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BRAIN WHITE MATTER DEVELOPMENT, ASSOCIATIONS TO MATERNAL PERINATAL PSYCHOLOGICAL DISTRESS AND EMOTIONAL ATTENTION AT THE AGE OF 5 YEARS

Venla Kumpulainen

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To my dear family

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ABSTRACT

Development of the brain white matter (WM) is highly plastic, and myelination continues from the second trimester into early adulthood which predisposes the brain to effects of both adverse and supporting factors during early life. Maternal perinatal psychological distress is acknowledged as an important contributor to the offspring's development. Furthermore, sex is known to affect the WM microstructure as well as the emergence of psychopathologies. Understanding the normal variation of microstructure in the developing brain WM is a prerequisite for recognizing alterations inflicted by early adversity that have possible long-term programming effects on behavioral and socio-emotional outcomes.

This study aimed to 1) investigate the incidence, risk factors and consequences of incidental findings in brain magnetic resonance imaging of infants; 2) optimize data acquisition parameters and pre-processing pipeline of diffusion tensor imaging (DTI) protocol applied with children; 3) describe the normal microstructural features of WM in infants and 5-year-old children; 4) investigate the associations between WM integrity and exposure to maternal perinatal psychological distress; 5) explore the associations of WM integrity and child's emotional attention.

Vacuum assistance and vaginal birth were observed to increase the risk for subdural hemorrhages (incidence 6.9%) with no effects on early neurological development. In 5-year-olds, higher WM integrity in widespread regions was observed in girls, and we found marked asymmetry in the WM, resembling patterns previously shown in adults. Maternal perinatal psychological distress showed sex- and timing-specific associations with WM integrity: prenatal symptoms predicting higher integrity in boys and postnatal symptoms lower integrity in girls. Maternal postpartum anxiety increased girls' vigilance toward fearful faces, which was also associated with reduced WM integrity. The results imply that maternal psychological distress affects WM development with effects especially on girls. Collectively, these studies provide fundamental insight for future studies addressing the mediating mechanisms and longer-term effects between the observed associations.

KEYWORDS: white matter; development; DTI; perinatal maternal psychological distress; emotional attention; sex difference; incidental finding

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VENLA KUMPULAINEN: Aivojen valkean aineen kehitys, äidin raskauden ympärillä esiintyvän psykologisen stressin vaikutus ja tunneperäinen huomion kohdentaminen 5-vuotiailla
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TIIVISTELMÄ

Aivojen valkean aineen kehitys jatkuu toiselta raskauskolmannekselta varhaiseen aikuisuuteen, mikä altistaa sen muovautuvuutensa vuoksi sekä epäsuotuisten että tukevien tekijöiden vaikutukselle varhaisen elämän aikana. Äidin raskauden ympärillä esiintyvä psykologinen stressi on tunnettu jälkeläisten kehitykseen vaikuttava tekijä. Lisäksi sukupuoli vaikuttaa valkean aineen rakenteeseen ja psykiatristen häiriöiden ilmaantuvuuteen. Kehittyvien aivojen rakenteen normaalivaihtelun ymmärtäminen on oleellista, jotta voidaan tunnistaa aikaisten vastoinkäymisten aiheuttamia muutoksia sekä niiden mahdollisia pitkäaikaisia ohjelmoivia vaikutuksia käytökseen ja tunnepohjaisiin toimintoihin.

Tämän väitöskirjan tavoitteena oli 1) raportoida vastasyntyneiden aivojen magneettikuvien sattumalöydösten esiintyvyyttä, riskitekijöitä ja neurologisia seurauksia; 2) optimoida lasten diffuusiotensorikuvantamisaineiston keräämistä ja esikäsittelyä; 3) tarkastella 5-vuotiaiden valkean aineen normaalipiirteitä; 4) tutkia äidin raskauden ympärillä esiintyvän psykologisen stressin vaikutusta jälkeläisten valkean aineen rakenteeseen; ja 5) selvittää valkean aineen yhteyksiä lapsen tunnepohjaiseen huomion kohdentamiseen silmänliikemittausten avulla.

Imukuppiavustus ja alatiesynnytys lisäsivät sattumalöydöksinä havaittujen kovakalvonalaisten vuotojen (6.9 %) riskiä, mutta eivät vaikuttaneet varhaiseen neurologiseen kehitykseen. 5-vuotiaiden tyttöjen valkean aineen integriteetti oli laaja-alaisesti korkeampi poikiin verrattuna, ja epäsymmetrisyys vastasi aiemmin aikuisilla havaittua rakennetta. Äidin psykologinen stressi liittyi jälkeläisten valkean aineen integriteettiin sukupuoli- ja ajankohtariippuvaisesti: pojilla raskaudenaikainen altistus lisäsi valkean aineen integriteettiä, kun taas tytöillä raskaudenjälkeinen altistus vähensi sitä. Äidin raskauden jälkeinen ahdistus lisäsi tyttöjen tarkkaavaisuutta pelokkaisiin ilmeisiin, joka liittyi myös alentuneeseen valkean aineen integriteettiin. Aiempia tutkimustuloksia tukien äidin psykologisen stressin havaittiin muovaavan valkean aineen kehitystä etenkin tytöillä, ja tämä luo pohjaa mekanismien ja kausaliteetin tarkastelulle myös tulevissa tutkimuksissa.

AVAINSANAT: valkea aine, kehitys, DTI, äidin raskauden ympärillä esiintyvä psykologinen stressi, tunneperäinen tarkkaavaisuus, sukupuolierot, sattumalöydös

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Abbreviations

ACC	anterior cingulate cortex
ACR	anterior corona radiata
AD	axial diffusivity
ADHD	attention-deficit hyperactivity disorder
ALIC	anterior limb of the internal capsule
ANOVA	analysis of variance
ANS	autonomic nervous system
BCC	body of the corpus callosum
BMI	body mass index
CG	cingulate gyrus
CING	cingulum
CRH	corticotrophin-releasing hormone
CST	corticospinal tract
DP	disengagement probability
DT	time for disengagement
DTI	diffusion tensor imaging
EC	external capsule
EPDS	Edinburgh Postnatal Depression Scale
FA	fractional anisotropy
FDR	false discovery rate
FFA	fusiform face area
FOV	field of view
FSL	FMRIB Software Library
GCC	genu of the corpus callosum
GLM	general linear model
GM	grey matter
Gwk	gestational week
HINE	Hammersmith Infant Neurological Examination
HPA	hypothalamic pituitary adrenal
ICC	intraclass correlation coefficient
IFOF	inferior fronto-occipital fasciculus

ILF	inferior longitudinal fasciculus
ILF/IFOF	inferior longitudinal fasciculus/inferior fronto-occipital fasciculus
IPH	intraparenchymal hemorrhage
MAD	mean absolute deviation
MD	mean diffusivity
MRI	magnetic resonance imaging
OFA	occipital face area
OR	odds ratio
PCR	posterior corona radiata
PFC	prefrontal cortex
PI	ponderal index
PLIC	posterior limb of the internal capsule
pSTS	posterior superior temporal sulcus
PTR/OR	posterior thalamic radiation and optic tract
RD	radial diffusivity
rlIC	retrolenticular internal capsule
ROI	region of interest
SCC	splenium of the corpus callosum
SCL-90	Symptom Checklist 90
SCR	superior corona radiata
SDH	subdural hemorrhage
SE-EPI	Spin Echo-Echo Planar Imaging
SES	socio-economic status
SFOF	superior fronto-occipital fasciculus
SGC	synthetic glucocorticoids
SLF	superior longitudinal fasciculus
SNR	signal-to-noise ratio
SPSS	Statistical Package for the Social Sciences
SSRI/SNRI	selective serotonin/serotonin-noradrenalin reuptake inhibitor
TBSS	tract-based spatial statistics
TE	time of echo
TFCE	threshold-free cluster enhancement
TR	time of repetition
UF	uncinate fasciculus
VBA	voxel-based analysis
VIF	variance inflation factor
WM	white matter

List of Original Publications

This dissertation is based on the following original publications:

I Kumpulainen V., Lehtola, S. J., Tuulari, J. J., Silver, E., Copeland, A., Korja, R., Karlsson, H., Karlsson, L., Merisaari, H., Parkkola, R., Saunavaara, J., Lähdesmäki, T., & Scheinin, N. M. Prevalence and risk factors of incidental findings in brain MRIs of healthy neonates – The FinnBrain Birth Cohort Study. *Frontiers in Neurology*, 2020; Jan 8;10:1347

II Kumpulainen V., Merisaari, H., Copeland, A., Silver, E., Pulli, E. P., Lewis, J. D., Saukko, E., Saunavaara, J., Karlsson, L., Karlsson, H., & Tuulari, J. J. Effect of number of diffusion encoding directions in Diffusion Tensor Imaging of 5-year-olds using Tract-Based Spatial Statistical analysis. *Eur J Neurosci*, 2022; Sep;56(6):4843-4868

III Kumpulainen V., Merisaari, H., Silver, E., Copeland, A., Pulli, E. P., Lewis, J. D., Saukko, E., Shulist, S. J., Saunavaara, J., Parkkola, R., Lähdesmäki, T., Karlsson, L., Karlsson, H., & Tuulari, J. J. Sex differences, asymmetry, and age-related white matter development in infants and 5-year-olds as assessed with tract-based spatial statistics. *Human Brain Mapping*, 2023; May;44(7):2712-2725

IV Kumpulainen V., Copeland, A., Pulli, E. P., Silver, E., Kataja, E.-L., Saukko, E., Merisaari, H., Lewis, J. D., Karlsson, L., Karlsson, H., Tuulari, J. J. Pre- and postnatal maternal depressive symptoms are associated with white matter integrity in 5-year-olds in a sex-specific manner. *Biol Psychiatry*, 2023; Dec 15;94(12):924-935

V Kumpulainen V.*, Kataja, E.-L.*, Pulli, E. P, Copeland, A., Silver, E., Häikiö, T., Saukko, E., Korja, R., Karlsson, L., Karlsson, H., Tuulari, J. J. Attentional bias toward fearful faces is associated with maternal postnatal distress and alterations in white matter microstructure in 5-year-old girls. *Preprint in bioRxiv. Submission to Human Brain Mapping*

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1 Introduction

The development of white matter (WM) is a dynamic process beginning during the prenatal period and continuing into early adulthood (Dubois et al., 2014; Lebel & Deoni, 2018). Plasticity during development predisposes white matter to influences of variable, both supporting and adverse, environmental factors that participate in the programming of the developing brain and behavioral outcomes. *In utero*, the fetus is exposed to maternal stress and agents transmitted by blood circulation, while the contributors after birth are more versatile. Perinatal maternal psychological distress has gained special attention as a risk factor for impaired neurodevelopment and psychopathology in the offspring (Buss et al., 2012).

Research of the white matter in pediatric populations with magnetic resonance imaging (MRI) requires adjusting the data acquisition and processing parameters appropriately for the developing brain. Currently, the optimization of MRI parameters has mainly relied on adult population studies. However, adult-based protocols are not directly applicable to pediatric populations in which, for example, intrascanner motion is a major complication (Baum et al., 2018), and methodological choices need to be accommodated accordingly. Additionally, incidental findings are common in MRI (Illes et al., 2006; Jansen et al., 2017; Vernooji et al., 2007), and as they may have grave and long-lasting implications on the families, researchers need to be prepared to handle them appropriately.

The developmental trajectory of normal WM maturation and additionally the emergence of later morbidity are affected by sex. Generally, studies have provided evidence of earlier white matter maturation in girls (Asato et al., 2010; Barnea-Goraly et al., 2005; Bava et al., 2011; Seunarine et al., 2016; Simmonds et al., 2014; Wang et al., 2012), but the results have varied widely between study populations. Furthermore, alterations in asymmetric patterns of white matter are observed in conditions like dyslexia, autism, and attention-deficit hyperactivity disorder (ADHD). In relation to this, normal features of WM lateralization during development are again a rather understudied topic. Both sex and asymmetric features are important contributors to be considered in WM developmental studies.

According to prior literature, exposure to factors such as early stress and inappropriate parental care inflict undeniable consequences on cognitive and socio-

emotional functions and predisposition to conditions such as depression and anxiety. However, their neural correlates have remained largely undetermined. Emerging evidence has associated prenatal exposure to maternal distress with alterations in WM integrity in the offspring (Borchers et al., 2021; Dean et al., 2018; Graham et al., 2020; Lautarescu et al., 2020; Hay et al., 2019; Marroun et al., 2018; Zou et al., 2019), but marked discrepancies between studies call for further investigations. Associations between maternal postpartum depression and WM changes have been under focus only in a few studies (Lebel et al., 2016; Zou et al., 2019; Borchers et al., 2021; Marroun et al., 2018), and results were again inconclusive, as associations were observed in three out of five reviewed studies. Maternal psychological distress has also been shown to affect emotional attention in the offspring. Maternal depressive and anxiety symptoms predicted attentional bias to fearful faces and threat signals in the offspring (Kataja et al., 2019; Morales et al., 2017), and the vigilance toward threat signals has been associated with increased risk for internalizing symptoms. In the prior literature, girls have been detected to be especially sensitive to maternal psychological distress (Braithwaite et al., 2016; Dean et al., 2018; Erickson et al., 2019; Quarini et al., 2016; Simcock et al., 2016; Wen et al., 2017).

Consequently, this thesis aimed to improve the methodological practices related to pediatric brain developmental studies first by investigating the prevalence, risk factors, and clinical significance of incidental findings in brain MRI of an infant population, and second, by evaluating and optimizing the data acquisition and pre-processing protocols of pediatric diffusion tensor imaging (DTI). Next, the study aimed to examine the normal variation in the integrity, sex differences, and the asymmetry of white matter in a healthy unselected pediatric population of infants and 5-year-olds. Finally, the aim was to investigate the effects of maternal psychological distress during the perinatal period on the white matter at the age of 5 years, and further examine these associations in the context of developing emotional attention at the age of five years.

2 Review of the Literature

2.1 MR Imaging of the Pediatric Brain

Magnetic resonance imaging (MRI) provides a versatile radiological tool to examine both the brain structure and function. The image contrast is generated by using high magnetic fields and radiofrequency (RF) pulses without ionizing radiation and is thus a safe and non-invasive method also for pediatric studies.

2.1.1 Technical Considerations

In MR imaging, the signal acquisition utilizes protons present mainly in the fat tissue and water. The protons have a property called "spin", which describes the precessional motion in a magnetic field at a characteristic frequency (Larmor frequency). A constant magnetic field (B_0) is applied to align the nuclear spins of the protons parallelly (parallel or antiparallel to the magnetic field). A radio-frequency pulse is used to excite the protons and the magnetization is tilted perpendicular to the magnetic field. After excitation, the proton spins attenuate to the equilibrium orientation with a rotational motion (T_2 relaxation) and induce a current to a coil which can be detected with receiving radio-frequency coils. Only the protons with a spin precession frequency matching the radiofrequency are excited, and the excitation thus depends on the local tissue properties. Spatial information is added by applying a magnetic field gradient before RF pulses (phase encoding gradient). A contrast between tissues can be adjusted by changing the amplitude and the timing of the RF pulse. Time of repetition (TR) refers to the time between subsequent RF excitations, and time of echo (TE) to the time between the excitation and the signal acquisition.

The quality of MR images depends on multiple factors. Increasing the magnetic field strength improves both the spatial resolution and signal-to-noise ratio (SNR) of the image. A thinner slice thickness and thus a smaller voxel size also improves the resolution, but simultaneously denotes longer imaging time, as more excitations are required to cover the region of interest. On the other hand, the smaller voxel size decreases the signal received and thus ultimately the SNR. Repetition and averaging can be used to improve the SNR, but this also lengthens the imaging time.

Additionally, both subject-related and sequence-specific artifacts limit imaging quality (Tamnes et al., 2017; Tokariev et al., 2020).

2.1.2 Incidental Findings

Incidental findings refer to previously undetected abnormalities found in situations with no purpose of discovering them (Illes et al., 2002). Part of incidental imaging findings may be of clinical relevance and, as they are usually discovered in healthy asymptomatic subjects, they pose various ethical and practical questions (Illes et al., 2006). In the field of MR imaging, incidental findings are continuously more frequent as the scanner hardware and consequently, the imaging resolution are improving. This is especially relevant in research-related scans using high-resolution MRI sequences as a common practice, as the detected prevalence of incidental findings is higher compared to MRI performed as a part of clinical screenings with lower resolution scanner hardware (4.7% and 1.7%, respectively) (Morris et al., 2009). Current problems regarding the incidental findings include scarce information on the consequences on an individual level, the best practices for sharing the information with the participants and guaranteeing that the study participants understand the possible repercussions of study participation in all aspects (Wardlaw et al., 2015). Furthermore, discussion on whether screening of incidental findings should be part of all brain MR imaging studies is currently ongoing (Li et al., 2021). This presumption of the screening duty would lead to the inclusion of MR sequences suitable for clinical evaluation (e.g., T1 weighted images) and a neuroradiologist's consultation in all study protocols.

Pediatric MR imaging raises additional ethical questions e.g., in situations where the participating child's wishes on hearing about the possible findings differ from those of parents (Kumra et al., 2006). The consequences of incidental findings particularly in pediatric subjects may be profound and cause a life-long need for follow-up which can, at worst, have detrimental effects on a child's development. While incidental detection of a treatable abnormality may result in overall net benefit with curative medical care being administrated in time, the treatment itself can also be harmful, and without knowledge of the natural course of the finding can cause net disadvantage (Dangouloff-Ros et al., 2019).

In the meta-analysis of incidental findings in pediatric brain imaging (Dangouloff-Ros et al., 2019), high-resolution MRI (magnetic field strength at least 3T and voxel resolution $2x2x2mm^3$) was observed to show a significantly higher prevalence of incidental findings compared to standard MRI resolution with a relative risk of 1.32. In conclusion, at least one incidental finding was detected in 16.4% of all participants in the reviewed studies, and 2.6% needed to be referred for further clinical evaluation (Dangouloff-Ros et al., 2019). Sex was not detected to

affect the prevalence of incidental findings (Dangouloff-Ros et al., 2019). The quality and prevalence of pediatric brain MRI incidental findings vary depending on the age of the study population. Intracranial hemorrhages are frequent in infant populations (Looney et al., 2007; Rooks et al., 2008; Sirgiovanni et al., 2014; Whitby et al., 2004), while venous anomalies, white matter hyperintensities (due to infection, inflammation, or injury) and tumors are emphasized in older children. Developmental cysts (pineal gland and arachnoid) are common benign findings in pediatric populations of all age ranges.

Intracranial hemorrhages are a relatively common finding in infants with brain MR scanning close to birth (at the age of 1 to 5 weeks). Prevalence estimates of neonatal incidental intracranial hemorrhages vary between 8 to 46% in previous studies (Looney et al., 2007; Rooks et al., 2008; Sirgiovanni et al., 2014; Whitby et al., 2004), in addition to which the detected locations and types of hemorrhages differ. Subdural hemorrhages (SDH) are the most common findings (Looney et al., 2007; Rooks et al., 2008; Sirgiovanni et al., 2014; Whitby et al., 2004) with the majority located posteriorly and infratentorially (Looney et al., 2007; Sirgiovanni et al., 2014; Whitby et al., 2004). This typical location differs from that of SDHs related to non-accidental head injuries (previously known as shaken baby syndrome), which are most often seen in the interhemispheric fissure and over the hemispheres (Ewing-cobbs et al., 2000; Poussaint & Moeller, 2002). Radiologically, birth-related intracranial SDHs are often bilateral and widely distributed, forming a thin film, with little indications for clinical interventions (Gabaeff, 2013; Squier & Mack, 2009). In addition to SDHs, minor incidental subarachnoidal and intraparenchymal hemorrhages may occur in infants (Looney et al., 2007; Tavani et al., 2003). Epidural hemorrhages are a very rare consequence of birth, but still of clinical significance, as they often require surgical interventions (Sharma et al., 2005). Recent findings suggest that the neonatal dural venous plexus is more extensive and immature compared to that of adults, especially in the regions of the tentorium and the posterior fossa, making the veins more vulnerable to injury (Mack et al., 2009). Intradural hemorrhage also often coincides with SDH, suggesting a role in the origin of the blood (Cohen & Scheimberg, 2009). The exact etiology of the bleeding could be direct pressure changes and/or occlusion of the veins due to pressure, or hypoxic damage to the veins (Squier & Mack, 2009).

Risk factors generally associated with intracranial hemorrhages in infant populations include vaginal birth (Looney et al., 2007; Rooks et al., 2008; Whitby et al., 2004), while the effect of assistance (vacuum assistance or forceps) during delivery has remained more controversial (Åberg et al., 2016; Ekéus et al., 2014; Looney et al., 2007; Rooks et al., 2008). Additionally, prolonged delivery and higher birth weight were associated with increased risk for intracranial hemorrhages in infants in one study (Rooks et al., 2008).

Apart from hemorrhages, cysts (1.9 to 57% of subjects) (Lind et al., 2010; Whitehead et al., 2013), developmental venous anomalies (1.59 to 1.9%), non-specific white matter abnormalities (0.18 to 1.9%) and Chiari I malformation (0.17 to 0.63%) (Jansen et al., 2017; Li et al., 2021) are relatively common intracranial findings also in older children. In the absence of mass effects and symptoms, there is usually no requirement for therapeutic interventions (Dangouloff-Ros et al., 2019). Central nervous system (CNS) tumors are the most common solid tumors in children (15 to 20% of all pediatric malignancies) (Udaka & Packer, 2018). Even though neoplasm is a rare incidental finding (0.18 to 0.20% of subjects) (Dangouloff-Ros et al., 2019; Jansen et al., 2017; Li et al., 2021), they have severe and profound consequences requiring efficient management plans to guide participants rapidly to further clinical evaluation.

Separate guidelines on the management of incidental findings are suggested by researchers. Informing participants in advance about the possibility of incidental findings, already in the recruitment phase is of major importance, and simultaneously willingness to hear about the possible incidental finding can be inquired (Schmidt et al., 2013; Seki et al., 2010). The possibility of incidental findings and their consequences need to be explained clearly in advance even though it may decrease the interest in participating (Kumra et al., 2006). Study participants are often volunteers with no prior indications for MR imaging. Participants were shown to overestimate the personal benefits of MRI even when informed explicitly in advance about the differences between clinical and research MR imaging and that the latter is not designed for guiding clinical decisions (Schmidt et al., 2013). One suggested alternative is to disclose incidental findings only if net benefit is expected (Wolf et al., 2008). On the other hand, not informing the participants of the findings is also problematic, especially as participants often expect benefits from participation (Kumra et al., 2006). Another published protocol recommended discussing the findings with multiple researchers and consulting a specialist (e.g., a pediatric neurologist) (Seki et al., 2010).

To summarize, the current occurrence estimates as well as knowledge of risk factors of incidental findings vary between studies. The majority of infants with incidental findings are asymptomatic. However, due to their high occurrence, researchers using brain MRI need to be prepared for the discovery of incidental findings. More accurate estimates of the prevalence, risk factors, and possible clinical implications of incidental findings would support designing better procedures for handling them.

2.1.3 Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is an MRI method in which the quantification of water molecule diffusion due to thermal motion is utilized in depicting the architecture of white matter fibers *in vivo (*LeBihan 2001, Basser et al 2000, Pierpaoli and Basser 1996; Phan et al 2009; Mori and Zhang 2006*)*. In the brain tissue, the water movement is restricted by cell membranes, myelin sheaths, and microtubules, and the directionality of diffusion can be used to describe the integrity and directionality of axons. The magnitude of diffusion in a voxel is determined from signal attenuation between two excitations and DTI thus has a relatively low SNR. More precisely, the protons are allowed to diffuse between two opposite dephasing and re-phasing gradients, and with more movement of protons in the measured direction, fewer return to equilibrium at the re-phasing stage resulting in no signal. Diffusion tensor imaging requires excitations in at least six unique directions to acquire information on the direction of diffusion, and the estimate of the orientation of the diffusion tensor improves by increasing the number of directions. Another parameter specific to DTI is the diffusion coefficient (b value), which is a combination of diffusion time, gradient duration, and gradient strength, and indicates the diffusion weighting of the image. Thus, a higher b value denotes stronger diffusion weighting but simultaneously leads to a loss of signal and deterioration of SNR.

Diffusion per voxel is described by a 3D tensor model in the shape of a diffusion ellipsoid. The diffusion is divided into three eigenvectors which represent the direction and magnitude of diffusivity along each orthogonal axis (λ_1, λ_2, λ_3). Scalar values, mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD), and fractional anisotropy (FA), are calculated based on eigenvectors to facilitate the description of diffusion properties (Figure 1). Mean diffusivity is the mean value of three eigenvectors, AD represents the longitudinal diffusivity along the longest axis of the ellipsoid (λ_1) and RD is the average value of two minor axes of the ellipsoid (λ_2, λ_3). Fractional anisotropy is the most used scalar, describing the directionality of diffusion (values range between 0 and 1, with 0 indicating totally random and 1 unidirectional diffusion), and is calculated based on all three eigenvectors.

Optimization of DTI acquisition protocol parameters and pre-processing pipelines has relied mostly on adult-population studies. Adult studies have shown that the reduction of diffusion encoding directions and non-uniform sampling (Landman et al., 2007) deteriorate the accuracy and precision of DTI scalar values, and generally overestimate FA values (Barrio-Arranz et al., 2015; Chen et al., 2015; Giannelli et al., 2010; Sairanen et al., 2017). The effect of decreasing the number of diffusion directions is emphasized in peripheral WM regions where anatomical variance is higher and partial volume effects might be more prominent (Sairanen et al., 2017).

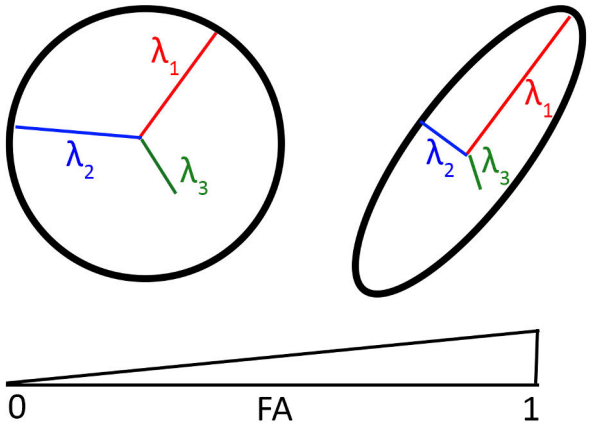


Figure 1. Directionality of the diffusion in a voxel is described with fractional anisotropy (FA) with values ranging between 0 (totally random diffusion) and 1 (unidirectional diffusion). The figure was created by Venla Kumpulainen.

Group comparisons of brain WM microstructural diffusion properties could be accomplished by a region-of-interest (ROI) analysis or a voxel-based analysis (VBA). However, tract-based spatial statistical (TBSS) analysis (Smith et al., 2006) is currently widely preferred as a standard methodological approach due to relieving problems with (minor) image misalignment and requirements for spatial smoothing before statistical analyses. In TBSS, a group-specific mean WM "skeleton" including only the core voxels of WM tracts is formed, the tract center estimates are projected individually, and voxel-wise group comparisons are performed only within the skeleton voxels. Even though TBSS is usually regarded to improve the sensitivity and objectivity of the results, the limitations and possible pitfalls must be considered carefully. As the method relies on FA maps, it has limited anatomical specificity, and there may be problems in segregating closely located WM tracts from each other. Additionally, observing the crossing and kissing of axons within a voxel is not possible with this method.

2.1.4 Special Features of Pediatric DTI

Diffusion tensor imaging is highly sensitive to disturbances such as intrascanner motion and subject-unrelated factors like artifacts related to magnetic field inhomogeneities and eddy currents that are induced by rapid switching of gradient coils (le Bihan et al., 2006). Scanning times are longer compared to e.g., T1 or T2 images due to the requirement of acquiring either multiple diffusion encoding gradient directions or repeating the sequences to improve the resolution and image quality. Thus, a prerequisite for successful DTI data acquisition is the subject's ability to lie immobile for a relatively long time. This combined with the general avoidance of anesthetics in pediatric research-related MRI with no clinical implications (Artunduaga et al., 2021)

places challenges, especially in scanning procedures of young children. Additionally, the lack of age-appropriate templates complicates the comparison between studies and recognition of WM regions (Dufford et al., 2022; Tamnes et al., 2017).

The repeatability of DTI results in pediatric populations has remained an understudied subject despite the special challenges associated with this subject group are usually acknowledged. To address this issue, the intrascan test-retest repeatability within our population was previously evaluated in a sub-study outside this thesis (Rosberg et al., 2022). Furthermore, investigation of the effect of the number of diffusion-encoding directions on the repeatability of DTI scalars would aid in designing age-appropriate data acquisition and pre-processing protocols.

2.2 White Matter Anatomy

Human brain WM is formed of a large network of axonal bundles that allow the exchange of information and communication between separate brain regions. Unlike assumed previously, WM structure is highly dynamic and correspondingly as important for brain function as grey matter (GM) which consists mainly of the neural cell bodies. While anatomy in the white matter can be defined in multiple ways, some of the most common anatomical divisions and areas are summarized below.

White matter tracts can be divided into three main categories: interhemispheric **commissural** pathways connect cortical areas of both hemispheres, **projection** fibers project from the cortex to subcortical nuclei and vice versa, and intrahemispheric **association** pathways connect cortical areas in each hemisphere (Aralasmak et al., 2006).

The corpus callosum (CC), the largest commissural tract, is an extensive interhemispheric bundle connecting the corresponding regions of the hemispheres (Aralasmak et al., 2006). It is further divided into four parts: 1. rostrum and genu of the corpus callosum (GCC) comprise the most anterior fibers, 2. body of the corpus callosum (BCC) forms the long middle part of the bundle and radiates as the corona radiata to the premotor and precentral cortices of frontal, parietal and temporal lobes, and 3. splenium of the corpus callosum (SCC) is the posterior part, which connects occipitotemporal cortices. Tapetum is a bilateral tract along which part of fibers from SCC radiate to temporal lobes, bordering lateral ventricles inferior-laterally (Aralasmak et al., 2006). The anterior and posterior commissures belong also to commissural tracts; the former connects temporal lobes traveling in front of the fornix and the latter connects hemispheres inferior to the pineal gland (Aralasmak et al., 2006).

The projection fibers include the bilateral corticospinal tracts (CST), which transfer information from the cerebral cortex to motor neurons and participate in the formation of voluntary movements. The internal capsule (IC) includes bidirectional connections between the cortex and subcortical GM nuclei and is further divided into

the anterior limb (ALIC), the posterior limb (PLIC), and the retrolenticular part (rlIC). The anterior limb connects parts of the frontal cortex to e.g., the thalamus, and is associated with different high-order functions such as emotional and cognitive processing, and decision-making (Safadi et al., 2018).

The association pathways include six bilateral fasciculi: (1) superior longitudinal (SLF; between temporoparieto-occipital regions and convexity of the frontal lobe), (2) inferior longitudinal (ILF; between the temporal and occipital lobe), (3) superior fronto-occipital (SFOF; between orbitofrontal and parieto-occipital areas), (4) inferior fronto-occipital (IFOF; between the prefrontal and posterior-temporal cortex), (5) uncinate (UF; between the frontal and temporal lobes) and (6) cingulum (CG; between the cingulate/parahippocampal gyri and the temporal/frontal/parietal lobe) (Aralasmak et al., 2006).

2.3 Development of White Matter Tracts

The human brain develops in a specified order with areas essential to survival maturing before birth, while higher-order structures related to more complex cognitive functions develop in prolonged timing. Postnatal brain development consists mainly of a decrease in the GM volume, and fine-tuning of the WM microstructure, mostly by increasing the volume by myelination, axonal growth, and synaptogenesis. Early childhood is especially a significant period for the development of the connectome and rapid changes in WM tracts occur with a consistent increase in the integrity of most WM regions.

All major brain white matter tracts are already formed at birth (Keunen et al., 2017; Wilson et al., 2021) and subsequent development entails mainly a refinement of the trajectories. The projection and commissural pathways are formed first during weeks 13 to 18 in the fetal development and association pathways later during weeks 24 to 32 postconception (Vasung et al., 2017). The myelination begins during fetal development, proceeding from the 20th postconceptional week to the 30th decade after birth (Barkovich et al., 1988). Particularly rapid changes in myelination occur during the first 2 years of life. After the rapid myelination phase, axonal packing, density, and increased spatial coherence have been suggested to drive changes in diffusion properties during later childhood (Moura et al., 2016).

The development of white matter structure during childhood has been investigated in several longitudinal research settings (Hermoye et al., 2006; Krogsrud et al., 2018; Lebel & Deoni, 2018; Löbel et al., 2009; McGraw et al., 2002; Muftuler et al., 2012; Qiu et al., 2008; Reynolds et al., 2019; Taki et al., 2013; Uda et al., 2015; Genc et al., 2017; Krogsrud et al., 2016; Moon et al., 2011; Sadeghi et al., 2015). Generally, a wide-spread increase in FA and a decrease in MD values are detected during childhood indicating an increase in white matter integrity and more

directional and efficient signal transmission. Major white matter tracts and trajectories of FA values between the ages of 5 and 32 years of life are depicted in Figure 2. The increase in FA is primarily driven by a decrease in RD and to a lesser extent changes in AD. Decrease of RD implies growth of axonal density and diameter and thickening of myelin sheaths. The white matter development follows non-linear trajectories; with younger children, the development can be described with linear models, but with older age groups (over 8 to 13 years) linear fitting could yield misleading results, and many studies report results from ordinary linear and higher-order, non-linear associations (Lebel et al., 2017).

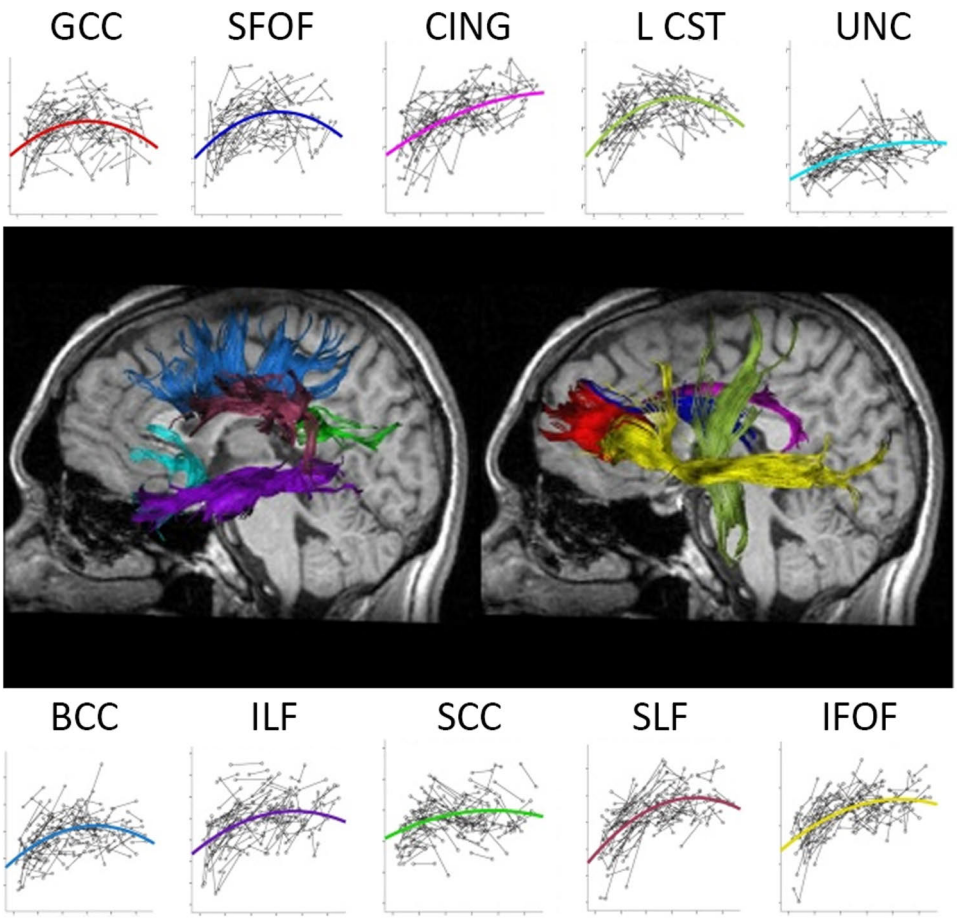


Figure 2. Major white matter tracts and the development of fractional anisotropy (y axis) values between ages 5 and 32 years (x axis). G/B/SCC = genu/body/splenium of the corpus callosum, SFOF = superior fronto-occipital fasciculus, CING = cingulum, CST = corticospinal tract, UNC = uncinate, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, IFOF = inferior fronto-occipital fasciculus. Figure adapted with permission from Tamnes et al., 2010.

Maturation of the white matter follows the general course of brain development advancing in caudo-cranial, central-to-peripheral, and posterior-to-anterior directions (Krogsrud et al., 2016). The adult-like white matter integrity is first reached in areas of the corpus callosum whereas fronto-temporal connections (e.g., the uncinate and the cingulum) present the most protracted developmental patterns (Asato et al., 2010; Lebel et al., 2008; Tamnes et al., 2010). During early childhood, the development is still ongoing in all white matter tracts (Reynolds et al., 2019). At the age of approximately six years, the early spurt phase is starting to level and the development approaches the plateau phase (Uda et al., 2015). One longitudinal study of 120 children showed the fastest development between ages 2 and 8 years in the occipital and limbic regions, with slower changes in both the callosal and fronto-temporal association tracts (Reynolds et al., 2019). During that period, the percent change of FA was highest in ILF, IFO, the cingulum, the fornix, and the uncinate (11.7 to 14.9%) and lowest in SCC (6.1%), followed by CST and BCC (9.0 to 9.6%). This may reflect that the period of fastest developmental changes in the corpus callosum is already completed, while the development of the association tracts is protracted and happens later.

The regional and temporal developmental patterns of the white matter reflect the progress of motor, cognitive, and behavioral skills during childhood. According to their developmental timing, WM tracts can be segregated into three, temporally partly overlapping main groups. First, the commissural and projection fibers, including mainly CC, and CST, reach high integrity during early childhood, with slower subsequent development and accomplishment of the plateau phase around the age of five to seven years. Sensory tracts mature first, supporting the later development of motor tracts (Lenroot & Giedd, 2006). The second group includes tracts in which the initial FA values in early childhood are low, but which demonstrate a rapid increase in FA during the first school years before adolescence. The group of white matter tracts that develop during this period includes part of the association tracts (ILF, IFOF, the cingulum, and the fornix), connecting the occipital and limbic areas. Lastly, the rest of the association tracts (including the uncinate and SLF) forming the fronto-temporal connections follow a prolonged developmental pattern from early adolescence to far adulthood (Reynolds et al., 2019).

In 3 to 6-year-old children, especially both gross and fine motor skills are improving (Grohs et al., 2018). This permits the child to practice essential skills like drawing, dressing up, and using cutlery, which are prerequisites for further social development and learning more elaborate abilities (reading, writing, etc.) during the school period. Practicing gross motor skills like running, jumping, and throwing not only enables the child to take part in hobbies that support the progress of social competence (Sigurdsson et al., 2002) but also supports the gradual progression toward independence. The motor performance in children correlates especially with the diffusion parameters in the

callosal motor fibers, the development of which occurs in concert during the preschool period (Grohs et al., 2018; Johansen-Berg et al., 2007). The initial FA of both the CC and the CST is higher and the increase rate is lower compared to other WM tracts between ages 3 and 8 years, which indicates the early timing of their development (Reynolds et al., 2019). Especially CST has a high maturation degree already at birth and during the first years of life (Lenroot & Giedd, 2006).

Preschool and the beginning of school between the ages of 5 to 8 years is an essential period for the development of various cognitive and behavioral skills. Visual processing, language skills including reading and writing, memory performance, and emotion processing are all among developing functions. Improving the integrity of ILF, IFOF, and the arcuate fasciculus (AF) between ages 5 to 8 years is associated with the development of language skills (Broce et al., 2019; Catani et al., 2007; Yeatman et al., 2012) and with left ILF, also with visual processing and recognition of objects (Ortibus et al., 2012). Further, the leftward lateralization of ILF during development is associated with reading skills (Broce et al., 2019; Yeatman et al., 2012). Additionally, limbic tracts including the cingulum, maturate during this period. In a study by Uda et al. covering the age range from 2 months to 25 years, they showed that limbic tracts develop before association tracts.

2.4 White Matter Characteristics in the Developing Brain

2.4.1 Sex Differences of White Matter

A plethora of both adult and pediatric population studies have indicated sexual dimorphism of the brain in multiple aspects (Cosgrove et al., 2007; Xin et al., 2019). Not only the overall brain volume (J. M. Goldstein et al., 2001; Lenroot et al., 2007) but also the proportion of white matter (Allen et al., 2003; Gur et al., 1999) is larger in males, while more specific regional differences of WM microstructure are detected between females and males. The peak volume of the female brain is reached earlier, at the age of 10 years, compared to 14 years of males (Lenroot et al., 2007). Prior studies of the WM microstructure have suggested that males have fewer but thicker fibers and possibly more myelination whereas the density and crossing of fibers are more extensive in females (Highley et al., 1999; Szeszko et al., 2003; Westerhausen et al., 2004).

Several developmental studies have indicated that the WM matures earlier in females during childhood (Asato et al., 2010; Barnea-Goraly et al., 2005; Bava et al., 2011; Seunarine et al., 2016; Simmonds et al., 2014; Wang et al., 2012). The more protracted development of WM in males is demonstrated as steeper and longer-lasting age-dependent changes of diffusion values in multiple longitudinal studies.

The FA in males aged under 8 years is generally lower compared to females, but the values converge over time, and discernible differences are no longer detected at ages between 10 to 14 years (Seunarine et al., 2016). On the other hand, some studies with similar wide age ranges have not detected developmental sex differences during late childhood and early adolescence (Eluvathingal et al., 2007; Lebel et al., 2008; Muetzel et al., 2008; Uda et al., 2015). The included age groups, the used ROI approach as well as the findings vary between separate studies even when developmental sex differences have been observed (Asato et al., 2010; Bava et al., 2011; Clayden et al., 2012; Reynolds et al., 2019; Wang et al., 2012), see a review of relevant literature in Table 1.

Table 1. Previous diffusion tensor imaging studies investigating sex differences in the white matter (WM) integrity in child and adolescent populations. N = number of subjects, RD = radial diffusivity, ILF = inferior longitudinal fasciculus, IFOF = inferior fronto-occipital fasciculus, FA = fractional anisotropy, SCC = splenium of corpus callosum, MD = mean diffusivity, CST = corticospinal tract, SLF = superior longitudinal fasciculus, SCR = superior corona radiata, UNC = uncinate, AF = arcuate fasciculus, IC = internal capsule, EC = external capsule, ↑ = higher, ↓ = lower.

Study	Age (years)	N	Females	Males
Asato et al. 2010	8-28	114	Earlier maturation in females (RD) only right SLF continued to mature after adolescence	most tracts continued to develop into adulthood (exception: right SLF and IFOF)
Bava et al. 2011	12-14	58	↑ FA in right SCR and bilateral CST ↓MD in right ILF and left forceps major	↑AD in right SLF, ILF, and forceps minor
Clayden et al. 2012	8-16	59		faster decrease in MD
Geng et al. 2012	0-2	211	↑FA in the right sensory tract ↑AD in right UNC	↑AD in right AF and right motor tracts
Herting et al. 2012	10-16	77		↑FA in all regions analyzed
Lebel et al. 2011	5-32	103	↑FA in SCC	↑FA in cingulum, bilateral CST, SLF, UNC
Reynolds et al. 2019	2-8	120	Earlier development ↓ global MD + in BCC, fornix, ILF, and SLF faster ↑ FA in CST	Faster, greater development ↑FA in GCC and CST faster ↓ MD in fornix, ILF, and SLF
Schmithorst et al. 2008	5-18	106	↑FA in SCC ↑MD in the right occipito-parietal and superior part of CST	↑ FA in frontal regions, in right AF and left parietal, and occipito-parietal WM ↑MD in right CST and frontal WM
Seunarine et al. 2016	8-16	53	↑ FA in females	↑ MD in CST, IC, EC, SLF, cingulum

The exact time point of diverging of the developmental trajectories between sexes is still elusive. One study of healthy infants observed minor sex differences in the lateralization of CST (Saadani-Makki et al., 2019), while a study of 0-2-year-olds showed girls to have higher FA in the right uncinate and lower FA in the right arcuate and motor tracts (Geng et al., 2012). Yet in another study of subjects aged between 2 months and 25 years, significant sex differences were not observed (Uda et al., 2015).

The basis of sex differences is likely related to gonadal hormones. Apart from adolescent puberty, sex hormone secretion is transiently activated also during prenatal development (gwk 10-24) and during the first 1-6 months after birth in so-called mini puberty (Becker & Hesse, 2020). In the absence of sex hormones during the immediate postnatal period, the brain follows a default developmental pattern, resulting in a female-like brain structure. However, the presence of testosterone, which is converted to estrogen in the brain, leads to masculinization of the brain. These hormonally active periods induce long-term programming effects on the developmental patterns and most likely form the basis of sex differences observed in the brain structure and function.

Higher initial FA values observed in girls have been partly suggested to derive from differences in exposure to gonadal hormones during the perinatal period (Genc et al., 2018). In animal models, researchers have detected differences in gene expression preceding gonadal differentiation (Dewing et al., 2003), suggesting there might be additional mechanisms unrelated to the sex hormones. Further, during puberty, the related hormonal changes may drive differences in the brain developmental trajectories during early adolescence (Herting et al., 2012; Seunarine et al., 2016). Considering the hormonal effects, breastfeeding during infancy was detected to increase the WM integrity of left BCC, SLF, and the cingulum in 8-to 10-year-old boys, but not in girls (Oddy et al., 2011; Ou et al., 2014). The effect was suggested to derive from neuroprotective estrogens received in milk.

Despite the sex differences of WM microstructure being investigated in several separate pediatric populations, the results, tract-specificity, and dynamics of differences are partly discordant. The sex differences in WM microstructure might be temporal features during development, and thus longitudinal studies of wide age ranges may not be optimal for observing them. Investigating the WM sex differences at a certain age would refine the current knowledge and aid in resolving the dynamics of changes.

2.4.2 Asymmetry within White Matter

Hemispheric asymmetry is a well-characterized feature of normal brain WM structure (Honnedevasthana Arun et al., 2021; Takao et al., 2011). In the light of

recent research, the WM lateralization has been shown to contribute to cognitive, and executive functions (Yin et al., 2013) and, for example, predisposition to diseases like ADHD (Yin et al., 2013) and autism (Carper et al., 2016; Liu, Tsang, Jackson, Ponting, Jeste, Bookheimer, Dapretto, et al., 2019). The role of WM lateralization in language functions has been consolidated in various studies (O'Muircheartaigh et al., 2013). However, only few previous studies have investigated the WM lateralization patterns in pediatric populations.

Lateralization of WM microstructure has been observed already during neonatal age (Song et al., 2015). Studies on pediatric populations have mainly focused on age groups over 5 years of age, and the sample sizes have been modest. Leftward asymmetry of FA was observed in populations of 5-17-year-olds in the internal capsule (Snook et al., 2005; Wilde et al., 2009), cingulate (Bonekamp et al., 2007; Wilde et al., 2009), SCR, the arcuate (Eluvathingal et al., 2007) and the uncinate (Eluvathingal et al., 2007). One study with a large age range (0-18 years, N = 42), observed widespread leftward asymmetries in IC, SFOF, IFOF, and the corona radiata. A more recent study of 0-6-year-old children observed also rightward FA asymmetries in the uncinate, fronto-parietal arcuate, and prefrontal cortico-thalamic projections, in addition to the leftward asymmetry of ILF, cingulate, and fronto-temporal arcuate (Stephens et al., 2020). Furthermore, they suggested the lateralization pattern to stay stable through the first 6 years of life.

In conclusion, WM lateralization is essential for normal cognitive functions, but previous pediatric studies have provided varying results on tract-specific asymmetries. While asymmetry pattern has previously been suggested to stay stable throughout development, at least the results from separate pediatric populations do not offer explicit support for this, and for example rightward asymmetries are rarely observed even though they are present in adult populations.

2.5 Effects of Perinatal Distress on White Matter Development

Increasing evidence has shown early life exposures to both adverse and supportive factors to have substantial and long-term effects on the development of brain functions and cognitive and behavioral outcomes. Perinatal maternal mental distress forms a significant subtype of early life stress as it is both common and associated with several negative effects on child development.

2.5.1 Prevalence of Perinatal Maternal Mental Distress

Depression and anxiety are frequent psychological disorders with high prevalence especially among young women (Kessler, Berglund, et al., 2005). Lifetime

prevalences for depression and anxiety disorders among adult populations are 20.8% and 28.8%, respectively. In addition, 8-38% of pregnant women meet the criteria for depressive disorder (Gavin et al., 2005; Lee et al., 2007; Records & Rice, 2007; Vesga-López et al., 2008; Yonkers et al., 2009), while the prevalence of depressive symptoms is higher, up to 70%. Additionally, postpartum depression is regarded as a major postnatal complication, with prevalence estimates up to 19% within the first 3 months postpartum (Gavin et al., 2005). In addition to genetic predisposition (Nestler et al., 2002), lack of social support (Verkerk et al., 2003), low socio-economic status (Lorant et al., 2003; Rich-Edwards et al., 2006), poverty, domestic violence (Leigh & Milgrom, 2008), as well as biological factors such as hormonal changes (Parry et al., 2003), nutrient deficiencies (Bodnar & Wisner, 2005), chronic diseases (Nestler et al., 2002) and medications (e.g., sedatives) increase the risk for depressive disorder. Several questionnaires have been developed and validated to facilitate the screening of depressive symptoms. In clinical and research settings, the most utilized are the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) and the Beck Depression Inventory (BDI) (Beck, 1961), which are also validated for use in obstetric populations.

Antenatal depression is highly comorbid with other psychiatric disorders (up to 60%), of which 80% are anxiety disorders (Glover, 2014; Wisner et al., 2013). However, they are suggested to have different influences on the brain development (Baker, 2013; Nolvi et al., 2016), and it would be optimal to include measures of both when studying their effects. Generalized anxiety symptoms during the perinatal period are common with prevalence estimates of 8.5-10.5% and associated symptoms include excessive worry, irritability, and problems with concentration and sleeping (Misri et al., 2015).

2.5.2 Mechanisms Transmitting Prenatal Maternal Mental Distress to the Fetus

In utero, the fetus is exposed to maternal cortisol and activity of the autonomic nervous system (ANS), both activated in stressful situations (Fatima et al., 2017; Field, 2011). Activation of ANS leads to changes in levels of neurotransmitters (Fatima et al., 2017). For example, increased exposure to norepinephrine leads to vasoconstriction in the placenta, which may induce growth restriction and result in low birth weight (Leuner et al., 2014).

Elevated cortisol levels have been suggested to mediate the stress-related effects between the mother and the offspring. Psychological distress as well as traumatic events are observed to induce higher cortisol levels. Prior studies have detected a correlation between offspring hypothalamus-pituitary-adrenal (HPA) axis activity and exposure to prenatal maternal stress (Zijlmans et al., 2015), which

has been suggested to modulate developing child's glucocorticoid receptor sensitivity to neurotransmitters and setting the baseline for the HPA-axis function. The activity of the HPA-axis is positively correlated with, for example, depression later in life. However, the results on direct associations between maternal cortisol levels and child outcomes have not provided concordant results and the effects of maternal HPA-axis activation are suggested to be transmitted through more complex mechanisms. Accumulating evidence indicates that the placental cortisol transfer regulates fetal exposure to cortisol (O'Donnell & Meaney, 2017). Maternal cortisol increases its' placental transmission by downregulating the cortisol-inactivating 11β-hydroxysteroid dehydrogenase (O'Donnell et al., 2012) and expression by stimulating placental corticotrophin-releasing hormone (CRH) production (Chrousos & Gold, 1992). Prenatally elevated cortisol levels are associated with increased cortisol levels in infants (Brennan et al., 2008), and further exposure to elevated cortisol levels has been associated with infant's negative reactivity (Davis et al., 2007) and childhood behavioral problems (Essex et al., 2002). Of note, exposure to synthetic glucocorticoids during pregnancy is similarly associated with poorer mental health during childhood and adolescence (Khalife et al., 2013).

Maternal mental health also affects the immune system activity. Psychological distress during pregnancy has been associated with elevated levels of serum inflammatory cytokines and further stimulated lymphocytes (Coussons-Read et al., 2005). The changes in the immune system are suggested to disrupt communication between the immune, endocrine, and nervous systems, which may partly affect the emergence of problems detected in individuals exposed to prenatal mental distress (Kohman et al., 2008).

Additionally, the effects of both prenatal (Cao-Lei et al., 2020) and postnatal (McGowan et al., 2009) stress are mediated by epigenetic changes such as differences in DNA methylation. This in part emphasizes the interactive effect of the genome and environmental exposures on developmental outcomes (Buss et al., 2017; Moog et al., 2022).

2.5.3 Effects of Postnatal Maternal Mental Distress

After birth, the significance of social environment and parent-infant interaction is emphasized instead of prenatal biological exposures. Maternal postnatal anxiety and depressive symptoms are related to several adverse effects on infant care practices and maternal involvement. Firstly, postpartum anxiety symptoms are associated with lower mother-child bonding which is suggested partly to stem from avoidance behavior and social withdrawal (Tietz et al., 2014). Mothers with general anxiety are less responsive to infant vocalization but simultaneously more controlling compared

to healthy controls (Stein et al., 2012). Secondly, maternal postpartum depression has been associated with lower sensitivity (Easterbrooks et al., 2000), less affectionate touching of the infant (Ferber et al., 2008), and less smiling, vocal, and visual communication (Field, 2010; Righetti-Veltema et al., 2002). Thirdly, parental depressive symptoms may lead to less enrichment activity in the forms of reading, telling stories, and playing (Paulson et al., 2006), and increase the risk for deprivation of health-promoting practices like breastfeeding (Akman et al., 2008) and visits to preventive health services (Minkovitz et al., 2005). Lastly, depressed mothers experience lower self-confidence (Reck et al., 2012), draw more attention to negative information, and are prone to negative misinterpretations (Everaert et al., 2017) which can be reflected as learned adverse behavioral manners in the child. These problems with care practices may lead to long-term effects in the offspring, including problems with social interaction, behavior, and cognitive skills (Field, 2010; Lovejoy et al., 2000), and further increase the susceptibility to mental health problems (Pawlby et al., 2009; Pearson et al., 2013).

Maternal psychological distress in the postnatal period has been shown to increase infants' tendency to more difficult temperament (McMahon et al., 2001; Mednick et al., 1996), as well as to be associated with less social engagement (Feldman et al., 2009; Kingston et al., 2012), increased fearful behavior (Kingston et al., 2012) and unmatured regulatory behavior (Feldman et al., 2009) during first years of life. Later on, children exposed to parental stress exhibit more behavioral problems (Giles et al., 2011; Ramchandani et al., 2005), and for example deteriorated fine and gross motor skills (Tuovinen et al., 2018). Additionally, a sex-specific association between exposure to parental stress and outcomes is observed, with girls showing more internalizing symptoms (Kessler, Wai, et al., 2005) and boys externalizing symptoms (Kramer et al., 2008; Ramchandani et al., 2005).

2.5.4 Effects of Prenatal Maternal Distress on White Matter Development

Albeit inconsistencies in the type of prenatal stress, the target WM tracts evaluated, and differences in the offspring age at the time of evaluation, previous studies have reported associations between maternal prenatal distress and WM microstructural properties (Table 2). These prior studies have mostly focused on the fronto-limbic regions (Hay et al., 2019; Lautarescu et al., 2020; Posner et al., 2016; Rifkin-Graboi et al., 2013; Sarkar et al., 2014; Wen et al., 2017) with known involvement in cognitive and emotional processing. Prenatal depressive and anxiety symptoms were mainly assessed during 2nd trimester or at multiple time points during pregnancy (Dean et al., 2018; Hay et al., 2019; Marroun et al., 2018; Rifkin-Graboi et al., 2013; Roos et al., 2022; Wen et al., 2017; Zou et al., 2019).

In infants, prenatal exposure to maternal mental distress has been associated with increased RD and MD in the left uncinate in premature infants at gwk 37-45 (Lautarescu et al., 2020) and right frontal WM at the age of 2-7 weeks (Dean et al., 2018). Maternal depression and anxiety assessed during the end of 3rd trimester were also observed to be associated with reduced FA in bilateral frontal WM and the fornix at the age of 2 weeks (Graham et al., 2020). In contrast, in another study, maternal prenatal depressive symptoms were associated with higher FA in the genu of corpus callosum (which was further associated with behavioral problems at the age of 18 months) (Borchers et al., 2021). In the most recent study of 70, 2–4-week-old, infants' prenatal depressive symptoms were not observed to associate with alterations in WM integrity. However, when evaluated at the age of 2-3 years, higher FA in widespread areas including the sagittal stratum and the corona radiata was observed in children of the same study population exposed to maternal depression (Roos et al., 2022).

Indeed, other studies have also observed WM alterations related to prenatal exposure to depressive symptoms in older children. At the age of 4 years, exposure to depression during 3rd trimester was associated with a decrease in FA in the amygdala-frontal tract and the cingulum (Hay et al., 2019). Similarly negative association between exposure to depressive symptoms during 2nd trimester and FA in the right cingulum in 6-9-year-old children (El Marroun et al., 2018), and between depressive symptoms and FA in the uncinate of 10-year-olds (Zou et al., 2019) have been observed.

To conclude, prenatal mental distress has potential programming effects on WM microstructure which are manifested after birth and postnatally. Due to variation in methodology, age groups, and covariates included, definitive conclusions of the extent, sex differences, and dynamics of the inflicted changes are difficult to make based on the current knowledge.

2.5.5 Effects of Postnatal Maternal Distress on White Matter Development

Effects of maternal postpartum depressive symptoms on offspring WM microstructure have been investigated only in a few previous studies (Table 2). Lebel et al. observed postnatal depression to be associated with decreased RD and MD in superior frontal WM in 2-5-year-old subjects (Lebel et al., 2016). Zou et al. showed that maternal postnatal depressive symptoms are associated with decreased FA in forceps minor and major, and in the uncinate at the age of 10 years (Zou et al., 2019). Additionally, Wen et al. observed a sex-specific positive association between maternal postpartum depression and FA of the right amygdala, only in girls (Wen et al., 2017). Contrarily, two studies observed no associations between maternal

postnatal depression and WM at the ages of 6-7 months (Borchers et al., 2021) and 6-9 years (Marroun et al., 2018). Interestingly, in studies with significant findings, the maternal assessment was arranged within the first 2-3 months after the birth, while no associations with distress scores were observed at later time points.

Table 2. Previous diffusion tensor imaging (DTI) studies investigating the effects of maternal perinatal mental distress on white matter (WM) integrity in the offspring. ROI = region-of-interest, TG = tractography, VBA = voxel-based analysis, TBSS = tract-based spatial statistics, rep = repetition, wk = week, gwk = gestational week, y = year, mo = month, FA = fractional anisotropy, MD = mean diffusivity, RD = radial diffusivity, AD = axial diffusivity, EPDS = Edinburgh Postnatal Depression Scale, SLE = Stressful Life Events, STAI = State-Trait Anxiety Inventory, CES-D = Center for Epidemiologic Studies Depression Scale, BDI = Beck's Depression Inventory, BSI = Brief Symptom Inventory, SSRI = selective serotonin/serotonin-noradrenaline reuptake inhibitors, UNC = uncinate, (dl)PFC = (dorsolateral) prefrontal cortex, CG = cingulate/cingulum, CR = corona radiata, EC = external capsule, SLF = superior longitudinal fasciculus, OR = optic radiation, ALIC = anterior limb of internal capsule, SFOF = superior fronto-occipital fasciculus, PTR = posterior thalamic radiation, ↑ = higher, ↓ = lower.

Study	Analysis method	Subjects Age	Stress Assessment	Results
Prenatal stress				
Borchers et al. 2021	TG	N = 37 (20 boys) 6.0-7.7 mo	EPDS during pregnancy	Prenatal depressive symptoms: ↑ FA (corpus callosum) ↓ RD (corpus callosum)
Dean et al. 2018	VBA	N = 101 (53 boys) 18-50 d	EPDS and STAI gwk 28 and 35	Depression and anxiety symptoms combined ↑ MD, RD, AD (right CR, EC frontal WM) ↑ RD (right SLF, OR) ↓ FA (EC, ALIC, SCR) Sex-specific correlations: Lower FA in girls, higher FA in boys exposed
El Marroun et al., 2018	TG	N = 636 (322 boys) 6-9 y	BSI gwk 20.6	↓ FA (right CG) ↑ MD (left UNC, bilateral CG)
Graham et al. 2020	TBSS and ROI	N = 34 (17 boys) 2 wk	STAI BDI	↓ FA (multiple areas: frontal, parietal, and temporal WM regions + limbic areas bilaterally)
Hay et al. 2019	TG	N = 54 (30 boys) 4 y	EPDS gwk 11, 16, 31	↓ FA (left CG) ↑ MD (left CG and bilateral UNC; stronger in boys; right amygdala pathway)
Jha et al. 2016	VBA	N = 68 (depression diagnosis/ exposure to SSRI + controls)	Diagnosis of depression or use of SSRI	No associations with untreated depression ↓ FA, ↑ MD, and RD in SSRI-exposed infants in multiple tracts

Study	Analysis method	Subjects Age	Stress Assessment	Results
Lautarescu et al. 2019	Tract-specific analysis	N = 251 (132 boys) 37-45 gwk Preterm	STAI (during scan) SLE (1 y prior scan)	↑ MD, RD, and AD (left UNC)
Posner et al. 2016	TG	N = 64 (27 boys) Mean 5.99 wk	CES-D gwk 34-37	↓ structural connectivity between the right amygdala and right ventral PFC
Rifkin-Graboi et al. 2013	ROI	N = 157 (82 boys) 0-2 wk	EPDS gwk 26	↓ FA (bilateral amygdala) ↓ AD (right amygdala) No interaction by child sex
Rifkin-Graboi et al. 2015	VBA	N = 54 (26 boys) 5-17 d	STAI and EPDS gwk 26-28	↓ FA (right: insula, dlPFC, UNC, CG)
Roos et al., 2022	TBSS	N = 70 (32 boys) 2-4wk N = 60 (36 boys) 2-3 y	BDI and EPDS 2nd trimester	In neonates: No association between depressive symptoms and WM 2-3-year-olds: ↑FA, ↓ MD, RD, and AD in sagittal stratum, SFOF, CG, CR and PTR
Sarkar et al. 2014	TG	N = 22 (12 boys) 6-9 y	SLE	↑ FA (right UNC) ↓ RD (right UNC)
Wen et al. 2017	ROI	N = 235 (88 boys) 4.5 y	EPDS gwk 26	No association between prenatal depressive symptoms and white matter
Zou et al. 2019	TG	N = 3469 (1717 boys) 10 y	BSI gwk 20 +2 mo +3 y postpartum EPDS 2 mo postpartum	Perinatal symptoms: ↓ FA (forceps minor, forceps major, UNC) No interaction by child sex
Postnatal stress				
Borchers et al. 2021	TG	N = 37 (20 boys) 6.0-7.7 mo	CES-D + EPDS 6 mo postpartum	No association between postnatal depression and FA
El Marroun et al. 2018	TG	N = 636 (322 boys) 6-9 y	BSI 3 y postpartum	No correlation to FA or MD
Lebel et al. 2016	TG	N = 52 (32 boys) 2.6-5.1 y	EPDS 2-3 mo postpartum)	↓ RD and MD in the superior frontal region
Wen et al. 2017	ROI	N = 235 (88 boys) 4.5 y	EPDS 3 mo postpartum	↑ FA (right amygdala, all subjects + girls, no correlation in boys)
Zou et al. 2019	TG	N = 3469 (1717 boys) 10 y	BSI (gwk 20 +2 mo + 3 y postpartum EPDS 2 mo postpartum	Perinatal symptoms: ↓ FA (forceps minor, forceps major, UNC; at child's age of 2 months)

2.5.6 Effects of Supportive Factors during the Postnatal Period

The postnatal environment modifies the association between prenatal stress and brain development and buffers against early adversities (Buss, Entringer, Swanson, et al., 2012; Nolvi et al., 2022). Resilience-promoting factors include, for example, a supportive and enriched environment, age-appropriate cognitive training, linguistic stimulation, and having a mother with higher sensitive and secure attachment. For instance, high parental bonding has been observed to reverse the association between lower birth weight and smaller hippocampus (Buss et al., 2007), and maternal prenatal anxiety was observed to be associated with child externalizing symptoms only when maternal sensitivity was low (Frigerio & Nazzari, 2021). Further, higher parental educational level has been observed to protect neurocognitive development in children born preterm or with lower birth weight (Beauregard et al., 2018a, 2018b; Bilsteen et al., 2021; Mallinson et al., 2019). High social support was observed to attenuate the association between maternal cortisol levels and infant cortisol reactivity (Thomas et al., 2018). Investigating the role of supportive factors in attenuating the effects of perinatal exposure to parental stress is complicated by the impact of parental stress also on the caregiving quality and parent-infant interaction, and that all children are not equally sensitive to environmental cues.

2.6 Development of the Emotional Attention

2.6.1 Development of Facial Expression Recognition System

The face-processing areas of the brain consist of distributed neural circuits. The occipital face area (OFA), fusiform face area (FFA), and posterior superior temporal sulcus (pSTS) are generally regarded as the core regions activated by visual face stimuli. OFA and FFA activation has been associated with the identification of invariant aspects of faces, while pSTS participates in the processing of more dynamic and changing characteristics like facial expressions. Additionally, the extended face system includes the amygdala, the insula, the medial prefrontal cortex (mPFC), the anterior paracingulate cortex, and the anterior temporal pole. The extended system participates more in the processing of the social and emotional contexts related to face recognition and is recruited in a task-specific manner, especially in adults. For example, the activation of limbic regions is related to situations with emotional valence (Gobbini & Haxby, 2007; Ishai et al., 2004), and the anterior cingulate cortex (ACC) to analyzing attitudes and if a person is trustworthy (Redcay et al., 2010).

The main connections of the face processing areas travel through ILF and IFOF, which connect the frontal/temporal and the occipital regions. While ILF participates in face recognition (Catani et al., 2003; C. J. Fox et al., 2008), visual perception (Ffytche & Catani, 2005), and visual memory (Ross, 2008), IFOF is particularly important for visual processing (C. J. Fox et al., 2008), attention (Doricchi et al., 2008) and recognition of emotional facial expressions (Philippi et al., 2009). Additionally, direct connections between OFA and FFA, and between early visual areas and the amygdala have been detected with tractography with predominance in the right hemisphere (Gschwind et al., 2012). This is in accordance with the previous notions suggesting right-sided dominance in the face processing (C. J. Fox et al., 2008).

The development of the face processing system is paramount for social interaction and communication skills. The face presents prompt cues of the identity, intentions, and emotional state of a person. The recognition of faces is developed early, as infants have been shown to prefer viewing faces versus other objects (Johnson, 2007), and the ability to identify a person by facial features is developed by the age of 3 to 5 months (Bhatt et al., 2005; Hayden et al., 2007). On the other hand, the activation patterns of face-selective regions reach adult-like functional specificity only during late adolescence (Cohen Kadosh et al., 2011; Scherf et al., 2007), even though the activity of FFA and the core face network is detected already at age of 7 years (Cantlon et al., 2011; Cohen Kadosh et al., 2011). The extended face network in children presents hyperactivation compared to selective activation in adults suggesting that the task-specific engagement of regions is matured during development (Haist et al., 2013).

Emotional facial expressions are essential non-verbal means of social interaction and for sharing feelings or emotional states between individuals. The processing of facial expressions includes the identification of emotional cues, responding with an adequate affective state, and adjusting the emotional behavior with inhibition when necessary (Phillips et al., 2003). Behavioral studies have provided evidence of infants' ability to categorize facial emotional expressions between the ages of 4 to 8 months (Barrera & Maurer, 1981; Caron et al., 1982; Nelson, 1987). Newborns show bias toward looking at happy faces as early as at the age of 4 to 6 months (Farroni et al., 2007; LaBarbera et al., 1976). However, the attentional bias is re-oriented to negative emotional expressions, especially to fearful faces, already during the first year of life (Vaish et al., 2008). This shift has been suggested to reflect the transition of a completely dependent infant requiring all resources from a caretaker to a more mobile individual with more emphasis on avoiding potential harm (Elam et al., 2010).

While attentional bias toward basic emotional expressions is detected in infants, emotional understanding develops only later during childhood (Denham et al., 2003;

C. M. Herba et al., 2006). The attentional bias to both happy and fearful faces is detected also among 5-year-olds (Elam et al., 2010). The recognition of emotional expressions follows different developmental trajectories in boys and girls (Mancini et al., 2013). For example, girls showed more accurate recognition of sad facial expressions at the age of 8 years, yet boys closed the gap by the age of 11 years (Mancini et al., 2013).

The accuracy of recognizing facial emotional expressions is improving during childhood (Chronaki et al., 2015; C. Herba & Phillips, 2004). Happiness is the emotion recognized earliest and with the most accuracy during childhood when assessed by comparing to the detection of facial expressions of sadness, fear, angriness, and disgust (X. Gao & Maurer, 2010; Mancini et al., 2013; Rodger et al., 2015). On the other hand, sadness is the emotional state with the highest misidentification rates and slowest improvement during childhood from the age of four years to adolescence (Chronaki et al., 2015; X. Gao & Maurer, 2010; C. Herba & Phillips, 2004). The identification of neutral facial expressions develops later between the ages of 8 and 11 years (Mancini et al., 2013). Apart from the improvement of recognizing the emotional state of other individuals, the affective reactions to experienced emotions are maturing during childhood (Mancini et al., 2013). The emotional arousal related to emotional facial expressions decreases while the child develops more mature ways of processing emotional information.

2.6.2 The Emotional Attention and its Neural Correlates

Literature on neural correlates in emotional processing has not revealed one specific brain region activated in variable emotional tasks. However, multiple areas are shown to activate consistently with emotional stimuli. Among these structures, the amygdala, its connectome (especially the uncinate fasciculus), and the prefrontal cortex (PFC) including the orbitofrontal cortex (OFC) are pivotal in both emotional perception and regulation, and they develop in divergent schedules with the amygdala maturing earlier in the childhood in contrast to PFC maturing throughout the childhood into the late adolescence (Pechtel & Pizzagalli, 2012; Qin et al., 2012).

Faces with emotionally relevant expressions have a greater tendency to capture attention in a reflexive, involuntary way when compared to neutral faces (Eastwood et al., 2003; E. Fox et al., 2001). This phenomenon is especially well-characterized with negative expressions, signalling potential threat and requiring immediate actions (Eastwood et al., 2003; E. Fox et al., 2001; Surguladze et al., 2003; Vuilleumier & Schwartz, 2001). The emotional valence has been detected to enhance the activation of the face-selective fusiform cortex, suggesting the existence of feedback connections between the amygdala and visual cortex (Ishai et al., 2004;

Vuilleumier & Pourtois, 2007). This top-down control can guide stronger engagement of attention when more salient facial stimuli are present. The attentive profile to faces also has practical implications. For instance, higher negative emotionality at the age of three years was also indicated to be associated with higher activation in both the amygdala and FFA, but in contrast, lower connectivity between the areas during face processing.

The amygdala is essential for emotion-related brain circuitry. Its connectivity to widely distributed structures (PFC, the insula, the cingulate gyrus) is under remarkable alterations during early childhood, making it especially susceptible to early life adversity (Gee et al., 2013; Qin et al., 2012). Previous studies have suggested that the amygdala receives input through subcortical sensory pathways and assessing the salience of the stimulus can influence orienting attention (LeDoux et al., 1983; Pasley et al., 2004). The rapid processing of stimuli does not necessarily reach consciousness, and the amygdala can thus direct the attention subconsciously to relevant and salient stimuli (Dolan & Vuilleumier, 2003; Garvert et al., 2014; Méndez-Bértolo et al., 2016; Pessoa & Adolphs, 2010).

The prefrontal cortex, which acts especially in the service of the executive functions, working memory, and the flexibility of goal setting, participates also in inhibition (the ability not to act by impulses). The reciprocal connections between OFC, the ventromedial PFC (vmPFC), and the amygdala are important for the regulation of emotional processes and dampening negative affect (Banks et al., 2007). The uncinate fasciculus is one of the major white matter tracts, which connects the prefrontal cortex and the amygdala and acts as a crucial link in emotion processing and regulation (Swartz et al., 2015). This connectivity changes during childhood and adolescence, and presumably tightens up the prefrontal regulation of the amygdala (Buhle et al., 2014; Wager et al., 2008; Silvers et al., 2017). Age-related decline in the amygdala activation to emotional faces has been associated with increased FA within the left uncinate in children and adolescents (Swartz et al., 2015).

In adult studies, the reduced WM organization in the cortico-limbic tracts, including the uncinate (Baur et al., 2013; Phan et al., 2009), is associated with increased trait anxiety (Kim & Whalen, 2009) and social phobia (Baur et al., 2013). Thus, the reduced suppression of the limbic circuit by the frontal control areas may lead to exaggerated arousal states. The WM integrity in the right uncinate during adolescence showed a negative correlation with the harm avoidance estimated at the ages 8-9 (Taddei et al., 2012). Apart from the uncinate, reduced integrity in the left ILF and IFOF was observed to correlate with responses to angry faces (Taddei et al., 2012). Another study showed the integrity of ILF to correlate positively with faster detection of anger or fear from facial expressions (Marstaller et al., 2016).

2.6.3 The Effect of Maternal Perinatal Depression on Emotional Attention Network

Early social interaction with parents is known to model infant's neural responses to emotional facial expressions (Taylor-Colls & Pasco Fearon, 2015). Even though emotional understanding develops later during childhood, attentional biases toward emotional expressions are observed already in infants (Denham et al., 2003; C. Herba & Phillips, 2004), and correspondingly environmental factors begin to adapt the infant's way of responding to signals.

Exposure to maternal postnatal anxiety was previously observed to be associated in 8-month-old infants with an increased probability of disengagement from faces in boys and contrarily increased attachment in girls (Kataja et al., 2019). Additionally, exposure to prenatal anxiety symptoms was associated with higher threat bias. Correspondingly, exposure to maternal anxiety symptoms during the postnatal period was associated with increased attentional threat bias in infants and toddlers of 4-24 months of age (Morales et al., 2017). Maternal cognitive bias toward fear and threat has also been observed to be transmitted from mother to the offspring (Fliek et al., 2017; Remmerswaal et al., 2016). High early-life stress has been associated with attentional avoidance of fearful expressions, which was suggested to mediate the association between stress exposure and social problems (Humphreys et al., 2016).

In the prior literature on emotional attention, girls have been detected to be especially sensitive to maternal psychological distress (Braithwaite et al., 2016; Dean et al., 2018; Erickson et al., 2019; Quarini et al., 2016; Simcock et al., 2016; Wen et al., 2017). Researchers have observed that daughters, but not sons, of depressed mothers attended selectively on sad faces (Kujawa et al., 2011).

2.6.4 Association between Emotional Attention and Psychological Symptoms

Early attentional patterns are suggested to shape the child's world for social processing and thus may inflict long-term effects on conventions of responding to environmental signals. Additionally, vigilance toward threat signals has been associated with increased risk for anxiety in children (Abend et al., 2018), and later avoidance of threats (Remmerswaal et al., 2016). An overview of previous literature considering attentional biases to threat or fear stimuli in pediatric populations is provided in Table 3.

Already during the first year of life, infant's attentional capacities are observed to associate with their emotional regulation abilities. Disengagement from distressing objectives is one of the first forms of self-soothing behaviors. In 8-month-old infants, lower attentional bias to fearful faces was related to early regulatory

problems in feeding, sleeping, and calming (Eskola et al., 2021). Furthermore, in this population, attentional bias for fear was related to higher socioemotional competence at the age of 2 years (Eskola et al., 2023). Contrarily, no associations were observed between attentional fear bias and socioemotional problems at this stage of development.

However, attentional bias to threatening signals has been associated with negative outcomes in relation to inhibition (Pérez-Edgar et al., 2010), internalizing symptoms, and anxiety in older age groups. That is, anxious children are observed to be faster in detecting fear (Simcock et al., 2020) and show stronger attention to all affective stimuli (Waters et al., 2004). Children with attentional bias to threat signals showed more irritability at the age of 6-14 years (Salum et al., 2017) and anxiety at the age of 13 (Abend et al., 2018). Further, attentional bias toward threat predicted an association between behavioral inhibition and anxiety symptoms in 5-7-year-old children (White et al., 2017). Additionally, anxiety symptoms have been associated with avoidance of negative emotions in 9- and 13-year-old children (Brown et al., 2013; Kallen et al., 2007). Thus, exploring the attention to affective stimuli in younger children may provide important cues for the development of emotional and psychological processing preceding the period when the child can verbally express his or her feelings and emotional states.

Table 3. Previous literature on the attentional threat or fear biases in pediatric populations. Studies on children aged under 5 years were excluded. fMRI = functional magnetic resonance imaging, FER = facial emotion recognition, CBCL = Child Behavior Checklist

Study	Age N	Method	Main results
Abend et al., 2018	Mean 13.4 years N = 1291	Dot-probe task + anxiety symptoms	○ Threat bias was positively associated with overall anxiety symptoms, social anxiety, and school phobia ○ No sex differences
Brown et al., 2013	8 years, twins N = 600	Dot-probe task for FER + parental report of child's anxiety symptoms	○ Attentional avoidance of negative faces (anger, fear, sad, disgust) in anxious children ○ Sex differences were not examined
Garcia & Tully, 2020	7-10 years N = 80	FER	○ Positive bias detected, happiness was recognized more accurately compared to sadness or anger ○ Anger was better recognized compared to sadness ○ No sex differences
Harrewijn et al., 2020	Mean 13.4 years N = 41	fMRI + Dot-probe task	○ Children with a bias toward threat were shown to switch from rest to threat processing more efficiently and thus might be prone to process threat signals ○ No sex differences

Study	Age N	Method	Main results
Humphreys et al., 2016	9-13 years N = 154	Dot-probe task for FER + CBCL + early life stress	○ High levels of early life stress associated with an attentional avoidance of fearful expression ○ This attentional bias was detected to mediate the association between early life stress and social problems ○ No sex differences detected
Kallen et al., 2007	10-13 years N = 44	Probe detection task + anxiety symptoms	○ Attentional bias away from threatening stimuli ○ Girls responded faster in disengage conditions, but this did not relate to anxiety scores
Pérez-Edgar et al., 2010	Mean 15 years N = 126	Dot-probe task for FER + child's temperament as toddler + CBCL at adolescence	○ Behavioral inhibition as toddler predicted increased attentional bias toward threat ○ Attentional bias to threat moderated the relation between childhood behavioral inhibition and social withdrawal as an adolescent ○ No sex differences
Salum et al., 2017	6-14 years N = 1872	Dot-probe task + CBCL	○ Increased attention bias toward threat signals (angry face) was associated with irritability ○ No sex differences
Simcock et al. 2020	12 years N = 40	FER task + psychological distress scale	○ Increased anxiety, depression, and somatization symptoms were associated both with poorer recognition of angry expressions and with faster recognition of fearful expression ○ Sex differences were not examined
Sylvester et al., 2017	Mean 12.9 years N = 52	fMRI dot-probe task	○ Threat avoidance associated with lower activation in occipital, parietal, and temporal lobes ○ Subjects with a history of depression/anxiety showed lower activity to happy, sad, and fearful facial expressions in the aforementioned regions ○ No sex differences
Waters et al., 2004	9-12 years N = 128	Dot-probe task	○ Attention toward fear-related pictures did not differ between anxious children and healthy controls ○ Anxious children showed stronger overall attentional bias to affective stimuli ○ Girls showed stronger attentional bias toward fear-related pictures than toward pleasant ones. No difference in boys.
White et al., 2017	5-7 years N = 268	Dot-probe task for FER + Behavioral inhibition symptoms + CBCL	○ No direct association between attention biases and reported anxiety symptoms ○ Threat and positive attentional biases moderated the association between behavioral inhibition and anxiety symptoms → in children with attention bias toward threat or away from positive, behavioral inhibition predicted anxiety symptoms ○ No sex differences

2.7 Alterations of White Matter related to Neurological and Psychiatric Disorders during Development

The basis of many neurological and psychiatric disorders is suggested to be embedded in early life. White matter changes in children and adolescents have been associated with the emergence of e.g., depression, anxiety, antisocial behavior, ADHD, and problems with executive functions, language development, and socio-emotional skills.

Generally, both depression and anxiety are associated with decreased integrity in multiple WM regions. In 7-year-old girls, the prevalence of internalizing symptoms correlated with decreased FA in the cingulum and the uncinate (Mohamed Ali et al., 2019). Depressive symptoms in subjects aged between 6 and 19 years have been associated with decreased FA in the CC (Aghajani et al., 2014; Henderson et al., 2013; Huang et al., 2011; LeWinn et al., 2014; Uchida et al., 2021), the corona radiata (Kliamovich et al., 2021; LeWinn et al., 2014), the internal capsule (Bessette et al., 2014; Henderson et al., 2013), SLF (Huang et al., 2011) and ILF (Bessette et al., 2014), in addition to the cingulum (Henderson et al., 2013; Huang et al., 2011; Hung et al., 2017; Uchida et al., 2021) and the uncinate (Aghajani et al., 2014; Cullen et al., 2010; Huang et al., 2011; LeWinn et al., 2014). Especially anxiety-related alterations are observed in the uncinate (Adluru et al., 2017; Kaczkurkin et al., 2020; Liao et al., 2014; Lichtin et al., 2021; Tromp et al., 2019) and in the cingulum (Kaczkurkin et al., 2020). Previous studies have also observed decreased integrity related to ADHD widely in separate regions of WM, including the CC, frontal WM, and the corona radiata (see a recent review of studies by Connaughton et al. (2022)).

In contrast, studies have provided evidence of increased WM integrity related to antisocial behavior in the uncinate (Pape et al., 2015; Sarkar et al., 2013), the CC (Grazioplene et al., 2020; Pape et al., 2015; Puzzo et al., 2018), the corona radiata (Pape et al., 2015; Puzzo et al., 2018), the internal capsule (Puzzo et al., 2018; Sarkar et al., 2016) and SLF (Sarkar et al., 2016), although also decreased FA has been observed in some studies (Breeden et al., 2015; Haney-Caron et al., 2014). Mixed results can be partly explained by comorbid ADHD symptomatology, as measures of antisocial behavior and ADHD show potential overlap as well as with heterogeneous study populations in relation to other symptoms and age ranges (see review by (Waller et al., 2017)).

Higher integrity, often related to the more advanced brain development of WM, is associated also with better inhibitory abilities (Olson et al., 2009; Seghete et al., 2013; Ursache & Noble, 2016), working memory (Krogsrud et al., 2018; Østby et al., 2011; Peters et al., 2014; Vestergaard et al., 2011), reaction speed (Fjell et al., 2012; Peters et al., 2014) and verbal performance (Sarkar et al., 2013).

2.8 Summary of Literature

The development of the white matter microstructure is a complex process during which diverse intrinsic and environmental factors contribute to the formation of coherent connections between brain regions. This further enables the progress of various cognitive and emotional functions. Certain constant factors such as sex are associated with white matter structure. Multiple studies have provided evidence of earlier white matter development in girls (Asato et al., 2010; Barnea-Goraly et al., 2005; Bava et al., 2011; Seunarine et al., 2016; Simmonds et al., 2014; Wang et al., 2012) – however, more research is required to establish the spatiotemporal features of these developmental sex differences. Previous adult studies have reported that the integrity of bilateral white matter tracts is lateralized (Honnedevasthana Arun et al., 2021; Takao et al., 2011), and alterations in this asymmetry pattern are associated with the emergence of conditions such as ADHD (Yin et al., 2013). Despite the asymmetry pattern is suggested to remain stable throughout the development, current pediatric studies have not provided explicit support for this statement (Bonekamp et al., 2007; Eluvathingal et al., 2007; Snook et al., 2005; Song et al., 2015; Stephens et al., 2020; Wilde et al., 2009).

Early exposure to adversity in the form of maternal psychological distress has been shown to inflict negative consequences in the offspring, for example in relation to the development of emotional skills and predisposition to psychiatric disorders (Feldman et al., 2009; Giles et al., 2011; Kingston et al., 2012; McMahon et al., 2001; Mednick et al., 1996). Prenatal maternal distress has been associated with the white matter microstructure in infants (Borchers et al., 2021; Dean et al., 2018; Graham et al., 2020; Lautarescu et al., 2020), and further with decreased white matter integrity in older children (Hay et al., 2019; Marroun et al., 2018; Zou et al., 2019). However, studies covering the exposure period immediately after birth are markedly scarce. Postnatal depression was observed to be associated with white matter structure when assessed immediately after birth (Lebel et al., 2016; Zou et al., 2019), while during later time points the current studies have not discovered significant associations (Borchers et al., 2021; Marroun et al., 2018). Psychological studies have observed girls to be especially sensitive to maternal distress during the postnatal period (Braithwaite et al., 2016; Dean et al., 2018; Erickson et al., 2019; Quarini et al., 2016; Simcock et al., 2016). Thus, investigating the timing and sex-specific neurodevelopmental correlates of early life exposures might be beneficial in unravelling the overall effects of early maternal distress on brain white matter morphology.

Attention to facial expressions is emerging during early development, and attentional biases provide a means to investigate emotional processing in infants and young children. Increased attention to threat has been associated with negative psychological features in children, e.g., irritability, behavioral inhibition,

internalizing symptoms, and anxiety. Further, maternal mental distress has been suggested to increase attention to threatening cues, with a stronger association in girls. The early social environment, in interplay with genetic predispositions and biological exposures, has been proposed to generate the foundation for the development of psychopathologies. Despite the observed associations in psychological studies, the information on the neural mechanisms mediating the interactions between early stress exposure, emotional attention, and the emergence of psychiatric disorders is limited.

3 Aims

In this thesis, the main aims were to first improve methodological conventions related to pediatric brain MR imaging by evaluating the prevalence and handling practices of incidental brain MRI findings along with optimization of the pediatric DTI data pre-processing pipeline. Secondly, this thesis aims to increase our understanding of the normal brain white matter development and bridge that information by exploring the associations between the WM, maternal perinatal well-being and emotional attention variables derived from eye-tracking measurements.

The specific aims were

1. To evaluate the prevalence and risk factors of incidental brain imaging findings in the infant population and to provide a recommended guideline for handling incidental findings in pediatric brain imaging. (Study I)
2. To provide a repeatable pre-processing protocol for pediatric diffusion tensor imaging study setting by evaluating the effect of the number of diffusion encoding directions and within-scanner movement on resultant scalar values. (Study II)
3. To describe the normative features of infants' and 5-year-olds' brain white matter tracts measured by tract-based spatial statistics (TBSS) as well as possible lateralization patterns and sex differences. (Study III)
4. To investigate associations between perinatal maternal psychological distress and the development of white matter. (Study IV)
5. To study, which white matter features (TBSS) of the children predict emotional attention and how it is associated with exposure to maternal perinatal psychological distress. (Study V)

4 Materials and Methods

All studies were performed in accordance with the Declaration of Helsinki. The studies were reviewed and approved by the Ethics Committee of the Hospital District of Southwest Finland ((07.08.2018) §330, ETMK: 31/180/2011). Both parents of the participating child signed a written informed consent form before MR scanning. The MRI scans were performed for research purposes without clinical indications, and this was also discussed with the parents before choosing to participate.

4.1 Subjects

The subjects were recruited from families participating in the longitudinal FinnBrain Birth Cohort Study (Karlsson et al., 2017). The FinnBrain Birth Cohort (www.finnbrain.fi) was established in 2010 to prospectively study the consequences of early exposure to stress. The initial recruitment occurred between December 2011 and April 2015 in maternity clinics in South-Western Finland among pregnant women who attended their first ultrasound visit (at gestational week (gwk) 12). The data for the current study is collected from two separate and partly overlapping study populations who attended an MRI scanning at the Turku University Hospital. The first population (studies I and III) consisted of infants and the second population (studies II-V) of 5-year-old children with their families.

4.1.1 Study I and III

A total of 189 families were recruited for an MR imaging visit at the Turku University Hospital. The enrolment was performed by a telephone call. The MRI acquisition occurred between November 2012 and January 2016. The MRI scan was successful with 180 (95.2%) subjects. The final number of subjects was 175 (94 males, 81 females), after the exclusion of five subjects due to major motion artifacts. All subjects were healthy Finnish neonates born from singleton pregnancies, and the MR imaging was performed from 2 to 5 weeks of age after birth. The participants were born full-term (between 37 and 43 gwks), with two exceptions born on gwk 36 and two with the information not available.

The information on the family characteristics was gathered as a part of the FinnBrain Birth Cohort Study protocol (e.g., maternal age, maternal pre-pregnancy body mass index, maternal educational level, monthly income, substance use during pregnancy, medical diagnoses and medications affecting central nervous system). The information on obstetric details was retrieved from the Finnish Medical Birth Register (the National Institute of Health and Welfare, www.thl.fi).

The exclusion criteria for the newborns were the following:

1. Sever perinatal complications with neurological consequences (e.g., hypoxia)
2. Scoring <5 in the 5min Apgar score
3. Diagnosed central nervous system anomaly
4. An abnormal finding in previous MR imaging
5. Birth weight under 1500 grams

The maternal exclusion criteria included:

1. Alcohol or drug abuse
2. Severe psychiatric disorders (past or present)
3. Epilepsy (and medication)
4. Medication for psychosis

Obstetric data included information on duration and mode of delivery, gestational age, use of anesthetics (epidural or spinal anesthesia/other anesthetics such as dinitrogen monoxide/no pain alleviation) or oxytocin induction during delivery, mother's parity, possible episiotomy, gestational age at birth, child's Apgar scores (1 min and 5 min), head circumference, birth weight, birth height and pH of the umbilical blood. Mode of delivery was categorized as: 1. vaginal, 2. assisted deliveries (vacuum assistance; no forceps-assistance used in any of the births), and 3. c-sections (elective or emergency sections).

4.1.2 Studies II-V

A total of 203 families attended MR imaging visits with 5-year-old children. The imaging visits were arranged in Turku University Hospital between October 2017 and March 2021. Due to the COVID-19 pandemic, the imaging visits ceased between March 2020 and May 2020. The recruitment process was carried out in two phases, and the family was instructed to discuss with the child about their willingness to attend in between two recruitment phone calls (assuring the child's assent). Demographical information of the participants in studies II-IV is provided in Table 4.

The following exclusion criteria were applied:

1. Birth before gwk 35
    - One exception was allowed born on gwk 33 due to inclusion to a separate nested population exposed to maternal prenatal glucocorticoid treatment
2. Major developmental disorder
3. Long-term diagnosis requiring constant contact with a hospital
4. Sensory abnormalities
5. Use of daily regular medication (with two exceptions)
    - Asthma inhalers were allowed
    - Desmopressin medication was allowed
6. Head trauma that had required inpatient care
7. Routine MRI contraindications
8. Metallic ear tubes

Table 4. Demographical information on 5-year-old subjects in sub-studies II-V. N = number, SD = standard deviation, BMI = body-mass index, EPDS = Edinburgh Postnatal Depression Scale, SCL-90 = Symptom Checklist 90, SES = socio-economic status (classified by educational level), NA = not available, SSRI/SNRI = selective serotonin/serotonin noradrenalin reuptake inhibitor.

	Study II	**Study III**	**Study IV**	**Study V**
N	**49**	**144**	**130**	**117**
Girls/boys (%)	21(43)/ 28(57)	68(47)/ 76(53)	63(48)/ 67(52)	55(47)/ 62(53)
Age (years; mean [SD])	5.03 [0.75]	5.38 [0.11]	5.36 [0.12]	5.25 [0.096]
Ponderal index (kg/m^3; mean [SD])	13.9 [1.43]	14.0 [1.28]	14.1 [1.29]	14.1 [1.26]
Maternal (mean [SD])				
○ Age at birth (years)	30.1 [4.19]	30.4 [4.80]	30.6 [4.72]	30.4 [4.85]
○ pre-pregnancy BMI (kg/m^2)	23.7 [3.71]	24.2 [4.10]	24.2 [4.12]	24.0 [3.94]
○ EPDS 2nd trimester	4.34 [4.03]	4.80 [4.22]	4.77 [4.24]	4.68 [3.91]
○ EPDS 3 months	3.74 [4.33]	4.26 [3.90]	4.16 [3.83]	4.40 [3.85]
○ SCL-90 2nd trimester	3.38 [3.62]	3.62 [3.75]	3.59 [3.83]	3.75 [3.83]
○ SCL-90 3 months	2.17 [3.16]	2.55 [3.50]	2.50 [3.46]	2.79 [3.62]
○ SES (low-middle/high/NA [%])	21 [42.9]/ 28 [57.1]/ 0	70 [48.6]/ 66 [45.8]/ 8 [5.56]	63 [48.5]/ 62 [47.7]/ 5 [3.8]	61 [50.8]/ 56 [46.7]/ 0
Exposures during pregnancy (yes/no/NA [%])				
○ smoking	4 [8.2]/ 45 [91.8]/ 0	8 [5.5]/ 134 [93]/ 2 [1.4]	7 [5.4]/ 123 [94.6]/ 0	6 [5.0]/ 109 [90.8]/ 2 [1.7]
○ SSRI/SNRI	2 [4.1]/ 42 [85.7]/ 5 [10.2]	6 [4.2]/ 128 [89]/ 10 [6.9]	4 [3.1]/ 118 [90.8]/ 8 [6.2]	4 [3.4]/ 103 [88.0]/ 10 [8.5]
○ glucocorticoids	4 [8.2]/ 45 [91.8]/ 0	14 [9.7]/ 130 [90]/ 0	10 [7.7]/ 120 [92.3]/ 0	11 [9.4]/ 104 [88.8]/ 2 [1.7]

4.2 Methods

4.2.1 Study Visits

4.2.1.1 Preparation and MR Imaging of Infants (Study I and III)

The infants and their families attended MRI scans 2-5 weeks after birth. The imaging was performed during natural sleep, which was proceeded by feeding with milk (breast milk or formula) and swaddling into sleep. Intrascanner movement was limited with a vacuum mattress wrapped around the infant, and both ear plugs or wax and earmuffs were used for hearing protection. The parent(s) were able to stay in the scanner room throughout the imaging, and they could stop the study at any point. The MRI compatibility of parents was confirmed before entering the scanning room (the existence of pacemakers, inner ear implants, or other metallic ferromagnetic devices prohibited from entering the MRI room).

4.2.1.2 Preparation and MR Imaging Visit at Age of 5 years (Studies II-V)

A careful preparation protocol was performed preceding each imaging visit to guarantee both the children's and parents' feelings of safety and comfort. First, a home visit by a study nurse providing more precise information concerning the visit was arranged. During the home visit, a member of the research staff was able to meet with the participating child and answer any remaining questions of the parents. The families were encouraged to practice the imaging visit in advance during the home practice period. We recommended families to build home mock scanners (e.g., a cardboard box with a hole for watching a movie through) and practice immobilization for example with a "statue game". Additionally, we suggested that the family would listen to the sounds of the MRI scanner beforehand. We introduced the visit for the participants as a "space adventure" but were prepared to adjust the setting individually to the child's own preferences.

The second part of the preparation involved a simulation at the imaging center with the aid of a wooden mock scanner head coil prior to scanning. Immobilization was practiced with the mock scanner and a toy brought by the participating child and the effect of moving the toy while taking photos with a cell phone was demonstrated to indicate the importance of staying still during the scan. Simultaneously, the staff members and the family could get to know each other better, which alleviated communication and increased the sensation of safety during the MR imaging. The families were also served lunch before the imaging to equalize blood sugar levels before scanning (for functional MRI). The duration of the preparation phase varied

between approximately 60 to 120 minutes, and it was aimed to be flexible and to proceed at the child's own pace.

The scans were performed awake or during natural sleep. The hearing protection was accomplished with a combination of earplugs and earmuffs. Before entering the scanner room, a staff member ensured that there were no metallic parts in the clothing or the pockets of the child or the parent. The participants were able to watch a television program of their choosing through a mirror-system of the head coil during the image acquisition. We noticed that it improved the overall compliance. The research staff was also able to communicate with the child through headphones through which the audio was channelled. One member of the research staff and a parent stayed in the scanner room, and the parent was able to touch the child's leg if the child wished this before the scan. A "signal ball" was given to the participant and throwing it in the case he or she wanted to stop, or a pause was practiced during training. The imaging was discontinued at any point if the child or the parent expressed unwillingness to continue. The total duration of the visit was approximately 3 hours on average and the maximum duration of the scanning protocol was 60 minutes.

4.2.2 MRI Sequences

4.2.2.1 Infants (Study I and III)

The MRI scans were performed with a Siemens Magnetom Verio 3T scanner (Siemens Medical Solutions, Erlangen, Germany) with a 12-element head/neck receiver coil. Acoustic noise during the scan was reduced by using a "whisper" gradient mode optimized 2D Dual Echo TSE (Turbo Spin Echo) sequence.

The following sequences were acquired: 1. T1-weighted sequence with time of repetition (TR)/time of echo (TE) = 1900/3.26 ms, voxel size 1.0×1.0×1.0 mm^3. 2. TR/TE = 12,070 ms and effective TE times of 13 and 102 ms were used to produce both PD-weighted and T2-weighted images from the same acquisition, voxel size 1.0x1.0x1.0mm^3. The total number of slices was 128. Diffusion-weighted imaging protocol was applied with a standard twice-refocused Spin Echo-Echo Planar Imaging (SE-EPI): TR/TE = 8500/90.0ms, field of view (FOV) = 208mm, 2.0x2.0x2.0mm^3 isotropic voxels, b value 1000s/mm^2, 96 noncollinear diffusion gradient directions and 9 b0 images (b = 0 s/mm^2). Additionally, field maps and functional resting-state images were acquired.

4.2.2.2 5-year-olds (Study II-V)

The MRI scans were performed on a Siemens Magnetom Skyra fit 3T scanner (Siemens Medical Solutions, Erlangen, Germany, the same scanner as for infant scans following an upgrade) using a 20-channel head/neck receiver coil. GeneRalized Autocalibrating Partially Parallel Acquisition (GRAPPA) was used to accelerate the image acquisition.

The following sequences were acquired: T1-weighted sequence with TR/TE = 1900/3.26ms, FOV 256mm, voxel size 1.0x1.0x1.0mm^3 and T2-weighted sequence (TR/TE = 6400ms/96.0ms, FOV = 230mm, voxel size 1.0x1.0x1.0mm^3. DTI protocol was applied with SE-EPI: TR/TE = 9300/87.0ms, FOV = 208mm, isotropic voxels with 2.0x2.0x2.0mm^3 resolution, b value 1000s/mm^2, 96 noncollinear diffusion gradient directions divided into three scanning sets (31, 32 and 33 directions) with 9 b0 images (3 b0 = 0s/mm^2 volumes scattered within each set). Additionally, multi-shell data including b values 650 and 2000 s/mm^2 was acquired from part of the participants (n = 70) with the following setting: 1) TR/TE = 5000/79.0ms, FOV = 208mm, isotropic voxels with 2.0x2.0x2.0mm resolution, b value 650s/mm^2, 34 noncollinear diffusion gradient directions, 4 b0 images, and 2) TR/TE = 5000/114ms, FOV = 208mm, isotropic voxels with 2.0x2.0x2.0mm resolution, b value 2000s/mm^2, 80 noncollinear diffusion gradient directions and 10 b0 images divided into two scanning sets.

4.2.3 Neuroradiological Review of MR Images

All brain MR images (T1 and/or T2) acquired were reviewed by a pediatric neuroradiologist for possible incidental findings. If incidental findings were found, a pediatric neurologist contacted the family so that the possible immediate questions or concerns of the parents were appropriately addressed.

4.2.4 Pre-processing of Diffusion Tensor Imaging Data (Study II-V)

The data were converted to NIfTI format and pre-processed using FSL 6.0 software (FMRIB software library, University of Oxford, UK). We chose not to perform distortion corrections due to the corruption of part of the field maps collected. Since our scans did not suffer from major distortions before corrections, we opted to leave this step out of the pipeline.

b0 images were reviewed by visual quality control and images with insufficient quality were manually excluded. Passed b0 images that included at least one image per imaging set were co-registered and averaged (FLIRT, FMRIB's Linear Image Registration Tool) and used to create a brain mask using Brain Extraction Tool (BET

version 1.0.0) (Smith, 2002) with settings -R -f 0.3 (with three exceptions of -f 0.2 due to problems with brain borderline recognition). The brain masks were quality-controlled visually.

Subsequently, DTIprep (https://nitrc.org/projects/dtiprep/ (Oguz et al., 2014) with default settings was used for quality control of the volumes. We chose to include the volumes with acceptable quality rather than to optimize the DTIprep sensitivity in detecting motion artifacts at the expense of decreasing specificity and thus missing volumes. During quality control, DTIprep was detected to retain directions with severe corruption with these settings. As optimization of sensitivity in detecting motion artifacts would have led to lower specificity and exclusion of volumes with good quality, we chose to perform a visual quality control to exclude residual motion-corrupted volumes.

After quality control, the same number of directions per subject was chosen by rejecting extra directions, and subjects with an insufficient number were excluded. The rejection was performed in a way that maximized the final angular resolution calculated with the spherical Voronoi algorithm in the Scipy Python library (Caroli et al., 2010; Millman & Aivazis, 2011). For studies III-V, 30 directions were used. In Study II, the effect of changing the number of directions on resultant scalars was investigated, and thus we formed a subset of subjects (N = 49) with 66 unique diffusion volumes and based on that permutated groups with 6, 9, 12, 15, 18, 24, 30, 36, 42, 48, 54 and 60 directions.

Motion and eddy current correction were performed with FSL tools with concurrent rotation of the directional vectors (.bvec file). DTIfit (FSL) was used for the computation of scalar maps (FA, MD, RD, and AD).

4.2.5 Tract-based Spatial Statistics and Region-of-Interest Analyses

Tract-Based Spatial Statistics (TBSS) pipeline of FSL (Smith et al., 2006) was used to estimate WM tract skeletons separately for each subset. TBSS utilizes nonlinear alignment of targets relieving problems of voxel-based analyses concerning imperfect brain-to-brain alignment and spatial smoothing and is thus a commonly used method for group comparisons. We chose to use a study-specific template, which is suitable for pediatric imaging data. Thus, in step 2 (tbss_2_reg), flag -n was used, which means identification of the “most representative” FA image to be used as a target and affine-aligning it into MNI152 standard space. After that, every image is transformed to the same space with nonlinear affine transformation to the target FA image, and subsequently mean FA skeleton across all subjects is formed (step 3, tbss_3_postreg, flag -S). The mean FA skeleton is formed with subjects included in each analysis and is thus specific for each of our study populations and study

questions. The mean FA skeleton was generally created with an FA threshold of 0.20 (which is commonly used in pediatric studies). In Study II, we evaluated the effect of changing the threshold and used skeletons calculated with thresholds 0.1, 0.125, 0.15, 0.175, and 0.3. Other scalar maps of MD, AD, and RD were co-registered on the mean FA image by using the "tbss_non_FA" script.

In region of interest (ROI) analysis, WM tracts were defined by the JHU-ICBM-DTI-81 white matter atlas (Mori et al., 2008). After assuring the alignment of the ROIs to the DTI data following spatial normalization to template space, tract-wise mean scalar values were extracted. See Table 5 for the WM tracts and abbreviations. The workflow and selection of the subjects are described in Figure 3 and examples of mean FA, mean FA skeleton, and mean FA with JHU-ICBM-DTI-81 atlas are provided in Figure 4.

Table 5. Abbreviations of white matter tracts.

Abbreviation	Tract name
GCC	Genu of the corpus callosum
BCC	Body of the corpus callosum
SCC	Splenium of the corpus callosum
CST	Corticospinal tract
ALIC	Anterior limb of the internal capsule
PLIC	Posterior limb of the internal capsule
rlIC	Retrolenticular internal capsule
ACR	Anterior corona radiata
SCR	Superior corona radiata
PCR	Posterior corona radiata
PCT	Pontine crossing tract
PTR/OR	Posterior thalamic radiation and the optic tract
EC	External capsule
CG	Cingulate
CING	Cingulum
UNC	Uncinate
ILF/IFOF	Inferior longitudinal fasciculus/inferior fronto-occipital fasciculus
SFOF	Superior fronto-occipital fasciculus
SLF	Superior longitudinal fasciculus

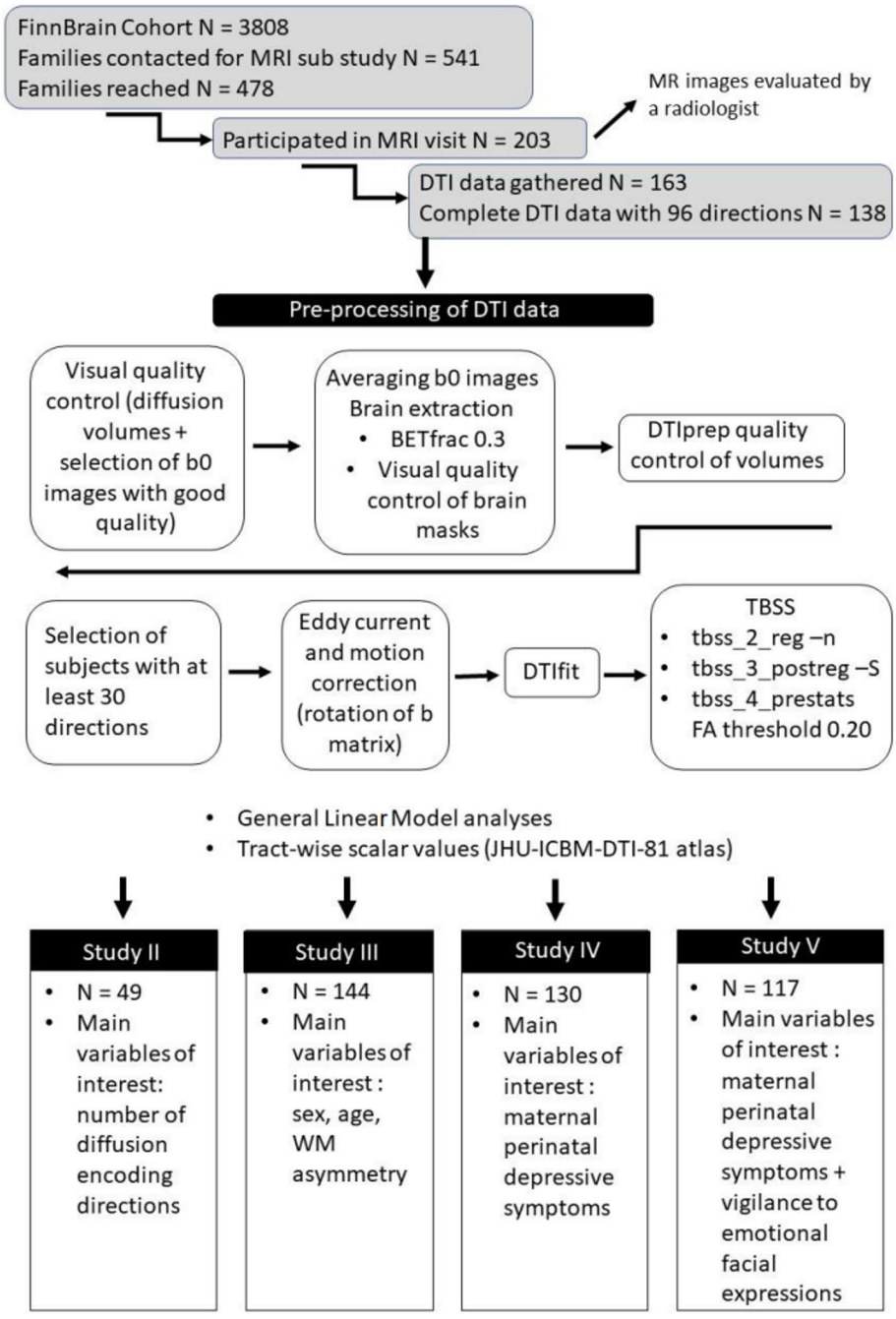


Figure 3. Workflow table of the diffusion tensor imaging data (5-year-olds), including subject recruitment, data acquisition and data pre-processing steps. The figure was created by Venla Kumpulainen.

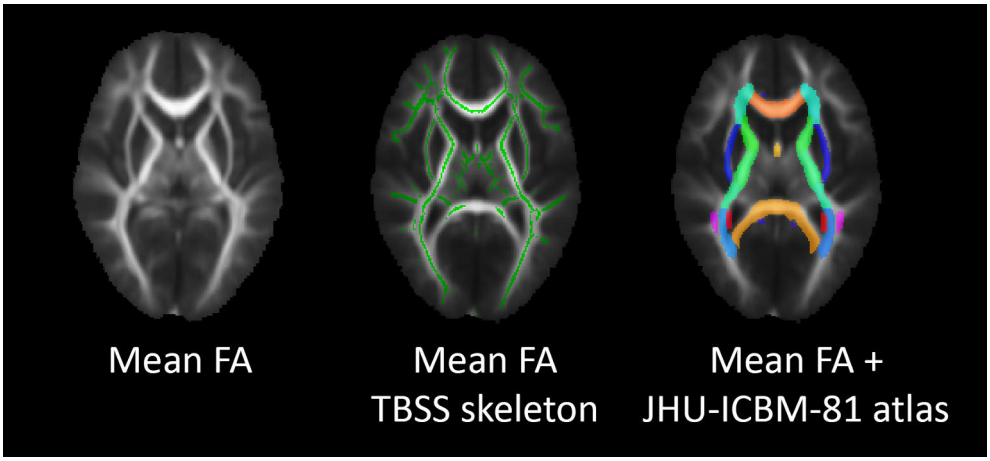


Figure 4. Example figures of 5-year-olds' pre-processed diffusion tensor imaging (DTI) mean white matter fractional anisotropy (FA) map, mean FA skeleton from tract-based spatial statistics (green) and mean FA map with JHU-ICBM-81 white matter atlas. The figure was created by Venla Kumpulainen.

4.2.6 Neurological Evaluation of Infants with Incidental Finding (Study I)

Families of infants with identified incidental brain MRI finding were offered a possibility of a neurological assessment visit for a pediatric neurologist. During the assessment, a complete somatic and neurological examination, and review of clinical history and developmental milestones were performed. Neurological development was examined with Hammersmith Infant Neurological Examination (HINE) (Haataja et al., 1999), and additionally standardized proforma of the Dubowitz (Haataja et al., 1999) was used for children aged 6 months or under to ensure the comparability of findings. Both the MRI findings, and the result of clinical examination were discussed with the parents, and they were also allowed to contact the pediatric neurologist after the visit (none of the families used this opportunity).

4.2.7 Assessment of Maternal Psychological Distress (Study IV and V)

Maternal depressive symptoms were assessed both during pregnancy (1st, 2nd, and 3rd trimester, at gwks 14, 24, and 34) and the postnatal period (3, 6, and 12 months postpartum) with Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987). The questionnaire was initially established to screen postnatal depression but has been validated also for use during pregnancy. The questionnaire includes 10 items, and the total score ranges from 0 to 30, with a score of 10 or higher is generally

suggested to indicate clinically significant symptoms of depression (Vázquez & Míguez, 2019).

Maternal anxiety symptoms were assessed at the same time points during pregnancy and 3 and 6 months postpartum with Symptom Checklist 90 (SCL-90) (Holi et al., 1998).

4.2.8 Eye-tracking Experiments (Study V)

Emotional attention was investigated at the age of 4-5 years using eye-tracking assessment to estimate the child's tendency to disengage from faces with emotional facial expressions (fearful, happy, neutral) and non-face distractors. The overlap paradigm (Peltola et al., 2009) with the following setting was used: a picture of a neutral, happy, or fearful face (of one female model) or a nonface control stimulus was shown in the center of the screen for 1000 ms. After that, a salient lateral distractor (i.e., geometric shape that started to flash after the child-directed attention toward it), was added on either side of the screen (at a visual angle of 13.6°) for 30000 ms. The experiment was repeated with 24 pictures, and the child's attention was captured at the center of the screen with a brief animation prior to each trial. The order of central stimuli was semi-randomized (no repetition of the same stimulus more than three times in a row).

The eye-tracking data was quality controlled with the following inclusion criteria: 1. Sufficient looking at the central stimulus (> 70% of time interval from onset of the trial to the end of the analysis period), 2. Sufficient number of valid samples with no gaps greater than 200 ms, 3. If disengagement occurred, the information of exact timing and assurance that the eye movement did not occur during missing or extrapolated gaze data was required. More in-detail description of quality control and pre-processing of eye-tracking is provided in previous studies (Kataja et al., 2022; Leppänen et al., 2015).

Based on trial-level data, mean disengagement probability (DP) for different conditions was analysed by coding the data into a binary disengagement value (0/1) based on whether the gaze shifted from the central to the lateral stimulus or not. Further, different attention bias indices were calculated by contrasting the face condition (neutral/happy/fearful) to the control picture, see Table 6 for eye-tracking variables.

Table 6. Eye-tracking variables and their abbreviations.

Abbreviation	Definition
Dp.1CS	Probability of disengagement from the control picture toward a distractor stimulus
Dp.2NE	Probability of disengagement from the neutral face picture toward a distractor stimulus
Dp.3HA	Probability of disengagement from the happy face picture toward a distractor stimulus
Dp.4FE	Probability of disengagement from the fearful face picture toward a distractor stimulus
Face bias	Probability of disengagement from the control picture versus neutral/happy facial expression)
Fear bias	Probability of disengagement from the fearful versus neutral/happy facial expression)
NE-bias	Attentional bias toward neutral face versus control picture
HA-bias	Attentional bias toward happy face versus control picture
FE-bias	Attentional bias toward fearful face versus control picture
Mean-DP-face	Average probability for disengagement from faces (neutral/happy/fearful)

4.2.9 Statistical Methods

4.2.9.1 Study I

Statistical analyses were performed with SPSS version 23 (IBM Corporation, Armonk, N.Y., USA). Group comparisons were performed with a two-sample independent t-test (for normally distributed data described with means and standard deviation, evaluated by Shapiro-Wilk test and Q-Q plots) and with a nonparametric Wilcoxon rank-sum test (for not normally distributed data, described with medians and median absolute deviation (MAD) scaled by factor k = 1.4826), and with Chi-square test for categorical variables. Multiple comparison corrections were not performed due to the small sample size as the study was exploratory in nature. The risk for incidental finding was estimated with odds ratio (OR) and the statistical significance with Boschloo's test (Boschloo, 1970).

4.2.9.2 Study II

Statistical analyses were performed with RStudio (version 1.3.1093). The mean, median, kurtosis, and skewness were calculated for each scalar (FA, MD, RD, AD) with the number of directions as a variable. Statistical differences between means and medians of scalars in subsets formed by different numbers of directions were estimated by 1-way ANOVA test, and with significant differences, followed by a post-hoc Tukey test to detect group-wise differences. False discovery rate (FDR)

correction was used (threshold $p < 0.01$). The intraclass correlation coefficient (ICC) (Shrout & Fleiss, 1979) was used for assessing the repeatability of results by changing the number of directions with a two-way random-effects model (ICC(2,1)). The ICC(2,1) was estimated over the following sets: 1. N6-to-N66 (including subsets with all permutated directions), 2. N12-to-N66 (including subsets with 12 to 66 directions), 3. N18-to-N166 and 4. N24-to-N66. The effect of the FA threshold on the results was estimated by multiple regression by defining the interaction of number-of-direction*threshold. Rotational and translational mean absolute motion (motion in relation to preceding DTI volume) was calculated in the x, y, and z axes during preprocessing, and the correlation between motion and resultant FA was calculated with Spearman rank correlation (the motion statistics were not normally distributed according to Shapiro-Wilk test).

4.2.9.3 Study III

Voxel-wise inter-subject differences of scalar values were estimated by General Linear Model (GLM) with FSL's randomise tool. For infants, sex, age from birth, and gestational age were explored as independent variables. For five-year-olds, sex, age at scan, handedness, maternal pre-pregnancy body mass index (BMI), ponderal index (PI), exposure to tobacco smoking during pregnancy, and maternal socio-economic status (SES) were explored as independent variables. Socio-economic status was evaluated by maternal educational level with a dichotomous scale (1. low [elementary school] and medium [high school or occupational education], 2. high [examination from a university or a university for applied sciences]). The analyses were performed with 5000 permutations and with threshold-free cluster enhancement (TFCE) as a multiple comparison correction method.

The following variables were included in sensitivity analyses: gestational age (birth before gestational week 35 for five-year-olds), maternal pre-pregnancy BMI, maternal age at birth, maternal SES, maternal pre- and postnatal depressive/anxiety symptoms (EPDS and SCL-90 scores at 2nd trimester and 3 months postpartum), prenatal exposure to tobacco smoking, synthetic glucocorticoids (SGC) and selective serotonin/serotonin-noradrenaline reuptake inhibitors (SSRI/SNRI) during pregnancy.

The lateralization of FA values was estimated by FSL's "tbss_sym". Lateralization was estimated by subtracting the right-sided FA values from the left-side ones, followed by a "one-sample t-test" randomise analysis (5000 permutations, TFCE correction).

Statistical analyses for tract-wise FA values extracted with co-registration to JHU-ICBM-DTI-81 atlas (Mori et al., 2008) for 5-year-olds and JHU Neonate atlas (Oishi et al., 2011) for infants were performed with SPSS version 27.0 (IBM Corp.

2020, Armonk, NY, USA). To estimate sex differences, a two-tailed independent samples t-test was used, and for asymmetric differences one-sample t-test. Bonferroni correction was used for multiple comparison correction, with the corrected p-value thresholded at 0.001 (0.05/36 tracts). Effect sizes were estimated with Cohen's d.

4.2.9.4 Study IV

Association between FA at the age of five years and early exposure to maternal psychological distress was estimated with GLM (FSL's randomise tool) in voxel-wise analysis. First-, second-, and third-trimester EPDS and SCL-90 scores were used as the main variables for prenatal exposure. For postnatal exposure, EPDS scores at 3, 6, and 12 months postpartum, and SCL-90 scores at 3 and 6 months postpartum were used. The analyses were performed for all subjects and girls and boys separately with 5000 permutations and TFCE correction.

The potential selection bias was evaluated by comparing subjects with usable DTI data (N = 130) and excluded subjects (N = 73) with independent samples t-tests for continuous variables and ANOVA for categorical variables. Age at scan was the only variable showing a statistically significant difference between groups, the included subjects were younger (5.37 years, SD 0.11, $p < 0.001$) compared to the excluded subjects (5.45, 0.15).

The following confounding factors were considered in the analyses: subject's age at scan, sex, maternal age at childbirth, maternal pre-pregnancy BMI, maternal SES, subject's PI, duration of full breastfeeding, the occurrence of an adverse life event during the preceding year (parental divorce, severe sickness, or death), prenatal exposure to tobacco smoking, SSRI/SNRI and SGC (exposures were self-reported). Correlation between variables was inspected with Spearman correlation. Due to the correlation between maternal BMI and the child's PI ($\beta = .30$, $p<0.001$), PI was excluded from the regression model to avoid possible multicollinearity. No multicollinearity between other covariates was detected (variance inflation factor [VIF] for all variables between 1.0 and 1.8). The categorical variables were dummy-coded for regression analyses.

The following covariate data were missing: maternal BMI (1 subject, 0.7%), SES (5 subjects, 3.8%), and SSRI/SNRI exposure (8 subjects, 6.2%). The data points were missing completely at random (Little's test) and were imputed with the regression method. The correlation of variables and data imputation was performed with SPSS (version 27.0.1.0, Armonk, NY: IBM Corp).

Spearman and partial correlations between separate WM tract mean FA values and EPDS/SCL-90 scores were calculated with SPSS with the same covariates as used in the regression analyses. False discovery rate (FDR) correction for multiple

comparisons was applied post hoc by tract. Statistical differences between girls and boys were estimated with independent samples t-test (two-tailed) for continuing variables and with ANOVA for categorical variables.

The interaction between sex and maternal depressive symptoms was examined by forming interaction variables (sex*2nd trimester EPDS and sex*3-month EPDS) which were used as the main covariate in regression analysis to explore their association with FA values. The aforementioned confounding factors were included in the analyses.

4.2.9.5 Study V

Group comparisons between girls and boys to determine whether they differed concerning demographical variables, maternal distress scores, or eye-tracking measurement results were performed with a two-sample independent t-test for continuous variables and with a Chi-square test for categorical variables using SPSS (version 27.0.1.0, Armonk, NY: IBM Corp). Statistically significant differences in disengagement probability and attentional biases between different facial expressions were examined with ANOVA, and post-hoc Tukey's HSD test (α level 0.05). Correlations between demographical variables, maternal distress scores, and eye-tracking measures were examined with Spearman rank correlation.

Voxel-wise analysis to investigate associations between DPs/attentional biases and FA values was performed with GLM (FSL's randomise tool, 5000 permutations, TFCE correction) for all subjects and girls and boys separately. The following confounding factors were included in the analyses: sex, child's age at scan, maternal pre-pregnancy BMI, maternal age, exposure to smoking, SSRI or GC during pregnancy, maternal 2nd trimester and 3 months postpartum EPDS, and SCL-90 scores.

5 Results

5.1 Incidental MRI Findings in Infants

5.1.1 Description of Incidental Findings

Within the sample of 175 infants, 13 (7.4%) subjects had an incidental finding. Hemorrhages were the most common finding (n = 12), and their prevalence was thus 6.9%. One subject with no hemorrhage had a caudothalamic cyst, and due to their high prevalence in normal brain development, this subject was excluded from subsequent analyses.

Subdural hemorrhages (SDH) were most common (n = 10, 5.7%), and mostly occurred simultaneously in multiple locations (n = 10 in the posterior fossa, n = 3 in the occipital region, n = 3 in the temporal region). Intraparenchymal hemorrhages (IPH) were combined with SDH in two subjects, and additionally, one isolated and one caudothalamic cyst-associated IPH were observed. Two subjects with SDH had also caudothalamic cysts. Demographical information on subjects and differences between subjects with incidental intracranial hemorrhage and subjects with no incidental finding is provided in Table 7.

Table 7. Demographical information on subjects and differences between subjects with or without hemorrhage as incidental findings. NA = not available, SD = standard deviation, BMI = body-mass index, CI = confidence interval, PRAQ-R2 = pregnancy-related anxiety questionnaire, 2nd trimester, Sig. = significance, $p < 0.05$ = *

	Hemorrhage n (%) = 12 (6.9)	**No findings** n (%) = 162 (93)	Sig.
male (%) female (%)	6 (50) 6 (50)	88 (54) 74 (46)	0.99
Mode of delivery: spontaneous vaginal delivery (%) vacuum assisted delivery(%) section (%)	 8 (67) 4 (33)* 0	 116 (71) 17 (11) 29 (18)	 0.029
Primigravida (%)	6 (50)	66 (41)	0.77
Anesthetics: epidural/spinal (%) no/mild (%)	 7 (64) 4 (36)	 95 (59) 65 (41)	 0.48 0.88
Length of pregnancy, days (mean [SD])	280 [6.16]	279 [8.30]	0.71
Maternal pre-pregnancy BMI (mean [SD])	24.7 [4.15]	24.4 [4.11]	0.83
Maternal age at birth (mean [SD])	29.7 [5.68]	30.2 [4.11]	0.74
Length of delivery (median [95% CI])	458 [297;744]	448 [455;553]	0.50
Artery pH (mean [SD])	7.20 [0.12]	7.27 [0.072]	0.16
Birth weight (g) (mean [SD])	3448 [490]	3531 [432]	0.53
Birth height (cm) (mean [SD])	50.2 [2.17]	50.5 [1.80]	0.39
Head circumference (cm) (median [95% CI])	34.75 [34.1;35.7]	35.0 [34.9;35.3]	0.47
Age at imaging (median [95% CI]) from due date (days) from date of birth (days)	 21.5 [17.9;25.2]* 22.0 [18.0;25.2]*	 25.0 [25.1;27.3] 26.0 [25.8;28.2]	 0.042 0.019
Apgar score 1 min (median [95% CI])	9.0 [6.25;9.08]	9.0 [8.25;8.66]	0.27
Apgar score 5 min (median [95% CI])	9.0 [7.23;9.27]	9.0 [8.69;8.91]	0.090
PRAQ-R2 (median [95% CI])	6.0 [4.71;8.57]	6.0 [6.41;7.28]	0.13

5.1.2 Risk Factors

The mode of delivery was associated with the risk of intracranial hemorrhage. No hemorrhages were observed in infants born with cesarean section. In addition to vaginal birth, vacuum assistance increased the risk for hemorrhages. Vacuum-assistance-associated risk for hemorrhages in general did not reach statistical significance with Boschloo's test (Figure 5) but it was presented as a risk factor for SDH and especially for temporal SDH.

Infant's sex, birth weight, birth height, gestational age, Apgar scores, duration of the delivery, maternal age, parity, and use of anesthetics or oxytocin were not related to the emergence of hemorrhages. The median age of infants was lower in the group with hemorrhages (median = 22.0 days, 95% CI [18.0;25.2]) compared to the group with no findings (26.0 days, [25.8;28.2], $p = 0.019$).

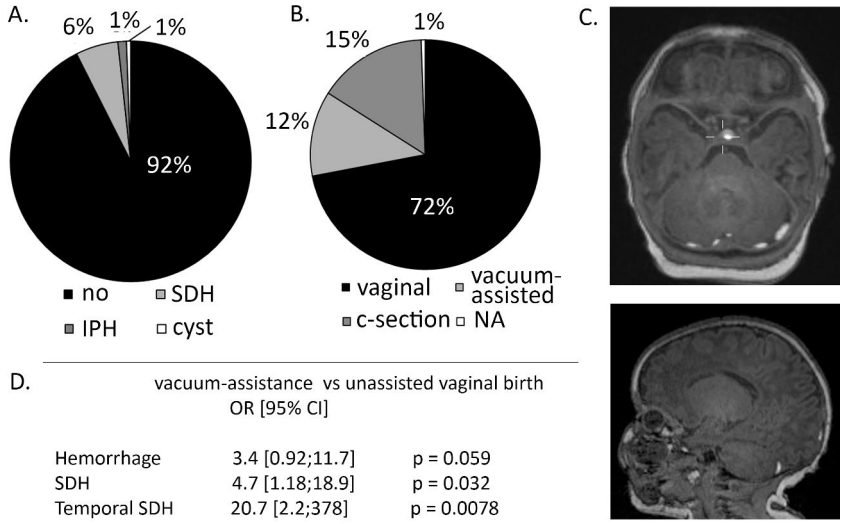


Figure 5. A. Pie chart shows the proportions of incidental findings in the study population (SDH = subdural hemorrhage 6%, IPH = intraparenchymal hemorrhage 1%, cyst 1%). B. Pie chart describes the percentages of different modes of delivery. C. Two T1-weighted MR images showed subdural hemorrhages in the posterior fossa. D. Odds ratios (OR) for hemorrhage between vacuum-assisted and unassisted vaginal births are provided with confidence intervals and p values. The figure is adapted from Study I.

5.1.3 Neurological Consequences

All infants with an intracranial hemorrhage observed at age 2-5 weeks, were initially discharged from the maternity hospital according to normal procedure (average stay at hospital 3.1 days, range 0-6 days), and no long-lasting symptoms or abnormalities were observed by healthcare personnel as per our inclusion criteria. One infant with posteriorly diagnosed cerebellar IPH had breathing difficulties requiring acute surveillance, which was assumed to be caused by an infection, and not related to the hemorrhage.

Eleven (85%) families attended the follow-up visit to a pediatric neurologist. Due to scheduling issues, the infant age at examination varied (7 to 54 weeks, mean 16.6 weeks), and thus two age-appropriate assessment protocols (Dubowitz neurological examination for infants aged 6 months or under (n = 9), and HINE for all subjects) were used to guarantee the comparability of the examination outcomes.

Significant clinically identifiable neurological symptoms, deficits in development, problems with general health, or clinically significant deviation in the Dubowitz or HINE scores were not observed in any of the 11 infants. Four infants had one deviant item in Dubowitz's neurological examination (mainly mild truncal hypotony; 1-2 deviant items are found in one-third of the normal population). In HINE, no marked delay in developmental milestones or behavior was detected (median score 65 in posture, movement, tone, and reflexes, which falls into the range

reported in normally developing 3- to 8-month-olds). Cranial nerve function was normal in all infants, but one infant showed mildly delayed motor and social development.

5.2 Optimised DTI Pre-Processing Protocol

The effect of the number of diffusion encoding directions on the repeatability of DTI scalar values in the TBSS skeleton was evaluated in the population of 5-year-olds (Figure 6 showing results in GCC with FA and MD). We conclude that a minimum of 18 directions is required for repeatable results with ICC(2,1) > 0.85 for FA values and increasing the number over it resulted in no additional advantage in terms of repeatability, either with TBSS skeleton or whole WM tract mean scalar values (Table 8 showing ICC(2,1) for FA and MD skeletons). Readers are referred to the original publication for a detailed report of the results (Kumpulainen et al., 2022). Sensitivity for the number of directions was higher with FA, RD, and AD, while MD was less dependent on the amount of diffusion encoding directions of the data. The FA threshold applied in TBSS was observed not to affect the number of directions required for reproducible results evaluated by the interaction model.

On average, 63 (range 41-95, SD 13.3) directions were retained after the exclusion of movement-corrupted diffusion volumes in the population with a total of 96 directions gathered. The residual motion after pre-processing remained low with translation movement ranging between 0.36 and 0.91 (± 0.16-0.26) mm and rotational movement between 0.13 and 0.20 (± 0.067-0.010) degrees. The residual motion was not detected to affect the FA values.

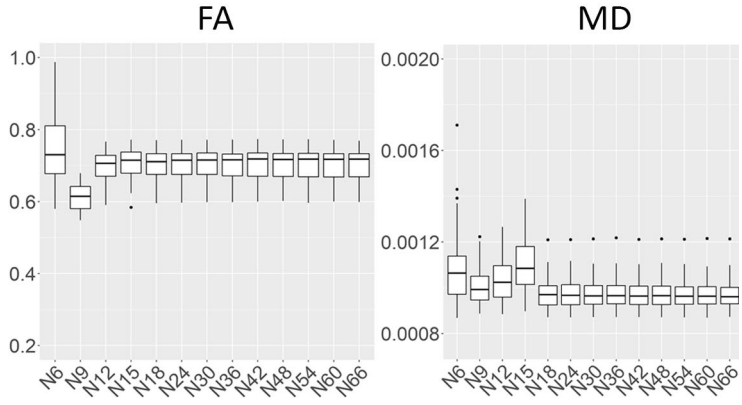


Figure 6. The effect of the number of diffusion-encoding directions (X axis) on the scalar values (Y axis; FA = fractional anisotropy, MD = mean diffusivity) in genu of corpus callosum. Plots show that the effect of using low number of directions affects most the FA and MD, and after 18 directions, increasing the number does not affect the results. The figure is adapted from study II.

Table 8. Intra-class correlation coefficients (ICC(2,1)) and 95% confidence intervals (CI) for the FA skeleton and MD skeleton extracted scalar values between different number of diffusion directions used for separate white matter tracts. See abbreviations in Table 5, page 52.

FA skeleton

	N6-to-N66 [CI]		N12-to-N66 [CI]		N18-to-N66 [CI]	
GCC	0.64	[0.54;0.74]	0.99	[0.98;0.99]	0.99	[0.99;1.00]
SCC	0.30	[0.21;0.42]	0.97	[0.95;0.98]	0.99	[0.99;.99]
CST R	0.14	[0.077;0.23]	0.74	[0.66;0.82]	0.87	[0.82;0.91]
ALIC R	0.29	[0.20;0.41]	0.95	[0.93;0.97]	0.97	[0.96;0.98]
PLIC R	0.31	[0.22;0.43]	0.96	[0.94;0.97]	0.98	[0.97;0.99]
CG R	0.23	[0.15;0.34]	0.86	[0.81;0.91]	0.94	[0.92;0.96]
SLF R	0.20	[0.13;0.30]	0.93	[0.90;0.95]	0.97	[0.96;0.98]
SFOF R	0.25	[0.16;0.36]	0.69	[0.60;0.78]	0.95	[0.93;0.97]

MD skeleton

	N6-to-N66 [CI]		N12-to-N66 [CI]		N18-to-N66 [CI]	
GCC	0.47	[0.37;0.59]	0.80	[0.73;0.87]	0.99	[0.99;1.00]
SCC	0.34	[0.25;0.47]	0.92	[0.88;0.95]	0.99	[0.99;0.99]
CST R	0.27	[0.19;0.39]	0.75	[0.67;0.83]	0.99	[0.98;0.99]
ALIC R	0.44	[0.34;0.56]	0.97	[0.95;0.98]	0.98	[0.97;0.99]
PLIC R	0.34	[0.24;0.46]	0.95	[0.93;0.97]	0.98	[0.97;0.99]
CG R	0.30	[0.22;0.42]	0.83	[0.76;0.88]	0.96	[0.95;0.98]
SLF R	0.69	[0.60;0.78]	0.93	[0.91;0.96]	0.98	[0.98;0.99]
SFOF R	0.15	[0.090;0.25]	0.16	[0.091;0.26]	0.97	[0.95;0.98]

5.3 Basic Features of White Matter Microstructure in Infants and 5-year-olds

Fractional anisotropy showed a significant increase in all WM tracts between birth and age of 5 years in two separate populations of infants (n = 166, 2-5 weeks of age) and 5-year-olds (n = 144, 5.1 to 5.8 years) (Table 9).

In infants, age from birth ($p < 0.05$ with gestational age as a covariate), and especially gestational age ($p < 0.001$ with age from birth as a covariate), showed a significant positive association with FA overall in WM tracts with regression analysis (5000 permutations, multiple comparison correction with TFCE), after controlling for sex, maternal age, and pre-pregnancy BMI, SES and exposure to SSRI, smoking, or glucocorticoids. Also, in 5-year-olds, the age was associated with an increase in FA in BCC ($p < 0.05$, 5000 permutations, TFCE correction), but the results did not remain significant after controlling for maternal age and pre-pregnancy BMI, SES, exposures to SSRI, smoking, or glucocorticoids during pregnancy ($p < 0.06$).

Table 9. Fractional anisotropy (FA) values and standard deviation (SD) per each white matter tract for infants and separately for 5-year-old boys and girls. The statistical difference between girls and boys was assessed with an independent sample t-test (two-tailed), p values provided (significant p-value with Bonferroni correction 0.001 (0.05/36), and effect sizes calculated with Cohen's d. See white matter tract abbreviations explained in Table 5, page 52. R = right, L = left

	infants		**5-year-olds**				**Difference between 5-year-old boys and girls**	
	All subjects		boys		girls		p value	Cohen's d
	FA	SD	FA	SD	FA	SD		
GCC	0.33	0.029	0.72	0.036	0.72	0.033	0.69	0.066
BCC	0.31	0.026	0.64	0.037	0.63	0.038	0.47	0.12
SCC	0.39	0.032	0.74	0.029	0.75	0.025	0.005	0.48
Fornix	0.24	0.020	0.44	0.043	0.45	0.041	0.25	0.19
CST R	0.24	0.024	0.49	0.028	0.49	0.024	0.67	0.072
CST L	0.24	0.027	0.51	0.028	0.50	0.027	0.29	0.18
ALIC R	0.29	0.020	0.54	0.025	0.54	0.023	0.73	0.059
ALIC L	0.26	0.020	0.52	0.027	0.52	0.023	0.52	0.11
PLIC R	0.39	0.024	0.65	0.020	0.65	0.020	0.57	0.095
PLIC L	0.38	0.024	0.66	0.021	0.66	0.021	0.95	0.010
rl IC R	0.38	0.024	0.54	0.026	0.55	0.028	**0.001***	**0.58**
rl IC L	0.36	0.022	0.56	0.023	0.57	0.024	0.007	0.46
ACR R	0.22	0.026	0.45	0.028	0.46	0.028	0.15	0.24
ACR L	0.22	0.025	0.44	0.027	0.45	0.028	0.049	0.33
SCR R	0.29	0.022	0.46	0.025	0.47	0.024	0.12	0.26
SCR L	0.28	0.021	0.48	0.022	0.48	0.024	0.85	0.031
PCR R	0.25	0.025	0.44	0.028	0.44	0.025	0.056	0.32
PCR L	0.27	0.026	0.44	0.027	0.44	0.030	0.41	0.14
PTR/OR R	0.31	0.024	0.57	0.032	0.59	0.029	**< 0.001***	**0.68**
PTR/OR L	0.32	0.026	0.57	0.034	0.59	0.030	**< 0.001***	**0.66**
ILF/IFOF R	0.29	0.027	0.50	0.026	0.52	0.030	**< 0.001***	**0.64**
ILF/IFOF L	0.30	0.027	0.50	0.026	0.52	0.026	**0.001***	**0.58**
CG R	0.25	0.043	0.41	0.037	0.41	0.039	0.86	0.029
CG L	0.27	0.035	0.41	0.037	0.41	0.036	0.27	0.19
CING R	0.19	0.026	0.46	0.038	0.46	0.035	0.46	0.12
CING L	0.20	0.026	0.49	0.039	0.48	0.035	0.45	0.13
Fornix/ST R	0.26	0.021	0.51	0.032	0.51	0.026	0.85	0.031
Fornix/ST L	0.31	0.023	0.52	0.032	0.52	0.025	0.96	0.009
SLF R	0.23	0.023	0.47	0.025	0.48	0.029	0.014	0.42
SLF L	0.24	0.022	0.47	0.025	0.48	0.029	0.097	0.28
SFOF R	0.34	0.030	0.47	0.041	0.48	0.036	0.47	0.12
SFOF L	0.19	0.020	0.45	0.045	0.45	0.037	0.031	0.36
UNC R	0.30	0.045	0.43	0.028	0.45	0.030	0.031	0.36
UNC L	0.26	0.051	0.45	0.028	0.45	0.035	0.19	0.22

5.3.1 Sex Differences

In the infant population, no sex differences were observed. However, at the age of 5 years, girls showed statistically significantly higher FA in multiple regions after controlling for gestational age, prenatal exposure to SSRI/SNRI, smoking or glucocorticoids, maternal age, pre-pregnancy BMI, SES, or maternal perinatal depressive symptoms in voxel-wise regression analysis (5000 permutations, $p < 0.05$, TFCE for multiple comparison correction, Figure 7). Additionally, statistically significant sex difference after Bonferroni correction in the tract mean FA between girls and boys were detected in right rlIC ($p = 0.001$), bilateral PTR/OR ($p < 0.001$), and bilateral ILF/IFOF ($p < 0.001$), and a trend toward statistical difference in SCC ($p < 0.005$; Bonferroni corrected p-value threshold 0.001). The sex differences were emphasized in the right hemisphere and posterior and temporal parts of the WM tracts. No regions with higher FA in boys were detected.

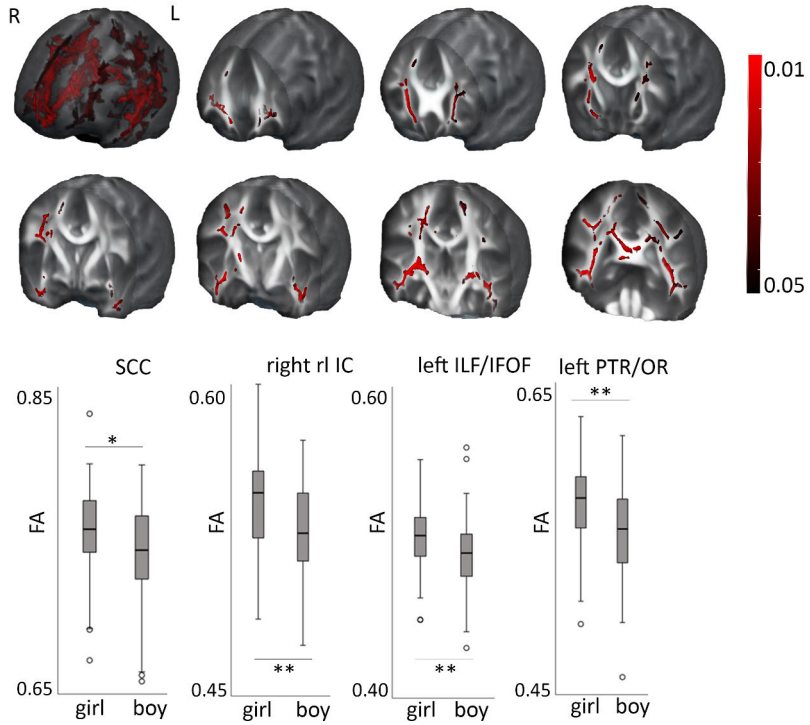


Figure 7. Sex differences with statistical significance ($p < 0.05$, multiple regression analysis) showing higher fractional anisotropy (FA) in girls (red areas with p-value < 0.05). Tract-specific differences between boys and girls investigated with extracted mean FA values and independent sample t-test showed statistically significant differences, right retrolenticular internal capsule (rl IC), left inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (ILF/IFOF) and left posterior thalamic radiation/optic tract (PTR/OR), and a trend toward significance in splenium of corpus callosum (SCC); * $p < 0.005$, ** $p < 0.001$, R = right, L = left. The figure is adapted from Study III.

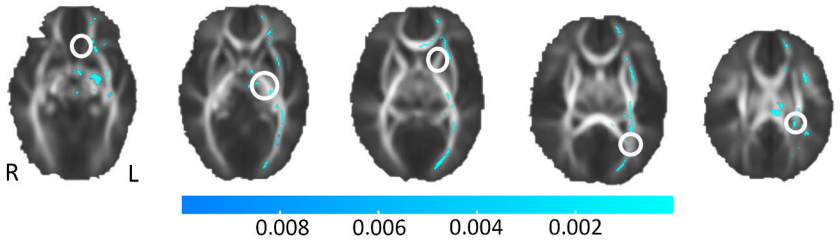
5.3.2 Asymmetry of White Matter

White matter showed highly lateralized microstructure both in the infant and in the 5-year-old populations (Figure 8). In infants, significant leftward asymmetry of FA was observed in PTR/OR (mean difference of FA (left-right) 0.0086, $p < 0.001$, Cohen's d 0.42) and PCR (0.0098, $p < 0.001$, Cohen's d 0.73), and significant rightward asymmetry in uncinate (-0.0051, $p < 0.001$, Cohen's d 0.84), PLIC (-0.0092, $p < 0.001$, Cohen's d 0.38), ALIC (-0.0245, $p < 0.001$, Cohen's d 1.2) and SCR (-0.0029, $p = 0.001$, Cohen's d 0.36). Voxel-wise multiple regression analysis showed additional clusters with left-right differences (5000 permutations, $p < 0.001$, TFCE for multiple comparison correction) after controlling for sex.

In 5-year-olds, asymmetry patterns observed with voxel-wise multiple regression analysis were widespread and covered regions in all WM tracts (5000 permutations, $p < 0.0001$, TFCE as multiple comparison correction) after controlling for sex. In a comparison of mean tract FA, leftward asymmetries were observed in the cingulum (mean difference of FA (left-right) 0.026, $p < 0.001$, Cohen's d 0.70), the uncinate (0.011, $p < 0.001$, Cohen's d 0.35), EC (0.022, $p < 0.001$, Cohen's d 1.0), SCR (0.010, $p < 0.001$, Cohen's d 0.42) and rightward asymmetries in ALIC (-0.022, $p < 0.001$, Cohen's d 0.90), SFOF (-0.028, $p < 0.001$, Cohen's d 0.71) and ACR (-0.0077, $p = 0.019$, Cohen's d 0.28). Significant sex differences in the lateralization pattern were not observed.

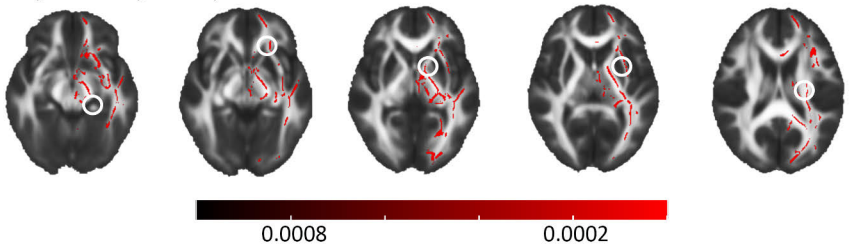
The observed lateralization patterns differed between the separate populations of infants and 5-year-olds, which was also repeated in the analysis of 22 subjects included in both populations. The asymmetries were more extensive in 5-year-olds, and rightward lateralization of PLIC, CST, and ILF/IFOF observed in infants shifted to leftward lateralization in 5-year-olds.

A Asymmetry in infants



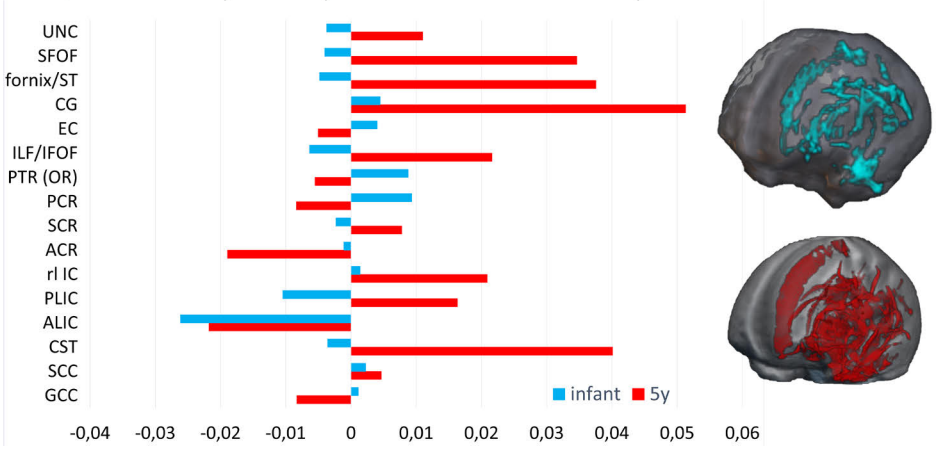
UNC	PLIC	ALIC	PTR/OR	PCR
L < R -0.00508	L < R -0.00919	L < R -0.0245	L > R 0.00860	L > R 0.00980
p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001
Cohen's d 0.84	Cohen's d 0.38	Cohen's d 1.2	Cohen's d 0.42	Cohen's d 0.73

B Asymmetry in 5-year-olds



CING	UNC	ALIC	EC	SFOF
L>R 0.0256	L>R 0.0106	L<R -0.022	L>R 0.022	L<R -0.0281
p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001
Cohen's d 0.70	Cohen's d 0.35	Cohen's d 0.90	Cohen's d 1.00	Cohen's d 0.71

C Comparison of asymmetry between infants and 5-year-olds



◄ **Figure 8.** White matter fractional anisotropy (FA) asymmetry in infants (A) and in 5-year-olds (B) (next page). A. Regions with statistically significant asymmetry in infants in multiple regression ($p < 0.01$, threshold-free cluster enhancement (TFCE) as multiple comparison correction) analysis shown in blue. Tract-specific difference investigated with tract mean FA comparing right and left tract (one-sample t test and Cohen's d for effect sizes), mean difference between left and right (negative values denote for rightward asymmetry). White circles show the location of tract below each image. B. Regions with statistically significant asymmetry in 5-year-olds (in red, $p < 0.001$). C. Comparison between FA asymmetry in infants (blue) and in 5-year-olds (red), left – right tract. UNC = uncinate, PLIC = posterior limb of internal capsule, ALIC = anterior limb of internal capsule, PTR/OR = posterior thalamic radiation and optic tract, PCR = posterior corona radiata, CING = cingulum, EC = external capsule, SFOF = superior fronto-occipital fasciculus, ILF/IFOF = inferior longitudinal fasciculus/inferior fronto-occipital fasciculus, SCR = superior corona radiata, ACR = anterior corona radiata, CST = corticospinal tract, SCC = splenium of corpus callosum, GCC = genu of corpus callosum, R = right, L = left. The figure is adapted from Study III.

5.4 Maternal Perinatal Mental Distress and Association to Brain White Matter Development

5.4.1 Correlation between Perinatal Mental Distress Scores and Study Variables

Maternal EPDS and SCL-90 scores were statistically highly correlated during both the pre- and postnatal period (Table 10). Maternal EPDS during 2nd trimester correlated with postpartum EPDS scores at 3, 6, and 12 months equally, with Spearman ρ 0.54, 0.50, and 0.53, respectively, and p-value < 0.001. SCL-90 scores correlated also statistically significantly with EPDS scores, during 2nd trimester with Spearman ρ 0.69 ($p < 0.001$) and at 3 months postpartum 0.52 ($p < 0.001$), showing clear 'comorbid prevalence' of depressive and anxiety symptoms.

Additionally, maternal pre-pregnancy BMI showed a statistically significant correlation with the child's PI (ρ 0.28, $p < 0.001$), which was present especially in the male offspring (ρ 0.36, $p < 0.001$, compared to ρ 0.19 in females). Maternal age also expectedly correlated with educational level (SES, ρ 0.24, $p < 0.05$). Sex-specific statistical correlations with α level 0.05 were also observed but only correlations between males' exposure to smoking and maternal age remained significant (ρ -0.30, $p < 0.05$), after bootstrapping with 95% CI and 1000 resampling.

Table 10. Correlation matrix showing Spearman correlation coefficients for study variables, separately for 5-year-old girls and boys. EPDS = Edinburgh Postnatal Depression Scale, SCL = Symptom Checklist 90, PI = ponderal index, SSRI = selective serotonin reuptake inhibitors, GC = glucocorticoids, SES = socio-economic status. * p < 0.05, ** p < 0.001

		EPDS 2nd trim	EPDS 3 mo	EPDS 6 mo	EPDS 12mo	SCL 2nd trim	SCL 3 mo	SCL6 mo	Child' s age	PI	Maternal BMI	Maternal age	Gest. age	smoking	SSRI	GC	SES
EPDS 2nd trim	girls	1.00															
	boys	1.00															
EPDS 3 mo	girls	.53**	1.00														
	boys	.57**	1.00														
EPDS 6 mo	girls	.40**	.69**	1.00													
	boys	.59**	.72**	1.00													
EPDS 12 mo	girls	.47**	.60**	.55**	1.00												
	boys	.61**	.60**	.65**	1.00												
SCL 2nd trim	girls	.74**	.53**	.40**	.60**	1.00											
	boys	.62**	.61**	.47**	.47**	1.00											
SCL 3 mo	girls	0.25	.53**	.32*	.46**	.47**	1.00										
	boys	.60**	.53**	.52**	.54**	.66**	1.00										
SCL 6mo	girls	.31*	.60**	.68**	.47**	.37**	.68**	1.00									
	boys	.75**	.66**	.74**	.73**	.76**	.74**	1.00									
Child's age	girls	.07	.15	.02	-.04	.09	-.03	-.13	1.00								
	boys	-.02	.04	-.02	.01	-.13	-.04	-.03	1.00								
PI	girls	-.10	.17	.01	.03	.05	.08	-.03	.09	1.00							
	boys	-.17	-.05	-.20	-.24	-.05	-.04	-.23	-.03	1.00							
Maternal BMI	girls	-.07	.12	.21	.17	.10	.11	.20	.13	.19	1.00						
	boys	-.08	.06	-.11	-.01	.12	.16	-.05	.01	.36**	1.00						
Maternal age	girls	-.16	-.15	-.05	-.25	-.10	-.17	-.04	-.25*	-.07	.08	1.00					
	boys	.10	.15	-.03	.14	.10	.01	.05	.01	.07	-.02	1.00					
Gest. age	girls	-.05	.10	.05	.04	-.02	.08	.03	-.07	.07	.25*	.02	1.00				
	boys	-.02	.02	-.08	-.19	-.11	-.09	-.13	.15	.09	.11	-.11	1.00				
smoking	girls	-.13	.16	.25	.07	-.20	.16	.25	-.23	.17	.07	.04	.03	1.00			
	boys	-.14	-.02	-.07	-.15	-.09	.11	-.08	.18	-.02	.23	-.30*	-.03	1.00			
SSRI	girls	.15	-.09	.08	.09	.09	.16	.17	.14	.02	-.13	-.21	-.13	-.04	1.00		
	boys	.11	.22	.09	.11	.24	.13	.17	.11	-.25*	-.13	.06	-.23	-.05	1.00		
GC	girls	-.21	.06	-.07	.02	-.02	.21	.03	.15	.15	.19	-.01	.07	-.07	-.06	1.00	
	boys	-.08	.01	-.13	.01	.00	.06	.02	.10	.01	.12	.05	-.30*	.17	.28*	1.00	
SES	girls	.19	.19	.02	.09	.22	.02	.08	.01	.05	-.02	.16	-.10	-.21	.02	.09	1.00
	boys	.07	.04	.00	-.03	.16	.07	.15	.10	.06	.05	.25*	.00	-.15	-.14	-.32*	1.00

	0.80-1.00
	0.60-0.79
	0.40-0.59
	0.20-0.39
	0-0.19

5.4.2 Associations between Prenatal Maternal Depressive Symptoms and White Matter Microstructure in 5-year-olds

Prenatal exposure to maternal depressive symptoms evaluated by EPDS in 2nd trimester was associated positively with FA in boys' WM in multiple regions ($p = 0.03$, 5000 permutations, TFCE correction; Figure 9A) after controlling for postpartum EPDS scores at 3 months in addition to general covariates (child's age, maternal age and pre-pregnancy BMI, SES, occurrence of adverse life event, duration of full breastfeeding and exposures to smoking, SSRI, or glucocorticoids). First or 3rd trimester EPDS showed no statistically significant association with FA in boys ($p = 0.14$ and 0.18, respectively).

In girls, no associations were observed. The association between 2nd trimester SCL-90 scores and FA did not remain significant after controlling for postpartum SCL-90 ($p = 0.61$ for all subjects, 0.42 for boys, 0.67 for girls). Table 11 shows the p-values of all regression analyses between FA and maternal psychological distress scores in boys and girls.

Table 11. Multiple regression analysis p values for associations between maternal mental distress scores at separate time points and fractional anisotropy values separately in boys and girls (5000 permutations). Pre/postnatal score denotes for corresponding 2nd trimester or 3-month postpartum score. All covariates include the child's age, maternal age and BMI, socioeconomic status, duration of full breastfeeding, the occurrence of stressful life events during the preceding year, exposure to smoking, SSRI, and glucocorticoids during pregnancy in addition to corresponding pre/postnatal scores. EPDS = Edinburgh Postnatal Depression Scale, SCL-90 = Symptoms Checklist 90

	Boys Positive association		**Girls** Negative association	
covariates	Age and pre/ postnatal score	All co-variates	Age and pre/ postnatal score	All co-variates
EPDS 1st trimester	0.13	0.14	0.44	0.35
EPDS 2nd trimester	**0.03**	**0.03**	0.73	0.90
EPDS 3rd trimester	0.18	0.18	0.39	0.48
Prenatal EPDS sum	0.27	0.29	0.56	0.61
Prenatal EPDS mean	0.26	0.25	0.54	0.57
EPDS 3 months postpartum (N = 130)	0.11	0.75	**< 0.01**	**< 0.01**
EPDS 6 months postpartum (N = 119)	0.46	0.62	0.19	0.20
EPDS 12 months postpartum (N = 119)	0.52	0.79	0.55	0.65
SCL-90 1st trimester	0.39	0.30	0.21	0.07
SCL-90 2nd trimester	0.34	0.42	0.14	0.67
SCL-90 3rd trimester	0.62	0.33	0.06	0.10
SCL-90 3 months postpartum	0.24	0.29	0.08	0.29
SCL-90 6 months postpartum	0.38	0.61	0.34	0.54

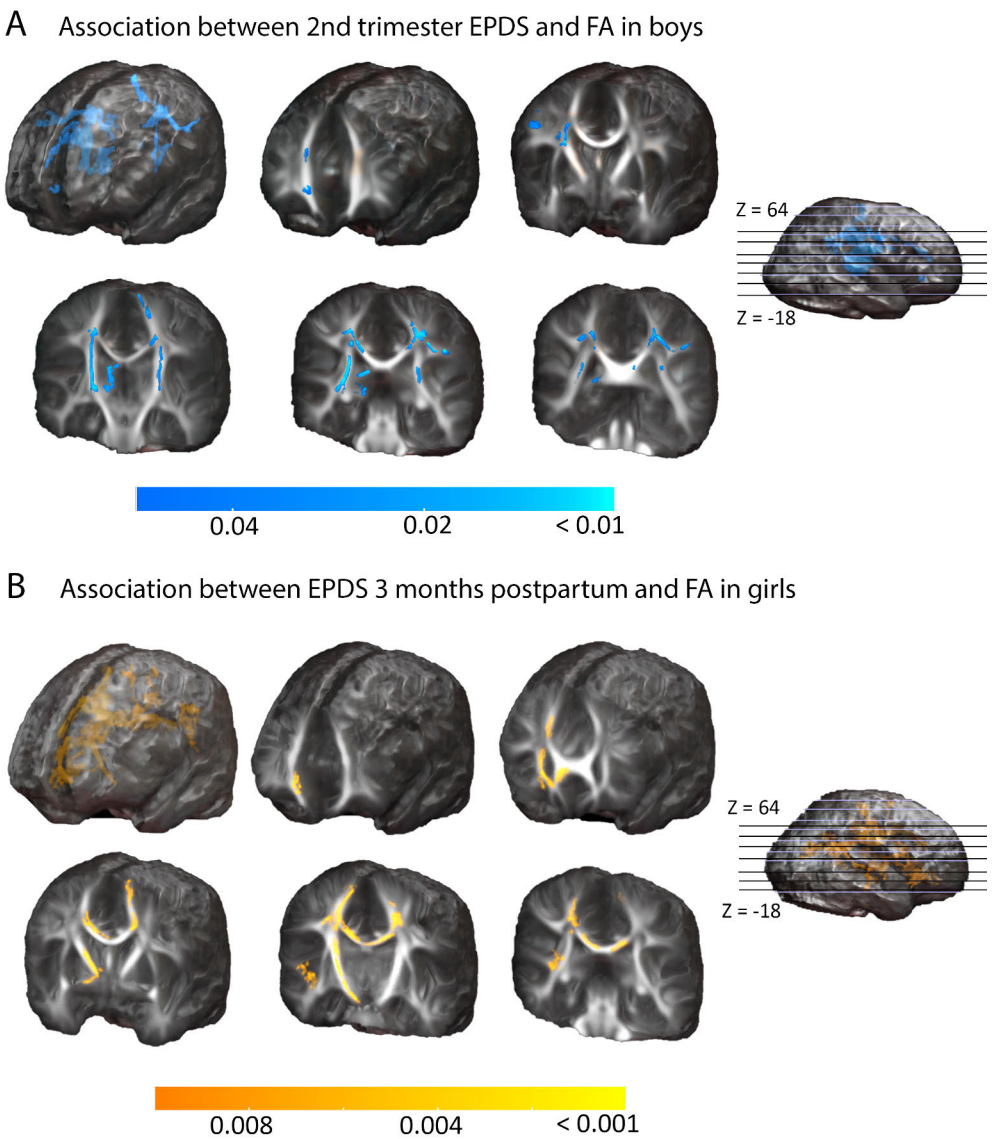


Figure 9. A. Positive association between 2nd trimester Edinburgh Postnatal Depression Scale (EPDS) score and fractional anisotropy (FA) observed in 5-year-old boys' white matter in multiple areas ($p < 0.05$, 5000 permutations; blue color bar) after controlling for postnatal EPDS at 3 months. B. Negative association between 3 months postpartum EPDS and FA observed in 5-year-old girls' white matter in multiple areas ($p < 0.01$, 5000 permutations, yellow color bar) after controlling for 2nd trimester EPDS. The figure is adapted from Study IV.

5.4.3 Associations between Postnatal Maternal Depressive Symptoms and White Matter Microstructure in 5-year-olds

Postnatal exposure to maternal depressive symptoms evaluated by EPDS at 3 months postpartum was associated negatively with FA in multiple WM clusters in girls after controlling for 2nd-trimester EPDS score ($p < 0.01$, 5000 permutations, TFCE correction; Figure 9B). No regions with positive association or statistically significant association in boys or all-subject groups ($p = 0.75$ and $p = 0.06$, respectively) were observed. Furthermore, the associations between FA and EPDS scores at 6 or 12 months postpartum did not reach statistical significance in girls ($p = 0.20$ and 0.65, respectively). A statistically significant association between postnatal SCL-90 scores and FA was not observed after controlling for 2nd trimester SCL-90 (in girls $p = 0.08$, in boys $p = 0.24$).

5.5 Association between Maternal Mental Distress and Vigilance toward Facial Expressions

Attention toward facial expressions among 5-year-olds was inspected by measuring the probability of disengagement from separate facial expressions (control, neutral, happy, fearful) (Table 12). Disengagement probability was statistically significantly lower from neutral (mean difference to control 0.15, $p < 0.001$), fearful (0.17, $p < 0.001$), and happy (0.081, $p = 0.042$) facial expressions compared to the control picture. Disengagement probability from happy faces was higher compared to fearful faces (DP -0.092, $p = 0.014$). Attentional bias to fearful faces was significantly higher compared to happy faces in all-subject groups (mean difference 0.092, $p = 0.034$).

Table 12. Disengagement probabilities (DPs) and attentional biases from facial expressions. Group comparison between girls and boys showed no statistically significant differences.

	Girls (N = 55)		**Boys (N = 62)**		**Group difference**	
	Mean	SD	Mean	SD	t	Sig.
Dp.1CS	0.81	0.21	0.83	0.20	-0.56	0.58
Dp.2NE	0.68	0.26	0.66	0.26	0.45	0.66
Dp.3HA	0.71	0.24	0.77	0.22	-1.35	0.18
Dp.4FE	0.62	0.23	0.67	0.25	-1.15	0.25
FE-bias	0.19	0.27	0.18	0.30	0.57	0.57
HA-bias	0.10	0.26	0.06	0.26	0.77	0.44
NE-bias	0.13	0.30	0.17	0.29	-0.77	0.44

Maternal postnatal mental distress at 3 months postpartum showed a statistically significant positive association with the attentional bias toward fearful expression in girls (association between FE-bias and SCL-90 score $\rho = 0.57$, $p < 0.001$, and between FE-bias and EPDS score $\rho = 0.34$, $p = 0.010$; Table 13). Prenatal mental distress was not associated with attentional biases in girls. In boys, no associations between maternal mental distress and attentional biases toward facial expressions were observed.

Table 13. Correlation matrix for girls' eye-tracking results, maternal psychological distress scores, and demographical variables with Spearman correlation ρ, p values < 0.05 marked with * and < 0.005 with **. CS = control stimulus, FE = fearful, NE = neutral, EPDS = Edinburg postnatal depression scale, SCL-90 = Symptom Checklist, mo = month, trim = trimester.

	DP. 1CS	**DP. 4FE**	**NE bias**	**HA bias**	**FE bias**	**EPDS 3mo**	**SCL 3mo**	**EPDS 2nd trim**	**SCL 2nd trim**
DP.1CS	1.00								
DP.4FE	.09	1.00							
NE bias	.59**	-.10	1.00						
HA bias	.44**	-.14	.47**	1.00					
FE bias	.61**	-.71**	.50**	.47**	1.00				
EPDS 3mo	.31*	-.14	.25	.17	.34*	1.00			
SCL 3mo	.43**	-.36**	.32*	.25	.57**	.51**	1.00		
EPDS 2nd trim	.18	.05	.23	.18	.08	.54**	.21	1.00	
SCL 2nd trim	.13	.00	.20	.07	.08	.58**	.51**	.70**	1.00

5.6 Association between 5-year-old Girls' Vigilance toward Fearful Faces and White Matter Microstructure

Attentional bias toward fearful facial expression was observed to show a negative association with FA in multiple WM regions in girls with multiple regression analysis (TFCE corrected, 5000 permutations, $p < 0.05$) after controlling for child's age, maternal pre-pregnancy BMI, maternal age, SES, exposure to smoking, SSRI and SGC and maternal EPDS and SCL-90 scores at 2nd trimester (Figure 10). The result did not remain significant after the inclusion of 3-month postpartum EDPS or SCL-90 scores in the regression model. The regions with significant associations included e.g., SCC, left anterior UF, left ALIC, left PLIC, and left PTR/OR. Statistically significant associations were not observed in boys.

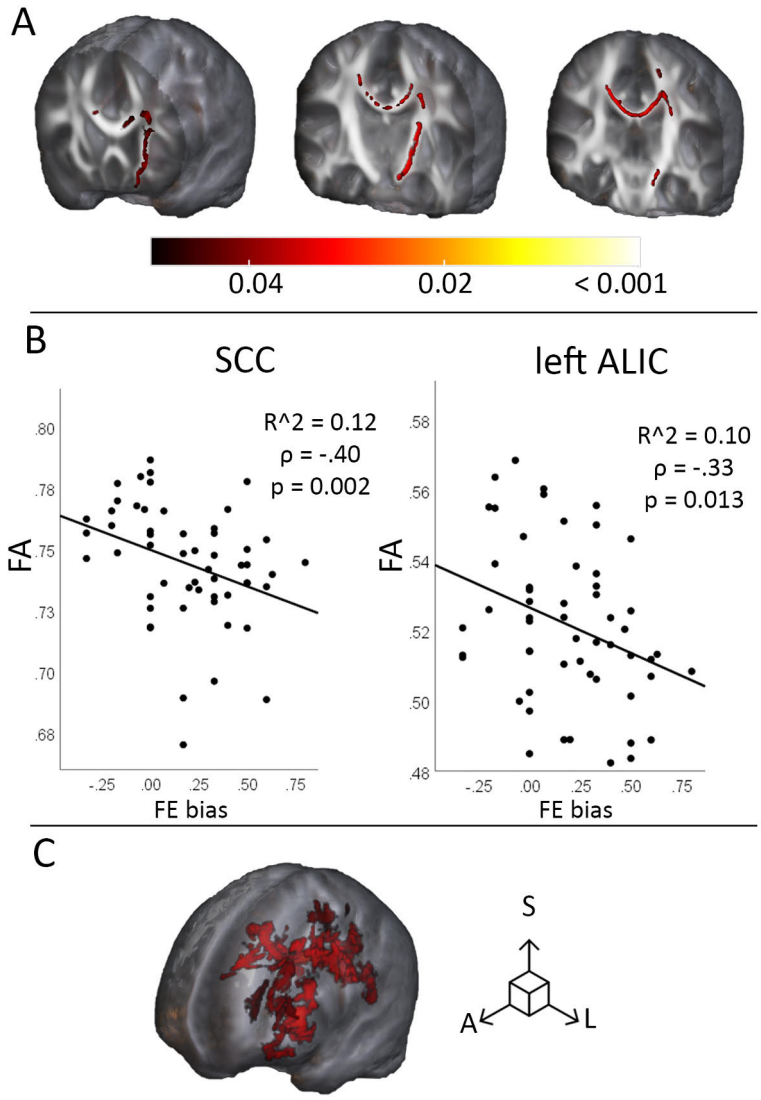


Figure 10. A. Negative association between bias to fearful faces (FE-bias) and fractional anisotropy (FA) in girls observed in regions shown in red ($p < 0.05$, 5000 permutations). B. Spearman correlation between FA and FE bias in splenium of corpus callosum (SCC) and in left anterior limb of internal capsule (ALIC) in girls. C. 3D depiction of areas with FA showing significant correlation with FE-bias. S = superior, A = anterior, L = left. The figure is adapted from Study V.

5.7 Association between 5-year-old Girls' Attention toward Faces and White Matter Microstructure

Face bias (disengagement probability from control picture vs neutral or happy faces) showed a negative association with FA in GCC in girls with multiple regression

analysis (TFCE corrected, 5000 permutations, $p < 0.05$) after controlling for child's age, maternal pre-pregnancy BMI, maternal BMI, SES, and exposure to smoking, SSRI and SGC during pregnancy (Figure 11).

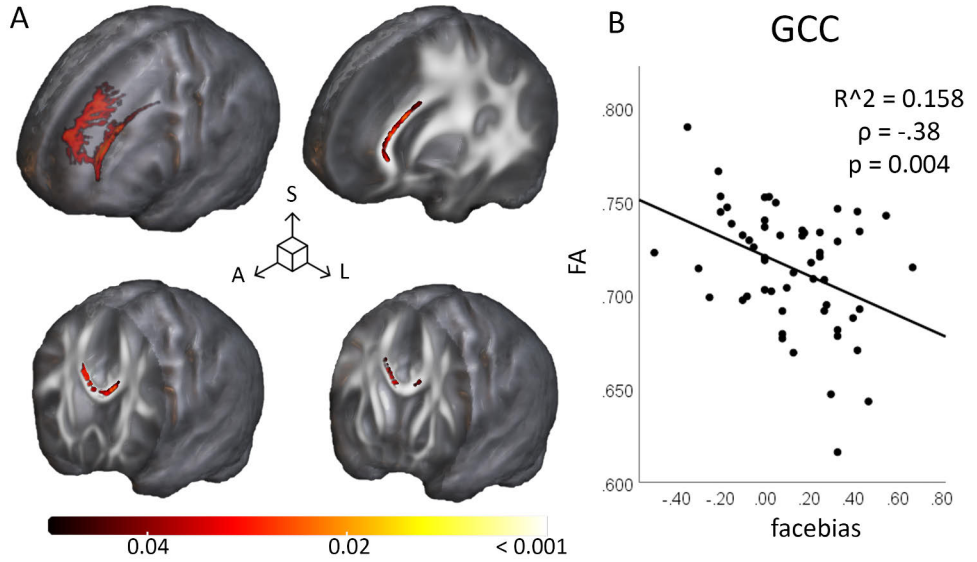


Figure 11. A. Negative association between bias to faces (face bias) and fractional anisotropy (FA) in girls observed in regions shown in red ($p < 0.05$, 5000 permutations). B. Spearman correlation between FA and face bias in genu of corpus callosum (GCC) in girls. The figure was created by Venla Kumpulainen.

6 Discussion

In this thesis, we disclose the importance of reporting methodological aspects and acknowledging the existence of incidental findings in pediatric brain MRI. We found that vacuum assistance and vaginal birth increased the risk for subdural hemorrhages while they were not associated with neurological consequences. Additionally, we found significant sex differences and asymmetric features in the WM at the age of 5 years. Higher WM integrity was observed in girls, while asymmetry of WM was tract-specific and showed no sex differences. The maternal psychological distress was observed to associate with the WM integrity in a sex- and temporal-specific manner: prenatal symptoms predicted higher integrity in boys and postnatal symptoms lower integrity in girls. Maternal postpartum anxiety increased girls' vigilance toward fearful faces, which was also associated with reduced WM integrity. The results drawn from this prospective study setting strengthen current knowledge of the developmental trajectory and normative features of the white matter in children. They further illustrate novel findings related to the sexually dimorphic characteristics and contributing factors behind the developmental variance of the white matter microstructure. Further, the results indicate that perinatal maternal mental health status inflicts long-term effects on white matter which may shape offspring's socio-emotional traits such as emotional attention.

6.1 Main Findings

6.1.1 Incidental Findings in Brain MRI of Infant Population

Several studies have explored incidental intracranial MRI findings in infant populations; however, the prevalence estimates have varied widely (8.1-47%) between prior studies (Carney et al., 2021; Looney et al., 2007; Malova et al., 2017; Rooks et al., 2008; Sirgiovanni et al., 2014; Tavani et al., 2003; Whitby et al., 2004; Wintermark et al., 2011), with the most acknowledged factors behind the differences being argued to relate to the scanning procedures, infants' age at scanning and practices during birth. In this thesis, we observed intracranial incidental findings in 7.4% of the participating infants and more specifically hemorrhages in 6.9%.

Vaginal birth and vacuum assistance were recognized to increase the risk of hemorrhages. Most essentially, the hemorrhages were not observed to compromise infant's health or affect the neurological development and were thus argued to have marginal clinical significance and no implication for changing the delivery practices.

The variance in the prevalence estimates of incidental hemorrhages is largely explained by age, as the highest prevalence was observed in the population with MRI scans within 3 days from birth (Rooks et al., 2008). Infants in our study population were scanned at the age of 2-5 weeks, by the time of which part of the minor hemorrhages may have been reabsorbed. The mode of delivery was also observed to affect the incidence of hemorrhages both in our and prior studies (Carney et al., 2021; Looney et al., 2007; Rooks et al., 2008; Sirgiovanni et al., 2014; Tavani et al., 2003; Whitby et al., 2004), and we detected hemorrhages in none of the infants born by c-section. Contrarily, in two studies (Carney et al., 2021; Rooks et al., 2008) hemorrhages were also observed after c-section. Events during labor contributing to the choice of delivery method are rarely reported or considered, which limits the comparison between studies, as those factors may also affect the risk for hemorrhages.

One previous study arranged a follow-up and observed all incidental birth-related hemorrhages to be resolved in 3 months (Rooks et al., 2008). This is valuable information especially in clinical settings, when evaluating the etiology of hemorrhages may also be required. Additionally, the distinct appearance of birth-related hemorrhages (wide distribution, posterior location, locating in multiple sites simultaneously, thin-film appearance) alleviates distinguishing them from non-accidental head injuries and prevents incorrect allegations of physical abuse.

As per our recommended protocol for handling of incidental findings, all families of infants with observed incidental findings (n = 13) were offered a visit to a pediatric neurologist. None of the infants presented clinical deficits or symptoms related to the finding at their follow-up appointment. Simultaneously, the parents were given information on the finding, and provided with an opportunity to contact a pediatric neurologist later, if they wished.

The usage and accuracy of MRI is continuously increasing, simultaneously increasing the emergence of incidental findings. The consequences of pediatric incidental findings may be grave, and the occurrence of a finding can cause a lot of stress for the participating family (Kumra et al., 2006; Li et al., 2021; Seki et al., 2010). Parental distress may affect parent-child bonding and attachment behavior (Mercer et al., 1986; Waisbren et al., 2003), and even in the case of benign findings, researchers should have sufficient resources to inform the parents of the positive prognosis. The information is recommended to be conveyed carefully with enough time and with the possibility to contact an adequate consultant upon request (Schmidt

et al., 2013). Information in a written form is not regarded as sufficient but face-to-face communication opportunity is recommended (Schmidt et al., 2013).

Considering this, a protocol for handling the incidental findings should be part of each research using MRI data, including appropriate follow-up and means to refer the subject to clinical care if required. Additionally, the possibility and potential repercussions of incidental findings should be informed in advance during the recruitment process. The applicability of these conventions related to the handling of incidental findings can be extended to cover all age groups of study subjects.

6.1.2 Pediatric DTI Data Pre-Processing Optimization

Comparability between separate DTI studies is complicated by wide methodological differences related to data acquisition, processing, and analysis methods, in addition to incomplete reporting of methodological choices and quality control protocols. To enhance reproducibility, several adult-population studies have recently aimed to optimize the DTI acquisition parameters and pre-processing pipelines in pursuit of a standardized protocol. However, due to structural and neurodevelopmental differences between children and adult brains, protocols designed for adults cannot be directly applied to pediatric populations. The guidelines for optimized parameter choices in pediatric DTI have been partly lacking. To respond to this need, we aimed in this thesis to evaluate the minimum number of diffusion encoding directions required for repeatable DTI scalar values with different FA threshold values, investigate the effect of intrascanner motion on DTI scalars and provide an optimized pre-processing protocol for DTI data. Our main finding was that a minimum of 18 directions is needed for providing reproducible FA values with TBSS in DTI data collected from 5-year-olds. Furthermore, after extensive pre-processing protocol including both manual and automated exclusion of volumes with poor quality, the residual motion did not have a statistically significant effect on the scalar values.

Number of diffusion gradients (Barrio-Arranz et al., 2015; Chen et al., 2015; Giannelli et al., 2010; Jones, 2004; Landman et al., 2008; Sairanen et al., 2017), b value (W. Gao et al., 2009) and voxel resolution (Fujiwara et al., 2008) have all been observed to influence on the resultant scalar values. Rejecting diffusion gradient directions has been shown to deteriorate both the accuracy and precision of DTI scalars, which was consistent with our findings. Decreasing the number of diffusion directions induced an increase in the variance of FA values especially in WM tracts with lower FA, again reflecting the results previously observed in adults (Chen et al., 2015; Sairanen et al., 2017). In addition, fluctuation of FA values was highlighted in tracts with low volume, which is partly explained by possible errors in the co-registration step and partial volume effects for example in cingulum bordering cerebrospinal fluid.

In the present study, TBSS was observed to reduce the variance inflicted on the FA values by decreasing the number of diffusion directions in the regions with high FA values compared to ROI analysis. This advocates the use of TBSS especially in situations when a low number of directions is available. Changing the FA threshold in TBSS did not affect the number of directions required, and thus the generally used threshold of 0.2 was chosen for analyses, as we observed TBSS skeletons of thresholds 0.1 and 0.15 to include voxels outside WM.

Within-scan motion places challenges on DTI, as the method is especially sensitive to motion artifacts (Basser & Jones, 2002). Motion artifacts have been indicated to distort DTI results (Farrell et al., 2007; Landman et al., 2008; Tijssen et al., 2009), and on the other hand, removing corrupted diffusion gradients randomly has been further shown to introduce bias to the scalar values (Ling et al., 2012). However, within-scan motion is an inevitable feature with young unsedated pediatric subjects, and the quality control of collected diffusion volumes is an essential step in data pre-processing. In the current study, an automatic quality control procedure (DTIprep) was applied but was observed not to remove all artifacts accurately while keeping all acceptable directions included, and thus was supplemented by manual verification of the passed volumes. On average, 30% of diffusion directions in this dataset were discarded in the quality control step. After the quality control steps were applied, the residual motion remained low and was not observed to influence the DTI scalar values. Related to this, the quality control of diffusion volumes and removal of motion-corrupted volumes has not been consistently reported in the pediatric DTI literature and requires additional attention in future studies.

To conclude, a minimum of 18 directions is recommended to be used in the TBSS analysis of children. However, as intrascanner motion is common in MRI of children, gathering extra directions is recommendable to simultaneously preserve the data quality and required number of directions.

6.1.3 Normative Features, Sex Differences, and Asymmetry of White Matter in Infants and 5-year-old children

A plethora of longitudinal studies have observed that the development of WM is accompanied by an increase in integrity, reflected as higher FA values and that the development proceeds with a temporo-spatially specific pattern that matches the maturation of motor, cognitive and socio-emotional skills (Hermoye et al., 2006; Krogsrud et al., 2016; Lebel et al., 2017; Lebel & Deoni, 2018; McGraw et al., 2002; Muftuler et al., 2012; Qiu et al., 2008; Reynolds et al., 2019; Rollins et al., 2010; Taki et al., 2013; Tamnes et al., 2010; Uda et al., 2015). Less is known about the sex differences and asymmetric features of WM during development. Additionally, longitudinal study settings have not been able to provide precise estimates on WM

microstructural properties at certain narrow age ranges of young children. In this thesis, we provide normative FA values in a healthy term-born population of Finnish infants (2-5 weeks of age) and 5-year-old children per separate WM tracts. Further, wide sex differences in 5-year-olds' WM microstructure were observed, with higher FA in girls, while in contrast no sex differences were observed in infants. Lastly, WM microstructure showed significant asymmetry at both age groups and with both rightward and leftward lateralized regions.

The observed sex differences were more extensive than previously described in the literature. We argue that this is related to the subject age: based on literature, boys' WM development is accelerated later than in girls, and thus the differences could be leveling off during later development (Seitz et al., 2021; Seunarine et al., 2016). These transient differences might, however, to some extent affect the variance in e.g., emotional processing Christov-Moore et al., 2014; Else-Quest et al., 2012), personality features (Schmitt et al., 2017; Weinstein & Dannon, 2015), temperament (de Boo & Spiering, 2009; Else-Quest et al., 2006; Olino et al., 2013) and behavior (Coe et al., 2020; Hines, 2010) known to exist between girls and boys.

White matter asymmetry is a well-known characteristic associated, for example, with language skills (Banfi et al., 2019). Considering the essential role in basic WM characteristics, the development and functional associations with WM lateralization have remained relatively understudied. In the current study, an asymmetric WM pattern was observed both in infants and in 5-year-old children, with no sex differences in either of the groups. The were some differences between infants and 5-year-olds, which might suggest that the WM asymmetry is developing still during the first years of life. The asymmetries at the age of 5 years resembled considerably the ones previously observed in adult populations (Honnedevasthana Arun et al., 2021; Takao et al., 2011), further suggesting asymmetry patterns to be a fundamental feature in brain WM. This finding highlights the role of WM asymmetry and depicts early childhood as an essential period for the appearance of diverging lateralization patterns, that may contribute to variation in cognitive measures, executive functions (Yin et al., 2013c), language development (Banfi et al., 2019; O'Muircheartaigh et al., 2013) and predisposition to disease associated with alterations in asymmetry patterns such as ADHD (Yin et al., 2013) and autism (Carper et al., 2016; Liu et al., 2019).

6.1.4 Effects of Maternal Perinatal Mental Distress on White Matter in Developing Brain

Early life adversity in the form of maternal perinatal mental distress is known to inflict negative consequences on cognitive, behavioral, social, and emotional functions in the offspring. In pursuit of resolving the neural correlates mediating the

association between maternal mental distress and alterations in e.g., socio-emotional skills, multiple studies have investigated the influence of prenatal maternal distress on WM development. The postnatal period has received less attention. In our sample of circa 5-year-olds, we observed significant sex-specific associations between maternal depressive symptoms and WM integrity. Prenatal depression showed a positive association with FA in multiple regions, but only in boys. In contrast, a negative association between girls' FA in widespread regions and maternal depressive symptoms at 3 months (but not 6 or 12 months) postpartum was observed. Maternal anxiety was not observed to associate with offspring WM integrity (when controlled for maternal depressive symptoms).

Several prior studies have shown girls to be especially sensitive to maternal psychological distress (Braithwaite et al., 2016; Dean et al., 2018; Erickson et al., 2019; Quarini et al., 2016; Simcock et al., 2016), both during and after pregnancy. One hypothesis (Sandman et al., 2013; Sutherland & Brunwasser, 2018) suggests that *in utero*, females are more responsive to early stress signals and adapt according to environmental requirements, which may increase later vulnerability to adversities (Clifton, 2010). In contrast, males are less adjustable, and environmental challenges may threaten their survival, leading to the survival of the fittest individuals.

Dean et al. found a corresponding sex-specific association between prenatal maternal distress and WM integrity in their population of 1-month-old infants: exposed females had a decrease and exposed males had an increase in FA (Dean et al., 2018). To our best knowledge, the current study is the first to observe different association patterns in girls and boys in relation to the timing of exposure to maternal depressive symptoms. Thus, these preliminary results suggest that boys' WM development is more vulnerable to long-term effects during pregnancy, while the first months after birth represent a critical period for girls.

It is also worthwhile to discuss the possible implications for the child phenotype concerning the observed white matter features. Prior studies have shown reduced that FA in multiple WM tracts to associate with internalizing symptoms like depression (Cullen et al., 2010; Henderson et al., 2013; Huang et al., 2011; Kliamovich et al., 2021; LeWinn et al., 2014; Mohamed Ali et al., 2019; Uchida et al., 2021) and anxiety (Adluru et al., 2017; Kaczkurkin et al., 2020; Liao et al., 2014; Lichtin et al., 2021). In the current study, reduced FA was observed in girls exposed to maternal depression, and on the other hand, depression and anxiety are overrepresented conditions in females. Thus, maternal mental distress may increase the risk of internalizing symptoms in female offspring through changes in white matter integrity. However, these preliminary conclusions are based on associations and future studies are required to further consolidate both the causality behind them and to investigate whether the WM changes observed in exposed subjects are manifested as psychiatric symptoms.

Increased FA was observed in prenatally exposed boys. Prenatal stress has been previously associated with accelerated WM maturation, which has been suggested to prepare the fetus for survival outside the womb. Even though higher FA is usually regarded to indicate the higher organization of WM, the advanced development may also denote diminished plasticity and make the brain less adaptable during later childhood. Higher FA is also associated with externalizing symptoms (Pape et al., 2015; Puzzo et al., 2018; Sarkar et al., 2013) which are more common in males.

The timing of exposure to maternal depression was observed to be essential. Accordingly with previous studies, alterations in WM were detected with postnatal exposure measured 3 months postpartum, but the effect did not remain significant at 6 or 12 months postpartum. Significant associations between postnatal depression and WM integrity have been observed when depression is measured 2-3 months postpartum (Lebel et al., 2016; Wen et al., 2017; Zou et al., 2019), but not at later time points (Borchers et al., 2021; Marroun et al., 2018).

To conclude, maternal depressive symptoms are associated with the WM integrity of the offspring in sex- and temporo-specific patterns and relate to alterations that in part may increase the offspring's predisposition to problems in socio-emotional functions.

6.1.5 Associations between 5-year-old Girls' Vigilance toward Fearful Facial Expression, Microstructure of White Matter and Role of Maternal Mental Distress during Postnatal Period

Maternal psychological distress has been shown to predict attentional bias to fearful faces and threat signals in the offspring (Kataja et al., 2019; Morales et al., 2017), and vigilance toward threat signals has been associated with increased risk for internalizing symptoms (Abend et al., 2018; Salum et al., 2017; Simcock et al., 2020; Waters et al., 2004). Based on the current knowledge, we investigated WM correlates between emotional attention and maternal postnatal psychological distress and found that 5-year-old girls' attentional bias to fearful faces showed a significant positive correlation with maternal anxiety and depressive symptoms assessed 3 months postpartum. Furthermore, attentional bias to fearful faces showed a negative association with girls' FA in multiple WM regions including SCC, left internal capsule, and fronto-occipital tracts. No correlations between boys' attentional biases or FA and maternal psychological distress were observed. Thus, girls' vigilance to fearful expression is associated with lower WM integrity, and this association was dependent on maternal postpartum depressive symptoms.

Besides attentional bias to fearful expressions, girls also showed a negative association between face bias (that is the probability of disengagement from the

neutral or happy face compared to the control picture) and FA of GCC. Reduced FA of SCC was also associated with attentional bias to fearful faces. The corpus callosum is known to be important for social functioning (Bridgman et al., 2014). Reduced FA of the corpus callosum is observed, for example, in depression (Aghajani et al., 2014; Ghazi Sherbaf et al., 2018; Henderson et al., 2013; Huang et al., 2011; LeWinn et al., 2014; Uchida et al., 2021). Research on patients with agenesis of the corpus callosum has further indicated the importance of this commissural tract in recognizing facial expressions (Young et al., 2019) and attentional vigilance to others' eyes (Bridgman et al., 2014).

The current finding further consolidates the evidence from prior studies of girls' sensitivity to maternal psychological distress. Further, as a novel finding, the vigilance to fearful faces was associated with reduced WM integrity. Immaturity of WM connections might imply weaker downregulation of neural activation to emotional stimuli and thus lead to an increased arousal state in the presence of emotional cues with lower social significance. The adherence to threatening emotional cues has been previously associated with negative outcomes including increased risk for internalizing symptoms. Based on the current results, it is possible that reduced WM integrity may transmit the long-term effects of maternal mental distress and by increasing the vigilance to negative emotions predispose the offspring to associated conditions. To endorse these preliminary findings, the follow-up of the current cohort is continued, and future investigations will show, whether the observed associations predicted the emergence of e.g., psychopathologies.

6.2 Limitations of the Studies

The studies included in this thesis have several shared limitations. The study population consists of healthy Finnish children drawn from a geographically restricted region (Southwest Finland) and extrapolating the results to other ethnicities or clinical applications requires caution. The socio-economic status of the families in the cohort is slightly skewed toward the higher end of the scale (Karlsson et al., 2017), and in this context, the cohort does not completely represent the Finnish clinical sample, for example, in relation to risk behavior. Information on many covariates relied on self-reports, and exposures to, for example, medications, smoking, or alcohol use were not objectively tested. Additionally, as the studies were cross-sectional, the exact timing, dynamics, and longer-term stability of the associations remain elusive.

In Study I, our prevalence estimates of incidental intracranial hemorrhages were lower compared to prior studies, and to one large population study published afterward (Carney et al., 2021). Several limiting factors may have led to an underestimation of the prevalence. The major limitation was related to the infants'

age at imaging. As the MRI was not initially designed to investigate the prevalence of birth-related incidental findings, the age range did not cover time immediately after birth and thus delivery associated hemorrhages may have been partially resolved, leading to an underestimation of their prevalence. Our MR sequences were not optimized for observing hemorrhages, and the inclusion of susceptibility-weighted imaging sequences may have increased the number of observed small hemorrhages. As per our inclusion criteria, infants with Apgar scores under 5 were excluded, which may have also led to the exclusion of infants with early signs of health problems. Follow-up imaging would have given information on the resolution dynamics of hemorrhages.

In DTI data acquisition of 5-year-olds (Study II-V), limitations are disclosed related to preprocessing and analysis methods. Acquired field maps were corrupted and hence field map correction was not performed for DTI data. However, artifacts in DTI volumes remained low after the preprocessing protocol, and lack of field map correction was not regarded to affect the data quality. The designed imaging session was relatively long, which may have increased subject attrition and increased movement during imaging.

In Study III, we used two separate study populations at the ages of 2-5 weeks and 5 years. Comparing the results between those two populations needs to be done with caution, as there are only 22 subjects included in both populations and the MR scanner was updated/upgraded between the imaging visits. As there is a limited number of follow-up data, making conclusions about the dynamics of developmental changes is challenging.

There are also several limitations related to the investigation of the effects of perinatal maternal distress (Study IV-V). The influence of genetics, paternal distress, or supporting factors such as daycare and involvement of grandparents were not considered in the scope of studies. Depression and anxiety are highly comorbid, and we were not able to separate their effects completely. Assessing the depressive and anxiety symptoms with self-report questionnaires provides both advantages and limitations to the interpretation of the results. As self-assessed, the main variables of depression or anxiety provide a realistic description of how mothers feel instead of using only information on diagnosis or medication of psychological distress, which does not necessarily illustrate the current mental state. On the other hand, questionnaire scores depend largely on other characteristics of subjects (how well they recognize their feelings, whether they are afraid of the consequences if revealing negative feelings, etc). Lastly, related to eye-tracking experiments (Study V), the use of mobile images could have increased the recognition of emotional expressions.

6.3 Clinical Implications and Future Research Perspectives

Previous literature has observed associations between exposure to maternal perinatal psychological distress and developmental problems in the offspring. As self-reported depressive and anxiety scores were used instead of diagnosis, the results indicate that already subclinical symptoms of psychological distress in mothers influence developing children. Sex differences in susceptibility to neuropsychological conditions as well as in the development of cognitive, behavioral, and socio-emotional skills are acknowledged likewise, while their neural foundation is just beginning to unravel. The results in this thesis further emphasize the sex-specific effects of maternal psychological distress and extend the evidence to associate early exposure to distress with the development of socio-emotional traits in 5-year-olds. The results consolidate the accumulating knowledge on the negative long-term effects of maternal indisposition on offspring development and address maternal well-being as a critical target for intervention in pursuit of supporting early brain development. In the support system, essential steps include screening and recognition of individuals with high risk for psychological distress and providing them with information and guidance to both prevent the emergence of depressive and anxiety symptoms and to enhance access to treatment when needed. Preventative actions reduced maternal postpartum depressive symptoms (Kozinszky et al., 2012), and it would be an interesting and important topic for future studies to investigate whether the WM alterations in the offspring could be reversed by treating and preventing maternal psychological distress. This kind of research would provide direct knowledge on the advantage of channeling more resources to preventative healthcare. Examining factors that increase resilience toward negative influences of maternal psychological distress was not in the scope of this thesis but investigating them in the future would also aid in finding targets for supportive interventions.

The finding of sex differences both in consequence of maternal distress and in normal WM maturation provide support for encountering and understanding cognitive and behavioral features of young children. This may in part assist in designing well-timed and appropriately targeted preventative protocols to meet the needs of developing children better. Simultaneously, encountering and treating children with stereotypical assumptions about their behavior based on sex needs to be avoided. Knowledge of sex differences in brain development could aid in finding individual strengths and focusing on them to support balanced development and coping with adversities (Määttä & Uusiautti, 2020).

In the near future, rapid advances in brain developmental research are expected. Open access databases, including Developing Human Connectome Project (dHCP, http://www.developingconnectome.org), Baby Connectome Project (BCP) (Howell et al., 2019), Healthy Brain and Child Development Study (Volkow et al., 2021), and

Adolescent Brain Cognitive Development (ABCD) Study (Casey et al., 2018), in addition to large multisite research collaborations such as Organization for Imaging Genomics in infancy (ORIGINs) (Alex et al., 2023), provide enormous potential for studying various aspects of brain development. Collaboration increases cost-efficiency, and large populations of harmonized multi-center data facilitate both the identification of heterogeneity in the sample and consistent differences between different phenotypes. Furthermore, sharing of data increases the reliability of new results, the populations are more comprehensive, and more attention is focused on improving and assessing the reproducibility of used analysis pipelines.

7 Conclusions

White matter in the brain is characterized by sexually dimorphic development as measured by microstructural features. The developmental trajectories within the white matter are associated with the consequences of early life exposure to perinatal maternal psychological distress. In contrast, asymmetry appears to be a fundamental feature of white matter, independent of sex and relatively stable during development past early infancy.

This thesis provided a report on the prevalence of incidental findings and describes how the local team handled them in practice. A key part of the described work is the methodological benchmarking of our diffusion imaging protocol and pipelines that form the basis for testing three research questions on typical brain development, effects of maternal perinatal distress, and exploration of brain correlates of attentional bias to emotional faces.

Maternal perinatal depressive symptoms are associated with white matter microstructure in the offspring, with prenatal depressive symptoms predicting higher white matter integrity in 5-year-old boys, and postnatal exposure to depressive symptoms, contrarily, associated with reduced integrity in 5-year-old girls. The timing of exposure is essential, as the first months after birth appear to inflict stronger effects. Whether these findings that implicate clear sex-specific brain phenotypes are later risk factors for multiple psychiatric conditions that have been linked with alterations in white matter integrity, remains however unanswered within the scope of the current study.

Exposure to postnatal maternal psychological distress, and specifically to anxiety, is associated with 5-year-old girls' vigilance toward fearful faces which was also associated with reduced white matter integrity. These associations in the brain were observed mainly in left-sided tracts and corpus callosum. Attentional bias to faces associated with reduced integrity of corpus callosum in girls. This further supports the observations of the sex-specific repercussions of early exposures and indicates that early maternal psychological distress modifies the emotional attention in girls. Increased sensitivity to threat signals has been linked with increased levels of internalizing symptoms. Investigating the possible role of observed white matter

alterations in mediating the association between allocated emotional attention and later psychological distress is to be addressed in future studies.

This thesis reports novel findings on sex- and temporo-specific patterns of white matter development, consequences of maternal perinatal psychological distress on white matter, and their associations with emotional attention at the age of 5 years. These novel findings contribute to understanding the sex-specific features of white matter development and provide preliminary evidence of alterations mediating the potentially long-term programming effects of exposure to maternal perinatal distress. Due to the exploratory nature and mainly cross-sectional setting, replication of the results and longitudinal follow-up studies are required to confirm the causality of observed associations. The current results provide an interesting initiative for future research on screening risk factors for psychiatric disorders embedded in early life.

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