

Structural Brain Development

Birth Through Adolescence

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Abbreviations

AD	Axial diffusivity
CT	Computed tomography
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
fMRI	Functional MRI
IQ	Intelligence quotient
MD	Mean diffusivity
MRI	Magnetic resonance imaging
PET	Positron emission tomography
RD	Radial diffusivity
ROI	Region of interest
TBSS	Tract-based spatial statistics
VBM	Voxel-based morphometry

12.1 INTRODUCTION

Human brain development is a dynamic process that begins *in utero* and continues prominently through childhood, adolescence, and young adulthood. While strongly influenced by genetic factors, the environment also prominently affects brain maturation by acting on the cellular and macroscopic levels. This experiential learning impacts both brain structure and function through forms of neuronal plasticity that continue throughout our lifetimes. However, despite the fact that investigating brain development is undoubtedly one of

the keys to appreciating how we emerge as unique human beings and how this process can go awry in disease, our understanding of this important period has historically been hindered by two main factors. First, there has been a lack of reliable postmortem data as, thankfully, children are generally healthy during development. Second, technological limitations of past methods such as positron emission tomography (PET) and computed tomography (CT) often imposed some modest risk of harm to the subject (e.g., ionizing radiation), which made the study of healthy, typically developing children ethically questionable. The situation changed dramatically with the dissemination of magnetic resonance imaging (MRI) technology during the 1980s, which not only offers higher-quality images of the brain parenchyma than ultrasound, x-ray, CT, or PET, but also does so in a way that is remarkably safe for the subject (see [Chapter 34](#)).

This discussion will begin with a review of the historical postmortem and histological literature, and will then move on to the groundbreaking neuroimaging investigations of the 1990s, that first examined brain development with this MRI technology. A collection of more detailed phenomena will then be examined, which have been uncovered with advanced brain mapping techniques and have come together as a set of classic features that characterize typical brain development. Finally, we will conclude with a discussion of the cutting-edge efforts being made to integrate these diverse observations within a more generalized ‘multimodal’ imaging framework and to relate them to advancements in cognitive development. A focus on prominent sex-specific, regional and temporal variations will be continually threaded throughout this discussion.

12.2 POSTMORTEM STUDIES AND HISTOLOGY

12.2.1 Comparison to MRI

Although datasets were sparse, postmortem and histological studies were able to provide key insight into normal brain structure and development, as well as pathology, decades before the introduction of neuroimaging methods like PET and MRI. Further, the rich literature that developed from this early effort has provided a strong foundation of data against which newer imaging modalities can be validated. Compared to a modern imaging method like MRI, there are several distinct advantages and disadvantages of these postmortem studies. Not only are datasets relatively small in postmortem samples, as mentioned above, but longitudinal studies – valued for their statistical power to detect changes over time within individuals among the highly variable population – are also impossible to conduct. Conversely, because postmortem methods can directly visualize the

brain tissue, spatial resolution far exceeds even the best neuroimaging protocol, and there is less validation needed to ensure that the raw signal being measured faithfully represents the underlying neuronal architecture. Artifacts, though, are an important concern for either method. While postmortem methods may introduce artifacts due to cell death, fixation/staining procedures, and morphological changes due to osmotic pressure and mechanical damage, MRI data suffer artifacts from other sources like magnetic susceptibility effects (signal loss in regions near large caverns of air), local image distortions caused by magnetic field inhomogeneities, and partial volume effects that occur when different structures fall within the same voxel. Many of these issues present less of a problem for the interpretation of larger data sets obtained with MRI, relative to postmortem data, as effects of artifacts generally become small as the number of samples becomes large. However, it should still be remembered that MRI only offers a wide-angle indirect view of tissue, which cannot reach down to the cellular level and must be observed through the complex lens of magnetic resonance.

12.2.2 Synaptogenesis and Pruning

By the time an infant is born, the human brain already contains on the order of 100 billion neurons ([Kandel et al., 2000](#)). The period of rapid overall brain growth that began *in utero* continues after birth through the first years of life. Surprisingly, however, postmortem studies during the early part of the twentieth century showed that total brain volume and weight actually plateau early and reach approximately 90% of their adult values by age 5 ([Dekaban, 1978](#); [Riddle et al., 2010](#); [Vignaud, 1966](#); and is discussed extensively in [Rubenstein and Rakic, 2013](#)).

Even during this early period of pronounced overall growth, brain development is characterized as a dynamic process with both progressive and regressive changes that are influenced by complex genetic influences as well as experience-dependent plasticity due to environmental influences. As the infant brain grows in size, it also grows in complexity. Neurons undergo dendritic branching, forming an arbor of neural connections through synaptogenesis and then ultimately refine this global brain network through the processes of myelination and synaptic pruning. Much of our understanding of the complex balance between synaptogenesis and synaptic pruning has evolved from the seminal histological work performed by Huttenlocher and colleagues, who mapped synaptic density in different areas of the brain throughout childhood. Overall synaptic density is comparable to the adult level at birth. It then rises even further through the first year of life to its peak at 12–18 months and then decreases during late childhood and

young adulthood towards a stable adult plateau of ~ 1 billion synapses $\cdot\text{mm}^{-3}$ (Huttenlocher, 1979). This has helped to form the theory that the flexible groundwork laid through an initial overabundance of connections gives way to a reduced – but more targeted and efficient – network through experience-dependent synaptic pruning. Interesting regional variations were also observed during these studies, with primary visual and auditory cortex reaching their peak synaptic densities earlier than prefrontal cortex (Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997; Huttenlocher et al., 1982). The extended period of synapse elimination also has regional variations, with pruning ending by age 12 in the auditory cortex but continuing through mid-adolescence in the prefrontal cortex. This temporal pattern parallels concurrent gains in the cognitive domains that are thought to relate to these regions (Luna et al., 2004; Spear, 2000).

12.2.3 Myelination

Myelination of axonal projections by oligodendroglia is also a prominent component of early brain development. This process begins *in utero*, continues rapidly through the first 5 years of life, and remarkably extends – although at a slower rate – through young adulthood. Intracortical histological preparations by Kaes in 1907 were some of the first to demonstrate this prolonged trajectory of myelination, along with its striking regional variability in timing (Kaes, 1907; Kemper, 1994). His work not only demonstrated earlier trajectories in some areas (posterior temporal, precentral, and postcentral cortex) than others (superior parietal, anterior temporal, and anterior frontal cortex), but also showed that regions with a more protracted developmental trajectory have more pronounced changes during older age. This has helped to form the ‘first-in-last-out’ theory of aging (Davis et al., 2009), which suggests that higher-order cognitive manifestations (e.g., problem solving and logical reasoning) – some of the last to develop (Luna et al., 2004) – are some of the first to degenerate in old age. Furthermore, the visible spread of myelin outwards into the cortex results in an apparent cortical thinning, which suggests that normal developmental decreases in cortical thickness (discussed in Section 12.4.3) may be due, in part, to this progressive increase in myelin and not simply to regressive changes like synaptic pruning and cell loss (see Rubenstein and Rakic, 2013).

These initial observations in intracortical tissue were extended to the white matter in the pioneering work performed by Yakovlev and Lecours in the 1960s. They demonstrated that white matter myelination begins *in utero* during the second trimester of pregnancy and continues throughout young adulthood (Yakovlev and

Lecours, 1967). Additionally, they extended the earlier observations of regional variations in the timing of myelination and described a general posterior-to-anterior trend in the timing of white matter myelination during development that has also been replicated in other samples (Kinney, 1988). Later independent research, targeting the hippocampal formation, has also noted striking increases in myelination, with a 95% increase observed in the extent of myelination relative to brain weight during the first two decades of life. Surprisingly, the authors noted that expanding myelination continued even through the fourth to sixth decades of life (Benes et al., 1994). Taken together, these observations suggest that structural white matter development, in the form of advancing myelination, proceeds in tune with overall cognitive development – with areas involved in lower-order sensory and motor function myelinating earlier than areas involved with higher-order executive function. This correlated timing implies there may be some relationship between advancing brain function and increased myelination; however, postmortem studies are limited from investigating this directly.

12.2.4 Sex-Specific Differences

A pronounced sexual dimorphism in overall brain size emerges during the first 5 years of human brain development, with males having brains that are, on average, approximately 10% larger than females at their adult plateau (Dekaban, 1978). This simple and widely reproducible observation has served as a catalyst for continued interest in the study of sex-specific differences during brain development in order to (1) map other detailed components of brain development that may also show sex-specific differences, (2) determine if there are any cognitive correlates with these findings (Kimura, 1996), (3) establish what – if not total volume of brain matter – are the driving structural contributors to individual cognitive differences in areas like language skills and overall intelligence, and, perhaps most importantly, (4) better understand and clinically address the range of neuropsychiatric disorders that tend to emerge during adolescence with prominent sex-specific affinities (Marsh et al., 2008). Interestingly, while some of this sex-specific variance in brain size can be attributed to height, which is consistent with broader trends across different mammalian species, there remains a significant sex-specific effect on brain size even when differences in body size are taken into account (Peters et al., 1998). Although the brains of adult males tend to be larger than adult females, this increase is actually smaller than what would be predicted based on differences in adult height alone. Histological findings indicating a 15% higher neuronal density in males than females are consistent with

this (Rabinowicz et al., 2002), although conflicting reports from other studies prohibit firm conclusions on this point (Haug, 1987; Pakkenberg and Gundersen, 1997). A consideration of the fact that females actually tend to be taller than males during late childhood, perhaps due to faster pubertal maturation in girls, further weakens the idea of such a simple allometric relationship when age-matched males and females are compared (Giedd et al., 2006). These discrepancies highlight the diversity that exists among the postmortem literature on the topic of sex differences in brain development, which is also likely to be influenced by a variety of confounds (including cohort effects and observational bias) that have made interpretation challenging (Peters et al., 1998). Additionally, these reports are limited to either simple global measures, like total brain volume or weight, or very local measures, like neuronal density, and generally do not account for regional variations in measures like cortical thickness and folding complexity (Luders et al., 2004; Sowell et al., 2007) (see Chapters 35 and 38).

12.2.5 Summary

The central theme that emerges from this early postmortem work is that brain development from birth through adolescence is a uniquely dynamic process, encompassing both progressive and regressive events, with varying magnitudes and timing across different regions of the brain. In particular, the concurrent decrease in synaptic density and increase in white matter myelination is consistent with the principle of selective specialization, which has been postulated to be the driving force behind the creation of cognitive networks and thought to form the foundation for higher cognitive processes (Fuster, 2002; Post and Weiss, 1997; Tsujimoto, 2008). The initial overabundance of neurons and synapses during infancy is thought to provide a flexible substrate through which activity-dependent plasticity can fine-tune neural network activity via processes like synaptic pruning, which continue robustly through adolescence and, in some form, throughout life.

12.3 IN VIVO VOLUME ANALYSES

With the development of MRI, not only were clinicians provided with a superior technology for the diagnosis of brain injury and disease (Barkovich, 2006; Panigrahy and Blüml, 2009; Prager and Roychowdhury, 2007), but researchers were also provided with an unparalleled technology for the study of typical brain development *in vivo*. This, together with the expansion of computing technology during the 1980s, led to the first wave of

structural neuroimaging studies aimed at extending previous postmortem results. Much of this early work utilized volumetric parcellation methods, whereby brain images are segmented according to different anatomical landmarks, and the volumes and tissue content (gray matter, white matter, cerebrospinal fluid) of these different regions are computed and compared between subject groups or throughout development. This parcellation step has been performed with a variety of methods, including the use of stereotactic coordinates (Jernigan et al., 1991a,b; Reiss, et al., 1996), manually drawn regions of interest (ROIs) (Giedd et al., 1996c; Sowell et al., 2002b), and automated protocols (Giedd et al., 1996a, 1999a) (see Chapter 28).

12.3.1 Gray Matter Decreases in Development

Given the previous postmortem observations of regional and temporal variations in synaptic density and myelination throughout the brain, the gray and white matter volume estimates extracted through these volumetric parcellation methods would be expected to show similar age-related developmental trajectories and regional differences. This was first demonstrated by Jernigan and Tallal, who observed that a group of children aged 8–10 had significantly more cortical gray matter than a group of young adults, as well as a higher gray matter to white matter ratio (Jernigan and Tallal, 1990). A subsequent study extended these findings to confirm that the group differences were due to continuous age-related decreases in gray matter volume with time – independent of brain size – and localized these effects to superior frontal and parietal cortices (Jernigan et al., 1991a,b). These studies marked the first *in vivo* morphological evidence in support of the earlier postmortem histological work by Huttenlocher and colleagues. While not a direct measure of synaptic density, the volumetric MRI finding of decreased gray matter volume is consistent with the regressive synaptic pruning changes previously described and aligns with the theory that evolutionarily more complex regions like the frontal lobe show more protracted timing in their development than evolutionarily simpler regions like primary motor/visual cortex. Even this early on, Jernigan and colleagues were also aware of the possible relationship between their *in vivo* MRI findings and the postmortem white matter myelination studies of Yakovlev and Lecours and suggested that an ‘apparent’ cortical thinning could be due, in part, to progressing myelination. Thus, a component of these observed changes might not be a gray matter loss, *per se*, but a transition of unmyelinated ‘gray’ matter into white matter, which, on MRI, would appear as a gray matter volume ‘loss’ during the childhood and adolescent years.

12.3.2 Regional and Temporal Dynamics

Since these initial observations of childhood and adolescent gray matter volume loss, other investigations have confirmed the general trend (Caviness et al., 1996; Giedd et al., 1999a; Ostby et al., 2009; Pfefferbaum et al., 1994; Reiss et al., 1996; Sowell et al., 2002b; Wilke et al., 2007) and extended these observations in several important ways. In a large cross-sectional sample of 161 subjects aged 3 months to 70 years, Pfefferbaum and others were able to demonstrate the early rise and plateau in total brain volume by approximately age 5, as well as the late childhood and adolescent decline in cortical gray matter volume. The extended age range of the sample allowed them to characterize the trajectory of the gray matter volume decline as curvilinear, which suggested an overall inverted ‘U’-shaped curve consisting of early childhood gray matter increases followed by a relatively early peak and then late childhood and adolescent reductions (Pfefferbaum et al., 1994). This general time course of cortical development is a feature that has gone on to become one of the hallmarks of structural brain development (Courchesne et al., 2000; Paus et al., 2001; Sowell et al., 2003).

Other studies have investigated the relative volume changes (controlling for global increases in total brain volume) more closely in broader age samples and in specific cortical and subcortical structures. In doing so, this work has demonstrated further heterogeneity in maturational timing and trajectory complexity across the brain. Importantly, the relative gray matter volume reduction during adolescence was confirmed to be most concentrated in the frontal and parietal lobes (Sowell et al., 2002b). Meanwhile, subcortical gray matter structures like the basal ganglia also generally showed a relative volume reduction, although with a simpler linear trajectory than the cortex over the age range of late childhood to young adulthood (Ostby et al., 2009; Sowell et al., 2002b). Tzirouchi et al. recently applied some of the modern spatial normalization methods to align each individual’s structural MRI brain data to a group average of all individuals studied and conducted an analysis in the vein of these classical volumetric studies by examining volume change over time in over 100 regions throughout the cortex. Using an exponential nonlinear function to model the upstroke portion of the developmental curve, they were able to estimate the age at which these different gray matter regions reached full development. In doing so, they provided a compelling demonstration of the previously theorized maturational sequence, with primary somatosensory and visual cortices maturing the earliest and then posterior-to-anterior and inferior-to-superior trends in the developmental timing of the remaining temporal, parietal, and frontal lobes (Tzirouchi et al., 2009).

12.3.3 White Matter Increases in Development

Interestingly, while gray matter volume was observed to peak early, researchers began to consistently observe that white matter volume continues to steadily increase roughly linearly from birth through adolescence and young adulthood (Caviness et al., 1996; Paus et al., 2001; Pfefferbaum et al., 1994; Sowell et al., 2002b; Wilke et al., 2007). The timing of these changes shows a posterior-to-anterior gradient, which generally parallels the overlying gray matter and has led to continued investigation into the interaction between these processes (Barkovich et al., 1988). The white matter volume increase is consistent with the widespread reports of relative gray matter reductions during later childhood and adolescence, as a protracted increase in underlying white matter volume (due, in part, to increased oligodendroglial wrapping of axonal fibers) will increase total brain volume and, therefore, decrease the relative gray matter volumes of specific structures compared to this total. The midsagittal corpus callosum was one of the first white matter areas to be examined in more detail, with volumetric analyses showing robust increases in total area throughout adolescence (Bellis et al., 2001; Giedd et al., 1999b) and a surprising anterior-to-posterior trend in the timing of the growth curve when the corpus callosum was subdivided into seven distinct segments (Giedd et al., 1996a). This protracted nature of white matter development is a thread that we will see repeated in the following sections, as imaging modalities and analysis techniques have advanced (Giedd et al., 1999a; Lebel et al., 2008b; Sowell et al., 2003), and as one that has gained increasing interest as more attention is being focused on the network properties of the brain as a potential, important mediator for the late cognitive development seen in domains like risk/reward processing, cognitive control, and working memory (Spear, 2000).

12.3.4 Sex Differences

Sex-specific differences in brain structure were also extended with these structural imaging techniques. Total brain volume was confirmed to be approximately 10% larger in males than females at the plateau of overall brain volume that is reached during childhood (Caviness et al., 1996; Courchesne et al., 2000; Durston et al., 2001; Gur et al., 2002; Lenroot and Giedd, 2010), and the significant sex-specific effect remains even when height and weight are covaried (Giedd et al., 1996b). However, more detailed regional volumetric observations of different cortical regions have been inconsistent – with varying reports of increased or decreased volumes in males and females that are further complicated by whether or not absolute or relative changes (to total brain volume differences) were reported (Sowell et al., 2007).

Despite this variation, strong evidence suggests that there may be sexual dimorphism in the timing of the developmental trajectory in the cortex, such that males and females have similar overall trajectories of regional brain maturation (both with an inverted 'U'-shaped curve) but differing gender effects with time because of a difference in the timing of this trajectory (Giedd et al., 1999a). Specifically, there appears to be approximately a 1–2 years' phase difference between girls and boys, with peaks in gray matter occurring earlier in girls than boys and regional variations in both phase and the actual differences between the sexes (Lenroot et al., 2007). Because this is a temporally dynamic period of development (and not a static one, e.g., like comparing fully mature adults), assessing sex differences during childhood and adolescence has become a more complicated problem, which requires the dissociation of phase differences (particularly those caused by differences in age of pubertal onset) from sex differences in the maturational trajectories. An additional challenge is identifying those differences that persist into adulthood and actually have functional relevance.

Observations of sex differences in subcortical regions have also been somewhat more reproducible. In particular, over the course of development, the amygdala seems to increase in volume more in males and the hippocampus more in females (Giedd et al., 1996b,c, 1997; Wilke et al., 2007). This is in line with animal studies that have shown high densities of steroid hormone receptors in the medial temporal lobe (Sarkey et al., 2008) and also that sex steroids exert trophic effects on these structures (Cooke, 2006; Galea et al., 2006; Zhang et al., 2008). In one recent study specifically targeted to investigate the degree to which the rise of gonadal hormones during puberty contributes to the emergence of these sex-specific differences, we examined subcortical volume measures among a group of 80 adolescent boys and girls matched on sexual maturity within a relatively narrow age range (Bramen et al., 2011). This focused analysis revealed an interaction between sex and the effect of puberty in predicting amygdala and hippocampal volumes: While females actually had larger left amygdala and right hippocampal volumes than boys during early puberty (relative to total brain size), by late puberty, the amygdala volume had increased in males but stayed relatively stable in females. In the right hippocampus, the effect of puberty was also to increase the volume in males but, surprisingly, to decrease the volume in females. This reiterates the importance of considering the timing in the interpretation of developmental phenomena like sexual dimorphisms. Furthermore, these results suggest that the sex-specific differences in amygdala volume previously observed across a broader age sample (Giedd et al., 1996c) are likely due, in large part, to the effects of puberty, but that the previous observation

of relatively larger hippocampal volumes in females may be due to nonpubertal influences, as the direct contribution of puberty, demonstrated in our recent observations, would be to blunt this effect. These findings are particularly important in the context of adolescent brain development, as maturation of these processing centers and their connections to areas like the prefrontal cortex may contribute to the dramatic changes seen in social and emotional domains during this period of development (Dahl, 2004; Steinberg, 2005). The caudate nucleus has also been shown to be relatively larger, controlling for total brain volume, in females across several distinct samples (Giedd et al., 1996b, 1997; Sowell et al., 2002b; Wilke et al., 2007). Put another way, the caudate is spared the reduction in volume that is typically shown by other structures in female brains. This observation of sexual dimorphism in the basal ganglia is also important, as it may relate to the emergence of similar sex differences in the incidence of several neuropsychiatric disorders (e.g., attention deficit hyperactivity disorder, Tourette syndrome) that are thought to involve these structures (Marsh et al., 2008) (see Chapters 35 and 38).

12.4 BRAIN MAPPING APPROACHES

12.4.1 Advantages

The early volumetric MRI imaging observations by Jernigan and others helped lay the foundation for the next wave of neuroimaging studies designed to further characterize the anatomical changes that occur during normal development. While the volumetric protocols were able to validate much of the classical postmortem literature, as well as provide further evidence for gray matter loss, white matter gain, and regional/temporal dynamics, they are unable to precisely localize where these maturational changes are taking place within the relatively large ROIs studied. Instead, these methods collapse entire regions of the brain down into one or several summary descriptive statistics that may not be characteristic of all functional and structural brain circuits within these large lobar regions. In contrast, newer methods like voxel-based morphometry (VBM) and cortical thickness analysis are distinct in that they allow for statistical analysis at many points throughout the entire brain volume or at many points across the entire cortical surface and allow the creation of whole-brain 'maps' to visualize these data. These enhanced analysis modalities, together with the traditional methods discussed in Sections 12.2 and 12.3, have contributed greatly to our understanding of normal brain development and provide an important context for the further study of neurodevelopmental and psychiatric disease (Eliez and Reiss, 2000; Marsh et al., 2008) (see Chapters 30, 35 and 38).

12.4.2 Voxel-Based Strategies

In VBM, the local fractional gray matter volume is analyzed in the neighborhood around each voxel in the brain to generate whole-brain maps of gray matter ‘density’ or ‘concentration’ (Ashburner and Friston, 2000). Spatial normalization algorithms are applied to align the brains of individual subjects so that each voxel then can be compared throughout development or between groups. Consistent with the previous volumetric studies and postmortem examples, whole-brain mapping strategies utilizing VBM show decreasing gray matter density during later development. In line with the coarse frontal and parietal lobar localizations of the earlier volumetric reports, the regions showing the most protracted changes in these new analyses include clusters in the dorsal frontal and parietal cortices during the transition from childhood to adolescence (Sowell et al., 1999a), as well as a distinct grouping of dorsal, medial, and orbital frontal cortical areas during the later transition from adolescence into young adulthood (see Figure 12.1; Sowell et al., 1999b). The relative specificity of these later changes to the frontal lobes is consistent with the similarly protracted time course of cognitive development in executive function domains, which are also typically thought to involve these frontal regions (Casey et al., 2005; Luna et al., 2004, 2010; Spear, 2000).

This notion of gray matter density was extended to allow for analysis on the cortical surface through the method of cortical pattern matching, where sulcal landmarks are manually identified and used to drive accurate nonlinear spatial normalization into a common template, while helping to account for regional, gender, and individual variability (Ashburner et al., 2003; Luders et al., 2004). Using this technique, protracted postadolescent gray matter density decreases were again demonstrated in dorsal frontal cortex (Gogtay et al., 2004; Sowell et al., 2001b), and, for the first time, shown to correlate significantly with underlying relative brain growth in these regions (Sowell et al., 2001b). This suggests the combined influences of both regressive processes like synaptic pruning, as well as progressive processes, like myelination, are acting in these areas. Using similar gray matter density measurement techniques, and a powerful longitudinal design that tracked individuals prospectively for 8–10 years, Gogtay et al. provided further evidence that the lower-order somatosensory and visual areas develop earlier than the higher-order association cortices that integrate these processes and also that phylogenetically older areas develop earlier than younger areas (Gogtay et al., 2004). Surprisingly, however, gray matter density increases were actually observed in bilateral perisylvian regions

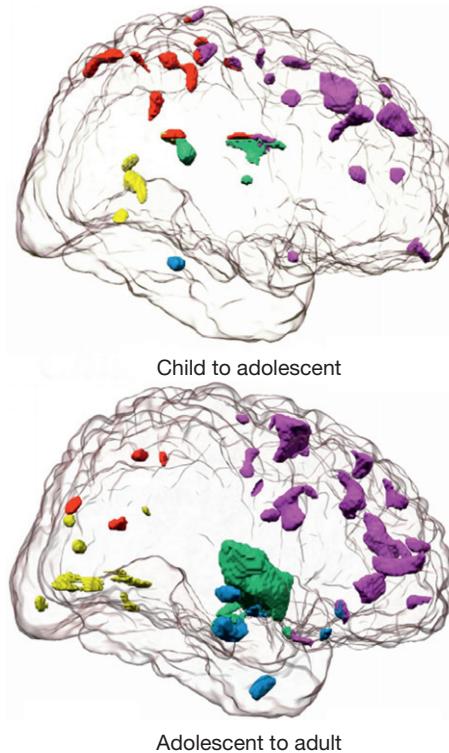


FIGURE 12.1 Gray matter density maturation. Voxel-based morphometry (VBM) measurements of fractional gray matter density/concentration show typical decreases during development. Colored volumes within a transparent cortical surface rendering represent the extent of significant decreases in gray matter density during the transition from childhood to adolescence (top panel) and adolescence to adulthood (bottom panel). Color-coding indicates which changes occurred in the frontal lobe (purple), parietal lobe (red), occipital lobe (yellow), temporal lobe (blue), and subcortical regions (green). Sowell ER, Thompson PM, Holmes CJ, Batt R, Jernigan TL, and Toga AW (1999a) Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. *Neuroimage* 9: 587–597; Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, and Toga AW (1999b) *in vivo* evidence for post-adolescent brain maturation in frontal and striatal regions. *Nature Neuroscience* 2: 859–861.

during the transition from adolescence to adulthood and shown to correlate with both lateralized differences in sylvian fissure morphology and concomitant local brain growth (Sowell et al., 2001b, 2002a). This suggests the presence of a particularly extended developmental trajectory in these gray matter regions beyond that in the dorsal frontal lobe and perhaps implies a unique position for these canonical language areas in the developmental landscape – with the typical inverse correlation between density and volume (decreasing density, increasing volume) reversed to give a direct relationship (increasing density, decreasing volume) in these areas during this age range (Sowell et al., 2003). Taken together, these findings again highlight both regional as well as temporal complexities to the normal developmental sequence of brain structure.

12.4.3 Cortical Thickness

The investigation of apparent cortical gray matter decreases during development reached full stride with the development of MRI cortical thickness measurement techniques. These automated algorithms extract mesh models of the white-matter/gray-matter boundary surface and the pial (i.e., cortical) surface and then directly calculate the cortical thickness at many points throughout the cortical sheet (see Figure 12.2; Fischl and Dale, 2000). Unlike the rather abstract interpretation of fractional gray matter ‘density’ estimates, cortical thickness estimates are in physical units of millimeters and validate exceptionally well against the historical postmortem cortical thickness maps – with average measurements in children ranging from 1.5 mm in occipital cortex to 5.5 mm in dorsomedial frontal cortex (see Figure 12.2; Sowell et al., 2004a; Von Economo, 1929).

In addition to their strong agreement with postmortem data in terms of absolute thickness estimates, reports using this method are also in line with the mounting evidence from postmortem, volumetric, and VBM density measurements, which support the picture that gray matter thickness peaks early and then declines due to a combination of progressive events, like enhanced myelin penetration into the cortical neuropil, and regressive events, like continued synaptic pruning (O'Donnell et al., 2005; Shaw et al., 2008; Sowell et al., 2004a; Tamnes et al., 2010). In a longitudinal study of

45 typically developing children aged 5–11 years, who were scanned 2 years apart, these techniques were able to demonstrate gray matter thinning of $\sim 0.15\text{--}0.30\text{ mm year}^{-1}$ coupled to relative brain volume increases in right frontal and bilateral parietooccipital regions (see Figure 12.3). This study was also able to reproduce the surprising earlier findings of gray matter increases in bilateral perisylvian language areas (Wernike's area) and extended these observations to the left inferior frontal gyrus – another language area (Broca's area) (Sowell et al., 2004a). Cortical thickening was estimated to be at a rate of $0.10\text{--}0.15\text{ mm year}^{-1}$ in these areas. This unique pattern of cortical thickening in the canonical language regions could be related to parallel gains in language processing made during this period of development. In another large longitudinal study of 375 children and young adults, changes in cortical thickness were modeled with a low-order polynomial basis set in order to investigate regional differences in the complexity of the developmental trajectory (Shaw et al., 2008). Patterns of varying complexity were found to parallel the established histological maps of cytoarchitectonic complexity and agree with the previous literature (Gogtay et al., 2004; Sowell et al., 2004a) – with simpler laminar areas, like the limbic cortex, having simpler trajectories and more complex laminar areas, like association cortex, having more complex trajectories. Although cortical thinning during adolescence reflects developmental processes like myelination and synaptic

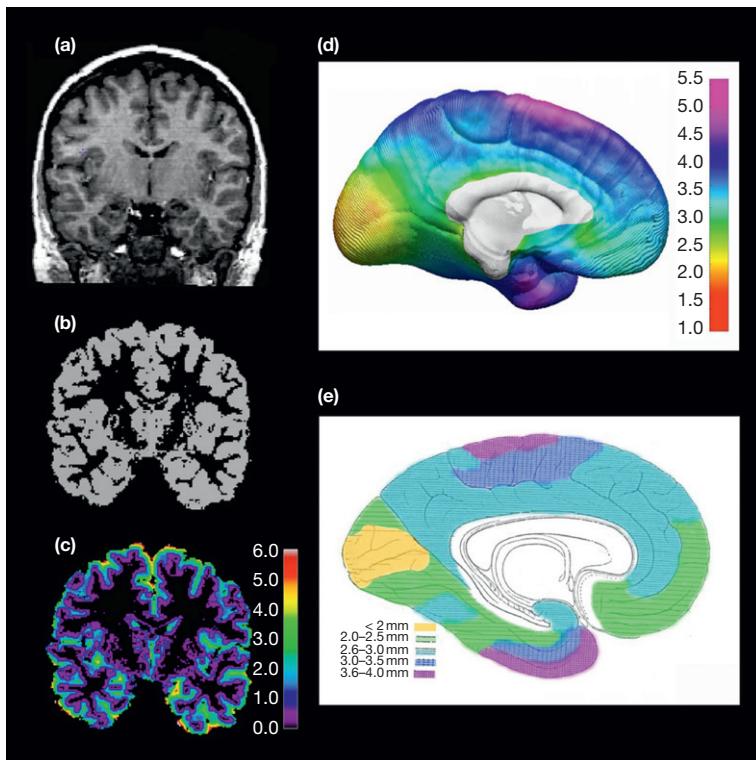


FIGURE 12.2 Cortical thickness analysis. (a–c) show a single representative slice for one subject: (a) Raw T1-weighted anatomical MRI scan. (b) Gray/white matter tissue segmentation. (c) Gray matter thickness image, with thickness (mm) coded by color (warmer colors overlie the areas with the thickest cortex). (d) shows an *in vivo* average cortical thickness map generated by performing this analysis on a cross-sectional sample of 45 subjects. The brain surface rendering is color-coded according to the underlying cortical thickness (mm) and the color bar on the right. The regional variations in cortical thickness can be compared to an adapted version of the classical Von Economo postmortem cortical thickness map (e), which has been color-coded in a similar manner over the original stippling pattern to highlight the similarity between the two maps. Sowell ER, Thompson PM, Leonard CM, Welcome SE, Kan E, and Toga AW (2004a) Longitudinal mapping of cortical thickness and brain growth in normal children. *Journal of Neuroscience* 24: 8223–8231; Von Economo CV (1929) The Cytoarchitectonics of the Human Cerebral Cortex. London: Oxford Medical Publications.

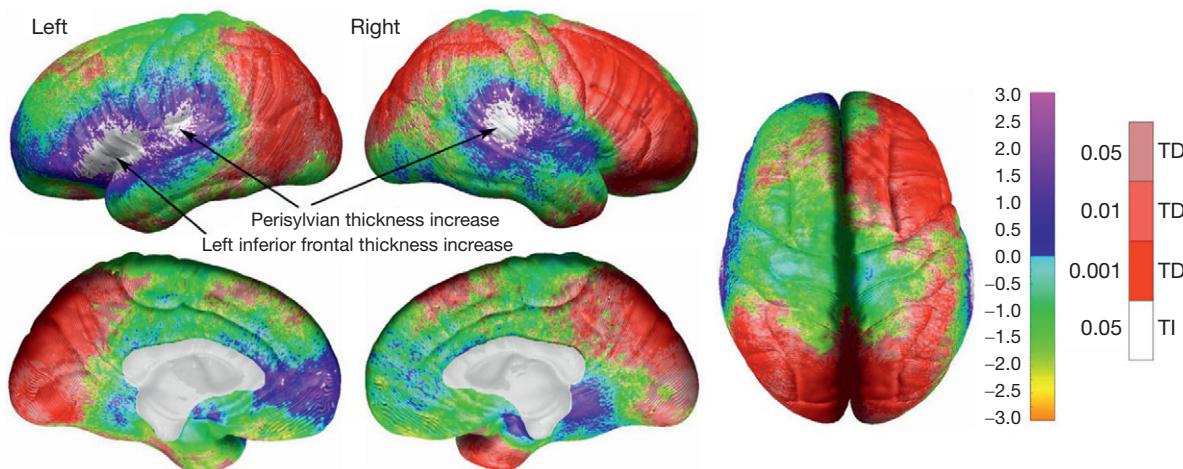


FIGURE 12.3 Gray matter thickness maturation. Statistical maps showing the significance of cortical thickness change in a longitudinal sample of 45 children scanned twice between the ages of 5 and 11. Areas showing significant thickness decrease (TD) are displayed in red, and areas showing significant thickness increase (TI) are displayed in white (see color bar and significance thresholds at right). Nonsignificant areas are coded by their t-statistic according to the left rainbow color bar. Arrows highlight the relative specificity of thickness increases during this age range to canonical language areas in the left inferior frontal gyrus (Broca's area) and perisylvian region (Wernike's area). *Sowell ER, Thompson PM, Leonard CM, Welcome SE, Kan E, and Toga AW (2004a) Longitudinal mapping of cortical thickness and brain growth in normal children. Journal of Neuroscience 24: 8223–8231.*

pruning, it is important to note that cortical thinning also continues in some form throughout the rest of the life-span (Sowell et al., 2003). This likely belies a shift in etiology to degenerative changes associated with aging (Sowell et al., 2004b), and recent work has sought to delineate this inflection point more precisely. By analyzing local gray and white matter signal intensities in the context of cortical thinning, the timing of the developmental peak was found to range from 8 to 30 years of age in different regions of the cortex, with the regional pattern following the general posterior-to-anterior gradient discussed in Section 12.3.2 (Westlye et al., 2010).

12.4.4 White Matter

Even before the widespread adoption of diffusion imaging, which will be discussed in Section 12.5, researchers were able to adapt traditional anatomical MRI analysis techniques to study white matter development (Wozniak and Lim, 2006). Magnetization transfer ratio imaging is sensitive to the 'bound' protons found on the phospholipids of myelin (Wolff and Balaban, 1989) and reflects the increasing myelination during early development (Engelbrecht et al., 1998) as well as the posterior-to-anterior trend in the timing of this process (Buchem et al., 2001). T2 relaxometry, which estimates the fraction of water in the brain, that is associated with the phospholipid bilayer of myelin (MacKay et al., 1994), has also been used to demonstrate the caudal-to-rostral wave of myelination (Lancaster et al., 2003). In an application of the VBM technology to the white matter, Paus and colleagues were able to powerfully interrogate the rather general 'global white

matter increases' observation previously described to obtain a much richer localization of the precise anatomical regions involved. In an 88-subject sample of children aged 4–17 years, they observed a prominent increase in white matter density in the internal capsule bilaterally, as well as the in left arcuate fasciculus, suggesting continued maturation of corticospinal and frontotemporal fibers through this age range (Paus et al., 1999). This work agrees with the postmortem data from Yakovlev and Lecours and demonstrates the unique progressive changes that occur in the white matter while the cortex shifts to undergo predominantly regressive events. Confirming the surprising corpus callosum results of the classical volumetric study by Giedd et al., which was discussed in Section 12.3.3, Thompson and colleagues applied a continuum mechanics approach to obtain maps of local tissue deformation in the corpus callosum during development. Their longitudinal design studied 6 children aged 3–11 with a follow-up interval of up to 4 years and again demonstrated an anterior-to-posterior wave in the timing of maximal local growth (see Figure 12.4; Thompson et al., 2000). This contrasts with the general posterior-to-anterior trend that has been observed in gray matter cortical regions and suggests a unique pattern of development in this region of interhemispheric fiber connectivity.

12.4.5 Sex Differences

Continuing the trend from volumetric results, VBM gray matter density and cortical thickness observations of sex-specific effects during development have also been variable (Wilke et al., 2007). However, this topic

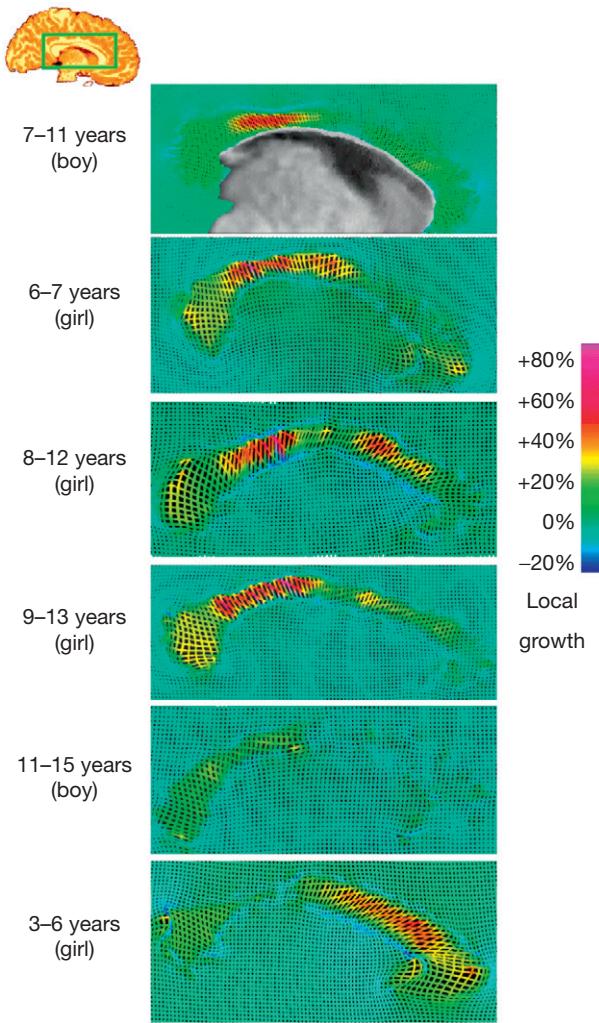


FIGURE 12.4 Corpus callosum maturation. Maps of the local volume changes in the corpus callosum are shown for six individuals aged 3–15 years, who were scanned twice longitudinally with an interval of up to 4 years. Maturation includes outward tissue expansion (warmer colors), with a dynamic wave in timing such that more frontal regions show prominent change early, and more posterior regions show prominent change later. Thompson PM, Giedd JN, Woods RP, MacDonald D, Evans AC, and Toga AW (2000) Growth patterns in the developing brain detected by using continuum mechanical tensor maps. *Nature* 404: 190–193.

remains a critical issue, as sex-specific differences in brain development are likely to contribute to the sexually dimorphic susceptibilities of a variety of psychiatric disorders – like schizophrenia and major depression – that emerge during adolescence (Durston et al., 2001; Lenroot and Giedd, 2010). Returning to the issue of gender differences in development, Sowell et al. analyzed cortical thickness and local brain size (taken as the distance from the center of the brain) in a large sample of 176 healthy subjects aged 7–87 years (Sowell et al., 2007). In line with previous studies, male brains were larger than females, at all locations. Strikingly, however, absolute cortical thickness was greater in females in right inferior parietal and posterior temporal regions even without accounting for the smaller overall size of female

brains. This finding was not significantly modulated by age and was demonstrated even more robustly across broad right temporal and parietal regions when an age-matched and brain-volume-matched subset of 18 males and 18 females was evaluated (see Figure 12.5). These findings suggest that there are both regional- and sex-specific differences in cortical thickness that appear relatively early in childhood, and support earlier reports of selective relative increases in gray matter volumes in females (Allen et al., 2003; Goldstein et al., 2001; Gur et al., 2002; Im et al., 2006; Nopoulos et al., 2000; Sowell et al., 2002b). Although the corpus callosum is also a frequent target for brain mapping research into sex-specific effects on brain development, no consensus has been reached and the topic remains frequently debated (Giedd et al., 2006) (see Chapters 35 and 38).

Because of the overall smaller brain volume in females, it has also been proposed that there may be evolutionary pressure to develop other compensatory mechanisms. Through sulcal delineation and cortical-pattern-matching techniques, it has been shown that females tend to develop a greater degree of cortical ‘complexity’ by young adulthood (Luders et al., 2004). This suggests that there is more cortical surface per unit volume in females and may be one mechanism through which female brains have become optimized for their smaller size.

An increasing focus is also being shifted away from sex-specific differences, *per se*, to the known differences in pubertal timing and sex steroid levels that are likely to be major contributors to observed sex-specific effects and their frequently observed modulation by age (Giedd et al., 2006; Lenroot et al., 2007). The emerging picture suggests that puberty and sex steroids do indeed have organizing effects on brain development (Bramen et al., 2011; Neufang et al., 2009; Peper et al., 2009a; Witte et al., 2010). One recent study of 107, 9-year-old monozygotic and dizygotic twin pairs noted strong overall heritability in regional brain volumes but also demonstrated decreased frontal and parietal gray matter density among the subgroup of individuals who had begun to develop secondary sexual characteristics of puberty (Peper et al., 2009b). Further investigation among the same cohort revealed that the serum level of luteinizing hormone, one of the first indicators of puberty, is associated with both increased overall white matter volume and increased white matter density in the cingulum, middle temporal gyrus, and splenium of the corpus callosum (Peper et al., 2008). The splenium observation is particularly intriguing, as this is the same region shown to have maximal growth over the 9–13 age range in a different study (Thompson et al., 2000). These results – observed between otherwise very well-matched groups – suggest that the onset of puberty and sex steroid levels may directly contribute to the decreases in gray matter and increases in white matter that are prominent features of normal brain development during late childhood and adolescence.

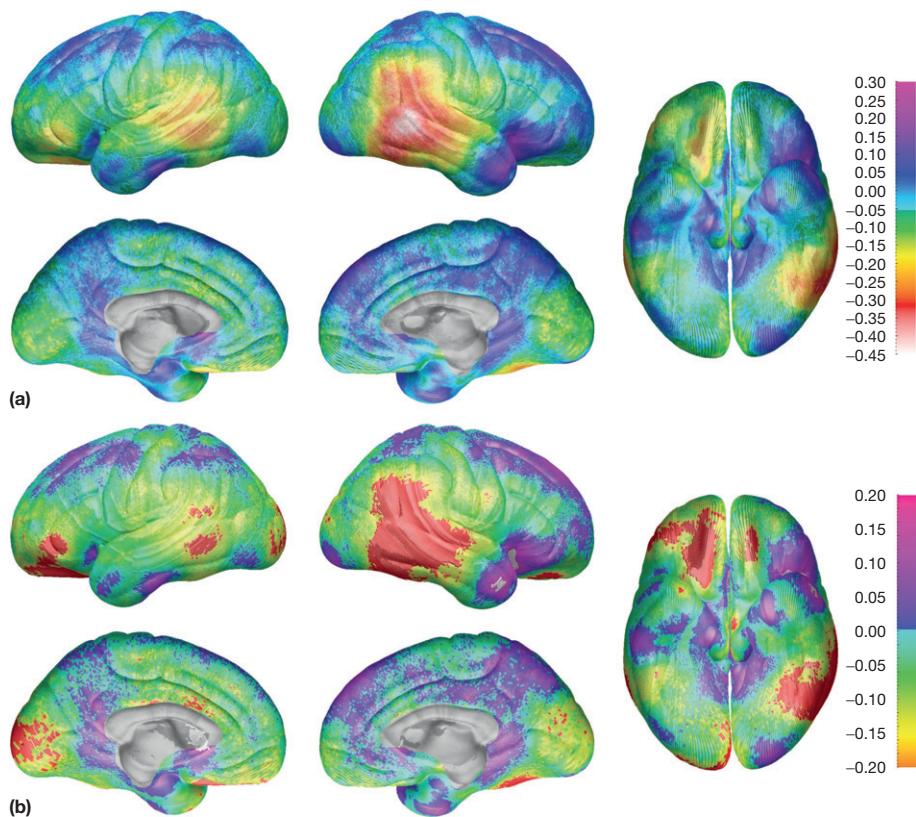


FIGURE 12.5 Sex-specific differences in cortical thickness. (a) Sex differences in cortical thickness (mm) among an age- and brain volume-matched sample of 18 males and 18 females. Warmer colors (<0 on the color bar at right) are regions where females have thicker cortex, and cooler colors (>0 on the color bar at right) are regions where females have thinner cortex, relative to males. (b) Statistical maps showing the significance of these sex differences. Areas where the cortex is significantly thicker in females are shown in red, and include right inferior parietal and posterior temporal, and left posterior temporal and ventral frontal regions. Areas where the cortex is significantly thinner in females are shown in white, and are limited to small regions in the right temporal pole and orbitofrontal cortex. The correlation coefficient is mapped for nonsignificant regions according to the color bar at right. Sowell ER, Peterson BS, Kan E, et al. (2007) Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. *Cerebral Cortex* 17: 1550–1560.

12.4.6 Summary

Taken together, these structural imaging studies represent a powerful evolution in our understanding of brain development during childhood and adolescence. The overall picture remains one of early overall brain growth, followed by a transition around age 5 to gray matter decreases coupled with persistent white matter increases. These processes continue through adolescence but relatively balance each other in magnitude. Thus, while overall net brain volume changes relatively little past the age of 5, adolescence remains a period of dynamic change beneath the pial surface.

12.5 DIFFUSION MRI

One of the remarkable discoveries to emerge from these developmental neuroimaging studies is the continued expansion of white matter volume well into adulthood (Giedd et al., 1999a; Sowell et al., 2003). This robust and protracted increase has rewritten the age

range associated with brain development (Pujol et al., 1993) and has driven an increasing focus on the white matter and its network connectivity as a possible mediator for the late cognitive gains seen in executive function domains during typical development (Liston et al., 2006), as well as a possible mechanism for neuropathology (Le Bihan, 2003) and training-induced increases in performance (Bengtsson et al., 2005; Carreiras et al., 2009).

12.5.1 Diffusion Tensor Imaging Theory

Simultaneously with this growing interest in studying the white matter, as it relates to connectivity between still-maturing brain regions and cognitive function, diffusion imaging was maturing as an MRI variation specifically tuned to examine the white matter (Basser et al., 1994; Bihan et al., 1986; Pierpaoli et al., 1996). Since the diffusion properties of water within neural tissue are affected by the geometry of the neuronal microenvironment, it is intuitive that diffusion imaging can provide a sensitive lens through which the microstructural properties of the white matter can be investigated. Specifically,

differences in microstructural properties like fiber coherence, axon packing, and myelination have all been shown to manifest as changes in the diffusion MRI signal (Beaulieu, 2002). By viewing this diffusion landscape within the brain from multiple angles, a more complete ‘tensor’ model of diffusion can be generated for each voxel (Basser et al., 1994). This can be thought of geometrically as a diffusion ellipsoid, with diffusion components in the radial (RD, radial diffusivity) and axial (AD, axial diffusivity) directions (see Figure 12.6). The size of this ellipsoid corresponds to the overall mean diffusivity (MD). The shape of the ellipsoid corresponds to the directionality of diffusion and is termed fractional anisotropy (FA). It can vary from 0, for perfectly isotropic diffusion, to 1, for perfectly anisotropic diffusion (e.g., the ventricles have low FA, while the corpus callosum has high FA). Because it has been shown to be sensitive to myelination, this FA metric has received considerable attention as a way to track the developmental maturation within the white matter and investigate disease. See Le Bihan (2003) for an excellent review.

12.5.2 Diffusion Parameters in Development

Using this unique framework, there has been a surge in research aimed at more deeply characterizing the normal developmental processes in these important regions

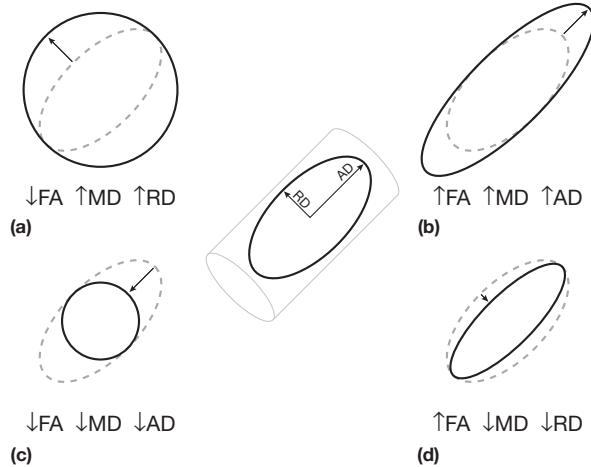


FIGURE 12.6 Diffusion tensor imaging (DTI) metrics. DTI metrics include fractional anisotropy (FA), which is a unitless measure of the directionality of diffusion, and mean diffusivity (MD), which is the overall magnitude of diffusion. The center panel shows a cross-section of the DTI ellipsoid model of diffusion, which is assumed to be oriented along the fiber axis (shown here as a cylinder). Individual diffusion components along the axial (AD) and radial (RD) directions contribute to the FA and MD values at each point in the brain. (a-d) show different changes in the individual diffusion parameters, and their varying effects on FA and MD. Note that changes in different diffusion components (AD or RD) can lead to the same effect on one diffusion metric, but have opposite effects on the other. (d) represents the prevailing regime during development, where decreasing RD – due, in part, to advancing myelination – leads to increasing FA (a more pointed ellipsoid) and decreasing MD (a smaller ellipsoid).

of connectivity that were previously obscured by low contrast within the white matter on traditional T1-weighted anatomical MRI. Similar to the general description in the overlying gray matter, the developmental trajectory within the white matter is both a nonlinear function of time and has prominent regional variations (Lebel et al., 2008b; Mukherjee et al., 2001; Snook et al., 2005). From birth, there is a rapid rise in diffusion directionality (FA; see Figure 12.7), coupled with a decrease in overall diffusivity (MD) (Bava et al., 2010; Engelbrecht et al., 2002; Hüppi et al., 1998; Löbel et al., 2009; Morris et al., 1999; Mukherjee et al., 2001; Neil et al., 1998; Schmithorst and Yuan, 2010; Schneider et al., 2004). In an interesting contrast to this general pattern within the white matter, gray matter cortical regions actually have been observed to have decreasing FA in a sample of preterm infants (McKinstry et al., 2002). This could reflect the fact that changes in FA are not highly specific for myelination and may also occur in response to cortical maturational processes, like synaptogenesis. Further, these observations may be related to the perinatal period of selective vulnerability in neural tissue, which has been demonstrated in animal studies and confirmed in humans through MRI (Miller and Ferriero, 2009). The white matter pattern of increasing FA and decreasing overall diffusion, although not universally reported in later development (Schneiderman et al., 2007), generally continues in a decelerating fashion throughout childhood, adolescence, and, in some areas, into adulthood (Bonekamp et al., 2007; Klingberg et al., 1999; Schmithorst et al., 2002; Zhang et al., 2007). There is a relatively stable plateau of these parameters during adulthood, which then eventually declines later in life (Davis et al., 2009; Salat et al., 2005). Accordingly, the developmental rising portion of this arc has been modeled as a linear (Snook et al., 2005), polynomial (Hsu et al., 2010), or exponential (Lebel et al., 2008b; Mukherjee et al., 2001; Schneider et al., 2004) function. The earliest reports utilized an ROI approach to look at diffusion properties averaged across specific anatomical locations and were able to reproduce the ‘increasing FA, decreasing MD’ pattern across a broad variety of regions within the brain and during different periods of development. In one example, Suzuki and colleagues examined ROIs placed bilaterally in the frontal and parietal white matter of 16 children and young adults. They observed increased FA and decreased overall diffusivity with age but went on to make the important determination that the etiology of these changes in FA and MD was a primary decrease in both radial (RD) and AD diffusion components, with a larger decrease along the radial direction (Suzuki et al., 2003). This explains the overall decreased diffusivity that was observed (both components decreased) but also the increased diffusion directionality (one component decreased more than the other). The dominance of changes in radial diffusivity (RD) during development is an important phenomenon that has been broadly replicated (Giorgio

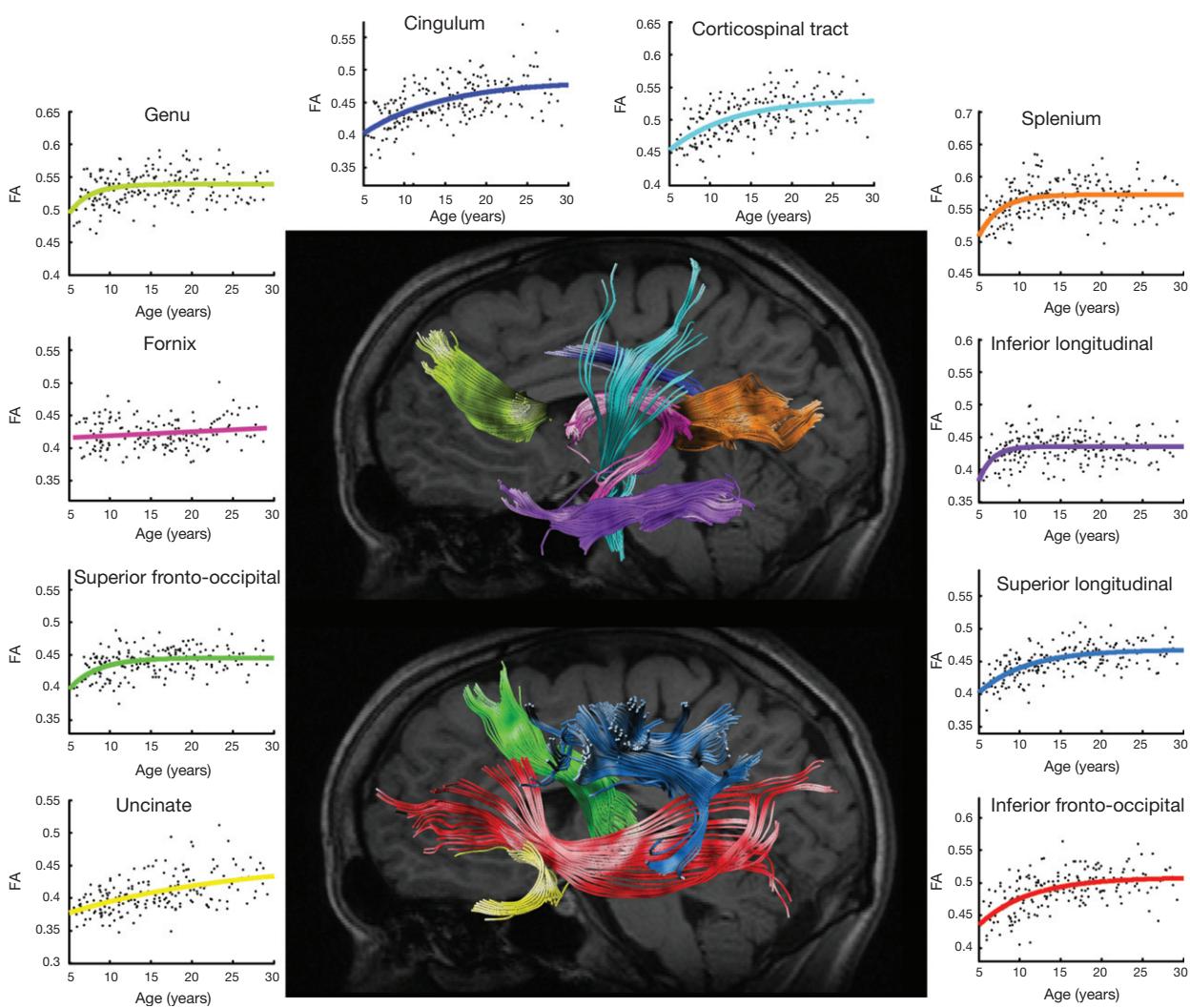


FIGURE 12.7 White matter maturation. Diffusion tensor imaging (DTI) tractography was used to identify ten major white matter tracts in 202 individuals aged 5–30 years (center panels show the extracted tracts for a representative subject). Broad age-related increases in fractional anisotropy (FA), a DTI index of white matter maturation that is sensitive to myelination, were observed across all tracts. Maturational trajectories generally followed an exponential rise, with regional variations in mean FA as well as developmental timing. The surrounding scatterplots demonstrate these relationships, and are color-coded according to the tracts in the center panels. Lebel C, Walker L, Leemans A, Phillips L, and Beaulieu C (2008b) Microstructural maturation of the human brain from childhood to adulthood. *Neuroimage* 40: 1044–1055.

et al., 2008; Lebel et al., 2008b; Löbel et al., 2009; Qiu et al., 2008), although not universally (Ashtari et al., 2007; Giorgio et al., 2010), and is thought to relate to the primary role that extended myelination plays during this age range (Song et al., 2002).

Paralleling the advancements made in the analysis of the cortex, methods have quickly adapted to include whole-brain mapping techniques that are able to examine the brain in a spatially continuous manner and better localize developmental changes. In general, these later efforts using VBM and similar techniques have both confirmed and extended the earlier ROI findings of broadly increasing FA and decreasing MD (Snook et al., 2007). Tract-based spatial statistics (TBSS) is an evolution of these methods that is tailored specifically to the analysis

of diffusion tensor imaging (DTI) data and has been used successfully to demonstrate age-related changes in diffusion imaging parameters (Bava et al., 2010; Burzynska et al., 2010; Giorgio et al., 2008, 2010). By projecting the imaging data onto a tract ‘skeleton’ consisting of the cores of the white matter tracts, TBSS avoids some of the alignment problems that arise when the high-contrast FA maps are compared using traditional voxel-by-voxel techniques (Smith et al., 2006, 2007). In a sample of 75 children through young adults that were analyzed using this approach, widespread FA increases and diffusivity decreases were again demonstrated spanning the frontal, temporal, and parietal lobes and the cerebellum (Qiu et al., 2008). Recognizing the need to synthesize these reports into a

normative reference standard against which to judge clinical abnormalities, effort has also been directed towards generating developmental brain atlases that integrate this diverse set of information (Hermoye et al., 2006; Löbel et al., 2009; Mori et al., 2008; Verhoeven et al., 2010).

12.5.3 Fiber Tractography

By making the assumption that the direction of the diffusion ellipsoid (i.e., the direction of principal diffusion) is pointing in the same direction as the neuronal fiber axis, streamlines can be generated passing from voxel to voxel along the path of principal diffusion. In this manner, the DTI technology has been extended to allow for *in vivo* fiber tractography (Behrens et al., 2003; Catani et al., 2002; Conturo et al., 1999; Mori et al., 1999). This allows for individualized measurements to be made that are tailored to each subject's anatomy, which circumvents many of the problems associated with attempting to register a diverse set of brains to a single template. Although these algorithms have generally validated well against postmortem dissections for many major white matter tracts, specific limitations related to issues, like partial volume averaging and complex fiber geometries, must be considered (Pierpaoli et al., 1996). Using this technology, together with standardized protocols for delineating the major white matter tracts of interest (Wakana et al., 2007), researchers have mapped the development of white matter fiber connectivity from before birth (Huang, 2010; Huang et al., 2006, 2009), through childhood, adolescence, and adulthood (Behrens et al., 2003; Liu et al., 2010; Wakana et al., 2004) and even through evolution (Rilling et al., 2008). Like other developmental neuroimaging efforts, these data provide important insight into human brain development in their own right and, additionally, serve as important normative markers against which pathology can be judged (Adams et al., 2010; Lebel et al., 2008a; Thomas et al., 2009). In a seminal report on the typical developmental trajectories within 10 major white matter tracts in a large sample of 202 subjects aged 5–30 years, Lebel et al. observed continually increasing FA in all regions (generally approximated well by an exponential function), but regional variations in timing such that the time to reach 90% of the adult plateau varied from approximately 7 years old in the inferior longitudinal fasciculus to beyond 25 years old in the cingulum and uncinate fasciculus (see Figure 12.7; Lebel et al., 2008b). Overall, they note that frontotemporal connections were the slowest to develop. In a representative example of the degree of intersubject diversity that exists even within tracts, DTI tractography has been used to

demonstrate lateralization of different white matter tracts (Bonekamp et al., 2007). In one particular study, left lateralization was shown for the arcuate fasciculus (temporoparietal part of the superior longitudinal fasciculus), with higher FA and more streamlines in the left hemisphere (Lebel and Beaulieu, 2009). These findings are in line with previous observations of left lateralization of perisylvian regions (Geschwind and Levitsky, 1968; Pujol et al., 2002) and are thought to relate to the left hemisphere language dominance that exists in the majority of the population. Interestingly, this same pattern has been demonstrated even in neonates, suggesting that the structural basis of left hemisphere language dominance is present long before the development of speech (Liu et al., 2010). Previous morphometric findings of local volume increases within the corpus callosum (Giedd et al., 1996a; Thompson et al., 2000) have also been explored with tractography. In a large sample of 315 subjects aged 5–59 years, Lebel and others demonstrated the typical trajectory of increasing FA and decreasing MD in the fiber tracts leading from all midsagittal sections of the corpus callosum (Lebel et al., 2010). They also observed an 'outer-to-inner' trend in the timing of these maturational arcs, which contrasts with the anterior-to-posterior volumetric trend observed on T1-weighted MRI (Thompson et al., 2000) and highlights the additional insight that can be uncovered when the full extent of a tract is considered.

12.5.4 Sex Differences

Diffusion imaging also reveals sex-specific structural differences within the white matter (Lenroot and Giedd, 2010; Schmithorst et al., 2008). In one tractography study of 114 children, adolescents, and young adults, Asato et al. found generally decreasing radial diffusivity (RD) and protracted maturation past adolescence, in projection and association fibers that included connections between the prefrontal cortex and the striatum. Furthermore, they observed that white matter microstructural maturation proceeded in parallel with pubertal changes, with females having overall earlier maturation of white matter tracts than males (Asato et al., 2010). This suggests that there may be hormonal influences on white matter maturation and that by considering these aspects, one may obtain a more appropriate estimate of developmental progress than by only considering chronological age. This notion is supported by concurrent findings with structural MRI that demonstrate that white matter volume increases during adolescence, especially in boys, are affected by testosterone levels and androgen receptor genes (Paus et al., 2010; Perrin et al., 2008).

12.5.5 Summary

Taken together, diffusion imaging studies generally show increasing diffusion directionality (FA) and decreasing overall diffusion (MD) during development. These changes are predominantly due to decreasing diffusivity in the radial direction (i.e. radial diffusivity; RD) from the fiber axis, which suggests a primary role for myelination in this process. These changes progress rapidly from birth through childhood and, eventually, level off to a relatively stable adult plateau. Paralleling what has been observed in the cortex and through volumetric observations, there are regional variations in the timing of this developmental trajectory that follow a roughly posterior-to-anterior trend. Sexual dimorphism is also present, with females exhibiting earlier white matter maturation than males – a trend that mimics their differences in pubertal timing.

12.6 CONNECTING DIFFERENT TECHNIQUES

12.6.1 Multimodal Imaging

Although the development of cortical gray matter and the development of white matter microstructure have been investigated independently, one needs to consider their dynamics jointly in order to determine what relationships exist between them. This challenge returns to one of the original questions that stemmed from the postmortem histological findings – that is, ‘To what degree do myelination and synaptic pruning (and other cellular processes) contribute to the decreasing gray matter and increasing white matter that is found during brain development?’ While these phenomena are undoubtedly linked, it remains unclear which is dominant and exactly how they interact. The maturation of DTI and structural MRI analysis techniques has now made it possible to investigate these questions using *in vivo* imaging data; however, in the end, it will likely be necessary to complete the circle and validate these observations back in histological preparations.

In a study focusing on adolescence, Giorgio et al. began by using the TBSS method, discussed in Section 12.5.2, to demonstrate broad increases in FA that were driven predominantly by decreases in radial diffusivity (RD). They then made an important and innovative step by incorporating both DTI tractography and gray matter VBM to show that the putative fibers leading from the white matter regions, with the strongest developmental effects, connect with regions showing significantly decreased gray matter density in the cortex. Further, they observed that the gray matter density decreases were significantly correlated with the FA

increases in the connected white matter (Giorgio et al., 2008). By following the structural connectivity present in the actual data, and using these patterns to guide their comparisons, this protocol links the concurrent phenomena of white matter FA increases and gray matter density decreases more convincingly than was possible with previous qualitative visual inspections. Tamnes et al. investigated this same general question in a different manner by integrating cortical thickness, volumetric, and DTI measurements derived from a single sample of 168 participants, aged 8–30 years (see Figure 12.8; Tamnes et al., 2010). As expected, they were able to demonstrate a combination of the phenomena seen in earlier individual studies, including broad cortical thickness decreases, white matter volume increases, FA increases (predominantly decreases in radial diffusion), and MD decreases. Most importantly, however, they were able to go on to demonstrate that, of the three measures, cortical thickness had the strongest relationship with age. Further, although the DTI and volume measures explained some of the variance in cortical thickness and each other, none of the measures were redundant. This implies that each may be sensitive to different microstructural processes and that all are useful indicators of brain development and microstructural integrity (Fjell et al., 2008). This reiterates the likely mixed regime of both synaptic pruning within the cortex and advancing myelination at the gray–white cortical interface, which contributes to the brain morphological changes seen during adolescence.

12.6.2 Brain–Behavior Relationships

While important neuroanatomical insights can be gleaned from these structural brain mapping observations, perhaps the most significant outgrowth of this research has been an expanded understanding of the cognitive and behavioral changes that accompany this underlying maturation of brain structure. There has been a long tradition of investigation into the cognitive correlates of brain structure, but unfortunately many of the early findings – which commonly focused on differences between ethnic or social groups – are unreliable because of data collection and analysis bias (Gould, 1978, 1981). With the advent of MRI, however, volumetric measurements of total brain size have shown a modest but reproducible correlation with general intelligence that emerges over the course of development (Peters et al., 1998; Reiss et al., 1996; Willerman et al., 1991; Witelson et al., 2006). However, the correlational nature of these findings does not at all suggest that groups with different brain sizes, like males and females, will have different intelligence. Indeed, independent of the possible relationships with neuroanatomy, it remains exceptionally controversial whether there is even any overall

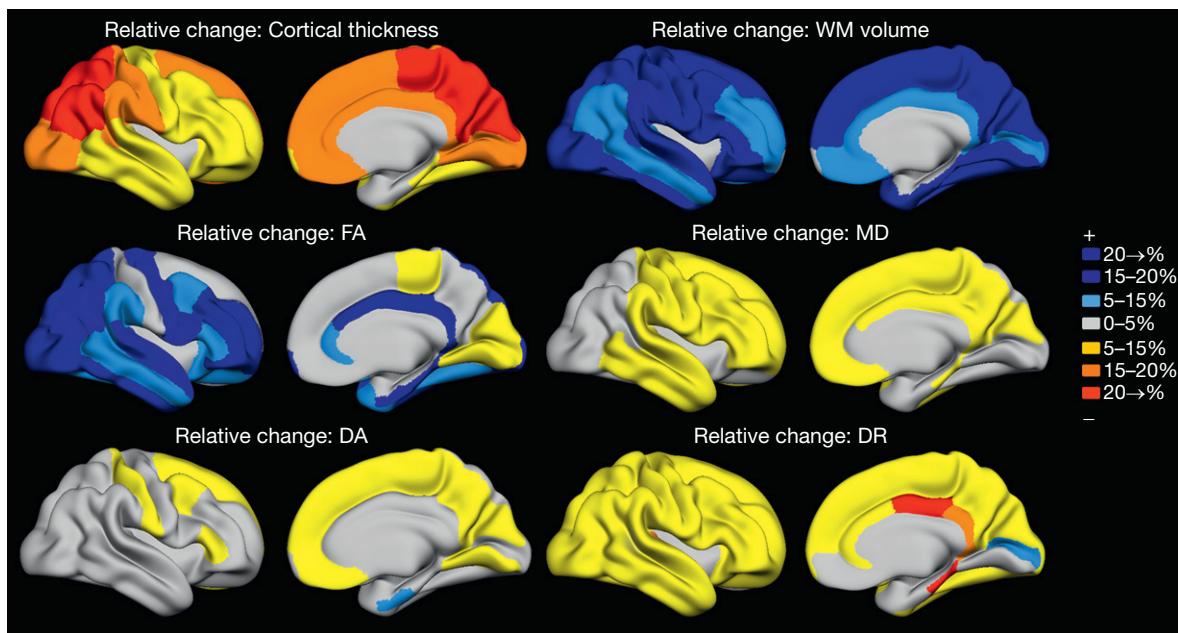


FIGURE 12.8 Multimodal imaging: volumes, cortical thickness, and DTI. Concurrent volumetric, cortical thickness, and diffusion tensor imaging (DTI) analyses were performed in the same sample of 168 participants aged 8–30. The percent changes in cortical thickness, white matter volume, fractional anisotropy (FA), mean diffusivity (MD), axial diffusion component (AD), and radial diffusion component (RD) are mapped by region and color coded according to the color bar on the right. Medial structures and corpus callosum are masked out. Tammes C, Ostby Y, Fjell A, Westlye L, Due-Tønnessen P, and Walhovd K (2010) Brain maturation in adolescence and young adulthood: Regional age-related changes in cortical thickness and white matter volume and microstructure. *Cerebral Cortex* 20: 534–548.

gender effect on intelligence (Blinkhorn, 2005; Hedges and Nowell, 1995; Irving and Lynn, 2006; Jorm et al., 2004; Lynn and Irving, 2004; Neisser et al., 1996) and, if so, whether the small effect magnitudes that have been reported are relevant, given the possible biases that may have contributed. An important additional phenomenon to consider is that both brain structure and intelligence are highly heritable (Shaw, 2007; Thompson et al., 2001). Both are further impacted by environmental influences in a process that begins *in utero*, continues throughout life, and contributes to individual variations in structural brain development and cognitive function that exist even among monozygotic twins. Although not exclusive, the orchestration of structural brain development by these genetic and environmental factors is one way in which they can converge to influence cognitive development (Toga and Thompson, 2005) (see Chapter 26).

Since there is evidence that brain development takes place through selective elimination and connectivity optimization, with prominent regional and temporal variability, it is not surprising that a global measure like total brain volume may not be the optimal choice for investigating the structural basis of cognitive development. Fortunately, the brain mapping strategies, discussed in Sections 12.3–12.5, have had more success examining brain-region-specific relationships between structure and function. This work has supported many

of the classical structure–function relationships discovered through lesion studies – for example, that the prefrontal cortex is related to cognitive control (Damasio et al., 1994) – and also has extended these findings by (1) providing more detail, (2) including more normative subjects without pathology, and (3) allowing for broader investigation in the pediatric population. In this way, these modern neuroanatomical imaging studies, together with complementary results from functional neuroimaging methods that can measure task-dependent blood flow response within the brain (Casey et al., 1995; Luna et al., 2010), have formed a powerful framework to investigate how brain development relates to cognitive function during childhood and adolescence. In this vein, continued investigation into the structural basis of general intelligence has revealed age-variable relationships between intelligence quotient (IQ) and regional brain structure. In line with the total brain volume results, a correlation between IQ and gray matter volume develops by adulthood (Wilke et al., 2003). However, regional relationships between IQ and gray matter structural measures appear earlier and have been reported to include the anterior cingulate during childhood (Wilke et al., 2003), the orbitofrontal cortex during adolescence (Frangou et al., 2004), and the frontal lobe – particularly the prefrontal cortex – by adulthood (Haier et al., 2004; Reiss et al., 1996; Thompson et al., 2001). Interestingly, these regional relationships between

gray matter development and IQ appear to be modulated by sex, although the specific regions reported to be most associated with IQ for each sex have been variable (Haier et al., 2005; Narr et al., 2007). In one important study, which investigated the relationship between cortical thickness maturation and IQ in a large longitudinal sample of 307 children and adolescents, IQ was observed to correlate most closely not with cortical thickness, *per se*, but rather with the shape of the developmental trajectory in cortical thickness change (see Figure 12.9; Shaw et al., 2006). The subjects that had the highest IQs tended to have the most dynamic cortical maturation, with more rapid cortical thickening during early childhood and more rapid cortical thinning during late childhood and adolescence. However, in terms of absolute thickness, the superior intelligence group actually had thinner cortex at the start of the age range studied (approximately age 7), peaked later, and then had relatively equal thickness to the others by the end of the age range (approximately age 19). This observation highlights the notion that, like the pattern of structural maturation itself, the relationships between brain structure and cognitive ability are complicated by their dependency on age during

the course of development. In another example, Choi et al. took a multimodal approach, as described in Section 12.6.1, and investigated correlations between intelligence and both cortical thickness and functional MRI (fMRI) blood flow response during a reasoning task. Because both sets of scans were performed on the same sample of subjects, the authors were able to go a step further than single modal studies and examine if different intelligence subcomponents correlated more with one imaging modality or the other. Their findings quite eloquently demonstrated that the *crystallized* component of intelligence (related to our ability to utilize previously acquired knowledge and past experiences) correlated more strongly with cortical thickness, while the *fluid* component of intelligence (related to our problem-solving and critical-thinking ability in novel situations, independent of past experience) was more strongly related to functional blood flow response (Choi et al., 2008). While the specific pattern and methodologies of these studies have varied widely, the common pattern that has emerged is a relationship between frontal lobe structural brain development and general intellectual ability.

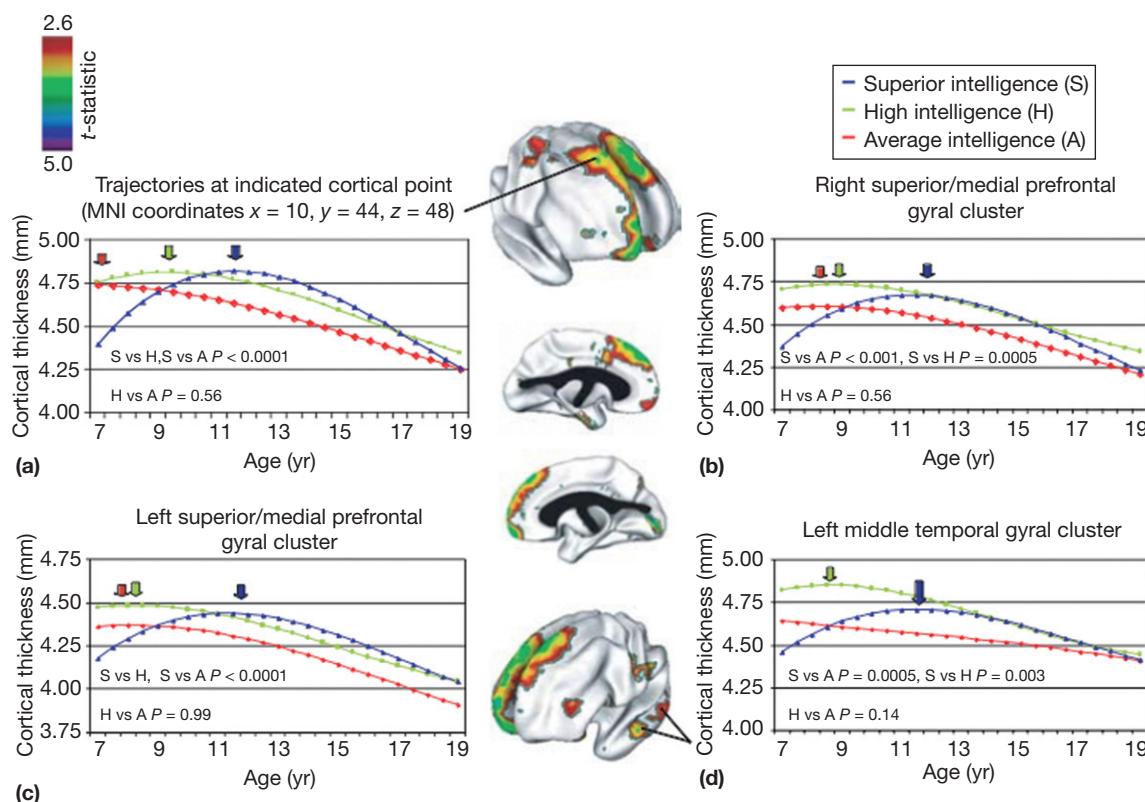


FIGURE 12.9 Trajectory of cortical thickness change versus IQ. Higher IQ was associated with a more dynamic trajectory (more rapid thickening and thinning) in cortical thickness maturation among a sample of 307 children and adolescents scanned longitudinally. The center panel shows regions where there was a significant interaction between IQ group (superior, high, or average) and a cubic age³ term in the regression analysis, which implies a varying trajectory shape in these regions. These individual trajectories are plotted in panels (a–d), and are color-coded according to intelligence group. Arrows indicate the age at peak cortical thickness for each trajectory. Shaw P, Greenstein D, Lerch J, et al. (2006) *Intellectual ability and cortical development in children and adolescents*. Nature 440: 676–679.

Other studies have investigated more specific cognitive functions and their relation to gray matter structure. In the same longitudinal sample of 45 typically developing children, that was described previously, we observed inverse correlations between performance on the vocabulary subtest of the Wechsler Intelligence Scale for Children (Wechsler, 2003) – a test of general verbal intellectual functioning – and gray matter thickness in left dorsolateral frontal and lateral parietal regions (see Figure 12.10; Sowell et al., 2004a). This is consistent with the language dominance of the left hemisphere and suggests a possible relationship between these concurrent structural and cognitive developmental processes. While originally interpreted as possibly relating to developmental cortical thinning, the results of the Shaw et al. (2006) study suggest that the individuals with the greatest verbal intellectual function here may still have been on the upstroke of their developmental arc in our much younger sample (age 5–11 years) and simply had thinner cortex at the time sampled. This nuance is also reflected in another study, which had an older sample (age 6–18 years), during the later period of development where increased cortical thickness is associated with higher IQ (Karama et al., 2009). Further studies, again in the young sample of 5–11-year-olds, have investigated even more targeted cognitive subtests, including phonological processing and motor speed and dexterity (Lu et al., 2007). Structural development in the inferior frontal gyrus (a phylogenetically more complex area that matures slower and is still on the upward stroke of cortical thickening) was expected to relate to advances in phonological processing, which has been shown to involve this area on functional imaging studies (Bookheimer, 2002) but not to relate to advances in motor processing.

Conversely, structural development in the hand motor region (a phylogenetically simpler area that matures earlier and is already experiencing cortical thinning) was expected to relate to advances in motor processing but not phonological processing. This predicted double dissociation was demonstrated as expected, which not only illustrates a specific alignment between language development and structural development in the inferior frontal gyrus but also reiterates the regionally specific definition of ‘structural development’ during childhood – with some cortical regions thinning but some relatively specific language areas still exhibiting thickening. A similar analysis has also revealed relationships between cortical thinning and both delayed verbal recall functioning and visuospatial memory ability, which is again consistent with the functional neuroimaging literature that suggests the dorsolateral prefrontal cortex is involved with memory recall (Casey et al., 1995; Sowell et al., 2001a). The relationship between cognitive development and structural brain development is further supported by intervention/training studies, which suggest even relatively short periods of cognitive or motor training can be associated with, at least, short-term morphological changes in brain structure (Draganski et al., 2004).

Diffusion imaging indicators of white matter development also relate to cognitive function. In a sample of 23 children and adolescents, there was a significant direct relationship between diffusion characteristics (FA) and working memory ability in inferior frontal and temporooccipital regions and the genu of the corpus callosum (Nagy et al., 2004). This relationship existed above and beyond the correlation of each individual measure with age, which suggests that the maturation

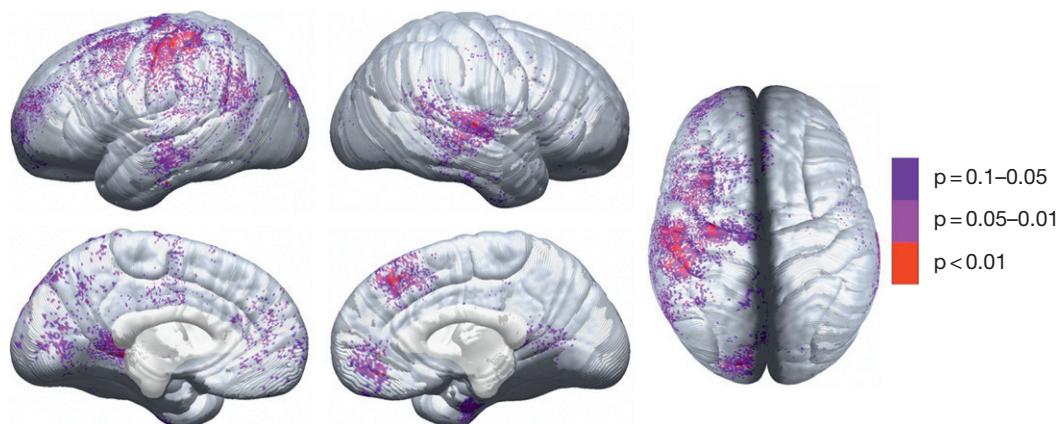


FIGURE 12.10 Cortical thickness versus language functioning. Statistical maps showing the significance of the relationship between changes in cortical thickness and changes in vocabulary scores in a longitudinal sample of 45 children scanned twice between the ages of 5 and 11. Areas with a significant negative relationship (cortical thinning was associated with improved language performance) are color-coded according to their P value, with the significance thresholds shown in the color bar on the right. No positive correlations were observed. Sowell ER, Thompson PM, Leonard CM, Welcome SE, Kan E, and Toga AW (2004a) Longitudinal mapping of cortical thickness and brain growth in normal children. Journal of Neuroscience 24: 8223–8231.

of the white matter in specific areas – as indexed by FA – may play a role in the development of (or simply reflect the development of) specific cognitive domains. In another study related to structure–function specialization within the brain, others have shown correlations between Chinese reading score and FA in the anterior limb of the left internal capsule and English reading score and FA in the corona radiata (Qiu et al., 2008). While a preliminary interpretation, this dissociation could represent that distinct brain networks are more or less involved with language development, depending on the specific language or mode of acquisition. For instance, it is quite reasonable to hypothesize that learning written Chinese, with symbolic characters representing whole words that are generally independent of pronunciation, could drive development (or reflect development) of different brain regions compared to learning written English, which uses an alphabetic system to describe how words sound. As a final example, in the arcuate fasciculus lateralization tractography study discussed in Section 12.5.3, greater leftward lateralization was associated with better performance on cognitive tests of receptive vocabulary and phonological processing (Lebel and Beaulieu, 2009). These studies suggest that diffusion imaging is not only a useful technique for tracking normal anatomical maturation within the white matter, but also that regional DTI metrics can provide reflections of cognitive development in specific domains.

12.7 CONCLUSIONS AND FUTURE DIRECTIONS

Our understanding of human brain development has accelerated over the last 20 years through the use of MRI and *in vivo* human brain mapping. Postmortem and histological studies have demonstrated that brain maturation, on the cellular level, encompasses both progressive and regressive events. These include synaptic pruning and protracted myelination, which continue to shape the underlying neural microstructure and regional brain morphology long after overall brain volume begins to plateau, around age 5. Brain development, in general, can be characterized as both nonlinear with respect to time, and also variable with respect to region. The hallmark of structural brain development during childhood is a striking change in the relative proportions of gray and white matter – with a peak and then decline in gray matter volume and cortical thickness but a relatively sustained increase in white matter beyond adolescence. Across these different regions, there is a general posterior-to-anterior and inferior-to-superior trend in the timing of maturation, such that primary somatosensory and phylogenetically older areas of the brain tend to

mature earlier than higher-order association cortices – particularly areas in the frontal lobe. Within the white matter, diffusion imaging indicators show decreasing diffusivity (MD) and increasing directionality (FA), which suggests that myelination continues through young adulthood and perhaps even beyond. Performance across a variety of cognitive domains has also been shown to relate to these structural changes, with the specificity of these relationships generally in line with classic functional neuroanatomical localizations.

Although the complexity of the regional and temporal patterns of structural brain development makes investigating and interpreting these brain–behavior relationships challenging, future work should continue to focus on the possible functional manifestations of structural brain development. Particularly, by integrating different structural and functional imaging modalities with thorough cognitive assessments, we can investigate the ways in which these processes interact with each other within a more inclusive framework that more realistically encompasses the full developmental landscape. With the increasingly broad array of radiological features of development that have been characterized, there is additionally a growing need to reintegrate a firm neurobiological understanding of the cellular mechanisms that facilitate these changes. Finally, effort should continue to be directed towards uncovering the ways in which this basic neuroscientific knowledge concerning human brain development can be translated into a better context for the understanding and clinical treatment of neurodevelopmental disorders.

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