Review article

New insights into the dynamic development of the cerebral cortex in childhood and adolescence: Integrating macro- and microstructural MRI findings

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ABSTRACT

Through dynamic transactional processes between genetic and environmental factors, childhood and adolescence involve reorganization and optimization of the cerebral cortex. The cortex and its development plays a crucial role for prototypical human cognitive abilities. At the same time, many common mental disorders appear during these critical phases of neurodevelopment. Magnetic resonance imaging (MRI) can indirectly capture several multifaceted changes of cortical macro- and microstructure, of high relevance to further our understanding of the neural foundation of cognition and mental health. Great progress has been made recently in mapping the typical development of cortical morphology. Moreover, newer less explored MRI signal intensity and specialized quantitative T2 measures have been applied to assess microstructural cortical development. We review recent findings of typical postnatal macro- and microstructural development of the cerebral cortex from early childhood to young adulthood. We cover studies of cortical volume, thickness, area, gyrification, T1-weighted (T1w) tissue contrasts such as a grey/white matter contrast, T1w/T2w ratio, magnetization transfer and myelin water fraction. Finally, we integrate imaging studies with cortical gene expression findings to further our understanding of the underlying neurobiology of the developmental changes, bridging the gap between *ex vivo* histological- and *in vivo* MRI studies.

1. Introduction

Childhood and adolescence represent remarkable periods of change. Early childhood involves extensive physical changes, major improvements in sensorimotor skills, and cognitive evolutions of self-awareness and language acquisition (Colson and Dworkin, 1997; McMurray, 2007; Rochat, 2003). Social bonding is another important childhood landmark, with play-time fostering several aspects of this development (Ginsburg et al., 2007). Adolescence, signifying the transitional period

between childhood and adulthood, brings forth a novel set of advancements. These include pubertal bodily and hormonal alterations, further development of complex and abstract thinking, heightened emotional reactivity, increases in certain risk-taking behaviors, an urge for independence, as well as major changes in socio-cultural roles and interpersonal relationships (Blakemore and Mills, 2014; Choudhury, 2010; Marshall and Tanner, 1970, 1969; Piaget and Cook, 1952; Silvers et al., 2012; Steinberg, 2008).

Childhood and adolescence are also central periods for brain

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reorganization and optimization (Blakemore, 2012; Brown and Jeri-gan, 2012; Lebel and Deoni, 2018). The cerebral cortex is a principal neural structure for our cognitive abilities (Harris and Shepherd, 2015; Rakic, 2009) and its spatiotemporal development is paralleled by qualitative and quantitative cognitive strides (Akshoomoff et al., 2014; Casey et al., 2005). Studying cortical maturation is therefore a natural step to understand cognitive development. Compared with closely related non-human primates, certain features of human cortical development appear temporally extended (Hawrylycz et al., 2012; Miller et al., 2012). One could speculate that this protracted development is advantageous, allowing for environmental experiences to foster adaptation and learning, while at the same time coming with certain costs. Indeed, childhood and adolescence are periods when many common mental disorders emerge (Kessler et al., 2005; Paus et al., 2008). The dynamic interplay of multiple genetic and environmental risk factors likely precipitates deviant pre- and postnatal neurodevelopment, and in turn emerging mental health problems (Paus et al., 2008). Put differently, most common mental disorders are today understood as neurodevelopmental in nature, and investigating brain development and its individual variation is consequently of high relevance.

Magnetic resonance imaging (MRI) can indirectly measure multifaceted properties and developmental processes of the cerebral cortex, while being in vivo and noninvasive (Lerch et al., 2017). Macrostructural or morphometric quantifications include cortical volume, its sub-components, namely thickness and surface area, as well as cortical gyrification indices (Desikan et al., 2006; Fischl, 2012; Fischl and Dale, 2000; Winkler et al., 2012). Beyond morphometric changes, newer less explored microstructural MRI measures are sensitive to “the brightness” or intensity variation in cerebral tissues, which is presumed to be of neurobiological relevance (Glasser and Van Essen, 2011; Salat et al., 2009; Westlye et al., 2010). It has also been shown that more specialized microstructural assessments that are sensitive to rapid T2 signal decay (Alonso-Ortiz et al., 2015) can successfully be applied to study cerebral cortical development.

To further our understanding of cognitive development and neurodevelopmental psychopathology, it is essential to determine first the characteristics of and variation in macro- and microstructural brain development. Recent studies have revised our knowledge of the developmental trajectories of cortical morphology (as discussed e.g. in (Mills and Tamnes, 2014; Walhovd et al., 2016a), yet dated descriptions of cortical thickness and volume development are still prevalent in the broader literature. Additionally, although reflecting partly separate underlying neurobiological and polygenic underpinnings (Panizzon et al., 2012; Patel et al., 2020), there are no previous literature reviews covering cortical developmental changes as assessed using signal intensity measures, magnetization transfer (MT) or myelin water fraction (MWF). Further, cortical structure and developmental trajectories could differ to some extent between males and females (Kaczurkin et al., 2019; Paus, 2010). Yet, beyond the consistent finding of larger brain volumes and cortical surface areas in males, results on sex differences in cortical development are difficult to reconcile (Jahanshad and Thompson, 2017; Paus et al., 2017; Wierenga et al., 2018). Another vital, but challenging task is to link developmental changes in morphology and microstructural measures to specific underlying neurobiological processes.

The objective of the current review is to summarize and discuss contemporary MRI research on typical development of the human cerebral cortex from early childhood to young adulthood. After a description of the anatomical and cellular architecture of the cortex, we review recent macro- and microstructural MRI findings across a range of imaging tools, the possible underlying neurobiological processes, and how different features of cortical development can be integrated. Finally, we will consider recent studies that have used transcriptomics to probe the neurobiological events underlying the development of the cerebral cortex. Of note, cortical developmental processes in childhood and adolescence are oftentimes continuations of processes beginning

before birth or in infancy. Research on fetal and neonatal brain development is not, however, covered in the current review due to differences in the scale and scope of the changes and in neuroimaging methods, but is reviewed elsewhere (Batalle et al., 2018; Lebel and Deoni, 2018; Makropoulos et al., 2018; Thomason, 2020).

2. The architecture of the human cerebral cortex

The cerebral cortex, constituting the outermost part of the brain, characteristically resembles a highly folded sheath, with peaks and valleys termed gyri and sulci, respectively (Destrieux et al., 2010). It consists of several cortical layers (six in the neocortex), with an average thickness of about 2.5 mm (Brodman, 1909; Palomero-Gallagher and Zilles, 2019). The cerebral cortex contains tens of billions of brain cells (Pelvig et al., 2008), including pyramidal- and interneurons neatly packed and organized column-wise for effective long-range and local signal transmission, respectively (Mountcastle, 1995; Rakic, 2009, 1995). The cortex also comprises dendrites, glial cells, and myelinated and unmyelinated axons (Nieuwenhuys, 2013). The specific cellular composition and distribution vary greatly depending on the cortical region and layer (Brodman, 1909; Palomero-Gallagher and Zilles, 2019), as does the layers functional role (Bastos et al., 2012) and structural connectivity (Rockland, 2015). There is, nevertheless, generally a profusion of neuronal cell bodies within superior cortical layers, and myelinated axons in deeper cortical layers. This is in part as subjacent white matter myelin penetrates the cortical neuropil (Nieuwenhuys, 2013), while many other cortico-cortical axons never leave, originating and terminating within the cortex (Paus et al., 2014).

The advancement of staining techniques in the late 1800s allowed for histological subdivisions of the full cortex (Palomero-Gallagher and Zilles, 2019). These atlases, still of high relevance today, are based on “cytoarchitecture”, meaning differences in cell types and the density of cell bodies, or “myeloarchitecture”, meaning the density and arrangements of myelinated fibers. The Brodman (Brodman, 1909) and Vogt (Nieuwenhuys, 2013) monographies are fine examples of such atlases. Using advanced MRI analysis programs, the cortex can be divided into finely grained sections using, for instance, markers of myelination, structural connectivity with other brain regions, functional specialization (Fan et al., 2016; Glasser et al., 2016; Yeo et al., 2011) or genetic influences (Chen et al., 2013, 2012). Another window into cortical organization and function is through its spatiotemporal maturational patterns in childhood and adolescence.

3. The morphological development of the cerebral cortex

Human corticogenesis starts early in the fetal period and involves a cascade of events, including the emergence of transient layers (Bystron et al., 2008). Neurons originating in the ventricular zone migrate to form the preplate, then, when the cortical plate is formed, the preplate separates into the marginal zone and the subplate (Chan et al., 2002; Miquelajáuregui and Varela-Echavarría, 2008). Despite later transformation or disappearance of the transient layers, cells from these compartments play central roles in cortical development and organization (Kostović, 2020; Molnár et al., 2020; Vasung et al., 2020).

Cortical macrostructure, or morphology, refers to the gross features of the cerebral cortex, such as size and shape. MRI studies of the morphology of the cerebral cortex and its postnatal development typically assess volume, thickness, surface area or folding, the latter also known as degree of gyrification (Hogstrom et al., 2013). A growing number of neuroimaging studies collecting or combining data in a large number of individuals (e.g. (Frangou et al., 2020)), also longitudinally (e.g. (Tamnes et al., 2017; Vidal-Pineiro et al., 2020)), have provided new insights into typical age-related differences and developmental trajectories of the different cortical components.

Generally, cortical morphology show rapid changes early in life (Gilmore et al., 2018), followed by protracted changes throughout

childhood and adolescence (Tamnes et al., 2017; Vidal-Pineiro et al., 2020; Vijayakumar et al., 2016). Development of cortical morphology is characterized by nonlinear changes, i.e. there may be periods of greater change, and by regionally specific patterns. Combined, these spatio-temporal patterns appear to progress in a back-to-front direction, and with sensorimotor regions maturing earlier than association cortices (Gogtay et al., 2004; Tamnes et al., 2013). The sequence of cortical maturation corresponds with functional maturation, where more basic and sensory functions mature earlier than higher-order cognitive functions, including social cognitive processes (Andrews et al., 2021; Gogtay et al., 2004). Although cortical morphology and its development have been related to sociodemographic variables, behavior, and cognition in healthy and clinical populations (e.g. (Alnæs et al., 2020; Chung et al., 2017; Ehrlich et al., 2012; Farah, 2017; Hooker et al., 2011; Schnack et al., 2015)), the relationships are complex and typically small (Dick et al., 2020; Paulus and Thompson, 2019; Walhovd et al., 2014).

Cortical volume can be defined as the product of thickness and surface area (Panizzon et al., 2009). Although novel methods for their joint analysis are available and appropriate in several cases (Doan et al., 2017; Winkler et al., 2018), it has become common to consider these measures separately. This is because they seem to be driven by biologically distinct processes (Rakic, 1988), may show differential sensitivity

to variation in cognitive abilities and mental disorders (Rimol et al., 2012; Schmaal et al., 2017; Schnack et al., 2015; Vuoksima et al., 2016), and have been found to have distinct sets of genetic influences, as inferred from twin and family studies (Panizzon et al., 2009; Winkler et al., 2010), and weak genetic correlations (Hofer et al., 2020). Although recent findings suggest a significant polygenic overlap between cortical thickness and surface area, the details of the molecular architecture underlying the two cortical features are quite different (Grasby et al., 2020; van der Meer et al., 2020). Importantly, cortical thickness and surface area also follow different developmental trajectories (Lyall et al., 2015; Tamnes et al., 2017; Wierenga et al., 2014) (see Fig. 1).

This section will provide an overview of morphological cerebral cortical development in childhood and adolescence by reviewing studies of gray matter volume, thickness, surface area, and gyrification. Given vast support for the distinctness of the two main components of volume, we discuss thickness and surface area in greater detail. Sex differences and biological factors underlying these developmental changes will also be discussed.

Fig. 1. Developmental trajectories for lobar measures cortical morphology in four independent longitudinal samples. The left panels shows cortical thickness, the middle panel shows cortical surface area, and the right panel shows cortical volume, all while controlling for sex. The thick colored lines represent fitted models, while the lighter colored areas correspond to the 95 % confidence intervals. The figure is adapted from Tamnes et al. (2017).

3.1. Volume

Cortical gray matter volume is typically estimated either using volume-based representations, such as voxel-based morphometry (VBM), or surface-based representations where volume is defined as the amount of tissue between the pial and the white surface (Winkler et al., 2018). Gilmore et al. (2012) examined development of cortical volume in 72 infants shortly after birth and at ages 1 and 2 years, and found substantially larger growth during the first compared with the second year, with relatively faster growth in association areas as compared with primary motor and sensory areas during the first two years of life. Beyond the infant and toddler periods, early studies assessing cortical volume development in youth reported an inverted U-shaped trajectory, with peak regional volumes in late childhood or early adolescence (e.g. (Giedd et al., 1999; Gogtay et al., 2004; Lenroot et al., 2007; Raznahan et al., 2011b)). More recent studies have not, however, identified peaks in overall cortical volume during these periods. For example, a study using four independent longitudinal samples with a total of 852 MRI scans from 391 participants aged 8–30 years (Mills et al., 2016) and a study with 202 scans from 135 individuals aged 7–23 years (Wierenga et al., 2014) both found monotonic non-linear decreases, indicating that cortical volume starts decreasing substantially earlier than previously reported. Developmental “peaks” have been identified in a few cortical regions, including anterior temporal cortices (Mills et al., 2016) and parts of the frontal cortex (Wierenga et al., 2014), but these are likely only exceptions from the general pattern of cortical volume development.

In terms of sex differences, studies converge on larger volumes in males (vs. females) examined at both gross and regional level (Kaczurkin et al., 2019; Lenroot et al., 2007; Mills et al., 2014; Raznahan et al., 2011b; Vijayakumar et al., 2016; Wierenga et al., 2014). Although inconsistencies exist regarding age by sex interactions on cortical volume, studies indicate that a few selected cortical regions may show different developmental trajectories in girls and boys (Paus et al., 2010; Vijayakumar et al., 2016; Wierenga et al., 2014).

3.2. Thickness

The influential radial unit hypothesis of cortical development posits that the three-dimensional architecture of the cerebral cortex can be traced back to the two-dimensional information of the proliferative units located in the ventricular zone; the site of origin in the ventricular zone gives information on X and Y axis of the cells, while Z-axis is determined by the time of their origin (Rakic, 1995, 1988). Cohorts of vertically arranged neurons, that share the same birthplace in the ventricular zone, migrate radially to the cerebral cortex. By this account, the thickness of the human cerebral cortex is principally determined by the number of cell divisions within proliferative units in the ventricular zone (Rakic, 1988). Cortical thickness shows considerable regional variation, ranging between 1 and 4.5 mm (Fischl and Dale, 2000). In MRI, a common method to assess cortical thickness is to use T1-weighted images to create models of the white and pial surfaces before calculating thickness as the shortest vertex-wise distance between these (Fischl and Dale, 2000).

Longitudinal MRI studies have found that cortical thickness increases during the first years of life, and especially during the first as compared with the second year (Li et al., 2015; Lyall et al., 2015). In many regions, cortical thickness also appears to peak between the first and second year, as demonstrated by Wang et al. (2019) in 43 infants aged 0–2 years and scanned up to 7 times, and by Li et al. (2015) in a sample of 73 infants aged 0–2 years with 219 scans.

After this initial thickening, current longitudinal studies, some of which include children from 4 years old, report monotonic thinning in most cortical regions from childhood to adulthood (Ducharme et al., 2016; Fjell et al., 2015; Mills et al., 2014; Vidal-Pineiro et al., 2020; Vijayakumar et al., 2016; Wierenga et al., 2014). Of note, and similar to

the discrepancy regarding cortical volume development, this is in contrast to some earlier pioneer longitudinal studies that reported peaks in thickness in late childhood or early adolescence (Raznahan et al., 2011ab; Shaw et al., 2007, 2008) (but see (Sowell et al., 2004; Tamnes et al., 2010)). Possible reasons for these discrepancies have been discussed elsewhere (Mills and Tamnes, 2014; Walhovd et al., 2016a) and include sample differences, image acquisition or processing differences, including different scanners, sequences and analysis tools, effects of variables such as head motion, and differences in statistical analyses and curve fitting. Generally, based on methodological advances and increased concern for data quality and focus on the importance of data quality assurance (e.g. (Alexander-Bloch et al., 2016; Ducharme et al., 2016; Gilmore et al., 2021; Rosen et al., 2018)), we believe that the results from studies from recent years that indicate peaks in cortical thickness during infancy or early childhood, followed by monotonic decreases in mid- and late childhood, adolescence and beyond are most likely to be true. As emphasized by Walhovd et al. (2016a), however, MRI-derived measures of cortical development are merely our best current approximations and do not directly reflect brain anatomy.

The apparent cortical thinning in childhood and adolescence also shows some spatiotemporal variation. For example, Zhou et al. (2015) scanned 90 individuals aged 5–32 years at two time-points and found slight acceleration in thinning during adolescence as compared with both childhood and young adulthood. In a study with four longitudinal samples with in total 854 scans from 388 participants 7–29 years old, Tamnes and colleagues (2017) found that the parietal lobe showed the largest annual decrease in cortical thickness, while the occipital lobe consistently showed the smallest decrease. Overall, studies of cortical thickness suggest a maturational posterior-to-anterior and/or sensory-to-association cortices temporal gradient (Walhovd et al., 2016a).

Regarding sex differences, a cross-sectional study of 805 two week old neonates did not find sex effects on average cortical thickness (Jha et al., 2019). Similarly, a cross-sectional study by Gennatas et al. (2017) found no differences between girls and boys in total cortical thickness in 1189 individuals aged 8–23 years. In a recent large scale cross-sectional lifespan study with 17,075 individuals, the estimated age-related slopes of cortical thickness were not different within the subsample of young females and males aged 3–29 years (Frangou et al., 2020). Many longitudinal studies similarly report no or only limited sex differences in the developmental trajectories for cortical thickness (Mills et al., 2014; Raznahan et al., 2011b; Vijayakumar et al., 2016). There are some exceptions however (Ducharme et al., 2016; Mutlu et al., 2013; Paus et al., 2017; Wong et al., 2018), but the region specific patterns of thickness change are not consistent across studies.

To conclude, beyond the first two years of life, current large-scale and longitudinal studies suggest monotonic apparent cortical thinning in youth development, with some spatiotemporal variation in rate. Girls and boys generally show similar overall cortical thickness and thinning, but likely with some differences in the pace of thinning during specific developmental periods.

3.2.1. Neurobiological processes underlying thickness development

From infancy to young adulthood, the MRI-observed changes in cortical thickness are thought to reflect different processes depending on developmental stage and likely to some extent cortical region. The radial unit hypothesis posits that cortical thickness is determined by the number of cell divisions within proliferative units in the ventricular zone (Rakic, 1988). Neurogenesis and neuronal migration are, however, largely concluded by the end of the first postnatal week (Hill et al., 2010; Rakic, 2009). The increases in cortical thickness during the first years of life (Li et al., 2015; Lyall et al., 2015) are thus likely the result of rapid increases in dendritic complexity, myelination, synaptogenesis, glial proliferation and axonal elongation (Huttenlocher and Dabholkar, 1997; Koenderink et al., 1994; Koenderink and Uylings, 1995; Mrzljak et al., 1991; Petanjek et al., 2011; Rakic et al., 1994). During the early

postnatal period, cortical thickness may also be impacted by the anatomical changes related to the dissolution of the subplate (Kostović, 2020; Marx et al., 2015; Sedmak and Judaš, 2021).

The two main candidate processes that underlie MRI-observed cortical thinning during childhood and adolescence focus on reorganization of dendritic arbour or pericortical myelination, while mechanical forces that alter cortical morphology have also been considered (Natu et al., 2019; Patel et al., 2019; Paus et al., 2008). Post-mortem histological studies have demonstrated increases in synaptic density in infancy, followed by a gradual decrease in synaptic and neural density through adolescence (Huttenlocher, 1979). Similarly, Petanjek et al. (2008) demonstrated, in their investigations of basal dendrites of pyramidal neurons, length related-, synapse number-, and dendritic spine overgrowth in childhood and early adolescence, followed by decreases in later adolescence. Additionally, emerging evidence suggest that microglia, the brain's resident immune cells, plays a role in monitoring synaptic function and in synaptic maturation and elimination (Paolicelli et al., 2011). However, developmental reductions in cortical thickness observed in MRI studies cannot be explained by small-scale changes at the synapse level (Bourgeois and Rakic, 1993; Paus et al., 2008). Instead, remodeling of dendritic arbour may be accompanied by reductions in the number of cortical glial cells, which may together explain some of the observed cortical thinning.

Myelination, the process of wrapping axons in a lipid rich sheath, is the second proposed mechanism that may explain the observed cortical thinning in MRI studies (Sowell et al., 2004). Myelin membranes contribute to the speed, reliability and frequency of information transfer and also provides structural support (Miller et al., 2012; Wake et al., 2011). Intracortical myelin content increases from early childhood in a general posterior to anterior fashion (Yakovlev and Lecours, 1967), but with additional regional specificity, as certain higher order regions continue to mature well into adulthood (Ritchie et al., 2018a; Williamson and Lyons, 2018). T1w voxel intensities increase in part as a function of increasing myelin content. Therefore, deep myelinated cortical layers could be misclassified by imaging software as white matter, thereby shifting the grey/white boundary outward (Norbom et al., 2020b). This would appear as cortical thinning, without necessarily implying actual loss of tissue (Natu et al., 2019; Sowell et al., 2004). Several studies support the notion of increased intracortical myelination explaining at least a portion of MRI-based cortical thinning (Natu et al., 2019; Whitaker et al., 2016), while other studies suggest that relations are likely more complex (Croteau-Chonka et al., 2016). Finally, mechanical changes that occur during development could also contribute to a thinner adult cortex (Hogstrom et al., 2013), although this view is challenged by findings of surface area remaining relatively stable from a young age, while cortical thinning continues across the lifespan (Amlien et al., 2016; Fjell et al., 2015). Importantly, proposed mechanisms of MRI-based developmental cortical thinning are not mutually exclusive, and could all contribute to a different extent, depending on developmental stage.

3.3. Surface area

According to the radial unit hypothesis, cortical surface area is principally determined by the number of contributing proliferative units (Rakic, 1988). In MRI studies, surface area is modelled based on the white surface, the pial surface or at times an average of the two called the "midthickness" (Fischl et al., 1999a, 1999b). Although methodological variations exist (Winkler et al., 2018), surface area is commonly estimated by assessing how much local distortion is needed to fit an individual brain to a standard template or atlas, resulting in a point-by-point expansion and contraction map (Fischl et al., 1999a; Hogstrom et al., 2013).

One of the few longitudinal studies of infants and toddlers (Li et al., 2013) demonstrated that during the first and second year postnatally, cortical surface area increases on average 80 % and 20 %, respectively.

During the first year, regions heavily involved in sensory processing expand the most, while regions involved in higher order functioning greatly expand during the second year. Studies covering childhood, adolescence and young adulthood suggest that surface area in most regions continues to expand somewhat, reaching peaks in late childhood or early adolescence, followed by stability or subtle decreases in late adolescence and adulthood (Amlien et al., 2016; Ducharme et al., 2015; Tamnes et al., 2017; Walhovd et al., 2016b; Wierenga et al., 2014). In terms of spatiotemporal patterns, surface area demonstrates a sensory-to-association gradient of maturation (Amlien et al., 2016; Cafiero et al., 2019; Li et al., 2013).

Studies consistently document larger total surface area in males as compared with females (Amlien et al., 2016; Vijayakumar et al., 2016; Walhovd et al., 2016b; Wierenga et al., 2014). Already shortly after birth, boys have 3.9 % larger surfaces (Jha et al., 2019), and they also show greater expansion of the cortical surface during the first two years of life (Li et al., 2013; Lyall et al., 2015). There is less consensus as to whether males and females have different developmental trajectories after year 2. A study by Raznahan and colleagues (2011) concluded that females reach maximal surface area earlier than males, while Mills et al. (2014) found this pattern only for certain regions. In contrast, Vijayakumar et al. (2016) found less increases in surface area in females in a few small regions. Several other studies have not observed any sex differences in surface area development (Amlien et al., 2016; Walhovd et al., 2016b; Wierenga et al., 2014).

To conclude, cortical surface area increases rapidly in infancy and continues expansion until late childhood or early adolescence, and while males on average have larger surface area than females, sex differences in development beyond early childhood is not supported.

3.3.1. Neurobiological processes underlying surface area development

The surface area of the human cortex is determined by the number of ontogenetic units (Rakic, 1988). Additionally, amplification of several types of radial glia cells likely plays a critical role (Borrell and Götz, 2014). As neurogenesis and neural migration is largely completed shortly after birth, MRI-observed postnatal surface area expansion is probably dominantly driven by local cellular events, including intracortical myelination, gliogenesis, synaptogenesis and dendritic arborization (Hill et al., 2010). Additionally, the width of cortical columns in newborns is about one third of that in adults (Buxhoeveden and Casanova, 2002), and infant areal expansion may thus be explained by increases in columnar width (Lyall et al., 2015).

The cellular processes underlying the more subtle surface area changes observed later in development are less well understood. Seldon (2005) suggested a model where increasing levels of pericortical myelin and axon caliber exert pressure on the cortical surface, causing it to stretch outward, like inflating a balloon. This in turn results in larger cortical surface area, and by extension less cortical folding and thickness. A study by Cafiero and colleagues (2019) demonstrated significant relations between cortical surface area expansion and subcortical myelinated white matter as indexed by T1 relaxation times. The authors speculated that areal expansion is needed to accommodate increasing amounts of axonal myelin, in line with Seldon's model (Seldon, 2005). However, this theory does not concord with observations indicating continued myelination into adulthood (Grydeland et al., 2019) and subtle reductions in surface area past early adolescence (Amlien et al., 2016; Ducharme et al., 2015; Mills et al., 2014; Raznahan et al., 2011b; Walhovd et al., 2016b; Wierenga et al., 2014).

3.4. Gyrification

One of the most apparent characteristics of the human cerebral cortex is its folded structure, a feature that both phylogenetically and ontogenetically in part is related to increasing brain size (Toro et al., 2008), and that mainly develops during the third trimester of fetal life (Armstrong et al., 1995). The spatial positions of sulcal pits, the local

deepest points of primary sulci that are believed to be the first folds that appear during early brain development, have been found to be temporally invariant across the second half of gestation and to be similar in the fetal brain in this period and in the adult brain (Yun et al., 2020).

Compared with the morphological features discussed above, developmental changes in the degree of folding across childhood and adolescence have been relatively less explored. Folding, or gyrification, can be quantified at different levels. An early approach was to calculate the ratio between the total cortical surface area relative to the “exposed” surface, also called the hull area (Elias and Schwartz, 1969; Zilles et al., 1988). This was first done globally for the whole cortex, but can also be done for lobes or regions. Building on this approach, Schaer et al. (2012, 2008) developed a method to calculate the local gyrification index, measuring the degree of folding at each specific point of the cortical surface, with higher values reflecting more folding. Other tools are also available for further quantification of aspects of sulcal morphology, including sulcal width, depth and length (Aleman-Gomez et al., 2013; Madan, 2019).

A longitudinal study of 73 infants and toddlers, followed over three time-points in the first two years of life, found that the degree of folding in the cerebral cortex, measured with the gyrification index, increased 16.1 % in the first year and 6.6 % in the second year (Li et al., 2014). The greatest increases were seen in lateral fronto-parietal-temporal cortices, precuneus, and posterior cingulate cortex. Studies capturing these early increases in folding and later developmental changes in the same individuals are lacking, but it is likely that the early increases are followed by decreases in gyrification from around age 4 years (Chen et al., 2012).

From middle childhood, during adolescence, and into young adulthood, longitudinal decreases in the gyrification index have been found at both the global and lobar level. At a global level, this was shown by Raznahan et al. (2011) using the large longitudinal Child Psychiatry Branch NIMH study with >1250 longitudinally acquired scans from 647 individuals aged 3–30 years. At the lobe level, a longitudinal study of 52 adolescents scanned twice found that the largest decrease in gyrification was in the frontal lobe (Aleman-Gomez et al., 2013). While significant sulcal widening was found in all lobes, this co-occurred with decreases in sulcal depth in the frontal and occipital lobes only. Partly inconsistent with this spatial pattern, Mutlu et al. (2013) analyzed 209 scans from 137 individuals between the age of 6–30 years and observed linear decreases in local gyrification index across the majority of the cortical surface, but no change in medial and inferior prefrontal, occipital and some lateral temporal cortices. Cross-sectional studies indirectly support the conclusion that cortical folding decreases across adolescence and with a somewhat slower pace in adult age, but also here, different spatial patterns are reported (Cao et al., 2017; Chung et al., 2017; Klein et al., 2014).

Effects of both sex and sex chromosome dosage on gyrification have been shown. The effects are largely consistent with normative scaling laws, with larger brains having disproportionately higher gyrification index due to a relative expansion of total versus hull area (Fish et al., 2016). There are also findings linking age-related decreases in local gyrification to cognitive development (Chung et al., 2017), but longitudinal studies on this are lacking.

To conclude, the degree of folding of the cerebral cortex increases in early childhood, but then decreases from onwards into young adulthood, and while main effects of sex have been found, these appear to be largely explained by normative scaling.

3.4.1. Neurobiological processes underlying gyrification development

The neurobiological and biomechanical processes underlying changes in MRI-based gyrification and sulcal morphology during childhood and adolescence are still unclear. Several theories on the folding of the cerebral cortex have been proposed, including explanations based on mechanical tension generated in axons that pull strongly interconnected regions together (Van Essen, 1997), or differential intracortical growth, where certain segments undergo more growth and

resulting in local bulges becoming gyri (Caviness, 1975), with some experimental animal studies and mathematical models being consistent with the latter (Bayly et al., 2013; Xu et al., 2010). There remains considerable controversy, however, over the phylogenetic and ontogenetic mechanisms that drive cortical folding (Lewitus et al., 2016; Mota and Herculano-Houzel, 2015; Zilles et al., 2013). Moreover, as highlighted by Cao et al. (2017), most of these theories focus on early brain development, while studies exploring the neurobiological processes explaining gyrification decreases later in childhood and during adolescence are scarce. The suggested possibilities overlap with explanations for developmental changes in surface area, either building on the balloon hypothesis discussed above (Seldon, 2007, 2005) or that dendritic arborization causes release of axonal tension which in turn results in decreasing gyrification (White et al., 2010). Both possibilities currently remain speculations.

3.5. The developmental relationships between brain morphology measures

Developmental changes in brain morphology in local regions do not happen in isolation, but rather in coordinated ways within structural networks (Alexander-Bloch et al., 2013; Khundrakpam et al., 2019). Such maturational coupling has been found to be stronger within association areas compared with primary sensory areas (Lerch et al., 2006; Raznahan et al., 2011a), to partly recapitulate known functional networks (Walhovd et al., 2015), and to be associated with cognition (Khundrakpam et al., 2017).

Beyond unimodal morphological assessments, a few studies have also explored the relations between different MRI macrostructural measures from childhood to young adulthood. Understanding these relationships and how they *change* during development may inform theories about the underlying neurobiology. Cortical volume is conceptually the product of thickness and surface area (Panizzon et al., 2009), while cortical folding has been described as the product of surface area and the square root of cortical thickness (Mota and Herculano-Houzel, 2015). Still, the relations between these brain morphology measures are dynamic across development. Lyall and colleagues (2015) examined relations between cortical thickness and surface area to overall cortical volume in the first two years of life. While they found very weak or no relations between cortical thickness and volume, strong relations were found between surface area and cortical volume in this age group. Furthermore, surface area expansion and cortical thickness growth did not appear to be strongly related. Later in childhood and adolescence, using four independent samples, Tamnes et al. (2017) demonstrated strong positive relations between cortical thinning and cortical volume decreases at the global, lobar, as well as at the vertex-wise level. Positive associations were found also for surface area and volume decreases, however; these relations were weaker. The associations between surface area decreases and cortical thinning were more topologically complex, and less consistent across samples. In general, negative relations were more widespread and identified mainly in gyral and insular regions, while positive relations were less prevalent and primarily located in sulcal regions.

To conclude, relatively few studies have assessed relations between common measures of cortical macrostructure and geometry, but existing studies suggest that the strength and direction of these relations may change as a function of age.

4. Microstructural development of the cerebral cortex

Brain microstructure refers to the small tissue subcomponents that together make up the gross shapes, or morphology (macrostructure), of the brain. In the following, microstructural cortical development from young childhood to young adulthood will be primarily assessed through an in-depth review of MRI signal intensity studies. Additionally, cortical MWF and MT will be covered. These methods are more specialized and sensitive to rapid T2 signal decay, which conventional neuroimaging

cannot detect (Alonso-Ortiz et al., 2015). Sex differences and biological processes underlying the microstructural changes will also be discussed.

4.1. Signal intensities

As detected from MRI, a prominent feature of brain development from childhood to young adulthood is an increase in its brightness. This increase is presumably due to changes in underlying tissue properties (Glasser and Van Essen, 2011). Measures of signal intensity are quantifications of precisely such variations, within and across brain matter. Morphometric measures are certainly also affected, albeit secondarily, by changes in intensity, as strong shifts are used to model the grey/white boundary and to classify voxels as belonging to one tissue class (e.g., grey matter) or another (e.g., cerebrospinal fluid or white matter).

Cortical grey matter intensities are calculated by sampling values across the full-, different fixed-, or percentage depths of the cortical mantle (Glasser and Van Essen, 2011; Salat et al., 2009). White matter intensities are calculated by sampling values extending a shorter millimeter distance into subjacent white matter (Jørgensen et al., 2016; Salat et al., 2009). Grey and white matter intensities can be investigated separately, but this is often challenging in practice as there are inherent intensity differences between individuals, due to individual optimization procedures during scanning (Westlye et al., 2010). Intensities must therefore be normalized, and although there is no convention, common procedures include using intensity values from the ventricles, eyeballs, white matter regions of interest (ROIs), global intensity across the entire head/brain, or outside of the skull. Nevertheless, these approaches have caveats, as normalization values themselves can be associated with other variables, such as age (Norbom et al., 2019), clinical status or head size.

Another approach is to compute a joint T1w grey and white matter intensity measure (Jørgensen et al., 2016; Salat et al., 2009). Grey and white matter can be combined using several slightly different formulas, and in the following they will all be covered by the term “T1w tissue contrasts”. It is also possible to compute a purely cortical measure using both the T1w and T2w modality, resulting in a T1w/T2w ratio (Glasser and Van Essen, 2011). Usually, a higher T1w tissue contrast indicates greater discrepancies between grey and white matter and vice versa. T1w/T2w ratio values above 0 indicate that T2w intensities are higher than that of T1w intensities. Consequently, there is an inverse relationship between T1w tissue contrasts and the T1w/T2w ratio.

A few early studies of T1 relaxation and T1w intensities within the adult lifespan, reported a progressive decrease in white- to grey matter contrast with increasing age, in specific white-, cortical- and subcortical grey matter regions (Magnaldi et al., 1993; Raz et al., 1990). Keeping several study-caveats in mind, this was the first documentation of intensity sequences being sensitive to fundamental age-related changes in brain tissue. Salat and colleagues (2009) extended this work, also in an adult sample, by performing vertex-wise analyses across the cortex and closely subjacent white matter, and found that age-related alterations in “grey/white ratio” occur in large portions of the cortical mantle.

4.2. T1w tissue contrasts and T1w/T2w ratio

There is presently only a single T1w tissue contrast study and no T1w/T2w ratio studies in youths employing longitudinal designs. Current knowledge about developmental changes in these measures has therefore mainly been indirectly inferred from cross sectional studies, of which highly powered ones are limited. One such T1w grey/white contrast (GWC) study of 1467 participants aged 8–23 years, reported a marked linear age-related decline in global GWC from late childhood to young adulthood (Norbom et al., 2019) (see also (Schwartz et al., 2014)). Occipital, pre- and postcentral cortical regions, parsed through independent component analysis, showed additional negative age effects, while the remaining regions showed either slight or marked linear positive associations with age, results that must be interpreted in

addition to the dominant global negative effect (Norbom et al., 2019). Individual differences in regional GWC were also associated with general cognitive ability in a bi-directional cortical pattern. Another GWC study had a partly overlapping sample, but also included younger children, including in a total of 2596 youths aged 3–23 years (Norbom et al., 2020b). This study corroborated age-related results of global GWC showing a steady linear decline with some regional variation, now from early childhood and until young adulthood. Consistent with the findings from Norbom et al. (2019), a separate study that was successfully able to predict age in youths using white/grey contrast, reported that residuals from their age-prediction were highly related to general cognitive ability (Lewis et al., 2018), further suggesting that T1w tissue contrasts are sensitive to aspects of neurocognitive development. However, it is not clear how the developmental patterns reported in these studies relate to grey and white matter intensities separately. A recent study assessed, for the first time longitudinally, GWC in 394 typically developing youths aged 4–22 years, with 1–3 repeated scans per participant resulting in a total of 819 scans (Drakulich et al., 2021). A best-fit vertex-wise model was employed across the cortex, and it was found that GWC nearly globally decreased with increasing age in a cubic (63 %), quadratic (20 %) or linear (16 %) fashion. Moreover, across development, males showed a limited and region-specific pattern of slightly higher GWC as compared with females.

A lifespan study of the purely cortical measure T1w/T2w ratio, which included a subsample of 85 youths aged 8–19 years, found a positive linear association between T1w/T2w ratio and age within this age-range (Grydeland et al., 2013). The effect was seen across large portions of the cortex, but was strongest in posterior frontal, parietal, and temporal cortices. Moreover, in the youth group, greater cognitive performance stability was associated with lower T1w/T2w ratio in occipital and parietal regions. Another overlapping lifespan study, which included a subsample of about 200 youths aged 8–23 years, reported that T1w/T2w ratio showed early prepubertal growth waves in primary sensory and motor cortices, and later post-pubertal growth waves in association, insular, and limbic cortices (Grydeland et al., 2019). A study of 1555 young adults aged 18–35 years, reported that higher age also in young adulthood was linearly associated with higher T1w/T2w ratio in widespread cortical regions (Shafee et al., 2015). A more recent study of T1w/T2w ratio, including young children, with a sample size of 621 youths aged 3–21 years, reported a near global age-related increase in T1w/T2w ratio across the cortical surface (Norbom et al., 2020a) (see Fig. 2). There was regional variation, and a general increasing gradient in the strength of the age association from inferior-posterior- to superior-anterior regions. Also, a negative association between T1w/T2w ratio and general and several specific cognitive abilities was found, mainly within anterior cortical regions.

Studies testing for possible sex differences in T1w tissue contrasts and T1w/T2w ratio in youth development generally report limited main effects (e.g. differences between girls and boys) and interaction effects (e.g. differential associations with age between girls and boys). Norbom et al. (2020b) found limited positive associations between sex and vertex-wise GWC, with boys having higher GWC than girls in occipital and insular subregions. In regards to T1w/T2w ratio, Norbom et al. (2020a) found no significant main effects of sex, but a small positive age by sex interaction, indicating that boys in late adolescence had relatively higher T1w/T2w ratio than girls in the frontal lobe and parts of the parietal lobe.

To summarize, cortical T1w tissue contrasts and T1w/T2w ratio appear to globally and steadily decrease and increase, respectively, from 3 years of age and until young adulthood. These cross-sectional findings indirectly indicate that as the brain matures, grey and white matter intensities become more similar, and the cortex appears brighter in T1w MRI derived images. Generally, early sensorimotor regions show the most rapid development in childhood, while association and limbic regions, as well as the temporal pole, show a more protracted development. The only longitudinal study of GWC generally concurs with-, yet

Fig. 2. T1w/T2w ratio, region and age-related differences. The figures on the left depict a mean T1w/T2w ratio map ($n = 621$, age = 3–21). As seen by the color bar, warm colors represent regions with higher T1w/T2w ratio, while cold colors represent regions with lower T1w/T2w ratio. The figures on the right depict a t-statistics map of the vertex-wise associations between T1w/T2w ratio and age. The t-statistics map is masked by familywise error corrected p-values, and as seen by the t-value color bar, warm colors represent a positive age association. The figure is adapted from [Norbom et al. \(2020a\)](#).

also modifies our understanding of GWC development, reporting that more than half of the brain shows a cubic developmental pattern. Sex related differences in intensity measures are generally sparse and somewhat conflicting, with reports of higher posterior GWC for boys as compared to girls, and higher frontal T1w/T2w ratio in late adolescent boys. Moreover, the few available studies that have examined associations between intensity measures and cognition indicate that these metrics are relevant for individual differences in both general and specific cognitive abilities in youth. GWC shows a bi-directional relationship with general cognitive functioning, while regionally lower T1w/T2w ratio, especially in frontal regions, has been associated with higher general- and specific cognitive abilities. The direction of these associations could indicate separate neurobiological underpinnings for cognitive and age-related findings, or be explained by an underestimation of the true cortical thickness (see ([Norbom et al., 2020a](#)) for in detailed discussion).

4.2.1. Neurobiological processes underlying T1w tissue contrasts and T1w/T2w ratio development

T1w tissue contrasts and T1w/T2w ratio have both been presumed to indirectly reflect differences in intracortical (and subjacent white matter) myelin content ([Glasser and Van Essen, 2011](#); [Salat et al., 2009](#)). Of note, while neuronal axons have diameters in the μm range, cortical microstructure is inferred from large tissue volumes, typically at about 1 mm voxel resolution ([Lazari and Lipp, 2021](#)). Such inferences are possible as macromolecules in the myelin sheath, including cholesterol, have a major influence on T1 longitudinal- and T2 and T2* transverse relaxation times ([Does, 2018](#); [Koenig, 1991](#); [Koenig et al., 1990](#)). Other signal influences include iron ([Miot-Noirault et al., 1997](#); [Stüber et al., 2014](#)) and water concentration ([Miot-Noirault et al., 1997](#)). Human histological studies have reported that T1 intensity profiles are highly similar to myeloarchitecture ([Eickhoff et al., 2005](#)) and that grey matter intensities in the motor-/somatosensory cortical regions are much more impacted by myelin as compared with iron ([Stüber et al., 2014](#)). Moreover, it has been reported that T1w/T2w values significantly differ between myelinated and demyelinated cortex ([Nakamura et al., 2017](#)), and that T1w/T2w ratio changes are driven by increased levels of myelin within deeper cortical layers ([Shafee et al., 2015](#)).

On the other hand, while there has been no assessments of T1w tissue contrasts, recent attempts have not revealed consistent links between T1w/T2w ratio and either myelin-related genes or other suggested MRI-based myelin proxies. For instance, studies have reported low and moderate correlations between T1w/T2w ratio and MT in white ($r = 0.38$) and grey matter ($r = 0.54$), respectively ([Hagiwara et al., 2018](#)),

and that T1w/T2w ratio only shows 11 % shared variance with MWF in all tested grey and white matter regions ([Uddin et al., 2019](#)). Similarly, while a study reported low to moderate correlations between T1w/T2w ratio and MWF in white matter ROIs, stronger relations were observed for T1w/T2w ratio and the intermediate T2 relaxation time constant, presumed to reflect instead intra and extracellular water mobility ([Arshad et al., 2017](#)). Of note, while a study of early white matter development found only weak relations between T1 relaxation time and MWF ([Deoni et al., 2012](#)), the same research group reported a strong relationship within the cerebral cortex, stating that while T1 is generally non-specific in nature, it may be an acceptable surrogate marker of cortical myelin content during early childhood ([Deoni et al., 2015](#)). A combined post-mortem and neuroimaging study reported that other molecular properties such as certain non-myelinating oligodendrocytes, molecular size, axon caliber, and even pH were more strongly associated with T1w/T2w ratio than myelin associated genes, and unexpectedly that the measure was not a proxy for iron content ([Ritchie et al., 2018a](#)). Similarly, another study found strong correlations between T1w/T2w ratio and dendrite density rather than myelin content ([Righart et al., 2017](#)).

Together, these findings demonstrate that intensity measures are by no means straightforward myelin proxies, and that histological validation studies are needed. Ideally by joint human post-mortem and MRI studies, where the tissue is processed both histologically as well as with neuroimaging, and where variance assessments control for confounders such as axon density and iron content ([Lazari and Lipp, 2021](#)). Other complicating factors, such as whether intensity measures capture the same underlying properties across the life-span and within and across brain matter, also need clarification. Moreover, novel neuroimaging methods are continuously developed in an attempt to increase micro-biological specificity.

4.3. Myelin water fraction and magnetization transfer

One of the more established proposed neuroimaging markers for myelin content is MWF ([Laule et al., 2008](#); [Mackay et al., 1994](#)). It is predominantly a white matter measure, with few studies assessing cortical MWF, let alone within typical development (but see ([Patel et al., 2019](#))). MWF is based on the notion that water trapped between lipid layers of the myelin sheath have shorter T2 relaxation time, while intra- and extra axonal water have much longer relaxation. MWF, based on the T2 sequence is the ratio of myelin water (the short T2 signal) relative to the total water content (the total T2 signal) ([Alonso-Ortiz et al., 2015](#)).

A cross-sectional cortical MWF study of 215 children aged 1–6 years

reported that already at one year of age, high MWF was found in somatosensory, motor, visual, auditory and superior temporal cortices (Deoni et al., 2015). In contrast, the temporal pole, prefrontal and association cortex showed relatively low MWF, but also a more protracted development, broadly mirroring established histological timelines of intracortical myelin. The study found no hemispheric or sex related differences (Deoni et al., 2015).

MT is another established proposed neuroimaging myelin marker, which also has been predominantly assessed in white matter. The measure, based on the T2 sequence, is based on hydrogen protons being present in three different forms within the brain, namely as “free water”, in “macromolecules” and between the two as “bound water” in hydration layers (Sled, 2018). While free water is unstructured with rapidly rotating molecules, protons in macromolecules and (to a lesser extent) bound water have highly restricted motion (Pike, 1996; Stanisz et al., 1999). To assess MT a targeted radio frequency (RF) pulse saturates the protons in macromolecules, which then partially transfer their magnetization onto protons in the other two sites. Another RF pulse now targeting free water protons is employed, resulting in a reduced signal due to the previous transfer of magnetization (Boer, 1995; Sled, 2018). The signal difference between these RF pulses is referred to as the magnetization transfer ratio (MTR). The cortical MT signal has also been associated with dendritic arbour (Patel et al., 2019).

A recent cross-sectional study of cortical MT in 297 youths aged 14–24 years found that association areas had lower MT as compared with primary cortical areas at age 14, but that association areas had faster rates of MT increases throughout adolescence (Whitaker et al., 2016). Moreover, at age 14 MT was highest in deeper cortical layers, possibly reflecting a greater density of myelinated fibers. Another study of 150 adolescents confirmed the age-related increase in average MT using longitudinal data (Patel et al., 2019). These findings were recently corroborated by an accelerated longitudinal study using an overlapping sample as employed by Whitaker et al. (2016) of 234 youths aged 14–27 years, which reported an overall developmental increase in mean MT, as well as independent increases in mid to deep cortical layers (Paquola et al., 2019). Both effects were particularly strong in uni- and heteromodal association cortices. Another accelerated longitudinal study, again with an overlapping sample of 288 youths, reported that early life economic disadvantage was associated with lower rates of MT in multiple cortical regions, including in mid- and posterior cingulate, precuneus, insular and prefrontal cortices (Ziegler et al., 2020). At present, few studies have explored MWF and MT in the cerebral cortex, yet both measures potentially give valuable information for assessing cortical microstructural properties, and may increase the neurobiological specificity of MRI studies of brain development. In one study that assessed both measures simultaneously, no relationship between the two measures was observed when correlated across the cerebral cortex, thus pointing to different neurobiological sources of MTR and MWF in cortical gray-matter (Patel et al., 2020).

5. Integrating macro- and microstructural development of the cerebral cortex

A few studies have attempted, through vertex-wise correlational and multimodal fusion methods, to explore the relationship between brain morphology and microstructure in children and adolescents. Indirectly these studies aim to improve the neurobiological specificity of age-related findings, as for instance illustrated by a cross-sectional lifespan study which was able to differentiate MRI-based cortical thinning in youth development from thinning in senescence through its inverse relationship with cortical grey matter intensities (Westlye et al., 2010).

A large cross-sectional study focusing on young adulthood found that the T1w/T2w ratio was negatively correlated with global cortical thickness ($r = -0.32$), but that the regional associations varied in direction (Shafee et al., 2015). Another recent study employing multimodal fusion to investigate the relationships between cortical thickness,

surface area and GWC in children and adolescents found several components that captured largely corresponding regions across modalities (Norbom et al., 2020b). In these instances, in accordance with the findings of Shafee and colleagues (2015), GWC and thickness generally showed directional weighting correspondence (i.e. higher thickness and GWC), which was opposite to that of surface area (i.e. smaller surface area). There was, however, an important exception to this finding, as one of the components reflecting global cortical thickness and GWC with opposite weighting showed a negative age association, indicating that the cortex becomes thinner and darker with increasing age. This could be additional evidence for the notion that as the intensity in deep cortical layers rises, these voxels are misclassified by imaging software as white matter, resulting in an outward shifting of the grey/white border and consequently an underestimation of the true cortical thickness and brightness (Norbom et al., 2020b). All findings considered, the cortex appears to become thinner and brighter from childhood to young adulthood, findings that in actuality might be over- and underestimated respectively.

Apart from intensity metrics, a cross-sectional study of adolescents and young adults found a strong negative association between cortical thickness and MT (Whitaker et al., 2016). This study also found that age-related thickness differences were significantly, but not entirely mediated by differences in MT, indicating that myelination is not the sole reason for developmental cortical thinning. Another study assessed multiple macro- and microstructural neuroimaging measures, including mean diffusivity, quantitative T1, and cortical thickness, within a region of the visual cortex in 27 children aged 5–9 years and 30 adults aged 22–28 years (Natu et al., 2019). Age-group differences were reported for quantitative T1 and MD in mid and deep cortical layers, both with a negative association. Further, these differences were related to cortical thickness, or more specifically to an increasing underestimation of cortical thickness. The study concluded, based on the multimodal pattern of results, albeit from a single cortical region, that the cortex does not thin during childhood but instead becomes more myelinated (Natu et al., 2019). Thus, recent multimodal studies consistently report that apparent cortical thinning in youth development is overestimated. If this is in part, or fully, due to pericortical myelination and the possible regional variation in these relationships, needs clarification.

6. Leveraging transcriptomics to probe the cellular neurobiology of cerebral cortical development

Recently, neuroimaging studies have begun to leverage cortical gene expression to understand the neurobiology underlying cortical structure in the developing brain. These studies build on previous work such as *ex vivo* histological studies of cortical neurobiology. To do so, inter-regional variations in MRI phenotypes are compared with inter-regional variations in gene expression. By establishing which genes have expression patterns similar to the profile of the imaging phenotype of interest, one can infer biological processes and cellular involvement underlying regional variations in brain structure and structural change. This burgeoning area of research has been facilitated by recent efforts to characterize the brain's transcriptome, that is, the total set of RNA transcripts expressed in the brain. In particular, the Allen Human Brain Atlas (<https://portal.brain-map.org/>) has contributed the most extensive spatial sampling across regions of the adult brain (Hawrylycz et al., 2015, 2012). With post-mortem MRI scans of six donor brains, and tissue samples additionally having been mapped to MNI coordinate space, this resource substantially aids in the comparison of gene expression with cortical brain phenotypes. Notably, the BrainSpan atlas (<https://www.brainspan.org/>) provides the most extensive spatial sampling of the developing human brain, from fetal development into adulthood (Kang et al., 2011; Li et al., 2018). These transcriptional resources have been used to study molecular features relevant to brain development, such as the relationship between sex and stress hormone receptor gene expression in association with cortical thinning during adolescence (French

and Paus, 2015; Parker et al., 2017, 2020b; Shin et al., 2018; Wong et al., 2018) or biological processes that are enriched among genes associated with cortical profiles of MT and areal expansion of the cortex (Reardon et al., 2018; Whitaker et al., 2016). It is important to note that, for these studies, the sources of gene expression (e.g., Allen Human Brain Atlas) differs from the source of brain phenotypes (i.e., study specific imaging).

This section will focus on reviewing studies that investigate the cellular neurobiology of cortical development using gene expression. Single-cell transcriptomic analyses of rodent and human brain tissue has provided several sets of genes specific to neural cell types (Darmanis et al., 2015; Lake et al., 2018; Zeisel et al., 2015; Zhang et al., 2014). Therefore, scientists can test which neural cell types contribute to the spatial variation in brain phenotypes by leveraging spatial gradients in cell-specific gene expression. This is accomplished using various methods that quantify the potential extent of cellular involvement such as over-representation analysis, gene set enrichment analysis, or virtual histology (Boyle et al., 2004; Maere et al., 2005; Shin et al., 2018; Subramanian et al., 2005).

6.1. Brain transcriptomics and the cellular neurobiology of cortical macrostructure

Cortical thickness and age-related thinning are the neuroimaging phenotype that have most often been associated with the transcriptional signatures of neural cells. From 4.5 years to 21 years of age, inter-regional patterns of cortical thickness have consistently been associated with the gradients in neuronal- and astrocyte-specific gene expression across three independent studies (Patel et al., 2020; Pecheva et al., 2020; Shin et al., 2018). The pattern of associations (i.e., greater expression, greater thickness) may suggest that regions with thicker cortex have greater neuronal and astrocyte cell densities. This is supported by histological evidence that more complex neuronal architecture and a larger population of glial cells are associated with thicker cortex (Carlo and Stevens, 2013; Goriounova et al., 2018). Additionally, spatial variations in cortical thickness have also been associated with transcriptional gradients in oligodendrocyte and microglial genes in infants and adolescents, respectively (Pecheva et al., 2020; Shin et al., 2018). Histological studies report that cortical myelin increases from birth through early adulthood, suggesting that oligodendrocytes play a role in shaping cortical morphology (Miller et al., 2012). Additionally, synapse formation early in life is followed by a period of elimination in childhood through early adulthood (Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997; Petanjek et al., 2011). Microglia play a major role at the synapse both in modulation of synaptic transmission and in synapse elimination (Kettenmann et al., 2013). Although cortical tissue is composed of neurons, glia, and vasculature, novel transcriptional evidence indicates that astrocytes and neuronal cells may contribute the most prominently to the spatial variations in cortical thickness in the developing brain.

Several studies have used gene expression to assess age-related changes in cortical thickness. Three independent investigations reported that, during childhood and adolescence, regional variations in cortical thinning were associated with the pattern of gene expression specific to neurons (Ball et al., 2020; Shin et al., 2018; Vidal-Pineiro et al., 2020). In particular, regions with lower pyramidal cell expression had greater cortical thinning (Shin et al., 2018; Vidal-Pineiro et al., 2020) (see Fig. 3). Therefore, this is in concurrence with hypotheses that suggest reductions in dendritic branching may underlie cortical thinning, as derived from post-mortem histology (Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997; Petanjek et al., 2011). With respect to glial cells, cortical regions with lower expression of astrocyte and microglia genes have greater cortical thinning (Shin et al., 2018; Vidal-Pineiro et al., 2020). Since these cells play a supporting role at the synapse, loss of spines may translate into local reductions in the involvement of astrocytes and microglia (Ben Achour and Pascual, 2010; Kettenmann et al., 2013). Consistent with histological studies describing

increases in myelination during maturation (Miller et al., 2012), regions of the brain with greater myelin-related gene expression have been associated with greater cortical thinning (Parker et al., 2020a). Moreover, greater oligodendrocyte gene expression in cortical regions with greater age-related decreases in thickness has been reported in male adolescents, but not females (Shin et al., 2018). One could speculate that as the human cortex develops, there might be reduced necessity of astrocyte and microglial support in cortical regions with greater myelination. Ultimately, this cascade of cellular effects, coupled with an outward encroachment of the grey/white boundary, may result in MRI-based cortical thinning during childhood and adolescence.

6.2. Brain transcriptomics and the cellular neurobiology of cortical microstructure

A number of studies have investigated the neurobiology of cortical microstructure during development using transcriptomic signatures of neural cell-types. For instance, greater oligodendrocyte gene expression has been associated with shorter T2 relaxation times, longitudinal increases in MT, higher T1w/T2w ratio, and greater MWF (Patel et al., 2020, 2019). Gradients in expression of oligodendrocyte genes and myelin-basic protein have also been linked to cortical variations in measures of MT during development (Paquola et al., 2019; Whitaker et al., 2016). Histological studies have reported that myelin content is associated with several of these imaging derived phenotypes, such as MT and MWF (Laule et al., 2006; Reeves et al., 2016). Histological evidence, however, also suggests that myelin content may not be the only source of signal for these measures of cortical microstructure (Reeves et al., 2016; Righart et al., 2017). Transcriptomic signatures of cell-types other than oligodendrocytes have also been associated with the signal of these neuroimaging phenotypes. A study of 507 males aged 18–21 years discovered that regions of the cerebral cortex with less astrocyte-specific gene expression had greater MWF and T1w/T2w ratio. These regions also had shorter T1 and T2 relaxation times (Patel et al., 2020). This is an example of how anti-correlated profiles of cortical phenotypes (i.e., MWF and T1w/T2w vs T1 and T2 relaxation times) will be co-localized with similar, but opposite, transcriptional gradients and therefore, may implicate the same cell-types. A study of cortical MTR reported that inter-regional variations were associated with pyramidal and ependymal cell-specific gene expression (Patel et al., 2019). Altogether, this may suggest that variations in neuronal and glial cell densities, the complexity of their cellular protrusions, and their macro- and micro-molecular contents may contribute to MRI derived measures of cortical microstructure. Therefore, many of the neuroimaging phenotypes thought to be associated with myelin content may in fact reflect a variety of other neural cells in addition to myelin producing oligodendrocytes.

Overall, studies leveraging transcriptomic signatures of neural cell-specific genes have provided insight into the neurobiology underlying spatial variations in cortical structure. Across development, these macro- and microstructural features share similarities in the cellular underpinnings contributing to their variation. Replication of these novel findings is warranted.

7. Discussion and conclusion

We have reviewed modern uni- and multimodal MRI research and reported on the current understanding of macro- and microstructural development of the human cerebral cortex from early childhood, through adolescence, and until young adulthood. Further, we have discussed the possible underlying neurobiological processes of changes in MRI metrics, bridging classic theories from *ex-vivo* histology to *in-vivo* findings from current transcriptomics research.

Concerning morphology, cortical volume increases in the first 2 years of life, before generally decreasing, while showing peaks in certain regions before late childhood. Similarly, beyond an initial increase in the first 2 years of life, the cerebral cortex shows a region specific pattern of

Fig. 3. Associations between cortical phenotypes and gene expression. Panel (a) illustrates the inter-regional variation in cortical thickness and the inter-regional variation in the stress-associated glucocorticoid receptor mRNA expression and a negative correlation of these two profiles ($r = -0.85$, $p = 1.46 \times 10^{-10}$). This section is adapted from Parker et al. (2020b, 2017) and Wong et al. (2018). Panel (b) depicts the basic components of the Virtual Histology technique. The inter-regional profile of cortical thinning is correlated with the inter-regional profile of an astrocyte-specific gene, *LXN*. The process is repeated for all astrocyte cell-specific genes. The density plot depicts the distribution of correlation coefficients with the mean represented by the vertical black line. The dark shaded area represents the 95 % confidence interval for the empirically derived null distribution of mean correlation coefficients. Panel (c) illustrates how the association of a single cortical phenotype and a single-cell specific gene panel is extended to multiple cortical thinning profiles and nine cell-specific gene panels. For the graph on the right, the x-axis represents the age at which the cortical thinning profile was derived. The y-axis represents the mean correlation between cortical thinning and panel gene expression (i.e., the vertical black line on the density plot). Y-axis values above 0 indicate that regions with greater gene expression have greater cortical thinning (or less thickening). Y-axis values below 0 indicate that regions with greater gene expression have reduced cortical thinning (or even thickening). Smaller circles indicate a $p < 0.05$ and larger circles indicate $p < 0.0001$. Sections b and c are adapted from Vidal-Pineiro et al. (2020).

monotonic cortical thinning across development, with possibly a slight acceleration in adolescence. Surface area massively increases the first- and to a lesser extent the second year of life, and in most regions probably continues to expand, reaching peaks in late childhood, followed by subtle decreases across adolescence. Cortical folding initially increases with a regional pattern, before likely decreasing after age 4 years. The complex multimodal relationship between these macrostructural measures appears to change in both strength and even direction as a function of age.

Microstructural changes include global steady decreases in cortical T1w tissue contrasts and increases in T1w/T2w ratio from 3 years of age and until young adulthood, indicating that the cortex becomes brighter, resulting in a blurring of the grey and white matter boundary. Early sensorimotor regions show rapid development in childhood, while higher-order association and limbic regions show protracted development. Concordantly, MWF and MT generally show similar developmental patterns as intensity metrics. In youth development, the complex relationship between macro and microstructural measures point to the cortex becoming thinner, larger in area during childhood and brighter.

While an increasing number of longitudinal studies have charted cortical macrostructural development (Gao et al., 2019; Vijayakumar et al., 2018), there are few developmental- and presently only a single longitudinal study employing MRI signal intensity metrics to probe cortical microstructural development. Strong relations between intensity metrics and age have however been found across childhood, adolescence and young adulthood, possibly even stronger than those seen for morphometric measures (Norbom et al., 2020b). Individual differences in signal intensity metrics in children and adolescents also show associations with cognitive abilities and neurodevelopmental psychopathology, but further studies are needed to understand the spatiotemporal dynamics of these relationships (Grydeland et al., 2013; Lewis et al., 2018; Norbom et al., 2020a, 2019).

It is challenging to link developmental changes in cortical macro- and microstructure to specific underlying neurobiological processes, and theories are often based on post-mortem histological- and indirect multimodal and quantitative MRI assessments. Novel transcriptomic studies have recently supplemented such studies. Transcriptomic studies have reported relations between cortical thinning in childhood and adolescence to lower pyramidal cell expression (Shin et al., 2018; Vidal-Pineiro et al., 2020), concurring with post-mortem theories of reduction in dendritic spines (Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997; Petanjek et al., 2011). Also, transcriptomic studies have found associations between cortical thinning and lower expression of astrocyte and microglia genes (Shin et al., 2018; Vidal-Pineiro et al., 2020) of which there might be reduced necessity for in regions with greater myelination. Concordantly, greater myelin-related gene expression has been associated with greater cortical thinning from late childhood to adolescence (Parker et al., 2020a). Of note, these studies are based on group-level regional associations and not on individual differences. Still, transcriptomic studies more broadly implicate the involvement of the cortical cellular environment, and appear to offer a highly fruitful link between *ex-vivo* post-mortem and *in-vivo* neuroimaging studies.

It is not unlikely that there would be sex-related differences in cortical structure and development, as there are well-known differences in the age of onset and duration of the pubertal period, as well as separate hormonal influences (Herting and Sowell, 2017; Marshall and Tanner, 1970, 1969; Peper et al., 2011; Peper and Dahl, 2013). Moreover, there are sex-related age of onset and overall risk discrepancies for developing several mental disorders (Häfner et al., 1993; Kessler et al., 2005), and studies have also reported subtle sex-related differences in selected cognitive functions (Jones et al., 2003; Sommer, 2004). It is therefore noteworthy that there appears to be limited sex-differences in cortical macro- and microstructural development. An exception is surface area, where young males have larger area (Amlien et al., 2016; Vijayakumar et al., 2018; Walhovd et al., 2016b; Wierenga et al., 2014),

and show greater areal expansion during the first years of life as compared to young females (Li et al., 2013; Lyall et al., 2015). However, recent studies measuring the spread instead of the center, indicate sex differences in inter-individual brain variability, suggesting that future studies should go beyond group-level mean differences (Forde et al., 2020; Ritchie et al., 2018b; Wierenga et al., 2020, 2018). Moreover, creating continuous instead of binary sex scores have also successfully captured inter-individual variability in several brain- and other phenotypes (Vosberg et al., 2020). Also, to capture effects of pubertal and hormonal changes on brain structure and development, studies with relatively more intensive longitudinal designs might be needed (Herting and Sowell, 2017). Nevertheless, female and male brains do not belong to distinct categories (Joel et al., 2015) and brain architecture typical of males are also typical of females, with substantially overlapping distributions (Alon et al., 2020; Vosberg et al., 2020). Rather, individual brains appear to be comprised of unique “mosaics” of features, some more common in each sex (Joel et al., 2015).

Further longitudinal studies are needed to more directly and accurately delineate the developmental trajectories of intensity based cortical microstructure. Future studies should also further investigate the multimodal relationships between cortical macro- and microstructural metrics longitudinally. These are as cross-sectional studies suggest complex and may involve age-variant relationships. Future studies should also integrate imaging modalities and seek to increase our understanding of the spatiotemporal dynamics of the relationships between brain structural and microstructural development and brain functional development, which involves increasing within-network connectivity, decreasing between-network connectivity and changes in neural responses during task performance (Fan et al., 2021; Mills and Tamnes, 2020; Overbye et al., 2018; Sherman et al., 2014).

Possible sex differences in cortical microstructure could be estimated through brain variability, and non-binary sex continuum approaches which have been profitable for assessing differences in cortical morphology. Beyond quantitative T1 and T2 approaches, the biological specificity of microstructural measures using the *weighted* sequences need stringent testing through both post-mortem and transcriptomics approaches. Further, prenatal and postnatal brain development is often explored separately due to the expertise of the researchers. Future collaborative efforts across these fields should seek to better integrate the study of brain developmental changes in utero and in infancy, childhood and adolescence. Of note, patterns of brain structural development discussed in this paper are largely based on group-level estimates. There is a growing emphasis on individual differences in brain structural development (Becht and Mills, 2020; Foulkes and Blakemore, 2018; Mills et al., 2021), and the importance of this heterogeneity in brain developmental patterns for cognition and behavior (e.g. (Bos et al., 2018; Schnack et al., 2015)). Relatedly, the neuroimaging literature increasingly considers the developing brain in context, probing the dynamic relations between brain structure and function and culture, ethnicity and socio-economic factors (Farah, 2017; Noble and Giebler, 2020; Qu et al., 2021). Growing insight into these complex relations may also shape the methods in pediatric imaging in the years to come (Zhao et al., 2019).

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Appendix A. The Peer Review Overview and Supplementary data

The Peer Review Overview and Supplementary data associated with this article can be found in the online version, at doi:<https://doi.org/10.1016/j.pneurobio.2021.102109>.

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