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Review

Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging

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Abstract

Advances in neuroimaging have ushered in a new era of developmental neuroscience. Magnetic resonance imaging (MRI) is particularly well suited for pediatric studies because it does not use ionizing radiation which enables safe longitudinal scans of healthy children. Key findings related to brain anatomical changes during childhood and adolescent are increases in white matter volumes throughout the brain and regionally specific inverted U-shaped trajectories of gray matter volumes. Brain morphometric measures are highly variable across individuals and there is considerable overlap amongst groups of boys versus girls, typically developing versus neuropsychiatric populations, and young versus old. Studies are ongoing to explore the influences of genetic and environmental factors on developmental trajectories.

Keywords: Brain; MRI; Pediatric; Development

Contents

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1. Introduction

Differences in cognition, behavior, and emotions between children, adolescents, and adults have been noted for millennia. Characterizing the neuroanatomical substrates of these differences has been more elusive. Data from animal and post-mortem studies has been able to tell us much about the basic processes underlying the development of the brain, but these types of studies are limited in what they can tell us about how individuals change over time, the extent of variability between individuals, what factors may impact that change, and the functional correlates of these differences. Magnetic resonance imaging (MRI) has opened the way for serial observations of brain changes during development in living people and thus the ability to address these questions. In this brief review we will first provide a context of the fundamental processes underlying brain formation, followed by a discussion of methodological issues in MRI. We will then summarize progress thus far on MRI studies of brain changes during development with an emphasis on the results from the longitudinal study of typically developing children and adolescents carried out by our group at National Institute of Mental Health (NIMH) over the past 15 years. We will conclude with a discussion of implications for brain–behavior relations and future directions.

2. Key events in brain development

The development of the nervous system occurs through the interaction of several synchronized processes, some of which are complete before birth, while others continue into adulthood. The first key event in the development of the central nervous system is the formation of a specialized fold of ectodermal tissue called the neural tube. The neural tube nears completion by 3–4 weeks of gestation (see Fig. 1) and is the basis for all further nervous system development. Birth defects such as spina bifida and meningomyelocele arise from abnormalities in neural tube formation (Victor et al., 2001).

From 4 to 12 weeks the neural tube differentiates into what will become various components of the nervous system. The forebrain and facial structures develop at one end, and the spinal cord at the other. The hollow center of the tube in the region that will become brain will eventually form the ventricles. Regions called *proliferative zones* form near the ventricles and give rise to young neurons. From 12 weeks to 20 weeks these neurons multiply and migrate from their origins to destinations in the cortex, moving along a scaffolding of glial cells (Rakic, 1990). After this migration, a period of rapid cell death occurs, reducing the neural number by half from 24 weeks of gestation to 4 weeks after birth. The cell bodies of the neurons are primarily found in the gray matter of the brain. Their myelinated axons form white matter.

Myelination occurs regionally beginning with the brain stem at 29 weeks (Inder and Huppi, 2000) and generally proceeds from inferior to superior and posterior to anterior. Proximal pathways tend to myelinate before distal, sensory before motor, and projection before association (Volpe, 2000). Although most major tracts are significantly myelinated by early childhood, axons within the cortex and in some regions such as the arcuate fasciculus, a white matter bundle near the temporal lobe, continue to myelinate into the second and third decades of life (Yakovlev and Lecours, 1967).

A third major developmental process is the proliferation and organization of synapses, which begins slightly later, around the 20th week of gestation. Synaptic density increases rapidly after birth, reaching by 2-years of age a

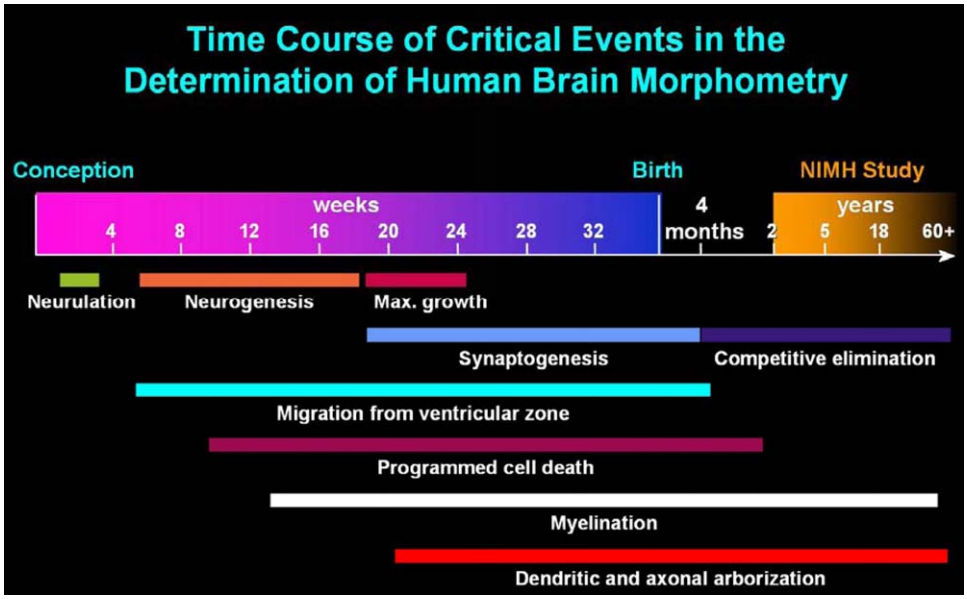

Fig. 1. Sequence of events in brain maturation.

level approximately 50% greater than that typically seen in adults (Huttenlocher, 1979). This is followed by a regionally specific loss of synaptic connections. For example, maximum synaptic density occurs in the visual cortex at 4 months postnatally, but it does not typically peak in the prefrontal cortex until 4 years of age.

Beginning at approximately 15 weeks the surface of the growing brain begins to fold into sulci and gyri (Levine and Barnes, 1999) The major sulci, except for the occipital lobe, are in place by 28 weeks of gestation, after which secondary and tertiary sulci are elaborated, with nearly all gyri present by birth. The sulcal and gyral patterns continue to increase in complexity after birth, likely related to changes in cell-packing density and maturation of subcortical tracts.

The dynamic interplay between progressive and regressive events results in relatively rapid brain growth in the first 2 years of life, by which time it has achieved 80% of its adult weight. By age 5 years brain size is approximately 90% of adult size (Dekaban and Sadowsky, 1978). However, significant remodeling of gray and white matter continues into the third decade of life, something that could not be fully appreciated until the MRI studies described below.

3. Methodology considerations in pediatric anatomical MRI studies

The brain is wrapped in a resilient membrane, immersed in a protective moat of fluid, and completely encased in bone. This protects the brain well from falls or attacks from predators but also creates a challenge for those interested in investigations of the organ responsible for our thinking and behavior.

Early methods of visualizing the brain in vivo, such as X-rays or computerized tomography, offered major advances but their use of ionizing radiation precluded their use in the study of healthy children. MRI has overcome this obstacle by providing exquisitely accurate pictures of in vivo brain anatomy without the same potential health risks. This has permitted not only the scanning of healthy children but also repeated scans of the same individuals over time. Such longitudinal data has proved indispensable in capturing the complicated and highly variable trajectories of anatomical brain development.

MRI is also a versatile imaging modality allowing assessment of physiology and characterization of many different aspects of tissue. In this paper we will focus on what is usually referred to as "anatomical" or "structural" MRI, the type whose output most closely resembles anatomy, as we would observe by visual inspection.

3.1. Image acquisition

Standard anatomical MRI acquisitions are typically designed to optimize discrimination between gray matter, white matter, and cerebrospinal fluid (CSF) as these three tissue types are used to define the boundaries of many brain structures. Anatomical MRIs are formed from three-dimensional volume elements called voxels. Each voxel is assigned a single value based on the average magnetic resonance characteristics present in the tissue corresponding to that voxel. The size of the voxel determines the spatial resolution, or the fineness of detail that can be distinguished in an image. Voxel sizes vary depending on the imaging parameters, magnet strength, the time allowed for acquisition, and other factors, but in most currently published structural MRI studies voxel sizes are on the order of 1–2 ml. Greater spatial resolution can be purchased with the currency of time, but this must be weighed against patient discomfort. Most structural pediatric MRI studies limit image-acquisition time to between 5 and 20 min.

Despite the impressively high resolution now obtainable with MRI scans, a reminder of the relative size of the cellular elements contained in a typical cubic millimeter voxel is in order. While cell densities vary in different regions of the cortex, a voxel this size in the cortical gray matter of a typical young adult would likely contain between 35 and 70 million neurons and up to twice as many glial cells (Pakkenberg, 1997). The number of synapses has been estimated on the order of 500 billion (Scheff et al., 2001). The same size voxel in white matter could contain up to 32 km of myelinated fibers (Marner et al., 2003). The amount of structural variation that can occur well below what is detectable on an MRI image should be kept in mind when inferring functional and behavior capabilities from anatomical MR images.

3.2. Image analysis

Fundamental components of structural MRI analysis include the segmentation of voxels into specific tissue types (e.g. gray matter, white matter, CSF, and etc.) and the identification and description of specific brain structures or areas of interest. Several techniques are currently available for tissue classification. The most common method at present is the use of computer algorithms that create an intensity histogram of all of the voxels in the image and then fit a Gaussian function to the distribution. The probability of a given intensity corresponding to a given type of tissue can thus be inferred and voxels are assigned to tissue types accordingly. Additional classification constraints using methods such as Markov random field modeling which allow information about neighboring voxels to affect classification can significantly decrease misclassification due to random noise in the image (Rajapakse et al., 1997; Zhang et al., 2001; Pham et al., 2000). Surface deformation techniques and probabilistic atlases can augment the classification by using prior knowledge of brain anatomy to inform whether a given location in the brain is likely to contain gray matter, white matter, or CSF voxels (Davatzikos, 1996; Collins et al., 1995).

A major potential source of error in voxel classification is alteration in voxel intensities due to regional differences

in the magnetic field at the time the image is acquired. These may arise from hardware problems, but are also unavoidably created by the presence of the head itself within the magnetic field. The different substances present within the head, ranging from the air in the sinuses to CSF and bone, each interact differently with the magnetic field and can perturb the intensity of the field, particular around complex areas such as the sphenoid region. Such effects become markedly stronger as field strengths increase. Bias field correction routines are now commonly used to identify and remove of this type of systematic distortion of image intensities (Zhang et al., 2001; Sled et al., 1998; Pham and Prince, 1999).

Once the voxels have been classified, the number of voxels in a given region can be counted to provide the gray and white matter volumes for that region. Lobar volumes are most commonly reported, but as resolution and labeling techniques improve smaller and smaller subregions can be accurately quantified. The "gold standard" for these types of analysis is still considered to be measurement by a trained human rater. Such an approach is labor-intensive and may not be feasible for use in studies with large numbers of subjects. In addition, some potentially informative features of brain anatomy such as cortical thickness or curvature are very difficult to quantify using this method. Continued improvements in the quality of MR images and computational resources, and development of new algorithms have made possible the many recent advances in the automation of image analysis and in the statistical analysis of the results, as seen in other manuscripts in this volume.

Another approach to comparing different brains is to create geometrical models of the brain or brain substructures can, which lend themselves to statistical analysis (see Fig. 2). The primary challenge to these approaches is to find a one-to-one correspondence between voxels in different brains. High individual variation in cortical sulcal and gyral folding patterns makes establishing this one-to-one correspondence difficult, although techniques to anchor the average shapes by aligning certain less variant sulci (Thompson and Toga, 1997; Thompson et al., 2004) or by using semi-automated deformable surface-warping methods (Liu et al., 2004) have greatly advanced the utility of these methods.

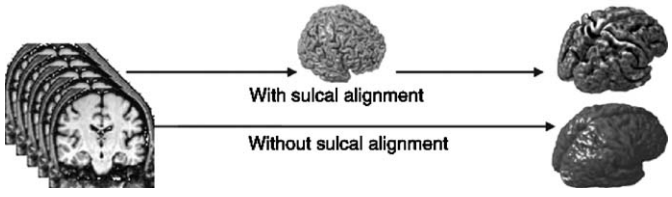

Fig. 2. Sulcal alignment: after careful separation of brain from nonbrain voxels, 38 sulcal curves on each subject's cortical surface are manually defined. The sulcal demarcations are used as anchors to create a deformation map, which warps the anatomy of one image onto another while matching sulcal demarcations.

Validation of MR image analysis techniques is hindered by lack of an absolute standard for comparison. Postmortem data are less than ideal on several counts. When removed from the intracranial cavity and the CSF in which it is immersed, the brain collapses on its own weight, distorting in vivo morphology. Fixation and drying processes affect different brain structures to different degrees, with gray matter and white matter shrinking at separate rates. Age is an important factor as younger brains have higher water content and are differentially affected by fixation processes. The standard for validation of automated measures for the quantification of many structures remains a comparison to results obtained from manual tracing by expert human raters.

4. Early pediatric brain anatomical MRI studies

The first MRI studies of brain development were reported in the 1980s and focused on qualitative descriptions of gray and white matter during the first 2 years of life (Barkovich et al., 1988; Holland et al., 1986; Johnson and Bydder, 1983; Levene et al., 1982; McArdle et al., 1987). With conventional MRI sequences the gray and white matter intensities during the first 6 months are reversed from the adult pattern (i.e. gray matter appears lighter than white matter). From ages 6 to 12 months there is a gradual and regionally specific transition to the adult pattern during which gray and white matter are not well differentiated. The findings are consistent with a decrease in water content in both white and gray matter, followed by the addition of macromolecular precursors to myelination and then myelination itself (Inder and Huppi, 2000; Paus et al., 2001).

Quantitative MRI studies of brain structure in typically developing children and adolescents were first reported in the 1990s. These confirmed the earlier postmortem findings that total brain volume was approximately 90% of adult size by age 5. White matter volume was generally found to be increasing and gray matter volume decreasing (Jernigan and Tallal, 1990; Reiss et al., 1996; Schaefer et al., 1990). These earlier studies provided seminal insights into anatomic brain development but were cross-sectional and underpowered to detect the more complicated developmental trajectories later confirmed by longitudinal studies.

In 1989, the Child Psychiatry Branch at the NIMH initiated the first large scale longitudinal study of normal and abnormal brain development. In the next section we will focus upon results obtained from this ongoing study.

5. NIMH pediatric brain imaging project

The long-term goals of the NIMH Pediatric Brain Imaging project are to (i) map the developmental trajectories of brain development; (ii) discern the genetic and environmental influences on these developmental pathways; and (iii) use knowledge of these influences to guide treatment interventions or optimize healthy brain

development. Initial cross-sectional data indicated that large sample sizes or a longitudinal study design would be required to characterize the developmental changes of the pediatric population (Kraemer et al., 2000). The feasibility of this type of longitudinal MRI study has been supported by the relative stability of morphologic measures from scans acquired at 2- to 4-week intervals (Giedd et al., 1995). This stability indicates that quantitative differences in longitudinal scans are reflections of genuine changes in brain structure and not from variability related to the scan-acquisition itself. As of December 2005 the data set included approximately 4000 scans from 2000 subjects, about half typically developing and half from various diagnostic groups, such as ADHD and childhood-onset Schizophrenia. This section will summarize results from the typically developing subjects of this project.

5.1. Study design and population

Healthy control subjects are recruited from the community and undergo physical and neurological exams, clinical interviews, family history assessment, and an extensive neuropsychological battery (Giedd et al., 1996a, 1999a). Approximately, 400 of the subjects are twins. Participants are asked to return for follow-up longitudinal testing and scans at approximately 2-year intervals.

5.2. MRI acquisition and image analysis

All images were acquired on the same General Electric 1.5 Tesla Signa Scanner located at the NIH Clinical Center. A three-dimensional spoiled gradient recalled echo in the steady state sequence, designed to optimize discrimination between gray matter, white matter and CSF, was used to acquire 124 contiguous 1.5-mm thick slices in the axial plane. Once the images are acquired, they are analyzed by a variety of automated parcellation and manual-tracing techniques through collaboration with several imaging centers throughout the world. Further details of the methods of image analysis are published elsewhere (Giedd et al., 1996a, 1999a; Zijdenbos et al., 1994; Chung et al., 2001). Analysis methods are applied to sub-samples of the available subjects depending on specific questions and the labor-intensiveness of the particular method used. As a consequence, because different methods of analysis used for different quantitative measures, and because automated measures are available for a greater number of subjects than manual measures, the samples presented in this manuscript are not identical. The number of subjects used for a given figure is given in that figure's legend.

5.3. Results

5.3.1. Total cerebral volume

Total cerebral volume peaks at 14.5 years in males and 11.5 years in females (Giedd et al., 1999b). By age 6 years the brain is at approximately 95% of this peak (see Fig. 3),

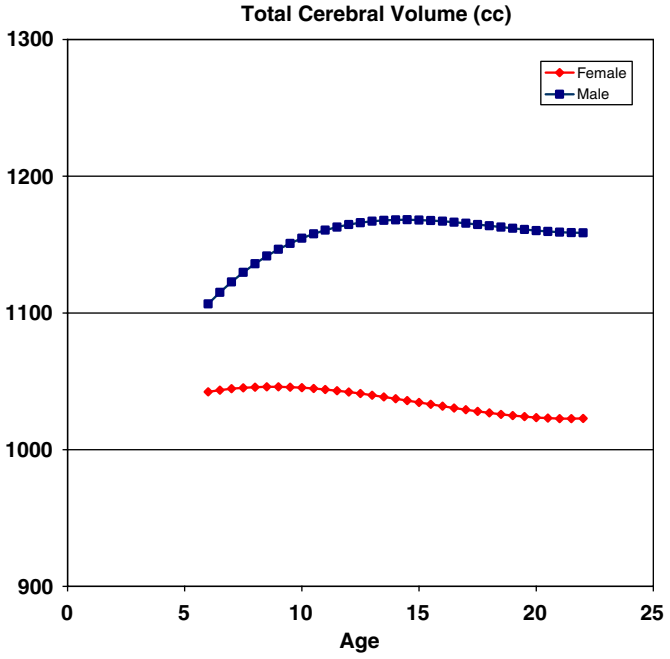

Fig. 3. Total cerebral volume (TCV) by age for 224 females (375 scans) in red and 287 males (532 scans) in blue.

consistent with earlier postmortem reports (Dekaban and Sadowsky, 1978). Male brains are approximately 9% larger on average than those of females. This difference is statistically significant, even when controlling for height and weight.

Total brain size differences should not be interpreted as imparting any sort of functional advantage or disadvantage. Gross structural measures may not reflect sexually dimorphic differences in functionally relevant factors such as neuronal connectivity and receptor density. This is further highlighted by the remarkable degree of variability seen in overall volumes and shapes of individual trajectories in this carefully selected group of healthy children. Healthy normally functioning children at the same age could have 50% differences in brain volume, highlighting the need to be cautious regarding functional implications of absolute brain sizes.

In anatomical MRI studies total cerebral volumes are usually further analyzed with respect to volumes of constituent tissues and structures, including the ventricles, gray matter, and white matter. The following sections will address these components.

5.3.2. Ventricles

Lateral ventricular volume increases across this age span (see Fig. 4), a fact not widely appreciated for children and adolescents. The naturally occurring enlargement of ventricles should be considered in interpreting the reports of increased ventricular volumes, or ventricular-to-brain ratios, reported for several neuropsychiatric conditions. Lateral ventricle volumes, perhaps because they share a

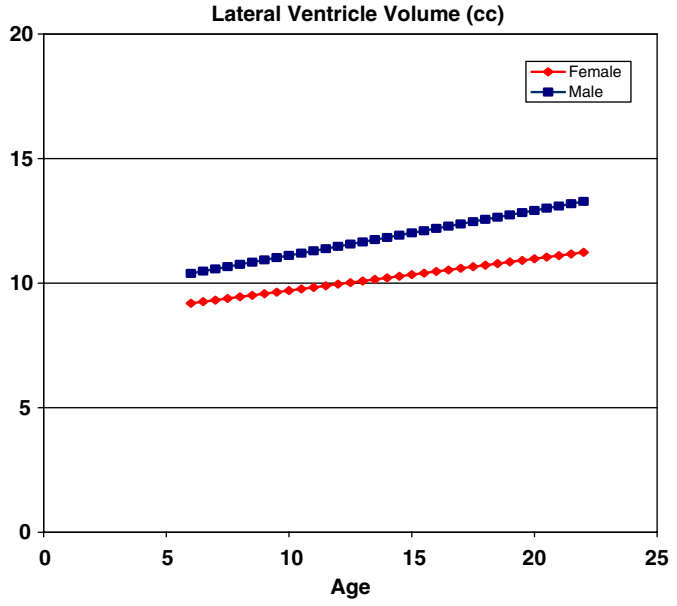

Fig. 4. Lateral ventricle volume by age for 224 females (375 scans) in red and 287 males (532 scans) in blue.

border with a myriad of other structures, tend to have the highest variability of brain morphometric measures.

5.3.3. Gray matter

5.3.3.1. Cortical gray matter. Cortical gray matter volume tends to follow an "inverted U" developmental course with volumes peaking at different times in different lobes (see Fig. 5). For instance, frontal lobe gray matter reaches its maximal volume at 11.0 years in girls and 12.1 years in boys; temporal lobe cortical gray matter peaks at 16.7 years in girls and 16.2 years in boys; and parietal lobe cortical gray matter peaks at 10.2 years in girls and 11.8 years in boys (Giedd et al., 1999b).

To explore cortical gray matter changes at a smaller spatial resolution we examined the change in gray matter density at the voxel level in a group of 13 subjects scanned 4 times at approximately 2-year intervals (Gogtay et al., 2004) (see Fig. 6). In accord with the previously described method (see Fig. 2) cortical landmarks were selected and used as anchors to aid registration between brains. The developmental trajectory of cortical gray matter followed a regionally specific pattern with areas subserving primary functions, such as motor and sensory systems, maturing earliest and higher order association areas, which integrate those primary functions, maturing later. For example, in the temporal lobes the latest part to reach adult levels is the superior temporal gyrus/sulcus which integrates memory, audio-visual input, and object recognition functions (along with prefrontal and inferior parietal cortices) (Mesulam, 1998; Calvert, 2001; Martin and Chao, 2001). The changes over time can be viewed as time-lapse movies (http://www.loni.ucla.edu/~thompson/DEVEL/dynamic.html).

Notably, late to reach adult levels of cortical thickness is the dorsolateral prefrontal cortex, involved in circuitry subserving control of impulses, judgment, and decision-making. The implications of late maturation of this area have entered educational, social, political, and judicial discourse in matters ranging from whether minors are cognitively mature enough to qualify for the death penalty to the age at which teenagers should be allowed to drive. In these debates there is a tendency to overestimate our understanding about the relationships between brain biology and behavior or cognition, especially on an individual basis. On the other hand, proper application of our growing knowledge of brain development and physiology will undoubtedly have increasing relevance in educational, judicial, and social domains. Exploring the nexus between advances in neuroscience and these other domains is likely to be a highly active endeavor in the years to come.

5.3.4. Subcortical gray matter

5.3.4.1. Basal ganglia. The basal ganglia consist of the caudate, putamen, globus pallidus, subthalamic nucleus, and substantia nigra. The basal ganglia have long been known to play a role in the control of movement and muscle tone but more recently have been shown to be involved in circuits mediating higher cognitive functions, attention, and affective states. Our group measured caudate nucleus volumes and found that like the cortical gray matter structures the caudate nucleus follows an inverted U-shaped developmental trajectory. Caudate size peaks at age 7.5 years in girls and 10.0 years in boys (see Fig. 7).

5.3.5. Amygdala and hippocampus

The temporal lobes, amygdala, and hippocampus subserve emotion, language, and memory, functions that change markedly between the ages of 4 and 18 years (Jerslid, 1963; Wechsler, 1974; Diener et al., 1985). In a previous cross-sectional study of a subset of this longitudinal data, amygdala volume increased with age significantly only in males and hippocampal volume increased significantly with age only in females (Giedd et al., 1996b). This pattern of gender-specific maturational volumetric changes is consistent with nonhuman primate studies indicating a relatively high number of androgen receptors in the amygdala (Clark et al., 1988) and a relatively higher number of estrogen receptors in the hippocampus (Morse et al., 1986), although direct links between receptor density and growth patterns have not been established. Quantification of the amygdala and hippocampus for the longitudinal sample is underway.

5.3.6. White matter

5.3.6.1. Lobar white matter volumes. In contrast to the inverted U shape of gray matter developmental curves, the amount of white matter in the brain generally increases throughout childhood and adolescence (see Fig. 8). Although the rate of white matter increase varies with age, we have not detected periods of overall white matter

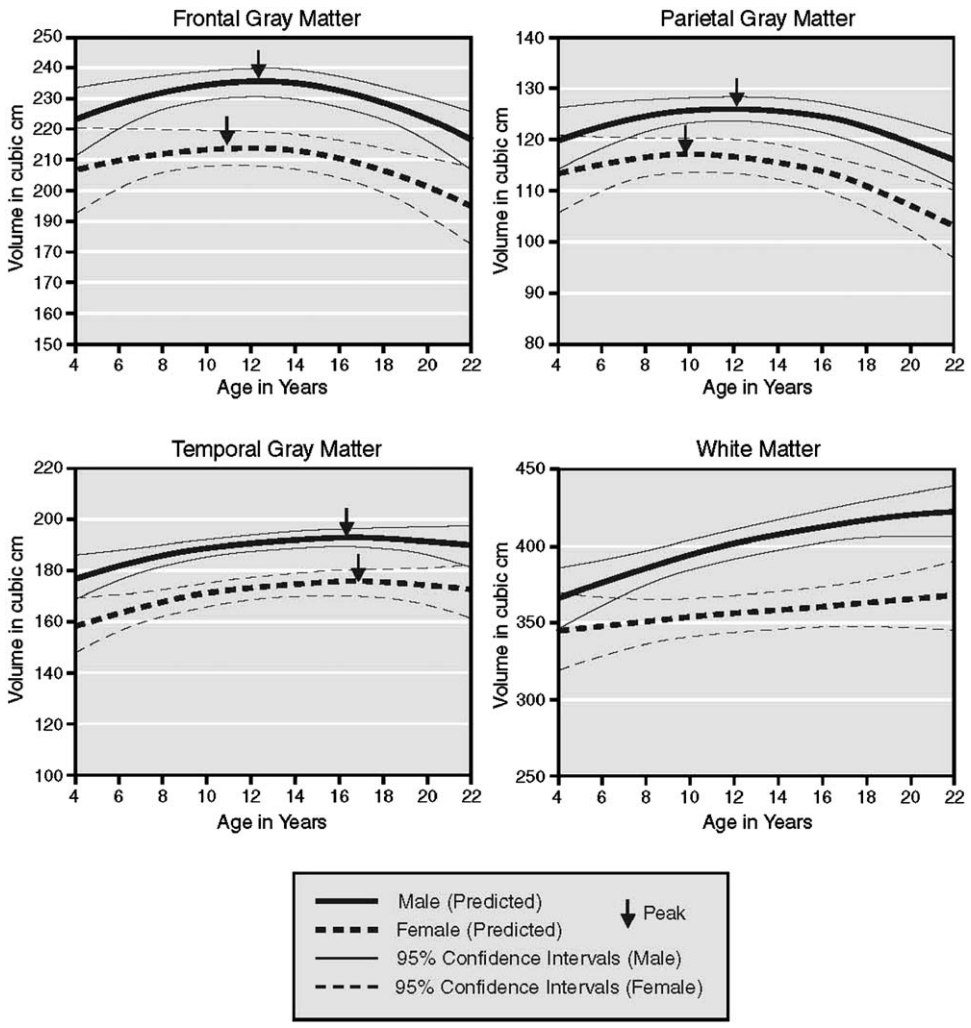

Fig. 5. Frontal GM, parietal GM, and temporal GM volumes: 243 scans from 145 subjects (scans acquired at approximately 2-year intervals). The arrows indicate peak volume. (I need to remove the WM figure from this panel as I show it in Fig. 8. I am rerunning these measures on the updated sample so that all will be consistent.)

reduction for any region within the age range we have examined (Giedd et al., 1999). Reports from other groups studying white matter changes in older populations have found that white matter does not begin to decrease until the fourth decade (Bartzokis et al., 2001). Unlike the lobar differences seen in gray matter trajectories, the white matter slopes are similar in frontal, temporal, and parietal lobes.

The differences in gray matter and white matter developmental trajectories belie the inseparable connection among neurons, glial cells, and myelin, which are components of the same neural circuits and share lifelong reciprocal relationships (Fields and Stevens-Graham, 2002). Neuron activity influences myelin production and the proliferation and survival of oligodendrocytes (Barres and Barde, 2000; Fields et al., 2001) while oligodendrocytes influence neurons via secretion of neuronal growth factors and influence axonal growth and clustering of ion channels (Du and Dreyfus, 2002). Proximal pathways tend to be myelinated before distal, sensory before motor, and projection before association (Volpe, 2000). Later-maturing myelin sheaths, such as those in association tracts and intracortical regions, tend to be thinner with greater axonal load per oligodendrocyte (Yakovlev and Lecours, 1967; Kinney et al., 1994), which may render them more vulnerable to environmental or aging-related factors (Bartzokis, 2004).

5.3.6.2. Corpus callosum. The most prominent white matter structure is the corpus callosum, consisting of approximately 200 million myelinated fibers, most of which connect homologous areas of the left and right cortex. The functions of the corpus callosum can generally be thought of as integrating the activities of the left and right cerebral hemispheres, including functions related to the unification of sensory fields (Berlucchi, 1981; Shanks et al., 1975), memory storage and retrieval (Zaidel and Sperry, 1974), attention and arousal (Levy, 1985), enhancing language and auditory functions (Cook, 1986). Several studies have indicated that corpus callosum development continues to

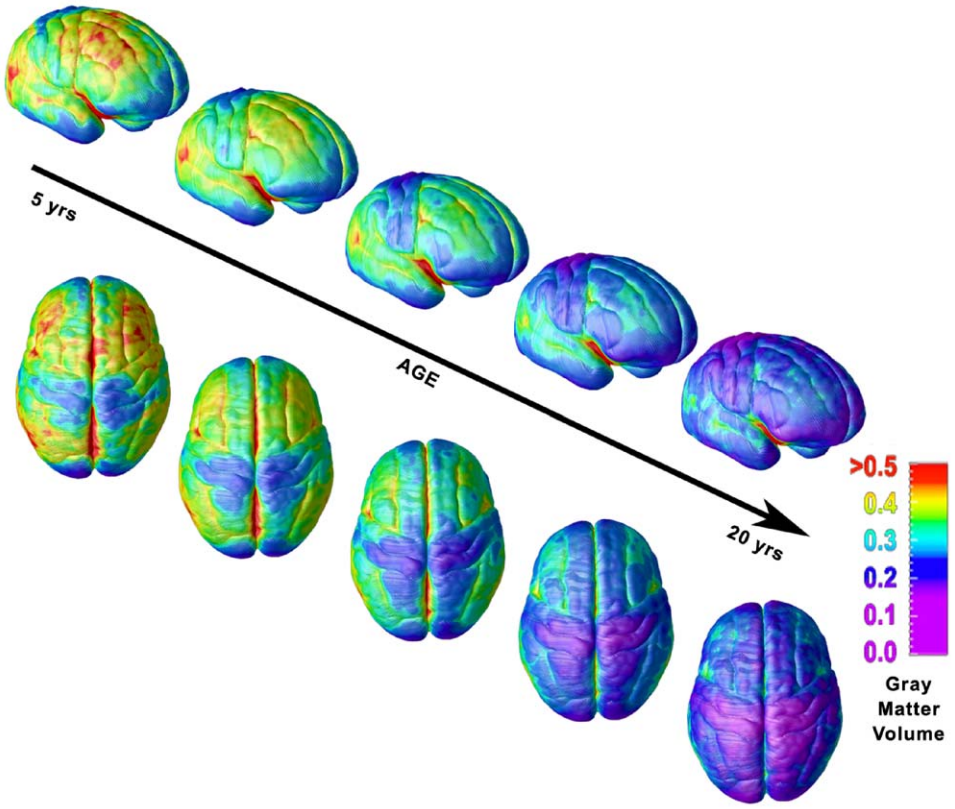

Fig. 6. Right lateral and top views of the dynamic sequence of gray matter maturation over the cortical surface. The side bar shows a color representation in units of GM volume. Fifty-two scans from 13 subjects each scanned 4 times at approximately 2-year intervals.

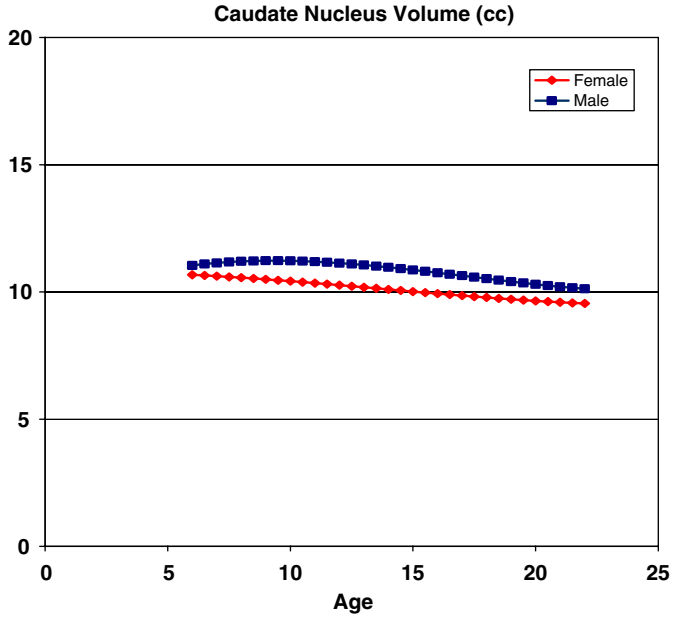

Fig. 7. Caudate nucleus volume by age for 224 females (375 scans) in red and 287 Males (532 scans) in blue.

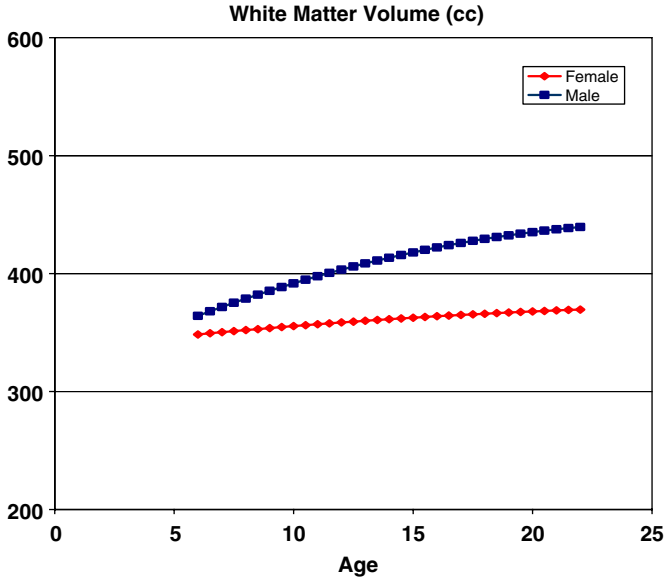

Fig. 8. White matter volume by age for 224 females (375 scans) in red and 287 males (532 scans) in blue.

progress throughout adolescence (Allen et al., 1991; Cowell et al., 1992; Pujol et al., 1993; Rauch and Jinkins, 1994) raising the question of whether this may be related to the improvement in these cognitive capacities seen during childhood and adolescence. Effects of sex have been widely debated with some authors finding gender-related differences (Cowell et al., 1992; de Lacoste et al., 1986; Holloway and de Lacoste, 1986; Clarke et al., 1989) while many have

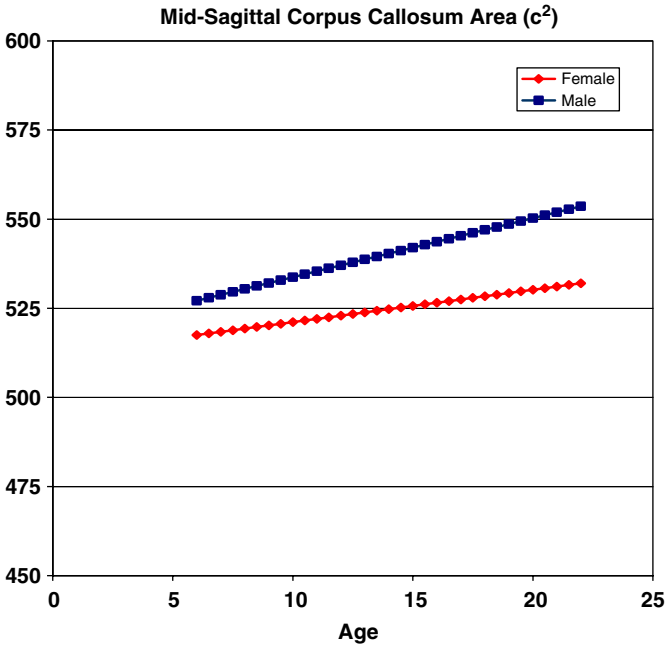

Fig. 9. Midsagittal corpus callosum area by age for 224 females (375 scans) in red and 287 Males (532 scans) in blue.

not (Bell and Variend, 1985; Witelson, 1985a, b; Oppenheim et al., 1987; Weis et al., 1988, 1989; Byne et al., 1988). In the NIMH sample total midsagittal corpus callosum area increased robustly from ages 4 to 18 years, but there were no significant gender effects (see Fig. 9).

5.3.7. Summary

Total brain size is 95% of maximum size by age 6, although cortical and subcortical components of the brain change dramatically during childhood and adolescence. Gray matter volumes follow inverted U-shaped developmental curves during childhood and are regional specific whereas white matter volume changes tend to be more linear and less variant across regions. Brain structure size and developmental trajectories are highly variable and sexually dimorphic.

6. Brain–behavior relationships

A primary aim of developmental studies of brain structure is to better understand developmental changes in cognition and behavior. Although few would argue that the brain is the physical substrate for cognition and behavior, relationships between the size of a particular brain area and these functions are rarely straightforward. It is a considerable challenge to relate brain function to distributed neural networks or to the complex interactions of neurons, neurotransmitter systems, and synaptic function within any given brain region. Nonetheless, correlations have been identified between some aspects of brain structure size and functional capacity. Several studies have shown that there are correlations of brain structural measures with IQ on both whole-brain and regional levels (Reiss et al., 1996; Haier et al., 2004; Posthuma et al., 2002; Thompson et al., 2001; Toga and Thompson, 2004).

Relationships between memory function and hippocampal size have also been noted in several animal models. Food-storing species of birds have larger hippocampi than related non-food-storing species (Krebs et al., 1989; Sherry et al., 1989), and in mammals, a similar example can be found in voles. Male voles of the polygamous species travel far and wide in search of mates; they perform better than their female counterparts on laboratory measures of spatial ability and have significantly larger hippocampi (Sherry et al., 1992). Conversely, in the monogamous vole species, which do not show male–female differences in spatial ability, no sexual dimorphism of hippocampal size is seen (Jacobs et al., 1990). In humans also, correlations between memory for stories and left hippocampal volume have been noted (Goldberg et al., 1994; Lencz et al., 1992). A study of taxi drivers in London found that they had larger posterior hippocampi than controls, thought to be related to their extensive amount of navigational memory required for their work (Maguire et al., 2000).

The realization of the amount of plasticity present in even the adult brain has also made clear that the relationship between factors affecting brain development and the resultant brain structures is staggeringly complex. As articulated by several investigators (Ansari and Karmiloff-Smith, 2002; Cicchetti and Cohen, 1995; Gottlieb and Halpern, 2002; Johnson et al., 2002; Karmiloff-Smith et al., 2004; Rutter and Sroufe, 2000; Sameroff and Mackenzie, 2003; Thomas and Karmiloff-Smith, 2002; Peterson, 2003), the structure of the brain at any time is a product of interactions between genetic, epigenetic, and environmental factors (“environmental” taken broadly as including both the outside environment and the internal physiological milieu). Stresses placed on the developing individual by a mismatch between his or her capacities and demands placed by the environment will result in compensatory physiological responses and behaviors that in time may affect brain structures. This can be part of a normal learning process, or, if the mismatch is too severe, can result in pathology. Influences of these compensations upon developmental trajectories may include a complete normalization, or only a partial return. The compensations themselves may even trigger environmental reactions that further divert the developmental trajectory from what would have been expected. It is not possible to determine ex post facto from a neuroimaging study which features are related to the initial perturbation or genetic anomaly and which to downstream effects—the “inverse solution” problem, as reviewed by (Courchesne, 1994). Longitudinal studies beginning as early as possible are the best means to try to tease apart how brain structure relates to other factors affecting the developmental trajectory (Peterson, 2003). Such studies may be logistically difficult, but as described previously, the few available to date have been fruitful in showing significant differences in trajectories

that were not apparent from previous cross-sectional studies (Giedd et al., 1999; Gogtay et al., 2004).

7. Conclusion and future directions

The field of pediatric structural neuroimaging has been growing rapidly in response to the realization of the complexity and potential malleability of postnatal brain development. There are now large-scale studies underway in several countries combining data from multiple sites in order to increase sample sizes and move towards the compilation of population-based measures of brain development. Advances in scanner technology are making it possible to obtain very high-resolution structural data within time frames feasible for pediatric populations. Although not reviewed here, recent years have seen the development of MRI-acquisition methods such as diffusion tensor imaging, magnetic resonance spectroscopy, and relaxometry that are able to augment structural data with information about microstructural and physiological aspects of brain development. The application of increasingly sophisticated image analysis and statistical modeling methods is allowing exploration of higher-level structural characteristics such as shape, symmetry, and complexity.

Remarkable advances in the field of pediatric neuroimaging have opened new windows into our understanding of the living growing human brain. The mapping of developmental trajectories in typical development lays the groundwork for the next stages of exploring the influences on those trajectories and ultimately using the knowledge to optimize brain development in healthy and clinical populations.

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