THE ILLUMINATION OF THE DEVELOPING BRAIN

Using MRI signal intensity contrasts to probe microstructural brain maturation, and associations with psychopathology and cognition

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2019

Series of dissertations submitted to the
Faculty of Social Sciences, University of Oslo
No. 773

ISSN 1564-3991

Cover: Hanne Baadsgaard Utigard.
Print production: Reprosentralen, University of Oslo.

Acknowledgements

It is perhaps slightly corny, but receiving the confirmation that I would be a PhD candidate is still one of the most memorable days of my life. The conscious choice of pursuing neuroscience on the other hand is elusive, apart from always wanting to study psychology, and never wanting to be a psychologist, which was confusing enough for my parents. This brings me to the first two people I would like to thank. Mom and Dad, you have never given any personal opinion concerning higher education or future professions, but always given your full support. Mom, thank you for listening to me ramble for countless pre-exam nights, as it was my only successful memorization technique. "..and then.. and then mom, are you listening?" Thank you dad, for being so so proud, and for bragging of me to anyone who will listen, including friends and family in Mauritius, stating that I am a psychologist and/or a medical doctor, both of which I am not. Thank you for working from a very young age, and I suspect, for giving me a curios mind, although you yourself never got the chance to study. I am the first Bonaventure to approach higher education not to mention possibly receiving a PhD, and I am so very proud.

I would sincerely like to thank the NORMENT neuroimaging group, and my group leader and co-supervisor Lars Tjelta Westlye in particular. You were my masters supervisor, helped me find a research assistant job vital to later receiving the PhD position, and now my PhD co-supervisor. There is too many aspects of this overall process that I want to recognize, including your constantly open office door, but as a true scientific writer, I want to say that: "In short", there is just nothing about me becoming a neuroscientist that you have not been a direct part of, and I am forever thankful. Also, working for you is downright inspiring.

I would also like to specifically thank my co-supervisor Nhat Trung Doan, for being very hands on during maybe the hardest part of this thesis, the first article. You stand out as a central figure whenever I think about this PhD period, and I hope I expressed that enough before you went to peruse your current job. Also, I would have never replaced Matlab for R, a.k.a the superior statistical tool, if it were not for your insistence.

I would also like to specifically thank my colleagues and co-authors: Dag it only takes you a split second to orient yourself in the broad landscape of questions I might have. Jarek, you have been vital for me during the last two papers, and helped me so much, and you are not even my supervisor. Dennis you are the genetics and for-loop-in-R guru, Torgeir you

always give great advice concerning figures, article titles, and tricky reviewer questions. Tobias, I would have gotten lost in the world of big-data if it were not for you, and your help during the review process is unparalleled. I would also like to thank my two office-partners in crime Knut and Luigi. Knut you assisted me in Matlab, and my articles would not have been the same without writing tips such as always finding the “rosinen i pølsa”. Luigi you are the tricky-FLICA-script-interpreter, and thanks for always sharing all your bread rolls with me.

Thank you to everyone else at NORMENT and to Ole A. Andreassen in particular for always thoroughly reading my articles and adding that clinical touch that might be lacking, as well as structuring advice that makes the article a more exciting read. A sincere thank you also to the Department of Psychology for their full support and academic education through my PhD.

I would also like to thank the Philadelphia Neurodevelopmental Cohort (PNC) study, and the Pediatric Imaging, Neurocognition, and Genetics (PING) study. I also want to recognize that without all the kids and adolescents giving their child- and informed assent, to do the boring task of laying still in a scanner for a very long time, I would not have been able to perform my research. Thank you!

Thank you to all my friends and family, and to Even the graphic design-expert in particular. And to Michael, for sitting quietly next to me (playing chess) while I was writing, and for making sure that every break was so fun. You keep me calm. Thank you B.

Lastly, and most importantly, I would like to sincerely thank Christian K. Tamnes, my main supervisor. I have felt safe, supported, and in competent hands through every single step of this journey, and I simply could not have done this without you. Since hiring me (although I said in my interview that “I am not so good in statistics”), you have red every single article draft, answered every email, and always made sure I was on top of all the practical aspects as well. You believed in me, and by doing so, made my scientist-dream come true. I am forever so very thankful, and will strive to make you proud.

Table of contents

1. General summary

Childhood and adolescence captures a remarkable period of change, and is also *the* central period for major reorganization and optimization of the cerebral cortex. This cortical maturation is mirrored by extensive cognitive improvements within the youth period. At a neurobiological level, several genetic regional and age specific processes are at work, in dynamic interplay with the environment. Moreover childhood and adolescence is a particularly sensitive period for developing mental health issues, possibly underpinned by genetic and environmental risk factors, which cause typical developmental processes to go awry. Intracortial myelination is one such candidate process. In youth, increasing levels of myelin gives rise to what appears as "brain illumination", or an increase in the signal intensity in the T1 weighted magnetic resonance image. There are newer microstructural MRI measures that are based on this intensity variation, but there is unfortunately a near a complete lack of highly powered developmental studies that employ them.

The current thesis is an exploration of typical cerebral cortical development, through the intensity contrast measures grey/white contrast (GWC) and T1w/T2w ratio. The relationship between these cortical patterns and cognitive abilities is also central for the current thesis, as well as searching for spatiotemporal patterns associated with emerging psychopathology. Large typically developing- and population based youth samples were employed, including very young children. Moreover, data-driven decomposition of-, as well as multimodal fusion including GWC was performed for the first time, in addition to the more conventional vertex-wise assessments of T1w/T2w ratio.

Main results from three papers will be integrated and discussed holistically in the current thesis. Within paper I my co-authors and I reported the novel finding that in development, higher age is associated with globally lower GWC. A specific regional bi-directional associations was also found, that beyond the global association, possibly reflect protracted and accelerated development. These regional findings were also neatly captured by an independent component within paper III. In paper II we reported that higher age was associated with almost globally higher T1w/T2w ratio, with a posterior to anterior direction in association strength. In sum, these findings indeed spatiotemporally converge with the protracted process of intracortical myelination. Within paper II we moreover found a negative association between T1w/T2w ratio and cognitive abilities, which possibly could indicate that

excess levels of intracortical myelin, beyond a certain developmental norm, is disadvantageous. Finally, within paper I we reported that clinical components capturing anxiety and prodromal psychosis were associated with highly overlapping regional GWC.

During the PhD project, I encountered several methodological challenges that will be thoroughly highlighted within the current thesis. These include studying development with a cross sectional design, MRI acquisition and analytical youth-related issues, and the close relationship between the developmental age range and cognitive abilities. Other central challenges included interpreting the GWC and T1w/T2w ratio results in a biologically meaningful way, as the underpinnings of signal intensity measures are not clear. In sum, GWC and T1w/T2w ratio shows a biologically relevant signal that is sensitive to individual differences in age-, cognitive abilities- and levels of symptoms of psychopathology. Future highly powered longitudinal studies are needed to replicate the findings of the current thesis, and studies are also urgently needed to give a better understanding of the biological underpinnings of intensity contrast measures as they are currently highly debated.

2. List of articles

Paper I:

Norbom, L. B., Doan, N. T., Alnaes, D., Kaufmann, T., Moberget, T., Rokicki, J., Andreassen, O. A., Westlye, L.T., Tamnes, C. K. (2019). Probing Brain Developmental Patterns of Myelination and Associations With Psychopathology in Youths Using Gray/White Matter Contrast. *Biological Psychiatry*, *85*(5), 389-398. doi:10.1016/j.biopsych.2018.09.027

Paper II:

Norbom, L. B., Rokicki, J., Alnæs, D., Kaufmann, T., Doan, N. T., Andreassen, O. A., Westlye, L.T., Tamnes, C. K. (under review). Maturation of Cortical Microstructure and Cognitive Development in Childhood and Adolescence: a T1w/T2w ratio MRI Study. Preprint: bioRxiv 681221. Doi:https://doi.org/10.1101/681221

Paper III:

Norbom, L. B., Rokicki, J., van der Meer, D., Alnæs, D., Doan, N. T., Moberget, T., Kaufmann, T., Andreassen, O. A., Westlye, L.T., Tamnes, C. K. (in preparation). Testing Relations of Multimodal Neuroimaging Measures and Polygenic Scores of Neuroticism in 2621 Children and Adolescents.

3. List of abbreviations

ABCD - Adolescent Brain Cognitive Development
CHOP- Children's Hospital of Philadelphia
CSF- Cerebrospinal fluid
DTI- Diffusion tensor imaging
FS- FreeSurfer
FWHM- Full width at half maximum
gF- General cognitive function
GLMs- General linear models
GM- Gray matter
GWAS- Genome-wide association studies
GWC- Gray/White Matter Contrast
HCP- Human Connectome Project
ICA- Independent component analysis
ICs- Independent components
LICA- Linked independent component analysis
MRI- Magnetic resonance imaging
PCA- Principal component analysis
PI- Principal investigator
PING- Pediatric Imaging, Neurocognition, and Genetics
PGS- Polygenic score
PNC- Philadelphia Neurodevelopmental Cohort
ROIs- Regions of interest
SD- Standard deviation
SNPs- Single-nucleotide polymorphisms
T1w- T1 weighted
T2w- T2 weighted
WM- White matter

4. Introduction

"People grow up, and when they grow up they change"
- Haruki Murakami, 1Q84

Childhood and adolescence captures a remarkable period of change. Early childhood involves physical increases in height and weight, major improvements in motor skills and cognitive revolutions such as acquiring language and self-awareness (Colson & Dworkin, 1997; McMurray, 2007; Rochat, 2003). Children also develop social bonds, and play-time fosters several aspects of this development (Ginsburg, 2007). Adolescence, which refers to the multifaceted transitional period between childhood and adulthood, comes with a novel set of challenges and advancements. These include major socio-cultural changes, increased emotional reactivity, urge for independence, complex and abstract thinking, and at times increased risk taking behaviors (Blakemore & Mills, 2014; Choudhury, 2010; Piaget & Cook, 1952; Silvers et al., 2012; Steinberg, 2008). This transitional period often co-occurs with pubertal onset, causing extensive sex related bodily alterations as well (Marshall & Tanner, 1969, 1970).

Within the brain, childhood and adolescence is *the* central period for major reorganization and optimization (Blakemore, 2012; Brown & Jernigan, 2012; Lebel & Deoni, 2018). The cerebral cortex undergoes a particularly lengthy developmental process, which is reflected in the major cognitive improvements of children, adolescents and young adults (Akshoomoff et al., 2014; Casey, Tottenham, Liston, & Durston, 2005). Indeed, the cerebral cortex is often credited as the basis for most of humans' unique cognitive capabilities (Harris & Shepherd, 2015; Rakic, 2009). At a neurobiological level, several genetically based regional and age specific processes are at work, underpinning this development, in dynamic interplay with the environment (Kremen et al., 2013; Natu et al., 2018; Nieuwenhuys, 2013; Petanjek, Judas, Kostovic, & Uylings, 2008).

Magnetic resonance imaging (MRI) is understood to indirectly capture numerous multifaceted properties and developmental processes of the cerebral cortex, and has the advantages of being *in vivo* and noninvasive. Standard cortical quantifications include

morphometric measures such as cortical thickness, surface area and gyrification. Fascinatingly, if assessing T1 weighted (T1w) MRI images, it appears as though the brain "illuminates", or becomes increasingly bright from childhood and through adolescence. There are newer and less explored MRI measures, which are based on these "illumination differences", or, more specifically, the intensity variation within the T1w and/or T2 weighted (T2w) image. Moreover, it has been argued that intensity measures indirectly reflect a central developmental process, namely cortical myelination (Glasser & Van Essen, 2011; Salat et al., 2009).

If one compares humans with closely related non-human primates, certain cortical developmental processes are exceptionally protracted in humans (Miller et al., 2012). Although this is clearly beneficial, as it allows environmental experiences to literally shape the brain and by extension for adaptation and learning, it does not however come without costs. Indeed, childhood and adolescence are periods of life with increased risk for developing many mental disorders (Kessler et al., 2005; Paus, Keshavan, & Giedd, 2008). There is reason to believe that a combination of genetic and environmental risk factors could cause certain underlying developmental processes to go awry, resulting in emerging mental health problems (Paus et al., 2008). One such candidate process is intracortical myelination, which could possibly be assessed indirectly with intensity measures (Insel, 2010; Paus et al., 2008). Still, there is a major disproportion between morphometric studies and studies exploring microstructure through intensity measures. Indeed, longitudinal or highly powered cross sectional intensity studies specifically investigating cortical development in childhood and adolescence are almost completely lacking.

"No escaping it-

I must step on fallen leaves

To take this path"

-Suzuki Masajo

In the following introductory sections, I will present and discuss central contextual information for the current thesis, starting by focusing on the cerebral cortex. This is followed by a description of how the cortex can be morphometrically and microstructurally quantified through MRI, emphasizing metrics employed in the current thesis. Then, a description of cortical development in youth is presented, followed by a section discussing probable morphometric and microstructural neurobiological underpinnings (which are too often neglected in neuroimaging papers). The controversy regarding possible underpinnings of intensity measures will be extensively covered in the methodological section. Thereafter possible sex differences in cortical development are discussed, followed by a section on the development of cognitive abilities, and their associations with cortical development. Finally, neurodevelopmental psychopathology will be introduced, including a discussion of possible transdiagnostic risk factors, and neuroticism specifically.

1. The cerebral cortex

The cerebral cortex constitutes the outermost part of the brain, and characteristically resembles a highly folded sheath, with peaks and valleys termed gyri and sulci respectively (Destrieux, Fischl, Dale, & Halgren, 2010). It consist of several and usually six cortical layers, with a total average thickness of about 2.5 mm (Amunts & Zilles, 2015; Brodmann, 1909). The cortex contains tens of billions of brain cells, including pyramidal- and interneurons neatly packed and carefully column wise organized for effective long-range and local signal transmission respectively (Mountcastle, 1995; Rakic, 1995; Rakic, 2009), as well as dendrites, glial cells, and myelinated and unmyelinated axons (Nieuwenhuys, 2013). Specific cellular composition and distribution vary greatly depending on the cortical layer and region considered (Brodmann, 1909), and so too the layers functional role (Bastos et al., 2012) and connectivity (Rockland, 2015). There is nevertheless generally a profusion of neuronal cell bodies within superior cortical layers, while myelinated axons are found in deeper cortical layers, as myelin originating in subjacent white matter (WM), and penetrates the periphery of cortical neuropil (Nieuwenhuys, 2013).

The function of the cerebral cortex is incredibly multifaceted, and includes integration of information across the full connectome, as well as sub-regions performing specialized

tasks, such as lower order sensory processing, but also elusive higher order processes like executive functioning (Friston, 2005; Goldman-Rakic, 1996; Woldorff et al., 1993).

There is no definite consensus regarding the spatial parcellation of the cerebral cortex. However, it can be divided into four different cortical lobes, or split into more fine grained sub-regions, based on differences in cytoarchitecture (of which the historical Brodmann atlas is a fine example (Brodmann, 1909)), myeloarchitecture, its connectivity with other brain regions, or regional functional specialization (Glasser et al., 2016; Palomero-Gallagher & Zilles, 2019). Although early cyto- and myeloarchitecturial discoveries were based on pioneering histological studies of postmortem cortical tissue, current diverse neuroimaging methods are indirectly sensitive to several of these underlying properties.

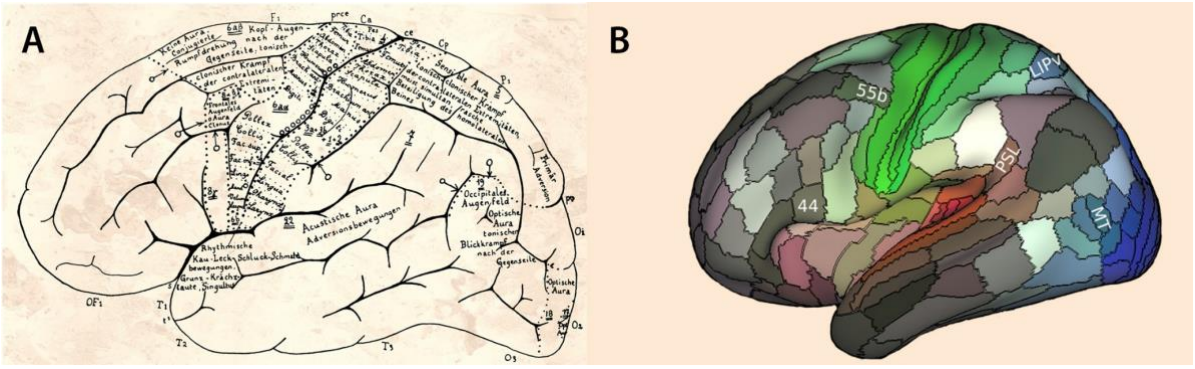

Figure 1. Cortical parcellations. (A) Shows the hand-drawn, myeloarchitectonic map by Oskar Vogt. (B) Shows the Human Connectome Project multimodal parcellation, which is also based on T1w/T2w ratio. Figure is adapted from Amunts and Zilles (2015) and Van Essen and Glasser (2018) with permission.

2. Cortical morphometric and microstructural measures

The cerebral cortex can be macrostructurally quantified *in vivo* and non-invasively with several diverse MRI measures, the most conventional being cortical volume, its substrates, thickness and surface area, and also global or local gyrification (Desikan et al., 2006; Fischl, 2012; Fischl & Dale, 2000; Winkler et al., 2012). There are also newer less explored measures of cortical and closely subjacent WM, which involves quantifying the signal intensity variation in the T1-weighted (T1w) and/or the T2-weighted (T2w) image (Glasser & Van Essen, 2011; Salat et al., 2009; Westlye et al., 2010) in order to probe cortical microstructure. For instance, cortical grey matter (GM) appears darker and brighter than WM

on the T1w and T2w image, respectively. This discrepancy reflects differences in several biological properties of which these images are sensitive (Glasser & Van Essen, 2011). If one uses perhaps the most commonly employed MRI analysis software package FreeSurfer (FS) as a basis (http://surfer.nmr.mgh.harvard.edu), these different metrics are mapped from the T1w (and T2w) volume and onto a 2D surface containing more than 300 000 vertices (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). In the following, I will describe some of these measures as they are estimated in FS in more detail.

2.1 Cortical thickness and surface area

Cortical thickness is calculated by first modeling the "white" surface i.e. the border between cortical GM and subcortical WM. This border is then nudged outward toward superficial layers of cortex creating the "pial" surface i.e. the boarder between cortical GM and cerebrospinal fluid (CSF). Cortical thickness is then defined as the vertex-wise shortest distance between the white and the pial surface (Fischl & Dale, 2000). Cortical surface area can either be based on the white surface, the pial surface or at times an average of the two called the "midthickness". The relevant surface is then mapped onto a standard template called "fsaverage", which is an average of multiple brains including both sexes and spanning a large age range (Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999). The amount of expansion and contraction needed for the individual surface to register successfully onto fsaverage is used to calculate the vertex-wise surface area (Dale et al., 1999; Fischl, Sereno, & Dale, 1999).

2.2 Intensity and contrast measures

Cortical GM intensity is calculated by sampling T1w values across the full or at different depths of the cortical mantle (Glasser & Van Essen, 2011; Salat et al., 2009). Similarly, WM intensity is calculated by sampling values from the grey/white boundary and extending a chosen shorter distance into subjacent WM (Jorgensen et al., 2016; Salat et al., 2009). GM and WM intensities can be investigated separately, but this is often challenging as participant specific optimization during image acquisition creates inter-subject intensity discrepancies (Westlye et al., 2010). There is no convention, but correction procedures include sampling of intensities from ventricles, eyeballs, or outside of the skull, however, not without caveats.

Another approach is to compute different kinds of ratios, either between GM and WM intensities yielding what is called gray/white matter contrast (GWC), or a purely cortical intensity measure using both the T1w and T2w modality, resulting in a T1w/T2w ratio (Glasser & Van Essen, 2011; Jorgensen et al., 2016; Salat et al., 2009). If one used the ratio calculations employed in the current thesis as a reference, high and low GWC would indicate that GM and WM are less and more similar, respectively. The T1w/T2w ratio is relative scale, with values generally falling within the boundaries of 0 and 1. A ratio below 0 would indicate that cortical T1 intensities are brighter than that of T2, and vice versa for ratio values above 0.

These morphometric and microstructural measures are understood to indirectly yet successfully capture fine-grained properties and processes of the cerebral cortex, and are thus useful for studying individual and developmental differences.

3. Morphometric and microstructural cortical development in childhood and adolescence

The major developmental optimization of the cerebral cortex can be explored through different morphometric and microstructural MRI metrics. These different metrics have been found to show distinct spatially heterogeneous trajectories which depends on age, and possibly, although less clear, also sex. As will be discussed in the methodological section, the gold standard for measuring development is undeniably the longitudinal design, with highly powered cross sectional studies as a decent alternative.

3.1 Cortical thickness and surface area

Groundbreaking longitudinal studies in the last decade have assessed cortical morphometric development early in life. One longitudinal study mapped the very rapid early changes in brain morphology by examining a large group of newborns aged 2 to 90 days old. The results showed that the brain's total volume increase approximately by a staggering one percent per day in the period immediately after birth (Holland et al., 2014). Other longitudinal studies within the first two years of life have reported that postnatal development of cortical thickness and cortical surface area consist of general increases, with reports of 36% and 115% overall

increase, respectively (Gilmore et al., 2012; Lyall et al., 2015). Unfortunately, there is a near complete discontinuity of longitudinal investigations of young children beyond year 2 and until primary school years. This is mainly due to movement related difficulties during image acquisition, and will be discussed in detail within the methodological considerations section.

Early longitudinal studies of older children and adolescents were conflicting regarding development of cortical thickness, with a number of studies reporting an inverted-U trajectory peaking in late childhood or early adolescence (Raznahan et al., 2011; Shaw et al., 2007; Shaw et al., 2008). For instance, a longitudinal study investigating 375 youths aged 4-33 years, reported that within most of the cortex, developmental thickness patterns were qubic, with an initial childhood increase until about year 10, followed by an adolescent decline (Shaw et al., 2008). A number of recent studies on the other hand, have reported a steady developmental decrease of cortical thickness, with slight regional variation (Ducharme et al., 2016; Fjell et al., 2015; Tamnes et al., 2017; Vijayakumar et al., 2016; Zhou, Lebel, Treit, Evans, & Beaulieu, 2015). One such longitudinal study, investigated 384 youths aged 5-22 years and reported that very few cortical regions showed a cubic trajectory for cortical thickness, and that the majority of cortical regions showed a linear monotonic decline (Ducharme et al., 2016).

There are fewer longitudinal studies that have investigated cortical surface area development, and results are quite discrepant. One study, which investigated morphometry, surface area included, within 90 youths aged 11-20 years, reported that in development, surface area non-linearly and at times regionally linearly increased across most of the cortex (Vijayakumar et al., 2016). This stands in contrast with a cortical morphometry study of 388 youths aged 7-29 years, from four samples that were analyzed separately. They reported relatively small but steady and nearly global decreases in surface area across samples, with the largest decrease found in parietal lobes (Tamnes et al., 2017). So too, a study of 90 normally developing youths aged 9-20 years, as a control for subjects with autism, reported that mean cortical surface area decreased with increasing age (Mensen et al., 2016). This partly converges with a study which followed 231 normally developing children from age 10 and until age 16 as controls for subjects with ADHD. It was reported that in normal development, lobar level surface areas showed an initial childhood increase before decreasing though the adolescent phase (Shaw et al., 2012). To complicate matters further, a study investigating local trajectories of surface area within 384 youths aged 4-22 years noted that

more than 50% of the cortical surface did not show significant changes. Changes in frontal and temporal regions however had negative linear-, inverted-U, and cubic age relations (Ducharme et al., 2015). It is possible that the discrepant results are related to differences in subject age, inter-individual differences, scanner and sequence related properties, and the actual method used to estimate surface area.

To summarize, arguably the current conventional understanding of cortical thickness development through childhood and adolescence is that it steadily decreases. It is nevertheless debated whether this reflects an actual or an apparent cortical thinning (Walhovd, Fjell, Giedd, Dale, & Brown, 2017). It appears that changes in surface area on the other hand (if present), is region specific and with separate age related trajectories. Arguably, it increases within the first years of life, possibly until mid-childhood, before steadily decreasing through adolescence. Theories concerning the biological underpinnings of area changes certainly would give rise to complex bi-directional changes, as discussed later.

3.2 GWC and T1w/T2w ratio

Unfortunately, longitudinal GWC and T1w/T2w ratio studies in youth or adulthood are nonexistent. There are also very few highly powered cross-sectional studies. Three cross-sectional studies have investigated age-related differences in GWC, or similar ratio and contrast measures in development. One cross-sectional study with 832 youths aged 3-22 years from the Pediatric Imaging, Neurocognition, and Genetics (PING), attempted to predict the chronological age of the subjects, using the closely related metric white/grey contrast. They reported a negative age association within cortical sensory processing regions, and a positive age relationship within cortical association regions (Lewis, Evans, & Tohka, 2018). It should be noted that one has to flip the direction of these results in order to concur with the GWC metric used in the present thesis. A different cross-sectional study investigated GWC during normal development, as a control for subjects with autism, and included a sample consisting of 82 typically developing participants aged 7 to 25 years. It was reported that the trajectory of GWC was complex and included both linear and non-linear age effects. The specific direction was not reported, but for regional clusters with age-by-group interaction effects, GWC was generally lower with higher age in normal development (Mann et al., 2018). Partly

in agreement with these findings, a final cross-sectional study explored the closely related metric grey/white ratio in 148 subjects across the adult life span, including a young adult group aged 20-39 years consisting of 41 subjects. Unfortunately, there were no applicable reports on this group specifically, but across the adult lifespan, it was reported that grey/white ratio was significantly higher with higher age including within large portions of the frontal lobe, as well as within inferior parietal, and superior temporal regions (Salat et al., 2009). Here too, results must be flipped in order to concur with the GWC metric, and can be translated to lower GWC with higher age, i.e. GM and WM was more similar.

Concerning T1w/T2w ratio, there are a few cross-sectional studies that have indirectly explored its development within childhood and adolescence, in part as one needs 2 modalities of sufficient quality, which is a challenge in of itself, but particularly when investigating children as it increases scan time thus acquiring children to lay still for a longer period. One such study, investigated T1w/T2w ratio across the lifespan, and included a subsample of 85 youths aged 8-19 year. It was reported that higher age was associated with higher T1w/T2w ratio across large areas of the cortex including posterior frontal, parietal, and temporal regions (Grydeland, Walhovd, Tamnes, Westlye, & Fjell, 2013). Accordingly, a different cross-sectional study, albeit investigating T1w/T2w ratio in 1555 subjects aged 18-35 years, reported that higher T1w/T2w ratio was significantly linearly associated higher age, in widespread cortical regions. (Shafee, Buckner, & Fischl, 2015). Additionally, a study investigated regional T1w/T2w ratio growth waves in 484 participants, aged 8-85 years. It was reported that age at peak growth had a bimodal distribution as there was an early pre-pubertal wave for primary sensory and motor cortices, and a later post-pubertal wave for association, insular and limbic cortices (Grydeland et al., 2019).

Importantly these “developmental” interpretations are based on cross-sectional and in some cases underpowered studies, which can have serious caveats (Kraemer, Yesavage, Taylor, & Kupfer, 2000; Schönbrodt & Perugini, 2013). Highly powered cross sectional intensity studies spanning the full developmental range is critically needed, as a supplement for more time-consuming but ideal future longitudinal studies.

To summarize, it appears that across childhood and adolescence GWC has a region specific bi-directional and at times non-linear trajectory, with a general decrease being a slightly more

consistent finding. This indicates that GM and WM becomes more similar across development, which aligns with theories concerning its neurobiological underpinnings. Concerning T1w/T2w ratio, this measure seems to generally show an age-related increase across childhood and adolescence, also concurring with the same main neurobiological theory.

4. Neurobiological underpinnings of morphometric and microstructural metrics in development

The underlying neurobiology of cortical structural MRI measures is logically highly complex as one is approaching the matter from a macro level. More specifically, at a typical 1mm isotropic voxel wise spatial resolution, with each voxel possibly containing as much as hundreds of thousands of brain cells (Ribeiro et al., 2013). Still, cortical thickness, cortical surface area, and signal intensity metrics are understood to reflect partly separate developmental neurobiological properties and processes of the cortex, and have also concordantly been described as having separate genetic underpinnings (Kremen et al., 2013; Panizzon et al., 2009; Panizzon et al., 2012).

4.1 Cortical thickness and surface area

Cortical thickness relates to the number of cells that are contained within the organizational columns of cortex (Rakic, 1995). In development, there has been two, on occasion opposing but in actuality not mutually exclusive theories regarding what cortical thickness reflects, namely pruning and/or intracortical and subjacent WM myelination. Pruning refers to the optimization of brain circuits by removing synapses, dendrites and even neurons that are in excess and inefficient (Natu et al., 2018). However, as synaptic boutons are incredibly small, and therefore only comprise a fraction of GM volume (Bourgeois & Rakic, 1993) it has been speculated that if pruning is detected on MRI, it should be coupled with additional associating processes, such as a reduction in glial cells (Mills & Tamnes, 2014). Several histological postmortem studies, including layer specific investigations within the frontal cortex have supported pruning during development, reporting that synaptic density increase during infancy, followed by a slow decline in both synaptic, as well as neuronal, density through adolescence (Huttenlocher, 1979). Similarly, investigations of basal dendrites of pyramidal

neurons have reported length related-, synapse number-, and dendritic spine overgrowth in childhood and early adolescence, followed by a decrease in later adolescence (Petanjek et al., 2008).

In development, cortical thickness has also been linked to axonal myelination occurring within deep cortical layers (Natu et al., 2018; Walhovd et al., 2017). Myelination is the vital process of covering some neuronal axons with myelin, a fatty sheath that amongst several benefits increases the speed and reliability of the nerve signal as well as provides structural support (Baumann & Pham-Dinh, 2001; Liu, Li, Zhu, Li, & Liu, 2019; Waxman & Bennett, 1972). A recent study of cortical thickness and magnetization transfer for indirect measures of intracortical myelin, reported that in adolescence, increasing intracortical myelination was a significant driver of cortical thinning, albeit the gene expression profiles related to these changes were not myelin specific (Whitaker et al., 2016). Of note, as myelin brightens the appearance of cortex, deep myelinated cortical layers are at times misclassified as WM, thereby shifting the grey white boundary outward, resulting in an underestimation of the actual cortical thickness (Sowell et al., 2004; Walhovd et al., 2017). A recent study attempted to tease apart if tissue growth or pruning underlay cortical thinning, as measured by decreased or increased T1 relaxation time, and the diffusion tensor imaging (DTI) measure mean diffusivity respectively. Tissue growth was reported as the underlying factor, and increased levels of myelin more specifically, as verified by postmortem cortical data (Natu et al., 2018).

Surface area is (rather than cell count) related to the amount of columns within cortex (Rakic, 1995). Again, there are two theories concerning the underpinnings of surface area changes during development, namely WM expansion and/or cortical pruning. The first "balloon model" (Seldon, 2005) proposes that as the myelin content and axon calibers within WM increase (Benes, 1989; Benes, Turtle, Khan, & Farol, 1994), and so too the myelin within cortical layers, it causes the cortex to laterally stretch and expand outward (Seldon, 2007), figuratively comparable to blowing up a balloon, increasing the distance between cortical columns and by extension cortical surface area. This column separation is understood to be advantageous as they become more functionally independent, thereby increasing the capacity of the area (Seldon, 2005). This does not however converge fully with the report of surface area expanding in childhood before possibly subtly decreasing in adolescence. It has therefore been argued that WM expansion is coupled with the additional process of cortical

pruning and dendritic arborization (Bourgeois & Rakic, 1993; Huttenlocher & Dabholkar, 1997; Petanjek et al., 2011). Pruning is understood to cause a widening of sulci and a decrease in their depth, resulting in the cortex becoming flatter and smoother (Klein et al., 2014). Indeed, sulcal widening has been reported to be associated with loss of surface area within the frontal cortex (Aleman-Gomez et al., 2013). Moreover, mean surface area has been reported to have complex interactions with gyrification, which both decreases during adolescence (Raznahan et al., 2011).

Summarized, probable factors underpinning the cortical thinning during childhood and adolescence are increased levels of intracortical myelin and arguably also synaptic pruning and associated processes to some degree. The complex developmental patterns of surface area reported in childhood and adolescence, are likely underpinned by increased WM and deep cortical layers myelinating and developing, thus pushing and expanding the surface area outward, coupled with pruning processes which reduce the cortical folding pattern and so too the surface area.

4.2 GWC and T1w/T2w ratio

Although presently debated, in development and beyond, the intensity measures GWC and T1w/T2w ratio have both been presumed to indirectly reflect differences in intracortical myelin (Glasser & Van Essen, 2011; Salat et al., 2009). As GWC also contains WM, recent papers typically clarify that GWC reflects differences in intracortical and closely subjacent WM myelin content.

The rationale for both intensity metrics is that cholesterol, which is an essential lipid constitute of myelin, is a major determinant of the intensity signal in T1-weighted MRI (Koenig, 1991; Koenig, Brown, Spiller, & Lundbom, 1990). Other constitutes include water concentration (Miot-Noirault, Barantin, Akoka, & Le Pape, 1997), and iron, the latter of which has been found to closely cohabit with myelin within the cortex (Fukunaga et al., 2010). Moreover, cortical GM intensities have been reported to specifically relate to myelin rather than iron content (Stuber et al., 2014), and to closely resemble histologically based myeloarchitecture (Eickhoff et al., 2005). Regarding T1w/T2w ratio, the described biological properties are believed to inversely co-vary with the T2 sequence and myelin in particular

(Glasser & Van Essen, 2011). An additional benefit of the T1w/T2w ratio is that it also increases contrast by mathematically cancelling scanner related intensity biases (Glasser & Van Essen, 2011). GWC and T1w/T2w ratio show overlapping patterns, and also concur with histological postmortem myeloarchitecture (Nakamura, Chen, Ontaneda, Fox, & Trapp, 2017). Moreover, a study, which computed T1w/T2w ratio separately at each side of the midthickness surface, reported that changes were driven for the most part, by alterations in deeper cortical layers, validated by high-resolution MRI scans of a postmortem brain tissue, to be caused by increased levels of myelin (Shafee et al., 2015).

Summarized, GWC and T1w/T2w ratio is understood to partly reflect intracortical (and closely subjacent WM) myelin content, as differences within the intensity signal of the T1w (and also the T2w) image, reflects cholesterol, a major constitute of myelin. As these measures are less explored and often within cross sectional adult samples, reports on the underlying biology have focused on individual differences in *content*, although the region specific *process* of intracortical myelination such as within prefrontal as well as association areas in temporal and parietal lobes, do extend into the 5th decade of life (Bartzokis, 2004). If one were to explore GWC or T1w/T2w ratio in youth samples, any age-related differences in content would arguably by extension be caused by the developmental process of myelination. Again, the topic of whether intensity metrics reflect myelin in the first place, is currently controversial and highly debated, and will be discussed further in the methodological section.

5. Sex differences in cortical development

The divergence between boys and girls increase extensively as they enter adolescence, and socio-cultural aspects, as well as differences in the onset of-, and the actual pubertal period, are understood to be underlying drivers (Blakemore & Mills, 2014; Marshall & Tanner, 1969, 1970). There have also been reports of sex specific differences in the onset of- and the overall risk of developing certain mental disorders (Hafner, Maurer, Loffler, & Riecher-Rossler, 1993; Kessler et al., 2005), as well as cognition specific abilities that favor males and females separately (Jones, Braithwaite, & Healy, 2003; Sommer, Aleman, Bouma, & Kahn, 2004). Due to these discrepancies and the relationship between specialized brain regions and cognition, it is therefore not unlikely that cortical structure and their developmental

trajectories differ between the sexes. A part from consistent reports that on average, males have larger brains than females (Davison Ankney, 1992), the possible sex related differences in morphometric development is difficult to integrate.

One of the previously described longitudinal cortical morphometry studies also investigated effects of sex across time. Surface area was reported to be significantly larger for young males within extensive parts of the cortex as compared to young females. No significant sex differences were however reported for cortical thickness, and the overall developmental trajectories for both measures were similar between the sexes (Vijayakumar et al., 2016). Similarly, a cross sectional study of 1189 subjects within the age range of 8 to 23 years also reported that there were no significant differences of total cortical thickness between the sexes during development (Gennatas et al., 2017). In part converging, a cross sectional study, of 442 youths aged 8-30 years, found no significant sex related lobar differences of cortical thickness. They did, however, report sex-by-age interactions for cortical surface area, primarily within frontal, parietal and temporal cortex, in the direction that young males had larger cortical surface until mid-adolescence, while young females had relatively stable surface area across development (Koolschijn & Crone, 2013). In contrast, a longitudinal developmental study with a sample size of 647 individuals aged 3-30 years, reported that at the mean age of the sample, cortical surface area and cortical thickness were significantly greater in males than females. Both measures followed inverted-u, and cubic developmental trajectories. For surface area alone, these trajectories had significantly different shapes as well as age-at-attained-peak between the sexes, which occurred earlier for young females as compared to young males (Raznahan et al., 2011).

Very little is known about possible sex differences in- or developmental trajectories of GWC and T1w/T2w ratio. Albeit, one previously described cross sectional study employing grey/white ratio, reported practically no sex differences in a group of 148 young adults aged 20-39 years (Salat et al., 2009).

To summarize, although there in childhood and adolescence appears to be morphometric sex related differences across time and possibly also of their developmental trajectories, results are often divergent. Once more, one should note that results are based on quite diverse age ranges, and at times cross sectional studies. Still, differences in cortical surface area appears

to be a more consistent finding as compared to cortical thickness, with the possibility that young males have larger surface area than young females through much- if not through all of adolescence. As it is currently not known whether there are microstructural developmental sex differences, as measured by intensity metrics, future longitudinal and highly powered cross sectional studies specifically investigating sex related differences in development are needed.

6. The developmental relationship between morphometric and intensity measures

Beyond separate explorations of morphometric and microstructural measures in childhood and adolescence, of which results are at times divergent, information about the intricate developmental relationships between them is even more limited. A few studies have attempted, through global, lobar or vertex-wise correlational methods to explore these morphometric and microstructural relationships. These assessments can be highly profitable, as illustrated by a lifespan study exploring the relationship between GM intensities and cortical thickness (Westlye et al., 2010). The study was able to untangle developmental cortical thinning, which is understood to be advantageous, from the disadvantageous cortical thinning in aging. It was reported that although appearing similar if investigating cortical thickness alone, developmental and aging related cortical thinning probably reflects separate underlying processes, as there was an inverse relationship with cortical intensity, which increased in adolescence and decreased in aging (Westlye et al., 2010).

Testing morphometric inter-relationships in development through global and lobar partial correlations, and vertex-wise general linear models (GLMs), a longitudinal study reported region specific relationships between changes in surface area and changes in cortical thickness. There was mainly a positive relationship between the two in anterior sulcal regions, and a negative relationship in posterior gyral regions (Tamnes et al., 2017). There are no morphometric studies investigating relations with GWC. However, a previously described cross sectional morphometric study also investigated relations to T1w/T2w ratio, and reported that T1w/T2w ratio was significantly associated with mean global cortical thickness, with a correlation of $r = -0.32$. Vertex-wise correlations, on the other hand directionally varied across the cortex (Shafee et al., 2015). It could therefore be argued, that during childhood and adolescence changes in cortical thickness might have complex bi-directional relationship with

changes in surface area, and additionally a moderate negative global relationship with T1w/T2w ratio, albeit indicated from a cross sectional study.

Beyond correlational approaches, a method called linked independent component analysis (LICA) (Groves, Beckmann, Smith, & Woolrich, 2011) is a profitable tool for exploring multimodal relationships, albeit in practice being more applicable for cross-sectional data. LICA is a data driven approach, which has been reported to neatly co-model several modalities into separate components of shared variance, with biologically meaningful patterns (Groves et al., 2012). Indeed cortical morphometric LICA studies have reported unique structural patterns sensitive to lifespan development (Douaud et al., 2014; Groves et al., 2012) including specific reports of components capturing local relationships between cortical thickness and surface area, within 484 healthy subjects ranging from 8 to 85 years (Groves et al., 2012). Unfortunately, although there are reasons to believe that interesting multimodal patterns are present between (and within) morphometric and microstructural measures, no previous FLICA studies have assessed GWC or T1w/T2w ratio.

7. Development of cognitive abilities in childhood and adolescence

Arguably, one of the most obvious advancements occurring from childhood to young adulthood is the dramatic shifts and improvements in cognitive abilities. Classical cognitive developmental studies have given important insight, such as Jean Piaget documenting for the first time, that object permanence, which is the understanding that non perceived objects may still exist, is learned within the first to years of life (Piaget, 1954). Piaget understood this period as being one of four developmental stages, with the final stage approximately occurring at 12 years of age, extending into adulthood (Piaget & Cook, 1952). Although one today has a more nuanced understanding of development, the rationale of concrete differences between young children and young adults still holds. These differences are of both of quantitative magnitude i.e. young adults can perform several cognitive tasks faster, more accurately and with less cognitive demand then children (Gur et al., 2012), and of qualitative magnitude i.e. young adults have the ability to grasp complex abstract concepts, which young children find difficult (Piaget & Cook, 1952).

Cognitive abilities can be hierarchically structured, with the bottom level consisting of quite specific abilities (Gustafsson, 1984). Although the specificity-based division varies,

modern cognitive test batteries often include several sub measures of executive functioning, memory, language, processing speed, and attention (Gur et al., 2010; Weintraub, Dikmen, et al., 2013). Cross sectional studies assessing these abilities in childhood, adolescence and young adulthood have reported large nonlinear improvement trajectories (Akshoomoff et al., 2014). One study investigated more than a 1000 youths aged 3-20 years, and reported large age related advancements across cognitive tasks. Measures of executive functioning, memory and attention were reported to show stronger improvement in younger as compared to older children, while tasks revolving language and processing speed showed continued increases into adolescence (Akshoomoff et al., 2014). Similarly a cross sectional study of 3,500 youths aged 8–21 years, reported age related improvements of speed and accuracy across all cognitive domains tested, albeit at a varying degree. The greatest maturational changes were reported for tasks revolving executive control, and the least for memory tasks (Gur et al., 2012). Longitudinal studies have reported highly similar results (Waber et al., 2007; Waber, Forbes, Almli, & Blood, 2012) including a study investigating several specific cognitive abilities in 385 youths aged 6-18 years. It was reported that across neuropsychological tests, there was generally a steep improvement from age 6 to 10 years, with a deceleration during adolescence (Waber et al., 2007).

Specific cognitive abilities are understood to recruit partly separate and specialized cortical regions and networks. Indeed, a pivotal longitudinal GM density study of 13 healthy children aged 4–21 years, scanned every 2 years for about 10 years, reported that cortical development appeared to follow regionally relevant milestones in cognitive development (Gogtay et al., 2004). The first to mature was cortical regions associated with more basic functions such as motor and sensory regions, neatly followed by areas involved in spatial orientation, language and certain subdomains of attention. Regions involved in taste and smell as well as visual cortical areas also showed early development. The latest to mature was cortical regions connected to executive function, other sub-domains of attention, and motor coordination. Moreover, it was reported that cortical maturation also concurred with the evolutionary sequence in which these regions are created (Gogtay et al., 2004). There have also been longitudinal investigations that have reported associations between cortical morphometry and improvements in cognitive abilities (see e.g. (Tamnes et al., 2013; Vijayakumar et al., 2014)).

Presented more than a century ago, and placed at the very top of the cognitive ability hierarchy, is the general cognitive ability, often termed the "g-factor" (Spearman, 1904). The rationale is that, as individual differences in more specialized cognitive abilities correlate at about r = 0.30 on average, a principal component or g-factor accounts for about 40% of the total variance (Carroll, 1993; Haworth et al., 2010). This also indicates that diverse cognitive abilities are underpinned by some of the same genes, and it has also been reported that the g-factor is highly heritable (Deary, Spinath, & Bates, 2006; Plomin & Spinath, 2004). Studies have also linked morphometric and microstructural brain development and level of general intellectual abilities (Shaw et al., 2006; Tamnes et al., 2010).

The protracted cortical development of humans is in principal advantageous, as it fosters adaptation, learning and extraordinary cognitive abilities. However, it is also understood to come with several human specific caveats.

8. Neurodevelopmental psychopathology

In closely related non-human primates, cortical development reaches adult-like levels already in puberty (Miller et al., 2012). In humans on the other hand, the developmental schedule is modified and extended, which from an evolutionary perspective has been highly advantageous and adaptive. Indeed, a plastic brain fosters learning, with the environment shaping brain circuit establishment and refinement (Miller et al., 2012). It might, however, simultaneously contribute to a human-specific vulnerability toward mental health issues (Miller et al., 2012; Paus et al., 2008). It is currently believed that a range of mental disorders are in fact neurodevelopmental. Autism spectrum disorders and ADHD often occur in childhood, while anxiety, mood disorders, psychosis, eating disorders, personality disorders and substance abuse disorders often occur in adolescence (Hafner et al., 1989; Kessler et al., 2005). Moreover, the peak age of onset for any mental health disorder has been reported to be 14 year of age (Kessler et al., 2005). A combination of genetic and environmental risk factors are probable underlying drivers, causing aberrations in typical developmental processes (Paus et al., 2008).

Structural neuroimaging studies, have reported a range of differences between subjects with mental disorders and healthy controls (see e.g. (Thompson et al., 2019)). Still, the results are at times highly discrepant and the majority of the time not diagnosis specific, as similar findings are reported across several disorders (which is subpar if one assumes that mental illnesses are distinct). Although several mental illnesses are understood to be neurodevelopmental, studies often include adult subject, as a confirmed diagnosis is set at this time, and as they can be more easily recruited through health facilities. Differences in medication status, as well as factors linked to being seriously ill for a long time, are often limitations of these studies. It is therefore beneficial to investigate subjects with increased risk of psychopathology, or subjects showing early prodromal symptoms. Subjects in risk studies usually have what is termed increased genetic risk i.e. has a close family member with a confirmed diagnosis, or increased clinical risk i.e. a help-seeking individual showing early signs of mental health issues (Satterthwaite, Wolf, et al., 2016).

"We all in the same game just different levels, dealing with the same hell just different devils"

-Jadakiss, Big dog status

Current diagnostic tools such as DSM-V, give rise to distinct diagnoses. This is subpar as there is large heterogeneity within diagnoses (Clark & Watson, 2006). It could be that several differing disorders are grouped together as they show in part similar symptoms, which is also reflected by subjects with the same diagnosis responding differently to the same medication. Moreover, there is large comorbidity across diagnoses, meaning that having one mental illness increases the change of having another (Caspi et al., 2014). Symptoms of many mental disorders additionally form spectra within the general population (Ferdinand, van Lang, Ormel, & Verhulst, 2006; Kelleher et al., 2012; Lubke, Hudziak, Derks, van Bijsterveldt, & Boomsma, 2009; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). Alternative dimensional models on the other hand, capture symptoms across diagnoses and compute an overarching "p-factor", and this factor has successfully been able to describe general psychopathology (Caspi et al., 2014). So too has "Internalizing" and "Externalizing"

from core domain models (Achenbach & Edelbrock, 1981), which capture vulnerability toward symptoms of mood- and anxiety disorders, and substance- and antisocial disorders, respectively (Caspi et al., 2014; Krueger & Markon, 2006). A population-based longitudinal study of 105 children scanned at about 8 years of age, and again a little over 1.5 years later, reported separate region specific decreases in cortical thinning for Internalizing and Externalizing symptoms, as reported by their mothers. The development of symptoms for these domains might therefore have unique neurodevelopmental patterns in late childhood (Whittle, Vijayakumar, Simmons, & Allen, 2019).

A role of personality has consistently been emphasized for etiologic models of psychopathology, and high levels of neuroticism shows the strongest and most consistent relation with several mental disorders (Brandes & Tackett, 2019; Kotov, Gamez, Schmidt, & Watson, 2010; Van Os & Jones, 2001). Strong links have also been reported between neuroticism and the overreaching p-factor (Caspi et al., 2014; Rosenstrom et al., 2018), as well as Internalizing from core domain models (Kotov et al., 2010), and Internalizing and neuroticism might also share underlying brain mechanisms (Hyatt et al., 2019). High levels of neuroticism could therefore be a transdiagnostic risk factor for much of neurodevelopmental psychopathology. The biological underpinnings of neuroticism is not known, but genetic differences account for approximately 40% of the trait variance (Lake, Eaves, Maes, Heath, & Martin, 2000; Wray, Birley, Sullivan, Visscher, & Martin, 2007). This could be explored through polygenic scores (PGS), which are genome-wide association studies (GWAS) identified trait-associated alleles of smaller effect (Dudbridge, 2013). Although no studies have investigated the relationship between brain structure and PGS for neuroticism in youths, one prior study did so in adults, and reported that there was a negative regional association between PGS for neuroticism and surface area (Opel et al., 2018). Studying how cortical developmental patterns are associated with the polygenic architecture of broad psychopathology-associated traits, could give novel insight into emerging atypical patterns.

5. Main research objectives

The overarching goal of the PhD project has been the following:

(1) Inform models of typical cerebral cortical development through intensity contrast measures in particular.

(2) Explore associations between cognition and cerebral cortical development as quantified by intensity contrast measures.

(3) Use typical cerebral cortical developmental patterns quantified by intensity contrast measures and multimodal integration, as a blueprint in the search for aberrant spatiotemporal patterns associated with emerging psychopathology.

9. Hypotheses and objectives for each article

9.1 Paper I

The main research objective for paper I was to investigate the sensitivity of GWC to individual differences in age, general cognitive abilities and risk of psychopathology in youths.

Hypothesis 1: There would generally be a negative association between GWC and age, possibly reflecting protracted intracortical myelination as compared to subjacent WM.
Hypothesis 2: Beyond the general negative age association, GWC would show regional age-related patterns.

Hypothesis 3: Youths with lower general cognitive ability, or higher amounts of psychopathology symptoms would show regionally higher GWC, possibly indicating lower levels of intracortical myelin as compared to subjacent WM.

Paper I fulfills all of the overarching aims of the current thesis i.e. informing models of typical cerebral cortical (and closely subjacent WM) development, as well as linking these developmental patterns to both general cognitive abilities and risk of psychopathology.

9.2 Paper II

The main research objectives for paper II was to investigate the sensitivity of vertex-wise T1w/T2w ratio to individual differences in age, sex and general as well as specific cognitive abilities.

Hypothesis 1: There would generally be a positive association between age and T1w/T2w ratio, putatively reflecting protracted intracortical myelination

Hypothesis 2: Beyond the general positive age association, T1w/T2w ratio would show regional age-related variation.

Hypothesis 3: Boys and girls would show similar age related associations with T1w/T2w ratio.

Hypothesis 4: There would be a positive association between cognitive abilities and T1w/T2w ratio.

Paper II fulfills two of the three overarching aims, i.e. informing models of typical cerebral cortical development, as well as linking these developmental patterns to both general and specific cognitive abilities.

9.3 Paper III

The main research objectives for the paper III was to investigate the relationship between cortical morphometry and microstructure by co-modeling cortical thickness, cortical surface area, and GWC using LICA, and testing resulting independent components (ICs) for associations between age, sex and PGS for neuroticism.

Hypothesis 1: GWC and cortical thickness would often be co-modeled within the same ICs, through shared variance.

Hypothesis 2: Generally, there would associations between age and ICs dominated by GWC and thickness, and additionally with ICs dominated by area for the youngest children.

Hypothesis 3: There would be associations between sex and ICs dominated by area.

Exploratory analysis of ICs and PGS for neuroticism: As no previous studies have linked PGS for neuroticism and brain structure in youth, we had no specific hypotheses concerning this exploration.

Paper III fulfills two of the three overarching aims, i.e. informing models of typical cerebral cortical (and closely subjacent WM) development, as well as linking these developmental patterns to PGS of neuroticism, understood to possibly be a transdiagnostic risk factor for psychopathology.

6. Methods

10. Sample

The samples for the current thesis consisted of the Philadelphia Neurodevelopmental Cohort (PNC) for paper I, Pediatric Imaging, Neurocognition, and Genetics (PING) for paper II, and a combination of the two samples for paper III. PNC and PING are both large-scale publicly available US developmental samples. In both studies, written informed consent was provided for subjects aged 18 years and above, while written parental informed consent was obtained for all remaining subjects, in addition to child assent for subjects aged 7-17 (Calkins et al., 2015; Jernigan et al., 2016).

PNC (Permission No. 8642) is a sample consisting of youths within the age range of 8-23 year, from the larger Philadelphia area in the US. The sample includes genetic-, cognitive- and clinical data, as well as multimodal imaging of 1601 subjects, which are all attained on a single scanner (Satterthwaite, Connolly, et al., 2016; Satterthwaite et al., 2014). The PNC initiative was implemented to explore associations between genetics and brain developmental trajectories as well as cognitive functioning in adolescence. Another central goal was to understand how aberrant developmental trajectories was associated with symptoms of psychopathology (Satterthwaite et al., 2014). Importantly, the PNC sample is therefore population-based. Contrasting standard recruitment procedures where subjects for instance respond to an advertisement or are recruited as they approach health services, seeking help for early symptoms of psychopathology, all PNC subjects were instead recruited while visiting the Children's Hospital of Philadelphia (CHOP). Participants were usually there for a general health check-up or standard pediatric care (Satterthwaite et al., 2014). Through this visit, they consented to be a part of a larger previous CHOP study and agreed to be contacted for future studies (Gur et al., 2012). Still, the sample could have a somewhat larger proportion of children with more complicated illnesses as they were given care at the CHOP (Satterthwaite et al., 2014).

PNC exclusion criteria included severe somatic illness, mental retardation, medical problems that could impact brain function, non-English proficiency and general MRI contraindications (Satterthwaite et al., 2014). For paper I and III we excluded 70 PNC subjects with quite severe medical health conditions based on a severity index rating, by trained personnel in the PNC study team (Merikangas et al., 2015).

PING (http://ping.chd.ucsd.edu) is a sample consisting of typically developing young children, adolescents and young adults within the age span of 3-21 years. The sample contains whole genome genotyping, standardized behavioral measures, and multimodal imaging for a large subgroup of 1239 subjects (Akshoomoff et al., 2014; Brown et al., 2012; Jernigan et al., 2016). PING is a multisite initiative, and for paper II subjects from 7 scanners were employed as we needed T1 as well as T2 sequences, while 10 scanners were employed for paper III. The PING initiative was implemented to improve the disparity in existing imaging samples consisting of adults and elderly participants as compared to the very limited data available from pediatric and adolescent participants. Across the US, subjects within the desired age range and with fluent English capabilities were recruited through local postings and outreach facilities.

PING exclusion criteria included preterm birth, diagnosis of mental disorders (not including ADHD as it is fairly common in (US) pediatric populations), mental retardation, somatic illness, daily illicit drug use by mother, or contraindications for MRI (Brown et al., 2012; Jernigan et al., 2016).

	PNC sample paper I	PING sample paper II	Combined PNC and PING sample paper III
N	1467	621	2621
Age range, years	8.2-23.2 (mean=15.1, SD=3.6)	3.2-21.0 (mean= 12.4, SD= 4.8)	3.0-23.2 (mean= 13.4, SD= 4.6)
Sex	Boys=691 Girls =776	Boys= 318, Girls = 303	Boys=1286 Girls = 1322 Not available = 4
Self-reported ethnicity	Hispanic/Latino= 86 Native Hawaiian/Pacific Islander= 3 Asian=0 Black/ African American= 674 Native American/ Alaska Native= 13 European American= 719 Other=58 Not Available=67	Hispanic/Latino = 140 Pacific Islander = 5 Asian = 88 African American = 102 Native American = 31 White = 426	Hispanic/Latino = 312 Native Hawaiian/Pacific Islander= 114 Asian = 278 Black/African American = 839 Native American/ Alaska Native = 66 European American /White = 1485 Other =58 Not Available = 70

Table 1. Sample demographic, from papers I, II and III. Total ethnicity numbers exceeds total sample sizes as several subjects reported as belonging to more than one ethnic group.

11. Clinical assessment and data-driven decomposition of psychopathology in paper I

Briefly, the clinical assessment entailed a computerized version of the neuropsychiatric interview Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS). For participants below 18 years of age, supplement information from collaterals were included, and for the youngest subjects the only source (Satterthwaite et al., 2014). 129 clinical symptom score items, from 18 clinical domains, were submitted to an independent component analysis (ICA) using Icasso (http://research.ics.aalto.fi/ica/icasso/) (Himberg, Hyvarinen, & Esposito, 2004), in an attempt to discover distinct domains and the empirical correlation structure of psychopathology across diagnostic boundaries, as is described in detail previously (Alnaes et al., 2018). The analysis generated seven psychopathology components. In addition, the mean subject weight across components were computed attempting to capture general psychopathology, conceptually similar to the p-factor.

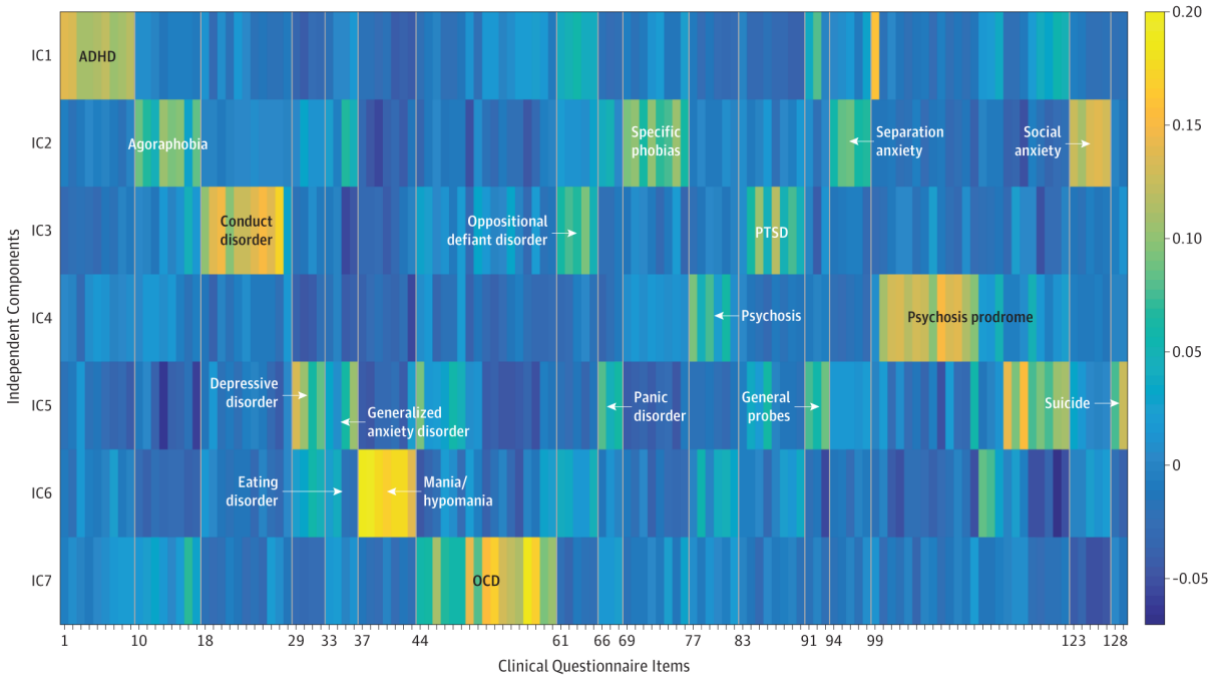

Figure 2. Overview of the clinical independent components (ICs). The figures shows the weights for 129 clinical items on the estimated clinical ICs. The color scale represents item loading on each IC. Attention-deficit/hyperactivity disorder, obsessive-compulsive disorder and posttraumatic stress disorder are abbreviated as ADHD, OCD, and PTSD, respectively. Figure from Alnaes et al. (2018) with permission.

12. Cognitive assessment and computation of specific and general cognitive abilities in paper I and II

Briefly, within paper I participants completed a computerized test battery evaluating a range of cognitive domains (Gur et al., 2012). Performance scores from 17 of these diverse tests were retrieved from a larger pool of PNC subjects consisting of 6487 individuals. As there were high correlations between age and test scores, all raw scores were age residualized by linear regression and standardized before being included in a principal component analysis (PCA) as reported previously (Alnaes et al., 2018). The first principal component was subsequently retrieved as a general measure of cognitive functioning (gF), conceptually similar to the g-factor.

Within paper II, subjects completed the computerized NIH Toolbox Cognition Battery (Akshoomoff et al., 2014; Weintraub, Bauer, et al., 2013; Weintraub, Dikmen, et al., 2013), and 8 sum scores were calculated from raw test scores as described elsewhere (Akshoomoff et

al., 2014). 78 sum score values in total, from 63 subjects were imputed in R using the "mice" package (Buuren & Groothuis-Oudshoorn, 2011) due to missing data. The first imputation from a total of five was chosen. Again, as there were high correlations between age and sum scores, all scores were residualized by linear and quadratic age by linear regression. In addition to employing separate sum scores, we also performed a PCA on sum scores in R (https://www.r-project.org/). The first principal component was subsequently retrieved as a general measure of cognitive ability and sign-flipped so that higher factor loading would represent better performance.

13. MRI

13.1 Care and safety procedures during image acquisition for PNC and PING

No subjects within the PNC or PING samples were sedated for imaging (Brown et al., 2012; Satterthwaite et al., 2014). Before image acquisition, subjects from the PNC sample were presented with a mock scanning session with a retired MRI scanner and head coil. These scannings were accompanied with auditory recordings of the noise that is produced by gradient coils for each pulse sequence. The mock scan was performed in an attempt to familiarize the youths with the MRI environment, and to practice laying very still (Satterthwaite et al., 2014).

Subjects from the PING sample were accompaniment by a parent or a technician into the scanning environment, and exposed, and habituated to the scanner before image acquisition. There were also opportunities for rests in between scans, or other behavioral support if needed. During scanning, all subjects were asked to lay as still as possible and the youngest subjects were given extra head padding. During the structural parts of the protocol, participants were presented with a movie of their choice with sound delivered via headphones to instill calmness and ease the passage of time (Brown et al., 2012).

13.2 MRI acquisition and processing

Our imaging samples were in total acquired on 11 separate 3T whole-body scanners. PNC was acquired on a single 3T Siemens (TrioTim) scanner, while the PING sample was attained on 10 separate scanners from Philips Medical Systems (Achieva), GE medical systems (Signa

HDx and Discovery MR750), and Siemens (TrioTim), of which only 7 scanners were used for paper II. T1 voxel sizes ranged from ≈ 0.9-1.2mm$^{3.}$ Stringent quality control of imaging data was performed for all papers through data-driven approaches combined with visual inspection. I refer to paper I, II and III for in detail documentation concerning MRI acquisition and stringent quality assessment.

Processing of T1 images were for paper I and III performed using the standard FS 5.3 (http://surfer.nmr.mgh.harvard.edu) "recon-all" pipeline. This pipeline performs volumetric and cortical surface segmentations and reconstructions, including modeling of the white- and pial surface (Dale et al., 1999; Fischl, 2012; Fischl et al., 2002; Fischl, Sereno, & Dale, 1999). Cortical thickness was for paper III computed as the shortest vertex-wise distance between the white and pial surface, while cortical surface area was computed by the amount of vertex-wise expansion and contraction needed to register to the FS common template fsaverage (Dale et al., 1999; Fischl, Sereno, & Dale, 1999).

Processing of T1 and T2 images were for paper II performed using the three step Human Connectome Project (HCP) pipeline (Glasser et al., 2013). The first "PreFreeSurfer" step produces an undistorted native structural volume space, aligns the T1 and T2 images, performs bias field correction, and a registration of the native- to the MNI space. Second, the "FreeSurfer" step, based on the FS 6.0 "recon-all" pipeline, performs volumetric and cortical surface segmentations and reconstructions. Lastly, the "PostFreeSurfer" step creates NIFTI volumes, GIFTI surfaces, registers surfaces to the HCP standard_fs_LR mesh, and creates the final brain masks and T1w/T2w ratio maps (Glasser et al., 2013).

13.3 GWC in paper I and III

GWC was assessed in paper I and III, using identical methods. As implemented previously (Jorgensen et al., 2016; Westlye et al., 2009), intra-subject signal intensities were extracted from the intensity normalized "nu.mgz" volume. This volume is created after performing corrections for non-uniformity in the original volume, but before any intensity scaling is performed. From this volume, vertex-wise GM intensities were sampled starting 10% from the white surface and extending a maximum of 60% into the cortical ribbon, resulting in six equally spaced sampling points. These starting and endpoints were chosen in order to capture as much of the layerwise structure of the cortex as possible, including highly myelinated

deeper layers, while at the same time minimizing partial volume effects from CSF. Still, as the first step started at only 10%, one should be aware of possible increased partial volume effects from WM.

Vertex-wise WM intensities were sampled starting close to the white surface and extending the fixed distance of maximum 1.5 mm into subcortical WM resulting in 10 equally spaced sampling points. The fixed distance could be problematic within the few areas where WM is less than 1.5 millimeters thick, but was chosen in order to retrieve a larger specter of intensities, not only within the same voxel, while also minimizing partial volume effects from GM. Then, intensity values across GM and WM sampling points were averaged separately, in order to obtain single vertex-wise intensity values for GM and WM. Finally, GWC was computed as: 100 x (white - gray)/[(white - gray)/2] (Jorgensen et al., 2016), so that higher and lower GWC values would indicate greater and smaller discrepancies between GM and WM respectively. GWC surface maps were smoothed using a Gaussian kernel of 10-mm full width at half maximum (FWHM).

13.4 T1w/T2w ratio in paper II

T1w/T2w ratio maps computed for paper II was based on methods described by Glasser and Van Essen (2011) and is part of the PostFreeSurfer step. It should be noted that we chose to remove the standard "t2pial" flag during the prior HCP processing step; "FreeSurfer" autorecon3. When employed, this flag additionally uses the T2 image for pial surface modelling, in addition to the T1 image. Although usually a benefit, the flag gave rise to sizable hemispheric differences in cortical thickness as well as moderate T1w/T2w ratio differences. This issue could be due to differences in image sequence- or voxel sizes as compared to HCP data, and the flag was therefore removed.

To achieve image division of the T1w and T2w sequence, a volume-to-surface mapping algorithm was applied to all voxel centers within the cortical ribbon. Ribbon voxels were selected within a cylinder centered on each vertex of the midthickness surface from the HCP pipeline output. The cylinder had a height and radius equal to the local cortical thickness and was in an orthogonal direction to the surface. To remove voxels with significant partial volume effects from blood vessels and CSF, individual voxels were excluded if the T1w/T2w ratio value exceeded ±1 standard deviation (SD) of all cortical ribbon values. The remaining

ribbon voxels were then averaged by a Gaussian weighted function to retrieve a single vertex-wise value. The medial wall was assigned values of zero (Glasser & Van Essen, 2011). The final HCP pipeline output included standard and bias corrected ratio maps, the first of which were used in all following analyses. Since we previously removed the t2pial flag, several T1w and T2w images were visually inspected separately. It appeared that although hemispheric discrepancies were now within normal range, the pial segmentation had suffered within sub regions of the medial occipital cortex for several subjects. This was as the T1w pial surface had captured dura, while the T2w pial surface had not, resulting in close to negative ratio values within these small sub-regions.

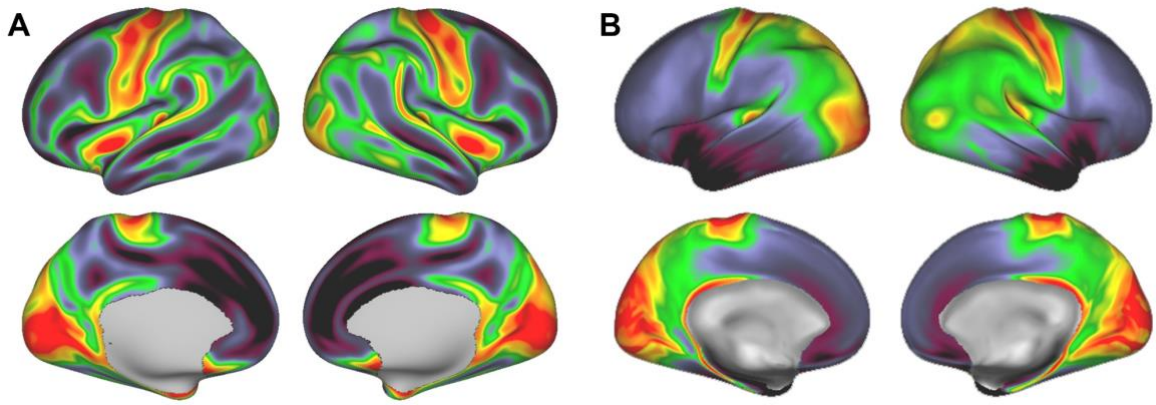

Figure 3. Mean grey/white matter contrast map vs. T1w/T2w ratio map. (A) Shows the mean gray/white matter contrast map of the full MRI sample in paper I (n=1467). Warm and cold colors represent regions with lower and higher gray/white matter contrast respectively. (B) Shows the mean T1w/T2w ratio map from the full MRI sample in paper II (n= 621). Warm and cold colors represent regions with higher and lower T1w/T2w ratio, respectively.

14. ICA on GWC maps in paper I

Paper I mainly consisted of ICA based decompositions of the GWC surface maps using Icasso (Himberg et al., 2004). Icasso based ICA creates spatially independent modes of variations, by running FastICA numerous times and pooling all the estimates together to form clusters (Himberg et al., 2004). In contrast to PCA, where components are orthogonal, ICA maximizes independence but allows components to correlate. ICA outputs "subject loading" which

numerically indicates which subjects have more or less of a corresponding spatial pattern that is presented for each IC (Groves et al., 2012).

For paper I, we ran Icasso testing several model orders spanning the range of 10-25, before pragmatically choosing a model order of 15, based on a compromise between data reduction and the total explained variance of the model. Based on previous studies using similar approaches for decomposition (Doan et al., 2017; Douaud et al., 2014; Groves et al., 2011) no residualization by sex or age was performed on the GWC maps before running Icasso, but were statistically accounted for or explored in all following analyses.

15. Co-modelling morphometry and microstructure through FLICA in paper III

In paper III cortical thickness, cortical surface area, and GWC were decomposed and co-modelled into spatially independent modes of inter-individual variation, through the data driven method LICA using "FLICA" (Douaud et al., 2014; Groves et al., 2012) (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FLICA), applying FSL (Groves et al., 2011; Smith et al., 2004). LICA can fuse several imaging modalities, and model them into a set of interpretable ICs, each characterizing a single biologically relevant form of variability. It is also efficient for detecting artifacts restricted to certain processing pipelines, as a given feature can be completely missing from a modality (Groves et al., 2012).

We ran the FLICA analysis in paper III, with 3000 iterations and a final model order of 60. This model was pragmatically chosen based on it having the highest cophenetic coefficient (Ray et al., 2013) as compared to model orders of 40 and 80, and the biological relevance of maps after visual inspection.

16. Polygenic scores for neuroticism in paper III

In paper III we calculated PGS for neuroticism in a subset of Caucasian participants (n= 880), using the PRSice v1.25 software, based on the item level and sum score GWAS on neuroticism from 2018 (Nagel, Watanabe, Stringer, Posthuma, & van der Sluis, 2018). Although the general notion is currently debated (Dudbridge, 2013), GWAS could be sensitive to proportions of trait variance (Smith et al., 2016) accounted for by genetic differences, which for neuroticism is about 40% (Lake et al., 2000; Wray et al., 2007). One

way to assess this variance is through PGS, i.e. the weighted sum of an ensemble of GWAS identified smaller-effects trait-associated alleles that by themselves do not reach strict significance thresholds (Dudbridge, 2013).

In paper III, PGS p-thresholds were calculated within the range of 0.001 and 0.5, using default PRSice v1.25 settings. We first chose a significance threshold of 0.05 based on statistical- as well as the convention of several previous GWAS studies (Nagel, Jansen, et al., 2018). However, as there are few indications of 0.05 consistently being the most suitable threshold we, based on a previous implementation (Alnaes et al., 2019), additionally performed a PCA in R (https://www.r-project.org/) across all p-thresholds. The first principal component explained 88.1% of the variance, and was extracted as a complementary and more liberal threshold, as the p-threshold 0.329 showed the highest contribution to the principal component.

17. Ethical considerations for the current thesis

There are several central ethical considerations one should be aware of when performing neuroimaging, as well as clinical and cognitive assessments, on youths and young children in particular. These considerations generally include issues related to a child's ability to understand and give assent, and the fact that a parent or guardian often consent on their behalf. In addition, issues concerning confidentiality or which actions to take when subjects report criminal, self-destructive or harmful behavior are central (Clark et al., 2018). There should also be guidelines concerning incidental findings on neuroimaging, psychiatric or cognitive tests. Still, as both the current samples were open access, I was as a researcher mostly removed from these issues in practice. There are, however, also central ethical considerations concerning open access data. These include secure data storage, confirmed anonymity, and also that open access might possibly give the study participant less control of what their data is being used for. This will be discussed below.

As previously described, written informed consent (18 years and above) or parental informed consent (subjects below 18 years) was obtained from all subjects in the PNC and the PING sample, as well as collecting child assent for subjects aged 7-17 (Calkins et al., 2015; Jernigan et al., 2016). The National Institutes of Mental Health, through the American Reinvestment

and Reconstruction Act of 2009, funded the PNC study (Satterthwaite, Connolly, et al., 2016). The PING study was funded by the National Institutes of Health grant, through the National Institute on Drug Abuse and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (Brown et al., 2012).

The PNC data was secured in a safe manner and due to concerns regarding confidentiality, in collaboration with funding agencies, it was decided that all data would be shared jointly though the "dbGaP" public repository. The data first underwent a multi-step process with multiple encrypted identifiers in order to de-identify participant data. Data is governed by policies such only being accessible to qualified investigators, defined as a person with principal investigator (PI) credentials. In order to access data the PI has to complete a request for data access, including a statement of what the research will be used for. If approved an institutional official must confirm that the data will only be used in accordance with the statement and that there will be no attempts to de-identify or transfer data to individuals not within the initial request (Satterthwaite, Connolly, et al., 2016).

The PING project has through funding partners made a major long-term commitment for preserving all data safely for future use. Data is governed by policies such only being accessible to qualified investigators, defined as a scientist at a postdoctoral level holding a research institution position. In order to access data, the researcher has to send a request with a brief description of what the data will be used for and agree to the PING data use agreement, which includes no attempts to de-identify or share data beyond individuals in the initial request. If the proposal is approved most sharable data is either available for download through the PING data portal platform "NITRC.org" or shipped to researchers on hard drives. After study completion the manuscript of the paper must be approved by the PING study team, and cannot be submitted or published online before this approval (Jernigan et al., 2016).

When our study team received the PNC and PING datasets, it was all stored and processed on a powerful research server with high security for sensitive personal information (TSD) or at a local highly secure cluster. Still, as pre-processed data are not always scull stripped, there are methods that technically would make it possible for individuals' accustomed to viewing structural images, to view facial attributes of the subject and by extension also probable sex and age range. This would directly breach consent to not attempt to de-identify data however, and would be highly unethical.

Typically, when a participant agrees to partake in a particular local study, it is due to philanthropic- or a particular interest, and based on concrete information about the goals of the study. Moreover, the data will typically only be used for that particular study, or stored for a set time interval for future use, also approved by the study participant. When the data is open access, however, the study participant has less control over what their data will be used for. Although researchers have to write a proposal in order access data, the proposal is obviously not approved by the participants, but rather by the main study team. The open access data could therefore theoretically be used for a study that a participant might find controversial or not wish to partake in. It is less straight forward, if at all possible to opt out of a particular study when their data is open access.

7. Summary of papers

18. Paper I: Probing brain developmental patterns of myelination and associations with psychopathology in youths using gray/white matter contrast

Background: Cortical myeloarchitecture develops substantially across childhood and adolescence, and when aberrant these trajectories are linked to numerous mental disorders. Differences between intracortical and closely subjacent WM myelination can be approximated through signal intensities in the T1-weighted MRI sequence.

Methods: We attempted to probe the sensitivity of GWC to age, as well as individual variation in psychopathology and general cognitive abilities in youths (8-23 years). Data-driven psychopathology and cognitive components were computed within a large population-based sample i.e. PNC (N = 6487, 52% female), before testing for relationships with regional GWC as established by an ICA in a subgroup of subjects with available MRI data (n = 1467, 53% female).

Main findings: Our analyses uncovered a global GWC component, with an age-related decline from late childhood and through adolescence. We additionally uncovered anatomically meaningful regional components with distinct age associations explaining unique variance beyond the global component. When co-varying for age and sex, we found a relationship between higher symptom levels of anxiety and prodromal psychosis as well as lower cognitive ability and higher GWC in insula and cingulate cortices and with lower GWC in pre- and postcentral cortices. Anxiety, prodromal psychosis, and cognitive ability was further related to several additional regional components.

Conclusions: Variation in independent GWC components reflect global and regional brain developmental processes, possibly related to differential intracortical and closely subjacent WM myelin content, and inter-individual differences in regional GWC are linked to psychopathology and gF.

19. Paper II: Maturation of cortical microstructure and cognitive development in childhood and adolescence: a T1w/T2w ratio MRI study

Background: The cerebral cortex undergoes extensive restructuring and optimization from early childhood and through adolescence. This cortical maturation is an essential feature of human brain development, understood to be the basis for immense developmental improvements of cognitive abilities. Beyond conventional cortical morphometric measures, the T1w/T2w ratio reflects partly separate underlying biological processes, and might give novel insight of typical neurocognitive development and developmental psychopathology.

Methods: Vertex-wise T1w/T2w ratio was computed across the cortical surface in 621 youths (3-21 years) from the PING study sample, and explored in association with individual variation in age, sex, and general as well as several specific cognitive abilities.

Main findings: Analyses revealed a positive association between T1w/T2w ratio and age, nearly globally across the brain surface, with a wide-ranging posterior to anterior direction in association strength. Additionally, boys in late adolescence had regionally higher T1w/T2w ratio as compared to girls. Across subjects, there was a negative relationship between T1w/T2w ratio and general-, as well as numerous specific cognitive abilities, mainly within anterior cortical regions.

Conclusion: The age-related cortical patterns of T1w/T2w ratio from young childhood and until young adulthood, converges with the protracted myelination of the cortex. Furthermore, the current study indicates that T1w/T2w ratio is a relevant neuroimaging marker for cognitive development.

20. Paper III: Testing relations of multimodal neuroimaging measures and polygenic scores of neuroticism in 2621 children and adolescents

Background: The trajectories of human brain development as captured by MRI derived morphometric measures, indicate distinct spatiotemporal courses. Additionally, as compared to conventional morphometric measures, the contrast between cortical grey- and closely subjacent white matter intensities (GWC) may reflect partly unique neurobiological properties. Uncovering the relationship between these morphometric and microstructural metrics in development may provide novel insight into the mechanisms of typical brain development. Moreover, exploring associations between these developmental patterns and the polygenic architecture of transdiagnostic factors, may give valuable insight into why numerous mental illnesses emerge during childhood or adolescence.

Methods: Within a large sample of young children, adolescents and young adults (n= 2621, 3-23 years), we multimodally fused MRI data and decomposed cortical thickness, cortical surface area, and GWC. We then tested for associations between these independent components (ICs) and age, sex and polygenic scores for neuroticism.

Main findings: There was a strong relationship between higher age and lower global GWC, with some region specific variation in association strength. Moreover, a separate component co-modelled globally thinner cortex with globally higher GWC. Boys had generally increased thickness across large cortical regions, but girls had region specific multimodal increases. There were no association with polygenic scores for neuroticism and any of the multimodal components.

Conclusion: The current study reveals that multimodal fusion is sensitive to age and sex related differences in morphometric and microstructural cortical patterns, in line with amongst others the protracted developmental process of intracortical myelination.

8. General discussion

While microstructural measures arguably reflect central underlying developmental processes and shows age-, cognitive ability-, and case-control related differential patterns in adults, there is a near complete lack of highly powered GWC or T1w/T2w ratio studies in development. In the three papers of the current thesis, my co-authors and I have attempted to study typical cortical development through the little-explored microstructural measures of GWC and T1w/T2w ratio, employing large samples and wide developmental age ranges, also including young children. Data driven components as well as vertex-wise measures revealed novel developmental patterns, as well as links to emerging mental health issues, and at times surprising associations with cognition. This will be discussed in detail below.

21. Typical cortical development measured through GWC and T1w/T2w ratio

In paper I ICA revealed one global and several regional and mostly bilateral and symmetrical components explaining variance beyond the global component. The global component showed a marked negative linear age association, as did regional ICs covering occipital, and pre- and postcentral cortices. The remaining ICs showed either slight or marked linear positive age associations. Interestingly, in paper III LICA revealed a particular IC, which neatly captured most of the separate regional ICs from paper I, and also showed and age trajectory that corresponded with the separate trajectories reported in paper I. Correspondingly, although with a different measure in paper II, vertex wise T1w/T2w ratio showed a near global positive age association, with a general posterior to anterior gradient in association strength.

Our results therefore indicate that in typical cortical (and subjacent WM) development, GWC and T1w/T2w ratio is nearly globally lower and higher respectively with higher age. This indicates that GM and WM becomes more similar, and T2w intensities become brighter than T1w intensities. Although linking these results to underlying neurobiology would be speculative, our results do correspond with the known protracted intracotical (and closely subjacent WM) myelination that occur in development (Bartzokis, 2004; Deoni, Dean, Remer, Dirks, & O'Muircheartaigh, 2015; Glasser & Van Essen, 2011). Moreover, the regional bi-directional relationships reported “on top” of the global changes in

paper I and III, could reflect accelerated and protracted regional development. For instance, components encompassing primary sensorimotor regions showed a negative associations with age in paper I and III. These regions are known to mature early and contain high amounts of myelin (Deoni et al., 2015; Glasser & Van Essen, 2011). The strongest association between age and T1w/T2w ratio was also positive and centered around the central sulcus. In comparison, the frontal lobe and temporal pole are known to continue intracortical myelination considerably longer than the age range of both our current samples (Bartzokis, 2004; Grydeland et al., 2013). Components capturing these regions in paper I and III showed positive age associations, which, together with the global negative age effect, might indicate regionally protracted development.

My co-authors and I are the first to report a global GWC decline with higher age in development, and the large sample sizes employed in paper I and III were probably beneficial for detecting such an association. Moreover our regional results contrast the study by Lewis and colleagues who reported scattered positive age associations within cortical sensory processing regions, and negative age relationships within cortical association regions assessed in the PING sample (Lewis et al., 2018). Our regional results do on the other hand concur with previous reports from Mann and colleagues (2018), and Salat and colleagues (2009). Our specific T1w/T2w ratio results also concur with previous reports of higher T1w/T2w ratio almost globally with higher age, but with region specific differences (Grydeland et al., 2013; Shafee et al., 2015).

22. Relationships between GWC, and T1w/T2w ratio and cognitive abilities in development

In paper I, we investigated the relationship between GWC and general cognitive abilities, while we in paper II investigated the relationship between T1w/T2w ratio and general as well as several specific cognitive abilities. In paper I, results showed as we hypothesized a negative association in insula and cingulate, superior parietal, right lateral posterior and visual cortices. Still, there were also regional positive associations in medial temporal, pre- and postcentral, and orbitofrontal cortices. In paper II permutation testing revealed a negative relationship between T1w/T2w ratio and general cognitive ability in the frontal lobe extending into left temporal pole and right parietal regions. Five specific cognitive sum

scores, specifically inhibition, attention, vocabulary, reading, and working memory, also yielded regional negative associations with T1wT2w ratio, spatially overlapping with the regions reported for general cognitive ability. This indicates that there is a regional bi-directional relationship between GWC and general cognitive abilities as well as a negative relationship between general- and specific cognitive abilities and T1w/T2w ratio.

While results in paper I was generally as hypothesized, the results in paper II was surprising. It does however converge with the only prior study investigating T1w/T2w ratio and intra-individual performance variability in response time in both youths and adults (Grydeland et al., 2013). Although the general conclusion was that higher T1w/T2w ratio was associated with higher performance stability, a regional and opposite relationship was reported for the young subgroup consisting of 8-19 year old youths.

It is difficult to interpret our results as being biologically underpinned by intracortical myelin content, as one would intuitively assume that "more is better". This probably is not the case however, as myelin also contains factors associated with inhibition of neurite growth. Excess myelin could consequently foster a permanent inhibitory environment for synapse formation resulting in lower neuronal plasticity (Snaidero & Simons, 2017). It could therefore be speculated that it is disadvantageous to have excess levels of intracortical myelin beyond a certain developmental norm. Still, it is not statistically straightforward to residualize effects of age from cognitive scores in a developmental sample, as correlations between the two are often extremely high. This could affect the direction of results and is discussed in detail in the methodological considerations section.

23. Relationship between GWC and risk of neurodevelopmental psychopathology

In paper I, results indicated that regional GWC was associated with two clinical ICs capturing symptom levels of several forms of anxiety, and positive prodromal symptoms of psychosis, separately. Higher levels of anxiety and/or prodromal psychosis were associated with higher GWC in left lateral posterior, insula and cingulate cortices. These clinical ICs were also associated with lower GWC in sensorimotor cortices, and each clinical IC additionally showed several unique regional bi-directional associations with GWC. As regional GWC associations often converged between the clinical ICs, our paper ads to the body of literature

that request a more nuanced understanding of symptomatology beyond being placed within distinct diagnoses.

Although our original hypothesis was that increased symptom burden would generally be linked to higher GWC, previous studies in adult samples have reported bi-directional associations of GWC in psychosis, and schizophrenia more specifically. One study reported decreased GWC in frontal and temporal regions (L. Kong et al., 2012), while a larger separate study reported the opposite i.e. increased GWC, yet in separate sensorimotor regions (Jorgensen et al., 2016). Our regional results are somewhat inconsistent with both these previous findings, albeit reported using adults with a set diagnosis and not in adolescent risk populations. Of note, while previous risk studies have typically employed genetic risk from family history, or clinical risk i.e. help seeking individuals who are already showing early mental health issues, the population based PNC sampling strategy assesses the continuum of mental health in youth (Satterthwaite, Wolf, et al., 2016). Thus, paper I might instead tap into markers of neural dysfunction at both an earlier age and stage of psychopathology development, as well as variation caused by symptom spectra within the general population (Insel, 2009; Satterthwaite, Wolf, et al., 2016).

Attempting to integrate our results with possible differences in intracortical as compared to WM myelin content is challenging, but there is accumulating evidence for abnormal intracortical myelination being a candidate mechanism for brain network dysfunction in neurodevelopmental disorders and psychosis in particular (Bartzokis, 2012). This has been reported in genetic association studies (Steen et al., 2017), postmortem studies (Tkachev et al., 2003; Uranova, Vikhreva, Rachmanova, & Orlovskaya, 2011), and there is also the notion that psychotropic medications have effects on myelin and its plasticity and repair (Bartzokis, 2011). Still, it is not intuitive to link the bi-directional results in paper I to abnormal differences in intracortical as compared to subjacent WM myelination, in anxiety and psychosis.

My co-authors and I are the first to report associations between regional GWC and individual differences in symptom levels of anxiety, and prodromal psychosis in youth. Still, future studies are needed to replicate these findings. Also, as GWC appears to capture a biologically relevant signal, that at times cannot be intuitively linked to intracortial and WM

myelin content, future studies are needed to give a better understanding of what this measure reflects in order to have practical consequences.

"Where I'm living is not a storybook world. It's the real world, full of gaps and inconsistencies and anticlimaxes."

-Haruki Murakami, 1Q84

24. Methodological considerations

While I was using large developmental samples during the current PhD project to explore GWC and T1w/T2w ratio in exciting new ways, I also encountered several methodological challenges that are important to highlight. The most central difficulties were all connected to the topic of interest, namely development. More specifically, studying development with a cross sectional design, and MRI acquisition and analytical youth-related issues. Moreover, the developmental age range is closely intertwined with nearly "everything else", or more specifically with several nuisance- and variables of interest. Other central challenges included interpreting the GWC and T1w/T2w ratio results in a biologically meaningful way. Lastly, PGS, which was employed in paper III, has been reported to explain minor amounts of variance accounted for by genetics. These challenges will all be discussed in the following.

24.1 The struggles of studying development

24.1.1 Studying development cross-sectionally

It is currently well documented and arguably a conventional understanding that cross-sectional developmental studies are sub-par as compared to investigating development longitudinally. More specifically, it is problematic to use data from a single time point per subject, for then to compare subjects across different ages before stating something about developmental trajectories within subjects (Kraemer et al., 2000). This is perhaps particularly challenging in developmental neuroimaging studies, as there are, within the same age range, large individual differences in brain structure (Mills & Tamnes, 2014), and possibly although

less explored also in the degree of change across time (Mills & Tamnes, 2014; Steen, Hamer, & Lieberman, 2007). Cross sectional studies therefore need a substantial amount of power in order to detect even small brain changes of interest (Schönbrodt & Perugini, 2013). For instance, assuming a 5% whole brain volume discrepancy between a patient and a control group, it has been reported that a cross sectional study would need a sample size of approximately 150 subjects in total to detect such differences, while it would be sufficient to recruit 5 patients and 5 controls for longitudinal investigations (Steen et al., 2007).

Researchers should therefore take specific steps to reduce cross-sectional-specific caveats, instead of nonchalantly reporting the design as a study limitation within papers. These steps include selecting a time scale, and correctly using terminology (Kraemer et al., 2000). Without detailing the statistical rationale, cross sectional studies should not use random time sampling, as it alters results by mixing within- and between -subject variation over time. One should instead report all results in time-matched and clearly defined groups (Kraemer et al., 2000). Of note, regional cortical thickness have for instance been reported to vary within only 24 hours (Elvsashagen et al., 2017). Moreover, when describing cross sectional results, one should not use terms such as "increases" or "changes" over time but instead use terms such as "age-related differences» or simply "high" and "low" (Kraemer et al., 2000).

It should still be noted that there are clear advantages to the cross sectional study design. In addition to savings in time and cost, cross sectional studies could be initially performed to inform longitudinal studies of what subject matters to approach. For the current papers, although large sample sizes were employed, we attempted to consistently use terms such as "high" instead of "increase". Still we often used the terms "development" and "maturation" which is imprecise and subpar terminology. Moreover, we did not match subjects by their scan time point and this is a study limitation for all papers within the current thesis.

24.1.2 MRI acquisition and analysis in children

The current developmental neuroimaging literature consist of early post-natal studies with an almost complete discontinuity until primary school years. While infants can be assessed during natural sleep, and tightly bound by wrapping a sheath around the full body which

inhibits movement while at the same time soothing the child, young children find it very difficult to lay still during image acquisition (Mills & Tamnes, 2018). Repositioning, fidgeting or even chewing is understood to create sufficiently poor quality data that could bias imaging results. Correspondingly, one study investigated the effects of head motions on morphometric measures as produced by FS 5.3 in 12 adults. Subjects were instructed to lay still for certain sequences and shake, nod or freely move their head, for others. When comparing the movement and non-movement sequences, it was reported that head movement gave rise to apparent volume loss as well as cortical thinning at varying regional degrees. Importantly, results remained even after including visual quality control, by a trained professional who excluded several poor quality images (Reuter et al., 2015). Still, in the reported study it appears that the subjects' heads were not padded within the head coil during image acquisition, which is an unusual practice. For the samples employed in the current thesis, all subjects were padded during acquisition. Moreover, deliberate large head movements such as nodding could be quantitatively different from subtle or involuntary head movements.

As compared to adults, younger children have differing tissue contrast, which are used by segmentation tools to model brain surfaces, and there are also differences in brain size-, shape-, and gyrification. Developmental imaging studies should therefore employ age-specific standard templates, as adult templates could result in inaccurate tissue segmentation (Cusack, McCuaig, & Linke, 2018).

Within paper II and III, we were able to include children with an age range spanning below primary school years. Several subjects were excluded due to movement, and although I was blind to subject-age during quality assessment, it was at times simply by viewing the image, clear that the subject was very young. Still, it should be mentioned that the PING study team appeared to have a particular focus on collecting decent quality data, as additional scans were consistently taken if the initial sequences showed movement artifacts. Moreover, in addition to visual inspection, quality assessment for all the current papers also included data-driven methods. For instance, the assessment tool employed in paper II and III has specific parameters understood to detect artifacts created by head motion (Esteban et al., 2017). As we did not use age-specific atlases during MRI analyses on the other hand, this is a limitation for all papers within the current thesis.

24.1.3 Untangling development from other variables of interest

Although biological age is an easily assessable metric that successfully captures development, it is clear that the developmental age range also shows close relationships with several other variables of interest and nuisance. This includes the negative relationship with head movement during MRI acquisition, and of course a strong positive association with cognitive abilities.

Within paper II, particular cognitive scores correlated above r=0.8 with age. After sum score residualization, we found a surprising negative association between T1w/T2w-ratio and cognitive abilities. This age-related dissociation between brain structure and cognition in development as compared to adults have been consistently reported, including within a separate T1w/T2w ratio study (Grydeland et al., 2013) but also in other morphometric studies. One such study investigated the association between IQ scores and thickness of the corpus callosum in a mostly adult sample, aged 16–44 years. As expected, emphasizing the relevance of functional interaction between hemispheres for cognitive abilities, they observed a positive association between IQ scores and region specific thickness (Luders et al., 2007). Using the same method in a sample of children and adolescents on the other hand, aged 6-17 years, the opposing effect was reported, i.e. a negative association between IQ and thickness within in the same corpus callosum regions (Luders et al., 2011). Interestingly, another developmental study attempted to re-investigate the reported negative association between IQ and corpus callosum thickness within a mixed cross-sectional and longitudinal sample of 495 participants, covering an age range between 6-22 years old (Westerhausen et al., 2018). Instead of deviation IQ measures, the study employed raw test scores before again associating regional corpus callosum thickness and cognition. Indeed, a positive association was now reported for both verbal and performance raw test scores. This association was not present if not considering the age of the participants within the analyses. Authors therefore concluded that there was no association that could not be explained by a temporal co-occurrence of development in cognitive abilities and corpus callosum maturation (Westerhausen et al., 2018).

Within paper II, rather than being nonexistent, the relationship between T1w/T2w ratio and cognitive abilities were in an unexpected negative direction. This could of course

be interpreted as excessive intracortical myelin, beyond a normative developmental range, being disadvantageous. Still it is not statistically straightforward to regress developmental age from another variable of interest when the two show high correlations. As we were concerned that the statistical regression itself could have caused a sign flipping of results, we additionally performed several tests on the raw cognitive scores. This included Gram-Schmidt orthogonalization of age and raw cognitive scores, in R, and also using a sliding window approach to investigate T1w/T2w ratio and raw cognitive scores in narrow age ranges. These results both showed corresponding directions to our original findings.

24.2 The controversy surrounding GWC, T1w/T2w ratio and intracortical myelin

Although the most common neurodevelopmental theory concerning the underpinnings of both GWC and T1w/T2w ratio relate to intracortical myelination, this notion has recently been disputed.

24.2.1 GWC

Beyond the signal of the T1w image reflecting myelin, and GM intensity showing histologically based myeloarchitectural patterns, it is not clear why the specific contrast between GM and WM is associated with intracortical myelin. First, one cannot assume that changes in GWC reflect shifts in myelin content solely within the cortex. This is both due to the inherent limitations in the biological specificity offered by MRI-based signal intensity measures, and since GWC essentially is a contrast between two tissue classes and may therefore capture variability in both GM and WM. Although deep WM myelination generally occurs earlier as compared to the protracted process of intracortical myelination, the WM sampled within GWC is within a short mm distance from the GM intensities "of interest". It would therefore not be sensible to state that alterations occurring that close in space are not a product of bother matter types.

One approach of delineating these effects would be to consider the GM and WM compartment independently. A complicating factor is that raw signal intensities are not constant across participants for the same underlying relaxation parameters due to session- and participant-specific optimization procedures performed during MRI acquisition. Thus, signal

intensities should be normalized to correct for inter-subject variations in scaling factors. In paper I we indeed attempted to test this empirically by normalizing GM and WM intensities by voxel intensities outside of the scull. These intensities unfortunately were also associated with age and using these for normalization would therefore unduly affect the results in the subsequent analyses. Instead, we plotted raw signal intensity scores sampled within different GM and WM regions and plotted them as function of age. With the important caveats described above in mind, the two tissue types showed overall similar age-associations. In paper I and III we therefore consistently referred to GWC changes as "differences between intracortical and subjacent WM".

24.2.2 T1w/T2w ratio

Although reported as a T1w/T2w ratio map within paper II, in actually it is outputted by the HCP pipeline as a "myelin map". The biological underpinnings of the T1w/T2w ratio is currently debated and likely complex. On the one hand, as described in the introduction, it has been reported that intracortical myelin content inversely co-varies with the signal in both the T1w and T2w MRI sequence. The measure also concurs with post mortem data. On the other hand, recent attempts have not been able to reveal close associations with T1w/T2w ratio and either myelin-related genes or more established myelin measures (Hagiwara et al., 2018; Ritchie, Pantazatos, & French, 2018; Uddin, Figley, Solar, Shatil, & Figley, 2019). For instance, an article investigated the regional correlations between magnetization transfer (MT) an imaging measure widely used for estimating myelin content and T1w/T2w ratio in 20 subjects age 25-71 years (Hagiwara et al., 2018). Investigations were performed in 48 WM regions of interest (ROIs) and 116 GM ROIs, 12 of which were subcortical. In WM, the study found only weak correlations between T1w/T2w ratio and MT ($r = 0.38$), and authors therefore concluded that T1w/T2w ratio might be less optimal for studying WM myelination. Still it should be noted that the correlation between the two measures within GM was $r= 0.54$.

Another study investigated the molecular basis and gene expression-correlates of T1w/T2w ratio, using the Allen Human Brain Atlas, which includes transcriptomic information and neuroimaging of six healthy adult postmortem brains. They also performed additional analyses replacing the post mortem brains with a mean T1w/T2w ratio map of more than a thousand individuals from the HCP sample. It was reported that the

most significant gene (SCARA5) was negatively correlated with T1w/T2w ratio across the six post mortem brains, suggesting unexpectedly that the measure is not a proxy for iron content (Ritchie et al., 2018). Moreover, they reported that certain oligodendrocytes, molecular size, axon caliber, and even pH were more strongly associated with T1w/T2w ratio than myelin associated genes. The oligodendrocytes in question were moreover understood to be primarily non-myelinating. It was therefore concluded that future studies were needed to show that T1w/T2w ratio reflects intracortical myelin content (Ritchie et al., 2018).

When writing the papers for the current PhD thesis, there has been a tough balance of associating results to possible underlying developmental process, of which cortical myelination is the main candidate, while at the same time clearly conveying that recent scientific attempts have not revealed close links between GWC and T1w/T2 ratio and intracortical myelin. This has been particularly problematic as there are no alternative developmental processes currently understood to underpin these measures. However, GWC and T1w/T2w ratio both clearly show a biologically relevant signal, sensitive to both cognition and mental health. Future studies are certainly needed to untangle the opposing reported associations (or lack thereof) between GWC and T1w/T2w ratio and intracortical myelin.

24.3 The issue of PGS and low explained variance

After initial excitement concerning the straightforward yet reasonable way to assess the polygenic architecture of complex traits such as neuroticism or mental health, several current studies have questioned the utility of PGS, reporting that scores explain very little of the known heritability in several complex traits. For instance, a combined meta-analysis of GWAS of neuroticism included almost 10 000 participants from the UK Biobank cohort, as well as more than 6500 participants from a Scottish cohort and almost 9000 participants from a Queensland Institute cohort. All participants were assessed using the same neuroticism instrument. It was reported that the UK biobank sample only explained about 1% of the variance in neuroticism within the two independent samples, and that most of the genome-wide significant alleles identified in the UK Biobank-only GWAS, were not independently replicated within the other independent cohorts (Smith et al., 2016). Moreover, a recent

attempt to apply polygenic scores to split-half samples failed to significantly predict any of the tested personality traits of the study, which included neuroticism (Docherty et al., 2016) . Beyond personality, PGS has been reported to explain only 12% of variance in actual educational attainment, and 7-10% of variance in actual cognitive performance (Lee et al., 2018). PGS have moreover been reported to only capture 2-7% of the explained variance of case-control differences in several mental disorders, including psychosis and mood disorders (Demirkan et al., 2011; Schizophrenia Working Group of the Psychiatric Genomics et al., 2014; Wray et al., 2018).

It could be that PGS studies are simply underpowered to detect the underlying variance in complex traits explained by genetics. Moreover, while GWAS, of which PGS is based on, only sample common variants and not the full genome, rare variants could be important contributors, which would account for the low explainability of PGS. The rationale is that from an evolutionary perspective, if a variant found in an individual is common, it should not have a large (negative) effect, if so it should have been selected against (Lupski, Belmont, Boerwinkle, & Gibbs, 2011). This notion corresponds with a recent study which obtained not only the common genetic variation typically assessed in GWAS, but whole-genome sequence data (thus including rare variants) from more than 20.000 individuals. It was reported that when only using common variants, the estimated heritability of height and body-mass index was 0.49% and 0.27% respectively, which replicated previous findings, but is well below the known heritability for these features. When employing the whole-genome sequence data on the other hand, estimates increased to 0.79% and 0.40% for height and BMI respectively (Wainschtein et al., 2019). Other factors that could explain the low explicability of PGS, are random “de novo” mutations occurring in the mothers stomach, when the sperm and egg fuse (A. Kong et al., 2012).

Our analyses in paper III revealed no association between PGS for neuroticism and any of the multimodal ICs. Null-findings remained after using the more liberal PCA threshold indicating that this is not due to the amount of single-nucleotide polymorphisms (SNPs) used to compute the PGS score. While PGS might show promise in the future (Martin, Daly, Robinson, Hyman, & Neale, 2019), it could currently be a premature measure and particularly for assessing the polygenic architecture of complex traits investigated in neuroscientific studies.

9. Concluding remarks

The essence of the current thesis has been to use structural MRI, and the intensity contrast measures GWC and T1w/T2w ratio in particular, to explore and give novel and nuanced insight of human cortical development from early childhood, through adolescence and until young adulthood. All three papers were based on large developmental samples, including young children, and investigated the signal intensity measures in, at times, novel ways through data-driven decomposition and multimodal fusion. By integrating the three papers, the current thesis has presented associations between age and global and region specific GWC. It has also reported a positive nearly global relationship between T1w/T2w ratio and age, as well as the quite unexpected association with cognitive abilities. In sum, these cortical and closely subjacent WM patterns spatiotemporally converge with the protracted developmental process of intracortical myelination. It was finally reported that clinical components capturing several forms of anxiety and prodromal psychosis were bi-directionally associated with highly overlapping regional GWC. Keeping several methodological challenges in mind, including the cross sectional study design, and the uncertainty concerning the biological underpinnings of signal intensity measures, I conclude that GWC and T1w/T2w ratio shows a biologically relevant signal that is sensitive to individual differences in age-, cognitive abilities- and levels of symptoms of psychopathology in development.

Future studies, particularly using large longitudinal samples, should replicate the findings of the current thesis. Indeed new initiatives such as the Adolescent Brain Cognitive Development (ABCD) study would be a unique opportunity for such replications as researchers will follow the brain development and health of more than 10,000 children starting at approximately 9 years of age, and continuing through adolescence (Casey et al., 2018). Coming investigations should also use multimodal integration to give additional insight about the relationship between intensity contrast and morphometric measures, as well as linking these relationships to brain function. Perhaps most urgently, studies are critically needed to untangle the discrepant reports concerning the underlying biology reflected by intensity contrast measures.

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