Fetal and Postnatal Development of the Cortex: MRI and Genetics

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Glossary

Folding of the cortex Process including the formation of the cortical sulci and gyri during brain development.

Primary, secondary, and tertiary folds Cortical folds that appear from 20w GA, from 32w GA, and around term age (~40w GA) respectively.

Nomenclature

DTI	Diffusion tensor imaging
GA	Gestational age
MRI	Magnetic resonance imaging
PTA	Post-term age
STS	Superior temporal sulcus
T1w/T2w images	T_1-/T_2-weighted images
w GA	Weeks of gestational age

Introduction

In the human brain, development of the cortex is a complex and long-lasting process that begins during the first weeks of pregnancy and lasts until the end of adolescence. It involves several overlapping mechanisms that proceed at different times and speeds among the cortical regions (e.g., the sensory regions develop early on and quickly, whereas the associative regions, like the frontal ones, develop later on and slowly). Since understanding normal development is essential before considering the complexity of pathological conditions, this article focuses on studies using magnetic resonance imaging (MRI) in healthy fetuses, newborns, infants, and children. In most of these studies, the main goal is to uncover in the human brain *in vivo* the well-known developmental processes described in the immature animal brain, despite challenges to test young children and especially infants (Dubois et al., 2014). Although the relationship between MRI structural markers and infant cognitive development is still unclear, these studies provide a first description of human cerebral maturation, useful for clinics. We here mainly review studies on the structural development of the cortex, assessed by T_1- and T_2-weighted (T1w and T2w) images and diffusion tensor imaging (DTI). We successively detail (1) how the cortex grows and gets convoluted, (2) the microstructural maturation of the gray matter, (3) the interhemispheric asymmetries in cortical development, and (4) how this development might be impacted by genetic, epigenetic, and environmental factors.

The Cortex Development: Structure and Morphology

The last weeks of pregnancy and the first postnatal months are marked by an intense increase in cortical volume and surface area, which progressively slows down after 2 years of age until adolescence.

The Early Cerebral Organization

Due to the differences in cellularity, membrane density, and water content of the different tissue compartments that affect contrasts and diffusion parameters, the last waves of neuronal migration are clearly visible with T1w and T2w MRI in fetuses as young as 20 weeks of gestational age (w GA) (Girard, Raybaud, & Poncet, 1995; Scott et al., 2011) and with DTI in preterm newborns (Maas et al., 2004; **Figure 1**). Successive layers are described from the center of the brain to its surface: the germinal matrix from where neuroblasts migrate in the subventricular and periventricular zones, the intermediate zone that gathers radial glia and the developing axonal fibers of the future white matter, the subplate zone where migrating neurons are waiting until reaching their final location in the cortical plate, and finally the thin cortical plate. Between 20w GA and 26w GA, the subplate is seen as a hyperintense layer whose volume increases, first globally in proportion with the supratentorial volume and secondly at different rates among brain regions (Corbett-Detig et al., 2011). It becomes progressively isointense and thus difficult to identify from 35w GA on, although it might still be present until the end of the first year, notably in the frontal regions (Kostovic et al., 2014).

Cortical Growth

Because contrasts in T1w and T2w images evolve with maturation (Dubois et al., 2014), the comparison of cortical volume across ages (**Figure 2(a)**) should remain cautious. *In utero*, the volume of the cortical plate increases from around 10 ml at 21w GA to 70 ml at 31w GA (Scott et al., 2011), and developmental rates differ among brain regions, with higher volume increases in the parietal and occipital regions than in the frontal lobe (Rajagopalan et al., 2011). In preterm newborns, the volume increases from around 25 ml at 29w GA to 250 ml at 48w GA (Kuklisova-Murgasova et al., 2011). During the first 2 years after term birth, brain growth is mainly due to gray

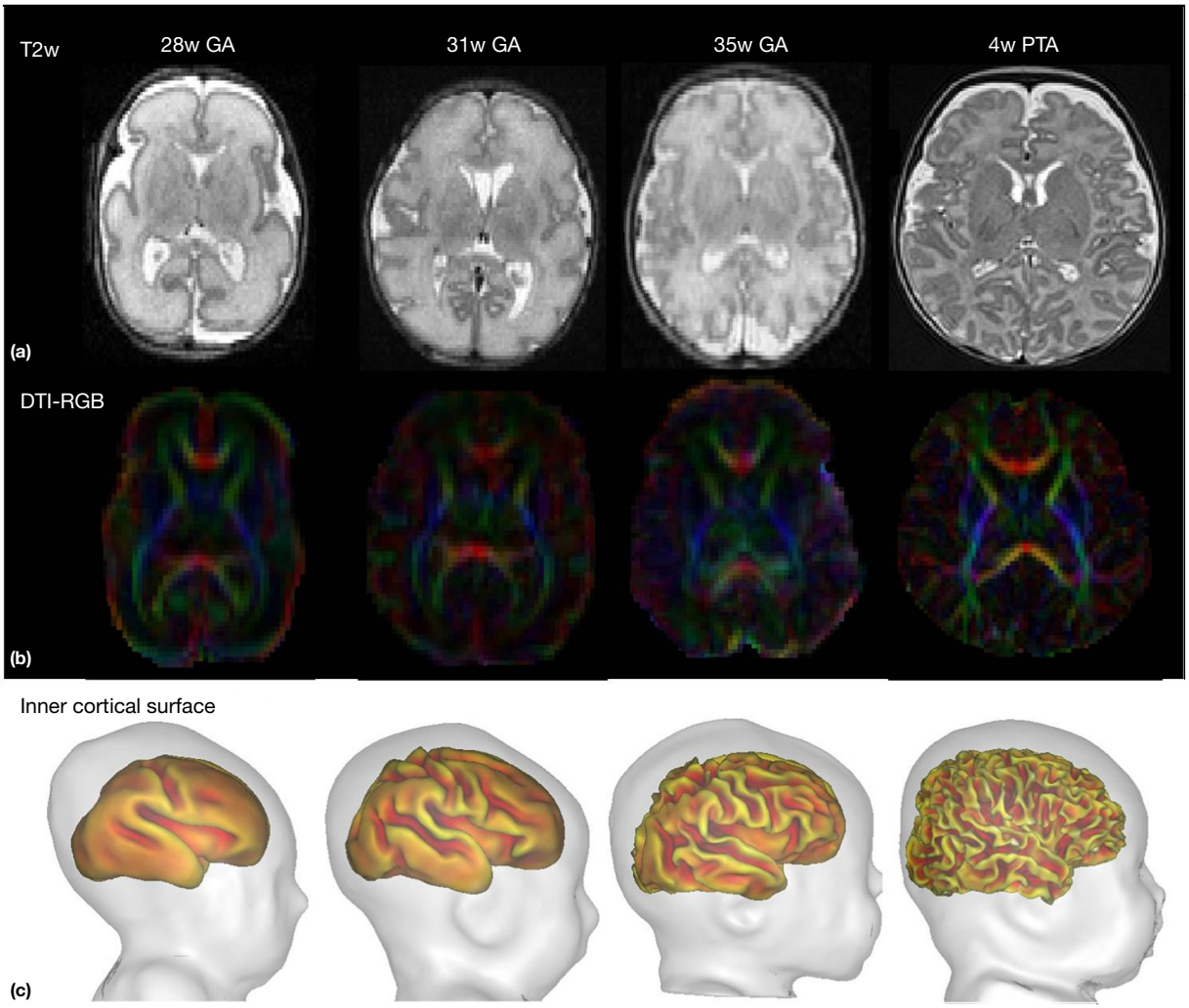

Figure 1 Structural imaging of the developing brain. T2w images (a), DTI-RGB directionality maps (b), and inner cortical surfaces (Dubois, Benders, Cachia, et al., 2008; Leroy, Mangin, et al., 2011) are presented for three preterm newborns of different ages and an infant aged 4w old (PTA: postterm age). Note that anisotropy decreases with age in the preterm cortex (b).

matter development (Gilmore et al., 2007; Knickmeyer et al., 2008) contrarily to the following years (Matsuzawa et al., 2001). The cortical volume increases much more during the first postnatal year (by around 106%) than during the second year (by 18%) and faster in the association cortices, particularly in the frontal and parietal lobes, relatively to the primary motor and sensory cortices (Gilmore et al., 2012; **Figure 3(a)**).

The preadolescent increase in cortical volume is followed by a postadolescent decrease, with different growth peaks across brain regions, varying from around 10 years (the female parietal lobe) to 17 years (the female temporal lobe) (Giedd et al., 1999; **Figure 2(a)**). Higher-order association cortices mature after lower-order somatosensory and visual cortices, and phylogenetically older regions mature earlier than newer regions (Gogtay et al., 2004).

Cortical Folding

Concurrently with brain growth, the cortex is getting folded during the last trimester of pregnancy. Dedicated tools and morphometric analyses have enabled to map in detail the developing cortical surface and growth patterns in fetuses as young as 20w GA (Habas et al., 2012) and in preterm newborns imaged shortly after birth (Dubois, Benders, Cachia, et al., 2008; **Figure 1(c)**). These *in vivo* studies confirm earlier postmortem observations (Chi, Dooling, & Gilles, 1977a) and show a precise calendar (with the appearance of primary folds around 20w GA, secondary folds around 32w GA, and tertiary folds around term), which can be used as a robust marker of brain maturation. Gyrification becomes manifest after 24w GA (Rajagopalan et al., 2011) and greatly heightens during the last weeks before term (**Figure 2(b)**; Angleys et al., 2014; Dubois, Benders, Cachia, et al., 2008). Although some variability is observed among individuals, the regional pattern is consistent over the brain surface: sulcation starts in the central region and proceeds first toward the parietal, temporal, and occipital lobes and second toward the frontal lobe (Dubois, Benders, Cachia, et al., 2008; Ruoss, Lovblad, Schroth, Moessinger, & Fusch, 2001).

At term, the cortical surface area is three times smaller than in adults, but the cortex is roughly similarly folded,

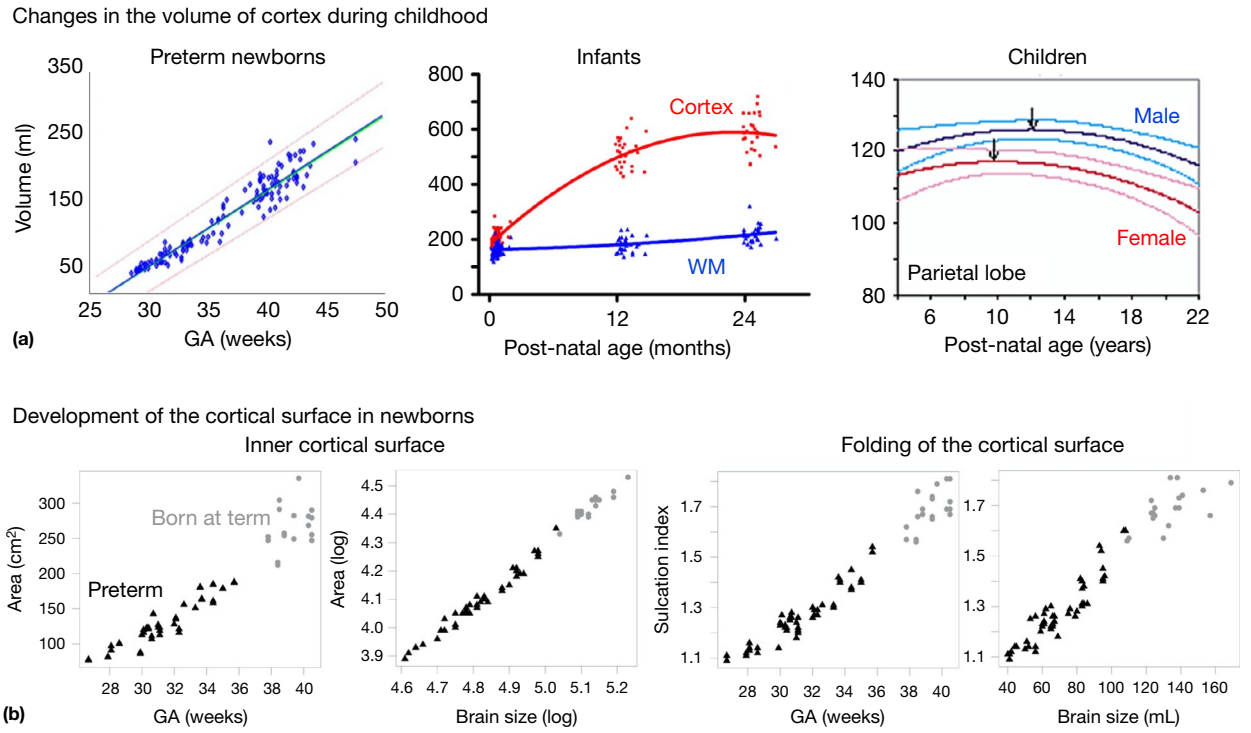

Figure 2 Changes in cortical volume, surface area, and folding during development. Cortical volume (a) increases during the preterm period (Kuklisova-Murgasova et al., 2011), infancy (Knickmeyer et al., 2008), and childhood, before decreasing during adolescence (Giedd et al., 1999). The increases in surface area and sulcation (b) are major during the last gestational weeks, going with the growth in brain size (Angleys et al., 2014).

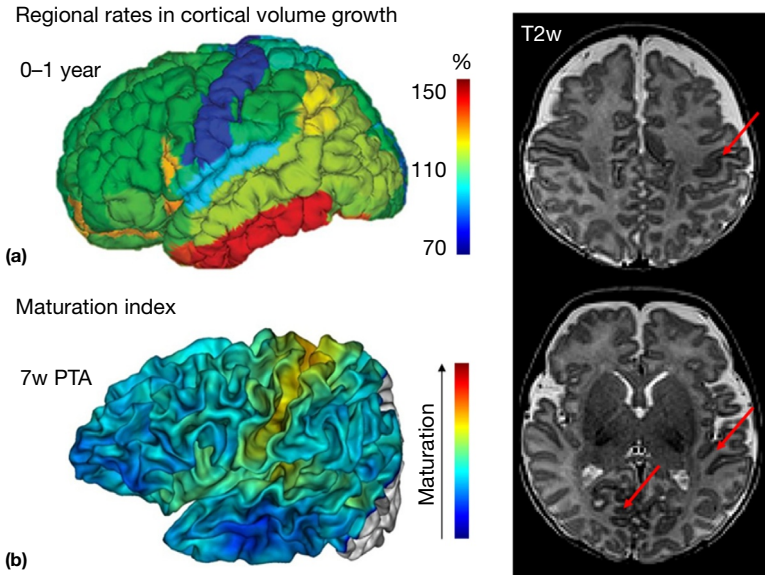

Figure 3 Asynchronous development of brain regions. During the first postnatal year, cortical regions demonstrate different rates of volume increase (a) (Gilmore et al., 2012) and maturation (b) (Leroy, Glasel, et al., 2011): primary sensorimotor regions grow less and appear more mature (red arrows on T2w images) than associative regions.

and the most variable regions among individuals are the same across newborns and adults (Hill, Dierker, et al., 2010). Noticing the nonuniform pattern of cortical growth among brain regions, Hill and colleagues proposed that it resembles the pattern of evolutionary expansion between human and macaque monkey, with phylogenetically recent regions being the least developed at birth (Hill, Inder, et al., 2010).

Modeling Cortical Development

Why does the human brain fold? The cortical structure appears as a closed surface, with fundamental mechanical properties of elasticity and plasticity (Toro & Burnod, 2005). Glial and axonal fibers might apply tension radially to this surface while it grows and consequently folds (Van Essen, 1997). According to genetic control or mechanistic constraints, the folding may organize around stable points, also called sulcal 'roots' (Regis et al., 2005) or 'pits' (Lohmann, Von Cramon, & Colchester, 2008) in the adult brain. So far, this hypothesis has been confirmed in preterm newborns, in whom stable inter-individual pits have been revealed along the central and superior temporal sulci using analyses of the surface curvature and depth (Operto et al., 2012) and also in infants in whom displacement field analyses have detected 'growth seeds' on longitudinal data (Lefèvre et al., 2009).

The Maturation of Cortical Microstructure

These macrostructural changes are the visible marker of the microstructural evolution, marked by synaptic outburst and pruning, modifications in dendritic branching, and fiber myelination.

Changes in Cortical Microstructure During the Preterm Period

In the developing brain of preterm newborns, DTI provides valuable information on cortical architecture and is sensitive to the regional heterogeneity in cortical development. The diffusion of water molecules is anisotropic in the cortical plate around 26w GA presenting a radial orientation of the tensor main direction and then becomes isotropic from around 36w GA (Dudink et al., 2010; Mckinstry et al., 2002; **Figure 1(b)**). This change is explained by the early radial deployment of glial fibers and apical dendrites of pyramidal neurons, followed by the elongation and complex branching of neuronal connections (basal dendrites for the pyramidal neurons and thalamocortical afferents). Besides, mean diffusivity increases between 26w GA and 32w GA and decreases thereafter, suggesting competing mechanisms (Mckinstry et al., 2002): decrease in cell density associated with programmed cell death, addition of neuropils between the neuronal somas, and decrease in water content. These changes are not uniform over the brain (Ball et al., 2013; Deipolyi et al., 2005), and they are not linear at least for some regions, such as the right superior temporal sulcus (STS) and lateral occipitotemporal gyrus (Aeby et al., 2012).

Cortical Maturation During Infancy

Accompanying the complex evolution of cortical microstructure, the dendritic and axonal fibers get myelinated. It is now possible to quantify this maturation *in vivo* by taking advantages of the changes in T_1 and T_2 signals induced by modifications in water and iron contents. For example, using normalized T2w images in infants, Leroy and colleagues recovered the regional asynchrony of maturation between primary and associative regions, as first described in postmortem studies (**Figure 3(b)**), and further uncovered a gradient of maturation within the linguistic network, the STS appearing less mature than the inferior frontal region (Leroy, Glasel, et al., 2011). Travis and colleagues also measured significant age effects within bilateral inferior lateral and anteroventral temporal regions and dorsomedial frontal and superior parietal cortices during the second postnatal year (Travis et al., 2013). T1w signal intensity and T1w/T2w myelin mapping reveal that cortical maturation is ongoing until 30 years of age in some brain regions and that occipital visual cortices display the earliest maturation, while superior frontal regions have the most protracted maturation (Grydeland, Walhovd, Tamnes, Westlye, & Fjell, 2013; Westlye et al., 2010). Besides, the magnetic susceptibility displays an exponential growth, suggesting a continuous increase in iron content (Li, Wu, et al., 2013).

Changes in Cortical Thickness During Childhood and Adolescence

In newborns, average cortical thickness is around 1.3 mm between 27 and 45w GA (Xue et al., 2007). It further increases with age, ranging from 1.5 mm in the occipital regions to 5.5 mm in the dorsomedial frontal cortex during childhood (Sowell et al., 2004). As for the cortical volume, this increase is followed during adolescence by an asynchronous decrease across brain regions (Shaw et al., 2007, 2008; Sowell et al., 2004). These thickness changes are correlated across regions linked with rich structural and functional connectivity (e.g., frontotemporal association regions; Raznahan, Lerch, et al., 2011).

It has been argued that cortical thinning would be an artifactual observation resulting from myelination that would blur the segmentation of the gray/white matter boundary on MR images. However, age-related evolutions of thickness and maturation are distinct over the life span (Westlye et al., 2010), and developmental patterns of superficial white matter diverge from the widespread changes in thickness (Wu et al., 2013). Relationships between cortical thickness, volume, surface area, and folding are also a matter of debate. Between 7 and 23 years of age, the regional patterns and timings of developmental trajectories differ for thickness and surface area, suggesting that these parameters rely on different mechanisms (Wierenga, Langen, Oranje, & Durston, 2013). Nevertheless, thinning seems associated with sulcal widening and gyral white matter expansion during adolescence, period when the cortex flattens (Aleman-Gomez et al., 2013). Nonlinear changes in cortical volume emerge from the complex age-dependent interactions of changes in thickness and surface area, also relying on gyrification (Raznahan, Shaw, et al., 2011).

Interhemispheric Asymmetries in Cortical Development

The two cerebral hemispheres do not develop symmetrically during the fetal and postnatal life, suggesting early structural bases of functional lateralization. Postmortem studies have described that the right hemisphere shows gyral complexity earlier than the left, while Heschl's gyrus and the planum

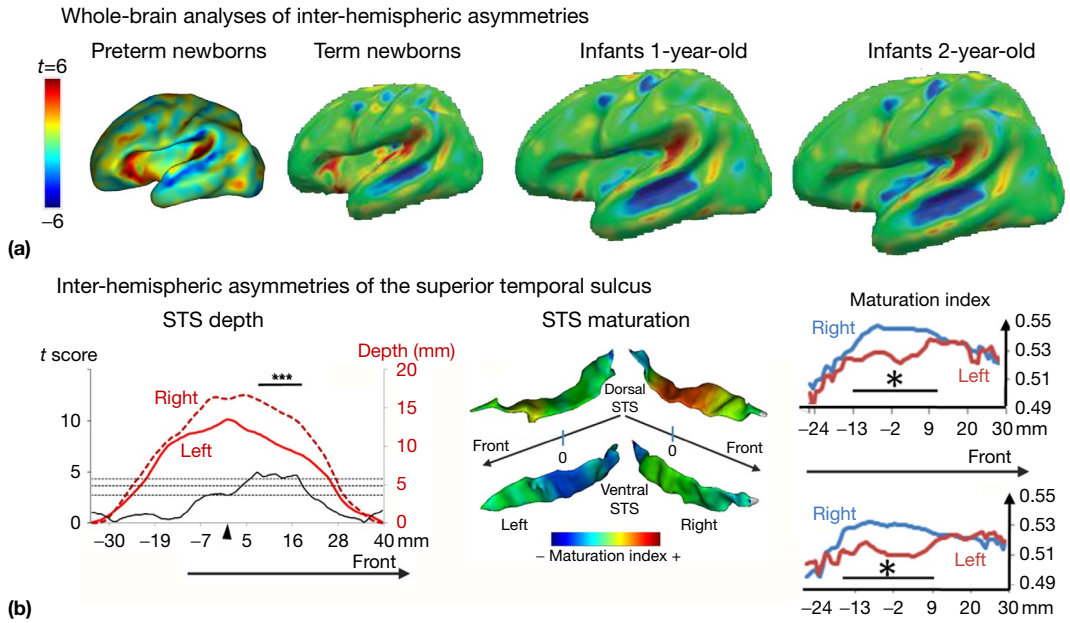

Figure 4 Interhemispheric asymmetries in cortical development. The cortex folds asymmetrically in perisylvian regions (a), as shown in preterm newborns (Dubois et al., 2010) and infants (Li, Nie, et al., 2013). Notably, the STS (b) is deeper (Glasel et al., 2011) and more mature (Leroy, Glasel, et al., 2011) on the right side than on the left.

temporale are more developed on the left side by 31w GA (Chi et al., 1977a; Chi, Dooling, & Gilles, 1977b). *In vivo* studies have confirmed these cortical asymmetries (**Figure 4**). STS folds earlier on the right side than on the left side in *in utero* fetuses (Habas et al., 2012; Kasprian et al., 2011) and in preterm newborns (Dubois, Benders, Cachia, et al., 2008), and the right STS remains deeper than the left in newborns at term (Hill, Dierker, et al., 2010), infants (Glasel et al., 2011; Li, Nie, et al., 2013), children, and adults (Leroy et al., in preparation), in association with an advanced maturation during infancy (Leroy, Glasel, et al., 2011).

The leftward elongation of the planum temporale and thickening of Heschl's gyrus are also detected early on (Dubois et al., 2010; Glasel et al., 2011; Hill, Dierker, et al., 2010; Li, Nie, et al., 2013). The posterior end of the sylvian fissure is shifted forward and upward in the right hemisphere of infants (Glasel et al., 2011; Li, Nie, et al., 2013), and this asymmetry increases with age (Sowell et al., 2002). Furthermore, the anterior region of the sylvian fissure seems to grow earlier on the left side (Dubois et al., 2010; Li, Nie, et al., 2013), close to Broca's region that matures before its right counterpart (Leroy, Glasel, et al., 2011). These maturational asymmetries in the posterior STS and Broca's region are finally associated with asymmetries in the arcuate fasciculus connecting these cortical areas (Dubois et al., 2009; Leroy, Glasel, et al., 2011).

Thus perisylvian regions involved in language processing in the left hemisphere and in social contact in the right hemisphere follow a different developmental calendar. The relation between structural and functional lateralization is still not clear (Dehaene-Lambertz, Hertz-Pannier, & Dubois, 2006), but early asymmetric expression of several genes, like LMO4 that is consistently more expressed in the right superior temporal regions than in the left regions of human embryos (Sun et al., 2005), suggests an evolutionary pressure on these regions.

Influence of Genetic, Epigenetic, and Environmental Factors

Several studies have related differences in cognitive performances with variations in cortical development during childhood and adolescence (Lu et al., 2007; Shaw et al., 2006). Nevertheless, the variability of detailed relationships among studies suggests that numerous factors affecting cognitive performances and brain development (e.g., socioeconomic status, education, birth weight, nutrition, and stress) should be taken into account. Furthermore, since age is the main variable driving brain changes, longitudinal studies should be preferred to isolate the crucial factors and their impact on precise structures along the developmental trajectory (Raznahan, Shaw, et al., 2011). Too numerous pathologies disrupt development; therefore, we will only focus on normal development, except for prematurity, a major societal issue.

Sexual Dimorphism

Whereas no difference in folding is detected among fetuses of the same age (Chi et al., 1977a), males already have larger cortical volumes than females after preterm (Dubois, Benders, Cachia, et al., 2008) or term birth (Gilmore et al., 2007). During childhood and adolescence, this dimorphism strengthens, with volumes being 10% larger in boys (Giedd et al., 1999) correlating with body mass index (Brain Development Cooperative Group, 2012). The age-related changes in volume peak slightly earlier (1–2 years) in girls, but the curve shape does not differ among genders (Giedd et al., 1999; Lenroot et al., 2007).

Girls tend to have larger gray matter volume relative to brain size than boys (Groeschel, Vollmer, King, & Connelly,

2010), and gender differences are more pronounced for volume and surface area than for cortical thickness (Wierenga et al., 2013), for which sex differences are region-specific (Sowell et al., 2007). During adolescence, the pattern of differences in cortical thickness between genders accelerates, notably a wave of maturation sweeps frontal subregions with a delay in males compared with females (Raznahan et al., 2010) probably related to the earlier female puberty. The acceleration of cortical thickness changes during this period is different across regions and is modulated by the level of cerebral androgen receptor signaling in both males and females (Raznahan et al., 2010). The effect of gender is strikingly different in the superior frontal region (accelerated loss in males relatively to females) and the parietal lobule (reverse pattern), suggesting possible relationship with gender cognitive differences (e.g., better social cognition in females versus better visuospatial cognition in males; Raznahan et al., 2010) despite no direct established correlation.

Besides hormonal influence, sex chromosome gene expression also directly influences gray matter volume in different brain regions (parietooccipital and temporoinsular), as demonstrated during the early stages of puberty in normal children and children with Turner syndrome (females missing one X chromosome) and Klinefelter syndrome (males having an additional X chromosome) (Hong et al., 2014). These developmental studies demonstrate the robust influence of hormones and sex chromosome gene dosages on cortical development and underscore the need to precisely match gender and age when evaluating normal or pathological brain functioning.

Genetic Influences

To assess how genetics and environment influence cortical development, most MRI studies have relied on the longitudinal follow-up of pediatric monozygotic and dizygotic twins. Cortical volume and depth are highly correlated within monozygotic twin pairs, but surface measures are more prone to environmental influences (White, Andreasen, & Nopoulos, 2002). The volume heritability decreases with age (Wallace et al., 2006), differently among brain regions (Giedd, Schmitt, & Neale, 2007). Cortical density is increasingly similar in subjects with increasing genetic affinity, particularly in the frontal, sensorimotor, and perisylvian language regions (Thompson et al., 2001). The degree of genetic influence on cortical thickness also differs among brain regions (Van Soelen et al., 2012): regions that develop earlier show greater genetic effects during early childhood, while later-developing regions are more heritable in adolescents than children (Lenroot et al., 2009).

So far, the heritability in cortical patterning has not been studied during development, but in adults, the similarity in sulcal graphs is higher in twin pairs than in unrelated pairs, suggesting a genetic influence on cortical folding (Im et al., 2011). Finally, genetics also influences interhemispheric asymmetries: asymmetries in the planum temporale and sylvian fissure are slightly heritable during childhood. However, heritability decreases when twins with discordant writing hand or large birth weight differences are included (Eckert et al., 2002), suggesting that prenatal and postnatal factors should not be neglected.

Intrauterine Environment and Gestational Duration

In agreement with postmortem studies (Chi et al., 1977a), an *in vivo* study of preterm newborns has shown a delayed but harmonious maturation in twins at birth in comparison with singletons (Dubois, Benders, Borradori-Tolsa, et al., 2008), whereas the gyrification of newborns with intrauterine growth restriction is discordant to the normal developmental trajectory. Within monozygotic pairs in a normal birth weight range, higher birth weight is associated with higher intelligence quotient in adolescence and with higher cortical volume and surface area notably in several perisylvian regions (Raznahan, Greenstein, Lee, Clasen, & Giedd, 2012). This relation is not observed in singletons and is weaker in dizygotic twins. These results highlight that a slightly more difficult prenatal environment interacting with genetic expression has a durable effect (although weak: two points of IQ in the aforementioned study).

Premature birth also strongly modifies subsequent brain growth, even in the absence of major destructive brain lesions. In comparison with normal newborns, preterm newborns at term-equivalent age show alterations in cortical volume (reductions in most brain regions except increases in occipital regions) (Padilla, Alexandrou, Blennow, Lagercrantz, & Aden, 2014), folding (Melbourne et al., 2014), and maturation (Ball et al., 2013), in a dose-dependent fashion related to the premature exposure to extrauterine environment (development increases with gestational age at birth). From 23 to 48w GA, the scaling exponent relating surface area and volume decreases with increasing prematurity (Kapellou et al., 2006).

Prematurity consequences further stretch to infancy and childhood, with early brain measures predicting future cognitive development. Cortical folding in preterms at birth correlates with cortical volume and neurobehavioral development at term-equivalent age (Dubois, Benders, Borradori-Tolsa, et al., 2008). Language abilities of 2-year-old infants born preterm are negatively correlated with DTI diffusivities measured in the left superior temporal gyrus at term-equivalent age, suggesting that the early stage of development of this region is crucial for later language acquisition (Aeby et al., 2013). The rate of microstructural maturation assessed between 27 and 46w GA predicts neurodevelopmental scores at 2 years of age (Ball et al., 2013). At 8 years of age, children born preterm demonstrate increased bilateral temporal lobe gyrification compared with term controls, and the left increase is negatively correlated with reading recognition scores (Kesler et al., 2006). Even in children born full term, a longer duration of gestation (until 41w GA) seems beneficial, being associated with region-specific increases in cortical density (Davis et al., 2011). These studies outline that cognitive functions have their roots in early development, but questions remain on the causal disturbing mechanisms of exposure, notably on the respective roles of microscopic brain lesions, to the too stimulating outside world versus to the maternal protective and filtering environment.

Conclusion

MRI now enables to map and characterize the dynamics of cortical development and the development of structural and

functional connectivity, highlighting the structural bases of cognitive development. These studies are challenging in healthy infants and require dedicated methodologies for image acquisition and postprocessing (Dubois et al., 2014), but it is worth the effort since markers of maturation are required to better understand pathological mechanisms or the deleterious effects of early disturbances such as prematurity. However, if clear effects of age, genes, hormonal status, or nutrition are observed on structural images, the causal relationships between these observations and cognition are still unknown due to the complex interactions between these factors and the delicacy of the neural circuitry still not captured by MR images.

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See also: **INTRODUCTION TO ACQUISITION METHODS**: Anatomical MRI for Human Brain Morphometry; Diffusion MRI; Myelin Imaging; **INTRODUCTION TO ANATOMY AND PHYSIOLOGY**: Brain Sex Differences; Cortical Surface Morphometry; Development of Structural and Functional Connectivity; Development of the Basal Ganglia and the Basal Forebrain; Embryonic and Fetal Development of the Human Cerebral Cortex; Gyrification in the Human Brain; Sulci as Landmarks; **INTRODUCTION TO CLINICAL BRAIN MAPPING**: Developmental Brain Atlases; **INTRODUCTION TO METHODS AND MODELING**: Cortical Thickness Mapping; Diffusion Tensor Imaging; Modeling Brain Growth and Development; Tissue Properties from Quantitative MRI.

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