Published in final edited form as:
Prog Brain Res. 2011 ; 189: 77–92. doi:10.1016/B978-0-444-53884-0.00019-1.

Postnatal brain development: Structural imaging of dynamic neurodevelopmental processes

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Abstract

After birth, there is striking biological and functional development of the brain's fiber tracts as well as remodeling of cortical and subcortical structures. Behavioral development in children involves a complex and dynamic set of genetically guided processes by which neural structures interact constantly with the environment. This is a protracted process, beginning in the third week of gestation and continuing into early adulthood. Reviewed here are studies using structural imaging techniques, with a special focus on diffusion weighted imaging, describing age-related brain maturational changes in children and adolescents, as well as studies that link these changes to behavioral differences. Finally, we discuss evidence for effects on the brain of several factors that may play a role in mediating these brain–behavior associations in children, including genetic variation, behavioral interventions, and hormonal variation associated with puberty. At present longitudinal studies are few, and we do not yet know how variability in individual trajectories of biological development in specific neural systems map onto similar variability in behavioral trajectories.

Keywords

MRI; DTI; brain development; cognitive development; individual differences; fiber tracts

Introduction

Human brain development is a protracted process, beginning in the 3rd week of gestation and continuing into early adulthood (Stiles, 2008). Recent studies using magnetic resonance imaging (MRI) have confirmed that biological development of the brain continues throughout childhood, and these studies provide evidence that different neural structures and systems exhibit different modal trajectories of maturation (Gogtay et al., 2004; Lebel et al., 2008; Westlye et al., 2010). During the school-age years, ongoing maturation in the brain's connecting fiber tracts is particularly striking (Lebel et al., 2008), and MRI measures of the structure in fiber tracts are correlated with behavioral indices that also change with age during this period (Madsen et al., 2010; Schmithorst and Yuan, 2010; Tamnes et al., 2010; Vestergaard et al., 2010).

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Many cross-sectional studies of normative samples have now examined age-differences on brain MRI as well as on cognitive measures. The primary aims of these studies are defining the modal course of brain and behavioral development and delimiting the normal range of brain structural indices and neurocognitive abilities across childhood (Waber et al., 2007). As the data accumulate, they will provide benchmarks for assessing developmental milestones, and may improve detection of pathology. However, due primarily to a lack of longitudinal studies, there is little evidence regarding the degree of interindividual variability in the trajectories of brain development, either with respect to the pace of biological brain development overall or to trajectories within specific neural systems. If the trajectories of brain maturation are substantially variable from one child to the next, and if these relate to the learning capacity of the networks, then it stands to reason that children will respond differently to the information they encounter depending on the phase of brain maturation in their neural systems. Though individual differences in cognitive development have been studied before, few studies have directly examined relationships between individual trajectories of cognitive and neural development. Indeed, advances in neuroimaging technology have only recently made it possible to examine the architecture of the brain in sufficient detail in the individual child to allow these associations to be studied.

The goals of this selective review are to describe the current status of structural imaging research on normal brain development in childhood and adolescence, and to review the evidence that links neural architectural variability in children to behavioral differences. Finally, factors that may play a role in mediating these relationships, such as genetic variation, neuroplastic responses to experience and learning, and hormonal alterations will be discussed, and some key questions to be addressed in future studies will be posed.

Changes in brain morphology during postnatal development

Before the advent of MRI, it was generally felt that biological development of the human brain was essentially complete by 6 years of age. Since MRI is a safe technique for use in children it has since been applied widely in pediatric imaging, and it reveals dramatic changes in the tissues of the developing brain during the postnatal brain growth spurt. These MRI signal changes reflect alterations in tissue chemistry that mark the proliferation of oligodendrocytes and deposition of myelin, and they reveal much about the timing and anatomical distribution of these processes (Barkovich, 2000, 2005). The visual appearance of the brain on MR images changes appreciably over the first 2–3 years of life, mirroring an orderly pattern of myelination in white matter regions. However, the changes in brain morphology that continue past this age are subtler, and were first appreciated only after quantitative morphometry techniques were applied in the early 1990s. At that time, we conducted MR morphometry studies comparing brain morphology in children and adults. Surprisingly, these showed that estimates of gray matter volumes, both in the cerebral cortex and in subcortical nuclei, were considerably larger in school-aged children than in young adults (Jernigan and Tallal, 1990; Jernigan et al., 1991). This suggested that tissue alterations related to brain maturation might be much more protracted during childhood than was generally supposed, and that some of these alterations might be regressive; that is, they might involve tissue loss. These findings were confirmed and extended by later studies (see Toga et al., 2006 for a review), but the underlying tissue alterations remain a matter of speculation (Paus et al., 2008).

The notion that the brain of a 6 year old is fully mature appears to have been engendered by two factors: the adult appearance of the brains at autopsy, and the fact that the size of the cranial vault increases very little after this age (Dekaban, 1978). However, MRI suggests that the latter probably reflects the combined effects of waning progressive changes (associated with continuing growth in white matter) and concurrent regressive changes

(perhaps associated with “pruning” of neuronal processes). There is ample histological evidence for ongoing myelination (Yakovlev and Lecours, 1967), and more limited, but persuasive, evidence for reduction of synaptic density in cortex during childhood (Huttenlocher and Dabholkar, 1997), but it remains unclear to what extent these factors, and perhaps others, contribute to the changing morphology observed with MRI. What is clear is that dynamic biological changes in the tissues continue throughout childhood and adolescence. Data shown in Fig. 1, plotting estimated volumes of brain structures across the lifespan, belie the dogma that the brain’s structure remains constant in childhood, and illustrate that during this period changes in brain structure are at least as dramatic as those at the end of life. The scatterplots illustrate results from our studies of a more extended age range, and show volumes of particular brain structures (from Jernigan and Gamst, 2005). Shown are continuous age-related decreases in apparent volume in frontal cortex, thalamus, and nucleus accumbens across the lifespan, and increases in cerebral white matter volume during childhood and early adulthood. All volumes are normalized for cranial volume-which does not change appreciably over this age range.

Recent MR morphometry studies provide more anatomical detail, emphasize the effects of ongoing myelination, and employ mapping methods for visualizing the pattern of age-related change (Giedd et al., 1996a,b; Ostby et al., 2009; Pfefferbaum et al., 1994; Shaw et al., 2008; Sowell et al., 1999a,b, 2002). By the end of the 1990s, morphometry studies of developing children had demonstrated a protracted course of postnatal white matter growth. It had also been established that the volume of tissue with the MR signal characteristics of “gray matter” declined concurrently in locations throughout the brain, for example, in cerebral cortex and deep nuclei. The most detailed studies, employing both high-resolution mapping techniques and longitudinal assessments (Gogtay et al., 2004; Sowell et al., 2004) began to reveal a modal pattern of childhood and adolescent changes in the cerebral cortex that included not only widespread, regionally specific, apparent cortical thinning, but more limited areas of cortical thickening as well. On average, cortical thinning appears to occur first in primary sensory-motor cortex and then to progress into secondary, and then multimodal cortical areas throughout childhood and adolescence.

An important issue germane to the interpretation of these effects is their relationship to myelination. At the most basic level, cortical “thinning” could simply reflect increased myelination in the white matter tracts coursing near the deepest layer of cortex. In other words the “gray” signal of the unmyelinated fibers could simply be becoming more “white” as myelin is deposited there. This is clearly a part of what is measured as cortical thinning with morphometry, especially in younger children. However, there is evidence that truly regressive changes also occur in some structures-probably due to loss or simplification of neuronal processes (dendrites and/ or axons). This can be inferred from the fact that the progressive changes that would be expected to result from continuing oligodendrocyte growth do not seem to increase cranial volume in late childhood (as though they were opposed by some regressive factor); and from the fact that there are modest but significant CSF volume increases adjacent to the cortical surface and in the ventricular system over this age range, as might be expected if neural elements in the adjacent tissues were lost (Jernigan et al., 1991; Sowell et al., 2002). Note that enlargement in CSF spaces usually occurs, ex vacuo, in the wake of brain tissue loss.

Using mapping methods, Sowell et al. (2004) reported similarities in the patterns of brain growth and cortical density reductions and interpreted this as evidence that local cortical thinning might bear a direct relationship to myelination of nearby fiber tracts; but the nature of this relationship remains unclear. It is possible that functional changes resulting from maturation of fiber tracts stimulate cortical thinning (or thickening), or, conversely, that increasing activity due to intrinsic cortical maturation stimulates myelination of the axons in

the maturing network. Studies of animal tissues in culture have identified neuron-glia signaling mechanisms that mediate effects of action potentials on oligodendrocyte differentiation and myelination (see Fields and Burnstock, 2006 for review). However, the control of these factors in developing brain tissues is still poorly understood. In summary, MR morphometry studies reveal a complex pattern of development in brain structure during childhood and hint that ongoing maturation of fiber tracts probably plays a key role. Only recently, however, has it become possible to examine the maturation of fiber tracts in more detail, using diffusion imaging methods (Basser et al., 1994; Mori and van Zijl, 1995).

Diffusion-weighted imaging of postnatal brain development

Diffusion MRI measures the diffusion of water molecules through the tissue. A common use of diffusion imaging involves fitting, for each voxel, a tensor that estimates proton diffusion (movement) along three principal axes (see Fig. 2 in DTI insert). This method is referred to as diffusion tensor imaging (DTI), and provides useful measures of magnitude (diffusivity) and directionality of diffusion. In voxels containing cerebrospinal fluid, water can diffuse freely and randomly, yielding high diffusivity values and little net directionality, that is, diffusion is isotropic (Fig. 2a). In gray matter, the mean diffusivity (MD) is lower, but also relatively isotropic. However, in white matter voxels containing organized fiber bundles, diffusion is hindered by the axonal membranes (and surrounding myelin sheaths), and to a greater degree in the direction perpendicular to the fibers than parallel to them, causing diffusion anisotropy (Beaulieu, 2009). The degree of diffusion anisotropy (i.e., the degree of net directionality of the diffusion) is typically indexed by the measure fractional anisotropy (FA). The phenomenon is illustrated graphically in Fig. 2. Proton diffusion in cerebral white matter of human newborns is generally high, and exhibits low anisotropy (Hermoye et al., 2006), probably because the relatively unmyelinated fibers have small caliber and there is high water content in the extra-axonal space (Fig. 2c). As the fiber tracts mature, and myelination proceeds, diffusivity declines, and anisotropy increases. By examining the change in detail, that is, by examining the three tensor eigenvalues separately, it has been shown that developmental increase in FA often reflects a decrease in all three diffusivities, which is, however, smaller in the principal eigenvalue (i.e., in diffusion along the long axis of the tracts). The interpretation is that with age the number of unrestricted water molecules in extra-axonal space declines while, simultaneously, diffusion within and/or along the membranes of the axons increases (Suzuki et al., 2003). The denser packing of axons that results from increasing myelination is likely to reduce diffusion by decreasing extra-axonal water. It is less well understood how alterations of axonal morphology or axoplasmic diffusion, for example, due to increasing axonal diameter, may contribute to changing tensor values. Also, FA clearly does not always index myelination; FA is low when the fibers within a voxel are not well aligned (e.g., where fiber tracts cross or exhibit high tortuosity) even if the fibers are well myelinated. Nevertheless, there is growing evidence that alterations reflected in and measurable with DTI continue throughout childhood and adolescence (Barnea-Goraly et al., 2005; Bava et al., 2010; Colby et al., 2011; Schneider et al., 2004; Snook et al., 2005). The anatomical pattern observed for FA increases in white matter suggests that FA reaches asymptote much earlier in some fiber tracts than others. For example, Lebel et al. (2008) observed earliest plateaus in FA in corpus callosum and visual system tracts, and a more protracted increase in FA in several cortical association tracts, especially those within the limbic system, the latter continuing to exhibit age-related FA increases well into adulthood.

Brain morphological correlates of behavioral differences in children

Since the evidence emerged that brain morphology continues to change throughout childhood, several studies have examined its relationship to developing cognitive functions

in young subjects. We conducted an early study of children and adolescents, and reported that memory retrieval abilities, as measured by the child version of the California Verbal Learning Test, were significantly related to estimates of frontal cortex volume even when the children's ages were taken into account; that is, the more closely these volumes resembled the thinner cortex of adults, the better the children's retrieval abilities (Sowell et al., 2001). This suggested to us that even among children of the same age, the maturational process that we were measuring as decreasing cortical volume was more advanced in some than others, and that this was associated with the efficiency of their memory retrieval. In other words, our speculation was that the association was mediated by developmental variability—since if it was mediated by trait (stable) variability in cortical volume, we would not have expected lower cortical volumes to predict better performance.

More recently, Lu et al. (2007) conducted a longitudinal imaging study of children who were on average 7 years old at the outset of the study. They showed that the degree of apparent thinning over a 2-year period in dorsal areas of frontal cortex was associated with improvement in fine motor dexterity; whereas, interestingly, apparent thickening in inferior frontal cortex was associated with improving phonological processing. Lee et al. (2007) recently reported that increased gray matter density in bilateral supramarginal gyri was predictive of larger vocabulary size in adolescents. It is unclear, however, whether this association represents activity-dependent neuroplastic change, a preexisting advantageous neural architecture, or whether it relates to the phase of maturation in this region.

Shaw et al. (2006) examined longitudinal change in cortical thickness in a large cohort of developing children. They compared children who scored high on IQ scores to groups of children with lower scores and found that both large early increases in cortical thickness and large later decreases in cortical thickness were associated with high IQ. This study suggests that developmental change in cortical morphology is relevant to cognitive development, and that behavioral differences in children may bear a stronger relationship to the course of neurodevelopmental change over time than to morphology at the time of assessment.

Diffusion imaging correlates of behavioral differences in children

Changes in apparent thickness of the cortex, and the behavioral correlates of these, may be linked to the ongoing maturation in fiber tracts recently described with DTI. Thus, the recent studies correlating fiber tract microstructure with task performance are of particular interest. An important recent observation linked the latency of the first positive wave (P1) of the visual evoked response to FA in the optic radiations in infants. This association remained significant after controlling for age and was relatively specific to FA variability in the visual pathways (Dubois et al., 2008), which exhibit rapid myelination during this age range. This result is significant because it suggests that increases in FA that occur in parallel with postnatal myelination are also accompanied by increased speed of neural conduction in these pathways.

Several early studies have linked FA values in white matter to performance on reading tasks in school-aged children (Beaulieu et al., 2005; Deutsch et al., 2005; Nagy et al., 2004; Niogi and McCandliss, 2006). Nagy et al. (2004) linked FA in temporal lobes to reading in children and adolescents while at the same time showing that FA in superior fronto-parietal regions was correlated with spatial working memory performance. Beaulieu et al. (2005) also observed an association between reading ability and FA in temporoparietal tracts in school-aged children, and these authors used tractography to locate the implicated region in the posterior limb of the internal capsule. Niogi and McCandliss (2006) examined individual differences in reading and working memory abilities in 6- to 10-year-old children and showed that both of these skills exhibited a relationship to FA in fiber tracts, but in distinct

locations. Better reading was associated with higher FA in a region within the left superior corona radiata, but not with FA in a more anterior (and bilateral) region of corona radiata; while better digit recall showed the opposite pattern of associations. This study demonstrates that the relationships between fiber tract parameters and performance differences cannot all be explained by global differences, for example, in myelination; but seem, instead, to exhibit anatomical specificity. Importantly, these relationships between fiber tract parameters and task performance do not appear to be mediated by chronological age, which was generally modeled as a covariate in these studies.

Spatial working memory performance improves significantly throughout the childhood years, and several lines of evidence, including the report by Nagy et al. (2004) cited above, implicate the left fronto-parietal cortices and connections within the superior longitudinal fasciculus (SLF) in these functions. We recently reported that in children 7–13 years of age higher FA in the left SLF was associated with better spatial working memory skills, and that this effect was independent of age (Vestergaard et al., 2010). The association also remained significant after controlling for a global measure of FA in fiber tracts throughout the brain, as well as after controlling for a measure of right SLF FA. This pattern suggested a considerable degree of anatomical specificity in the relationship between left SLF FA and spatial working memory performances.

Cognitive control of behavior and the capacity to inhibit prepotent responses also shows marked development in the course of childhood. Behavioral motor control has been investigated with several paradigms, among them the stop-signal task, which provides a measure of a subject's ability to inhibit a prepotent manual response, that is, the stop-signal reaction time (SSRT) (Logan and Cowan, 1984). There is evidence that responding is mediated by a premotor-striatal-pallidal-motor cortical network; whereas for response inhibition, a primarily right-lateralized network has been implicated, involving the inferior frontal gyrus (IFG) and the presupplementary motor area (pre-SMA), as well as the subthalamic nucleus (Aron and Poldrack, 2006; Aron et al., 2007a,b). When the stop-signal task is administered in typically developing children, robust improvement in response inhibition (decreasing SSRT) is observed across the childhood years (Madsen et al., 2010; Tillman et al., 2008). Recently, we showed that in our sample of 7- to 13-year-old children, higher FA in the white matter underlying both the right IFG and the right pre-SMA was significantly correlated with better response inhibition (Fig. 3), and both of these effects remained significant after controlling for age or for global FA (Madsen et al., 2010). Moreover, the associations were mainly driven by variability in perpendicular diffusivity, consistent with the possibility that they are mediated by reduced extra-axonal space associated with continuing myelination or other factors that increase fiber packing density. Interestingly, the contributions of FA in the white matter underlying the right IFG and right pre-SMA to the prediction of response inhibition appeared to be additive, that is, both contributed significantly as simultaneous predictors of SSRT.

Taken together, these links between behavioral measures and diffusion parameters suggest that behavioral individual differences in school-aged children are mirrored by biological differences in the neural systems that mediate the behaviors. Further, studies in which several functions have been measured in the same group of children suggest that behavioral profiles, that is, patterns of relative strengths and weaknesses in performance across tasks, are linked to corresponding patterns within the biology of the neural systems relevant to the different functions measured.

Observations such as these, of correlations between measures of structural connectivity and behavioral measures, have also been made in older adolescents. A recent study (Ashtari et al., 2007) focused on fiber tract maturation in late adolescent males and measured both FA

and parallel and perpendicular diffusivities. Voxel-wise analyses revealed distributed clusters of increasing FA and increasing parallel diffusivity, with little change in perpendicular diffusivity, across the adolescent age range of the subjects. Though this pattern diverges to some extent from the pattern most often observed in younger groups (i.e., greater change in perpendicular diffusivity), it is not yet clear whether it signals a fundamental difference in the biological basis for white matter development during this age range. The authors speculate that age-related changes in fiber tracts may be more strongly related to fiber organization than to myelination during adolescence. In any event, both FA and parallel diffusivity in arcuate fasciculus and frontal regions were correlated with age-adjusted scores on the Information subtest of an intelligence test, a measure of semantic memory, again suggesting that these structural differences are linked to differences in cognitive functions among adolescents. Additionally, in a large cohort of healthy subjects between 8 and 30 years of age, verbal and performance intelligence scores were positively related to FA and negatively related to MD and perpendicular diffusivity, predominantly in the left hemisphere (Tamnes et al., 2010). Again, the associations were independent of age and sex. Moreover, verbal, but not performance abilities, were associated with developmental differences in diffusion measures in widespread regions in both hemispheres.

Though the focus of this review is on pediatric studies, it should be noted that a growing literature documents associations between the pattern of structural connectivity in the brain and behavioral differences among adults as well as developing children and adolescents. One interesting study (Powell et al., 2006) examined the degree of connectivity between superior temporal and inferior frontal regions in both hemispheres and reported increased left hemispheric connectivity in right-handed adults. Further, there was evidence that the structural asymmetry in these fronto-temporal tracts (probably within the arcuate part of the superior longitudinal fasciculus) was related to differences among the subjects in the degree of functional asymmetry observed on fMRI during language tasks. Other investigators (Gold et al., 2007) have reported that individual differences in speed of lexical decisions is related to FA variability in the region of the superior longitudinal fasciculus. Thus, differences in connectivity that give rise to variability in diffusion parameters appear to relate to behavioral differences in adults as well as in children.

In summary, studies of diffusion parameters in brain fiber tracts of children are consistent with the notion that the microstructural attributes of specific tracts relate to individual differences in performance on cognitive tasks on which children continue to improve during childhood in several neuropsychological domains: visual processing, language (particularly phonology and reading), spatial working memory, cognitive control of responses, and verbal and performance intelligence. It is reasonable to hypothesize that these associations, which appear to be independent of chronological age, are mediated, at least to some extent, by developmental variability (i.e., variability among children of similar age in the phase of maturation within their fiber tracts), though the evidence available at present does not compel that conclusion. Of course, even if the variability mediating the associations is developmental, it is entirely open to question how practice and increasing expertise relate to biological indices of tract maturation. The nature and timing of maturational processes that are under genetic control could promote learning, and experience (or training) could stimulate biological development of the tracts. The processes underlying these brain–behavior associations probably involve both additive and interactive effects of these factors. Finally, it is not yet known whether the associations could be mediated to some extent by earlier developing, and more stable, underlying differences between children in brain connectivity, since such differences can also result in altered diffusivities (Dubois et al., 2008). In the next section, we shall review reports that provide clues about the kinds of factors that may affect the neural architectural parameters that have been shown to be

correlated with behavioral performance in children. Most of these factors have been identified in studies of adults, but a few have also been studied in children.

Intrinsic and environmental factors linked to variability in neural architectural features

Genes

Global and regional brain volume and cortical thickness measures are highly heritable (Baare et al., 2001; Peper et al., 2007; Thompson et al., 2001). Recent adult twin studies employing morphometry methods sensitive to cortical arealization indicate that cortical area, like cortical thickness, is highly heritable, but that, importantly, the two neural architectural features exhibit little genetic correlation and thus are likely to be mediated by variation in different sets of genes (Panizzon et al., 2009). Moreover, evidence suggests that genetic influences on cortical thickness are not uniform but regionally specific, that is, different sets of genes (and their expression) appear to contribute to thickness in different brain regions (Rimol et al., 2010b). The availability of MR brain morphometry and genome-wide genotyping in a few large adult cohorts has made it possible to begin to examine the genetic associations of neural architectural phenotypes. Two recent reports describe associations between common genetic variation and cortical surface area. Common genetic variants in the regions near genes related to microcephaly were associated with sex-linked cortical surface area expansion (Rimol et al., 2010a). In a second study, variation in the gene MECP2 was also linked to a specific pattern of cortical area expansion in adult males within the general population (Joyner et al., 2009; Rimol et al., 2010a). Although mutations in this gene have been linked to mental disorders in children (Moretti and Zoghbi, 2006), these newly demonstrated effects of common MECP2 variability in males have not yet been linked to individual differences in cognitive or social-emotional functions in children or adults; however, such studies raise important questions about the nature of gene-experience interactions that may contribute to evolving behavioral phenotypic differences in children. Unfortunately, the lack of pediatric cohorts with both MRI and genetic data impedes further research on these questions at present, and it is not yet clear when during brain development neural phenotypes, such as the pattern of cortical arealization associated with variations in microcephaly genes and MECP2, first emerge.

Experience

Several recent studies have attempted to determine whether plasticity related changes in specific gray and white matter regions can be observed after intensive behavioral interventions or training. Draganski et al. (2004) compared cortical volume before and after young adults learned a juggling task. They reported gray matter volume increases after training in the mid-temporal area (hMT/V5) bilaterally and the left posterior intraparietal sulcus, regions known to be involved in visuomotor functions. Juggling training was also reported to increase FA in the white matter underlying the posterior intraparietal sulcus, and the FA increase appeared to be more strongly related to the time spent on the training than to actual progress or outcome of the training (Scholz et al., 2009). Others have studied the effect of cognitive training on brain micro-structure. Recently, Takeuchi et al. (2010) administered a working memory training program over a 2-month period and performed diffusion imaging before and after the program. They reported associations between the amount of time spent on the training and increases in FA in the white matter underlying the intraparietal sulcus and in the anterior body of the corpus callosum. To date, most intervention studies have been performed in adults, and studies examining the relationship between intervention and brain morphological changes in children and adolescents are sparse. In a recent study, a group of 8 to 10 year old children who were poor readers received 100 h of intensive reading instruction. They were compared to groups of poor and

good readers who did not receive any training (Keller and Just, 2009). Before receiving instruction, poor readers had significantly lower FA in the left anterior centrum semiovale relative to the good readers. Receiving the instruction was associated with significantly better performance on the Woodcock reading mastery test as well as with increases in FA and decreases in perpendicular diffusivity in the left anterior centrum semiovale. The authors speculated that the changes in FA and perpendicular diffusivity could be due to myelination or changes in axonal density or diameter. Further, the increase in FA was associated with improvement in phonological decoding ability.

Puberty

A major developmental milestone of childhood is the onset of puberty and adolescence. Puberty onset is associated with elevated levels of gonadal steroid hormones, such as testosterone and estradiol, which have organizational and activating effects on the nervous system (Sisk and Zehr, 2005). Information regarding the effects of sex steroids on brain development generally comes from animal studies (McCarthy, 2009; Stein, 2008). Besides well-established organizational effects of sex steroids on neural circuits and behavior in the prenatal and immediate postnatal period, it is now recognized that steroids also play an important organizational role in adolescence (Sisk and Zehr, 2005). The role that steroids play in observed sex-specific changes in human brain structure and function (Lenroot and Giedd, 2010; Luders and Toga, 2010; Paus, 2010) is largely unknown and only very recently direct empirical studies have been undertaken (Lenroot and Giedd, 2010; Neufang et al., 2009; Peper et al., 2009; Perrin et al., 2009; Raznahan et al., 2010; Witte et al., 2010). Sex-specific effects of testosterone and estrogen have been found in the amygdala and hippocampus (Neufang et al., 2009), structures that are known to exhibit gender dimorphism in adults. Corrected for age, global gray matter volume has been negatively associated with estradiol levels in girls, and positively with testosterone levels in boys (Peper et al., 2009). Moreover, Perrin et al. (2008) showed that testosterone-related increases of white matter volume were stronger in male adolescents with a lower versus higher number of CAG repeats in the androgen receptor gene. Because magnetization transfer ratio imaging (sensitive to the amount of myelin) provided no support for the role of myelination in this growth, the authors speculated that testosterone might affect axonal caliber rather than the thickness of the myelin sheath. Recently, using a longitudinal design, variation in androgen signaling was shown to have sex-linked, regionally varying effects on cortical thickness in adolescents (Raznahan et al., 2010). Finally, steroid hormone levels have also been shown to exert regional effects on gray matter volume in a sample of young adults (Witte et al., 2010).

Important remaining questions

We have summarized the evidence for continuing age-related alteration of brain morphology, and ongoing biological alterations in brain fiber tracts, over a protracted period extending throughout adolescence. In addition, we have described a growing body of evidence suggesting that, in children, individual differences in cognitive task performance can be associated with variability in brain morphology and with diffusion imaging parameters from brain fiber tracts. The associations usually persist after controlling for age and gender and they appear to be relatively anatomically specific. However, we do not yet know how to interpret these associations. In this respect, several relevant factors that could mediate these associations have been linked to variability in the same imaging measures. On the one hand, reports of correlation between genetic variation and cortical surface area suggest that some relevant variation may be of genetic origin. However, other studies suggest that significant variation in cortical thickness and white matter diffusion parameters can arise from experience-dependent neuroplastic responses. Imaging studies of effects of hormonal changes suggest that these could also play a role in the development of individual differences. Critical questions that should be addressed in future studies are the degree to

which these and other factors may explain suggest brain–behavior relationships in children. Almost certainly, genetic variation contributes to behavioral differences by influencing biological processes that themselves involve constant interaction with the child's environment. Among these processes are those that are influenced by changing hormone levels in adolescence. Many other factors are also likely to contribute. However, the relative contributions of intrinsic and extrinsic factors, and the nature of the interactions between them, are important questions to answer, because these interactions are likely to be the most promising targets for interventions to improve the lives of children.

One question with important implications for child development and education is whether differences in the rate of neural development *per se* explain some of the behavioral differences among children. Only longitudinal studies can tell us whether individual differences among children in the course of their cognitive development are mirrored by developmental differences in relevant neural systems, and how such associations relate to and modify associations with other, more stable, neuroarchitectural attributes. The school-age period is a time of significant developmental change in both cognitive abilities and neural systems. Yet information on links between these processes is sparse. There is a need to document the degree of temporal congruence between developmental change in the behavioral profiles of individual children and changes in the brain systems that support specific cognitive functions. This approach must differ in an important way from previous studies, because it must focus on concordance between brain and behavioral development at the individual, rather than the group, level of analysis. In order to more clearly convey this important distinction, consider the hypothetic outcome of assessments (e.g., of indices of fiber tract development) at 5 time points for three children (as illustrated in Fig. 4). For this illustration, the children's scores are constrained to lie on the mean of the distribution both at baseline (Time 1) and at the final assessment (Time 5). Previous behavioral research suggests that children differ in their cognitive abilities and that these differences are to a considerable degree persistent across development. Some imaging studies have related differences in brain structure to these behavioral differences. However, these studies tell us very little about the hypothetical differences illustrated in Fig. 4, which are, by definition, independent of persistent differences. The question we must answer is whether, independent of "intercept" differences, "trajectory" differences such as these, in development of a given fiber tract (or neural system) map onto similar trajectories for behavioral measures. Further we need to address whether such trajectory differences between children are expressed similarly across different brain (and behavioral) systems? In other words, would the graphs of these three childrens' trajectories consistently look like those in the left panel across different fiber tracts and behavioral domains, or could the child whose data are presented with a solid line in the left panel show a different developmental pattern for another fiber tract (as shown with a solid line in the right panel)? It is our contention that virtually no information that addresses these questions presently exists, and that the answers are potentially very important.

Acknowledgments

This work was supported by grants from the Lundbeck Foundation and by grants from the National Institute of Child Health and Human Development and the National Institute of Drug Abuse: R01-HD25077, R01 HD060595, RC2DA029475, R01HD061414.

Abbreviations

CSF	cerebrospinal fluid
DTI	diffusion tensor imaging

FA	fractional anisotropy
IFG	inferior frontal gyrus
MD	mean diffusivity
MR	magnetic resonance
MRI	magnetic resonance imaging
pre-SMA	presupplementary motor area
SLF	superior longitudinal fasciculus
SSRT	stop-signal reaction time

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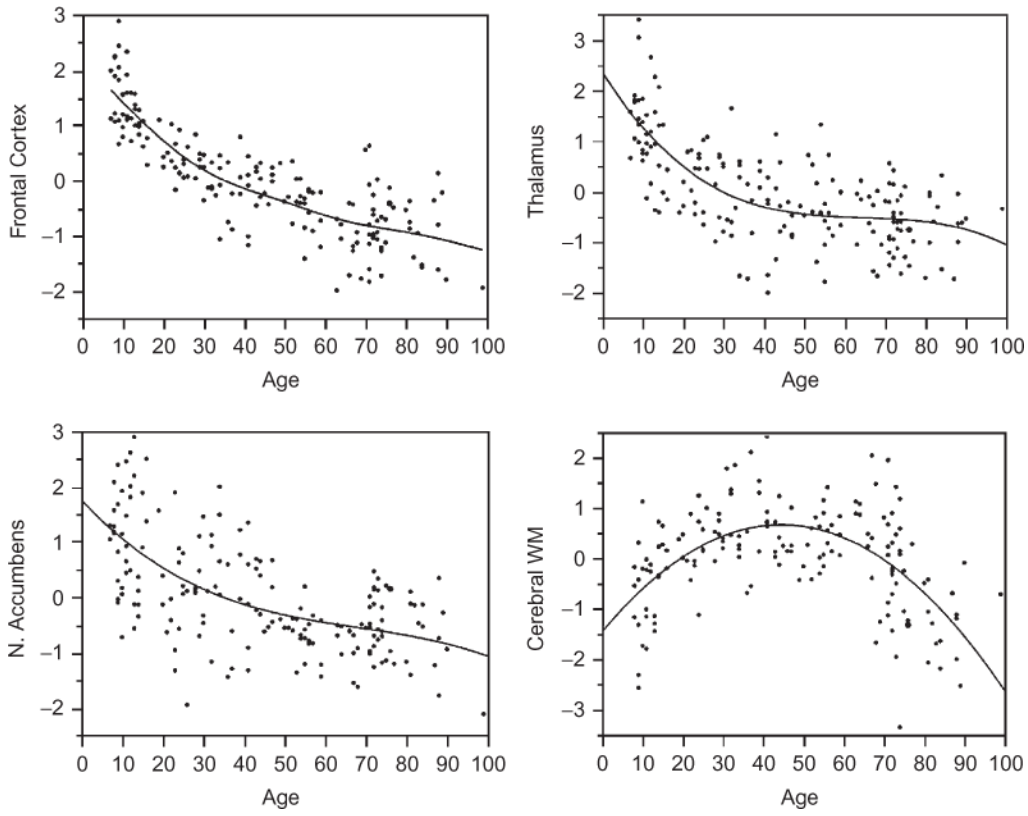

Fig. 1.

Estimated volumes of brain structures in normal volunteers are plotted against age. The volumes in the figures are presented as standardized residuals (removing variability associated with volume of the supratentorial cranial vault). They are, from left, volumes of frontal cortex, thalamus, nucleus accumbens, and cerebral white matter. Note the rapid age-related change (and striking individual differences) in the childhood and adolescent age range.

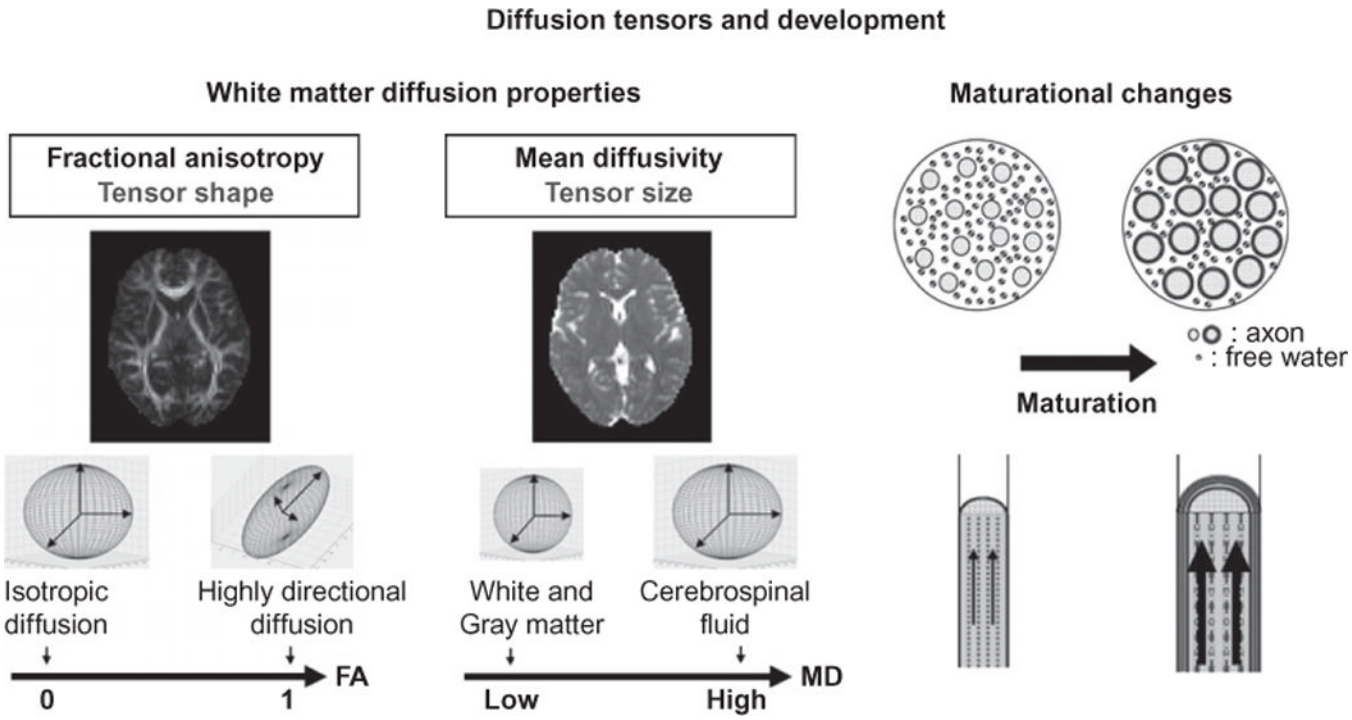

Fig. 2.
Tutorial box

(a) Tensor size reflects magnitude of diffusion.

- Tensors for voxels in CSF spaces are large and spherical (or isotropic): all 3 eigenvalues the same and all high.
- Tensors in gray matter are smaller (less free water) but also isotropic: all 3 eigenvalues the same and all low.

(b) Tensor shape reflects directionality of diffusion.

- Tensors for voxels in fiber tracts are elongated (or anisotropic) presumably because diffusion of water molecules is higher within axons and along the axonal and myelin surfaces than perpendicular to the fiber tracts: principal eigenvalue (parallel diffusivity) higher than others (perpendicular diffusivity) — high “fractional anisotropy.”

(c) As fiber tracts mature, axons and their myelin sheaths become larger and the water in extra-axonal space decreases.

- Less free water reduces all 3 eigenvalues (as in (a))
- But because diffusion along fiber membranes is preserved or increased, principal eigenvalue (parallel diffusivity) is decreased less than other eigenvalues (perpendicular diffusivity).
- Therefore, perpendicular diffusivity and fractional anisotropy are most affected by fiber tract development. Alterations of fiber organization (coherence, tortuosity) may also contribute to anisotropy.

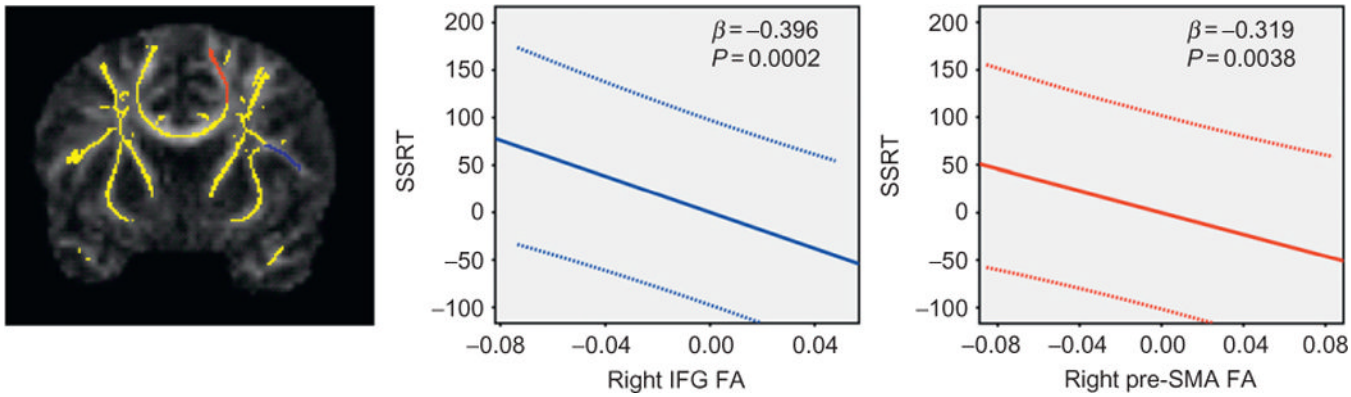

Fig. 3.

Left: Group mean tract skeleton (black) identified using Tract Based Spatial Statistics; tract segments in the white matter underlying the right inferior frontal gyrus that served as right IFG region-of-interest and the right presupplementary motor area that served as right pre-SMA region-of-interest are shown in white. Middle and right: Leverage plots illustrating the semipartial correlations of FA in the right IFG and right pre-SMA (respectively) with the stop-signal reaction times. Standardized regression coefficients (and associated *p*-values) are given from simultaneous regression analysis predicting the stop-signal reaction time. FA in both regions accounts for significant variability: higher FA is associated with lower stop-signal reaction times, that is, a reduction in the time needed to cancel or suppress a prepotent motor response.

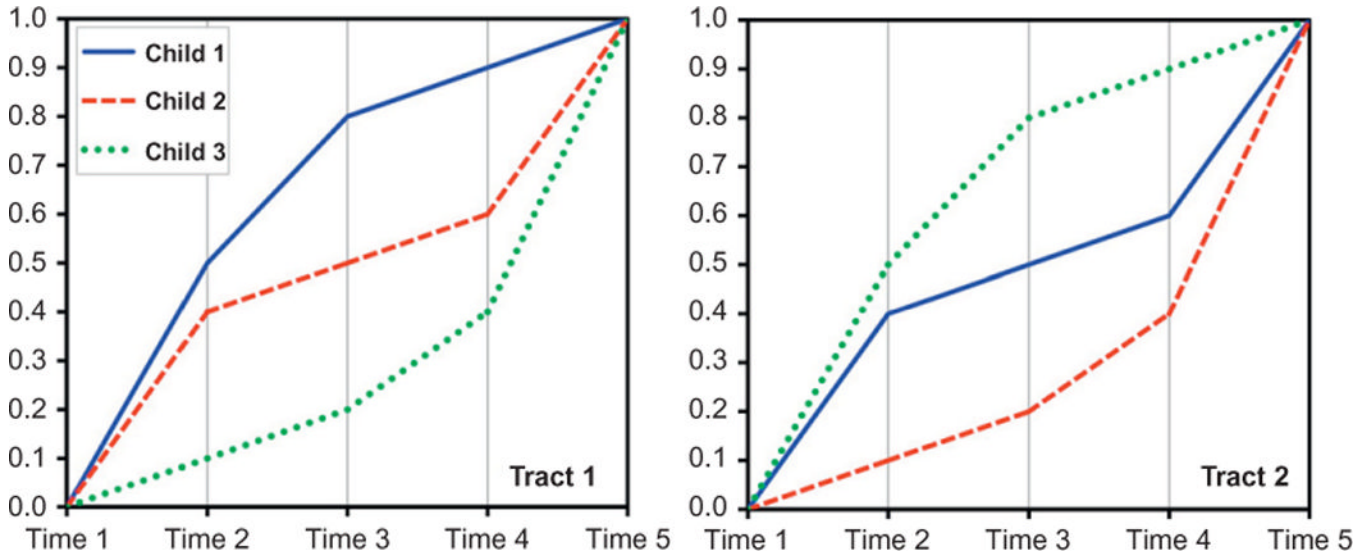

Fig. 4.

Both figures depict hypothetical results of five longitudinal assessments in each of three children (each child's data shown in different line style and/or color). Scores are of a hypothetical index of the status of maturation in two fiber tracts, one on right and another on left. Scores are constrained to be equal both at baseline and at the final assessment, but the differences illustrated are in the trajectories (or time courses) of development. The contrast between the data for the fiber tract shown on the left and that shown on the right illustrates the possibility that individual differences in rate of development in one neural system may not generalize to those in others.