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PRENATAL MATERNAL HEALTH AND CHILD BRAIN STRUCTURE: IMPLICATIONS FOR NON-VERBAL ABILITY AND OPTIMIZING SUBCORTICAL SEGMENTATION

The FinnBrain Birth Cohort Study

Elmo P. Pulli

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To my mom and dad

UNIVERSITY OF TURKU
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ELMO PULLI: Prenatal Maternal Health and Child Brain Structure:
Implications for Non-verbal Ability and Optimizing Subcortical Segmentation
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ABSTRACT

Brain development starts in utero, and the fetal brain can already be affected by the environment, including chemical exposures and maternal health characteristics. These factors range from exposures to large quantities of teratogens (such as alcohol) to variations in the behaviors and characteristics of healthy individuals (such as age, diet, and subclinical levels of depressive and anxiety symptoms), which can nonetheless have long-lasting adverse effects.

In this thesis, we reviewed the literature on the effects of prenatal exposures on human neurodevelopment, as well as cognitive, behavioral, and health outcomes. In Study I we found that prenatal exposures are often reported poorly in infant neuroimaging studies and gave recommendations for reporting in future studies.

In Study II, we examined which early life factors predicted cortical structure in 5-year-olds. The results from Study II were utilized to make an informed decision regarding confounders in future studies in the 5-year-old neuroimaging sample of the FinnBrain Birth Cohort study. In Study III, we explored the cortical structural correlates of non-verbal ability in 5-year-olds. The findings were generally in line with prior results from adult and adolescent studies, with the important addition of a positive association between gray matter volume and surface area in the right medial occipital region and non-verbal ability as well as visual abstract reasoning ability.

Finally, in Study IV, we compared the results from two common segmentation tools, FSL-FIRST and FreeSurfer, against manual segmentation in the hippocampus and subcortical structures. Overall, the agreement with manual segmentation was good, although results were suboptimal for the hippocampus, amygdala, and nucleus accumbens, and careful visual quality control is still recommended.

This thesis summarized different perinatal factors affecting the developing brain, and ensured the high quality of our neuroimaging data. This foundational work, together with the multidisciplinary, longitudinal data collection in the FinnBrain Birth Cohort study, can be used to discover how environmental factors affect brain development.

KEYWORDS: brain, neuroimaging, structural magnetic resonance imaging (sMRI), cerebral cortex, hippocampus, amygdala, gray matter, FreeSurfer, FSL, intelligence, cognitive ability, prenatal stress, prenatal exposures, prenatal environment

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Psykiatria
ELMO PULLI: Äidin raskausajan terveys ja lapsen aivojen rakenne:
yhteydet ei-kielellisiin taitoihin ja subkortikaalisen segmentaation optimointi
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TIIVISTELMÄ

Aivojen kehitys alkaa kohdussa ja jatkuu läpi elämän. Jo sikiöaikana aivot ovat alttiina ympäristön vaikutuksille, ml. kemialliset altisteet sekä äidin terveyteen liittyvät tekijät. Nämä altisteet vaihtelevat suurista annoksista teratogeeneille (esim. alkoholille) eroihin terveiden yksilöiden ominaisuuksissa ja toiminnassa (esim. ikä, ruokavalio sekä vähäiset masennus- ja ahdistusoireet ilman mielenterveyshäiriön diagnoosia), joilla voi kuitenkin olla kauaskantoisia seuraamuksia.

Tässä väitöskirjassa teemme katsauksen raskaudenaikaisten altisteiden vaikutuksista yksilön kehitykseen sekä siihen liittyviin muutoksiin aivoissa. Tutkimuksessa I toteamme, että raskaudenaikaiset altisteet kuvataan usein puutteellisesti vauvojen aivokuvantamista koskevissa tutkimuksissa ja annamme suosituksia raportoinnista.

Tutkimuksessa II tutkimme varhaisten altisteiden yhteyksiä 5-vuotiaiden aivojen rakenteeseen. Tämän tutkimuksen tulokset ohjasivat kontrolloitavien muuttujien valintaa. Tutkimuksessa III tutkimme aivokuoren rakenteen yhteyksiä ei-kielelliseen kognitiiviseen kyvykkyyteen 5-vuotiailla. Tulokset olivat pitkälti linjassa aiempien, vanhemmilla osallistujilla tehtyjen tutkimusten kanssa. Uutena tuloksena löysimme yhteyden oikean takaraivolohkon mediaalisen osan tilavuuden ja pinta-alan olevan yhteydessä ei-kielelliseen kyvykkyyteen sekä erityisesti näönvaraiseen päättelyyn.

Tutkimuksessa IV vertailimme kahta yleistä segmentointityökalua (FreeSurfer ja FSL-FIRST) käsin tehtyyn segmentaatioon hippokampuksessa ja aivokuoren alaisissa tumakkeissa. Tulokset vaihtelivat paljon rakenteesta riippuen. Huolellista laadunvarmistusta aivoalueiden koon määrityksen yhteydessä suositellaan vahvasti.

Tämä väitöskirja antaa kokonaisvaltaisen ymmärryksen aivoihin vaikuttavista varhaisen elämän altisteista. Yhdessä korkealaatuisen aivokuvantamisdatamme sekä muun FinnBrain-syntymäkohortissa kerättävän aineiston kanssa tätä tietoa voidaan hyödyntää useissa tulevissa aivojen kehitystä selvittävissä tutkimuksissa.

AVAINSANAT: aivot, aivokuvantaminen, rakenteellinen magneettikuvantaminen, aivokuori, hippokampus, mantelitumake, harmaa aine, FreeSurfer, FSL, älykkyys, kognitiivinen kyvykkyys, raskaudenaikainen stressi, raskaudenaikaiset altisteet, raskaudenaikainen ympäristö.

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Abbreviations

ADHD	Attention deficit hyperactivity disorder
BMI	Body mass index
COMT	Catechol-O-methyltransferase
CT	Cortical thickness
DNA	Deoxyribonucleic acid
DSC	Dice score coefficient
DTI	Diffusion tensor imaging
ENIGMA	Enhancing Neuro Imaging Genetics Through Meta Analysis
FA	Fractional anisotropy
fMRI	Functional magnetic resonance imaging
FSL	FMRIB (fMRI of the brain) software library
GM	Gray matter
GP	Globus pallidus
ICC	Intraclass correlation coefficient
IL-6	Interleukin-6
IQ	Intelligence quotient
LBW	Low birth weight
MPRAGE	Magnetization prepared rapid gradient echo
MRI	Magnetic resonance imaging
NICU	Neonatal intensive care unit
PCC	Pearson correlation coefficient
PIQ	Performance intelligence quotient
Qdec	Query, design, estimate, contrast
ROI	Region of interest
SA	Surface area
SES	Socioeconomic status
SNRI	Serotonin–norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
WM	White matter
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence, third edition

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Pulli, E. P., Kumpulainen, V., Kasurinen, J. H., Korja, R., Merisaari, H., Karlsson, L., Parkkola, R., Saunavaara, J., Lähdesmäki, T., Scheinin, N. M., Karlsson, H., & Tuulari, J. J. (2019). Prenatal exposures and infant brain: Review of magnetic resonance imaging studies and a population description analysis. *Human Brain Mapping*, 2019; 40(6): 1987–2000.

II Silver, E., Pulli, E. P., Kataja, E.-L., Kumpulainen, V., Copeland, A., Saukko, E., Saunavaara, J., Merisaari, H., Lähdesmäki, T., Parkkola, R., Karlsson, L., Karlsson, H., & Tuulari, J. J. (2022). Prenatal and early-life environmental factors, family demographics and cortical brain anatomy in 5-year-olds: an MRI study from FinnBrain Birth Cohort. *Brain Imaging and Behavior*, 2022; 1: 1–13.

III Pulli, E. P., Nolvi, S., Eskola, E., Nordenswan, E., Holmberg, E., Copeland, A., Kumpulainen, V., Silver, E., Merisaari, H., Saunavaara, J., Parkkola, R., Lähdesmäki, T., Saukko, E., Kataja, E.-L., Korja, R., Karlsson, L., Karlsson, H., & Tuulari, J. J. (2023). Structural brain correlates of non-verbal cognitive ability in 5-year-old children: Findings from the FinnBrain Birth Cohort study. *Human Brain Mapping,* 2023; https://doi.org/10.1002/HBM.26463 [online ahead of print]

IV Lidauer, K., Pulli, E. P., Copeland, A., Silver, E., Kumpulainen, V., Hashempour, N., Merisaari, H., Saunavaara, J., Parkkola, R., Lähdesmäki, T., Saukko, E., Nolvi, S., Kataja, E. L., Karlsson, L., Karlsson, H., & Tuulari, J. J. (2022). Subcortical and hippocampal brain segmentation in 5-year-old children: Validation of FSL-FIRST and FreeSurfer against manual segmentation. *European Journal of Neuroscience*, 2022; 56(5): 4619–4641.

1 Introduction

Our development as individuals is affected by the complex interplay of our own biology (e.g., genes) and the environment (e.g., home environment and schooling). The fetal origins hypothesis or the developmental origins of health and disease hypothesis (also known as the Barker hypothesis; Barker, 1995) suggests that the environmental factors that predispose us to different health outcomes in later life already take effect in the fetal period. A growing body of evidence shows that different exposures indeed predispose the individual not only to birth defects (in certain situations such as excessive alcohol exposure) but also to more subtle risks of adverse outcomes in later life (including normal variation in healthy individuals, such as mental distress and nutritional status).

Knowledge of the adverse effects of different prenatal exposures can guide professionals in clinical decision-making. For example, mental health conditions such as depression (approximately 7% prevalence in the Finnish adult population, more common in females; Markkula et al., 2015) and anxiety disorders (approximately 4% prevalence in the Finnish population, more common in females; Pirkola et al., 2005) are common, including among pregnant females. In clinical practice, different medications can be used in the treatment of these conditions, and some of the most common medications include selective serotonin reuptake inhibitors (SSRIs). When mental health issues that cannot be treated without medication are present during pregnancy, the fetus is exposed to either the medication or the untreated medical condition, and the potential harmful effects of both should be known so that informed decisions can be made regarding the treatment.

Neuroimaging has emerged as a valuable tool to gain knowledge of the neurobiological basis of different risks associated with prenatal exposures. Magnetic resonance imaging (MRI) can be used to examine brain structure and function noninvasively in vivo. Unlike in X-ray imaging or imaging methods utilizing radioactive substances, such as positron emission tomography, MRI does not use ionizing radiation, making it an ideal tool for pediatric imaging, including imaging done for research purposes.

In the series of studies included in this thesis, we reviewed the current literature on the effects of different prenatal exposures on neurodevelopment, and we used that information to identify the relevant covariates for structural brain imaging in our own sample of typically developing 5-year-olds from the FinnBrain Birth Cohort study. Furthermore, the high quality of data was ensured by utilizing manual editing and quality control protocols established in our previous work (Pulli et al., 2022). Finally, this knowledge was applied to explore the cortical structural brain correlates of cognitive ability (focusing on non-verbal ability).

2 Review of the Literature

2.1 Early-life Brain Development

Brain development starts during the fetal period and continues throughout life. The brain develops most rapidly during the first years of life: total brain volume increases by 101% during the first year and by another 15% during the second year, reaching over 80% of adult brain volume by the age of 2 years (Knickmeyer et al., 2008).

The developmental trajectories of the brain vary based on metric and region. Total gray matter (GM) volume shows a strong increase starting from the fetal period, and it reaches its peak at approximately 6 years of age (Bethlehem et al., 2022; Courchesne et al., 2000). In terms of regional variation, frontal and temporal regions show peak volumes in late childhood, while parietal and occipital volumes are already decreasing by the age of 5 years (Aubert-Broche et al., 2013; Bethlehem et al., 2022). In addition to volume, cortical GM development can be assessed by measuring surface-based measurements, including surface area (SA) or cortical thickness (CT).

Cortical volume is a combination of the two surface-based measurements, CT and SA, which reflect different biological features of the cortex. Specifically, CT is thought to reflect underlying biological processes, including myelination (Natu et al., 2019), synaptic overproduction, and eventual pruning (Tierney & Nelson, 2009; Vidal-Pineiro et al., 2020), while SA reflects the number and spacing of cellular columns (Hill et al., 2010; Rakic, 1988). This difference is also reflected genetically, as both CT and SA are highly heritable (0.81 and 0.89, respectively), but almost unrelated to each other (correlation 0.08; Panizzon et al., 2009) in adults, although the heritability of different brain metrics varies at different stages of development (Lenroot et al., 2009), and significantly higher correlations have been observed in the neonatal period (correlation 0.65; Jha et al., 2018) and in childhood/adolescence (correlation 0.63; J. E. Schmitt, Neale, et al., 2019).

Cortical SA shows global increase in early childhood, and it reaches its peak at approximately 10 to 12 years of age (Bethlehem et al., 2022; T. T. Brown et al., 2012; Raznahan et al., 2011; Wierenga et al., 2014). There has been controversy regarding the developmental trajectory of CT, with estimates of the age of peak CT varying from early to late childhood (Walhovd et al., 2016). However, a recent study

combining data from over 100 studies and 100,000 scans has concluded that CT peaks as early as the second year of life (Bethlehem et al., 2022). Growth charts of the brain (from Bethlehem et al., 2022) are presented in Figure 1.

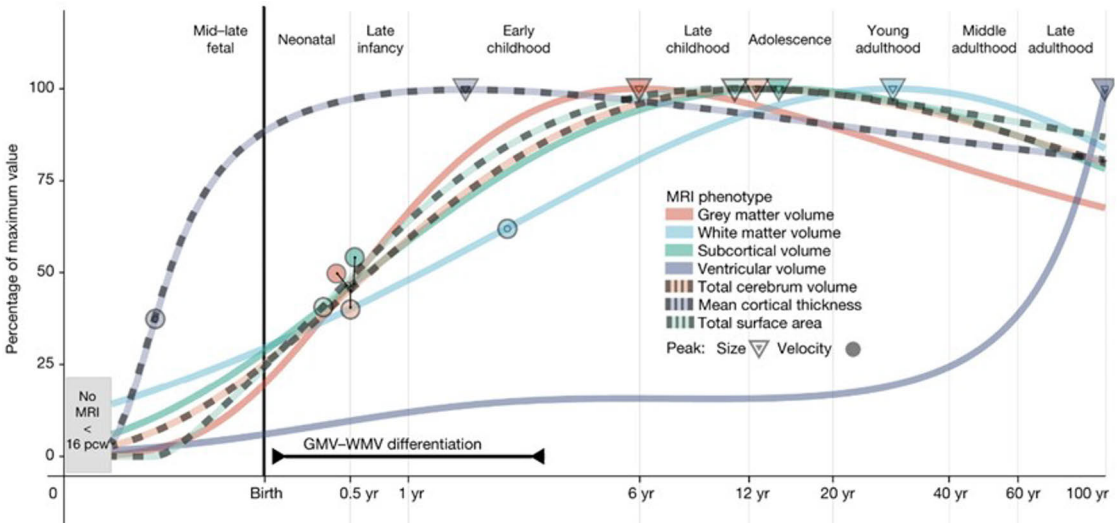

Figure 1. Trajectories of growth for different brain metrics over the human lifespan. Figure 1 is a modified version of a figure (only part of the figure is used) from an article by Bethlehem et al. (2022), which is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

2.2 Pediatric Structural Neuroimaging

2.2.1 Magnetic Resonance Imaging

MRI can be used to examine brain structure and function noninvasively in vivo. Unlike in X-ray imaging or other methods utilizing radioactive substances, such as positron emission tomography, MRI does not use ionizing radiation, making it an ideal tool for pediatric imaging, including imaging done for research purposes. Children and their brains are growing and changing throughout their childhood, presenting us not only with different opportunities and interesting research questions at different stages of development, but also with unique methodological challenges, especially in the younger age groups. This review will focus on the challenges in neuroimaging of young children (approximately 5 years of age), as per the age group studied in our original publications (Studies II, III, and IV). For a review and summary of neuroimaging studies across a wider age range, see Copeland et al. (2021).

There are multiple methodological challenges in pediatric neuroimaging studies that may affect the quality of data and comparisons between studies. Questions related

to safety and other ethical concerns have been comprehensively answered in an article by Korom et al. (2022). One of the biggest challenges is for the child to lie still while awake, as head motion can cause artifacts in brain images (Barkovich et al., 2019; Blumenthal et al., 2002; Poldrack et al., 2002; Theys et al., 2014). One study by Blumenthal et al. (2002) found that mild, moderate, and severe motion artifacts were associated with 4, 7, and 27% loss of total GM volume in segmentation, respectively. Furthermore, subtle motion can cause bias even when a visible artifact is absent (Alexander-Bloch et al., 2016). Another core challenge is the variation in preprocessing and segmentation techniques (Hashempour et al., 2019; Phan et al., 2018; Schoemaker et al., 2016), due to a lack of a gold standard processing pipeline for pediatric brain images. Furthermore, several segmentation protocols have been developed for adult brains, but they cannot be directly applied in segmenting child brain images because children's MR images have different contrast and comparatively lower resolution than adults' images (Gousias et al., 2012; Moore et al., 2014; Morey et al., 2009). Therefore, some studies rightfully emphasize the importance of a validated quality control protocol (Schoemaker et al., 2016).

2.2.2 Surface-based Analyses

FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) is an open source software suite for processing brain MRI images that is commonly used in pediatric neuroimaging (Al Harrach et al., 2019; Barnes-Davis et al., 2020; J. M. Black et al., 2012; Boutzoukas et al., 2020; Clark et al., 2014; El Marroun, Tiemeier, Franken, et al., 2016; Garnett et al., 2018; Ghosh et al., 2010; Y. J. Lee et al., 2017; Nwosu et al., 2018; Phan et al., 2018; Ranger et al., 2013; Roos et al., 2014; Wedderburn et al., 2020), and it has been validated for use in 4–11-year-old children (Ghosh et al., 2010). FreeSurfer utilizes surface-based parcellation of cortical regions based on cortical folding patterns and a priori knowledge of anatomical structures (further technical information in Dale et al., 1999; Fischl et al., 1999). The FreeSurfer instructions recommend visually checking and, when necessary, manually editing the data. The manual edits can fix errors in the automated segmentation such as skull-stripping, white matter (WM), or pial errors (errors in the outer border of cortical GM). The FreeSurfer instructions suggest that this process takes approximately 30 minutes. Meanwhile, Ross et al. (2021) report 9.5 hour editing times per image. Similarly, in our experience, the 30-minute timeframe seems far too short for careful quality assessment and editing, and time consumption does pose one of the most important practical challenges in manual editing of neuroimaging data.

Another key challenge is the fact that the edits may lead to inter- and intra-rater bias. Nevertheless, effects of motion artifacts must be considered in the segmentation process (Blumenthal et al., 2002), as some systematic errors in pial border,

subcortical structures, and the cerebellum have been observed in structural brain images of 5-year-olds without manual edits (Phan et al., 2018). There is some controversy regarding the benefits of manual editing (Beelen et al., 2020; Guenette et al., 2018; McCarthy et al., 2015; M. C. Ross et al., 2021), as errors that can be manually fixed are often small and therefore only have minor effects on CT, SA, or volume values. Consequently, they tend not to affect the significant findings in group comparisons (McCarthy et al., 2015; M. C. Ross et al., 2021) or brain–behavior relationships (Waters et al., 2019).

In summary, the benefits of manual editing seem minor, and it is unclear whether it is worth the commitment of time and resources. Although the effects on brain metrics have been relatively small in previous studies, it is noteworthy that systematic manual edits of the segmented images can help with quality control, as they simultaneously maximize the chance to find segmentation errors that can be subsequently fixed. We have explored this issue in our previous study (Pulli et al., 2022), and we decided to use manual editing in our 5-year-old sample to optimize segmentation of both cortical and subcortical structures.

2.2.3 Volumetric Analyses

Surface-based approaches are excellent for the cerebral cortex, but not applicable for subcortical segmentation, where volume is the main structural measurement. In addition to subcortical structures such as the basal ganglia and the amygdala, hippocampal segmentation is also often approached volumetrically. Notably, diffusion tensor imaging (DTI) can be used to measure microstructural qualities (e.g., Cai et al., 2021), but methodological issues regarding DTI measurements are outside the scope of this thesis.

Manual segmentation is currently considered the gold standard in volumetric segmentation (Makowski et al., 2018; Schoemaker et al., 2016). The most important limitations are that it is highly time consuming and requires expertise for adequate results. Notably, in our experience, both the time and the expertise required are higher than in manual editing in surface-based analyses. Another major downside is that estimating the shapes and sizes of the structures is, by nature, dependent on the rater, which may cause reproducibility issues.

Several software tools have been developed for automated segmentation of the brain. In accordance with the methods used in Study IV, we will focus on FSL-FIRST and FreeSurfer. FSL-FIRST from the FMRIB (Functional MRI of the Brain) Software Library (Patenaude et al., 2011) is a segmentation tool that uses the template based on manually segmented images to construct the shape of the automated segmentation models. It utilizes the active appearance model combined with a Bayesian framework, which allows probabilistic relationships between voxel

intensity and the shapes of different structures (Patenaude et al., 2011). FreeSurfer uses a five-stage volume-based stream for segmenting subcortical structures. Final segmentation is based on a subject-independent probabilistic atlas and subject-specific values. Both FSL-FIRST and FreeSurfer use a training dataset for the basis of segmentation and utilize probabilistic computing to determine the final shape and volume of each structure. Both software tools have been widely used in pediatric neuroimaging for pediatric volumetric subcortical brain segmentation (Barch et al., 2019; Grohs et al., 2021; Sandman et al., 2014; Z. Wang et al., 2022), despite having been originally developed for adult brain imaging. Most of the studies in the field do not use manual segmentation as a control for segmentation accuracy.

Both FreeSurfer and FSL-FIRST typically overestimate subcortical volumes (Cherbuin et al., 2009; Doring et al., 2011), which has been documented in pediatric populations on the hippocampus and amygdala (E. R. Mulder et al., 2014; Schoemaker et al., 2016). The study by Schoemaker et al. (2016) also found that the consistency between manual segmentation and FreeSurfer was better than between manual segmentation and FSL-FIRST in children aged 6–11 years. Although the reliability of these segmentation methods has been assessed in multiple studies in the medial temporal lobe structures such as the hippocampus, there has been little research including the striatal structures.

2.3 The Effects of Prenatal Environment

There are two major categories that constitute the prenatal or in utero environment: chemical exposures and maternal health characteristics. The first category includes, for example, exposure to maternal alcohol use, tobacco smoking, or illicit drug use (illicit drugs are here defined as all drugs of abuse except alcohol, nicotine products, and prescription drugs used for medical purposes, and this definition will be used throughout the text). Maternal health characteristics include, for example, somatic and psychiatric disorders, age, and obesity. Notably, somatic disorders (as well as the medications that can be used to treat them) form extraordinarily large and heterogeneous categories with a lot of variation in their relevance for brain development. Therefore, they are outside the scope of this thesis. Further, this literature review is not intended to cover all prior literature in any of the individual exposures, but rather to highlight the multiplicity of ways they can affect offspring development and hence to provide a rationale for neuroimaging research in these topics.

Overall, the presented studies are correlational, and this brings a general limitation that causal chains remain uncertain in most existing studies. Further, postnatal life might modify the associations between prenatal factors and later child outcomes. Additionally, some prenatal exposures can continue postnatally and affect child development via different mechanisms, for example, suboptimal parent–child

interaction in depression (Ferber et al., 2008; Paulson et al., 2006). These two limitations apply to the literature and are, in general, hard to overcome in human studies. This review focuses on early life development (infant and child studies), where the postnatal environment has had a relatively smaller effect.

2.3.1 Prenatal Chemical Exposures

In Finland, the prevalence of both alcohol and tobacco exposures during pregnancy (any amount) is estimated to be approximately 14% (Frederiksen & Nissinen, 2020). In the Finnish 15–64-year-old general population in 2018, the annual prevalence of illicit drug use was as follows: marijuana 8.2%, amphetamines 1.7%, cocaine 0.9%, and opioids (in 2017) 0.8% (United Nations Office on Drugs and Crime, 2022). Based on United States (US) survey data, substance use drops significantly during pregnancy (alcohol from 51.5% to 9.8%, tobacco products from 16.6% to 10.8%, and illicit drugs from 18.9% to 7.7%) on a population level, but does not stop completely (Substance Abuse and Mental Health Services Administration, 2023). Notably, there is a lot of variation between estimates based on surveys and toxicological samples (Tavella et al., 2020, estimate 7.4 times higher prevalence of drug use based on toxicological samples compared to self-reports).

2.3.1.1 Alcohol Exposure

Alcohol was identified as a teratogen in 1973 (K. L. Jones et al., 1973; K. L. Jones & Smith, 1973). In extreme cases, individuals may be born with fetal alcohol syndrome with neurobehavioral effects, such as cognitive impairment, and physical effects, such as distinct facial anomalies including short palpebral fissures, thin vermilion border, and smooth philtrum (Mattson et al., 2019). Individuals without the characteristic facial anomalies often go undiagnosed despite showing neurobehavioral deficits of fetal alcohol spectrum disorders (Chasnoff et al., 2015). Some of the possible neurobehavioral effects include deficits in cognitive ability, executive functioning, learning, visual–spatial reasoning, memory, mood regulation, behavioral regulation, attention, impulse control, communication, daily living skills, and motor skills.

Children with prenatal alcohol exposure are overrepresented, for example, among children in care and special education (Popova et al., 2019), and they often require social and vocational support (Popova et al., 2023). As such, prenatal alcohol exposure constitutes an important public health problem. Considering that alcohol use is common among the general population (Substance Abuse and Mental Health Services Administration, 2023) and a large number of pregnancies are unplanned (Finer & Zolna, 2016), prenatal alcohol exposure can happen accidentally and is

difficult to prevent completely, but with public health action, the impact could be made smaller. There is no safe level of alcohol consumption during pregnancy (Lees et al., 2020) and, therefore, important preventive measures include public health campaigns (B. Jacobsen et al., 2022), advisement from healthcare professionals (Lees et al., 2020), large-scale early pregnancy screening (Popova et al., 2023), and screening newborns with known alcohol exposure for signs such as growth restriction (Edwards et al., 2023; Popova et al., 2023).

Although alcohol is a well-known teratogen, partly due to the facial anomalies in severe cases (Mattson et al., 2019), the neurodevelopmental effects still often go unnoticed by healthcare professionals (Chasnoff et al., 2015). This exemplifies why developmental research on prenatal exposures is important. The goal is to make the adverse effects widely known, so that protective measures can be targeted towards those at risk.

2.3.1.2 Tobacco Exposure

Tobacco smoking is a major risk factor for low birth weight (LBW; Janisse et al., 2014; Kramer, 1987). More specifically, maternal smoking has been associated with reduced growth in head circumference, abdominal circumference, and femur length (Jaddoe et al., 2007). The mechanisms for growth restriction include decreased oxygen and nutrients from the mother to the fetus (Lambers & Clark, 1996). Prenatal tobacco exposure also affects neurotransmission (Slotkin, 1998) and metabolism (Cajachagua-Torres et al., 2022). Furthermore, prenatal tobacco exposure is associated with increased risks of preterm birth (Philips et al., 2020) and sudden infant death syndrome (Anderson et al., 2005; K. Zhang & Wang, 2013). One of the adverse outcomes in later childhood is an increased risk of obesity (Philips et al., 2020). Philips et al. (2020) found that this risk was present even when the mother stopped smoking during the first trimester. Furthermore, among non-smoking mothers, paternal tobacco smoking was associated with childhood overweight. Passive smoking exposure is one possible explanation, but this finding implies that some of the risks may be transferred via pathways other than direct exposure to tobacco smoke, such as genetic, epigenetic, or social effects. Moreover, maternal (and paternal) tobacco smoking during pregnancy is associated with an increased risk of hypertension (De Jonge et al., 2013) and type 2 diabetes (Jaddoe et al., 2014) in adulthood. In both studies, correction for current body mass index (BMI) significantly attenuated the associations. Finally, a study with over 50,000 participants ages 0–7 years found prenatal tobacco exposure (≥20 cigarettes per day) to be associated with LBW and increased risk of childhood obesity, but not conduct problems or cognitive development (Gilman et al., 2008). However, there are studies linking prenatal tobacco exposure to cognitive and behavioral developmental outcomes.

Behaviorally, prenatal tobacco exposure has been linked to increased internalizing and externalizing symptoms in 2-year-olds (Carter et al., 2008), activity, inattention, and behavioral problems at 6 years of age (Cornelius et al., 2007), which persist into later childhood (Cornelius et al., 2011). These studies controlled for confounders such as sociodemographic factors and other substance use (except Carter et al., 2008, where there was not enough drug use to include in analyses). Notably, tobacco use was measured via self-report, presenting some questions regarding reliability. One study found a connection between prenatal tobacco exposure and increased conduct problems in 5–7-year-olds, half of which was due to genetics (Maughan et al., 2004). Gatzke-Kopp et al. (Gatzke-Kopp & Beauchaine, 2007) suggest a direct role of cigarette smoke in the risk of childhood externalizing symptoms, based on mothers who did not smoke but who had exposure to environmental tobacco smoke. Notably, one of the common sources of passive smoking exposure is the partner living in the same household, which in many (although not nearly all) cases is the biological father, meaning that the effect of (epi)genetic and social factors cannot be excluded based on these findings. Overall, there is strong evidence that prenatal tobacco exposure is linked to both restricted fetal growth and higher childhood obesity risk (Gilman et al., 2008), as well as adverse cognitive and behavioral outcomes in children and adolescents (Alhowail, 2021; Sikic et al., 2022) and the mechanisms are likely related to direct chemical exposure as well as genetic and sociodemographic risk factors.

2.3.1.3 Illicit Drug Exposures

“Illicit drugs” is a term that encompasses an extraordinarily large group of different substances, and the health effects of each cannot be covered in this literature review. Instead, we will focus on the most common and clinically relevant ones: marijuana, amphetamines, cocaine, and opioids.

Marijuana was the most commonly used illicit drug in the US sample in 2021: 7.2% of pregnant females used marijuana compared to 2.3% who used any other illicit drugs (Substance Abuse and Mental Health Services Administration, 2023). One important methodological challenge is that marijuana use is often combined with smoking tobacco as well as multiple socioeconomic and social factors (El Marroun et al., 2008), which complicates differentiating the specific effects of marijuana. The long-term effects of prenatal marijuana exposure are poorly understood (El Marroun et al., 2018). In pediatric studies, prenatal marijuana exposure has been associated with, for example, reduction in head circumference in neonates (Calvigioni et al., 2014), delayed mental development at 9 months of age (use during the third trimester, specifically; no longer present at 19 months, see Richardson et al., 1995), increased aggressive behaviors in 18-month-old girls (but

not in boys; see El Marroun et al., 2011), increased externalizing behavior symptoms at ages 6 and 10 years (Calvigioni et al., 2014), and worse executive functions at 9–12 years of age (Fried et al., 1998). For a review, see Grant et al. (2018). Moreover, maternal marijuana use during pregnancy has also been associated with increased psychotic-like experiences by the age of 10 years (Bolhuis et al., 2018), although evidence for increased risk of schizophrenia is weak (Alpár et al., 2016). In that study (Bolhuis et al., 2018), similar effects were seen for marijuana use exclusively before pregnancy and paternal marijuana use during pregnancy, suggesting mechanisms other than solely direct intrauterine exposure, such as genetic vulnerabilities. Finally, there is some evidence that the effects of prenatal marijuana exposure are long-lasting, as prenatally exposed young adults show different neural activation during a visuospatial working memory task, although task performance did not significantly differ from the unexposed group (A. M. Smith et al., 2006). In summary, the effects of prenatal marijuana exposure are mixed, and longitudinal follow-up studies in large cohorts are needed to better understand its real-life consequences.

Amphetamine-type stimulants (e.g., methamphetamine) are among the most commonly used groups of illicit drugs worldwide (United Nations Office on Drugs and Crime, 2022). Similar to marijuana use, concurrent cigarette smoking and polydrug use are very common with methamphetamine. In one of the few studies exploring the combined risk, exposure to methamphetamine together with tobacco was associated with delayed neurological development during the first months of life (L. Chang et al., 2016). Methamphetamine exposure together with alcohol has been associated with lower general cognitive ability in 5–15-year-olds (Sowell et al., 2010), although another, much larger study did not find associations between methamphetamine exposure and cognitive development at 3 years of age (L. M. Smith et al., 2015). Prenatal methamphetamine exposure alone has been associated with lower birth weight and higher neonatal mortality (Y. Zhang et al., 2021), and decrements in attention, visual motor integration, verbal memory, and long-term spatial memory in a small sample (n = 28) of 3–16-year-olds (L. Chang et al., 2004). Connections to behavioral problems (L. M. Smith & Santos, 2016) and lower cognitive ability have been observed at different stages throughout childhood (Kwiatkowski et al., 2014; Y. Zhang et al., 2021), but high-quality follow-up studies are rare and implications for adult life are still poorly understood.

Prenatal cocaine exposure has been associated with lower birth weight (although some studies suggest this is attributable to polydrug exposure rather than cocaine, specifically; Richardson & Day, 1994), but there is no convincing evidence of increased risk of malformations at birth (L. M. Smith & Santos, 2016). Neonates show higher excitability (Tronick et al., 1996), increased irritability (Eyler & Behnke, 1999), and differences in motor development and activity (Eyler & Behnke, 1999; Lester et al., 2002), with the effect on motor development continuing into later

infancy (A. Salzwedel et al., 2020). In later childhood, prenatal cocaine exposure is related to poorer auditory attention and narrative memory skills (Beeghly et al., 2014), poorer language skills (Lambert & Bauer, 2012), and increased attention deficit hyperactivity disorder (ADHD) symptoms (Ackerman et al., 2008; Linares et al., 2006; L. M. Smith & Santos, 2016), while the evidence for alterations in cognitive development is conflicting (Lambert & Bauer, 2012; L. M. Smith & Santos, 2016). In adolescence, prenatal cocaine exposure has been associated with increased externalizing behaviors, poorer mood (in a temperament survey, see Richardson et al., 2015), and increased risk of substance abuse (Min et al., 2014; L. M. Smith & Santos, 2016). The literature on the long-term effects of prenatal cocaine exposure is conflicting, and the effects depend on the dose and timing of the exposure (E. J. Ross et al., 2015).

The connection between opioid use and impaired fetal growth (both LBW and smaller head circumference) is well established (Mactier & Hamilton, 2020), including for mothers in methadone maintenance (Mactier et al., 2014). Neonatal opioid withdrawal syndrome is common after opioid-maintained pregnancies, and it presents with symptoms including irritability, tremors, poor feeding, vomiting, and diarrhea, as well as fast heart rate and breathing (Mactier & Hamilton, 2020). Methadone is associated with longer lasting treatment of the offspring withdrawal symptoms than buprenorphine (H. E. Jones et al., 2010). Furthermore, visual problems such as nystagmus are more common in prenatally opioid-exposed children (Mactier & Hamilton, 2020; Rosen & Johnson, 1982). Prenatal opioid exposure is consistently linked to poorer outcomes in cognitive, psychomotor, and behavioral development (Mactier & Hamilton, 2020; Monnelly et al., 2019; Yeoh et al., 2019), and offspring are more likely to be impaired in school readiness assessment at 4.5 years of age (S. J. Lee et al., 2020).

In summary, prenatal exposure to illicit drugs has been associated with a wide variety of adverse developmental outcomes, but there still seems to be a lack of large follow-up studies. There are a few important factors to consider that complicate research in this field. First, illicit drugs are quite rare compared to alcohol and tobacco, which are legal in most places around the world. Consequently, the potential pool of participants for these studies is naturally smaller. Second, high-risk behaviors (such as illicit drug use) tend to cluster and are more common among people of lower socioeconomic status (SES), including educational level and occupation. Limited resources may make it difficult for participants to commit to a long follow-up (practical issues such as lack of transportation may affect the ability to participate; Eskenazi et al., 2005). Third, the prevalence of multidrug use makes it more difficult to separate the effects of individual substances. In all studies on the effects of prenatal drug exposure, it is important to consider this option and to control for other drug exposures in analyses (Konijnenberg, 2015). With a proper statistical approach,

it is possible to identify the effects of individual substances on behavioral and brain metrics even in samples that are heterogeneous in their drug use profiles (A. Salzwedel et al., 2020). Finally, the effects of prenatal drug exposures depend on the dose and timing of the exposure. This information is practically impossible to gather from later self-reports, especially considering that self-reports of drug use are known to be very unreliable (Tavella et al., 2020). Gathering objective data (e.g., urine toxicology samples) has to be included in the study design for a more accurate measurement. Still, this is subject to the same limitations as drug testing in clinical contexts. For example, if the participant knows when the test is coming, they can use drugs normally and only abstain for the necessary period before the test to give a negative sample, while surprise tests or too frequent testing might negatively affect the participant retention rate in the study.

2.3.1.4 Environmental Toxins

Prenatal exposure to different environmental toxins can also affect the development of the individual. For example, exposure to air pollution (e.g., polycyclic aromatic hydrocarbons and nitrogen dioxide) is associated with LBW (Pedersen et al., 2013; Stieb et al., 2012), preterm birth (Sapkota et al., 2012), and decrements in general cognitive ability (Suades-González et al., 2015). Pesticides are commonly used in agriculture, and the most common type of exposure is through diet (Sokoloff et al., 2016). Some studies on the effects of pesticide exposure have associated it with lower cognitive ability in 1-year-olds (Engel et al., 2011) and 7-year-olds (Bouchard et al., 2011), but not with ADHD or autism spectrum disorder symptoms during childhood (van den Dries et al., 2019). Finally, exposure to lead, a potent neurotoxin, is still a problem in many places around the world and can lead to preterm birth (Khanam et al., 2021) and attenuated mental development in infancy (Gardella, 2001) and toddlerhood (Jian'an Liu et al., 2014). Importantly, the changes related to low-dose lead exposure seem to be reversible if the exposure is discontinued after birth (Gardella, 2001). One important limitation in all these environmental exposure studies is the requirement for toxicological samples, as people (at least in general) have no idea how much exposure they have, for example, to pesticides. Air pollution is an exception, as it can also be estimated based on the home address (e.g., in Lubczyńska et al., 2021), assuming such data is available in the region. Most of the other exposures in this review can be assessed using self-report (although they may not be as reliable as toxicological measurements; Tavella et al., 2020), making it easier to collect data in cohort settings and possible to collect data retrospectively or from registries.

2.3.2 Maternal Health Characteristics

2.3.2.1 Depressive Symptoms and Medication

Depression is a common and strongly familial disorder (Weissman et al., 2016). There is strong evidence that maternal depression during pregnancy is associated with increased risk of socioemotional problems in infant, child, and adolescent populations (OR = 1.79, see meta-analysis by Madigan et al., 2018). Maternal prenatal depression does not seem to affect infant attachment (Śliwerski et al., 2020; Tharner et al., 2011). Differentiating the effects of depression from depression medications such as SSRIs is an important question as it affects the treatment choices during pregnancy. In one study (El Marroun et al., 2012), maternal depressive symptoms were associated with decreased fetal body and head growth (measured using ultrasonography), but SSRI use was only associated with decreased head growth. This was in line with previous research linking untreated depression to restricted fetal growth (Davalos et al., 2012). Another study (El Marroun et al., 2017) explored the effects of maternal depressive symptoms (with and without SSRIs) on child neurobehavior. Exposure to untreated depressive symptoms was associated with shifting problems and emotional control problems at 4 years of age, while SSRI use was not (both compared to unexposed controls). Neither group differed from controls in non-verbal ability at 5 years or neuropsychological function at 7 years of age. In a Finnish register-based study, prenatal SSRI exposure was associated with increased cumulative risk of depression by 15 years of age, compared to individuals with exposure to psychiatric disorder (a mood disorder in almost all cases) but no SSRIs or antipsychotics (Malm et al., 2016). An increased risk of anxiety, autism spectrum disorders, or ADHD was not observed (Malm et al., 2016). El Marroun et al. (n = 5,976; 2014) found a connection between prenatal SSRI exposure (but not depressive symptom exposure without SSRIs) and an increase in autistic traits at 6 years of age, compared to controls with no exposure to SSRIs or significant depressive symptoms. In the same study, those with exposure to depressive symptoms but not SSRIs showed an increased risk of affective problems compared to unexposed controls, while those with SSRI exposure did not. In this case, the mothers using SSRIs exhibited lower levels of depressive symptoms than those not on medication. In this literature, it is important to remember that medication does not necessarily lead to remission of symptoms. Hence, in some cases, individuals may be exposed to both psychotropic medication and high levels of symptoms. Some studies also report no effects of exposure to treated or untreated depression (Davalos et al., 2012; Hermansen et al., 2016). In summary, maternal prenatal depression is associated with adverse outcomes. Based on the limited evidence that exists regarding SSRI medication, at least there does not seem to be convincing evidence that it is more harmful than untreated depression.

2.3.2.2 Distress and Anxiety

Early life stress has multiple possible definitions, but in this literature review, we will mostly focus on anxiety-related measurements. Anxiety is a normal part of life. Anxiety disorders include abnormally high levels of anxiety either generally or in specific situations. Anxiety disorders are relatively common during pregnancy, with estimates ranging from 4.4% to 39% (Goodman et al., 2014). In previous studies, anxiety symptoms have been related to multiple adverse outcomes (Van den Bergh et al., 2005), including increased risk of preterm birth (E. J. . Mulder et al., 2002), abnormalities in neuromotor development at 3 months of age (Van Batenburg-Eddes et al., 2009), higher infant negative behavioral reactivity at 4 months of age (Davis et al., 2004), and lower task orientation and motor coordination at 1 year of age, as well as attenuated mental development at 2 years of age (Brouwers et al., 2001) and more emotional problems at 4 years of age (O'Connor et al., 2002). There is strong evidence that maternal anxiety during pregnancy is associated with an increased risk of socioemotional problems in infant, child, and adolescent populations (OR 1.50, see meta-analysis by Madigan et al., 2018). One study compared the effects of objective (questions related to the participant's objective exposure to a natural disaster: the 1998 ice storm in Québec, Canada) and subjective stress (questions related to distress after trauma; in this case, the natural disaster). Objective stress but not subjective stress was significantly negatively associated with productive and receptive language at 2 years of age (Laplante et al., 2004). This highlights the challenge with the variation of different types and measurements of stress.

Benzodiazepines (and closely related medications) can be used to treat anxiety symptoms. They are assumed to not cause congenital malformations, and one study did not find them to be associated with oppositional defiant disorder, aggressive behavior, or anxiety at 6 years of age, independent of prenatal anxiety symptoms (Radojčić et al., 2017). There is limited evidence that prenatal exposure to benzodiazepines may be associated with increased risk of ADHD and autism spectrum disorders (Chen et al., 2022). The study was based on a Taiwanese database, including data from more than one million children (76,411 of them exposed to benzodiazepines). Benzodiazepine use was associated with increased risk (regardless of timing and whether the exposure was to short- or long-acting benzodiazepines), but effect sizes were small (hazard ratio between 1.1 and 1.3) and, more importantly, the risk did not significantly differ from unexposed siblings, suggesting parental genetic and environmental factors explain the increased risk (Andrade, 2023; Chen et al., 2022). Importantly, benzodiazepine use in late pregnancy can cause withdrawal symptoms and abnormal limpness (in the body, limbs, and head) in the newborn (McElhatton, 1994), and the necessity of benzodiazepine use during pregnancy should be considered carefully.

2.3.2.3 Obesity, Nutrition, and Inflammation

Pre-pregnancy obesity has been linked to being born large for gestational age, and pre-pregnancy underweight to being small for gestational age (Z. Yu et al., 2013). Moreover, both high pre-pregnancy BMI and excessive gestational weight gain have been associated with an increased risk of childhood obesity (Godfrey et al., 2017; Z. Yu et al., 2013), and the increased risk seems to continue into adolescence and adulthood (Godfrey et al., 2017). Obesity itself is a major risk factor for multiple adverse health outcomes to the individual, which makes it hard to assess the direct effects of maternal obesity on outcomes such as hypertension or adult-onset diabetes. Furthermore, maternal obesity has been linked to an increased risk of multiple psychiatric and neurodevelopmental disorders (including, for example, autism spectrum disorders; Y.-M. Li et al., 2016), as well as a decrease in cognitive ability (Edlow, 2017). Some of the potential mechanisms include dysregulation in neural, glucose, insulin, insulin-like growth factor 1, and leptin signaling, as well as low-grade neuroinflammation (Edlow, 2017; Hellström et al., 2016).

In contrast to overweight individuals, maternal underweight and undernutrition increase the risk of the offspring being born small for gestational age (R. E. Black et al., 2013). Some studies have found associations between LBW and poorer psychomotor development (Tofail et al., 2012). Undernutrition can also accentuate the effects of other maternal diseases such as anemia (Patel et al., 2018). Low maternal vitamin D levels have also been linked to poorer language development at 6 months of age (Hanieh et al., 2014). However, the mechanisms and effects of specific nutritional deficiencies are outside the scope of this literature review.

The role of (subclinical) inflammation in the risk of many disorders is of great interest to many researchers. Prenatal exposure to a maternal diet with more inflammatory potential has been associated with a slightly increased risk of depression, anxiety, aggressive behavior, and ADHD symptoms in school-age children (in a study combining data from multiple large cohorts; see Polanska et al., 2021). Polanska et al. used the Dietary Inflammatory Index, in which multiple food parameters are given inflammatory potentials based on their effects on selected cytokines (Shivappa et al., 2014). Proinflammatory substances include carbohydrates, cholesterol, and saturated fat. The potential health effects of a high-fiber diet have been explored in a mouse model, showing that good nutrition could protect the offspring from the adverse effects of maternal obesity (X. Liu et al., 2021). In addition to obesity and nutritional sources, proinflammatory states can be caused by prenatal stress (Marques et al., 2015) and maternal infections, such as the human immunodeficiency virus infection, which can affect infant neurodevelopmental outcomes even when the infant is uninfected (Tran et al., 2016; Wu et al., 2018). Indeed, there is evidence that maternal inflammation in general increases the risk of adverse outcomes such as increased risk of autism spectrum

disorders and schizophrenia (Estes & McAllister, 2016). This makes proinflammatory markers such as interleukin-6 (IL-6) interesting targets for study (A. M. Graham et al., 2018; Ishihara & Hirano, 2002). The effects of IL-6 on the developing brain are supported by animal research, in which an IL-6 injection causes behavioral deficits in wild-type offspring but not in IL-6 knock-out offspring (S. E. P. Smith et al., 2007).

2.3.2.4 Demographic Factors

In addition to health conditions, certain demographic factors can affect offspring development. Here, we only focus on maternal age at birth and SES.

Advanced age at childbirth is associated with an increased risk of impaired fetal growth, congenital anomalies, and pregnancy complications (Cooke & Davidge, 2019). Some of the hypothesized mechanisms include deficiency in cardiovascular adaptations to pregnancy and placental dysfunction (Cooke & Davidge, 2019). Alternatively, it has been proposed that the risks for offspring might be mostly induced by deoxyribonucleic acid (DNA) reprogramming (Tarín et al., 2017). Notably, high paternal age is also associated with multiple negative outcomes, implicating mechanisms other than biological changes associated with maternal aging, whether social or (epi)genetic (Gale-Grant et al., 2020). Beyond the perinatal period, higher maternal age has been associated with an increased risk of autism spectrum disorders (after correction for confounders; Sandin et al., 2012) and an increased long-term risk of cardiovascular disease (Cooke & Davidge, 2019). Notably, 35 years is typically considered a cutoff for an advanced maternal age at which the risks start to increase (Cooke & Davidge, 2019; Falster et al., 2018). There is some evidence that an increasing age up to approximately 30 years of age may even be a protective factor for child development (Falster et al., 2018), although it is important to consider the protective effects of SES, which tend to increase with age (e.g., higher income and level of education). Further, an increased risk of offspring ADHD has been observed in teenage mothers, based on Swedish national register data (Z. Chang et al., 2014). Importantly, an increased risk was seen in all children of mothers who began childbearing as teenagers, suggesting the role of genetic or environmental risk factors. For ADHD risk, genetic influence explained 73% of the variance. Similarly, for age at first childbirth, genetics were the most important explanatory variable (49%), although nuclear family environment also had a large role (44% of the variance compared to only 2% for ADHD risk). Overall, both particularly young or old ages during gestation have been linked to an increased risk of adverse developmental outcomes, and the mechanisms differ at least partially (i.e., placental dysfunction and cardiovascular adaptation seem to play a role at an older

age, while risks associated with teenage pregnancy seems to stem from genetic and environmental risk factors).

SES is a complex phenomenon due to the multiple different approaches to measuring it. Some of the most obvious options are income, occupation, and educational level. However, even a measurement as simple as income raises many issues. First, median income levels vary a lot by region, let alone in the global environment, making comparisons of uncorrected data meaningless in more heterogeneous samples. Second, in more prosperous regions, income is not so much a measure of deprivation and could rather be considered a proxy for the educational level and cognitive ability of the parent, as well as for general good health behaviors (Lynch et al., 1997; Okamoto, 2021). Furthermore, some individuals have children before completing their education or reaching their target occupational position, meaning that they may exhibit many of the beneficial characteristics and behaviors while still having low income at their current stage in life. Third, it is unclear whether the use of household income or only maternal or paternal income is a better measurement. Household income is confounded by the issue that some households are single-parent households, heavily skewing the measurement. On the other hand, income data from only one parent may not reflect the total household income, especially in cases where one parent (typically the mother) stays at home raising the children. Furthermore, the number of children in the household affects how much financial freedom a certain income brings. In many cases, first-hand income data may not be available from both parents, limiting the reliability of household income as a measurement. Occupation is another commonly used measurement (Okamoto, 2021), but rank-ordering different occupations is a relatively subjective process. Nevertheless, rankings such as the Hollingshead Index of Social Status (Hollingshead, 1975) are available. Educational status (highest degree or years of education) is a comparatively simple measurement of SES.

Higher SES has been associated with, for example, increased healthy behaviors such as eating breakfast and regular tooth brushing in adolescents (Okamoto, 2021), better language abilities in 3–21-year-olds (Norbom et al., 2022), lower risk of obesity in 0–15-year-olds (Ding et al., 2021), lower risk of intellectual disability in school-age children (T. Yu et al., 2021), and, interestingly, increased risk of autism spectrum disorders in school-age children (Durkin et al., 2010; T. Yu et al., 2021). However, in the last case, the possibility of underdiagnosis in the lower SES groups is an important confounding factor. Notably, differentiating the effects of prenatal and postnatal environments is increasingly difficult as children age. As such, neuroimaging in early life can help identify the effects of SES on brain development, and the developmental trajectories of specific changes can be further explored.

2.4 Brain Changes Associated with Prenatal Exposures

2.4.1 Prenatal Chemical Exposures

2.4.1.1 Alcohol Exposure

Prenatal alcohol exposure has previously received little attention in brain imaging of children under 5 years of age (see Donald, Eastman, et al., 2015, for a review), but recently more research has emerged. Structurally, prenatal alcohol exposure has also been linked to a decreased corpus callosum area in neonates (n = 43; Jacobson et al., 2017). Another study (n = 73; Donald, Fouche, et al., 2016) found that prenatal alcohol exposure was associated with reduced overall GM volumes, most notably in bilateral amygdalae, the left hippocampus, and the left thalamus at 3 weeks of age, and with slightly delayed socio-emotional development compared with control infants at 6 months of age. The findings of lower total GM volume are consistent with results in older children, which suggests that they are pervasive (n = 67; Archibald et al., 2001; n = 84; Nardelli et al., 2011). A large study of adolescents (n = 9,719; Lees et al., 2020) found increased cortical SA and volume in those with prenatal alcohol exposure, which seems to be in conflict with most prior literature reporting a negative association between GM volumes and prenatal alcohol exposure. However, there are multiple important differences to consider. The timing of neuroimaging is important, as both decreased GM volume in neonates and increased GM volume in adolescents indicate delayed development. Among studies in older children and adolescents, one study had congruent findings, showing larger regional volumes in alcohol-exposed participants (n = 41; Sowell et al., 2002), but most studies tend to find decreased volumes related to prenatal alcohol exposure (n = 67; Archibald et al., 2001; n = 84; Nardelli et al., 2011; n = 99; F. F. Roussotte, Sulik, et al., 2012). The first difference to consider is the severity of exposure. Lees et al. (2020) observed an inverted U-shape association between alcohol exposure and volume and SA in some regions. Archibald et al. (2001) studied fetal alcohol syndrome individuals, and Roussotte et al. (2012) found associations between facial abnormalities and brain volumes, meaning that the alcohol exposure was larger than for the average participant in the Lees et al. study. Furthermore, Archibald et al. found that in comparison to total cerebral volume, only WM was lower in those exposed to alcohol. Similarly, in Nardelli et al. (2011), who studied participants with fetal alcohol spectrum disorders, the difference in cortical GM did not remain significant after controlling for total intracranial volume, while total and subcortical GM volumes did. These findings suggest that even at larger alcohol doses, the effects

on cortical GM may be relatively small compared to the other parts of the brain (including the cerebellum, Archibald et al., 2001).

DTI studies on the topic have found lowered axial diffusivity values in infants with prenatal alcohol exposure (n = 58; Donald, Roos, et al., 2015; n = 20 Taylor et al., 2015). Additionally, one neonatal functional MRI (fMRI) study (n = 27; Donald, Ipser, et al., 2016) found increased connectivity in somatosensory, motor, brainstem, thalamic, and striatal intrinsic networks at 2–4 weeks of age, while a large study of young adolescents (n = 9,719; Lees et al., 2020) found no differences in resting state functional connectivity between those with prenatal alcohol exposure and controls. Findings in both structural and functional imaging studies strengthen the notion that prenatal alcohol exposure affects the developing brain. In summary, structural neuroimaging studies support the idea that timing and dose matter (Archibald et al., 2001; Lees et al., 2020; Nardelli et al., 2011; F. F. Roussotte, Sulik, et al., 2012), and that there is no safe level of alcohol use during pregnancy (Lees et al., 2020). Both GM and WM structure are affected by prenatal alcohol exposure in multiple studies (see Lebel et al., 2011, for a review), while the evidence for functional differences is limited, possibly due to the relatively small number of studies.

2.4.1.2 Tobacco Exposure

One study by Knickmeyer et al. (n = 756; 2017) found marginal associations between maternal smoking and reduced GM, WM, and intracranial volumes in infants. Changes in GM volumes were mediated by birth weight, which is not surprising considering that the effects of smoking are partially due to growth restriction from hypoxemia (Lambers & Clark, 1996; Slotkin, 1998). However, intracranial volume and WM volumes were not mediated by birth weight, suggesting another mechanism not related to overall growth restriction (Knickmeyer et al., 2017). One study observed lower CT in the left superior parietal, left superior frontal, and right caudal middle frontal regions in 6–8-year-olds (n = 264; El Marroun, Tiemeier, Franken, et al., 2016). Another study by El Marroun et al. (n = 226; 2014) examined the structural correlates of continuous prenatal tobacco exposure in 6–8-year-olds. Exposure throughout pregnancy was associated with smaller cortical GM volumes and total brain volumes, as well as with cortical thinning in the superior parietal, superior frontal, and precentral regions, and thinning in the latter two regions was associated with affective problems (El Marroun, Schmidt, et al., 2014). Brain development in those whose mothers quit smoking during pregnancy resembled that of unexposed controls (El Marroun, Schmidt, et al., 2014). Similarly, Zou et al. (2022) studied the effects of continuous maternal prenatal smoking in a large sample (n = 2704) of 10-year-olds and discovered smaller GM, WM, and total brain volumes, smaller SA, and less gyrification in the exposed children. The associations were not explained by paternal smoking or smoking-

associated DNA methylation patterns from cord blood. Moreover, smoking only during the first trimester was not associated with brain structure. Together, these results (El Marroun, Schmidt, et al., 2014; R. Zou et al., 2022) imply that quitting smoking during pregnancy can be beneficial for offspring development. In contrast to alcohol use, there is currently no evidence that cortical morphology predicts future tobacco use (Boer et al., 2022). Overall, current neuroimaging literature shows a consistent pattern of smaller brain volumes in children exposed to tobacco prenatally, as well as lower regional CT. This is in line with literature showing fetal growth restriction (Jaddoe et al., 2007) and reduced head circumference, specifically (Roza et al., 2007). Adolescent studies show altered response to reward in the ventral striatum (n = 354; Muller et al., 2013) and increased fractional anisotropy (FA) in anterior WM regions (n = 67; L. K. Jacobsen et al., 2007), but developmental DTI and fMRI studies are scarce (Castro et al., 2023; Ekblad et al., 2015). One difficulty in tobacco exposure research is the prevalence of multidrug exposure. However, that issue should affect structural neuroimaging studies and even studies outside the neuroimaging field almost equally. Another possibility is publication bias. It is possible that there were no significant findings in prior examinations, and hence the results were never published.

2.4.1.3 Illicit Drug Exposures

Relatively little is known about the effects of prenatal marijuana exposure on offspring neurodevelopment. Prenatal marijuana exposure has been associated with higher CT in 6–8-year-olds (n = 263; El Marroun, Tiemeier, Franken, et al., 2016) and altered brain activation during a working memory task in young adults (n = 31 in both studies; A. M. Smith et al., 2006, 2016). Notably, the altered activity does not necessarily correlate with difference in task performance (A. M. Smith et al., 2006, 2016). Similarly, a study in 3-month-olds (n = 133; A. Salzwedel et al., 2020) found that prenatal marijuana exposure was linked to altered resting state functional connectivity in sensorimotor and dorsal attention networks, but not with cognitive, language, or motor development. On the contrary, behavioral changes related to prenatal cannabis exposure can be present without observable changes in functional imaging (n = 672; Cioffredi et al., 2022). The morphology of the orbitofrontal cortex has been consistently linked to a higher risk of future marijuana use in adolescence (Boer et al., 2022; Cheetham et al., 2012; Luby et al., 2018; Spechler et al., 2019; Wade et al., 2019). Overall, the literature on prenatal marijuana exposure is conflicting, showing both brain differences without behavioral correlates and vice versa. For a better understanding of long-term consequences of prenatal marijuana exposure, prospective longitudinal follow-up studies are needed (El Marroun et al., 2018).

Prenatal methamphetamine exposure has been associated with decreased subcortical volumes in neonates (n = 39; Warton et al., 2018) and children aged 3–

16 years (n = 28; L. Chang et al., 2004) and in children exposed to methamphetamine and alcohol, as opposed to children with exposure to just alcohol (as well as compared to unexposed controls, see Sowell et al., 2010, n = 61), in children aged 5–15 years. In the same study (Sowell et al., 2010), volume increases were observed in the cingulate and perisylvian regions in children exposed to methamphetamine and alcohol compared to the other groups. Furthermore, volumetric differences in the bilateral occipital, right thalamus, and left inferior temporal fusiform regions that were seen in both exposure groups were also associated with lower cognitive ability (Sowell et al., 2010). It is important to note that the findings of increased cortical volumes may be related to the fact that in almost all participants in Sowell et al. (2010) had exposure to alcohol, which has been associated with increased cortical volumes in late childhood and early adolescence (n = 9,719; Lees et al., 2020). Furthermore, prenatal methamphetamine exposure has been associated with lower FA and higher diffusivity values in striatal, limbic, and frontal regions in 6–7-year-olds (controlled for nicotine exposure; Roos et al., 2015, n = 32) and WM microstructure alteration in widespread regions (see Y. Zhang et al., 2021 for a review). One study by Chang et al. (n = 139; 2016) examined the effects of prenatal methamphetamine and tobacco exposures, performing repeated scans during the first 6 months of life. Sex-dependent variations in FA and diffusivity values were seen widely in the corona radiata. The findings in boys reversed by 3 months of age. The findings in girls were also seen in the group that was only exposed to tobacco and not methamphetamine. This finding highlights the usefulness of repeated early scans, as some of the findings may disappear, although the exposure has adverse effects lasting into later childhood (Kwiatkowski et al., 2014; L. M. Smith & Santos, 2016). Finally, fMRI studies have shown abnormal activations during a working memory task, as well as poorer performance compared to unexposed controls, in 7–15-year-olds (n = 50 in both studies; F. F. Roussotte et al., 2011; F. F. Roussotte, Rudie, et al., 2012), but the fMRI literature on methamphetamine exposure is currently limited compared to structural and DTI studies (see Moghaddam et al., 2021, for a review).

Cocaine, like many other drugs, is often used in combination with other substances. Hence, three studies compared infants with prenatal cocaine exposure, infants with similar substance exposure without cocaine, and control subjects with no prenatal exposures to illicit drugs, alcohol, or tobacco (n = 119; Grewen et al., 2014; n = 152 in both studies by A. P. Salzwedel et al., 2015, 2016). Grewen et al. (2014) linked prenatal cocaine exposure to smaller GM and larger cerebrospinal fluid volumes in frontal and prefrontal regions. Salzwedel et al. (2016) found increased connectivity between the anterior thalamus and frontal cortex, and that hyper-connectivity was associated with poorer cognitive and fine motor development. On the other hand, Salzwedel et al. (2015) only found cocaine-specific effects on functional connectivity in a subregion of the amygdala–frontal network, while

changes related to common drug exposure were widespread. One study in 8–10-year-olds discovered that prenatal cocaine exposure was associated with smaller cortical, thalamic, and putaminal GM volumes (n = 21; Akyuz et al., 2014). One study in adolescents found an association between smaller CT in the right dorsolateral prefrontal cortex and prenatal cocaine exposure after controlling for covariates (n = 40; Jie Liu et al., 2013), while another found decreases in some frontal cortical region volumes, including the bilateral caudal middle frontal and left lateral orbitofrontal regions (n = 40; F. Roussotte et al., 2012). While the neonate studies have sample sizes of over one hundred, the reliability of findings from older children and adolescents is limited by small sample sizes of a few dozen or fewer participants. Nevertheless, the structural studies show a consistent pattern of lower CT and volumes, similar to tobacco. On the fMRI side, Salzwedel et al. (2015) found limited cocaine-specific effects compared to multidrug exposure, and this finding is supported by their later work (n = 133; A. Salzwedel et al., 2020), in which prenatal cocaine exposure had the lowest effect of all studied exposures (including alcohol, nicotine, marijuana, opiates, and SSRIs).

There is some neuroimaging research on the effects of prenatal opioid exposure, although the studies are limited by samples sizes of a few dozen or fewer participants (see Mactier & Hamilton, 2020, for a review). Prenatal opioid exposure has been associated with smaller total brain and basal ganglia volumes in neonates (n = 16; Yuan et al., 2014), higher mean diffusivity in the bilateral longitudinal fasciculus in infants (n = 20; Walhovd et al., 2012), lower FA in widespread WM regions in neonates, although only the anterior and posterior limbs of the interior capsule and the inferior longitudinal fasciculus survived adjustment for head size (notably, polydrug use was common in the sample, Monnelly et al., 2018, n = 40), smaller basal ganglia and thalamus volumes in 10–14-year-olds (n = 32; Sirnes et al., 2017), and increased prefrontal activation and poorer performance in a working memory-selective attention task in 10–14-year-olds (n = 23; Sirnes et al., 2018). As with many other drugs, frequent polydrug use complicates the differentiation of the effects of specific substances. In summary, the literature on opioid exposure shows many similarities with other drugs discussed in this review. Lower GM volumes, alterations in WM microstructure (typically lower FA and higher diffusivity), and poorer task performance were coupled with functional abnormality in the brain.

2.4.1.4 Environmental Toxins

Prenatal and postnatal exposure to air pollutants has been associated with variations in GM (n = 3,133; Lubczyńska et al., 2021) and WM (n = 2,954; Lubczyńska et al., 2020) in 9–12-year-olds. One study examining prenatal exposure, specifically, found lower CT in multiple bilateral regions, and the decrease in the right precuneus and

the right rostral middle frontal region partly mediated the differences in inhibitory control in 6–10-year-olds (n = 783; Guxens et al., 2018). Notably, studies done late in life are subject to the limitation that participants also have long exposure to air pollutants postnatally.

Briefly, some other environmental toxins that could have adverse effects on offspring neurodevelopment include pesticides. Higher prenatal organophosphate pesticide levels have been associated with lower CT in the frontal and parietal regions, and larger SA in widespread regions in 6–11-year-olds (n = 40; Rauh et al., 2012), as well as lower FA and higher mean diffusivity globally in 9–12-year-olds (n = 518; van den Dries et al., 2020). Finally, the GM volume reductions associated with early lead exposure are still visible in early adulthood, and the effect seems to increase with age (see Horton et al., 2014, for a review).

2.4.2 Maternal Health Characteristics

2.4.2.1 Depressive Symptoms and Medication

The neural correlates of prenatal exposure to maternal depression symptoms have been explored in multiple studies. Higher maternal depression symptoms have been associated with decreased FA in the fornix and bilateral frontal regions at 2 weeks of age (n = 34; most participating mothers had subclinical levels of depressive symptoms; R. M. Graham et al., 2020), lower FA and axial diffusivity in the right amygdala in 6- to 14-day-olds (no differences in volume, n = 157; Rifkin-Graboi et al., 2013), higher fiber density in the bilateral uncinate fasciculus, as well as fiber density and fiber cross-section in the left dorsal cingulum in neonates (the latter did not survive correction for multiple comparisons; see Lautarescu et al., 2022, n = 413). In older children, prenatal exposure to depressive symptoms has been linked to increased FA in widespread WM tracts (5-year-olds, n = 130, effect seen in boys only; Kumpulainen et al., 2023). In functional imaging studies, exposure to prenatal maternal clinically relevant depressive symptoms was associated with amygdala hyperreactivity to angry and fearful faces (6-9-year-olds, n = 39; van der Knaap et al., 2018). Notably, exposure to postnatal maternal depressive symptoms (at 3 years) did not explain this connection. The literature on amygdala connectivity is conflicting, showing reduced (preschoolers, n = 128, effect only seen in girls; Soe et al., 2018), increased (infants, n = 24; Qiu et al., 2015), and increased negative (neonates, n = 64; Posner et al., 2016) connectivity (in resting state) to the frontal cortex, among other regions (see Lautarescu, Craig, et al., 2020 for a review). In a structural neuroimaging study of 6–9-year-olds, maternal depressive symptoms were associated with lower CT in the superior frontal gyrus and larger SA in the left caudal middle frontal region (n = 654; El Marroun, Tiemeier, Muetzel, et al., 2016). Lower

regional CT values have also been observed in preschool (right frontal and temporal regions, n = 52; Lebel et al., 2016) and school ages (right frontal lobe, n = 81; Sandman et al., 2015). In summary, lower CT in frontal regions has been observed repeatedly, but overall the structural neuroimaging literature is limited (Lautarescu, Craig, et al., 2020). Although these findings are limited to certain regions, lower CT in childhood indicates accelerated cortical development, which has been associated with suboptimal outcomes (n = 307; Shaw et al., 2006). This is likely due to a tradeoff between accelerated development for increased odds of early survival and reproduction, and developmental plasticity that can lead to better outcomes in the long term (Callaghan & Tottenham, 2016; Sandman et al., 2013). Findings from a recent DTI study also support this proposition (n = 130; Kumpulainen et al., 2023), while fMRI studies have discordant findings from different ages, and more research is needed to make interpretations from the point of view of the stress acceleration hypothesis (Callaghan & Tottenham, 2016).

Genetic and other individual differences can affect the neuroimaging correlates of prenatal maternal depression. Wang et al. (2018) and Qiu et al. (2017) examined the effects of different genetic variants on amygdalar and hippocampal morphology. Wang et al. (n = 161; 2018) discovered that infant right hippocampal volumes correlated positively with prenatal maternal depressive symptoms in low genetic risk individuals, and negatively in high genetic risk individuals in an Asian cohort. High and low genetic risk were defined by FKBP5 genotype (the FKBP5 gene regulates the hypothalamic–pituitary–adrenal axis function). On the other hand, Qiu et al. (2017) discovered that right amygdalar and right hippocampal volumes correlated positively with maternal depressive symptoms in infants with high genetic risk, and negatively in infants with low genetic risk for major depressive disorder (calculated from multiple risk genes) in their Asian cohort (n = 168 infants), while the direction of this interaction effect on the right amygdala volume was the opposite in their US cohort (n = 85 infants). One study in a Finnish sample (n = 105; Acosta et al., 2020) found an interaction effect between genetic risk and prenatal depressive symptoms for the right amygdala that was in the same direction as in the US cohort in Qiu et al. (2017), although this finding did not survive correction for multiple comparisons. This exemplifies the issue that even the same single nucleotide polymorphisms in certain genes may have opposing effects on the risk of psychopathology in groups from different backgrounds (Domschke et al., 2007). Importantly, publication bias and statistically under powered studies have been shown to sometimes overestimate the effect sizes in gene–brain interaction studies (as noted in the meta-analysis by Murphy et al., 2013). Finally, these findings are subject to the general factors that influence between-study comparisons in neuroimaging, such as differences in image acquisition/processing and statistical approach (sample characteristics, confounders, correction for multiple comparisons), as well as methodological limitations affecting

gene research, such as a specific single nucleotide polymorphisms not covering all the relevant variance in the function of the gene (Domschke et al., 2007).

SSRI medications are sometimes prescribed to pregnant mothers suffering from depression. A study by Jha et al. (2016) compared brain volumes and DTI parameters of infants with prenatal SSRI exposure (n = 27) to their matched controls (n = 54), and infants of mothers with a history of depression but no current pharmacotherapy (n = 41) to their matched controls (n = 82), attempting to separate the effects of the SSRI exposure from the effects of maternal qualities. Widespread differences were seen in DTI values between SSRI-exposed infants and controls, while no differences were seen between those with a maternal history of depression and their controls (Jha et al., 2016). Effects were particularly pronounced in mean diffusivity and radial diffusivity values in the corticofugal and corticothalamic tracts. One study of neonates (n = 98) found that SSRI exposure was associated with increased volume in the right amygdala and insula, as well as increased WM structural connectivity between the two, compared to neonates exposed to untreated maternal depression and unexposed controls (n = 98; Lugo-Candelas et al., 2018). Another study by Salzwedel et al. (n = 152; 2016) found marginally significant, constant drug–drug interactions between SSRIs and cocaine on thalamocortical connectivity measures. While the limited neuroimaging studies point to abnormal neurodevelopment that is different from that seen in unmedicated cases, the literature is too limited to draw conclusions regarding the potential harm of SSRIs, especially considering the lack of convincing evidence of adverse real-life outcomes. Furthermore, while an untreated depression group is included in these studies, it is notable that the medicated individuals may suffer or have previously suffered from more severe depression, hence the need for medication even during pregnancy. Finally, one aspect to consider when starting SSRI (or other antidepressant) medication during pregnancy is the fact that pharmacotherapy does not always results in remission of the depressive symptoms, in which case the fetus may be exposed to both the medication and high levels of depressive symptoms.

2.4.2.2 Distress and Anxiety

Prenatal distress can be examined using many different measurements. For example, prenatal exposure to stressful life events has been associated with higher FA in the right uncinate fasciculus in 6–9-year-olds (n = 22; Sarkar et al., 2014), and perceived maternal stress during pregnancy has been associated with lower CT in multiple clusters throughout the cortex in 7-year-olds and increased depressive symptoms in adolescence, and many frontal and temporal regions were associated with both stress exposure and future depressive symptoms (n = 74; Davis et al., 2020). However, in this literature review, we will focus on the effects of anxiety symptoms.

Higher maternal state and trait anxiety symptoms have been associated with decreased FA in the fornix and bilateral frontal regions at 2 weeks of age (n = 34; anxiety symptoms considered clinically elevated in only 15% of the participants; R. M. Graham et al., 2020), higher uncinate fasciculus diffusivity values in preterm infants (n = 251; Lautarescu, Pecheva, et al., 2020), and slower growth of the bilateral hippocampi during the first 6 months of life (n = 35 infants with repeated scans; Qiu et al., 2013). Pregnancy-related anxiety has been associated with sex-specific alterations in the volume of the left amygdala in 4-year-olds (n = 27; Acosta et al., 2019) and widespread decreases in cortical GM volumes in 6–9-year-olds (n = 35; Buss et al., 2010). For a review of neuroimaging findings on prenatal stress exposure (including depressive symptoms), see Lautarescu et al. (2020). Only one of the reviewed articles (Buss et al., 2010) covered differences in cortical anatomy, finding decreased regional volumes in many parts of the brain. The participants were at an age where some cortical regions are still increasing in volume while others are decreasing (Bethlehem et al., 2022), meaning this finding does not directly fit into the stress acceleration hypothesis network (Callaghan & Tottenham, 2016), although separation from different forms of distress such as perceived stress and depressive symptoms (where the structural findings were in line with the stress acceleration hypothesis) is somewhat artificial. Findings regarding the amygdala were similar to those following prenatal exposure to depressive symptoms (Acosta et al., 2020; Qiu et al., 2017), supporting the idea that there is substantive overlap in the neuroimaging findings following different forms of prenatal distress. Finally, the hippocampus demonstrated slower growth after prenatal maternal anxiety exposure (Qiu et al., 2013). Considering that lower hippocampal volume has been associated with increased internalizing problems in adolescence (n = 179; Koolschijn et al., 2013), these findings present a potential neurobiological mechanism for the increased risk of psychopathology in individuals exposed to maternal anxiety symptoms prenatally.

Similar to the effects of depressive symptoms, genetics can affect how anxiety exposure affects the brain between individuals. One study found differences in the association between early life stress and right amygdala reactivity, based on polygenic variation in hypothalamic–pituitary–adrenal activity in young adults (Di Iorio et al., 2017). Moreover, findings by Qiu et al. (n = 146; 2014) show that prenatal anxiety is differentially associated with CT, based on catechol-O-methyltransferase (COMT) gene haplotype. In the brain, the product of the COMT gene breaks down certain neurotransmitters such as catecholamines and is particularly important in the prefrontal cortex. An interaction effect between maternal anxiety and *val*158*met* single nucleotide polymorphism in the COMT gene was observed in the right ventrolateral prefrontal cortex. In this area, higher prenatal maternal anxiety was associated with a thicker cortex in higher activity genotypes (*val* homozygotes) that cause decreased dopamine signaling, and with thinner cortex in lower activity

genotypes (*met* homozygotes). COMT is a gene linked with both psychiatric outcomes in later life and structural findings in early life, and it is therefore an example of how neuroimaging might provide useful biomarkers to identify those at risk more accurately.

2.4.2.3 Obesity, Nutrition, and Inflammation

Maternal obesity has become recognized as a factor affecting early brain development. A study by Ou et al. (n = 28; 2015) examined how maternal adiposity affects WM maturation in 2-week-old infants. Maternal fat percentage correlated negatively with FA values in anterior parts of the brain, suggesting poorer maturation in infants of obese mothers. Another neonate study associated maternal obesity with decreased CT in the left frontal cortex (n = 44; Na et al., 2021). A neonatal fMRI study by Li et al. (n = 34; 2016) found that maternal obesity was associated with decreased functional connectivity in the prefrontal network, more specifically in the bilateral dorsal anterior cingulate, although only the left side remained significant after controlling for covariates. In summary, neonate studies find attenuated GM and WM maturation and altered functional connectivity (n = 21; Rajasilta et al., 2021; n = 45 infants with MRI data; Spann et al., 2020). Altered functional connectivity seems to persist into later childhood, as one study of 4–6-year-olds found maternal obesity to be associated with decreased neuronal activity in the left posterior cingulate gyrus, in addition to decreased activity in the left anterior prefrontal cortex and the left medial frontal gyrus (n = 101; Shapiro et al., 2020). On the other end of the weight spectrum, children of underweight mothers and those with no gestational weight gain showed lower total brain volumes at 10 years of age (n = 2,797; Silva et al., 2022), although these connections did not survive correction for multiple comparisons. Finally, one study found that maternal pre-pregnancy BMI was associated positively with FA values and negatively with diffusion values in widespread WM tracts in 10- and 26-year-olds (n = 2,466 and n = 437, respectively) but not in 6-year-olds (n = 116; Verdejo-Román et al., 2018). Notably, effect sizes were small, and there was no overlap in the tracts identified in different cohorts. Finally, maternal pre-pregnancy BMI (n = 231; Rasmussen et al., 2023) and fatty acid concentration during pregnancy (n = 94; Rasmussen et al., 2022) have been associated with differences in neonate hypothalamic structure. Furthermore, the increased mean diffusivity in the neonate hypothalamus predicted childhood overweight (Rasmussen et al., 2022), offering a possible biological basis for the increased childhood obesity risk in the offspring of obese mothers, although more studies are needed to confirm this finding.

Obesity is associated with an increased risk of many metabolic and cardiovascular diseases, such as hypertension. There has been some exploration of

their effects on offspring neurodevelopment. For example, higher maternal diastolic blood pressure in early pregnancy has been associated with lower WM mean diffusivity at 10 years of age (n = 2,797; Silva et al., 2022). However, a detailed breakdown of the effects of maternal somatic diseases is outside the scope of this literature review.

A proinflammatory environment can result from multiple causes, including the aforementioned obesity (see Choi et al., 2013, for a review) and malnutrition (see Marques et al., 2015, for a review). Other potential causes are prenatal distress (Marques et al., 2015) and maternal infections (Tran et al., 2016; Wu et al., 2018). One study by Graham et al. (n = 86; 2018) examined the effects of maternal systemic IL-6 levels on the neonatal amygdalar volumes and functional connectivity, as well as impulse control, at 2 years of age. Larger neonatal right amygdalar volume mediated the association between higher maternal IL-6 levels during pregnancy, and poorer impulse control in offspring at 2 years of age, which was in line with previous research linking adversity and increased amygdalar volumes (n = 78; Tottenham et al., 2010; n = 57; Vassilopoulou et al., 2013). Another study by the same group (n = 84; Rudolph et al., 2018) found widespread associations between maternal IL-6 levels during pregnancy and neonate functional connectivity patterns. They also utilized machine learning to predict maternal IL-6 levels based on neonatal functional connectivity. Some of the strongest effect sizes were seen in networks that have a role in attention systems, such as the salience network and the dorsal attention network, both proposed to have a role in executive functioning. In line with the functional connectivity findings, they also found a negative correlation between IL-6 levels and visuospatial working memory at 2 years of age (Rudolph et al., 2018). In another neonate study (n = 36; Spann et al., 2018), immune activation (measured using both IL-6 and C-reactive protein concentrations) was associated with altered salience network connectivity with widespread regions. Surprisingly, a positive association was observed between immune activation (including IL-6, specifically) and cognitive performance at 14 months of age, in contrast to the negative association with working memory that was seen in the Rudolph et al. study (2018). While cognitive ability and working memory are distinct constructs, they are highly intercorrelated (Kane et al., 2005), and hence an opposite relationship to maternal immune activation is surprising. In addition to relatively small sample sizes (especially in Spann et al., 2018, n = 36), the postnatal environment is one potential confounder. Neither study considered environmental effects such as parenting behaviors or socioeconomic characteristics. This is especially relevant considering that Spann et al. (2018) recruited teenage mothers, which is a population with increased risk for adverse outcomes in offspring (Z. Chang et al., 2014), and parental age as such also constitutes a confounder that may be related to the discordant findings. Finally, one study explored the associations between maternal IL-6 levels,

uncinate fasciculus microstructure in infancy, and socioemotional/cognitive development at 12 months of age (n = 86; Rasmussen et al., 2019). Average IL-6 level during pregnancy was negatively associated with cognitive development but not with socioemotional development. It was also associated with lower uncinate fasciculus FA values in neonates but a faster increase in FA during the first year. A faster increase in the left uncinate fasciculus was associated with worse cognitive performance at 12 months and mediated the effects of higher IL-6 levels on cognitive performance. The observation that FA at 12 months was not associated with cognitive performance but with the speed of FA increase further emphasizes the utility of studying trajectories of brain development rather than just differences in values cross-sectionally. Various inflammatory biomarkers present interesting avenues for future studies.

2.4.2.4 Demographic Factors

Maternal and paternal age have been associated with brain volume in children and adolescents (n = 171, many with repeated scans; Shaw et al., 2012). Shaw et al. (2012) present an inverted U-shape relationship between parental age and cortical GM volume, wherein the volume peaks at 33–34 years of parental age, which is in line with previous findings linking adverse outcomes with both particularly young (Z. Chang et al., 2014) and old (Cooke & Davidge, 2019) ages at childbirth. In neonates, higher paternal age has been associated with decreased FA in the corticospinal tract, the corpus callosum, and the optic radiation, which were also associated with worse cognitive performance at 18 months (n = 275; Gale-Grant et al., 2020). In a study by Knickmeyer et al. (n = 756; 2017), maternal and paternal age were not significantly associated with infant brain volumes. There is relatively little pediatric neuroimaging literature exploring the effects of parental age, and more studies are needed.

Higher maternal SES has been associated, for example, with larger cortical and deep GM volumes in term-born infants (n = 44 African-American girls; Betancourt et al., 2016), higher total WM and GM volume in neonates (Knickmeyer et al., 2017), and higher bilateral hippocampal volumes in 4–18-year-olds (n = 317, SES measured using household income; Hanson et al., 2011). On the other hand, higher paternal education has been associated with lower CT in neonates globally, as well as regionally in many frontal regions (n = 805; Jha et al., 2019), and with higher total GM volume and intracranial volume in neonates (Knickmeyer et al., 2017). Overall, there is a trend of higher brain volumes associated with higher SES. One finding that deviates from this trend is the lower infant CT found by Jha et al. (2019). A study of 4–18-year-olds (n = 283; Lawson et al., 2013) found that higher parental SES was associated with higher CT in the left superior frontal and right anterior cingulate

regions. CT findings are congruent with the stress acceleration hypothesis (Callaghan & Tottenham, 2016), with higher family SES (meaning less stress, generally speaking) associated with slower CT development, presumably allowing more plasticity and better adaptation to the environment. However, results from volumetric studies do not fit this narrative, as smaller volumes in relation to lower SES is a common finding. In cortical measurements, GM volume is more closely linked to SA than CT, and CT and SA develop largely independently of each other (Winkler et al., 2010). Therefore, SES may affect the development of CT and volume in different ways. One possible explanation is that decreased volumes reflect suboptimal environmental stimulation, which has been linked to worse language skills in childhood and adolescence (n = 110; Farah et al., 2008). Notably, a positive association with the paternal education has been observed in neonates, and even regarding intracranial volume (association not mediated by birthweight, see Knickmeyer et al., 2017), which is harder to explain with environmental stimulation, but rather suggests genetic effects. Considering that cognitive ability predicts academic achievement and income (M. I. Brown et al., 2021), both cognitive ability and brain volume are highly heritable (Deary et al., 2006; Plomin & Von Stumm, 2018), and higher brain volume is associated with better cognitive ability (McDaniel, 2005). Higher brain volumes (GM, WM, and intracranial) in the children of high SES parents could be one of the neurobiological mechanisms mediating the beneficial effects of SES.

In adolescents, one task-fMRI study found that greater parental (average of maternal and paternal) education was associated with increased activity in parts of the frontal–subcortical pathway during successful response inhibition (n = 81, males only; Cascio et al., 2022). Furthermore, studies have found relatively consistent associations between SES and frontal SA in adolescence (see Rakesh & Whittle, 2021, for a review) but at this stage in life, the postnatal effects of SES are a major confounding factor, and the literature on adolescents and adults will not be covered here in greater detail.

2.5 Child Characteristics

Many of the prenatal exposures covered above increase the risk of being born preterm, LBW, or small for gestational age. It is estimated that more than 10 million babies are born preterm every year globally, and approximately 1 million children die each year due to the complications of preterm birth (Perin et al., 2022; Walani, 2020). Both the prevalence and mortality caused by preterm birth are higher in low- and middle-income countries (Walani, 2020). Preterm birth (especially very preterm) has been associated with poorer cognitive, language, social, and motor development in later childhood (Aylward, 2014; Brydges et al., 2018; Lean et al.,

2018; Ream & Lehwald, 2018). LBW is often comorbid with preterm birth, and there is evidence of similar adverse neurodevelopmental outcomes (Oudgenoeg-Paz et al., 2017), even continuing into adulthood (Eryigit Madzwamuse et al., 2015). Being born small for gestational age also has an increased risk of neonatal mortality (A. C. C. Lee et al., 2017).

Two large neuroimaging studies by Knickmeyer et al. (2017) and Jha et al. (2019), with sample sizes of 756 and 805, respectively, examined the effects of prenatal environment and family characteristics on infant brain morphology. They found gestational age at birth and birth weight to be the most important predictors of SA and all brain volumes (GM, WM, and intracranial volume), alongside sex and age at scan, either from birth (Jha et al., 2019) or from conception (Knickmeyer et al., 2017). Both sex and age at scan are outside the scope of this literature review, as they are not affected by prenatal exposures. Gestational age at birth was more specifically associated positively with SA (Jha et al., 2019), but negatively with regional CT (Jha et al., 2019) and GM, WM, intracranial, and cerebellar volumes (Knickmeyer et al., 2017). Furthermore, effects of parental education and maternal ethnicity were partially mediated by birthweight (Knickmeyer et al., 2017), suggesting the role of general susceptibility at least in addition to potential specific effects of these demographic factors. Current literature on 10-year-olds supports the idea that a positive association between gestational age at birth and regional and global brain volumes persists into late childhood, even among term-born children (n = 3,079; El Marroun et al., 2020; n = 101; Nivins et al., 2023). Furthermore, a recent meta-analysis suggests that the profile of adverse effects of preterm birth and LBW remains similar through development (Christians et al., 2023). Overall, the studies on preterm birth and LBW demonstrate a pattern of consistently lower brain volumes, similar to that seen in many prenatal exposures that increase the risk of preterm birth and LBW, such as tobacco and opioid exposures.

2.6 Cognitive Ability

Cognitive ability is an important predictor for many important life outcomes (Plomin & Von Stumm, 2018), such as school and academic performance (Deary et al., 2007; Neisser et al., 1996; Strenze, 2007), educational attainment (M. I. Brown et al., 2021), occupational status (M. I. Brown et al., 2021; Lang & Kell, 2020; Schmidt & Hunter, 2004; Strenze, 2007), job performance (Bertua et al., 2005; Neisser et al., 1996; Schmidt & Hunter, 2004; N. Schmitt, 2014), income (M. I. Brown et al., 2021; Furnham & Cheng, 2017; Lang & Kell, 2020; Neisser et al., 1996), life expectancy (Batty et al., 2007; Whalley & Deary, 2001), and other psychiatric and somatic health outcomes (e.g., alcohol use, see Batty et al., 2006; and obesity, see Chandola et al., 2006). Cognitive ability is considered a stable (Deary et al., 2013; Gow et al., 2011)

and highly genetically determined (Deary et al., 2006; Plomin & Von Stumm, 2018) individual characteristic in adult populations, while environmental factors play a greater role the younger the subjects are (Haworth et al., 2009; Plomin et al., 1997; Plomin & Von Stumm, 2018).

Cognitive ability can be measured, for instance, using age-appropriate Wechsler Intelligence Scales originally developed by David Wechsler. In Study III, we used the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) meant for children from 2 years 6 months to 7 years 3 months of age (Wechsler, 2009). There are also the Wechsler Intelligence Scale for Children meant for older children and adolescents, and the Wechsler Adult Intelligence Scale for adults. In WPPSI-III, the completion of the core subtests yields Full Scale Intelligence Quotient (IQ), Verbal IQ, and Performance IQ (PIQ) composite scores. All composite scores have a mean of 100 and an SD of 15 and are corrected by age. The WPPSI-III consists of different subtests for children under 4 years and over 4 years of age. As per the subjects' age in our Studies II, III, and IV, we will focus on the latter. The core subtests of WPPSI-III for children between 4 years and 7 years 3 months of age include: 1) three performance domain subtests: Block Design, Matrix Reasoning, and Picture Concepts; 2) three verbal domain subtests: Information, Vocabulary, and Word Reasoning; and 3) the Coding subtest, which is a Processing Speed Quotient subtest that contributes to the Full Scale IQ (Freeman, 2013). The WPPSI-III also includes supplemental tests that can be used to substitute for core subtests (e.g., Similarities, a verbal domain subtest) or derive additional composite scores: Processing Speed Quotient and General Language Composite. There are also optional subtests that cannot be substituted for core subtests. Tests can change between the core, supplemental, and optional categories based on age at testing. Importantly, PIQ (or verbal IQ) can be estimated from two subtests. In Study III, PIQ was estimated using the Block Design and Matrix Reasoning subtests.

2.7 Brain Correlates of Cognitive Ability

A consistent but modest positive correlation between total brain volume and cognitive ability has been consistently observed in prior studies (this correlation is higher in adults than in children; McDaniel, 2005). However, with advancements in neuroimaging technology, we have the capability to answer more specific questions: what regions and qualities in the brain are associated with cognitive ability?

2.7.1 The Parieto–Frontal Integration Theory

The Parieto–Frontal Integration Theory (P–FIT) model proposes that cognitive ability is consistently associated with structural and functional features of a network

including widespread frontal and parietal regions, the anterior cingulate cortex, and sensory regions within the temporal and occipital lobes (Jung & Haier, 2007). Jung and Haier formulated this model by reviewing the literature including structural and functional MRI studies, as well as positron emission tomography studies. Studies in children were not excluded from the review, but even the studies with the youngest populations were focused on older children and adolescents (Frangou et al., 2004; Schmithorst et al., 2005; Schmithorst & Holland, 2006; Shaw et al., 2006; Wilke et al., 2003), and most of the studies were of adult populations. A summary of the regions involved in the neuroimaging studies of cognitive ability in the review by Jung and Haier (2007) is shown in Figure 2.

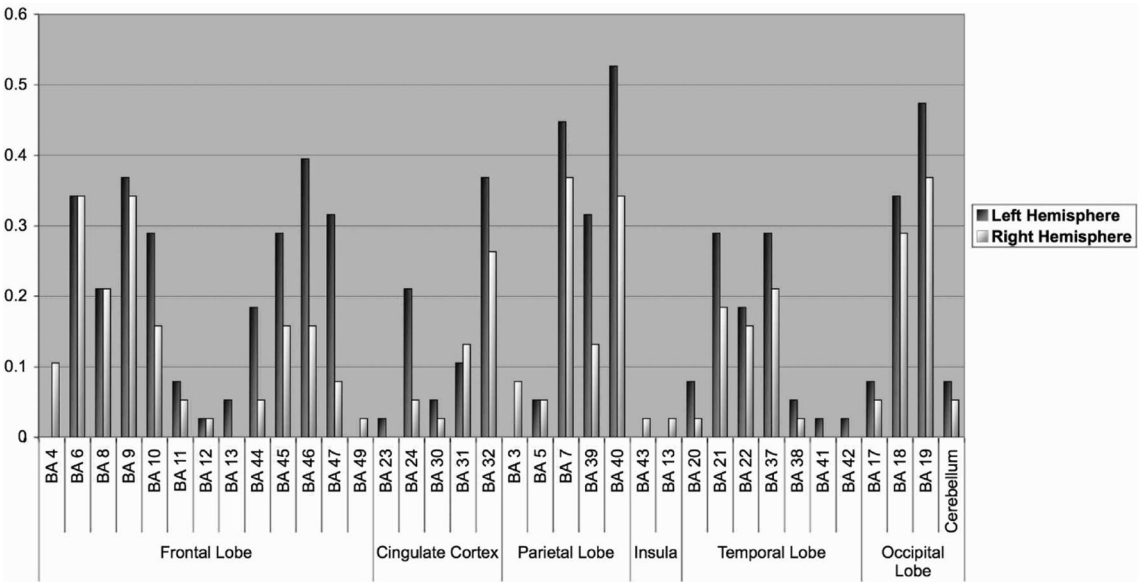

Figure 2. Graphical representation of the proportion (Y-axis) of all reviewed structural and functional magnetic resonance imaging as well as positron emission tomography studies describing relationships between intelligence and/or reasoning and discrete Brodmann areas by lobe. Brodmann areas that were identified in more than 25% of the studies were considered part of the Parieto–Frontal Integration Theory (P–FIT). Figure 2 is a copy of a figure from an article by Jung and Haier (2007) and has been reprinted with the permission of the copyright holders. © *Cambridge University Press 2007*

A more recent meta-analysis of structural and functional neuroimaging studies was generally in good agreement with the P–FIT model (Basten et al., 2015; notably, they excluded child and adolescent studies from their review). However, there were interesting discrepancies between structural and functional findings in the two reviews (Basten et al., 2015; Jung & Haier, 2007): Basten et al. found consistent structural but not functional associations in the temporal and occipital regions, while

the opposite was true in the review by Jung and Haier. Basten et al. speculate that these differences may be a by-product of the selection of more task-based studies by Jung & Haier, leading to activation of sensory regions. Furthermore, while both reviews agree that frontal and parietal regions are important, Basten et al. did not find structural associations in the parietal regions, which the authors speculate might be related to differences in spatial resolution in comparisons (Basten et al., 2015). These discrepancies were not totally surprising considering that previous studies that have shown that structural and functional changes may not happen in the same regions (Haier et al., 2009). Furthermore, Basten et al. (2015) added the posterior cingulate cortex into the model of intelligence. The posterior cingulate cortex is part of the default mode network (Greicius et al., 2003; Hagmann et al., 2008) and one of the areas that typically decreases in activation during attention-demanding tasks (Fox et al., 2005; Heuvel et al., 2009; Langer et al., 2012; Song et al., 2008), including in children (DeSerisy et al., 2021).

Most studies in these reviews use full-scale IQ as the measurement of cognitive ability. However, it is possible to explore verbal and non-verbal ability separately. Based on current evidence in school-age children and adolescents, verbal ability is associated with structural and functional neural features in language areas (Khundrakpam et al., 2017; Qi et al., 2019; Ramsden et al., 2011), while non-verbal ability is associated with structural and functional features in (pre)motor areas (Kim et al., 2016; Ramsden et al., 2011).

2.7.2 Structural Pediatric Neuroimaging and Cognitive Ability

In line with the P–FIT model, previous studies on school-age children and adolescents have found positive associations between general cognitive ability and GM volume in the frontal (Pangelinan et al., 2011; Reiss et al., 1996) and parietal lobes (Pangelinan et al., 2011). One study found prefrontal cortical GM volume to predict approximately 20% of the variance in cognitive ability (greater volume predicted higher cognitive ability) in children between the ages 5 and 17 years (Reiss et al., 1996). Additionally, studies of children and adolescents have found negative associations between general cognitive ability and the volumes in the right middle temporal gyrus (Yokota et al., 2015; participants separated into clusters with different profiles of cognitive ability), as well as positive associations between general cognitive ability and GM volumes in the whole brain and the bilateral cingulate gyrus (effects were driven by the adolescents, Wilke et al., 2003). There is some evidence that SA is also positively associated with general cognitive ability from birth to 11 years of age (Girault et al., 2020; Schnack et al., 2015; Sølsnes et al., 2015) and that children with higher cognitive ability reach the

maximal SA faster (Schnack et al., 2015). Furthermore, greater prefrontal SA has been linked to higher general cognitive ability in children aged 9–11 years (Vargas et al., 2020). However, pediatric studies examining the connection between SA and cognitive ability are scarce relative to studies using CT as a brain measure of interest.

Similarly in line with the P–FIT model, greater CT in the frontal and parietal regions may predict later higher verbal ability in infants (Girault et al., 2020) or academic achievement in adolescents (Meruelo et al., 2019). Similarly, studies have found positive associations between non-verbal ability and CT in the frontal regions in 4–7-year-old children (with low SES; see Leonard et al., 2019) and adolescents (Schilling et al., 2013). On the other hand, a study of 12–14-year-olds found negative associations between general cognitive ability and CT in the bilateral parietal regions (Squeglia et al., 2013). Similarly, one study found negative associations between CT and working memory in 4–8-year-olds in the superior and middle frontal, superior parietal, and anterior cingulate regions (Botdorf & Riggins, 2018), while another found no correlations between CT and working memory in any brain regions in 6–16-year-olds (Faridi et al., 2015). Furthermore, a recent longitudinal study in children and adolescents found positive correlations between general cognitive ability and CT mostly in the superior frontoparietal cortex, frontopolar cortex, and language centers (J. E. Schmitt, Raznahan, et al., 2019), which are among the areas typically associated with cognitive ability, according to the P–FIT model (Jung & Haier, 2007). Notably, correlations were modest in young children but became stronger at approximately 10 years of age (J. E. Schmitt, Raznahan, et al., 2019). Some other studies have also focused on this dynamic development of CT in childhood and adolescence. One study found greater vocabulary improvement associated with greater thinning between the ages 5 and 11 years in widespread brain regions, especially in the left hemisphere (Sowell et al., 2004). In another study, the correlation between general cognitive ability and CT was negative until about 8 years of age, and it then turned positive (Shaw et al., 2006).

In summary, most studies examining brain structure and cognitive ability are conducted in samples with wide age ranges, typically focusing on late childhood and adolescence, while such research in younger age groups is scarcer. Notably, studies with wider age ranges risk conflating findings from different age groups, and studies with large samples from a limited age range are warranted to better explore the neural basis of cognitive ability at the specific developmental stage. To the best of our knowledge, there are no previous large neuroimaging studies focusing solely on typically developing 5-year-olds.

2.8 Summary of the Literature Review

A vast array of different prenatal factors can affect development of the individual and their brain. These factors range from exposures to large quantities of teratogens (such as alcohol) to variations in the behaviors and characteristics of healthy individuals (such as age, diet, and subclinical levels of depressive and anxiety symptoms), which can nonetheless have long-lasting adverse effects.

Neuroimaging can be used to gain more knowledge of the neurobiological origins of the differences in cognitive and behavioral outcomes in later life. In the case of prenatal exposures, imaging in early life is the best option, as the effects of the postnatal environment are minimized. MRI can be done safely on children of all ages with age-appropriate adjustments (Copeland et al., 2021; Spann et al., 2022), which makes it an excellent tool for developmental neuroscience. The reviewed literature focused on the first years of life, so that the majority of the studies have been carried out with prepubescent children as participants.

Pediatric neuroimaging as a field faces some characteristic methodological challenges related to factors such as poorer image quality and lack of age-specific analysis tools. Poorer image quality due to factors such as increased motion raises the question of what constitutes optimal quality control in pediatric samples, and whether manual editing or segmentation could be used to improve image quality.

Cognitive ability predicts multiple important outcomes and is related to brain structure and function. However, the underlying neural characteristics of cognitive ability in young children are still poorly understood. Even the large studies with longitudinal samples have only started the follow-up at around the age of 5, but typically have few participants this young. Five years is also a particularly interesting age to study the structural brain correlates of cognitive ability, as the children are old enough to both cooperate in cognitive assessment to be reliably evaluated and to lie still in the MRI scanner while awake. Furthermore, 5-year-olds have yet to start school in Finland, meaning most of them have not gone through the formal learning of academic abilities such as reading (Chyl et al., 2021) and arithmetic (Hashimoto et al., 2022).

3 Aims of the studies

The aim of this thesis was to identify important background factors that affect brain development based on previous literature, and to subsequently explore whether these factors affect structural brain development in 5-year-olds from the FinnBrain Birth Cohort study. Utilizing this information in statistical analyses, our aim was to map the structural correlates of non-verbal ability in 5-year-olds, which is an age group that has previously received little attention. Finally, knowing the limitations of current brain image segmentation software, we aimed to compare the quality of two commonly used software tools (FreeSurfer and FSL) against manual segmentation of subcortical structures. The goal was to assess in which structures automatic segmentation is satisfactory and which might still require editing or, at least, careful quality control.

The specific aims of the studies were:

I. To review the literature on the effects of various prenatal exposures on the developing brain. Additionally, to explore how the confounding effects of these exposures are considered in pediatric neuroimaging studies.

II. To explore the effects of demographic factors (of child and parent) on cortical morphometry in typically developing 5-year-olds.

III. To identify the cortical structural correlates of non-verbal ability in typically developing 5-year-olds.

IV. To compare FSL-FIRST and FreeSurfer against the gold standard manual segmentation of the hippocampus and subcortical structures in typically developing 5-year-olds.

4 Materials and Methods

4.1 Ethical Considerations

All studies were conducted in accordance with the Declaration of Helsinki. The neuroimaging measurements for Studies II, III, and IV were approved by the Joint Ethics Committee of the University of Turku and the Hospital District of Southwest Finland (ETMK: 31/180/2011). The neuropsychological measurements for Study III were approved by the Joint Ethics Committee of the University of Turku and the Hospital District of Southwest Finland (ETMK: 26/1801/2015).

Study I was a literature review; no original data was collected for the study and therefore it did not have to be approved by an ethics committee.

Written informed consent was acquired from both parents at the beginning of the MRI visit. Child assent was confirmed during the recruitment process. The participating family was free to stop the visit at any time for any reason.

4.2 Participants

4.2.1 The FinnBrain Birth Cohort study

The participants for Studies II, III, and IV are a part of the FinnBrain Birth Cohort Study (www.finnbrain.fi), which prospectively examines the influence of genetic and environmental factors on child development and later health outcomes (Karlsson et al., 2018). Pregnant females (n = 3,808) attending their first trimester ultrasound at gestational week 12, their spouses (n = 2,623), and babies to-be born (n = 3,837; including 29 twin pairs) were recruited in Southwest Finland between December 2011 and April 2015. Ultrasound-verified pregnancy and sufficient knowledge of Finnish or Swedish language were required for participation. The cohort study includes several follow-up studies. The participants that attended the neuroimaging visit as part of the 5-year-old data collection were included in Studies II, III, and IV. In the data collection, a neuropsychological visit preceded the neuroimaging visit, and data from that visit is used in Study III.

The participants were first recruited for the neuropsychological assessments at 5 years of age. The participants recruited for this visit were focus cohort families

(highest or lowest quartile scores of maternal prenatal distress; please see Karlsson et al., 2018, for more details) and families who had actively participated in previous FinnBrain study visits. For the neuropsychological visits, 1,288 families were contacted and informed of the study, and of these families, 974 (75.6%) were reached by telephone. From all the contacted families, 545 (42.3%) participated in a study visit (304 boys (55.8%), mean age 5.01 (SD 0.08), range 4.89–5.37 years). For the 5-year-old neuroimaging visit, we primarily recruited participants that had attended the neuropsychological visit. For the neuroimaging visits, 541 families were contacted and 478 (88.4%) of them were reached. In total, 203 (37.5%) participants attended imaging visits (113 boys (55.7%), mean age 5.40 (SD 0.13), range 5.08–5.79 years). Altogether 196 participants attended both visits.

We originally aimed to scan all subjects between the ages of 5 years 3 months and 5 years 5 months; however, there was a pause in visits due to the start of the COVID-19 pandemic, and subsequently many of the participants were older than planned when they were scanned (152/203 [75%] of the participants attended the visit within the intended age range).

The exclusion criteria for the neuroimaging study were: 1) born before gestational week 35 (before gestational week 32 for those with exposure to maternal prenatal synthetic glucocorticoid treatment), 2) developmental anomaly or abnormalities in senses or communication (e.g., blindness, deafness, congenital heart disease), 3) known long-term medical diagnosis (e.g., epilepsy, autism), 4) ongoing medical examinations or clinical follow-up in a hospital (meaning there has been a referral from a primary care setting to special health care), 5) child use of continuous, daily medication (including per oral medications, topical creams and inhalants; one exception to this was desmopressin medication, which was allowed, as it has not been linked to altered brain development and is a commonly used medication for nocturnal enuresis, a relatively common condition that does not in isolation indicate an atypical neurological development in 5-year-olds (Van De Walle et al., 2010)), 6) history of head trauma (defined as concussion necessitating clinical follow-up in a health care setting or worse), 7) metallic (golden) ear tubes (to ensure good-quality scans), and routine MRI contraindications.

Out of the 203 participants that attended the neuroimaging visit, 173 had a high-quality T1-weighted image and were consequently potential participants in the structural neuroimaging studies. The background information of these participants is presented in Tables 1 and 2. For the background characteristics of the specific samples used in the studies, see the original publications (Studies II, III, and IV).

Table 1. Participant demographics (continuous variables). Number of participants = 173.

VARIABLE	MEAN	SD	MIN	MAX
Age at scan (years)	5.40	0.13	5.08	5.79
Ponderal index	14.06	1.20	11.21	17.63
Gestational age at birth (weeks)	39.69	1.68	33.57	42.29
Birth weight (grams)	3524	504.7	1790	4980
Maternal age at term (years)	31.12	4.70	19.10	41.95
Paternal age at birth (years)	31.74	4.98	20.00	44.00
Maternal bmi before pregnancy	24.23	4.31	17.49	41.95
5 minutes apgar score	9.09	0.70	4	10

Table 1 footnote | Abbreviations: SD = standard deviation, BMI = body mass index. Ponderal index was calculated using the following formula: weight in kilograms divided by height in meters cubed. Height and weight were acquired during the neuroimaging visit. The participants kept indoor clothes on during the weighing. Maternal BMI before pregnancy data was missing from one participant. Table 1 is original content made by the author for this thesis.

Table 2. Participant demographics and maternal medical history variables (categorical variables). Number of participants = 173

VARIABLE	NUMBER	PERCENT
Sex		
Male	95	54.9
Female	78	45.1
Maternal education level		
Low	36	20.8
Middle	48	27.7
High	89	51.4
Paternal education level		
Low	32	18.5
Middle	40	23.1
High	43	24.9
Missing	58	33.5
Maternal monthly income, estimated after taxes (euros)		
≤ 1,500	55	31.8
1,501–2,500	93	53.8
2,501–3,500	15	8.7
≥ 3,501	3	1.7
Missing	7	4.0
Maternal background		
Finnish	162	93.6
Other	5	2.9
Missing	6	3.5
Gestational age at birth		
≥ 37 weeks	164	94.8
< 37 weeks	9	5.2

VARIABLE	NUMBER	PERCENT
Neonatal intensive care unit admission		
Yes	26	15.0
No	146	84.4
Missing	1	0.6
Alcohol use during pregnancy		
Yes, continued to some degree after learning about the pregnancy	15	8.7
Yes, stopped after learning about the pregnancy	30	17.3
No	117	67.6
Missing	11	6.4
Tobacco smoking during pregnancy		
Yes	11	6.4
No	162	93.6
Illicit frug use during pregnancy		
No	162	93.6
Missing	11	6.4
Ssri/snri medication during pregnancy		
Yes	6	3.5
No	150	86.7
Missing	17	9.8
Pregnancy complication		
Yes	26	15.0
No	146	84.4
Missing	1	0.6
Mode of delivery		
Vaginal	139	80.3
C-section	33	19.1
Missing	1	0.6

Table 2 footnote | Abbreviations: SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin–norepinephrine reuptake inhibitor. Maternal and paternal education data were combined from questionnaire data from 14 weeks gestation or 5 years of child age by choosing the highest degree reported. The three classes are: Low = Upper secondary school or vocational school or lower, Middle = University of applied sciences, High = University. On the question about alcohol usage, four subjects answered that they did not use alcohol during pregnancy, but also answered that they stopped using alcohol when they learned about the pregnancy. These were classified as “yes, stopped when learning about the pregnancy”. SSRI/SNRI medication indicates use at either 14 or 34 weeks gestation. The data for maternal monthly income estimate, alcohol use, and illicit drug use are from questionnaires at gestational week 14. The pregnancy complications include a diagnosis (according to ICD-10) for O12 (Gestational edema and proteinuria without hypertension), O13 (Gestational hypertension without significant proteinuria), O14 (Severe pre-eclampsia), O24 (Diabetes mellitus in pregnancy, childbirth, and the puerperium), O46 (Antepartum hemorrhage, not elsewhere classified), or O99.0 (Anemia complicating pregnancy, childbirth and the puerperium). Paternal age at birth was counted as full years. Sex, birth weight, maternal BMI before pregnancy, and tobacco smoking data (combined with questionnaire data) were retrieved from the National Institute for Health and Welfare (www.thl.fi). Table 2 is original content made by the author for this thesis.

4.2.2 Study II

For Study II, 30/203 participants were excluded due to a missing or poor quality T1-weighted image, and a further three participants were excluded due to being born before gestational week 35. Subsequently, the sample size for analyses was 170 participants.

4.2.3 Study III

For Study III, only participants with an adequate quality T1 image (n = 173/203, assessed by the author Elmo P. Pulli as described in our earlier work (Pulli et al., 2022)) and successful assessment of cognition (n = 166/173) were included. Additionally, one participant was excluded due to scoring below 4 scaled score in the verbal ability test Similarities and below the standard score 70 in PIQ (calculated from Block Design and Matrix Reasoning scaled scores and the estimated scaled score for a third non-verbal subtest; see a more detailed description later in Methods), leaving us with a final sample size of 165 participants. A few participants were missing one of the non-verbal tasks, and missing data was not imputed. Consequently, the sample sizes were 164 for the Matrix Reasoning task, 160 for the Block Design task, and 159 for PIQ.

Potential selection bias in the sample was assessed: Mothers of the children who did not participate in the neuropsychological visits (out of the 1,288 contacted families) had a lower education level ($\chi2(2) = 30.94$, $p < 0.001$), had a lower monthly income ($\chi2(3) = 11.65$, $p = 0.009$), and were younger ($t(1286) = -4.130$, $p < 0.001$) compared to the mothers in the families that participated in the neuropsychological visits.

Mothers of the children who participated in the neuropsychological visits but not in the neuroimaging visits were older ($t(369) = 1.97$, $p = 0.047$) but did not differ in education level or monthly income compared to the mothers in the families that participated in the MRI visit.

The children who participated in the neuropsychological visits but not in the MRI visits did not differ in PIQ, Block Design, or Matrix Reasoning performance from those that participated in the MRI visit.

4.2.4 Study IV

For Study IV, we used a subsample of 80 participants. This was considered a large enough sample for reliable statistical analyses, while avoiding excess manual segmentation, which is extremely time-consuming, even though the *FSL None* output was used as the basis for manual editing to save time. We selected the first 80 participants who were visually confirmed to have a high enough quality T1-weighted image for manual segmentation of the subcortical structures.

4.3 Literature Search – Study I

We focused on studies that used MRI techniques to assess brain development in healthy term-born infants up to 2 years of age. Two years was a good compromise between a range that is large enough to result in a good number of original studies (e.g., compared to a search only focusing on neonates) while also limiting the search to participants who are young enough so that the postnatal environment and life events have limited effects on the results. To identify relevant articles, we conducted a PubMed search using the following terms: ("Magnetic Resonance Imaging" [Mesh] OR MR imaging* OR MRI OR fMRI OR DTI OR "diffusion tensor imaging") AND ("Brain/growth and development" [Mesh] OR brain growth* OR brain developm*) AND ("Infant" [Mesh] OR infant* OR toddler* OR neonat* OR newborn*). To keep the search comprehensive, no search term referred to the prenatal time, in utero environment, or maternal characteristics. This was important, as we were also interested in how these factors were reported in other MRI studies on healthy term-born infants. The only filter used was the time of publication, which ranged from January 1, 2012, to March 31, 2018, the search being performed on April 1, 2018. We chose to review the most recent findings in hope of capturing a methodologically comparable set of studies.

Our search resulted in 905 articles. In the screening phase, our major goal was to exclude all studies outside the set age range and/or involving "abnormally" developing participants, that is, infants with congenital disease or malformation, premature birth (preterm), or LBW. We considered the latter two categories abnormal, as both conditions are linked with increased risk of adverse developmental outcomes, and their developmental trajectories are likely different from those of term-born infants (Inder et al., 2005; Linsell et al., 2015). We went through titles and abstracts for initial screening. Subsequently, we identified 193 potentially relevant articles. The other 712 were excluded, as presented in Figure 3. During screening, if a publication met more than one of our exclusion criteria it was excluded based on the highest priority criterion that it met. If an exclusion criterion was clear from the title, we did not search the abstract for a higher priority criterion. Exclusion criteria are presented in detail in the Supporting Information Material. Exclusion criteria at this phase, in descending order of priority, were:

1. Publication was a duplicate of another publication found in this search.
2. Publication was not written in English.
3. Publication was a review article.
4. Subjects were nonhuman animals. Studies were also excluded if both humans and other animals were studied.

5. The study focused on preterm (born before 37 weeks gestational age [GA]) or LBW (birth weight <2,500 g) subjects of any age.
6. The study focused on the effects of a certain disease or treatment.
7. Living 0- to 2-year-olds were not MRI scanned in the study.

In total, 193 articles passed the screening process. To identify the appropriate studies, we did assessment for eligibility using full articles. In addition to excluding studies in which participants were not healthy term born infants up to 2 years of age, we also excluded studies in which the examination of brain development between 0 and 2 years of age was peripheral due to the main focus being on a new method or on a population with a wider age range. This was done to maintain focus on the effects of prenatal factors on early brain development. The assessment for eligibility consisted of three steps:

1. We implemented all the same criteria as we did in the screening phase.
2. We excluded methodological articles regarding either creation, comparison, or optimization of scanning sequences, analysis pipelines, statistics, atlases, or practicalities of the pediatric MRI imaging procedure.
3. We excluded articles in which the age of the participants extended beyond the 2-year timepoint or conversely to the fetal period.

We identified 19 studies that focused on infants with a certain in utero chemical exposure, or infants of mothers with certain characteristics. The flowchart of study selection is presented in Figure 3. We summarized these 19 articles to show how the prenatal factors they examined may affect early neurodevelopment and, therefore, to provide a basis for why these factors should be reported in all pediatric neuroimaging studies.

In a complementary approach, we performed a population description analysis among the articles identified during the literature search. In addition to the aforementioned 19 articles, we found 48 articles that focused on other aspects of early brain development. Altogether, 67 articles were used in the population description analysis, in which we examined how the reviewed prenatal factors were generally reported in MRI studies on infants of up to 2 years of age. In the population description analysis, we went through both the articles and their supplementary materials to gather the information on participant characteristics.

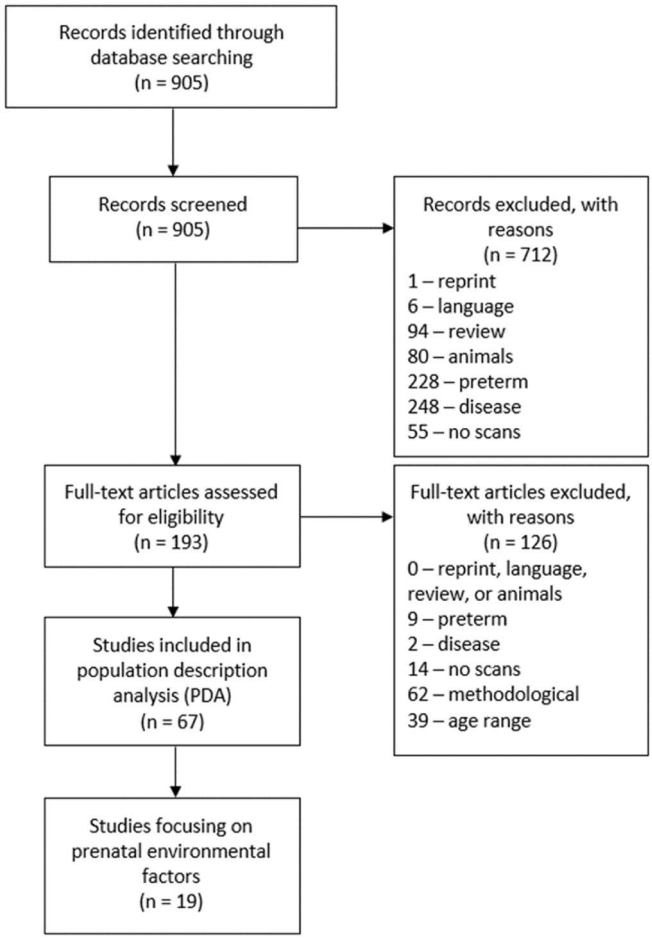

Figure 3. A flow diagram outlining the study selection process. Reprinted from Study I with the permission of the copyright holders.

We aimed to cover a wide variety of studies both qualitatively and thematically to get a sample that represents the infant/pediatric neuroimaging field. To minimize selection bias, we selected studies using predefined search terms and exclusion criteria. Therefore, we decided to conduct a structured review. We concluded that this approach was sufficient to describe the current trends in population descriptions. Of note, we considered performing a systematic review, but soon discovered that it is not feasible due to the small number of studies on a single prenatal exposure. While some articles relevant to prenatal effects of the environment might have been left out of the sample, findings from studies outside our search are discussed where appropriate. For the purposes of the population description analysis, we believe this is a representative sample of the research done during the chosen period and can be used to accurately describe current trends in the infant neuroimaging field.

4.4 MRI Data Acquisition – Studies II-IV

The neuroimaging data used in Studies II, III, and IV are from the same FinnBrain 5-year-old data collection.

4.4.1 Neuroimaging Visits

All MRI scans were performed for research purposes by the research staff (a research nurse, four PhD students, and two MR technologists). Each family was personally contacted and recruited via telephone calls by a research staff member. The scan preparations started with the recruitment and at-home training. We explained the image acquisition process to the parents and advised them to present the process to their children and confirm child assent before the follow-up phone call, which was used to confirm the willingness to participate and to set the scan date. Thereafter, we advised the parents to use at-home familiarization methods such as showing a video describing the visit, playing audio of scanner sounds, encouraging the child to lie still like a statue ("statue game"), and practicing with a homemade mock scanner, such as a cardboard box with a hole to view a movie through. The visit was marketed to the participants as a "space adventure," which is in principle similar to the previously described "submarine protocol" (Theys et al., 2014), but the child was allowed to come up with other settings as well. A member of the research staff made a home visit before the scan, to deliver earplugs and headphones, to give more detailed information about the visit, to answer any remaining questions, and for familiarization with the research staff.

At the start of the visit, we familiarized the participant with the research team (a research nurse and a medically trained PhD student) and acquired written informed consent from both parents. This first portion of the visit included a practice session using a non-commercial mock scanner consisting of a toy tunnel and a homemade wooden head coil. Inexpensive non-commercial mock scanners have been shown to be as effective as commercial ones (Barnea-Goraly et al., 2014). The participants brought at least one of their toys that would undergo a mock scan (e.g., an MRI-compatible stuffed animal they could also bring with them into the real scanner). The researcher played scanner sounds on their cell phone during the mock scan, and the child could take pictures of the toy lying still and of the toy being moved by the researcher to demonstrate the importance of lying still during the scan. Communication during the scan was practiced. Overall, these preparations at the scan site were highly variable as we did our best to accommodate the child's characteristics (e.g., taking into account physical activity and anxiety) in cooperation with the family. Finally, we served a light meal of the participant's choice before the scan.

The participants were scanned awake or during natural sleep. One member of the research staff and the parent(s) stayed in the scanner room throughout the scan. The

participants wore double hearing protection and were able to watch and listen to a movie or television show of their choice during the scan. Participants were given a "signal ball" to throw in case they wanted to stop or pause the scan. If the research staff member noticed movement, they gently reminded the participant to stay still by lightly touching their foot, which was practiced earlier in the visit. The practical steps to limit head motion during the scan and decrease participant anxiety were based on earlier research (Epstein et al., 2007; Greene et al., 2016).

All images were viewed by one neuroradiologist (Riitta Parkkola), who then consulted a pediatric neurologist (Tuire Lähdesmäki) when necessary. The protocol with incidental findings has been described in our earlier work (Kumpulainen et al., 2020). In the whole neuroimaging sample of 203 participants, there were 13 participants with incidental findings (6.4%). These participants were not excluded from the sample but went through the same quality control procedure as all the other images (described in detail elsewhere in Methods).

4.4.2 MRI Sequences

Participants were scanned using a Siemens Magnetom Skyra fit 3T with a 20-element head/neck matrix coil. We used the Generalized Autocalibrating Partially Parallel Acquisition technique to accelerate image acquisition (a parallel acquisition technique factor of 2 was used). As part of a max 60-minute scan session, we acquired high resolution T1-weighted images with the following magnetization prepared rapid gradient echo (MPRAGE) sequence parameters: repetition time = 1900 ms, echo time = 3.26 ms, inversion time = 900 ms, flip angle = 9 degrees, voxel size = 1.0 x 1.0 x 1.0 mm^3, field-of-view 256 x 256 mm^2. For other acquired sequences, see the original publications. The scans were planned as per the recommendations of the FreeSurfer developers (https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki?action=AttachFile&do=get&target=FreeSurfer_Suggested_Morphometry_Protocols.pdf, at the time of writing).

4.5 MRI Preprocessing and Analysis

4.5.1 The Semiautomated Protocol of FinnBrain Neuroimaging Lab

4.5.1.1 Automatic FreeSurfer Preprocessing

The automatic cortical reconstruction and volumetric segmentation for all images in Studies II, III, and IV were performed using the FreeSurfer software suite, version 6.0.0. We selected the highest quality T1-weighted image and then applied the

"recon-all" processing stream with the default parameters. The protocol has been described in Studies II, III, and IV, and further technical details can be found in the publications of FreeSurfer developers (Dale et al., 1999; Fischl et al., 1999).

4.5.1.2 Manual Edits and Freeview Quality Control Protocol

After the automatic FreeSurfer segmentation, we used Freeview to view and edit the images using the standard command recommended by the FreeSurfer instructions with the addition of the Desikan–Killiany atlas (Desikan et al., 2006) overlay. The full protocol was described in our earlier work (Pulli et al., 2022). Images with excess motion artifacts or large unsegmented regions (extending over multiple gyri; examples provided in Figure 4) were excluded, and a dichotomous pass/fail scale was used. The images that passed the initial quality check were then manually edited (the time required for manual editing ranged from approximately 45 minutes to over 3 hours, taking approximately 2 hours on average). All images were examined in all three directions, one hemisphere at a time, and the edits were made for every slice regardless of the region of interest (ROI) in question. Subsequently, we ran the automated segmentation process again, as suggested in the FreeSurfer instructions. The images were then inspected again for errors.

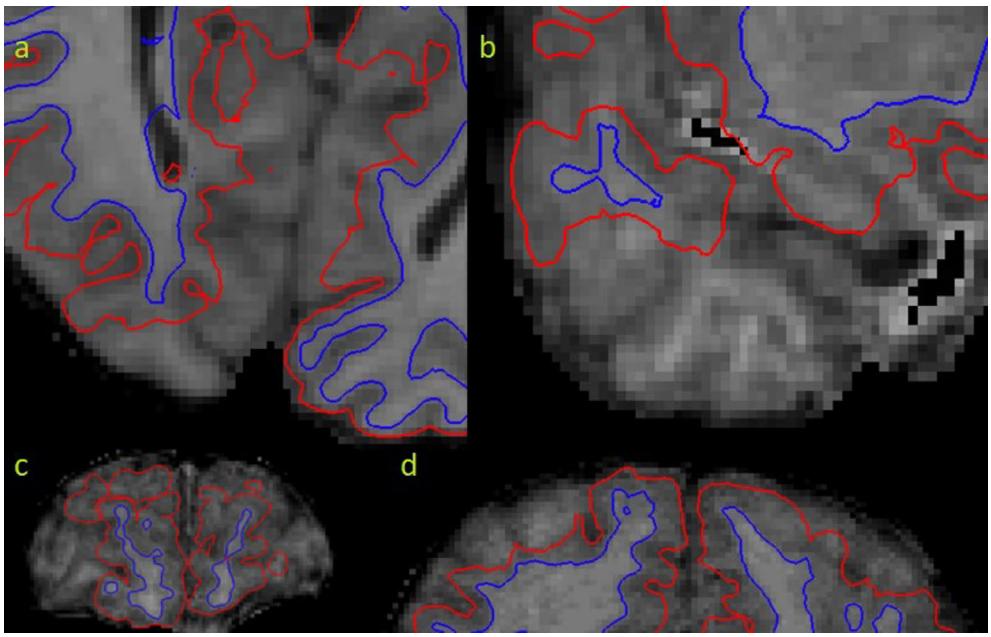

Figure 4. Large, unsegmented areas in the occipital (A), temporal (B), and frontal (C and D) regions. These errors that leave areas over multiple gyri unsegmented lead to exclusion of the whole image. Reprinted from Pulli et al. (2022) with the permission of the copyright holders.

4.5.1.3 Errors in Borders

The automatically segmented images were visually inspected, and the found errors were either manually corrected or the ROI with the error was simply excluded, depending on the type of error (exclusions based on the ENIGMA quality control protocol, which is presented later). Excess parts of the skull were removed where the pial border was affected by them (Figures 5A,B). Arteries were removed to avoid segmentation errors between arteries and WM (especially relevant for structures adjacent to the circle of Willis and the insulae) by setting the eraser to only delete voxels with intensity between 130 and 190 in the brainmask volume. The arteries were removed throughout the image whether they caused issues in the segmentation in that specific slice or not. An example can be seen in Figure 5C. In cases where an error appeared in a junction between ROIs, all adjoining ROIs were excluded.

One typical error was that parts of the superior sagittal sinus were included within the pial border. We stopped editing the superior sagittal sinus after an interim assessment, as it was an arduous task with little effect on final results. Briefly, the change in CT between manually edited and unedited images was compared in regions adjacent to the superior sagittal sinus in participants with ($n = 95$) and without ($n = 26$) superior sagittal sinus edits. The only significant difference was the left cuneus ($p = 0.009$), where the superior sagittal sinus edits made the cortex thinner (mean change 0.013 mm), while the lack of edits resulted in a thicker cortex (mean change 0.011 mm). The finding did not survive Bonferroni correction. Full analysis is presented in Pulli et al. (2022) supplementary materials (Data sheet 2, pp. 10–14).

Some error types could not be fixed easily. Figure 5D shows the pial border cutting through the cortex. In these cases, the remaining GM mask is too small, and this error cannot be easily fixed in Freeview. Manual segmentation of a T1 image is not recommended in the FreeSurfer instructions, as it is labor intensive and hard to conduct reliably with 1 mm^3 resolution. Additionally, the WM mask edits recommended in FreeSurfer instructions would not fix all cases in which the cortical segmentation is too thin, as the WM mask often seemed adequate in the regions with this type of error. Therefore, we simply had to exclude the ROI(s) in question.

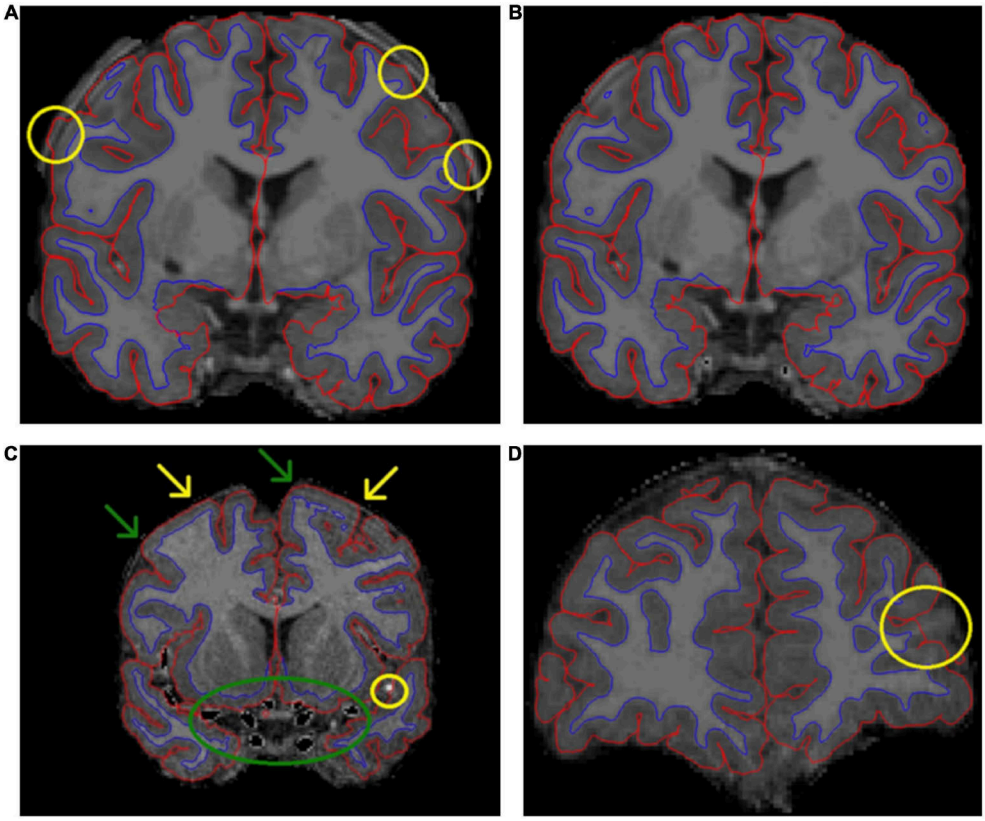

Figure 5. A presentation of some common errors and fixes related to the pial (red) border and non-brain tissues. (A) Demonstrates how skull fragments can cause errors in the pial border (yellow circles). (B) Presents the same subject with skull fragments removed, and the pial border now looks correct. (C) Presents removal of arteries (green circle). We removed voxels with an intensity between 130 and 190, and therefore some parts of arteries were not removed (yellow circle). (C) Additionally demonstrates the challenges with artifacts, meninges, and the pial border. In some areas, the pial border may extend into the meninges (yellow arrows). Meanwhile, at the other end of the same gyrus, the border may seem correct (green arrows), which, together with visible motion artifacts, makes it difficult to fix these errors manually. (D) Presents the pial border cutting through a gyrus. Reprinted from Pulli et al. (2022) with the permission of the copyright holders.

Small errors in the WM–GM border were ubiquitous. The corrections were made by erasing excess WM mask. This process is demonstrated in Figure 6. The WM–GM border was inspected after the manual edits. Particularly prevalent errors in the WM–GM border throughout the brain, as markers of motion artifacts, led to exclusion of the whole brain (as in Figure 7).

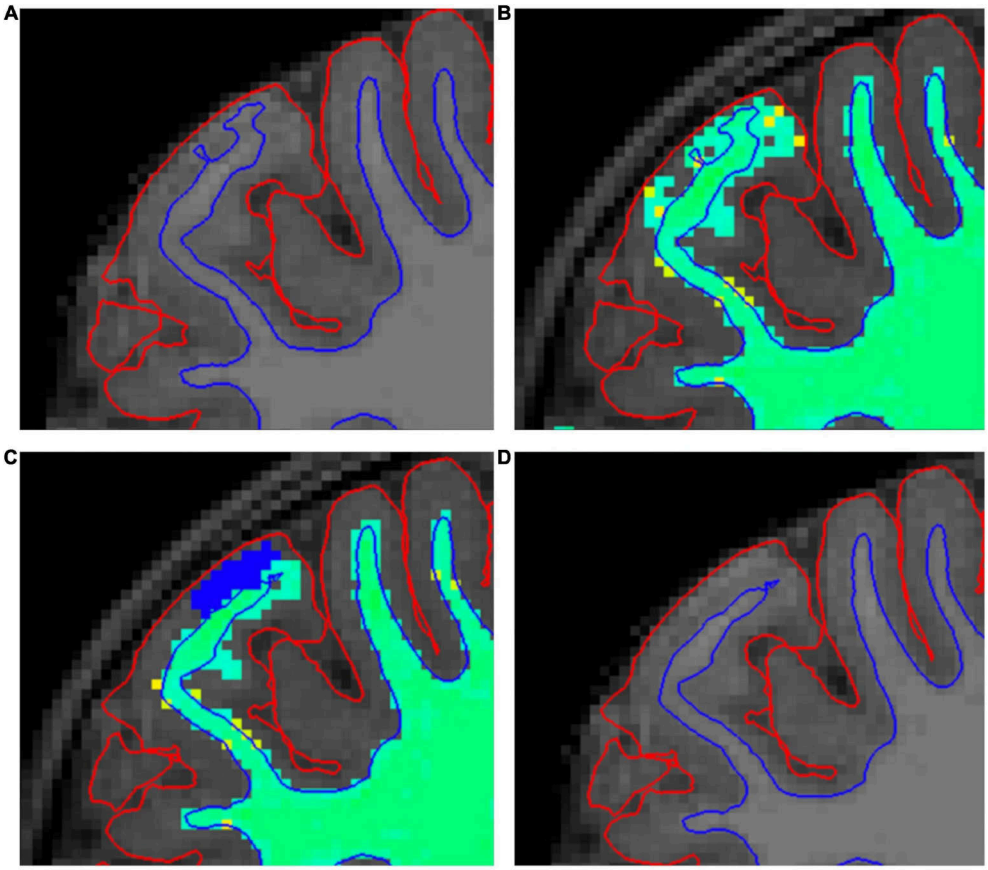

Figure 6. A demonstration of our white matter (WM) mask editing protocol. (A) Shows a typical error in the border between white and gray matter (WM–GM border, the blue border), where it goes too close to the pial (red) border. Errors such as this are searched for in the "brainmask" volume (A,D). (B) Shows the same error in "wm" volume with "Jet" colormap (B,C). (C) Shows how we fixed these errors by erasing the erroneous WM mask (blue voxels). (D) Shows the final result after the second recon-all. Reprinted from Pulli et al. (2022) with the permission of the copyright holders.

Furthermore, there are some error types that cannot be easily fixed but also do not warrant exclusion. One such problem is that the pial border often extends into the cerebrospinal fluid or meninges around the brain. The issue with this type of error is that sometimes the real border between GM and the surrounding meninges cannot be denoted visually, and therefore the error cannot be reliably fixed. This problem is further complicated by the fact that motion artifacts may mimic the border between the GM and meninges, making visual quality control challenging.

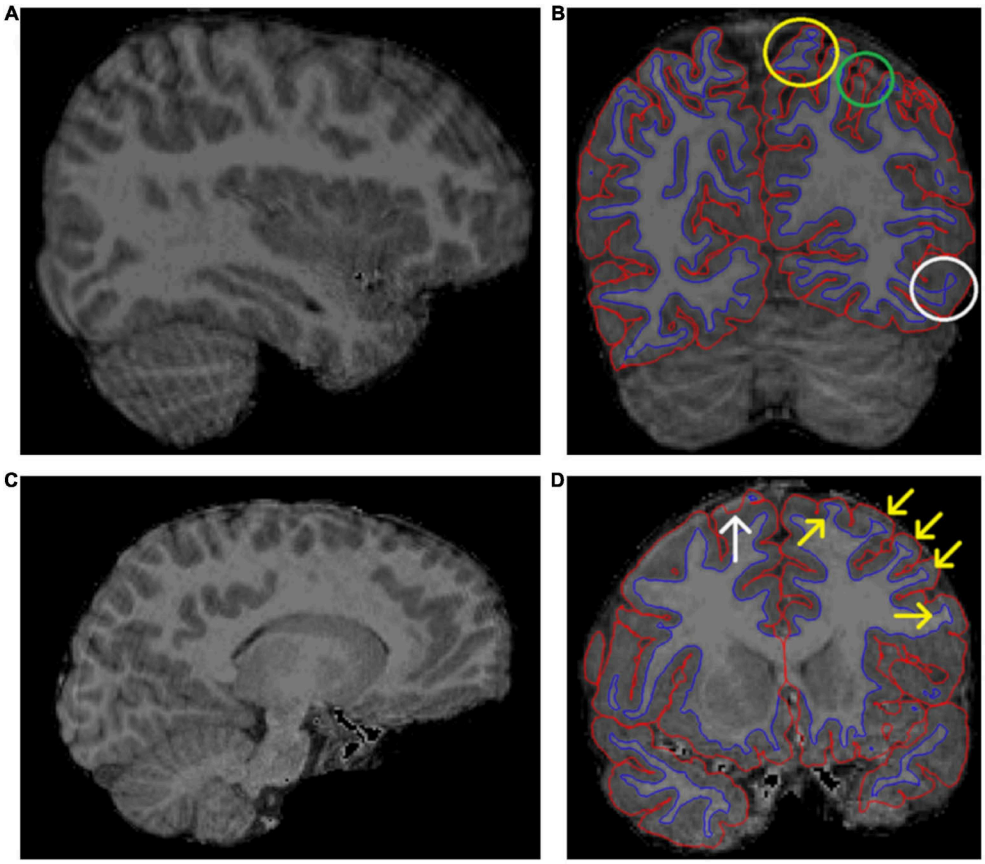

Figure 7. Two examples of excluded brain images. (A) Shows “waves” or “ringing” throughout the image, marking motion artifacts. (B) Shows the same subject as in panel (A) in a coronal view with borders visible. This image shows motion artifact related errors in the border between white and gray matter (WM–GM border), denoted by the yellow circle. Additionally, there is a potential unsegmented area due to motion artifacts (green circle) and poor contrast between WM and GM (white circle). (C,D) Show another excluded subject. The motion artifact in panel (C) is not as pronounced as in panel (A). However, (D) still shows some typical errors for images with large artifacts. There is a clear pial error (white arrow). Additionally, the yellow arrows show typical cases, where the “ringing” causes the WM mask to “widen” where the actual WM meets the ringing motion artifact. Reprinted from Pulli et al. (2022) with the permission of the copyright holders.

4.5.1.4 Errors in Cortical Labeling

A common issue was the presence of WM hypointensities in the segmented images. These errors were typically small and did not cause errors in pial or WM–GM borders, and in those cases did not require exclusion. Sometimes the WM–GM border was affected, in which case we tried to fix it by editing the WM mask, and when unsuccessful, we simply excluded the ROI in question from the analyses

(Figures 8A,B). Hypointensities often appeared in ROI junctions, leading to the exclusion of multiple regions due to one error. Of note, these errors can only be seen with the anatomical labels as overlays, unless they affect the WM–GM border.

One typical error occurred at the posterior end of the lateral ventricles, where it may cause segmentation errors in the adjacent cortical regions, typically the precuneus and the lingual gyrus (Figures 8C,D).

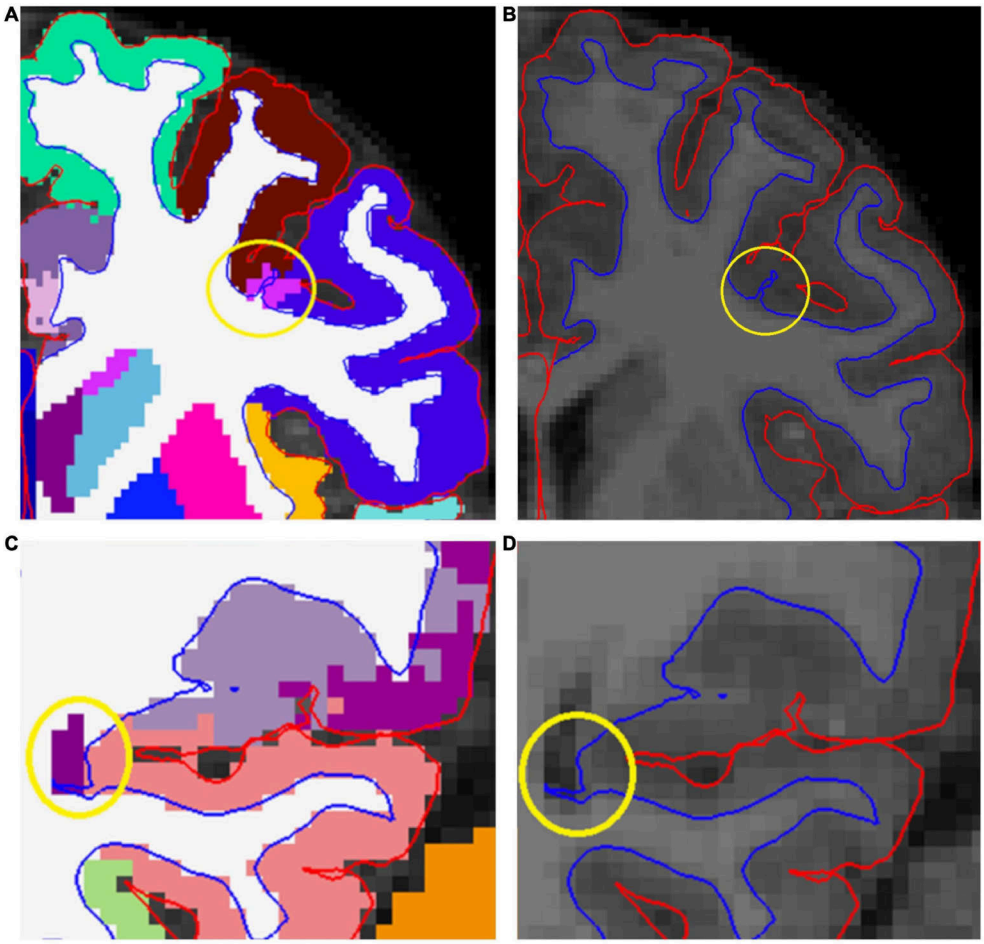

Figure 8. (A,B) Show a white matter (WM) hypointensity that affects the border between white and gray matter (WM–GM border), denoted by a yellow circle. (C,D) Show how the posterior part of the lateral ventricle causes distortion to the WM–GM border (yellow circle). Reprinted from Pulli et al. (2022) with the permission of the copyright holders.

4.5.1.5 The ENIGMA Quality Control Protocol

The term ENIGMA stands for "Enhancing Neuro Imaging Genetics Through Meta Analysis," a large international consortium (http://enigma.ini.usc.edu). After the quality control that entailed manual edits, we conducted a quality check using the ENIGMA Cortical Quality Control Protocol 2.0 (April 2017). First, the FreeSurfer cortical surface measures were extracted and screened for statistical outliers using R (R Core Team, 2022) and visualized via Matlab (Mathworks) and bash scripts. Second, visual representations of the external 3D surface and internal 2D slices were generated and visually inspected according to the ENIGMA instructions in https://drive.google.com/file/d/0Bw8Acd03pdRSU1pNR05kdEVWeXM/view (at the time of writing). The ENIGMA cortical quality control instructions remark that certain areas have a lot of anatomical variation and therefore it is possible to be more or less stringent in the quality control. Considering this and the fact that the example images provided in the ENIGMA instructions are limited in number and as such cannot show every variation, we deemed it necessary to describe how we implemented these instructions in our sample, specifically.

4.5.1.6 The External View in ENIGMA

We started by viewing the external image. The pre- and postcentral gyri were assessed for meninge overestimations, which can manifest as "spikes" or flat areas. These error types were rare in our sample. These cases were excluded as instructed.

The supramarginal gyrus has a lot of anatomical variability, and when quality checking it, we decided to be lenient, as suggested in the ENIGMA instructions. We only excluded cases in which the border between the supramarginal and inferior parietal regions cuts through a gyrus, leading to discontinuous segments in one of the regions (Figure 9A). In some rare cases, this type of error also happened with the postcentral gyrus, and these cases were also excluded. Similarly, in cases with supramarginal gyrus overestimation into the superior temporal gyrus, we only excluded clear errors (examples in Pulli et al., 2022).

One commonly seen error is insula overestimation into the midline (Figure 9B). In these cases, we excluded the insula and the region(s) adjacent to it in the midline (e.g., the medial orbitofrontal region in the case of Figure 9B).

The border between the superior frontal region and the cingulate cortex is one typical place for errors. This was typically seen in the left caudal anterior cingulate (Figure 9B), where we excluded cases in which the border did not follow the sulcal lines anteriorly (as was demonstrated in the image examples in the ENIGMA instructions). In rare cases, the border between the posterior cingulate and the superior frontal region was affected, and these were also excluded.

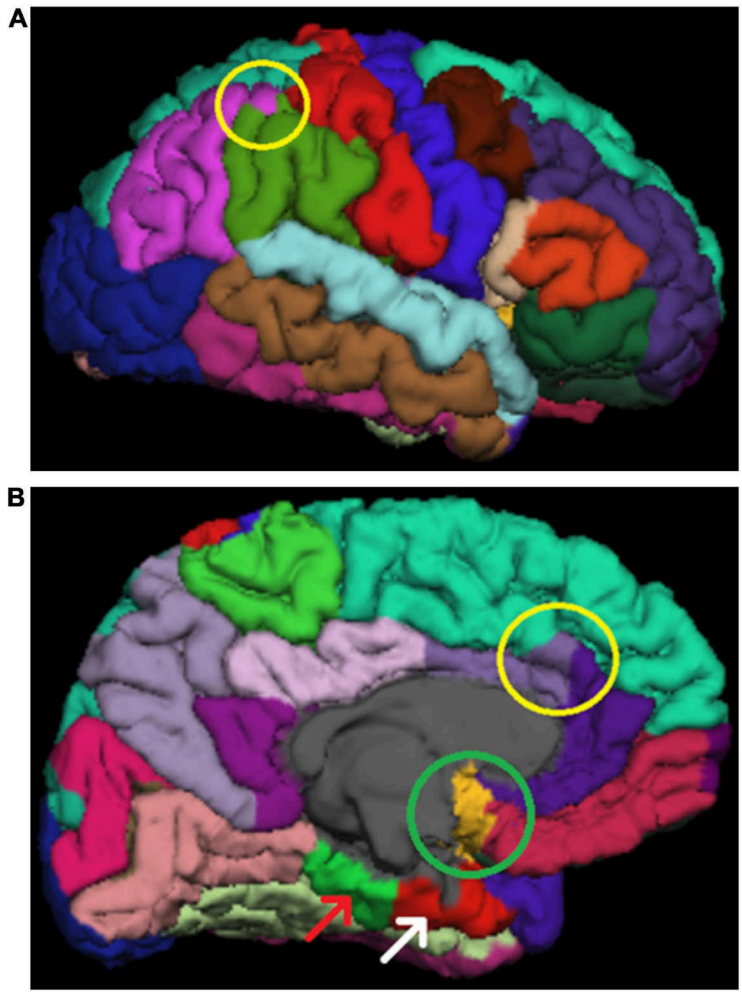

Figure 9. (A) Shows an error (yellow circle) in which the inferior parietal region (purple) cuts through a whole gyrus in the supramarginal region (green). This region has a lot of variation and only clear errors led to exclusion in our ENIGMA quality control protocol. (B) Shows insula overestimation in the midline (green circle). Furthermore, poor image quality can be seen the areas adjacent to the base of the skull, such as the parahippocampal (green region denoted by a red arrow) and entorhinal (red region denoted be a white arrow) cortices. Additionally, there is an error in the border between the superior frontal gyrus and the caudal anterior cingulate. This border should follow the sulcal line. The rostral anterior cingulate was not considered erroneous in these cases. Reprinted from Pulli et al. (2022) with the permission of the copyright holders.

The pericalcarine region was accepted when the segmentation was confined to the calcarine sulcus as instructed. Therefore, we excluded cases in which the pericalcarine region extended over a whole gyrus into the lingual gyrus or the cuneus.

Cases of superior parietal overestimation, as well as errors in the banks of the superior temporal sulcus, were excluded as instructed. Both errors were rare in our sample.

The border between the middle and inferior temporal gyri was not assessed, as the instructions suggested that most irregularities seen there are normal variants or relate to the viewing angle. Similarly, we did not quality check the entorhinal and parahippocampal regions in the external view.

4.5.1.7 The Internal View in ENIGMA

In the internal view, regions with unsegmented GM were excluded. These errors often reflect WM hypointensities seen in Freeview.

Temporal pole underestimations were sometimes seen. However, the cases were rarely as clear as presented in the instructions. Therefore, we had to use both coronal and axial views to assess the situation and make exclusions when both views supported an error in segmentation.

One of the errors commonly seen in our sample was an erroneous pial surface delineation in the lateral parts of the brain. This was particularly prevalent in the middle temporal gyri. Notably, it is possible to attempt to fix these types of topological errors by, for example, using control points or brainmask edits. Some previous studies (e.g., M. C. Ross et al., 2021) have done this. They reported an average editing time of 9.5 hours, approximately quadruple our editing time, and concluded that their edits did not affect their conclusions. Therefore, this type of edit was omitted as too time-consuming and challenging compared to the expected effect on the results. The ROIs affected by these errors were excluded from the analyses. This error was assessed from 2D slices, wherein what seems to be an error may be caused by partial volume effects. Consequently, we only made exclusions when clear errors were seen in two adjacent slices. A particularly clear example of this can be seen in Figure 10, where the WM extends outside the segmentation.

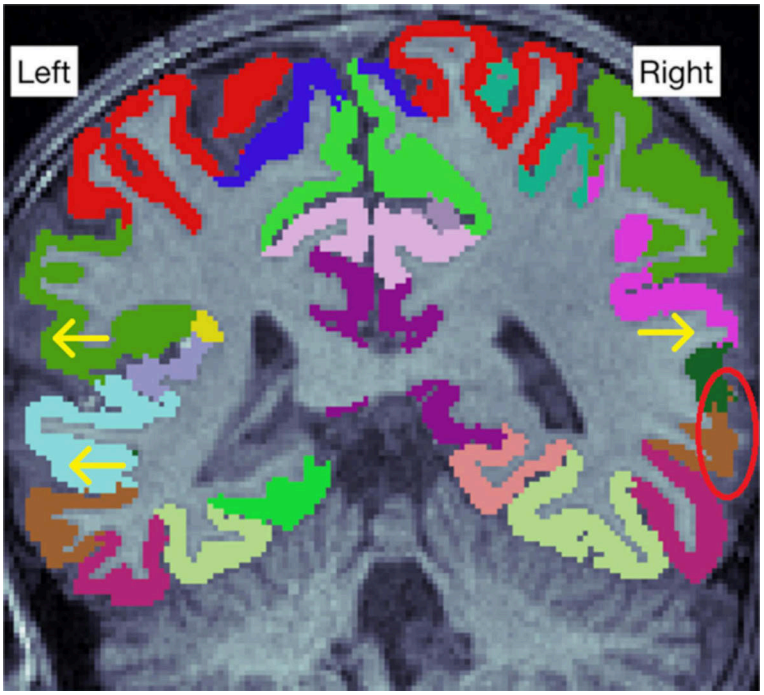

Figure 10. There are some visible errors in the lateral parts of the image (arrows). An especially clear error is denoted by the red circle, where some white matter is seen outside the cortical segmentation. Reprinted from Pulli et al. (2022) with the permission of the copyright holders.

4.5.1.8 Statistical Outliers in ENIGMA

After the systematic viewing of all the problem regions, we inspected the statistical outliers, as recommended in the ENIGMA quality control protocol. This rarely led to new exclusions, as many of the statistical outliers were among the excluded subjects or the outliers were ROIs in which the instructions did not give any tools to assess whether they were correct. Therefore, we simply had to double check the internal view to rule out segmentation errors.

4.5.2 Study II

The neuroimaging data was preprocessed, manually edited, and quality checked as described above. However, in Study II, instead of analyzing each ROI specifically, we were interested in the gross cortical anatomy, and we divided the brain into the following ROIs: total cortical volume, left and right hemispheres separately, and lobe division bilaterally into the four main lobes (frontal, temporal, parietal, and occipital). We included all the MRI data that passed the FinnBrain quality control

protocol (on a whole brain pass/fail scale). We confirmed that typical errors in borders and cortical labeling were located inside the main lobes instead of in the areas between lobes or between hemispheres. The ROI selection was justified by the notion that prior work (Jha et al., 2019) reported associations that reflected gross anatomy in the main results. In addition, ROI analyses based on Desikan–Killiany atlas labels present multiple comparison issues, and we decided to not pursue such analyses.

4.5.3 Study III

The neuroimaging data was preprocessed, manually edited, and quality checked as described above. Additionally, we pre-smoothed fsaverage surfaces, as instructed in the FreeSurfer manual for vertex-wise statistical analyses (described in more detail in Statistical analyses).

4.5.4 Study IV

The automatic segmentation with FreeSurfer was done as described above. The volumes were extracted using the 'asegstats2table' command.

4.5.4.1 Automated Segmentation Using FSL-FIRST

The automated segmentation of the subcortical structures was performed using FSL-FIRST 5.0.9 (Patenaude et al., 2011), a freely available automated segmentation tool provided by the FMRIB Software Library (FSL). FSL-FIRST uses a training data-based approach combined with a Bayesian probabilistic model to determine the most probable shape of the structure given the intensities of the T1 image. FSL-FIRST makes use of the adult MNI152 template space (MNI = Montreal Neurological Institute), but the segmentation model has been trained using a large set of manually labeled T1-weighted MR images from children and adults (Patenaude et al., 2011). For more technical details, see Patenaude et al. (2011). We segmented the T1-weighted images using FSL-FIRST with three different boundary correction settings. The *FSL Default* method uses different options based on empirical observations for each different structure. The *FSL Fast* option uses an FSL-FAST-based tissue-type classification to determine the final shape of the model. The *FSL None* method uses no boundary correction settings. After running the pipelines, a voxel count was performed to estimate the volumes produced by each different method.

4.5.4.2 Manual Segmentation

Manual segmentation was done by editing the output from *FSL None*, because this required the least amount of manual editing (based on visual assessment). The subcortical structures were segmented by a single expert rater (Kristian Lidauer) using the software FslView (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FslView). The rater was experienced in manual segmentation of infant brain MR images and templates (Acosta et al., 2020; Hashempour et al., 2019) across a period of two years before starting Study IV (2018–2020).

The use of initial estimates from FSL-FIRST significantly reduced the working time compared with full manual segmentation, as the main task left for the investigators was correcting the borders. This process was guided by prior work on striatal structures (Perlaki et al., 2017) and the thalamus (Owens-Walton et al., 2019; Power et al., 2015), as well as the amygdala and the hippocampus (Hashempour et al., 2019).

The edits were documented for 40 randomly chosen subjects from the total of 80, to highlight important areas for quality control. The anatomical delineations that we incorporated are in line with prior work (de Macedo Rodrigues et al., 2015). Manual edits were performed in a slice-by-slice manner to carefully trace the correct anatomical border, and reviewed in axial, coronal, and sagittal planes for 3D consistency of the segmentations. Finally, all segmentations were checked for accuracy by senior a scientist (Jetro J. Tuulari). The accuracy check was performed using fsleyes, and it entailed: 1) selection of a reference segmentation with all structures accurately delineated, 2) opening three segmentations at a time and comparing them against the reference segmentation, and 3) checking bilateral structures from each one by browsing the structure in all 3D planes and checking the borders with intermittent opening and closing of the overlay to check the consistency of the borders. This process took about 15 minutes per three segmentations (approximately 7 hours in the final round of quality control).

To assess any bias that might occur with FSL-FIRST-based initial estimates, we re-segmented 20 randomly chosen subjects using automated FreeSurfer segmentations as the base for manual delineation. We also re-segmented 10 randomly chosen subjects (using *FSL None* initial estimates) to assess intra-rater accuracy.

A voxel count was then concluded using fslmaths to estimate the volumes of the manually segmented structures.

4.6 Cognitive Assessment – Study III

4.6.1 Neuropsychological Study Visits

The neuropsychological study visits for 5-year-old children included neurocognitive testing, eye-movement tracking, mother–child interaction assessment, and questionnaires filled out by the parents. Neurocognitive testing included assessments of the child's general cognitive ability (WPPSI-III subtests Block Design, Matrix Reasoning, and Similarities), executive functioning, and self-regulation, of which only the non-verbal tasks from the general cognitive ability assessments were used in Study III.

In the pilot study, another verbal WPPSI-III subscale (Information) was collected, but the study visit was too long for the children. Subsequently, Information was left out. As at least two subscales are required to reliably estimate verbal ability, Study III focused solely on non-verbal ability based on the available data.

The approximately two-hour-long study visits were conducted and video recorded by graduate students in quiet examination rooms, and the data collection was overseen by PhD students/psychologists. The graduate students were trained by PhD students/psychologists prior to data collection, to ensure unified test administration among all students, and to ensure that the students had sufficient interaction skills to scaffold the children's motivation and mood during the study visit. Written informed consent was provided by the parents prior to the study visit, and after the study visit, the parents received feedback on the child's performance on some of the assessment methods.

4.6.2 Assessment of Non-verbal Ability

Non-verbal ability was assessed using the Finnish version of WPPSI-III, which is a standardized and widely used measure of cognitive ability in young children from ages 2 years and 6 months to 7 years and 3 months (Wechsler, 2009). A composite sum score of non-verbal ability (PIQ; mean 100) was estimated using two subtests: the Block Design task measuring visuospatial ability and the Matrix Reasoning task measuring visual abstract reasoning. The standardized scale scores corresponding to the raw scores of the subtests were based on Finnish norms and result in a mean of 10, reflecting standardized mean performance in the population at each age. Additionally, analyses of the subtests were conducted separately to get further information on the possible subtest driving the findings.

The PIQ scores were: mean = 104.7, SD = 15.4, range 68–146. Block Design scores: mean = 10.5, SD = 3.3, range 3–19. Matrix Reasoning scores: mean = 10.8, SD = 2.8, range 1–18. These results suggest a normally distributed cognitive ability

in the sample of the present study. The Pearson correlation between PIQ and Block Design was 0.809 ($p < 0.001$); between PIQ and Matrix Reasoning it was 0.711 ($p < 0.001$); and between Block Design and Matrix Reasoning it was 0.164 ($p = 0.039$).

4.7 Statistical Analyses

4.7.1 Study II

Statistical analyses were conducted using IBM SPSS Statistics 27.0 (IBM Corp., Armonk, NY, USA). Neuroimaging data was confirmed to be normally distributed using JASP Statistics 0.14.1 (https://jasp-stats.org/), based on visual assessment, skewness, kurtosis, and Shapiro–Wilk p-values. Correlation matrices with Pearson correlation were created for cortical volumes and SAs with JASP Statistics. Lateralization calculations for hemispheres and lobes were carried out using JASP statistics for descriptive purposes. Lateralization indices were also confirmed to be normally distributed based on the same criteria as the initial neuroimaging data.

A total of 170 subjects' MR images passed the inclusion criteria and the FinnBrain quality control protocol (Pulli et al., 2022) and were selected for the statistical analyses. Brain variables included cortical volumes and SA for the following regions: total cortex, both cortical hemispheres, and the four main lobes bilaterally. The refence article by Jha et al. (2019) was set as a basis for selecting the variables, resulting in 16 demographic variables. Categorcial variables included: sex, neonatal intensive care unit (NICU) admission, mode of delivery, maternal and paternal education level, maternal smoking during pregnancy, diagnosis of gestational diabetes during gestation, and the use of SSRI or serotonin–norepinephrine reuptake inhibitor (SNRI) medication during pregnancy. Continuous variables included: birth weight, gestational age at birth, postnatal age at MRI, ponderal index at MRI, maternal age at child's birth, paternal age at child's birth, maternal BMI before gestation, and 5 min Apgar score. The following variables were considered too unreliable or otherwise suboptimal in our questionnaire data, and were excluded: maternal and paternal psychiatric history, household income, gestation number, and number of siblings.

Linear regression models were carried out using each brain variable separately as a dependent variable and the group of 16 demographics as independent variables. Stepwise linear regression models were applied. Raw p-values are reported due to the exploratory nature of Study II. The Bonferroni corrected p-value at alpha level 0.05 over the 22 comparisons over the 11 regression models × 2 brain measures (SA, volumes) was $p < 0.002$.

4.7.2 Study III

Statistical analyses concerning demographics and ROIs were conducted using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Scatter plots and the related statistics were created using JASP version 0.16.1.0 (JASP Team, 2022). Statistical significance in all analyses was calculated two-tailed at alpha level 0.05.

4.7.2.1 Vertex-wise Analyses

For the purposes of Study III, we pre-smoothed fsaverage surfaces, as instructed in the FreeSurfer manual, for analyses with Query, Design, Estimate, Contrast (Qdec), which is a single-binary application included in the FreeSurfer software suite (www.surfer.nmr.mgh.harvard.edu). Qdec is a graphical user interface for a statistics engine running a vertex-by-vertex general linear model. For display purposes, we used the standard FreeSurfer's fsaverage in MNI305 space (MNI = Montreal Neurological Institute). We tested for clusters with statistically significant associations between non-verbal ability and cortical GM volume, SA, and CT. The data was smoothed with a kernel of 10 mm full width at half maximum. A Monte Carlo Null-Z Simulation was run with a z-value threshold of 1.3, corresponding to $p = 0.05$ (Hagler et al., 2006). After the simulation, a z-value threshold of 1.3 was used for statistically significant clusters. For confounding factors and performed sensitivity analyses, please see "Confounders." Age at scan was squared for the purposes of running Qdec. In the sensitivity analyses, we added the potential confounders to the model one at a time (continuous factors) or excluded the exposed group from the analysis (categorical factors).

4.7.2.2 Region of Interest-based Analyses

Additionally, we calculated partial correlations (controlling for participant sex, maternal education level, maternal age at term, participant ponderal index at scan, and participant age at scan) between 1) all cognitive measurements (PIQ, Block Design, and Matrix Reasoning), and 2) a multitude of brain metrics, including volume, SA, and CT in all 68 ROIs in the Desikan–Killiany atlas (Desikan et al., 2006), as well as total SA (separately for both hemispheres), mean CT (separately for both hemispheres), brain volume (excluding ventricles), and estimated total intracranial volume; in total, 210 brain metrics per cognitive measurement. We excluded poor-quality ROIs from this analysis, as described in our earlier work (Pulli et al., 2022). For this part of the analysis, we corrected for multiple comparisons using the Benjamini–Hochberg procedure (Benjamini & Hochberg, 1995) across all 630 comparisons. Adjusted p-values < 0.05 were considered significant.

4.7.3 Study IV

All statistical analyses and plotting of the results were performed using R tools v.4.0 (R Core Team, 2022) and R-Studio 1.3 (https://rstudio.com/). For the plots and following analyses, we used irr, ggplot2, gridExtra, grid, and gtable libraries.

The volumetric difference between automated segmentation and manual segmentation was calculated as a percentage using the following equation (Schoemaker et al., 2016): $\%VD = [(V_a - V_m)/V_m] \times 100\%$, where V_a is the automatically segmented volume and V_m is the manually segmented volume. A negative result indicates that the automated method underestimated the volume, whereas a positive value shows that the automated method overestimated the volume.

Pearson correlations were calculated to measure the strength of the association between manual segmentation and the different automated techniques for each individual structure. A strong correlation would indicate good consistency between methods. To estimate reproducibility between different techniques and estimation bias, we computed intraclass correlation coefficients (ICC). We used a two-way mixed effect model with absolute agreement and average measures (ICC Type A, k), as specified by McGraw and Wong (1996), which is a model not defined in the commonly used Shrout and Fleiss (1979) convention. A high value would confirm good reproducibility between two raters. There are no fixed guidelines on how to interpret ICC values, but in previous studies, a coefficient of 0.70 has been considered as the minimum for establishing adequate reliability between two raters (Terwee et al., 2007).

To determine the spatial overlap of the structures, we conducted Dice score coefficient (DSC) analysis between manual and automated segmentation methods. The value of DSC ranges from 0, indicating no spatial overlap between structures, to 1, indicating complete overlap (K. H. Zou et al., 2004).

The same correlations and DSC were also calculated for comparison between manual segmentation based on either *FSL None* or FreeSurfer and automated segmentation, and between intra-rater segmentations.

To assess the adequacy of the sample size, we performed a split-half analysis, in which we divided the whole sample ($n = 80$) into two randomly selected subsamples ($n = 40$). Then, we compared the volumetric differences and correlations of these subsamples to each other.

5 Results

5.1 Study I: Effects of Prenatal Exposures on the Developing Brain

In the literature review, we summarized the neuroimaging correlates of multiple prenatal exposures, including alcohol (Donald, Fouche, et al., 2016), tobacco (L. Chang et al., 2016), illicit drugs (L. Chang et al., 2016; Grewen et al., 2014; A. P. Salzwedel et al., 2016), certain pharmaceuticals (Monnelly et al., 2018; Spann et al., 2015), depressive symptoms (Qiu et al., 2017; C. Wang et al., 2018), SSRIs (Jha et al., 2016), anxiety symptoms (Qiu et al., 2013, 2014), maternal obesity (X. Li et al., 2016; Ou et al., 2015), maternal inflammation (A. M. Graham et al., 2018), SES (Betancourt et al., 2016; Jha et al., 2019), and other demographic characteristics (Jha et al., 2019; Knickmeyer et al., 2017).

Furthermore, we examined how prenatal factors (and key infant characteristics) were reported in a set of 67 studies on typically developing term infants under 2 years of age. Studies in which individual development was not the main research question were excluded, as the reporting in them differs significantly from studies on brain development. The excluded articles include, for example, methodological articles, where participant sex was reported in only 29/62 (47%), and age at birth as mean and SD and/or as range in only 13/62 (21%) of the studies. The reporting of background information in the identified studies is summarized in Table 3.

Table 3. Reporting of maternal and infantile characteristics in the studies included in the population description analysis.

CHARACTERISTIC	N	DESCRIPTION
Infant sex	63	Reported
	4	Not reported
Age at scan	15	Gestational, postmenstrual, or corrected
	34	Days after birth/chronological or not specified
	9	Both above
	9	Vague
Ga at birth	12	Mean and SD
	19	Exact range or at least one border stated
	31	Both above
	5	Vague or not stated
Birth weight	18	Mean and SD
	16	Limited (either range, lower border, or weight “appropriate for GA”)
	19	Both above
	14	Not reported
Prenatal alcohol	7	Amount of alcohol users/use reported in some way
	9	Used as a reason for exclusion
	5	Implied as a reason for exclusion
	46	Not reported
Prenatal smoking	11	Amount of smoking/smokers reported in some way
	5	Used as a reason for exclusion
	6	Implied as a reason for exclusion
	45	Not reported
Illicit drugs	5	Amount of users/use reported in some way
	16	Used as a reason for exclusion
	4	Implied as a reason for exclusion
	42	Not reported
Medications	4	Used maternal medications reported in some way
	12	Some maternal medications used as reasons for exclusion
	2	Both above
	49	Not reported
Maternal disease	5	Psychiatric and/or neurological conditions generally reasons for exclusion
	9	Medical conditions generally reasons for exclusion
	10	Both above

CHARACTERISTIC	N	DESCRIPTION
	23	Certain maternal diseases reported as number of patients or excluded
	20	Not reported
Ses	37	Reported in some form
	30	Not reported
Ses measures	11	Maternal years of education
	16	Maternal education level or highest degree
	4	Paternal years of education
	1	Paternal education level or highest degree
	19	Household income
	2	Maternal income
	7	Hollingshead's Index of Social Status
	4	Maternal IQ
	3	Class
	2	Marital status
	1	Scottish Index of Multiple Deprivation
	1	Home literacy questionnaire
Race/ethnicity	5	Both race and ethnicity
	30	Race or ethnicity
	32	Not reported
Maternal age	16	Mean and SD
	7	Limited
	7	Both above
	37	Not reported
Maternal weight	4	BMI or weight, and other measure (fat%, weight gain during pregnancy)
	4	Only BMI or weight
	1	Only “other measure”
	58	Not reported

Table 3 footnote | Abbreviations: N = number of studies; SD = standard deviation; GA = gestational age; SES = socioeconomic status; IQ = intelligence quotient; BMI = body mass index. The category “SES measures” allows one article to fit multiple descriptions, as it describes all the metrics used to assess SES or a characteristic approximating it. All other characteristics were categorized such that every article only fits one description. The Scottish Index of Multiple Deprivation is an official government index used to identify areas of deprivation. Modified from Study I with the permission of the copyright holders.

5.2 Studies II–IV: Findings from the FinnBrain Birth Cohort Study

Studies II, III, and IV included the FinnBrain 5-year-old structural neuroimaging sample, with only minor differences in the included participants (e.g., based on the availability of non-neuroimaging data). The descriptive statistics regarding the samples are presented in the original publications.

5.2.1 Cortical Findings

In Study II, cortical metrics were assessed using lobar (frontal, parietal, temporal, and occipital, for both hemispheres separately) and global (total brain, right, and left hemisphere volume and SA) metrics. In Study III, cortical development was assessed with a vertex-wise approach using Qdec, which is not limited to predefined ROIs. These are complementary approaches to the study of cortical structural brain development.

5.2.1.1 Volume

In Study II, occipital lobe volume (bilaterally) had a relatively weak correlation with total brain volume (left 0.61 and right 0.633) compared to all other volumes (e.g., left and right frontal lobe 0.932 and 0.912, respectively), suggesting that the occipital lobe (where the most significant findings in Study III were located) develops relatively independently of the rest of the cerebral cortex. A full correlation matrix in presented in original publication II. Although some lobes developed relatively independently from the brain as whole, the left and right counterparts had high correlations (ranging from 0.83 in the temporal lobe to 0.944 in the frontal lobe). The temporal lobe had bigger volumes on the left, and all other lobes had bigger volumes on the right (effect relatively small).

Predictors for cortical volume at 5 years of age included sex (larger volumes in males), maternal education level (larger volumes in children of highly educated mothers), and maternal age at birth (positive association). Predictors of cortical volumes for different cortical regions are presented in Table 4. Only sex survived correction for multiple comparisons (except it did not survive correction for multiple comparisons in bilateral temporal lobes). Notably, only sex predicted occipital lobe volumes.

Table 4. Predictors of 5-year-old cortical volumes. Standardized coefficients (β) reported for statistically significant results.

PREDICTOR	SEX	MATERNAL EDUCATION	MATERNAL AGE
Total brain	0.369	0.212	ns
L-hemisphere	0.367	0.222	ns
R-hemisphere	0.385	ns	0.217
L-frontal	0.419	0.197	ns
R-frontal	0.396	ns	ns
L-parietal	0.294	0.217	ns
R-parietal	0.307	0.215	0.250
L-temporal	0.192	0.226	ns
R-temporal	0.252	0.236	ns
L-occipital	0.258	ns	ns
R-occipital	0.230	ns	ns

Table 4 footnote | Abbreviations: L = left, R = right, ns = not significant ($p > 0.05$). In sex, a positive value indicates larger volume in males. Table 4 is original content made by the author for this thesis.

In Study III, PIQ was positively associated with cortical volume in the left caudal middle frontal (peak z-value = 1.67, size = 950.9 mm^2) and right medial occipital (peak z-value = 4.00, size = 1639.8 mm^2) regions. Clusters are shown in Figure 11. For subtask-specific results, see original publication III.

Finally, in Study III, smaller cortical ROIs (according to the Desikan–Killiany atlas) were explored. The correlations between ROI-based cortical volumes and non-verbal cognitive ability measurements were estimated (controlling for the same variables as in the vertex-wise analyses). There were no results that survived a correction for multiple comparisons (results not shown).

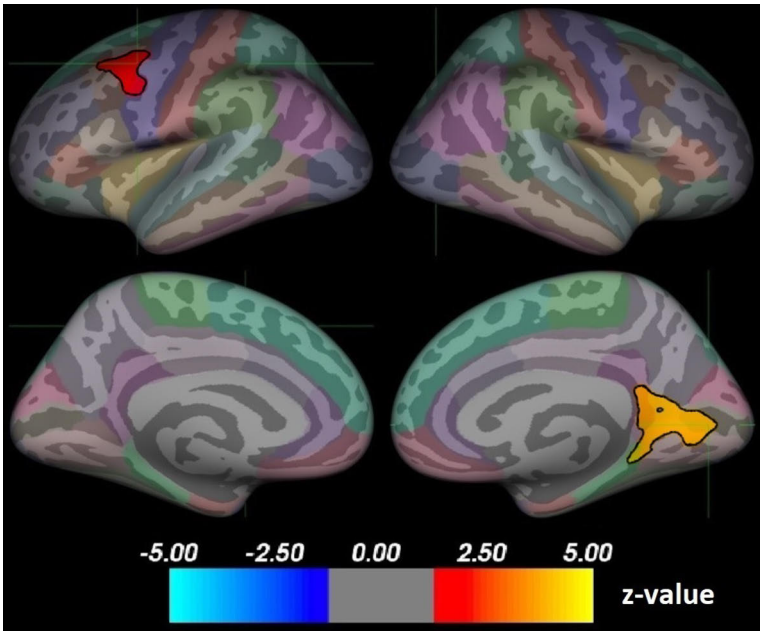

Figure 11. Associations between performance intelligence quotient (PIQ) and cortical gray matter volume. Results corrected for multiple comparisons using Monte-Carlo Null-Z simulation. The position of the green crosshair indicates the most statistically significant vertex in statistically significant clusters. The left hemisphere is on the left and the right on the right side. Color coding of regions according to the Desikan–Killiany atlas. Modified from Study III with the permission of the copyright holders.

5.2.1.2 Surface Area

In Study II, total SA had a strong correlation with frontal lobe SA (0.940 left, 0.921 right), a moderately strong correlation with temporal lobe SA (0.874 left, 0.886 right), and a relatively weak correlation with occipital lobe SA (0.649 left, 0.659 right). Highlighted regions were based on those that had findings in Study III. These results suggest that, just as with volume, the occipital lobe develops relatively independently from the rest of the cerebral cortex. A full correlation matrix is presented in original publication II. Although some lobes developed relatively independently from the brain as whole, the left and right counterparts had high correlations (ranging from 0.870 in the occipital lobe to 0.937 in the frontal lobe). The temporal lobe had bigger volumes on the left, and all other lobes had bigger volumes on the right (effect relatively small).

Predictors for cortical SA included sex (larger in males), NICU admission (larger SA in those with NICU admission), maternal smoking during pregnancy (smaller SA in those with tobacco exposure), maternal BMI before pregnancy (positive association), and 5 minutes Apgar score (negative association). Predictors of cortical SA for different cortical regions are presented in Table 5. Only sex survived

correction for multiple comparisons (except it did not survive correction for multiple comparisons in bilateral occipital lobes).

Table 5. Predictors of 5-year-old cortical surface areas. Standardized coefficients (β) reported for statistically significant results.

PREDICTOR	SEX	NICU ADMISSION	MATERNAL SMOKING	MATERNAL BMI	5 MINUTES APGAR
Total Brain	0.463	0.175	ns	ns	ns
L-Hemisphere	0.454	0.174	ns	ns	ns
R-Hemisphere	0.473	0.205	-0.179	ns	ns
L-Frontal	0.454	ns	ns	ns	ns
R-Frontal	0.418	ns	ns	ns	ns
L-Parietal	0.408	0.232	-0.186	ns	ns
R-Parietal	0.448	ns	-0.247	0.157	-0.229
L-Temporal	0.380	ns	ns	ns	ns
R-Temporal	0.450	ns	-0.182	ns	ns
L-Occipital	0.327	ns	ns	ns	ns
R-Occipital	0.349	ns	ns	ns	ns

Table 5 footnote | Abbreviations: L = left, R = right, NICU = neonatal intensive care unit, BMI = body mass index, ns = not significant ($p > 0.05$). Maternal smoking means smoking during pregnancy. BMI is pre-pregnancy. In sex, a positive value indicates larger volume in males. Table 5 is original content made by the author for this thesis.

In Study III, PIQ was positively associated with SA in the left caudal middle frontal (peak z-value = 2.05, size = 870.7 mm^2), left inferior temporal (peak z-value = 1.37, size = 692.4 mm^2), and right medial occipital (peak z-value = 3.70, size = 1239.1 mm^2) regions. These clusters are shown in Figure 12. The subtask results are presented in original publication III. Apart from the cluster in the left inferior temporal region, the results were similar to those seen in volume analyses.

Finally, in Study III, smaller cortical ROIs (according to the Desikan–Killiany atlas) were explored. The correlations between ROI-based cortical SA and non-verbal cognitive ability measurements were estimated (controlling for the same variables as in the vertex-wise analyses). There were no results that survived a correction for multiple comparisons (results not shown).

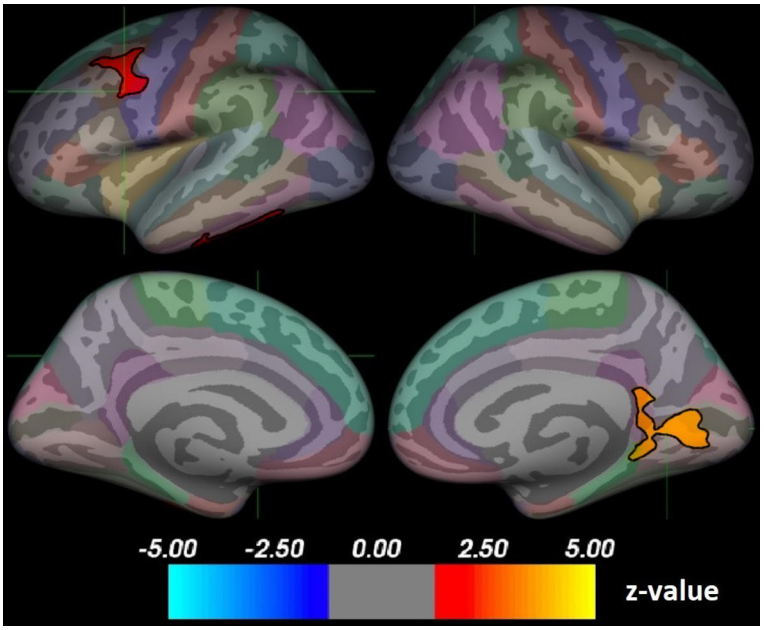

Figure 12. Associations between performance intelligence quotient (PIQ) and cortical surface area (SA). Results corrected for multiple comparisons using Monte-Carlo Null-Z simulation. The position of the green crosshair indicates the most statistically significant vertex in statistically significant clusters. The left hemisphere is on the left and the right on the right side. Color coding of regions according to the Desikan–Killiany atlas. Modified from Study III with the permission of the copyright holders.

5.2.1.3 Cortical Thickness

CT was only examined in Study III. There were no associations between PIQ and CT. Associations were only found in the Block Design subtask. Positive correlations were observed in the left precentral and the right postcentral gyri. The results are presented in original publication III.

Partial correlations between CT from bilateral Desikan–Killiany ROIs and measurements of non-verbal cognitive ability were measured (controlling for the same variables as in the vertex-wise analyses). There were no results that survived a correction for multiple comparisons (results not shown).

5.2.1.4 Study III Sensitivity Analyses

In sensitivity analyses, one additional variable at a time was added to the analysis to explore potential confounding effects. The results from Study II were used to select these variables: maternal pre-pregnancy BMI, 5 minutes Apgar score, prenatal tobacco exposure, and NICU admission were found to be significant predictors of cortical volume or SA in Study II. Additionally, we explored the effects of

gestational age at birth, prenatal alcohol exposure, and pregnancy complications (based on previous studies). There were no large differences to the basic statistical model (results not shown).

5.2.1.5 Study III *Post Hoc* Analyses

Based on a visual assessment of the results after the Monte Carlo simulation, it seemed that the positive association between volume/SA and the medial occipital region may have been driven by the Matrix Reasoning subtask (see original publication III). To further explore this, we visually compared the regions before the Monte Carlo simulation (Figure 13), which revealed similar clusters in PIQ and Matrix Reasoning analyses, but totally different results in Block Design analyses, supporting the idea that the Matrix Reasoning task drove the observed effect.

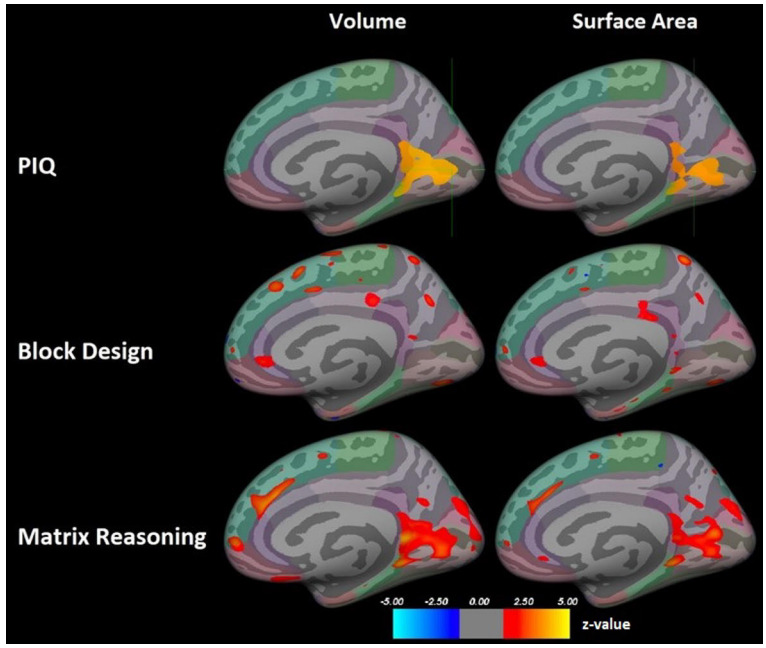

Figure 13. An exploratory analysis showing correlations between performance intelligence quotient (PIQ) and volume (left) as well as surface area (SA; right) in the medial occipital region of the right hemisphere (top row). The PIQ results are from Figures 12 and 13 and have been corrected for multiple comparisons using the Monte Carlo simulation. The bottom two rows show the same region for the two subtests without correction for multiple comparisons. In both volume and SA, the results seem to be driven by the Matrix Reasoning subtest. The z-value threshold for all images is 1.3. Color coding of regions according to the Desikan–Killiany atlas. Modified from Study III with the permission of the copyright holders.

5.2.2 Subcortical Findings

Unlike with cortical analyses, subcortical metrics were not examined in relation to non-neuroimaging measurements. Instead, the goal of Study IV was to assess the accuracy of two common automatic segmentation tools against manually corrected segmentations.

5.2.2.1 Volumetric Differences

FSL None produced generally the highest values among the FSL-FIRST pipelines. Some FSL-FIRST pipelines produced the exact same results in some structures due to the utilization of the same boundary correction options. FreeSurfer produced higher values than any of the FSL-FIRST pipelines for the amygdala, putamen, and globus pallidus (GP). Compared to manual segmentation, most structures were overestimated by all pipelines. Exceptions were the caudate nucleus by FreeSurfer, *FSL Default*, and *FSL Fast*, as well as the putamen, GP, and thalamus by *FSL Fast* (all bilaterally). All volumetric segmentation results can be seen in Table 6.

Table 6. Comparison of mean (standard deviation) volumes and percentage of volume difference between manual segmentation and the pipeline.

STRUCTURE	MANUAL	FSL DEFAULT	FSL FAST	FSL NONE	FREESURFER
Volume (SD)					
L-hippocampus	3109.89 (444.14)	3412.41 (441.28)	3412.41 (441.28)	4244.95 (575.67)	4076.74 (384.19)
R-hippocampus	3150.08 (425.61)	3551.45 (415.35)	3551.45 (415.35)	4434.70 (531.64)	4189.92 (393.52)
L-amygdala	892.89 (169.80)	1096.85 (203.91)	1096.85 (203.91)	1377.63 (232.26)	1540.28 (214.03)
R-amygdala	845.36 (174.28)	1053.94 (194.49)	1053.94 (194.49)	1306.54 (228.94)	1734.00 (193.02)
L-thalamus	7354.33 (723.20)	8194.63 (665.97)	6713.21 (547.86)	8194.63 (665.97)	7751.61 (565.98)
R-thalamus	7274.78 (691.27)	8053.54 (653.88)	6612.65 (528.49)	8053.54 (653.88)	7714.82 (577.31)
L-putamen	4899.50 (508.16)	5152.74 (509.74)	4695.56 (482.28)	5152.74 (509.74)	5178.54 (570.61)
R-putamen	4924.40 (530.36)	5250.24 (541.97)	4656.94 (501.47)	5250.24 (541.97)	5283.99 (580.31)
L-gp	1644.91 (159.43)	1775.01 (152.92)	1377.19 (150.87)	1775.01 (152.92)	2064.27 (241.91)
R-gp	1664.09 (171.18)	1780.10 (165.80)	1348.86 (153.55)	1780.10 (165.80)	1938.86 (188.74)
L-caudate	4018.88 (428.88)	3870.68 (441.35)	3870.68 (441.35)	5014.68 (577.25)	3931.77 (426.83)

STRUCTURE	MANUAL	FSL DEFAULT	FSL FAST	FSL NONE	FREESURFER
R-caudate	4222.35 (464.31)	4016.30 (511.14)	4016.30 (511.14)	5059.09 (643.09)	4052.67 (419.55)
L-accumbens	523.96 (100.67)	610.65 (128.79)	610.65 (128.79)	804.31 (136.64)	568.37 (114.45)
R-Accumbens	428.64 (86.09)	534.33 (96.44)	534.33 (96.44)	675.84 (117.69)	635.37 (97.09)
L-Cau+Acc	4542.85 (469.18)	4481.33 (497.87)	4481.33 (497.87)	5818.99 (641.97)	4500.13 (484.39)
R-Cau+Acc	4650.99 (480.17)	4550.63 (531.08)	4550.63 (531.08)	5734.93 (659.63)	4688.39 (472.09)
Combined Mean	3204.58	3453.78	3110.79	3794.57	3618.68
% volume difference (SD)					
L-hippocampus		13.61 (9.31)	13.61 (9.31)	41.15 (10.62)	37.10 (20.12)
R-hippocampus		13.45 (10.27)	13.45 (10.27)	41.58 (12.75)	34.55 (16.01)
L-amygdala		24.65 (21.68)	24.65 (21.68)	56.56 (23.88)	77.02 (34.11)
R-amygdala		27.02 (22.55)	27.02 (22.55)	57.75 (27.28)	112.00 (40.58)
L-thalamus		11.73 (5.75)	-8.49 (4.43)	11.73 (5.75)	5.96 (8.72)
R-thalamus		10.93 (4.85)	-8.90 (4.06)	10.93 (4.85)	6.52 (8.08)
L-putamen		5.24 (2.06)	-4.13 (2.38)	4.24 (2.06)	5.81 (6.76)
R-putamen		6.69 (2.45)	-5.39 (2.80)	6.69 (2.45)	7.49 (6.98)
L-gp		8.08 (3.89)	-16.28 (4.28)	8.08 (3.89)	26.00 (14.00)
R-gp		7.16 (4.38)	-18.92 (4.58)	7.16 (4.38)	17.17 (12.02)
L-caudate		-3.50 (7.15)	-3.50 (7.15)	25.14 (11.12)	-1.99 (6.12)
R-caudate		-4.89 (6.49)	-4.89 (6.49)	19.91 (9.84)	-3.72 (7.00)
L-accumbens		17.58 (18.59)	17.58 (18.59)	55.34 (20.97)	10.79 (24.05)
R-accumbens		26.13 (15.34)	26.13 (15.34)	60.02 (22.24)	52.08 (27.03)
L-cau+acc		-1.17 (7.26)	-1.17 (7.26)	28.44 (10.89)	-0.80 (6.06)
R-cau+acc		-2.12 (6.31)	-2.12 (6.31)	23.47 (9.47)	1.03 (6.60)
Combined mean		11.71	3.71	29.09	27.63

Table 6 footnote | The volumetric unit used is 1 voxel (= 1 mm^3). Abbreviations: SD = standard deviation; L = left; R = right; GP = globus pallidus, Cau+acc = combined volume of the caudate and nucleus accumbens; Combined mean = mean of all structures combined. Modified from Study IV with the permission of the copyright holders.

5.2.2.2 Volumetric Correlation Analysis

Pearson correlation coefficients (PCC) between manual segmentation and the different pipelines were satisfactory overall. The PCC ranges per pipeline were as follows: *FSL Default* from 0.61 in the left amygdala to 0.98 in the bilateral putamen, *FSL Fast* from 0.61 in the left amygdala to 0.97 in the left putamen, *FSL None* from 0.67 in the bilateral amygdala to 0.98 in the bilateral putamen, and FreeSurfer from 0.34 in the left amygdala to 0.84 in the right putamen and the left caudate. Combined means were 0.83 for *FSL Default*, 0.82 for *FSL Fast*, 0.82 for *FSL None*, and 0.60 for FreeSurfer. For all structures in all pipelines, $p < 0.001$. From these results, it can be observed that smaller structures such as the amygdala produced lower values than

other structures. In summary, all FSL-FIRST pipelines produced similar PCCs and higher than FreeSurfer, except in the bilateral caudate nucleus, where the results were similar between FSL-FIRST and FreeSurfer.

Additionally, we performed ICC (A, k) measurements to assess the agreement between different segmentation methods. Results were generally similar to those in PCC analyses, where FSL-FIRST performed better than FreeSurfer overall. In ICC (A, k) analyses, *FSL None* also performed worse than the other FSL pipelines. ICC (A, k) values for all structures and pipelines are presented in Table 7. PCC results for all regions and pipelines are presented in original publication IV.

Table 7. Comparison of intraclass correlation coefficient analysis between manual segmentation and automated segmentation pipelines

STRUCTURE	FSL DEFAULT	FSL FAST	FSL NONE	FREESURFER
ICC (A, K)				
L-hippocampus	0.75	0.75	0.34	0.20
R-hippocampus	0.68	0.68	0.28	0.23
L-amygdala	0.55	0.55	0.29	0.09
R-amygdala	0.58	0.58	0.31	0.07
L-thalamus	0.66	0.72	0.66	0.66
R-thalamus	0.69	0.70	0.69	0.66
L-putamen	0.93	0.95	0.93	0.84
R-putamen	0.90	0.92	0.90	0.82
L-GP	0.82	0.53	0.82	0.26
R-GP	0.85	0.46	0.85	0.39
L-caudate	0.85	0.85	0.37	0.90
R-caudate	0.89	0.89	0.53	0.85
L-accumbens	0.69	0.69	0.33	0.58
R-accumbens	0.65	0.65	0.31	0.27
L-CAU+ACC	0.87	0.87	0.31	0.91
R-CAU+ACC	0.91	0.91	0.43	0.90
Combined mean	0.75	0.71	0.54	0.49

Table 7 footnote | Intraclass correlation coefficients (ICC) (Type A, k) computed between manual and automatic segmentation volumes. Abbreviations: L = left; R = right; GP = globus pallidus, Cau+acc = combined volume of the caudate and nucleus accumbens; Combined mean = mean of all structures combined. Modified from Study IV with the permission of the copyright holders.

5.2.2.3 Dice Score Coefficient Analysis

DSC values between automated pipelines and manual segmentation were good overall. FSL-FIRST provided slightly higher scores overall than FreeSurfer for all structures. All automated pipelines produced relatively low scores for the smaller structures such as the amygdala and nucleus accumbens. The DSC ranges per pipeline were as follows: *FSL Default* from 0.73 in the bilateral amygdala to 0.98 in

the bilateral putamen and the left GP, *FSL Fast* from 0.73 in the bilateral amygdala to 0.95 in the bilateral putamen, *FSL None* from 0.71 in the right amygdala to 0.98 in the bilateral putamen and the left GP, and FreeSurfer from 0.60 in the right amygdala to 0.89 in the right thalamus. Combined mean DSC values for different automated methods were as follows: *FSL Default* 0.89, *FSL Fast* 0.87, *FSL None* 0.88, and FreeSurfer 0.77. For DSC values of all structures and pipelines, see original publication IV.

5.2.2.4 Intra-rater Bias Assessment

There were no significant differences in volumetric segmentations ($p > 0.05$ for all structures). The largest differences were observed in the hippocampus, amygdala, and nucleus accumbens. Correlations were strong across the board: combined mean PCC 0.87 (range from 0.63 in the left nucleus accumbens to 0.98 in the right putamen), ICC (A, k) 0.90 (range from 0.70 in the right hippocampus to 0.99 in the right putamen and the left GP), and DSC 0.93 (range from 0.82 in the left amygdala to 0.98 in the bilateral putamen and the left GP). For intra-rater results from all structures, see original publication IV.

5.2.2.5 Summary of Manual Segmentation

The hippocampus and the amygdala required the most edits. There were two common types of error in the hippocampus that required major manual corrections in most subjects: 1) The lateral anterior superior border was overestimated in 88% and 90% of the subjects in the left and right hippocampus, respectively; and 2) the inferior posterior area was too large in 75% and 80% of the subjects in the left and right hippocampus, respectively. The amygdala also required major edits in all participants. The lateral superior border was overestimated in all subjects, and the anterior side was underestimated in 83% and 38% of the subjects for the left and right amygdala, respectively. The lateral inferior edge was too large in 53% and 45% of the subjects for the left and right amygdala, respectively. For edits regarding the thalamus and the caudate, see original publication IV. Other structures rarely required edits, and even in those cases, the edits were typically minor.

Finally, we wanted to assess whether choosing *FSL None* as a basis for manual segmentation might have caused some bias towards FSL-FIRST rather than FreeSurfer. Segmentations based on FSL-FIRST and FreeSurfer were generally in good agreement, with volumetric differences of <15% in all structures except for the amygdala, where FreeSurfer resulted in 25.6% and 40.7% larger volumes for the left and right amygdala, respectively. PCC, ICC (A, k), and DSC values between FSL-FIRST and FreeSurfer-based segmentations were generally good, the lowest values

being in the bilateral amygdala and nucleus accumbens. Furthermore, we provide images of example segmentations so that the reader can visually assess the potential bias in segmentation (see original publication IV for detailed results and example images).

6 Discussion

6.1 The Role of Prenatal Exposures

In this work, we have shown that multiple different prenatal exposures can affect individual neurodevelopment, as well as cognitive, behavioral, and health outcomes. MRI is an excellent tool for exploring the possible biological mechanisms that predispose an individual to different outcomes in life.

While it is known that prenatal exposure to alcohol, tobacco, illicit drugs, and various maternal characteristics can affect neurodevelopment, Study I showed that these are rarely considered as potential confounders in neuroimaging studies. For example, prenatal exposures to alcohol, tobacco, and illicit drugs, as well as maternal age and weight status, were each reported in less than half of the studies identified in the review. Methodologically, prenatal alcohol, smoking, and illicit drug exposures are challenging, as the researchers often have to rely on self-report (especially in general population samples), which is unreliable. First, there is the possibility that the participant is lying about their substance use, which is an unfixable problem in all questionnaires. For example, in studies exploring illicit drug use during pregnancy, those using toxicological analysis show 7.4 times higher prevalence than questionnaire studies (based on a review of 70 studies; see Tavella et al., 2020). Second, there is recall bias, especially in questions assessing the extent of alcohol or drug use. At the other end of the spectrum of methodological difficulty, we have maternal age at birth (or term). If the mother's birthday is known, there is no ambiguity in measurement (except with how leap years are dealt with; nonetheless, the margin of error there is negligible). This information can often also be confirmed (or gathered) directly from clinical or register data. In our studies, for example, obstetric data were retrieved from the National Institute for Health and Welfare (www.thl.fi). Notably, some of the exposures (such as pesticide exposure) require toxicological measurements to be reliable, and that type of data cannot be expected to be available in all studies.

In Study II, we examined which prenatal exposures and child characteristics were associated with brain cortical volume and SA at 5 years of age. Significant predictors for SA were sex, NICU admission, prenatal tobacco exposure, maternal BMI, and 5 minutes Apgar scores. Significant predictors for cortical GM volume

were sex, maternal education level, and maternal age. These factors partially differed from those seen in infants (Jha et al., 2019). Both Study II and Jha et al. (2019) measured cortical SA. Jha et al. found birthweight, gestational age at birth, postnatal age at scan, and sex to predict total SA. Out of these, sex was the only one that was also identified in our study. Birthweight makes a lot of sense in the infant study, as soon after birth, birthweight is highly correlated with the body and head size of the participant (Jha et al. did not analyze head circumference separately), which is logically associated with larger SA. Variation within the normal range of birthweight is not expected to cause long-lasting effects on the brain. Postnatal age at scan is obviously relevant in developmental studies (e.g., a newborn brain and a 10-year-old brain are vastly different), but it was not a significant predictor in Study II (for either brain metric). At the age of 5 years, both cortical volume and SA are still increasing, but the rate of increase is not particularly fast (compared to the first year of life). In Study II, most participants were scanned within a 2-month age range, which makes the age differences so small that they may not be statistically significant anymore. In contrast, Jha et al. scanned infants between 6 and 144 days of postnatal life, a time period characterized by exceptionally fast brain growth (Knickmeyer et al., 2008). Gestational age at birth is a similar case, as longer gestation increases the postmenstrual or postconceptional age at scan, which makes a bigger difference in the first weeks of life compared to the effect at 5 years of age. Furthermore, in our sample, the mean gestational age at birth was 39.7 weeks, compared to 37.3 in Jha et al., which further decreases the role of (potentially long-lasting) adverse effects of preterm birth in our sample. If we include regional SA results from Jha et al., they also found maternal and paternal ethnicity to be significant predictors. However, the effects of ethnic background were not considered due to a very high level of ethnic homogeneity (sample 97% Finnish).

Outside SA, the comparisons between Study II and Jha et al. are more difficult, due to the different cortical brain metric (volume and CT, respectively), which may be responsible for some of the incongruencies. However, the common predictors of cortical structure at different ages are still worth discussing. In the study by Jha et al. (2019), significant predictors for global CT included age at scan (which was discussed earlier), maternal ethnicity (not tested in Study II), and paternal education, as well as gestational age at birth (discussed earlier). Paternal education is an interesting one, because the study found an association between maternal education and volume (both studies tested for educational level of both parents). Jha et al. performed sensitivity analyses switching paternal education for maternal education in regional CT models, and the results were largely similar. This was not particularly surprising, considering that maternal and paternal education level were highly correlated (Pearson $r = 0.70$). Jha et al. used a statistical approach that does not allow highly intercorrelated predictors in the model, which is most likely the reason why

maternal education was not a significant predictor (especially considering the sensitivity analyses), and hence our findings are mostly in agreement. Furthermore, the positive association between maternal education and cortical GM volume was in line with earlier studies linking higher SES to higher brain volumes at different stages of development (Betancourt et al., 2016; Hanson et al., 2011; Knickmeyer et al., 2017).

Finally, we found some significant predictors of brain volumes that were not identified by Jha et al. (2019), including NICU admission, 5 minutes Apgar score, maternal smoking, maternal pre-pregnancy BMI, and maternal age at childbirth. Notably, NICU admission was the only one that was significant for total SA, while the others were only significant for certain lobes (maternal age for volume, others for SA). Both NICU admission and Apgar score are thought to reflect issues immediately after birth. Therefore, it was surprising to see that the effects were in different directions. Apgar predicted smaller SA in the right parietal lobe, while NICU admission predicted larger SA in total brain and both hemispheres, but notably not in the right parietal lobe. The negative association could be region-specific, although it is unclear why smaller SA would only be seen in the right parietal lobe. An Apgar score of seven or lower has been associated with an increased risk of abnormal MRI findings in neonates admitted to NICU (Aoki et al., 2020), although none of them required treatment based on the findings, and the long-term significance is not clear. NICU admission marks a very heterogeneous group of participants, ranging from individuals needing treatment for life-threatening conditions to rather minor issues in early development. Notably, individuals with known neurological issues have been excluded from Study II, and the predictive value of NICU admission should not be based on conditions with severe, persisting effects (e.g., cerebral palsy). There is some evidence that individuals admitted to NICU are at a higher risk for adverse neurodevelopment, but most research is focused on specific conditions that often lead to NICU admission (Liebowitz et al., 2023). Lacking access to medical records, it is difficult to say why NICU admission predicted larger volumes in 5-year-olds. Similar to Apgar score, maternal pre-pregnancy BMI was also only associated with right parietal lobe SA, specifically (positive association). Obesity in infant studies has consistently shown attenuated GM (Na et al., 2021) and WM (Ou et al., 2015) development, while larger right parietal SA at 5 years of age indicates accelerated development. As prior literature on cortical structure in older children is lacking, and we did not collect behavioral measurements in Study II, it is difficult to say whether this could be a maladaptive acceleration of growth. For the same reasons, it is difficult to hypothesize why this effect might be limited to the right parietal region. One methodological limitation to consider is the relatively small sample size of 170, as opposed to 805 in Jha et al. (2019), meaning the effect could be more widespread, but insufficient statistical

power limited the findings to the right parietal lobe. Maternal tobacco smoking was associated with smaller SA in multiple lobes. Tobacco exposure did not affect brain structure in Jha et al., but it did in a similar infant study examining the effects of multiple parental and infant characteristics (Knickmeyer et al., 2017). Furthermore, our finding was in agreement with other research linking tobacco exposure to smaller SA in children (R. Zou et al., 2022). Finally, maternal age associated positively with right hemisphere and right parietal lobe volumes. This finding fits with the limited existing literature on the effects of maternal age. Shaw et al. (2012) observed an inverse U-shape relationship between maternal age and offspring cortical GM volume, where the highest GM volumes were seen at approximately 33 years of maternal age at birth. In Study II, the mean maternal age was 30.6 years, and therefore the positive association was not surprising.

The information from Study II was utilized when planning statistical analyses for Study III. In addition to basic child information (sex, age at scan, and ponderal index at scan), we decided to control for maternal education level and maternal age at term in all analyses. The other variables that were significant predictors have some limitations that led to them being considered only in sensitivity analyses (instead of as confounders in all analyses). First, NICU admission is a very heterogeneous group in terms of the severity of the reason for admission, which complicates interpretation of the results. Second, 5 minutes Apgar score had little variation, with almost all participants being in the normal range (2/173 scored below seven), meaning that the differences would not be considered clinically significant (Watterberg et al., 2015). Finally, prenatal tobacco exposure is rare in our general population sample (11/173, 6.4%), and hence our sample lacks statistical power in assessing the effects of tobacco exposure. Nevertheless, sensitivity analyses with relevant factors (such as NICU admission, 5 minutes Apgar, and prenatal tobacco exposure) are a consistent part of our statistical approach.

6.2 Methodological Issues in Structural Pediatric Neuroimaging

6.2.1 Surface-based Analyses

One of the key methodological difficulties in pediatric neuroimaging is the variation in preprocessing and segmentation techniques (Phan et al., 2018), due to a lack of a gold standard preprocessing pipeline. In our earlier work (Pulli et al., 2022), we explored the feasibility of using FreeSurfer for cortical surface-based analyses.

There is a limited number of previous studies focusing on the effects of manual edits (Beelen et al., 2020; McCarthy et al., 2015; M. C. Ross et al., 2021). The procedure in all of them roughly resembles the FreeSurfer instructions for manual

editing and quality control. In all these studies, the main conclusion (regarding manual editing) was that it did not significantly affect the results/conclusions, even if there were significant differences in the CT, SA, or volume values. Notably, most of these studies were done on adolescents (M. C. Ross et al., 2021) or adults (McCarthy et al., 2015; Waters et al., 2019). Older participants move less during the scan, leading to fewer errors in segmentation, which may explain some of the differences.

Nonetheless, we found manual edits necessary in our sample (Pulli et al., 2022). We found more significant results in the unedited than in the edited images (regarding sex differences or structural asymmetry). Some of this effect could be due to a decrease in statistical power following the ROI exclusions. However, this effect was also seen in regions with few exclusions, meaning it is not the only reason and suggesting that the lack of quality control may lead to some false positive findings. Furthermore, some results were only seen in quality-controlled images. Notably, these regions include the left inferior and middle temporal gyri, which are regions that were often excluded due to erroneous segmentation, suggesting that the lack of quality control could also lead to false negative findings in some cases. In conclusion, manual editing and quality control can affect the results of surface-based analyses (Pulli et al., 2022).

Quality control and possible manual editing are often not reported in great detail (Barnes-Davis et al., 2020; Boutzoukas et al., 2020; Kamson et al., 2016). This leads to two main issues: 1) there is no widely accepted way to assess errors in automated segmentation, and 2) other researchers have no knowledge of whether manual editing happened and how adequate image quality was assured, complicating the comparisons with prior studies. While a single original study such as Pulli et al. (2022) alone cannot create a commonly accepted way to perform editing and quality control, it can solve the second main issue, making the detailed protocol of the FinnBrain Neuroimaging Lab publicly available. This protocol was utilized in Studies II and III of this thesis.

6.2.2 Volumetric Analyses

In our previous work (Pulli et al., 2022), we attempted to use control points to correct certain errors in subcortical labeling. This was largely unsuccessful, and therefore we decided to assess the quality of FreeSurfer (and FSL-FIRST) subcortical labeling against the gold standard manual segmentation in Study IV.

In Study IV, we compared two automated segmentation tools, FSL-FIRST (with three different pipelines) and FreeSurfer, against manual segmentation in subcortical areas in typically developing 5-year-olds. In our results, *FSL Default* and *FSL Fast* pipelines performed more accurately overall than *FSL None* or FreeSurfer. In line

with previous studies, automated methods tended to overestimate volumes in most structures (Grimm et al., 2015; Hashempour et al., 2019; Nugent et al., 2013; Pipitone et al., 2014). The overestimation was most prominent overall with FreeSurfer and *FSL None*. Excluding the *FSL None* pipeline, FSL-FIRST produced generally better agreement across the structures than FreeSurfer, which was in contrast to previous studies, which found the opposite to be the case (Morey et al., 2009; Schoemaker et al., 2016). Inter-rater variability may explain some of these differences, as it is one of the key challenges with manual segmentation. The differences may be more pronounced in smaller and less visually distinct structures such as the amygdala. In these instances, the rater must, to an extent, rely on general anatomical knowledge instead of the intensities of the MR image to determine the exact shape of the structure. This is even more significant in pediatric MR images acquired during infancy, because the structural MR images have different contrast and comparatively lower resolution than adult images (Gousias et al., 2012).

Both the hippocampus and the amygdala were overestimated by all automated segmentation methods in Study IV. The most accurate were the *FSL Default* and *FSL Fast* pipelines with moderate overestimation, while *FSL None* and FreeSurfer overestimated both structures greatly. In line with previous studies, the hippocampus was segmented more accurately than the amygdala (Akudjedu et al., 2018; Doring et al., 2011; Pipitone et al., 2014; Schoemaker et al., 2016).

For the other subcortical structures, the thalamus was most accurately segmented by FreeSurfer, with only slight overestimation. The putamen was segmented more accurately than the GP by all methods in Study IV. FSL-FIRST results were very highly correlated with manual segmentation for both the putamen and GP, while with FreeSurfer, this was the case for the putamen but not for GP. The caudate nucleus was segmented accurately overall, whereas the nucleus accumbens was overestimated by all methods in Study IV.

In summary, FSL-FIRST can be used to segment subcortical nuclei reliably in pediatric samples. Hippocampal segmentation achieved acceptable reliability (ICC > 0.70), while amygdalar segmentation requires further effort. The segmentation of the amygdala can be improved using multi-template approaches (Acosta et al., 2020) or cutting-edge approaches relying on machine learning (Y. Wang et al., 2022).

6.3 Structural Correlates of Cognitive Ability

In Study III, we examined the associations between non-verbal ability and cortical brain structure (volume, SA, and CT) in a sample of typically developing 5-year-olds. We hypothesized, based on the P–FIT model, that non-verbal ability would be positively correlated with volume and SA in the frontal and parietal regions. In line with the hypothesis, we found that the volume and SA of the left caudal middle

frontal gyrus were positively associated with non-verbal ability. Additionally, we found significant positive associations with right medial occipital structure and left inferior temporal SA. Furthermore, we expected to find associations between non-verbal ability and CT in the frontal and parietal regions. Two significant positive associations with visuospatial ability measures utilizing only one task were found, but there were no associations with the overall non-verbal ability of the child. Altogether, this is the first study to examine the cortical structural correlates of non-verbal ability in a large sample of typically developing 5-year-olds. Our results suggest that some of the structures identified in studies of older participants are associated with non-verbal ability at this stage of development.

We found associations between non-verbal ability and both volume and SA in the caudal middle frontal gyrus. The posterior parts of the caudal middle frontal gyrus form a part of the premotor cortex, which is, in addition to cognitive ability (Jung & Haier, 2007; O'Boyle et al., 2005), also a relevant region for mathematical ability (Navas-Sánchez et al., 2016), working memory (an fMRI study, Osaka et al., 2004), and speech perception (based on transcranial magnetic stimulation studies; see Meister et al., 2007; Sato et al., 2009). The premotor cortex is especially often observed as relevant in functional brain studies focusing on cognitive ability (Jung & Haier, 2007; Osaka et al., 2004), while prior structural findings are comparatively scarce. In conclusion, our results support the previous studies in proposing that the positive association between non-verbal ability and SA may already be observable at 5 years of age, which is in line with the finding that children with higher cognitive ability reach peak SA faster (Schnack et al., 2015).

Volume and SA in the right medial occipital region, including parts of the pericalcarine, isthmus of cingulate gyrus, precuneus, and lingual regions, were associated with non-verbal ability, and more specifically with visual abstract reasoning rather than visuospatial ability. Some studies in adults have found associations between general cognitive ability and lingual gyrus volume (Colom et al., 2006b), as well as more widespread occipital GM volumes (Colom et al., 2006a; Haier et al., 2004). Notably, Colom et al. only found associations with visuospatial ability (visual abstract reasoning ability not tested; Colom et al., 2006a), while our results in the occipital lobe were driven by visual abstract reasoning ability. Furthermore, in previous articles, the associations between general cognitive ability and occipital brain metrics have generally been found on the lateral rather than the medial surface (Colom et al., 2006a; Karama et al., 2009). To the best of our knowledge, this is the first study to link right medial occipital cortex volume and SA to non-verbal ability in children, and thus, these areas should be included among the hypothesized structures related to non-verbal ability specifically.

We found a positive association between non-verbal ability and SA in the inferior temporal gyrus. The inferior temporal gyrus, as well as the medial occipital

region, has a key role in the ventral visual pathway (Kravitz et al., 2013), which is a network responsible for object recognition. On a related note, it has a role in visual and auditory word processing (Cohen et al., 2004). In children with a family risk of dyslexia, a smaller SA was observed, even when controlling for their reading ability (Beelen et al., 2019). Additionally, one pediatric neuroimaging study found a positive association between general cognitive ability and inferior temporal CT in children (Karama et al., 2009). In theory, one would expect the structural and functional characteristics of the system responsible for object and pattern recognition to affect performance in tasks that require pattern recognition (such as the tests used in Study III). However, current information on the roles of the temporal and occipital cortices for non-verbal ability is conflicting (for review, please see Basten et al., 2015; Jung & Haier, 2007), and little is known about the role of these regions during childhood cognitive development.

We also found positive associations between CT and visuospatial ability in the left precentral and right postcentral gyri. One previous study found widespread positive associations between the Wechsler Abbreviated Scale of Intelligence score and CT in 6- to 18-year-olds (Karama et al., 2009). In their 6- to 12-year-old sample, the main overlap with our results is the positive association in the right postcentral gyrus. In contrast, Botdorf and Riggins (2018) found no associations between general cognitive ability and CT in the fronto–parietal regions but did find negative associations between CT and working memory (corrected for general cognitive ability) in multiple regions, including the right postcentral gyrus, in a sample of typically developing 4–8-olds. The primary somatosensory area is not commonly associated with cognitive ability in structural neuroimaging studies but when it is, the findings tend to be in the right rather than in the left hemisphere (Haier et al., 2004; Jung & Haier, 2007; Karama et al., 2009).

The most recent studies suggest that CT peaks at a very young age, possibly even before 2 years of age (Bethlehem et al., 2022; Frangou et al., 2022). Therefore, in a simplistic "more advanced is better" interpretation, participants with higher non-verbal ability would be further along the developmental trajectory and have lower CT. Some studies have indeed found higher general cognitive ability (Schnack et al., 2015; Squeglia et al., 2013) and working memory (Botdorf & Riggins, 2018) to be associated with lower CT in children and adolescents. However, the positive associations seen in Study III, while in agreement with many previous studies (Girault et al., 2020; Leonard et al., 2019; Meruelo et al., 2019; Schilling et al., 2013), contrast the idea that more advanced development would necessarily correlate with higher cognitive ability. One option to consider is that individuals may have different growth trajectories depending on cognitive ability. Shaw et al. (2006) have shown that children with higher general cognitive ability reach their peak CT later, while Khundrakpam et al. (2017) suggest different CT coupling between the cortical

regions between ages 6–18 years, based on verbal ability. Meanwhile, other studies have found positive associations between general cognitive ability and CT in multiple brain regions in 6–18-year-olds (Karama et al., 2009, 2011), 9–24-year-olds (Menary et al., 2013), and adults (Bajaj et al., 2018), suggesting that individuals with higher general cognitive ability may retain greater CT, although there have been conflicting results in adult studies, too (Tadayon et al., 2020). Overall, the results regarding cognitive ability and CT in children are currently inconsistent, and more studies are needed. There are currently some large multisite neuroimaging projects devoted to longitudinal data collection of the developing brain, such as the HEALthy Brain and Child Development consortium (HBCD; Volkow et al., 2021) and the Adolescent Brain Cognitive Development consortium (ABCD; Hagler et al., 2019; Volkow et al., 2018), which will provide crucial information on developmental trajectories of the brain.

6.4 Limitations

6.4.1 Study I

We must point out that this review is not exhaustive for any of the prenatal exposures, as it uses a limited time range and relies on only one database, PubMed. Nonetheless, we believe that this comprises a methodologically comparable set of studies representative of the infant neuroimaging field at large and that it can be used to assess the shortcomings in population descriptions of recent studies and to highlight the importance of the prenatal period in brain development.

6.4.2 Study II

Some of the demographics were obtained from questionnaires from mothers during pregnancy (including paternal information), which creates important reliability considerations of varying scales. For example, self-reports of drug use are unreliable (Tavella et al., 2020), while some other data can be assessed more reliably and the alternative options may be very limited, for example, with maternal depressive symptoms. We were interested in how the important predictors from infant studies (Jha et al., 2019) are still relevant at 5 years of age. Therefore, the 5-year time gap between questionnaire data collection and imaging sessions was justified. Longitudinal design would be optimal for this purpose, and such studies are warranted in the future. In addition, the sample size was limited for some variables (e.g., maternal smoking and gestation diabetes). Even though the demographics matched satisfactorily compared to previous work (Jha et al., 2019), the brain variables differed between the studies (volume and SA in our study, as opposed to

SA and CT in Jha et al. (2019)), which is in our view age-appropriate. The rationale for the choice of brain metrics was that the reference article (Jha et al., 2019) studied infants, and at that stage of development, both CT and SA essentially measure how quickly the brain is growing (as both metrics are at a stage of rapid growth; Bethlehem et al., 2022). As CT is already declining at 5 years of age, making the results more challenging to interpret, we decided to use SA and cortical volume, as they better capture the amount of brain growth in our sample. Examining the effects of demographic and obstetric factors on other cortical metrics, such as CT and gyrification, can provide useful information in future studies. Most of these limitations can likely be addressed in large open science data sets such as the developing Human Connectome Project (Fenchel et al., 2020).

6.4.3 Study III

Both a strength and a limitation of Study III is the limited age range in a cross-sectional setting. While the strength lies in the possibility to understand the neural correlates of non-verbal ability at this specific age relevant for later development, it precludes true longitudinal and developmental interpretations. Especially with CT, it seems to be the case that longitudinal modeling is needed to find the potential individual differences in growth trajectories and how they might relate to non-verbal ability. On the other hand, to our knowledge, this is the first neuroimaging study to explore the association between non-verbal ability and structural brain development in a large sample of typically developing 5-year-olds. The small age range provides an opportunity to get an accurate image of brain structure at this stage of development. Another limitation is the generalizability of the results, especially to clinical samples. The participants in the final sample were born at a higher gestational age and had fewer visits to the NICU, suggesting that many participants with even slight issues during pregnancy or the perinatal period were not included in the sample. Furthermore, our sample is highly ethnically homogenous, and the results are not necessarily generalizable to populations of different backgrounds. Finally, while the sample is larger than in any prior neuroimaging studies exploring cognitive development in young children, it is not as large as recommended in current best practice (Marek et al., 2022). Marek et al. ran correlational analyses in three large open access datasets and concluded that effect sizes in brain-wide association studies are much lower than are often reported in current neuroimaging literature (with sample sizes ranging from dozens to hundreds), and sample sizes of thousands are required for good reproducibility. In the context of Study III, this indicates a risk of false positives and effect size overestimation. One step to alleviate this issue when working with or collecting smaller datasets is to make the data collection and processing streams compatible with larger datasets (as FinnBrain 10-

year data collection has done with regard to the ABCD study), although this is still not optimal as in-sample associations still remain larger than out-of-sample replications (Marek et al., 2022). The estimates are further biased by the fact that standard, widely used neuroimaging analysis approaches are not designed to estimate the effect sizes of brain-outcome relationships (Reddan et al., 2017). Standard approaches instead rely on a probabilistic approach, in which magnitudes are only reported for significant voxels in brain-wide analyses, leading to effect size estimation (Bowring et al., 2021). Novel statistical approaches could alleviate the limitations related to smaller sample sizes (Bowring et al., 2021).

6.4.4 Study IV

Study IV presents a few notable limitations. First, the sample size is limited due to the time-consuming manual segmentation process, but it is likely sufficient for building study-specific templates, which is a potential goal for applied studies. Second, all manual segmentations were performed by a single rater, which might lead to some systematic biases in delineation of anatomical borders in MR images. However, this risk is attenuated by the expert review. On a related note, the manual segmentation was done by editing models produced by *FSL None*, which might cause the manual segmentations to have a bias towards FSL-FIRST. However, this was explored by segmenting a subsample based on FreeSurfer automated segmentation, and the results were generally similar. There were some differences in structures that are smaller and harder to delineate, such as the amygdala and the nucleus accumbens. Some variance is to be expected simply due to technical challenges when performing the manual segmentation using two different editing tools. Most importantly, automated FreeSurfer segmentation vastly overestimated amygdalar volumes even when compared with the manual segmentation based on it. Therefore, regardless of the initial estimate, the conclusion is that visual inspection of subcortical structures is strongly advised.

6.5 Future Directions

We have shown that prenatal exposures are associated with individual neurodevelopment, and we have identified the most important predictors for cortical structure in typically developing 5-year-olds. This information has been (Study III) and will be utilized in our future publications. We used FreeSurfer with a semiautomated segmentation and quality control protocol that has been established as an appropriate tool for surface-based analyses in pediatric neuroimaging in our previous research (Pulli et al., 2022). In Study IV, we expanded on this research by assessing the performance of FreeSurfer in volumetric analyses. Overall, FreeSurfer

performed satisfactorily, but the results were not optimal for the amygdala, the hippocampus, and the nucleus accumbens. Hence, careful visual inspection of the automated segmentations is still strongly advised. Future research should investigate the benefits of using custom subcortical atlases to improve the accuracy and reliability of automated segmentation methods especially for the amygdala and the hippocampus (Acosta et al., 2020).

The findings presented in this thesis provide a great opportunity to explore childhood neurodevelopment in the FinnBrain Birth Cohort study. As for prenatal exposures, the FinnBrain cohort is not optimal for studying most of the chemical exposures, as the number of exposed participants is relatively small (alcohol, tobacco, illicit drugs, and most medications) or the data has not been collected (e.g., pesticide levels). On the other hand, the cohort is well suited to study the effects of maternal (and some paternal) characteristics. Distress measurements (depressive and anxiety symptoms) have been collected at multiple timepoints pre- and postnatally, and SES data are available (measured using maternal education level). Furthermore, multiple biological samples, such as serum and hair cortisol samples, have been collected. In addition, FinnBrain has ongoing data collection (currently in ca. 9-year-olds), measuring multiple aspects of child development, including psychological development (e.g., cognitive skills, executive functioning, temperament, social–emotional attention and abilities), language development, pediatric health, and biological sample collection (e.g., fecal samples). The knowledge from this thesis combined with our previous work (Pulli et al., 2022) creates a strong basis for future studies. With this holistic understanding of different factors affecting the developing brain, our high-quality neuroimaging data, together with the multidisciplinary, longitudinal data collection in the FinnBrain Birth Cohorts study, can be used to explore various new aspects of early brain development and the possible mediating and moderating roles of different brain structures.

Our findings have implications beyond the scope of our own future research. In Study I, we identified issues in the reporting of background information in recent studies, and we provided recommendations for reporting in future studies. Specifically, we recommended that all infant neuroimaging studies report age at MRI scan (both from birth and from conception), gestational age at birth, sex, birth weight, maternal age, maternal weight status (BMI), race/ethnicity, and SES, and either report drug, alcohol, and tobacco use during pregnancy or mention them as exclusion criteria. In Study II, we observed different predictors of brain structure from those in prior infant studies (Jha et al., 2019). Understandably, there are some differences between age groups. For example, reporting age both from birth and from conception becomes less important as the participants age. Nevertheless, as we have shown in this thesis, many prenatal exposures, such as alcohol and tobacco

exposures, have effects that last beyond infancy into childhood, and hence considering these potential confounders is still important in this age group.

Moving forward, longitudinal studies are going to be paramount in pediatric neuroimaging. While some exposure–brain and brain–behavior relationships in younger children (especially in children under 5 years of age) are still so poorly understood that cross-sectional studies can provide important preliminary information, many phenomena are best modeled longitudinally. There are currently some large multisite neuroimaging projects devoted to longitudinal data collection of the developing brain, such as the HEALthy Brain and Child Development consortium (HBCD; Volkow et al., 2021) and the Adolescent Brain Cognitive Development consortium (ABCD; Hagler et al., 2019; Volkow et al., 2018), which will provide crucial information on the developmental trajectories of the brain.

7 Conclusions

The major findings of the studies are as follows:

I. Based on the literature review, we recommend that all infant neuroimaging studies report age at MRI scan (both from birth and from conception), gestational age at birth, sex, birth weight, maternal age, maternal weight status (BMI), race/ethnicity, and SES, and either report drug, alcohol, and tobacco use during pregnancy or mention them as exclusion criteria.

II. The factors that predicted brain structure were different from those in infants (in previous studies). We identified child characteristics and prenatal exposures that predicted cortical GM volume and SA at 5 years of age. In the future, researchers will likely benefit from including similar early life and family variables in statistical analyses in studies on cortical anatomy between 0 and 5 years of age.

III. We explored the cortical structural neural correlates of non-verbal cognitive ability in 165 typically developing 5-year-olds from the FinnBrain Birth Cohort study. The findings were generally in line with the literature from adult and adolescent studies, with the important addition of a positive association between volume / SA in the right medial occipital region and non-verbal ability, as well as visual abstract reasoning ability specifically. This finding adds to the literature by discovering a new region that should be considered in future studies exploring the mediating or moderating roles of cortical structure for cognitive development in young children.

IV. We evaluated the accuracy of two automated segmentation tools, FSL-FIRST and FreeSurfer, against manual segmentation in typically developing 5-year-olds. Overall, the automated tools performed relatively well, but the performance changed vastly based on the structure. Small and visually indistinct structures such as the amygdala and the nucleus accumbens were inaccurately segmented by all

automated methods. On the other hand, the segmentation of the putamen and the caudate were performed accurately with most of the automated methods, yielding relatively good consistency and reproducibility with manual segmentation. The use of these automated segmentation tools in neuroimaging studies still requires caution, and careful visual inspection of the automated segmentations is still strongly advised.

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