Building brains; What can we conclude about children's educational success by looking at their brain structure, cognitive abilities, and socioeconomic background?

Langensee, Lara

2024

Document Version:
Publisher's PDF, also known as Version of record

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What can we conclude about children's educational success by looking at their brain structure, cognitive abilities, and socioeconomic background?

Larissa Langensee

LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 10th of June 2024 at 09.00 in Fernströmsalen, Forum Medicum, Sölvegatan 19, 223 62 Lund

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Organization: LUND UNIVERSITY

Document name: Doctoral Dissertation **Date of issue** 10.06.2024

Author(s): Larissa Langensee **Sponsoring organization:**

Title and subtitle: Building brains; What can we conclude about children's educational success by looking at their brain structure, cognitive abilities, and socioeconomic background?

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Classification system and/or index terms (if any) Supplementary bibliographical information

Language: English **Number of pages**: 79

ISSN and key title: 1652-8220

ISBN: 978-91-8021-581-7

Recipient's notes Price Security classification

Signature Date 2024-04-24

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Coverphoto by Larissa Langensee

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ISBN 978-91-8021-581-7
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2024

Table of Contents

1 Abstract

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2 List of publications

I. Langensee, L., Rumetshofer, T., Behjat, H., Novén, M., Li, P., & Mårtensson, J. (2022). T1w/T2w ratio and cognition in 9-to-11-year-old children. *Brain Sciences*, *12*(5), 599.

II. Langensee, L., Spotorno, N., & Mårtensson, J. (2023). Beyond the language network: Associations between reading, receptive vocabulary, and grey matter volume in 10-year-olds. *Neuropsychologia*, *191*, 108719.

III. Langensee, L., Rumetshofer, T., & Mårtensson, J. (2024). Interplay of socioeconomic status, cognition, and school performance in the ABCD sample. *Npj Science of Learning, 9*(1), 17.

3 Svensk sammanfattning

Skolor behöver vara inkluderande och erbjuda alla barn de bästa möjliga förutsättningarna för att deras skolgång ska bli framgångsrik. Grunden för att kunna skapa sådana inlärningsmiljöer är att förstå vad som ligger bakom barns framgång i skolan. Varför lyckas vissa utan större problem att ta sig igenom sin utbildning, medan andra har det svårt? En bra utbildning har ofta stor påverkan även senare i livet, till exempel i form av vilka typer av jobb och inkomstnivåer som är nåbara, samhällsstatus, men också välbefinnande och psykosocial hälsa. En välutbildad befolkning är även en tillgång för samhället i stort då den främjar ekonomisk tillväxt såväl som jämställdhet och delaktighet. Men hur blir framgång i skolan till? Hur skiljer sig de som klarar sig bättre i sin utbildning från dem som måste kämpa sig igenom? Vad finns det för aspekter inom individen och i deras omgivning som avgör om de blir framgångsrika i sin utbildning? Dessa frågor utgör fundamentet för denna avhandling.

Olika metoder för hjärnavbildning, som till exempel magnetresonanstomografi, MRT eller magnetkameror, har blivit vanliga som forskningsverktyg inom kognitiv neurovetenskap. Forskare använder till exempel MRT för att studera hjärnan i syfte att förklara olika psykiska och neurologiska sjukdomar och deras symtom. På liknande sätt har olika mått av hjärnans struktur använts även i friska populationer för att undersöka hur neurala faktorer hänger ihop med olika förmågor och beteenden, till exempel kognition eller inlärning. Parallellt har det dock publicerats studier som ifrågasätter pålitligheten av just den forskning som hittat kopplingar mellan beteende och hjärnstruktur. Stora mängder data, ”Big data”, föreslås ofta som en lösning till problemet. Det är därför viktigt att avgöra vad stora mängder hjärndata tillför i studier av lärande och utbildning, och om det är meningsfullt att studera hjärnans struktur för att förklara varför vissa klarar sig bättre i skolan än andra. Det finns bevis för att socioekonomisk status påverkar framgång i skolan och att de som är ekonomiskt välställda har bättre odds att få bra betyg än de som växer upp under mindre fördelaktiga förhållanden. Är detta samband oundvikligt eller finns det faktorer som kan bryta ett sådant samband och motverka negativa effekter av en ogynnsam uppväxt på akademisk framgång?

Med hjälp av data från ABCD studien (Adolescent Brain Cognitive Development) försökte vi att komma till botten med dessa frågor. Vi använde två olika MRT-tekniker för att undersöka om det finns samband mellan strukturen i den gråa

substansen hos barn och deras kognitiva förmågor. Inspirerad av djurstudier som pekade på korrelationer mellan myelin, ett essentiellt isolerande hölje runt nervbanor, och inlärning, tittade vi på huruvida T1w/T2w kontrasten, som sägs återspeglar myelin i hjärnbarken, kan kopplas till barns prestation på olika kognitiva test. Trots ett stort urval såg vi inga sådana korrelationer. På liknande sätt visade vi att gråsubstansvolym inte lämpar sig för att förklara skillnader i språklig förmåga hos barn. Vi studerade även om individuella kognitiva förmågor interagerar med föräldrarnas socioekonomiska status i deras effekt på barns prestationer i skolan. Medan kognitiv förmåga inte bekräftades som skyddsfaktor mot effekter av socioekonomisk status på betyg i skolan, så hittade vi små men robusta effekter på skolframgång av både kognitiv prestationsnivå och socioekonomisk bakgrund. Sammantaget bekräftar resultaten i denna avhandling befintliga reservationer mot att använda MRT för att förklara skillnader i beteende och prestationsnivå, åtminstone bland friska barn. Trots att mått på kognition och socioekonomisk status också har brister, har de visat sig vara mer kraftfulla för att förklara komplext beteende, samtidigt som de är billigare och mindre påfrestande än MRT.

4 Abbreviations

ABCD	Adolescent Brain Cognitive Development
CNS	central nervous system
CSF	cerebrospinal fluid
DUC	data use certification
FDR	false discovery rate
FSL	Functional magnetic resonance imaging of the brain Software Library
FEW	family-wise error
HCP	Human Connectome Project
IRB	institutional review board
MRI	magnetic resonance imaging
MTR	magnetization transfer ratio
MWI	myelin water imaging
NDA	National Institute of Mental Health Data Archive
NIH	National Institute of Health
OL	oligodendrocyte
OPC	oligodendrocyte precursor cell
PALM	permutation analysis of linear models
ROI	region of interest
SES	socioeconomic status
VBM	voxel-based morphometry

5 Introduction

Why do some people succeed in school, reaching high levels of formal education, while others have a hard time? What are the influencing factors that determine how well people navigate the challenges of the formal education system? Questions like these have inspired the work on the present thesis. Being well-educated is linked with numerous advantages, not only on an individual level in the form of better opportunities for employment and income, higher societal status, and positive health outcomes, but also for society overall by promoting economic growth and fostering equality and empowerment among its citizens. According to a meta-analytic review, math, reading, and attention skills at the beginning of school, predict later school achievement across sexes and levels of socioeconomic status [1]. But what other factors determine if someone completes their education successfully? Is it useful to look at the brain to understand educational success? Are there external parameters that can sway one's educational trajectory?

Most people have an intuitive appreciation for the fact that cognition and intelligence play a significant role for someone's educational achievements throughout their lives. Intelligent people have an easier time to navigate the tasks and challenges that schooling and formal education present them with. Perhaps this even works like a feed-forward loop where someone with good preconditions for doing well in school, gradually becomes more intelligent through their continuous successes in school. Turning towards the brain to help answer some of these questions and to explain interindividual differences in cognitive abilities and academic performance is an obvious choice. Thanks to the advent and widespread availability of modern neuroimaging technologies, they have become a mainstream research tool in cognitive neuroscience. For clinical questions, scientists frequently look at the brain to explain diverse pathologies and disorders, and the symptoms and divergent behaviors that go hand in hand with them. Similarly, empirical research has tied various measures of brain structure to cognitive performance, which, in turn, is a well-established predictor and outcome of education. Accordingly, it is conceivable that higher educational attainment would go hand in hand with corresponding neural manifestations. In this spirit, educational neuroscience has established itself as a research area that studies the brain in all its facets to better understand the neural factors that are associated with learning outcomes and education. At the same time, there has recently been a surge in studies questioning the reliability of links between behavior and brain structure. Large sample sizes are

often proposed as a solution for addressing this issue. It is crucial to determine whether this claim proves to be true in the context of learning and education and if studying brain structure is useful for explaining individual differences in terms of how well someone does in school. But what about other factors, like the environment someone is growing up in? There is evidence that socioeconomic status influences educational success and that those that are financially well-off are more likely to do well in school than their peers from a less advantageous background. Is this an inevitable association, or are there protective factors that can break the unfortunate relation between a disadvantaged upbringing and poorer educational outcomes?

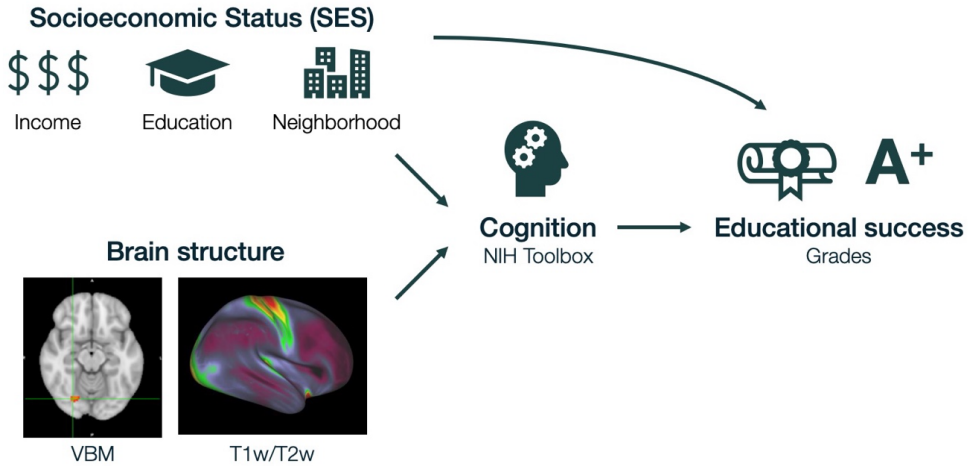

Figure 1: Schematic overview of the core ideas underlying this thesis. The primary concept of interest is educational success, quantified by means of grades, which in part can be explained terms of individual cognitive abilities as well as socioeconomic background. Cognitive abilities in turn have been associated with both socioeconomic status and brain structure. In this work, socioeconomic status is operationalized by parental education and income as well as neighborhood status. Brain structure is measured by means of estimated grey matter volume (VBM) and cortical myelin content (T1w/T2w ratio). Cognitive abilities are assessed by seven tests contained in the NIH Toolbox Cognition Battery which tap into attention, executive function, language, memory, and processing speed.

Investigating these questions and hypothesized relationships has been the objective of this thesis, summarized in Figure 1. We used two neuroimaging measures to explore how grey matter and cognitive abilities relate to one another. To account for environmental variables, we studied if individual cognitive abilities interact with parental socioeconomic status in their effect on children's performance in school. In the following sections of the thesis, you will read about what we presently know about how factors inside and outside an individual can influence their educational success. First, a brief overview of how educational success is defined and measured is presented. This is followed by an introduction to the concepts of cognitive abilities

and intelligence, as well as socioeconomic status. Features of brain structure relevant to cognition are then discussed together with a section on using magnetic resonance imaging (MRI) to image grey matter and myelin.

5.1 What is educational success?

Before we attempt to answer who is successful in their education and why, it is worth contemplating what educational success means. What comes to mind are acquisition of knowledge and skills, as well as passing exams and graduating from courses or programs. Some researchers go a step further and consider factors that are much more difficult to quantify, like academic self-efficacy, engagement, or satisfaction [2]. Unsurprisingly, a broad concept like *educational success* does not come with a simple definition. This is also reflected in the literature, where a variety of different indicators of educational success are used, as well as inconsistent terminology. Besides educational, or academic, success, the terms attainment and achievement feature frequently, two terms which are not easily distinguished. Some argue that the former is concerned with formal qualifications and learning objectives, like obtaining degrees or diplomas, while the latter should be seen as a reflection of performance ability [2]. Other research defines educational achievement by means of clear criteria, such as the highest level of completed education [3] or grades [4]. This substantial overlap between the two terms is reflected by the fact that they are often used interchangeably [5]. Nevertheless, the most widely used measure of educational success are, as you might expect, grades either from specific courses or in the form of a grade point average [2], thus gearing the field towards objective accomplishment criteria.

5.2 Cognitive abilities and intelligence

Cognitive abilities and intelligence impact many life outcomes, not least individual educational trajectory [6–8]. The two concepts are interrelated, reflected in the fact that they are occasionally used interchangeably [9]. Different approaches to defining them have been proposed. While cognitive abilities refer to various mental processes necessary to store and process information, such as attention and working memory, intelligence is typically viewed more broadly. British psychologist Charles Spearman famously conceptualized it as a combination of several task-specific factors and one general factor – accounting for the fact that an individual's performance on different cognitive tests typically correlates [10]. The two can be divided into crystallized and fluid abilities, where the former refers to someone's ability to think logically and to deal with novel stimuli, while the latter concerns

acquired knowledge. Even though other variables, such as personality factors, also have an impact, empirical evidence implies intelligence as the strongest predictor of academic success and suggests it should be defined comprehensively and operationalized with both verbal and non-verbal measures to maximize its predictive value for school performance [8, 11, 12]. Effect sizes tend to be medium, with the exact numbers varying from study to study, for example as a function of school subject, behavioral measure, or analytical approach. Several reviews and meta-analyses have found robust links between executive functioning and school achievement, especially in math, across a broad age range of elementary school students [13–15]. At the same time, transfer effects between executive function training paradigms and academic performance have not been observed, possibly because interventions should be focused more on encouraging the engagement of executive functions rather than improving them [16].

Math and language performance are typically used as indicators of academic achievement, even though the two abilities do not appear to be independent of one another [17]. In a recent meta-analytic review inadequate reading skills have been shown to go hand in hand with deficits in many non-verbal cognitive domains, such as attention, memory, and inhibition, possibly because cognitive deficits hamper the development of language skills which in turn could adversely affect cognitive development [18]. In line with this, a recent review concluded that the relationship between cognitive ability and school achievement is bidirectional, meaning both interact during development – contrary to the traditional view that cognitive abilities precede academic success [7]. The data is less conclusive when it comes to how the effect of cognitive ability on school performance changes over time [8, 11]. There is some evidence that the correlation between intelligence and some cognitive abilities (working memory and reasoning) and academic achievement increases with age, while the picture is less clear for executive functioning [7, 8].

In conclusion, the link between cognition and intelligence on the one hand and academic achievement on the other is well established in the literature, with some level of uncertainty with respect to the magnitude of the effect. Correlations appear to be reciprocal and have been shown across a wide range of ages, various aspects of cognitive abilities and measures of academic achievement.

5.3 Socioeconomic variables

5.3.1 Measures of socioeconomic status (SES)

In educational research, there is no way around considering to what extent a child's academic trajectory is affected by their socioeconomic standing, that is, their parents' level of education, the type of job they have, and how much money they

make. Much like cognition and intelligence, socioeconomic status is not a unidimensional entity. And even though it is commonly used in educational research and beyond, there is considerable variety when it comes to how to define it. Typically, it is operationalized by level of education, income, or occupation – and studies use one, a combination, or all of these as they see fit. Increasingly, factors beyond an individual's home environment, for example information on school quality, neighborhood status or eligibility for free or reduced lunch (although this has been criticized [19]), are also being considered [20, 21].

5.3.2 Links between SES and educational attainment

Much like with cognition and intelligence, links between socioeconomic background and school performance are consistently reported in the literature, starting during early school years, and persisting, albeit attenuated, all the way to university [21, 22]. While links between SES and academic achievement have been observed reliably for decades, their reported strength varies quite significantly and some meta-analytic evidence point towards rather moderate effect sizes [21, 23, 24]. An evident reason underlying this disparity is the large variety in how both SES and academic achievement are conceptualized and operationalized. It has also been shown that the way SES is measured influences the estimated size of its correlation with academic achievement, with continuous SES variables producing higher effect sizes than discrete categories [21]. It even makes a difference where the SES data comes from, with information coming from parents producing larger effects compared to when it comes from children or other sources [21]. Other contributing factors are the grade the student is in, the geographical location of their school, whether they belong to a minority group, and whether individual students or schools are used as unit of analysis (with the latter producing larger effect estimates) [21].

Evidence suggests that the reciprocal relationship between cognitive abilities and school performance is less pronounced in children that are socioeconomically disadvantaged [7]. At the same time, lower socioeconomic status often co-occurs with poorer performance on various cognitive measures. Mechanisms suggested to explain these findings are better access to high-quality teaching material, psychosocial resources, and intellectual stimulation available to children that are socioeconomically well off. Beyond that, parent's social capital has also been suggested to come into play [21].

There is ample evidence that parents play a crucial role in their children's education. SES has been found to correlate with parent's involvement in their children's education, which in turn has been found to be linked to their performance in school, though not as strongly as one may be inclined to believe [25, 26]. A cross-national analysis of data from the 2012 PISA (OECD's Programe for International Student Assessment) study revealed that access to cultural and, to a lesser extent, educational resources, correlates with children's performance in math, reading (or some other

indicator of verbal/language skills), and science. This association is at the basis of both the direct and indirect effects that parental occupation status has on children's performance in school [27]. Parents' level of education is also linked with children's academic achievement, though primarily through its connection with occupational status [27]. While these resource-related factors likely explain the bigger part of the performance difference between low and high SES children, additional forces do seem to be at play, for instance psychological variables, like self-concept or how flexible, respectively fixed students' beliefs about their academic abilities are [28, 29].

Furthermore, it has been shown that factors outside the individual, such as a positive school and classroom climate, school, and curriculum type, as well as the socioeconomic status of a school contribute to offset the negative effects of low SES on academic performance [30–32]. To sum up, even though true effect sizes are still uncertain, after decades of research, there is little doubt that a child's socioeconomic background affects their odds to succeed in school.

5.4 Brain structure – the macro and the micro level

The brain, our body's most complex organ, underpins every aspect of our lives. It plays a vital role in processes ranging from those typically beyond our awareness or deliberate control, like respiration or cardiovascular function, to more conscious acts like learning to walk, writing music or remembering our spouse and family. During childhood and adolescence, the brain undergoes extensive development, reorganization, and rewiring, correlating with profound changes observable at the level of biology, physical appearance, behavior, cognition, and numerous other abilities [33–36]. The timelines vary between different structural indices and areas of the brain, and their corresponding overt changes. Sensorimotor skills develop earliest and fastest, mirrored by corresponding changes on the neural level. Associative and limbic areas are characterized by slower, and more prolonged development, in line with relatively later refinement of higher cognitive and emotional functions [37]. Generally, somatosensory, motor, and phylogenetically older regions mature earlier than higher-order association cortices [38, 39] in parallel with the typical sequence of behavioral, cognitive, and psychosocial development [39, 40].

5.4.1 Grey matter

5.4.1.1 Grey matter development during childhood

The mammalian brain is made up of three main components: grey matter, white matter, and cerebrospinal fluid (CSF). The outermost layer of the brain, the cerebral cortex, is 1-4.5 mm thick and has long been regarded the site of higher cognitive

function [41, 42]. It is primarily made up of grey matter, which in turn, consists of neurons, glia cells, blood vessels, dendrites, and myelinated and unmyelinated axons [43]. Structural changes in the brain during development are visible across a range of different grey matter indices, including cortical volume, cortical thickness, gyrification, and surface area [44–46]. Each of these metrics follows a characteristic pattern over time, though there is substantial variability between individual people when it comes to these trajectories, both in terms of their size and direction, especially at the transition between developmental phases [47]. There is also evidence that points towards greater variability in brain structure among males compared to females [48]. Small but consistent sex differences have been observed reliably across the life span with respect to overall brain volume [49, 50], whereas the picture is more complex in terms of individual indices of grey matter morphology and their developmental trajectories for boys and girls [51–56].

Unlike white matter, which typically increases linearly in volume throughout childhood and adolescence before leveling off in adulthood, grey matter metrics follow a non-linear trajectory, with decreases in cortical thickness and volume during childhood, adolescence, and young adulthood after an initial increase in cortical thickness during the first two years of life [45, 57, 58]. After some years of more gradual gains, cortical thickness, volume, and surface area reach a peak around early puberty, after which a gradual decrease sets in, with flatter slopes for surface area compared to the other two [45, 47, 59]. Compared with white matter, grey matter development is characterized by considerably more regional, temporal and interindividual variability [47, 60] and varying slopes [61]. The temporal cortex stands out, because while following a similar overall trajectory as the frontal and parietal cortices it reaches its peak grey matter volume markedly later than the other two [62]. Grey matter in posterior cortical regions follows a more linear growth over the course of development at least until age 20 without evident leveling or decline [62]. Frontal and parietal regions have been shown to reach their peak earlier in females than males, possibly caused by an earlier onset of puberty differences in hormones [62].

Cortical grey matter volume is the product of cortical thickness and surface area. Thanks to its characteristic folding pattern the cortical surface area can grow without an increase in overall brain volume. These structural metrics follow distinct developmental trajectories and are thought to reflect different underlying neurobiological maturational processes [56]. Both cortical thickness and surface area grow substantially during the first two years of life as the brain develops rapidly. [63]. After that, cortical thickness has been shown to change differently depending on brain region, with fronto-parietal and cingulate areas exhibiting a more consistent decrease in thickness, compared to sensorimotor, limbic and association cortices which initially increase in thickness before experiencing a more moderate thinning [64]. Some data also suggests that posterior brain regions are characterized by initial cortical thinning and followed by thickening between age 1 and 5 [55]. Surface area

on the other hand increases steadily in the anterior part of the cortex until about age 13 when it starts levelling off, more posterior regions of the cortex on the other hand roughly remain steady throughout that same period [64]. When it comes to the cellular changes giving rise to the macroscopic shifts, which we can detect by means of neuroimaging, synaptogenesis, myelination, and selective pruning, are developmental key processes that can lead to cortical thinning [65–67]. Dendritic branching and axonal sprouting also occur, although these mainly take place during prenatal and early postnatal development [67].

In contrast to grey matter in the cortex, grey matter deeper within the brain is, simply put, involved in more fundamental functions, such as regulating emotion, relaying sensory input to relevant parts of the brain, and basic physiological functions [68–70]. However, cortical, and subcortical grey matter are heavily interconnected and functionally integrated [71]. Even subcortical grey matter structures have been shown to follow an inverted-U-curve during development with extensive expansion in volume during the first year after birth [33, 72], though some findings point towards linear relationships [73]. There is evidence that the developmental trajectories of subcortical structures are not a function of age to the same extent as those of cortical grey matter, though the strength of the relationships differs between different structures of the basal ganglia [73].

5.4.1.2 Links between grey matter and cognitive abilities during childhood

A landmark study from the early 2000s found that the relationship between intelligence and cortical morphology changes over the course of childhood and adolescence, with a negative correlation between cortical thickness and intelligence during earlier childhood gradually transforming into a positive one [74]. More intelligent children were also characterized by a higher degree of cortical plasticity, especially in prefrontal regions [74]. Cortical thinning during childhood has robustly been linked to improved cognitive abilities across a range of functional domains. For instance, cortical thinning in left lateral dorsal frontal and parietal regions has been shown to correlate with improved vocabulary performance [75]. Similarly, cortical thinning in right anterior cingulate and inferior frontal gyrus, respectively superior parietal cortex, was found to correlate with improved cognitive control and working memory in 5-to-10-year-old children [76]. Evidence linking cognitive abilities to grey matter volume is less conclusive, with both positive and negative correlations occurring. One study found improved reading proficiency to be tied to grey matter volume in left superior temporal cortex [77]. At the same time, decreases in grey matter volume in left inferior parietal lobule as well as pre-and postcentral gyri were associated with better reading performance [77].

5.4.2 Myelin

5.4.2.1 What is myelin and why do we need it?

Myelin, which can be found in both white matter and grey matter, is a fatty substance insulating the axons of the central and peripheral nervous system. It is essential for efficient signal transmission between disjoint parts of the brain because it helps optimize the speed at which action potentials can travel along axons. It has also been hypothesized that myelin helps maintain and stabilize the brain's circuitry by inhibiting synaptic plasticity [78]. Myelin is thus a major determinant behind healthy brain function and has more recently also been implied as a critical component for learning and memory [79]. Studying myelination to understand both healthy and pathological brain function has a long history. German neuroanatomist Paul Flechsig with his mapping of the chronology of early myelination at the turn of the 20th century was a pioneer in investigating myelin as an influencing factor behind neural transmission [80–82]. Traditional histological techniques have been complemented by immuno-chemistry and electron microscopy methods in more recent times [83]. These techniques provide important insights into myelin function and plasticity, since they can visualize myelin directly, but they come with one obvious drawback: they cannot be used in vivo. Consequently, cognitive neuroscientists have resorted to neuroimaging as an alternative approach. You will soon learn more about this.

At birth, the human brain contains very limited quantities of myelin [84]. The process of myelination starts during the third trimester of pregnancy and progresses in a predetermined spatiotemporal order [84–86]. During development, myelin gradually wraps around the axons in the CNS, forming an insulating layer around them. This supports a swift and, likely even more importantly, well-synchronized propagation of electrical signals across the neuronal pathways, which in turn facilitates communication between spatially distributed brain regions [87, 88]. The bulk of myelination takes place during early childhood [84, 89–91]. However, it has been shown to continue for several decades, albeit to a lesser extent [87]. Moreover, oligodendrocyte precursor cells (OPCs) are present in the adult brain, and continue to proliferate and differentiate into oligodendrocytes, a cell type responsible for generating myelin [92, 93]. There is also mounting evidence that neural activity can modulate OPC activity and foster the formation of new myelin [94–96].

5.4.2.2 Dynamic myelin changes in response to behavioral stimulation

For a long time, researchers have assumed that the myelin sheaths around the brain's interconnecting nerve pathways are more or less stable in adults [97]. The validity of this long-held view though, is increasingly being called into question. Animal studies show that neural activity can affect myelin formation in the brain, and that this has impact on behavior. For example, the development of remote, but not recent, fear memories is hampered in transgenic mice that are unable to produce new myelin

[93]. This finding suggests that proliferation and differentiation of OPCs into mature oligodendrocytes and subsequent formation of new myelin is necessary for preservation of fear. Interestingly, immediate recall of fear memories was unaffected, suggesting that myelination is a fundamental prerequisite for their consolidation. Whether or not the same is true for other types of memories, remains to be investigated.

In order to learn a skill, the formation of new myelin is required and performing a recently acquired skill prompts new myelin forming cells (i.e., oligodendrocytes) to develop, which in turn leads to structural changes in white matter [98]. After several hours of training, motor learning was impaired in transgenic mice in which OPCs were unable to proliferate and differentiate into oligodendrocytes [98, 99]. Another rodent study demonstrated a connection between a motor learning paradigm and white matter structural indices, as captured by ex vivo MRI, in pathways implicated in the task [100]. Subsequent myelin staining techniques revealed higher myelin staining density in the white matter of those parts of the motor cortex that were associated with the execution of the task in the trained group as compared to a control group. Presumably there are different cellular or molecular processes underlying different stages of learning and memory formation, each of which follows its own time course – proliferation and differentiation of OPCs into oligodendrocytes in a matter of hours with subsequent myelination by mature oligodendrocytes over the course of a few weeks [93].

Animal research has provided valuable insights into the microstructural processes that underlie experience-dependent structural plasticity and its behavioral correlates – but its potential is naturally limited when it comes to answering questions about uniquely human abilities and behaviors, such as language, mathematical abilities, or the acquisition of musical expertise. It is uncertain to what extent the adult human brain can form new myelin in response to neural activity [101]. It is plausible that some of the structural changes captured by neuroimaging methods are indicators of remodeling of pre-existent myelin (for example through changes to thickness or internode length of the myelin sheaths) rather than the development of new myelin [101].

5.5 Imaging the brain with MRI

Continuous advancements in neuroimaging, especially magnetic resonance imaging (MRI), have enabled scientists to study many aspects of brain structure and function in-vivo and have significantly improved our understanding of how the brain's developmental trajectory looks throughout life, both in health and disease [102–104].

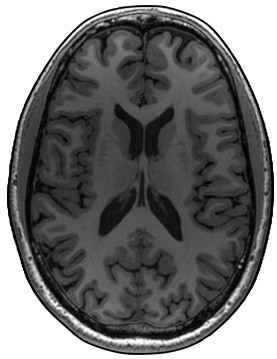

Figure 2: Example of T1-weighted MRI image.

MRI uses strong magnetic fields to detect signals from water-bound protons, which are abundant in the human body [43]. The signal differs depending on the environment these water-bound protons are in, which gives MRI its unique soft tissue contrast and ultimately enables clear visualization of brain anatomy, see example in Figure 2. A big advantage of MRI compared to other imaging methods (such as positron emission tomography, PET), is that it does not rely on ionizing radiation or the use of external contrast agents. This makes it possible to study vulnerable populations, like small children or patient groups.

Broadly speaking, MRI techniques can be categorized as either functional or structural. Functional MRI involves acquiring a series of low-resolution images over time to study the brain in action, such as monitoring blood flow, to infer information about neural activity. Structural MRI on the other hand, looks at gross anatomical features and is used to measure the volume or shape of a certain organ or region. Finally, there is a subset of structural MRI techniques which goes beyond anatomical structures and instead aim to provide information about the tissue microstructure on a voxel level, such as myelin, axonal diameter, or water content. These methods include quantitative MRI techniques, such as relaxometry, as well as diffusion MRI, among many others. The following two sections will provide an overview of how MRI can be used to capture brain structure at varying levels of detail, both by means of traditional morphometric measures and more novel microstructure indices that attempt to come closer to the anatomical phenomena that underlie gross structural features.

5.5.1 Grey matter MRI

MRI can be used to visualize and quantify cortical and subcortical grey matter. T1-weighted images, such as MPRAGE [105] or MP2RAGE [106], are used for this purpose as they provide strong contrast between white and grey matter. Since the cortex is only a few millimeters thin, high-resolution images are required, typically

at least 1x1x1 mm^3, see example in Figure 2. Based on these images, advanced image processing methods are used to compute different measures of the size and shape of grey matter, such as cortical thickness, surface area, gyrification, and grey matter volume [43]. These analyses can be based on either a volume- or surface-based approach. Volume measures can be computed both for the entire brain, types of tissue or specific subregions [43]. Common surface-based measures are cortical thickness, surface area and gyrification, all of which can be calculated in slightly different ways [43].

5.5.2 Myelin MRI

The contrast between white and grey matter in MRI is mainly produced by the different myelin content in the tissues. However, the image intensity in a single T1-weighted image does not give a quantitative estimate of focal myelin content. This issue has spawned a growing interest in a different type of MRI measures. These methods aim to complement traditional morphometric measures of grey matter by enabling inferences about underlying cellular processes or anatomical structures through biophysical models of the MRI signal obtained from multiple images with different contrasts. Myelin imaging is one such application. The reason myelin can be imaged using MRI is that it has a strong effect on the MR signal, in particular the relaxation times, the main determinant behind the image contrast [83]. There are numerous methods proposed for imaging myelin including relaxometry [107], magnetization transfer ratio (MTR) [108], cortical myelin mapping [109, 110] (namely T1w/T2w ratio which you will soon read more about), and diffusion MRI. Neither diffusion MRI nor MTR are specific to myelin and can reflect other tissue properties [111, 112]. Myelin water imaging (MWI), a type of relaxometry, and quantitative magnetization transfer methods have been shown to have high sensitivity to myelin at the same time as producing reliable results across different scan sites which makes them especially promising as biomarkers for myelin-dependent pathologies, such as multiple sclerosis and schizophrenia [83, 113, 114]. Myelin water imaging holds a lot of promise as a quantitative myelin measure. Its applicability used to be limited by long scan times, however, recent work using advanced reconstruction methods [115], has significantly reduced acquisition times, making the use of MWI viable even in vulnerable individuals, like children and clinical populations. However, just like other MRI metrics, myelin measures from MWI can be affected by other factors than purely the myelin content of the tissue which complicates the interpretation of the findings [116].

5.5.2.1 Myelin throughout the life span according to MRI evidence

MRI-based myelin measures have been applied frequently within clinical research on pathologies related to myelin, most prominently multiple sclerosis, an autoimmune disease characterized by focal areas of myelin damage, i.e., lesions [117–

[120]. Studies of brain development during childhood – the most crucial phase of life when it comes to the formation of new myelin [121] – have also begun to exploit the potential of myelin imaging. Myelin has been shown to increase steadily until about the third decade of life, around which it starts plateauing before gradually decreasing during older age [122]. Similarly, myelin imaging has been used to investigate the role of myelin on a wide range of cognitive functions and behaviors – in adults as well as in children, in health as well as in disease - indicating a clear association between myelin and performance in several different cognitive domains [87, 123–127]. At the same time, aberrant myelin has proven promising as biomarker for various neuropsychiatric and neurological disorders [125, 128–132]. Currently, evidence for an association between myelination and learning in humans is still scarce. Studying white matter variations in schizophrenia patients, researchers coincidentally observed that myelin water fraction in the control group positively correlated with age and years of education [133].

5.5.3 Methodological issues in neuroimaging research

5.5.3.1 Analytical issues in brain-behaviour association studies

Since MRI became widely available as a research tool at the onset of the new millennium, cognitive neuroscientists have been enthusiastic about its potential to help them get to the bottom of the causes of interindividual differences in human behavior, personality, and performance. Inspired by early studies tying brain lesions to behavioral deficits [134, 135], countless studies have been published attempting to relate various types of behavioral performance indices to underlying differences in healthy brain structure and function. A lot of times, the findings of such studies have proven to be difficult to replicate[136], leaving the community collectively scratching their heads. Methodological approaches and minimum standards have been an avidly discussed topic in the cognitive neuroscience community ever since the onset of the replication crisis. This has curbed the initial enthusiasm whilst increasingly calling the conventional approaches of one-on-one mapping of behavior to brain structure into question. A 2022 hallmark study [137] pooled data from three publicly available neuroimaging datasets and used the resulting sample of roughly 50.000 participants to quantify effect sizes in brain-behavior association studies and to examine how sample sizes affect their replicability. The results suggest that brain-behavior correlations in healthy individuals tend to be weak, reinforcing the findings of an earlier study [138]. At the same time, the likelihood of discovering significant brain-behavior associations using an exploratory approach is low [138]. Significant findings from underpowered studies inflating effect size estimates along with variability of included populations are likely contributors to the persistent replication struggle. Sample sizes to reliably detect such small brain-behavior associations in healthy populations will have to be significantly larger than what has typically been the case in behavioral neuroimaging studies [137].

5.5.3.2 Limitations of MRI as a research tool

Thanks to MRI, we now know a great deal about how different parts of the brain expand, respectively shrink throughout the lifespan [45, 59, 139]. However, despite this significant progress, numerous questions remain unanswered. Researchers around the world are trying to understand the cellular and physiological mechanisms that underpin gross structural changes and different types of observable behavior [140, 141]. While a spatial resolution of 1 mm^3 (typical in structural MRI) may seem detailed, one such unit of analysis, a voxel, can contain tens of thousands of cells of varying types [43]. Thus, any attempt to resolve information on a cellular level is limited by averaging over a relatively coarse resolution. Furthermore, MRI is non-quantitative and inherently unspecific, reflecting the combined effect of a variety of possible underlying biological and anatomical phenomena. For instance, a challenge in imaging myelin content is differentiating it from naturally co-occurring substances, most prominently iron, especially in the cortex [142, 143].

For clinical practice, where diagnostic decisions are based on qualitative assessment on a case-by-case basis, these confounders are often not important. But for research purposes, where quantitative metrics are obtained from each image, methodological choices at various levels matter. Everyone's brain is different, which makes reliable comparisons of brain structure metrics between individuals a nontrivial challenge. Different approaches have been developed to make this possible, most of which feature some form of registration of individual brain images to a common template, prior to subsequent analyses. Once images from multiple individuals are aligned in the same space (known as registration, or spatial normalization) and statistical maps have been computed, further difficulties arise due to the sheer amount of data one is faced with. Like pixels in a digital photograph, MRI images consists of hundreds of thousands of small constituting elements (voxels or vertices, depending on whether one is conducting their analyses in volume- or surface space). Comparing brain features across individuals or over time is often done at a voxel level and essentially results in having to conduct the same statistical hypothesis test many times. Dealing with such large quantities of data necessitates specific correction procedures and statistical thresholds to limit the risk of false positives (Type I Error). These decisions are far from straight straightforward and to a great extent up to a researcher's personal preference. This considerable analytical freedom can heavily influence an individual study's results and makes comparisons across different studies a challenge [144–146].

Another complicating factor is that scanner vendor and pulse sequence can affect images and quantitative results [147], and similarly choice of post-processing software has been shown to have an impact [148–151]. Efforts to harmonize data acquisition and to standardize analytical procedures in MRI research, for instance through the BIDS (Brain Imaging Data Structure) initiative [152] or HCP-style data [153] – which you will read more about in a moment – will be essential to foster

consensus within the community, which will help to keep analytical challenges at bay and to take full advantage of the data that is available.

5.5.4 Large-scale datasets

A growing trend in the recent past that promised to remedy a lot of the above issues concerning reproducibility in neuroimaging, are large-scale data initiatives. Prominent examples are the UK Biobank [154] , the Human Connectome Project (HCP) [155], and the Adolescent Brain Cognitive Development (ABCD) study [156]. The UK Biobank aims to improve our understanding of the underlying causes of various diseases and health conditions during middle and later adulthood by gathering a wealth of data, including but not limited to genetic and biological samples, cognitive assessments, and lifestyle factors [157]. About 20% of the overall 500,000 participants also undergo a comprehensive neuroimaging protocol[158]. The Human Connectome Project (HCP) is a consortium effort aimed to map out the brain's functional and structural connectivity by collecting and analyzing multimodal neuroimaging data from over 1000 healthy young adults. Since its inception, the project has been refunded multiple times and has been supplemented with several connectome-related sub-studies focusing on ageing and specific pathological populations. The ABCD study [156], which the work in this thesis is based on, is another well-known instance of a large-scale, multi-site neuroimaging project intended to collect multifaceted data from thousands of individuals. The project's overarching aim is to identify protective and risk factors that affect children's physical and mental well-being during adolescence. The size of the ABCD dataset does not only provide an opportunity to uncover structural brain-behavior associations in healthy, typically developing children, despite expected small effect sizes, but also the chance to put the reliability of the results to the test at the same time. Some previous research has focused on empirically testing the replicability of structural brain behavior associations [136, 159], though sample sizes in neuroimaging studies typically do not leave room for including a replication element to confirm initial results within the same investigation.

Thanks to multi-site projects like these, the neuroimaging community not only gets access to large, rich datasets, providing increased statistical power and enabling replicability studies, initiatives like the HCP or the ABCD are also pioneering with respect to introducing standardized procedures for data collection across sites and timepoints. The HCP consortium for instance has established a standard for data acquisition and image processing which they actively encourage others to follow [153]. Central preprocessing of the images provides interested researchers the possibility to work with quality-controlled data at the same time as it limits some of the analytical degrees of freedom.

6 Aims

What is it that sets apart people who excel in their educational journeys from those who do not? And how do we as a community investigate these factors in a reliable way? These are the central questions that brought about the present work. Given the broad nature of these questions, it is, of course, impossible to clarify them conclusively within a single thesis. Instead, we aim to provide additional evidence on the way towards increasing our understanding about this complex topic. In the search for answers, we first turned towards MRI as a forever promising research tool, hoping that we can find some answers by looking at the brain. Other obvious candidates influencing educational attainment were cognitive abilities and socioeconomic circumstances. Using a large, well-known dataset, we set out to test different methods to narrow down underlying factors of educational success. This did not only allow us to exclude the possibility that null findings were the result of too little data, but also provided us with the opportunity to directly put the robustness of our findings to the test – in the spirit of the much-discussed replication crisis within cognitive neuroscience.

The individual papers included in this thesis were written in pursuit of the above aims by targeting the specific objectives listed below:

- Test the suitability of T1w/T2w ratio for investigating links between children's cortical myelination and their cognitive abilities in a large sample of similar age (Paper I)
- Investigate associations between grey matter volume and language ability (Paper II)
- Scrutinize the robustness of whole-brain voxel-based morphometry analyses (Paper II)
- Test whether the effect of socioeconomic variables on school performance of typically developing children differs based on their cognitive performance (Paper III)
- Explore whether the effect of children's socioeconomic background on their grades varies as a function of time (Paper III)

7 Ethical considerations

Since the work in this thesis is based on the publicly available ABCD dataset, one could assume that researchers do not have to deliberate ethical issues that are usually considered when conducting a study. Questions one reflects over when applying for local ethical approval in conjunction with doing research involving humans do not arise in the same way because they have already been addressed by those that are overall responsible for the study and data collection in question. The scientists in charge of a large-scale study need to weigh benefits against potential risks of psychological or physical harm, something that carries weight particularly when under-age participants are involved. In neuroimaging studies, for instance, odds are that incidental findings will be brought to light, blurring the lines between scientific research and clinical routine [160]. It is vital that routines are in place for when unexpected findings come up. For the ABCD study, ethical review and approval was managed primarily by the central Institutional Review Board (IRB) at the University of California San Diego, where the study's overarching coordinating center is located, and in some cases by local IRBs directly at the sites. Children participating in the ABCD study provided informed assent in addition to their guardians signing informed consent forms.

The ABCD study collects a lot of sensitive information from participants, including biomedical data like MRI images and genetic information, but also questions regarding, among others, mental health history or substance use. Collecting this type of data from children and adolescents can lead to ethical challenges. For instance, if a child reveals information about potential risk factors, such as suicidal ideation, researchers must balance protecting participant confidentiality against possibly needing to disclose information to parents to not jeopardize children's health and well-being [161]. The ABCD consortium follows established biomedical ethical principles and has developed specific procedures and guidelines for local investigators to follow when ethical dilemmas arise [161]. Big, open neuroimaging datasets pose additional challenges, not only from an ethical but also a legal angle, with the objective of ensuring participants' privacy and controlling motives for secondary data use. Individual participants must be protected as much as the communities they belong to, especially when marginalized groups are concerned [160].

Like many other large-scale studies, the ABCD dataset is shared via a repository that is managed by the National Institute of Mental Health Data Archive (NDA;

https://nda.nih.gov, last accessed on 21 April 2023) and access to it requires an agreement between the researcher's home university, providing institutional sponsorship, and the NIH. This is done via a Data Use Certification (DUC) which specifies the targeted research questions as well as who will have access to the data. The DUC is updated on a yearly basis, including a progress report. It also stipulates adherence to best practices when it comes to secure data storage in agreement with local as well as national and international regulations. Ensuring that the terms and conditions of the agreement are followed, is one of the most important responsibilities of a researcher when working with a public dataset.

8 Materials and methods

8.1 The ABCD dataset

The Adolescent Brain Cognitive Development (ABCD) study is an NIH-funded longitudinal, multi-site research project that follows nearly 12,000 participants, aged 9-to-10 years at the onset of the study, to identify biological and environmental variables that affect an individual's developmental trajectory, health, and well-being [156]. At present, it is the largest, most comprehensive study investigating brain health in children and adolescents. Starting in 2017, data is collected over the course of ten years at regular intervals, the timing of which depends on the type of data, at 21 sites (22 at the beginning) across the United States. When it comes to race and ethnicity, the children included in the sample come from diverse backgrounds, aimed to reflect the proportions found in the general population in the US [162]. Cognitive performance data is collected yearly, MRI data every second year. In addition, various other types of data, such as biospecimens, mental and physical health, substance use and physical activity as well as information on the participants' familial, cultural, and socioeconomic background, are also available. Some of these are complemented by questionnaire data obtained from the children's parents. Furthermore, data from external sources is also available, supplying additional information about the participants' place of residence, for instance with respect to education, employment, and housing quality. The Covid-19 pandemic prompted efforts to adapt the existent procedures and to conduct testing and assessments remotely whenever possible. The study protocol has also been supplemented with a questionnaire targeting behaviors and experiences in response to the pandemic.

The infrastructure to store and share all the data that the ABCD study generates is provided and managed by the NDA. Data is made available to researchers with an up-to-date DUC through annual releases. Following in-house quality control procedures, these annual releases contain curated and tabulated behavioral and questionnaire data as well as pre-processed imaging data. In addition, these releases also include raw imaging data. The data that was used for the present dissertation stems from the third (Paper I and II) and fourth (Paper III) annual release. Besides the annual releases, raw imaging data is also shared on an ongoing basis, in the form of so-called "Fast track releases".

The papers included in this thesis are based on subsets rather than the entire ABCD cohort. Due to computational constraints, Study I and II are based on a random

sample of one, respectively two thousand participants. These subsamples were reduced to account for specific inclusion criteria, which are described in more detail in the respective papers. Since no imaging data was used in Study III, computing power was not an issue, and the sample was thus derived from the complete ABCD cohort.

8.2 Education measure

The ABCD study provides data on children's academic performance by means of self-reports. Both the children themselves and their caregivers are asked to rate their overall performance in school during the last year on a scale from 1 (corresponding to an A+) to 12 (corresponding to an F). For our analyses, we recoded these number grades to the common American 5-point letter scale from A to F to aid interpretability. While this is a possibly less accurate measure than information directly from the schools, evidence suggests overall good correspondence between self-reported and actual grades despite a tendency to overestimate one's performance [163]. Other findings suggest some caution when it comes to using self-reported grades as an indicator of true performance due to systematic variations based on age, ability, and performance level [164, 165]. In the case of the ABCD study, children and parents provide information regarding school performance overall, rather than on different subjects individually, which has previously been shown to have higher validity as a reflection of actual attainment [165]. For this thesis, school performance data from two timepoints, two and three years after the baseline assessment, were used.

8.3 Cognitive measures

Cognitive ability in the context of the ABCD study is assessed yearly through the NIH Toolbox Cognition Battery, a collection of several measures evaluating both fluid and crystallized aspects of cognition [166, 167]. The individual tests included in the battery measure attention (Flanker Inhibitory Control and Attention Test), executive function (Dimensional Change Card Sort Test, Flanker Inhibitory Control and Attention Test), expressive and receptive language (Oral Reading Recognition Test, Picture Vocabulary Test), memory (List Sorting Working Memory test, Picture Sequence Memory Test), and processing speed (Pattern Comparison Processing Speed Test). In addition to individual test scores for each of the measures, each assessment also yields three composite scores: fluid, crystallized and total. These summarize an individual's performance across either all fluid test domains (attention, executive function, memory, processing speed), all crystalized

(expressive and receptive language), or the entire test battery. For the ABCD study, all tests are performed on an iPad with English as instructional and test language.

8.4 Socioeconomic variables

Accounting for the multi-faceted nature of socioeconomic status, the ABCD study contains several measures characterizing a participant's background. At an individual level, data on parental education and employment status as well as household income is available. For Paper III, data on parental education as well as household income were used. Total income per household for the previous 12 months was divided by the 2017 federal guideline for poverty for the respective number of people living in a household to account for the number of people supported by a given income. The resulting figure represents an income-to-needs ratio (ITN) where a ratio <1 indicates that a household is living below poverty level, while values >1 indicate an income above poverty level.

In addition to data from individual households, the Area Deprivation Index (ADI) provides information about the level of socioeconomic disadvantage in the neighborhood a participant's residence is located in. The ADI data is not collected by ABCD researchers but is instead derived from the American Community Survey (www.census.gov/programs-surveys/acs, last accessed on 5 January 2024). It aggregates data about the amount of deprivation present in an area, by assessing factors like housing quality, education, employment, and income. The ADI ranks neighborhoods across the United States and assigns national percentiles to each area. Accordingly, affluent neighborhoods receive low ADI scores, disadvantaged neighborhoods are given high ADI values.

8.5 MRI-based measures of brain structure

This thesis takes a multimodal approach to characterizing grey matter structure using two techniques which describe grey matter at different levels of detail. The first is Voxel Based Morphometry (VBM) which looks at brain structure on a macroscopic level to study how the size of brain regions differs between individuals or groups. The second is the T1w/T2w ratio which attempts to provide information about grey matter on a microscopic level, as a proxy for myelin. In the following, you will learn about both methods separately in more detail.

8.5.1 Voxel-based morphometry

Voxel-based morphometry (VBM) was first proposed as an objective way of quantifying brain structure in the early 2000s [168, 169] to enable comparisons between groups or individuals. It is typically used to characterize grey matter and it is one of the most widely used techniques of neuroimaging researchers to study brain structure, with well over 6000 studies published between 1993 and late 2020 using the method [146]. VBM is an automated technique that takes a mass-univariate approach, computing grey matter probability across the entire brain independently in every voxel. Various software packages are available for running VBM with different processing options, but the basic steps look as follows, also summarized in Figure 3.

1. Segmentation: The image is segmented into white matter, grey matter, and cerebrospinal fluid based on intensity values as well as priors [170].
2. Non-linear spatial normalization: The T1-weighted image is normalized to a common template, also called template space.
3. Modulation: This step applies a correction to compensate for enlarging or compressing native brain regions to fit them to the template by multiplying a voxel's intensity value by the Jacobian of the deformation field in each voxel, the result of which is that each voxel's concentration is scaled relative to the amount of deformation that was applied to it.
4. Smoothing: A Gaussian kernel is used to smooth the image, thereby assigning each voxel the weighted average intensity of its surrounding voxels, which helps to make up for inaccuracies induced by the normalization.

This workflow results in individual probability maps that quantify the likelihood that a given voxel is grey matter. Based on these maps, voxel-wise statistical analyses can be performed to make inferences about local tissue differences between individuals or groups as well as relationships to other variables, like clinical scores or phenotypical manifestations. Since statistical tests are typically performed separately at each voxel, correction procedures to account for multiple comparisons, by controlling either the Family-wise error rate (FWER) or False Discovery Rate (FDR), are needed [171]. Following VBM, local grey matter can be characterized as either concentration or volume, depending on whether modulation is included in the processing [170, 172, 173].

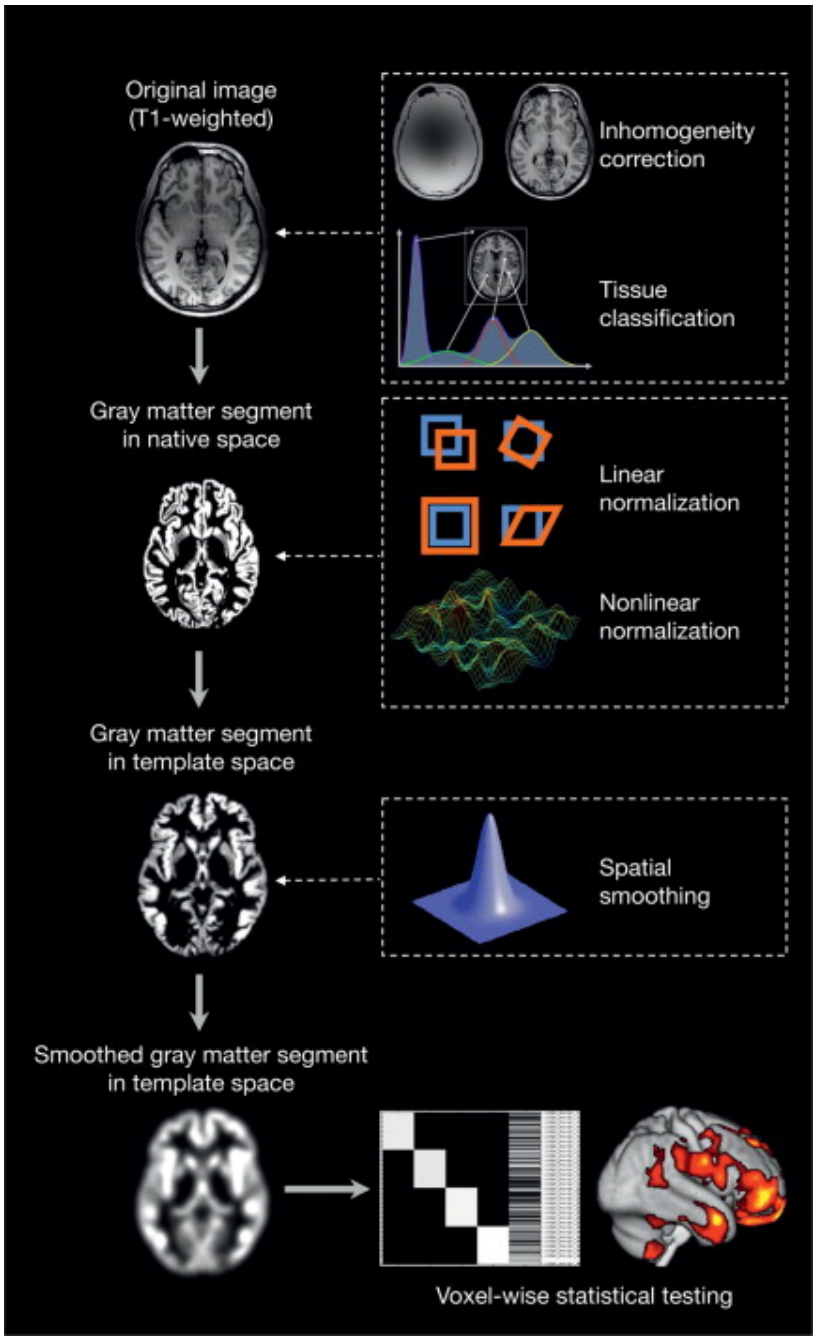

Figure 3: General overview of the main steps included in the VBM workflow. Note that minor variations exist between common software packages. Reprinted from Brain Mapping, Vol 1, F. Kurth, E. Luders, C. Gaser, Voxel-Based Morphometry, 345-349, Copyright (2015),

Since it was first described, VBM has become widely used and accepted in the neuroimaging community as a tool to characterize brain morphometry. The technique is attractive because it is automated, objective[170, 173], and well-suited for exploratory studies. At the same time, it has drawn criticism for producing false positives due to normalization and segmentation errors (especially in areas with low contrast), risk of partial volume effects where different types of tissue exist in a single voxel, and for having little power to detect differences in areas of high interindividual variability. Compared to surface-based approaches, VBM has also been criticized for lacking specificity, since grey matter is represented by a measure that subsumes information on thickness, surface area and folding of the cortex [174]. It also respects anatomical boundaries less well than surface-based analyses [140]. Results are typically difficult to compare across studies due to researchers' freedom in terms of customizing individual pipelines by adjusting parameters for acquisition, preprocessing and statistical analysis which has been shown to produce divergent results, thus causing problems with reproducibility [146, 151, 175, 176].

8.5.2 T1w/T2w ratio

Myelin is one of the most important tissue components which drives image contrast in MRI of the brain, as previously discussed. Both T1- and T2-weighted images are affected by myelin, in opposite direction. Image intensity increases in T1-weighted images, while it decreases in T2-weighted images with increasing myelin content. Dividing the intensities of a T1-weighted and a T2-weighted image, i.e., computing a T1w/T2w ratio, to map cortical areas based on their myelin content was first proposed a little over a decade ago [110]. There are several reasons behind why the ratio image is said to reflect cortical myelin content: lipids contained in myelin have been identified as the main driver behind the T1w and T2w image contrast between grey and white matter, T1 signal intensities can be used to delineate cortical myelin content, while the T2 signal is inversely proportional to myelin [177]. The images are first linearly co-registered, and then divided by one another voxel-by-voxel. The resulting ratio image is characterized by increased contrast to noise ratio for myelin at the same time as some MR-related intensity bias is attenuated [110]. More specifically, since both input images are assumed to be equally affected by receive field (B_1^-) bias, its influence is removed in the ratio image [110].

Neuroimaging software can be used to compute 3D models of the brain from MR images, namely segmentation of tissue types and parcellation of individual brain regions. A critical step for computing accurate T1w/T2w ratio maps is the reconstruction of the inner and outer cortical surface. Issues can arise due to susceptibility artifacts in the input images and poor surface reconstruction [110]. Erroneously low T1w/T2w ratio values and cortical thickness estimates can arise in regions where the cortex is very thin and heavily myelinated, since the intensities of heavily myelinated grey matter and white matter are not vastly different which can

make it difficult for the analysis software to place the surfaces correctly [110]. Areas where the cortex is both thick and lightly myelinated can receive inflated T1w/T2w ratio values, because the intensity of the more exterior layers of grey matter resemble those of CSF more than deeper layers of grey matter, thereby risking that the pial surface is placed incorrectly [110]. With some exceptions, T1w/T2w ratio is negatively associated with curvature-corrected cortical thickness, partially because heavily myelinated parts of the cortex are often comparably thin, but also since deeper, more heavily myelinated cortical layers can be mistaken for white matter during segmentation [110].

It is easy to recognize why T1w/T2w ratio as an index of myelin content is attractive: the two structural images are standard elements in most MRI examinations, their acquisition is comparably fast, even at high resolution which makes clinical applications feasible [178]. On top of that, computing the ratio is relatively simple using well-established pipelines [179], compared to many of the more specific, quantitative myelin measures that often require long acquisition times and complex modeling [114][163]. For cognitive neuroscientists, the most significant limitation of the technique is that it is calculated based on raw, unitless intensity values and affected by numerous non-biological factors [110, 177], thus impeding comparisons across individuals, scanners, sequences or timepoints [177]. Like all other MRI metrics, the T1w/T2w ratio is not a direct measure of myelin, and its sensitivity has been contested, suggesting it may reflect axonal diameter and dendrite density rather than myelin content [174]. Nevertheless, numerous studies have been published in the recent past, using T1w/T2w ratio as a semi-quantitative proxy for cortical myelin, exploring its relationship to development, ageing, as well as its associations with behavior and performance [58, 120, 177–182], personality traits [183], pathologies involving suspected or confirmed myelin dysfunction [184–189] and other living circumstances and experiences [190]. T1w/T2w ratio has also been used to study subcortical and white matter myelination [180–183], even though doubts as to whether the measure can accurately reflect myelin in white matter have been raised [178, 181]. Concurrently, various approaches have been designed and tested to mitigate some of the drawbacks of the technique through different bias correction, intensity calibration, and standardization procedures [177, 184, 185] to alleviate non-systematic variations and to facilitate comparisons between individuals, studies, and sites [186].

8.6 Analytical approach

8.6.1 Study I

Following previously shown associations between learning and myelin, the objective of Study I was to explore whether better cognitive abilities could be tied to local T1w/T2w ratio, as a proxy for cortical myelin. The work is based on cognitive performance and MRI baseline data from 960 ABCD participants (511 boys). T1 and T2 weighted structural images were used to compute individual T1w/T2w ratio maps. Using permutation based general linear modelling in FSL PALM [187], we tested for positive and negative associations between T1w/T2w ratio across the brain and each of the seven cognitive tests from the NIH toolbox. To account for possible scanner effects, scanner site was included in the models as confounder. In a supplementary analysis, we also included age, sex, and SES as covariates of no interest in addition to scanner site.

8.6.2 Study II

To further probe relationships between grey matter and cognition, we used VBM to assess grey matter volume in the same sample of children that was studied in Study I (N = 939). Using permutation based general linear modelling in FSL randomise [188], we correlated voxel-wise grey matter with children's performance in the two crystalized cognition domains (vocabulary and reading skills). As in Study I, we included scanner site as covariate of no interest in the model. We then ran the same analysis with fluid cognitive abilities and total grey mater volume included in the model as additional covariates of no interest, to evaluate if associations between language abilities and grey matter volume are robust even when other variables are factored in. Following this, we supplemented the whole-brain VBM analysis by attempting to replicate the significant clusters we found initially in a second, equivalent subset of ABCD data (N = 926) when using a ROI-based approach. We extracted median grey matter volume from all relevant areas and tested if they covary with language performance scores, with and without fluid cognition and total grey matter volume taken into account.

8.6.3 Study III

Effects of SES on school performance are well-established in the educational science literature. The aim of Study III was to test whether these links vary as a function of children's cognitive ability. For this purpose, we used cognitive performance, SES, and school performance data from 5001 children participating in the ABCD study. Children's cognitive abilities were represented by their individual

total composite scores, a value summarizing their performance across all seven NIH toolbox measures. SES was assessed in terms of parental level of education, income-to-needs ratio, and neighborhood deprivation. School performance was operationalized as average grades reported by the children. Cognitive and SES data stems from the baseline assessment, while grade estimates were derived from the 2- and 3-year follow-up data collection. We created ordinal logistic regression models where letter grades served as dependent variable and cognition scores and the three SES variables were used as predictors. In separate models, we tested main effects of SES on grades, possible interactions with cognitive ability as well as the relationship between SES and grades over time.

9 Results

9.1 Study I

Testing correlations between T1w/T2w ratio cortical maps and children's performance on the seven NIH cognition measures did not yield any statistically significant associations at an α-threshold of 0.05, irrespective of whether demographic variables (age, sex, and SES) were included in the models as confounders or not. Similarly, neither sex, age, nor SES were associated with T1w/T2w ratio [189].

Based on the absence of any statistically significant relationships despite using a large sample, we conclude that T1w/T2w ratio is not a suitable metric for associating variations in children's cortical myelin with interindividual differences in cognitive abilities. Given that the individual T1w/T2w ratio maps conformed well to the spatial patterns expected based on the existent literature on cortical myelin (see Figure 4), with primary sensory and motor cortices being the most heavily myelinated regions, there were no major issues on the level of the image post-processing. Nonetheless, Study I suggests that cortical T1w/T2w ratio is not appropriate for establishing statistical associations between cortical myelin and

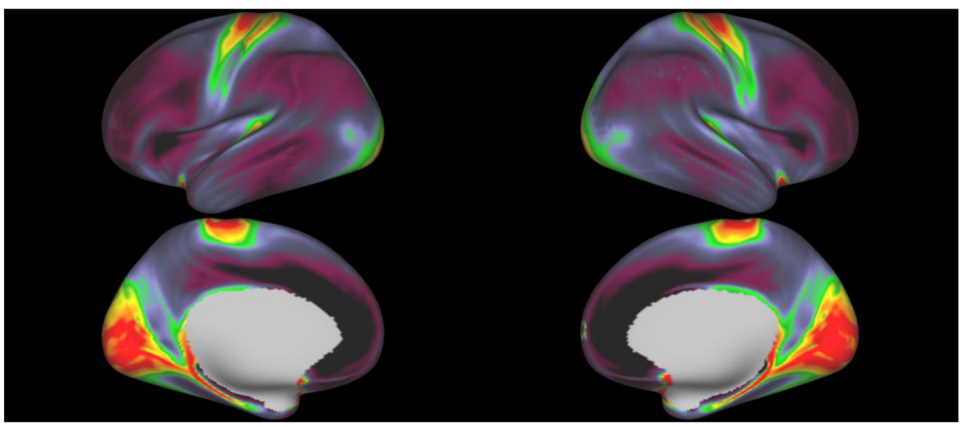

Figure 4: Average cortical myelin map from the sample used in Study I. From Langensee et al. [186], distributed under a CC-BY 4.0 DEED license.

behavioral scores. As it currently stands, it is not possible to determine if this is the result of methodological issues, whether variations in cortical myelin are too small in this age-homogenous sample to tie them to behavioral differences, or if perhaps correlations between cognitive abilities and cortical myelin truly are absent in this age range.

9.2 Study II

After correcting for multiple comparisons and thresholding the *t*-statistical maps at $\alpha = 0.05$, we saw a negative correlation between receptive vocabulary and a large predominantly right-hemispheric cluster including parts of the amygdala, the anterior parahippocampal gyrus, the temporal pole, and the medial orbitofrontal cortex. We also found a positive relationship between children's reading performance with regional grey matter volume in a cluster in the middle of the right occipital fusiform as well as lingual gyrus. Including total grey matter volume and fluid cognitive abilities in the analysis as confounders, produced three significant positive associations between regional grey matter volume and receptive vocabulary. The first cluster was located around the occipital fusiform gyrus and the temporal occipital fusiform cortex of the right hemisphere, stretching into the cerebellum. The second and third cluster were both located in the left cerebellum. Similarly, reading performance correlated positively with grey matter volume in two clusters, the first one in the right hemisphere occipital fusiform gyrus and lingual gyrus, the second one in the right cerebellum.

The replication analysis in the second subset of data yielded a mixed picture. The two clusters derived from the analysis not factoring in total grey matter volume and fluid cognition were both successfully replicated. In contrast, only one of the five clusters that emerged from the extended models (including not only scanner site but fluid cognition and total grey matter volume as covariates of no interest) was replicated in the second sample. Multiple regression analysis identified total grey matter volume and fluid cognitive abilities as the most robust predictors of both vocabulary and reading performance, though with negligible effect sizes for total grey matter volume. In addition, grey matter volume in a cluster in the left cerebellum was associated with vocabulary scores, and grey matter volume in the right occipital fusiform and lingual gyrus was predictive of reading abilities in boys [190].

9.3 Study III

Ensuing from literature implying cognitive abilities and socioeconomic background as critical determinants for an individual's educational success, the goal of Study III was to determine whether cognitive performance interacted with parental socioeconomic status in their effect on educational achievement. Using ordinal logistic regression analysis, we looked at whether the effect of three indices of socioeconomic status (parental education, income-to-needs ratio, and neighborhood deprivation) on grades varied as a function of overall cognitive ability. All three SES measures were significantly associated with children's grades at two timepoints, though interactions between SES and time were not confirmed. After including cognitive abilities in the models, parental education and income-to-needs ratio still proved to be significant predictors of grades at both timepoints, while neighborhood deprivation did not. Cognitive performance scores were the strongest independent predictor of grades at both timepoints, though we also saw some evidence for an interaction between cognitive abilities and parental education.

10 Discussion

In the wake of MRI scanners becoming more and more widely available, the technique has been applied enthusiastically and celebrated by many cognitive neuroscientists as a kind of magic bullet. The fact that we suddenly could get a, somewhat, direct look at the living brain certainly deserved some excitement. Understandably, attempting to explain all kinds of behavioral, cognitive, or emotional traits and functions, ranging from typical to pathological, by relating them to their "neural substrates" has become immensely popular among neuroimaging researchers in the last two decades. More recently however, the tides have started to turn. Inadequate sample sizes, suboptimal statistical testing procedures and publication bias have led to a much-discussed replication crisis. One vital remedy for this crisis were meant to be increasing sample sizes, either from large-scale, multi-center studies or from collaborative efforts to combine and share datasets across sites. This dissertation makes it clear that even when a much bigger than average participant pool is available, neither macro- nor microstructural brain metrics are guaranteed to generate robust explanations of behavioral differences – in line with recent work that reached a similar conclusion based on investigating cortical thickness data [137].

10.1 Summary of findings

The present work employed two different structural MRI indices, namely VBM and T1w/T2w ratio, to investigate associations between brain structure and cognitive performance in children. Yet, it did not reveal any robust correlations between these indices in specific areas of the brain and cognitive abilities. Rather than clarifying how children's brain structure relates to their behavior, this thesis illustrates the problems that are associated with using exploratory studies to study correlations between a behavioral phenotype and brain structural indices. Our findings are a testament to the methodological difficulties associated with brain-wide association studies [137] and the evolving idea within the cognitive neuroscience community of what constitutes a large sample size [191]. The early days of neuroimaging research were characterized by samples that nowadays can seem suitable for a pilot study at best and typical sample sizes have continuously been growing since [192]. However, the first two papers included in the present work clearly show that even sample sizes

that are far beyond average still do not necessarily provide sufficient of a foundation to allow inferences about relationships between brain structure and behavior – at the very least when employing a mass-univariate approach in healthy, similarly aged children. Ultimately, we cannot be certain where the null results originate from. There is a good chance that the brains of children that are cognitively stronger differ in some way from those that are weaker. However, what we can state, based on the present work, is that neither T1w/T2w ratio nor VBM appear to be adequate tools to make these differences visible. While the two brain structure metrics that were used in this work did not contribute to a better understanding of children's cognitive abilities, both socioeconomic status and cognitive performance helped explain some variance in how well the children did in school. In other words, socioeconomic status and cognitive ability have proven more useful and cost-efficient for explaining interindividual differences in educational attainment than MRI data.

The fact that we did not find robust links between brain structure and behavior does not imply that all MRI research involving small sample sizes is automatically unreliable. But for results from a limited number of participants to be robust, targeted questions and carefully designed experiments are essential [137, 193]. Broad, exploratory questions cannot be answered based on limited sample sizes and, as this thesis demonstrates, even a dataset that is much larger than what is typically available does not guarantee robust results. While the human neuroscience community as a collective is currently pushing for larger and larger datasets and population-based research, some have made a stand against this trend and instead advocate for deep imaging, that is, gathering a substantial amount of data from only a few individuals [194–197]. Instead of aiming to collect MRI data from as many participants as possible, the goal is to follow only a few people and to scan them as many times as possible. This approach promises to illustrate details and nuances on the level of individual brains, rather than averaging across a larger number of brains at the expense of interindividual variability. If participants are followed during a longer period, this type of study design has the potential to reveal novel insights about how the brain changes over time at a level of detail that is not attainable through more conventional neuroimaging study designs that usually gather data for a very limited number of timepoints.

10.2 Large datasets

Large, multimodal imaging datasets have fueled much research and enabled many new perspectives and insights into the brain's inner workings [139, 198–200]. While multisite studies like the ABCD are great in many ways, the price one pays for working with a large, longitudinal sample is that the data that is collected is meant to cater to a broad range of research aims. Rather than being designed specifically for the questions that this work has attempted to answer (or for that matter any study

in particular), the MRI sequences and behavioral measures available through the ABCD study represent a lowest common denominator, intended to be applicable in as many different contexts as possible. At the start, any researcher intending to make use of the ABCD sample should ask themselves whether the available data really is appropriate to answer the questions they are interested in. Although T1w/T2w ratio has become a popular tool to study potential relationships between myelin and a range of traits, behaviors, and psychological and clinical variables, the metric has received criticism and its ability to represent myelin content has been contested.

ABCD and other large cohorts measured with neuroimaging are valuable for the scientific community and provide many unique opportunities to generate new knowledge, but they also carry a high risk that many new insights will be extracted from the same pool of participants. Even though the ABCD has taken measures to ensure the included children reflect the diversity of the population of the US, some selection bias will be unavoidable. For instance, although the acquisition sites are spread across the contiguous US (excluding Hawaii and Alaska), they inevitably must be located at a university with access to MRI equipment and expertise. Accordingly, children living in urban and metropolitan areas will be overrepresented compared to those from rural areas, far away from the draw area of a sizeable research university. Similarly, the ABCD sample is skewed towards high socioeconomic status. Large-scale neuroimaging projects will have to become more diverse, representing heterogeneous populations and living conditions, to generate truly generalizable knowledge. Nonetheless, at present the community still suffers from a persistent bias towards *weird* societies (western, educated, industrialized, rich, democratic) [201], representing only a small fraction of the diversity of human behavior and ability – contradictory to the goal of many neuroscientists trying to find the neural correlates of interindividual differences. The effect of socioeconomic background on educational attainment for example has been shown to vary vastly depending on which region of the world is being considered [202] – the present findings need to be viewed with this in mind. Some similar large neuroimaging initiatives have gotten under way in other parts of the world, though presently still not quite of the same magnitude as the likes of ABCD and HCP [203]. Large-scale neuroimaging studies give way to a vast number of publications based on the same data – from a statistical point of view, conducting many statistical tests is bound to lead to some positive findings. Which of these ultimately will be revealed to be false positives, and which will be corroborated as a reflection of true phenomena remains to be seen.

A central downside of working with a large, public dataset is the lack of control over many key variables. Consider, for instance, the age of the sample, especially with respect to Study II and its focus on language performance. Aged between 9 and 11 when first entering the study, ABCD participants can be assumed to already have achieved the most important milestones of speech and language development. The first few years of life, including prenatal development [204], are the most critical

when it comes to language acquisition and the corresponding modifications going on at a neurobiological level. Language lateralization, for instance, has been shown to be established at around age 5, with limited changes after that [205]. At around 10 years of age, a lot of neural and behavioral changes have already taken place and in many ways these children already start to resemble adults in their brain structure and performance patterns [206, 207]. A younger cohort may have been more insightful, when it comes to how language abilities are reflected in the brain specifically during key developmental periods, but scanning younger children comes with its own difficulties and limitations.

10.3 Analytical approach

10.3.1 Strengths

All three papers included in this dissertation are based on large samples. While researchers typically do not undertake new projects, hoping for null results, if nothing else, the sample sizes of the three studies in this dissertation, make it difficult to blame the lack of significant relationships on insufficient data quantities. Alternatively, if 1000 children in fact are not enough data to illustrate links between their brain structure and their cognitive abilities, because effect sizes are so small, then one is left to wonder whether it is useful to look at the brain to explain differences in cognition in healthy children in the first place, at the very least with the measures that were used in this work.

As outlined earlier, there is uncertainty when it comes to the robustness of the cognitive neuroscience literature, with many published findings not withstanding replication attempts. Based on this, we saw a need to directly investigate the reliability of the results we obtain using standard methods. Living up to previously raised demands [138], Study II includes an independent confirmatory analysis to verify the robustness of the initial findings and to put their generalizability to the test. In the wake of the recent machine learning boom, cross-validation methods like k-fold or leave-one-out have become popular to evaluate the performance of one's model on unseen data. Owing to the amount of data available, rather than dividing our sample in a test and a training set, we drew two random samples and treated them as entirely separate – using one group of participants to locate regions of interest and a second batch to assess the generalizability of the initial results. The results from our replicational analysis clearly suggest that analytical choices influence the outcome of an analysis and thus corroborate existing doubts about the reliability of the cognitive neuroscience literature.

The brain-behavior analyses in this work were based on two different approaches to quantify brain structure in the same sample of children. Using both VBM and

T1w/T2w ratio as structural metrics combines a well-established with a more novel technique that quantify grey matter in different ways. While VBM can quantify regional differences in grey matter volume at a macroscopic level, T1w/T2w ratio aims to provide information about underlying microstructure, promising to bring cognitive neuroscientists closer to the cellular events underlying behavioral phenotypes. Even more so than T1w/T2w ratio, VBM is a standard tool for exploratory analyses of neuroimaging data [140]. Some of the advantages of the technique are that it can be used to study the entire brain, even though it is typically used to look at grey matter. Like T1w/T2w, VBM is semi-quantitative. It enables researchers to conduct exploratory, unbiased analyses in an automated way without requiring prior assumptions. Nonetheless, both point towards the same general conclusion, namely that these brain structural indices are not suitable measures to explain individual behavioral differences among children on the spectrum of typical development at a population level.

Even though T1w/T2w ratio was not confirmed as a valid indicator of cortical myelin for interindividual comparisons, the null results are still an important finding during a time in which this metric has been applied widely to study the underlying neural variables of phenotypical or behavioral differences in various populations [58, 124, 208–210]. The community actively encourages publication of null findings to produce a more realistic literature about structural brain-behavior relationships [138]. In this spirit, Study I can hopefully contribute to creating much-needed balance in the available literature on T1w/T2w ratio and its (lack of) suitability for explaining variations in human behavior.

10.3.2 Limitations

Quite often there is no direct correspondence between behavior on the one hand and brain structure and function on the other [211]. Various structural correlates can generate the same type of behavior, a concept known 'multiple realizability' [211]. In other words, a specific cognitive or mental function can be expressed by different underlying patterns of neural activity and brain structural substrates. With this in mind, it makes sense that trying to explain variations in something as complex as cognitive abilities by mapping them one-to-one to a corresponding brain region is a too simplistic approach – a notion that has been gaining increasing traction among cognitive neuroscientists [135, 138]. The practice of trying to match a specific cognitive skill to localized brain structure subserving it – sometimes referred to as *blobology* – is quickly becoming obsolete. Both imaging studies in this thesis are based on mass-univariate analyses, an approach that has been popular in human neuroscience for some time, but that has attracted criticism in recent years [135, 137, 193]. Thanks to the increasing availability of larger datasets, multivariate pattern analysis and machine learning approaches, such as deep learning models [212], have become a viable alternative to more traditional approaches [135]. At the same time, systems or

network neuroscience has started to get established as a more realistic and insight promising approach [213]. Rather than looking at selected areas in isolation, network neuroscience views the brain as complex network characterized by numerous connections (edges) between different regions (nodes). Not least thanks to continuously increasing computing power, dynamic simulations of neural circuit activities based on mathematical modelling have been gaining popularity among researchers.

The phenomena that were studied in this dissertation are complex and multifaceted. Neither brain structure, nor cognitive abilities, socioeconomic status or educational success are concepts that can be easily summarized, described, or measured – which makes studying them systematically a considerable challenge. This is complicated further by the countless interdependencies between each of these variables. It is therefore not surprising that complex questions cannot be answered comprehensively by reducing the problem to only looking at a few selected factors and testing handpicked relationships between them. For instance, different aspects jointly make up an individual's socioeconomic status. Thus, even under tighter experimental control, unraveling the specific contributions of each of these and establishing causality is challenging. Equivalently, it is difficult to determine the individual effects of different SES variables on education since they typically co-vary [214]. In this thesis we used income-to-needs ratio, parent education and neighborhood deprivation to account for children's SES. While this is supposed to provide an insight into socioeconomic conditions from varied angles, all three variables correlate substantially, which is why it is tricky to make definite statements about the explanatory power of each of them when trying to explain grades. Similarly, cognition and school grades are not neatly discernible phenomena [7]. Brain maturation, cognitive development, and education unfold in parallel and with numerous interactions. All three continuously interact, ideally by reinforcing one another, or, in less fortunate cases, aggravating each other.

This thesis reports primarily cross-sectional observations on brain-behavior relationships; it did not test effects of any intervention or experimental (or naturally occurring) manipulation. Correlational approaches, by nature, suffer from a lack of experimental control, which hampers the exclusion of possible alternative explanations for the observed outcome [134]. In fact, lack of tight experimental control is a major additional parameter distinguishing typical smaller-scale studies from their large, multi-site counterparts [215] – other than the obvious difference in amount of data that is generated. It is also possible that approaching the questions this thesis was aimed at from a more dynamic perspective would have made a difference in the extent to which brain structure can be used to explain differences in behavioral performance. Rather than comparing static snapshots of a specific moment in time during a child's development, it may have been more informative to instead look at how scores changed over time, to see whether a statistical association emerges between structural reorganization in the brain and development

of performance during a given time frame. Previous research that adopted this type of approach found that decreasing cortical volume was correlated with vocabulary and math performance in school-aged children, while reading and writing skills were not [216]. This research also found associations between vocabulary performance and grey matter volume collected at the same timepoint – unlike what we saw in Study II – possibly because their sample was somewhat less homogeneous in age than ours (9-16 years old as opposed to 9-11).

The main criticisms of MRI as a research tool are its lack of tissue specificity and lack of quantitative reference point for the image intensity, it is therefore difficult to say anything conclusive regarding the cellular features and mechanisms that underlie the image features we see [217]. Even though many standard structural indices based on MRI images appear quantitative on the face of it, some lack a measurement unit that would make them comparable across studies and sites. Neither VBM nor T1w/T2w ratio provide a pure reflection of any cellular or anatomical constituent. Rather, they are conglomerate measures whose values are influenced by various factors, from multiple different underlying neurobiological components to practical aspects such as experimental set-up, hardware or a participant's head size. In deep grey matter for example, signal intensities can be confounded by colocalized iron which affects T2w more than T1w signals [218], and while T1w intensities are driven by myelin content, it is not the only factor that affects the image intensity [218]. VBM is also not specific with respect to the underlying tissue properties the values reflect[140]. Different cellular processes, like cell density or myelination, affect relaxation times and will thus affect a voxel's intensity and consequently VBM results [140].

Various novel MR sequences have been put forward in the last couple of years aimed to make MRI data more conclusive when it comes to the underlying tissue properties it visualizes. Among these, T1w/T2w ratio has been proposed as a semi-quantitative metric for myelin [110]. The initial purpose was to use the contrast to parcellate the cortex. However, it has now eagerly been applied by many scientists who used the technique to study various behavioral phenomena and their relation to myelin, even though it was not originally designed for this purpose [58, 124, 209, 219]. T1w/T2w maps may be a useful tool for researchers that can provide novel information, which could contain biological information, but caution is warranted. It is uncertain to what extent T1w/T2w ratio can reflect myelin content across individuals, and its interpretation across different studies is complicated and fraught with methodological challenges. While the simplicity of computing the T1w/T2w ratio is alluring, its main inherent problem is that image intensities are session-specific and standardizing them reliably is not trivial [37, 218]. While the uncorrected T1w/T2w ratio might not live up to these high hopes, it clearly signals an ambition to transition from traditional neuroimaging methods towards more biologically specific variants. At the same time, there are active attempts to tweak and modify the measure to extend its initial realm of application [185].

Measuring myelin in-vivo is an area of active research and it remains to be seen which or if only one metric is established as the go-to method. As previously mentioned, there are a range of potential candidates for quantitative myelin imaging, but the major limitation is time [114]. The T1w/T2w ratio does not introduce additional scan time since the sequences are already acquired as part of the standard protocol. Other myelin specific technique would typically involve at least 10 min extra scan time, which is a problem especially in young cohorts who may experience a scan session as psychologically more demanding than adults. Furthermore, longer scan sessions, and long sequences increases the risk of motion artefacts, which already is a concern in pediatric imaging. In conclusion, while T1w/T2w ratio might not be the best method for myelin imaging, it remains a viable solution among the methods currently available, especially for cortical myelin imaging which requires high resolution. It may well be though that trading a portion of the sample size in Study I for a myelin technique with higher specificity could have been a worthwhile deal.

Much like the MRI measures mentioned above, psychological measures are indirect and imperfect reflections of the underlying systems and functions they are aimed at revealing, so any explanatory story based on them will become blurred by noise [138]. Inconclusive cognitive neuroscience literature is presumably at least in part the result of both its target phenomena and the way we attempt to study them [138]. It is widely accepted within the cognitive neuroscience community that to counteract this, large datasets are essential to reveal reliable associations between brain structural indices and behavior in healthy individuals [138]. This dissertation highlights that even a sample of nearly 1000 children is not sufficient to reveal robust associations between brain structure and cognition when looking across large areas of the brain. Two different structural MRI indices, one morphological and one microstructural, failed to provide distinguishing information between levels of cognitive ability. Noise is a factor that hampers the reliability of both neuroimaging and neuropsychological measurement instruments, thus making it difficult to establish clear links between the two.

11 Conclusion

While this thesis might raise more questions than it answers, it highlights important methodological issues within behavioral neuroscience, and challenges MRI's status as a panacea, readily available to answer any kind of question about human behavior and function one may have. In relation to the aims set out in this thesis we found that T1w/T2w ratio is not a suitable metric to link children's cortical myelin to interindividual differences in cognitive abilities. VBM does not robustly explain unique variability in children's language abilities. Rather, associations between grey matter volume and language performance vary as a function of statistical choices. Large samples do not guarantee robust links between brain structure, as measured by VBM and T1w/T2w, and behavior. Only weak evidence was found for cognition affecting the relationship between SES and grades. Both SES and cognitive abilities uniquely affect grades. This effect was present across timepoints but did not change as a function of time.

11.1 Outlook

Going forward, ultra-high field MRI promises exciting opportunities for cognitive and educational neuroscientists. Thanks to improved signal-to-noise it allows imaging myelin at a much more detailed level, for example laminar organization of the cortex or myelin patterns along superficial and deep white matter, ideally by creating detailed phenotypes of a limited sample to enable sketching short- and long-term myelination trajectories [83]. The continuous development of more advanced sequences, such as quantitative MRI, also holds a lot of promise for better in-vivo imaging of myelin in the brain. Combining different imaging techniques, including non-MRI-based methods, into a multimodal approach within the same protocol will also be essential for understanding the cellular processes that underlie gross structural changes and developmental behavioral shifts. A lot of efforts are invested into trying to overcome MRI's lack of specificity. Novel quantitative sequences [220] and data-driven, multivariate analytical approaches [211] are promising developments for maneuvering the neuroimaging community out of its replication crisis.

A vital benefit of the ABCD dataset is the fact it not only includes a large sample, but that data is collected several times over the course of ten years. Longitudinal research is rare in cognitive neuroscience, especially studies that collect data at more

than two timepoints. Once data collection is completed in the study, and MRI data from 10 years is available, this will offer rare opportunities to model longitudinal development in a large cohort across five timepoints. Following up the questions in the present work from a longitudinal perspective, looking at the development of brain structural indices and behavioral performance over time rather than looking at one specific moment in time, could provide new insight, and maybe reveal a larger explanatory power of VBM and T1w/T2w than was observed in this thesis. Following animal research that uncovered associations between myelin and learning, studying children as they grow up and continue to refine their cognitive abilities while their school education proceeds, will be a vital puzzle piece to corroborate that links between myelin and performance also occur in humans and can help confirm our hypothesized positive relationship between myelin and educational attainment. At the same time as myelin measures can inform us about the micro level processes behind healthy learning, they can also yield important information about developmental learning disorders, such as dyslexia or dyscalculia.

A more targeted study looking at myelin, cognition, and educational success in conjunction could help answer a lot of outstanding questions. Including a more precise estimate of myelin content will be essential to confirm that the lack of associations between T1w/T2w ratio and cognitive performance in Study I points towards T1w/T2w ratio's limited ability to represent myelin content rather than to a correlation that is indeed absent. Ideally, such a study would include more than one metric targeting myelin to not only reveal links between the concurrent development of myelin and cognitive abilities during mid-childhood, but simultaneously offer an important empirical foundation to better understand how different indices that claim to estimate myelin relate to each other. This could be combined with finer grained and objective measures of educational success, such as data directly from schools divided by subject areas, as well as data on a national level from placement exams.

The quest remains to understand how complex processes like learning and education are reflected in the brain. We have taken important steps toward this goal by showing that experimental approaches that have been prevalent in the community for a while are unlikely to provide useful, novel insights – not even when a large pool of participants is available.

12 Acknowledgments

They say Rome wasn't built in a day – and neither was this dissertation. While I may have had my moments of doubt about ever reaching graduation day, the people below have not, and for that I will always be grateful.

Johan, referring to you as my supervisor has always felt like an understatement. Throughout these years you have featured in so many different roles that I have lost track: mentor, academic parent, deputy dad, big brother, running buddy, friend – the list goes on. Thank you for making sure that these past couple of years were, although often challenging, first and foremost always fun. Thank you for your unconventional approach to supervision, for patiently listening to all my rants and for having faith in me, especially when I did not. The way you work towards your goals while staying true to yourself will remain an inspiration to me. While this marks the end of an era, I am positive that my lengthiest and best emails to you are yet to be written.

Thank you to my co-supervisors Marianne and Ping who, despite hectic schedules as scientists, have always made time to provide guidance when I needed it. Not being able to draw on your experience and expertise more after switching topic is one of my biggest regrets with regards to this dissertation. Hamid and Micke, thank you for helping me bring the first publication of this dissertation to life. The example you set both as scientists and humans will continue to inspire me. I also want to extend gratitude to everyone involved in the ABCD study – funders, scientists, parents, and, most of all, the participating children. Without you, this thesis would have been even more delayed.

Thank you to the resident grumpy, old men at the office, Theo and Nicola, for equal amounts of banter and support. Thank you, Nicola, for being an inexhaustible source of neuroimaging, statistics, and psychology knowledge, for every time you showed up at work with croissants out of the blue and for reluctantly accepting every hug that I forced upon you. Theo, without your wizardry I never would have been able to navigate the maze that is the ABCD data. Thank you for never saying no when I needed help with figuring out why my scripts weren't working, for valuing quality coffee breaks as much as me and for ensuring that our office was the greenest and

coziest in the building. Our time at the Austrian-German HQ and your one-of-a-kind laugh have been some of the highlights of my PhD student days.

Thank you to all the kind faces in and around the MR pavilion who have made the last couple of years so much brighter. Osa, thank you for being thoughtful and caring and for dragging me out on walks when I wanted them the least and needed them the most. I am sorry you were bestowed with the questionable honor of being the only artistically inclined member aboard HMS Impeccable – it remains to be seen if I will ever get a nicer birthday card than the one you gave me in 2022. Thank you to Linda, Boel, and Titti for being the soul and backbone of the pavilion and for featuring in many dear memories from a dark MR basement and sunny lunches down by the pond. Thank you to Geraline for much needed laughter at work – I could not be happier that our friendship outlasted our time as colleagues.

Thank you to friends, scattered across Sweden, Poland, Switzerland, Denmark, and Germany. Even though I will not mention you all by name, I trust that you will recognize that this is directed at you. Whether you have shared the highs and lows of being a PhD student, or whether you have provided much needed grounding outside the world of academia – I do not want to imagine this journey without you.

Thank you to my family. To my dad, who is not around to see me graduate, but who has instilled the belief in me that with hard work and dedication there is no limits to what I can achieve. To my mum, the strongest and most independent woman I know, for unconditional love and support and for providing a world where science and publications do not matter. To my sister, for a bond that is inexplicable in the best kind of way and for never forgetting my childish candy preferences.

Emil. A lot with respect to this thesis did not pan out as planned, but crossing paths with you has by far been the best unexpected side effect of this journey. Thank you for how masterfully you have balanced the fine line between kicking my butt and giving me grace these past few months. Your patience, love, and encouragement, during tough moments have meant the world and I cannot wait to spend the rest of my life showing you how grateful I am.

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Printed by Media-Tryck, Lund 2024 NORDIC SWAN ECOLABEL 3041 0903

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FACULTY OF MEDICINE

Department of Clinical Sciences, Lund

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2024:86
ISBN 978-91-8021-581-7
ISSN 1652-8220