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Anatomical Brain Magnetic Resonance Imaging of Typically Developing Children and Adolescents

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Many psychiatric disorders, including some with adult onset such as schizophrenia, are increasingly being conceptualized as stemming from anomalies of neurodevelopment. To explore neurodevelopmental hypotheses of illness, it is useful to have well-characterized data regarding typical maturation to serve as a “yardstick” from which to assess possible deviations. Studies of typical development, and the influences on that development, may also unveil the timing and mechanisms of brain maturation guiding the way for novel interventions.

In this overview, we will touch on methodological issues relevant to magnetic resonance imaging (MRI) studies of brain anatomy, summarize MRI findings of neuroanatomic changes during childhood and adolescence, and discuss possible influences on brain development trajectories.

As indicated in the previous articles of this series, one of the first steps in measuring brain morphometric characteristics in a conventional anatomic MRI is to classify (or “segment”) individual voxels (the smallest elements of different MRI signals—usually approximately 1 mL) as corresponding to CSF, white matter (WM), or gray matter (GM). Once categorized by tissue type, various parcellations can be performed to derive volumes at the level of lobes (e.g., frontal, temporal, parietal, occipital); regions defined by gyral, sulcal, or GM, WM, and CSF boundaries (e.g., caudate nucleus); or individual voxels.

Segmentation and parcellation of MRIs was originally exclusively done by trained individuals outlining particular regions of interest (frequently abbreviated as ROIs) by hand. Although having a highly trained individual manually identify brain regions is considered the closest thing to a “gold standard” available, the time and anatomic expertise necessary for training raters and performing this type of analysis can be prohibitive. This has motivated many laboratories to develop computer algorithms capable of automatically classifying regions of MRI images as belonging to different tissue types and anatomic regions. The rapid progress in this area has made it feasible to perform the type of large scale studies necessary to capture many of the changes associated with typical and atypical brain development. Automated methods have also opened the door to innovative ways of looking at brain structure, such as analyzing the shape and thickness of the cortical sheet.

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However, the fidelity of automated methods depends on the clarity of the borders between structures, which in turn is determined by a combination of the anatomy of a particular structure and the quality of the MRI image. For example, the amygdala and hippocampus are difficult for automated methods to separate properly because they represent adjacent GM structures. In cases such as these, hand measurements may still be the best approach, although even human raters may need considerable experience before they can consistently identify the borders of such structures on conventional MRI.

The data for this overview are largely derived from 387 typically developing subjects (829 scans) participating in an ongoing longitudinal study at the Child Psychiatry Branch of the National Institute of Mental Health. Begun in 1989 by Markus Kruesi, M.D., and Judith Rapoport, M.D., the study design is for participants aged 3 to 30 years to come to the National Institutes of Health at approximately 2-year intervals for brain imaging, psychological and behavioral assessment, and collection of DNA. The emphasis on this single source is not to devalue the many excellent contributions of other investigators but to provide an integrated account from the world's largest collection of child and adolescent brain MRI scans with data acquired using uniform screening/assessment batteries, the same scanner, and the same methods of image analyses. We have supplemented with references to studies by other laboratories, although a complete review of the field is beyond the scope of this article.

TOTAL CEREBRAL, CEREBELLAR, AND VENTRICULAR VOLUME

In the Child Psychiatry Branch cohort, total cerebral volume peaks, on average, at 10.5 years in female subjects and 14.5 years in male subjects.¹ By age 6 years, the brain is at approximately 95% of this peak (Fig. 1). Cerebellum volume peaks approximately 2 years later than cerebral volume.² Lateral ventricular volume has the most differences between individuals³ and increases throughout healthy child and adolescent development. These typically occurring increases should be considered when interpreting the ventricular enlargement widely reported in patient populations.

Sowell and coworkers⁴ measured changes in brain volume in a group of 45 children scanned twice (2 years apart) between ages 5 and 11 years. Using a different method, in which the distance was measured between points on the brain surface and the center of the brain, they also found increases in brain size during this age range, particularly in the frontal and occipital regions.

Caviness et al.,⁵ in a cross-sectional sample of 15 boys and 15 girls aged 7 to 11 years, found that the cerebellum was at adult volume in the female subjects but not in the male subjects at this age range, suggesting the presence of late development and sex dimorphism.

WHITE MATTER

The white color of WM is produced by myelin, fatty white sheaths formed by oligodendrocytes that wrap around axons and drastically increase the speed of neuronal signals. The volume of WM generally increases throughout childhood and adolescence,¹ which may underlie greater connectivity and integration of disparate neural circuitry. An important feature that has only recently been appreciated is that myelin does not only maximize speed of transmission but also modulates the timing and synchrony of the neuronal firing patterns that create functional networks in the brain.⁶ Consistent with this, a study using a measure of WM density to map regional WM growth found rapid localized increases between childhood and adolescence. Corticospinal tracts showed increases that were similar in magnitude on both sides, whereas tracts connecting the frontal and temporal regions showed more increase in the left-sided language-associated regions.⁷

GRAY MATTER

Whereas WM increases during childhood and adolescence, the trajectories of GM volumes follow an inverted U-shaped developmental trajectory. The different developmental curves of WM and GM belie the intimate connections among neurons, glial cells, and myelin, which are fellow components in neural circuits and are linked by lifelong reciprocal relations. Cortical GM changes at the voxel level from ages 4 to 20 years derived from scans of 13 subjects who had each been scanned 4 times at approximately 2-year intervals are shown in Figure 2 (animation is available at <http://www.nimh.nih.gov/videos/press/prbrainmaturing.mpeg>).⁸ The age of peak GM density is earliest in primary sensorimotor areas and latest in higher-order association areas such as the dorsolateral prefrontal cortex, inferior parietal, and superior temporal gyrus. An unresolved question is the degree to which the cortical GM reductions are driven by synaptic pruning versus myelination along the GM/WM border.⁹ The volume of the caudate nucleus, a subcortical GM structure, also follows an inverted U-shaped developmental trajectory, with peaks similar to the frontal lobes with which they share extensive connections.

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INFLUENCES ON DEVELOPMENTAL TRAJECTORIES OF BRAIN ANATOMY

Gene and Environment

By comparing how alike monozygotic twins are versus dizygotic twins, we can estimate the relative contributions of genetic (i.e., “heritability”) and environmental effects to the brain imaging findings.¹⁰ Importantly, we can also assess gene-by-environment interactions and the effects of age and sex on heritability. The current sample size from our ongoing longitudinal study is approximately 600 scans from 90 monozygotic and 60 dizygotic twin pairs. Heritability for total cerebrum and lobar volumes (including GM and WM subcompartments) ranged from 0.77 to 0.88.¹¹ Highly heritable brain morphometric measures provide biological markers for inherited traits and may serve as targets for genetic linkage and association studies.^{12,13} Multivariate analyses, which allow assessment of the degree to which the same genetic or environmental factors contribute to multiple neuroanatomic structures, indicate that a single shared genetic effect accounts for 60% of the variability in cortical thickness.¹⁴

Age-related changes in heritability may be linked to the timing of gene expression and related to the age of onset of disorders. In general, heritability increases with age for WM and decreases for GM volumes,¹¹ whereas heritability increases for cortical thickness in regions within the frontal, parietal, and temporal lobes (Fig. 3).¹⁵ Knowledge of when certain brain structures are particularly sensitive to genetic or environmental influences during development could have important educational and/or therapeutic implications.

Male/Female

Given that nearly all neuropsychiatric disorders have different prevalence, age of onset, and symptoms between the male and the female subjects, sex differences in typical developmental brain trajectories are highly relevant for child psychiatry. Consistent with the adult neuroimaging literature,¹⁶ mean total cerebral volume was approximately 10% larger in the male subjects. Also, GM volume peaks generally occurred 1 to 3 years earlier for the female subjects.¹

The rapid development of the brain over the first few years of life and the recognition of the importance of early events in neurodevelopmental disorders such as autism have led to increased interest in scanning infants and young children. A study by investigators at the University of North Carolina of 74 neonates who underwent imaging within the first weeks of life found rapid growth of cerebral volumes; sexual dimorphism of brain volumes was already

present, with intracranial volume being significantly larger in the male subjects, even after correction for differences in birth weight.¹⁷

Total brain size differences between the male and the female subjects should not be interpreted as imparting functional advantage or disadvantage. Gross structural measures may not reflect sexually dimorphic differences in functionally relevant factors such as neuronal connectivity and receptor density. Whether, or how, to adjust for this total brain size difference in assessing subcomponents of the brain (i.e., are certain brain structures “relatively” larger in the female subjects) strongly affects what is reported as sexually dimorphic in the literature.

An interesting approach to address this scaling issue was reported by Sowell et al.¹⁸ who found that regionally specific sex differences detected in a sample of 176 people between 7 and 87 years of age (i.e., right parietal and posterior temporal cortex thicker in female subjects) were replicated in a subset of 18 male and 18 female brains that did not differ in total brain size.

DISCUSSION

The general pattern for typical brain development in the first 25 years of life is a roughly linear increase in WM volumes and regionally specific inverted U-shaped developmental trajectories for GM structures, with peak volumes occurring in late childhood or early adolescence. A prominent theme is that, in neuroimaging, as in life, it is often more about the journey than the destination. This theme is relevant in studies of typical development where there are strong age-by-heritability interactions in twin studies, sexual dimorphism is greater for the paths of development than final size, and age-by-cortical thickness developmental curves are more predictive of IQ than cortical thickness at age 20 years.¹⁹ The “journey not just destination” theme is also highly relevant in studies of psychopathology where it is the trajectories of development that most distinguish controls from those with attention-deficit/hyperactivity disorder or childhood-onset schizophrenia.

Adequately characterizing developmental trajectories requires either large cross-sectional samples or longitudinal studies, both of which pose substantial methodological challenges. Differences in subject and control selection criteria, image acquisition, and image analysis techniques contribute to the high rate of nonreplication in the pediatric neuroimaging literature and make valid meta-analytic studies difficult. A six-site neuroimaging study of control pediatric subjects using standardized methodology across the sites is underway and should further illuminate the nuances of typical brain development.²⁰

Although group average brain anatomy differences have been reported for nearly all neuropsychiatric disorders, the large overlap of values between clinical and control populations currently precludes diagnostic use (except to rule out possible central nervous system insults such as tumors, intracranial bleeds, or congenital anomalies as etiologies for the symptoms). There is no identified “lesion” common to all, or even most, children with the most frequently studied disorders of autism, attention-deficit/hyperactivity disorder, childhood-onset schizophrenia, dyslexia, fragile X, juvenile-onset bipolar disorder, posttraumatic stress disorder, Sydenham chorea, or Tourette’s syndrome. Neuroimaging is currently most useful to explore the core nature of the illnesses and to provide endophenotypes, biological markers that are intermediate between genes and behavior. Endophenotypes may also help identify subtypes of illnesses that have different pathophysiology, prognosis, or treatment response.

The future of pediatric neuroimaging is likely to see a growing number of studies combining multiple imaging modalities on the same individuals (e.g., structural MRI, functional MRI, diffusion tensor imaging, magnetization transfer imaging, electroencephalography, and magnetoencephalography). This provides a “greater than the sum of its parts” synergy because information from each modality informs interpretation of the others. Also, combining imaging

with postmortem studies of animals will be instrumental in clarifying the mechanisms driving the imaging findings such as discerning the degree to which cortical GM changes as detected via MRI are related to arborization/pruning of neurons or to encroachment of WM on the inner cortical border. Another important direction for future neuroimaging studies will be increased integration with social and educational science, which has remained relatively separate despite the shared goal of successfully guiding people through the childhood and adolescent years in preparation for the adult world.

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REFERENCES

1. Lenroot RK, Gogtay N, Greenstein DK, et al. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. *Neuroimage* 2007;36:1065–1073. [PubMed: 17513132]
2. Mackie S, Shaw P, Lenroot R, et al. Cerebellar development and clinical outcome in attention deficit hyperactivity disorder. *Am J Psychiatry* 2007;164:647–655. [PubMed: 17403979]
3. Lange N, Giedd JN, Castellanos FX, Vaituzis AC, Rapoport JL. Variability of human brain structure size: ages 4 to 20. *Psychiatry Res* 1997;74:1–12. [PubMed: 10710158]
4. Sowell ER, Thompson PM, Leonard CM, Welcome SE, Kan E, Toga AW. Longitudinal mapping of cortical thickness and brain growth in normal children. *J Neurosci* 2004;24:8223–8231. [PubMed: 15385605]
5. Caviness VSJ, Kennedy DN, Richelme C, Rademacher J, Filipek PA. The human brain age 7–11 years: a volumetric analysis based on magnetic resonance images. *Cereb Cortex* 1996;6:726–736. [PubMed: 8921207]
6. Fields RD, Stevens-Graham B. New insights into neuron-glia communication. *Science* 2002;298:556–562. [PubMed: 12386325]
7. Paus T, Zijdenbos A, Worsley K, et al. Structural maturation of neural pathways in children and adolescents: in vivo study. *Science* 1999;283:1908–1911. [PubMed: 10082463]
8. Gogtay N, Giedd JN, Lusk L, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A* 2004;101:8174–8179. [PubMed: 15148381]
9. Sowell ER, Thompson PM, Tessner KD, Toga AW. Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: Inverse relationships during postadolescent brain maturation. *J Neurosci* 2001;21:8819–8829. [PubMed: 11698594]
10. Neale, MC.; Cardon, LR. North Atlantic Treaty Organization. Scientific Affairs Division. *Methodology for Genetic Studies of Twins and Families*. Kluwer Academic Publishers; Dordrecht: 1992.
11. Wallace GL, Schmitt JE, Lenroot RK, et al. A pediatric twin study of brain morphometry. *J Child Psychol Psychiatry* 2006;47:987–993. [PubMed: 17073977]
12. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 2003;160:636–645. [PubMed: 12668349]
13. Schmitt JE, Lenroot RK, Wallace GL, et al. Identification of genetically mediated cortical networks: a multivariate study of pediatric twins and siblings. *Cereb Cortex* 2008;18:1737–1747. [PubMed: 18234689]
14. Schmitt JE, Wallace GL, Rosenthal MA, et al. A multivariate analysis of neuroanatomic relationships in a genetically informative pediatric sample. *Neuroimage* 2007;35:70–82. [PubMed: 17208460]
15. Lenroot RK, Schmitt JE, Ordaz SJ, et al. Differences in genetic and environmental influences on the human cerebral cortex associated with development during childhood and adolescence. *Hum Brain Mapp* 2009;30:163–174. [PubMed: 18041741]
16. Goldstein JM, Seidman LJ, Horton NJ, et al. Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. *Cereb Cortex* 2001;11:490–497. [PubMed: 11375910]

17. Gilmore JH, Lin W, Prastawa MW, et al. Regional gray matter growth, sexual dimorphism, and cerebral asymmetry in the neonatal brain. *J Neurosci* 2007;27:255–1260.
18. Sowell ER, Peterson BS, Kan E, et al. Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. *Cereb Cortex* 2007;17:1550–1560. [PubMed: 16945978]
19. Shaw P, Greenstein D, Lerch J, et al. Intellectual ability and cortical development in children and adolescents. *Nature* 2006;440:676–679. [PubMed: 16572172]
20. Evans AC. The NIH MRI study of normal brain development. *Neuroimage* 2006;30:184–202. [PubMed: 16376577]

Fig. 1.

Mean volume by age in years for male subjects ($n = 475$ scans) and female subjects ($n = 354$ scans). Middle lines in each set of three lines represent mean values, and upper and lower lines represent upper and lower 95% confidence intervals, respectively. All curves differed significantly in height and shape. Figure adapted from Lenroot et al., 2007.¹

Fig. 2. 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 gray matter volume. (From Gogtay et al.8)

Fig. 3.

Age-related changes in heritability for younger and older children. Variance component estimates are calculated using the AE model, because the shared environment component did not significantly affect results. Estimates of variance components were computed separately for younger children (aged 5–11 years) and for older children and adolescents (aged 12–19 years). Columns a and b show areas that are significantly heritable for younger (a) and older (b) age groups. Column c is a map of differences in heritability, created by subtracting the values for the younger group from those of the older group. Arrows indicate regions in which heritability changes between age groups. Numbers to the left of the scale bar indicate degree of statistical significance. Numbers to the right of the scale bar indicate the magnitude of the

difference in heritability: light green, yellow, and red regions indicate heritability increasing with age; dark green, blue, and purple regions indicate decreasing heritability. A false discovery rate threshold of $q = 0.05$ was applied to significance maps. (From Lenroot et al.15)