-018-0268-x

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1653. Parkkila, Karri (2021) Biomarkers and clinical parameters in comprehensive cardiovascular risk estimation

1654. Korkalainen, Noora (2022) Long-term neurologic and cardiovascular outcome in fetal growth restriction : a longitudinal study from prenatal period to early school age

1655. Kiiskilä, Jukka (2022) Association of mitochondrial DNA haplogroups with endurance performance

1656. Kyrklund, Mikael (2022) Antibody response to oxidized epitopes and oral bacteria in atherosclerosis

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1658. Kanavakis, Georgios (2022) Associations of facial profile and occlusion in the Northern Finland Birth Cohort 1966

1659. Khakpour, Shahab (2022) Multi-component finite element analysis of low-energy acetabular fracture : computational study of pelvic girdle fracture mechanism

1660. Tapio, Joona (2022) Role of HIF-P4H inhibition and hemoglobin levels in metabolic diseases

1661. Pihlaja, Toni (2022) Varicose vein disease : postoperative care and treatment of venous ulcers

1662. Heula, Anna-Leena (2022) Meningeal protein synthesis in chronic subdural hemorrhagies : analysis of proteins and evaluation of their clinical significance

1663. Erikson, Kristo (2022) The brain as an end organ in sepsis?

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