The Adolescent Brain: Insights from Neuroimaging

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Abstract Adolescence is a time of dramatic changes in body, behavior, and brain. Although the adolescent brain has different features than those of a child or mature adult, it is not broken or defective. The changes in the teen brain have been exquisitely forged by evolution to facilitate the survival of our species. During the second decade of life the brain does not mature by becoming larger; it matures by becoming more specialized and its subcomponents becoming more "interconnected." Recent advances in neuroimaging and the application of graph theoretical methods of analysis are enabling scientists to characterize these changes in connectivity and how they vary by age, sex, health/illness, and other cognitive or behavioral measures.

Introduction

Adolescence is the transition from our caregiver-dependent childhood to independent functioning as an adult; thus it is defined by both biological and social factors. The timing of this transition may vary across individuals and cultures but in general is thought to begin around the onset of puberty and encompasses the teenage years. Adolescence is a time of change, both physical and psychological. The path to independence is usually accompanied by behaviors and attitudes that are different from their parents, and often these differences are ridiculed as evidence that the teenage brain is "broken" or "defective." Although adolescence is a peak time for the emergence of psychopathology, the many dynamic brain changes occurring during the second decade are also part of the pattern of healthy development and are integral to our success as a species.

In this chapter, we will review aspects of adolescent brain changes derived from our ongoing longitudinal magnetic resonance imaging (MRI) study of brain development that has been conducted since 1989 at the Child Psychiatry Branch of the

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National Institute of Mental Health. The data set encompasses approximately 8,000 images from 3,000 subjects (longitudinal data acquired at approximately 2-year intervals): ¼ from healthy singletons, ¼ from healthy twins, and ½ from one of 25 clinical populations (e.g., autism, ADHD, childhood-onset schizophrenia). Our focus on this data set is not meant to slight the many other excellent studies but to provide one perspective from a single, fairly large project that has used standardized methods of image acquisition and analysis.

The organization of the chapter is to first describe the developmental trajectories of specific brain regions during typical childhood and adolescence and then to discuss the implications of the findings for clinicians, teachers, parents, and the youth themselves.

Total Cerebral Volume

In the NIMH Child Psychiatry Branch study data, total cerebral volume increases during childhood, reaches a peak at age 10.5 in girls and 14.5 in boys, and subsequently slightly declines through the second and third decades (Lenroot et al. 2007). Total brain volume is 95 % of its peak size by age 6. Brain size varies markedly from person to person, with as much as a two-fold difference among healthy subjects of the same age. This high variability extends to measures of brain substructures and has important implications for the interpretation and utility of brain imaging results.

Group-average brain size is approximately 10 % larger in males (see Fig. 1a). The magnitude of this difference is relatively stable from birth across the life span. This difference in brain size should not be interpreted as necessarily imparting any sort of functional advantage or disadvantage, as large-scale brain measures may not reflect sexually dimorphic differences in functionally relevant factors such as neuronal connectivity and receptor density.

The sex difference in total brain volume is not solely attributable to the larger body size of males. This is especially evident in our pediatric population, where the brain size difference persists despite little difference in body size. In fact, both in our sample and according to published normative data from the Centers for Disease Control, because of an earlier growth spurt, females tend to be slightly taller than males from ages 10–13 years. Across species there is a relationship between brain size and body size, but in individual humans the growth trajectories are quite dissimilar, with body size increasing through approximately age 17.

Total brain size difference between males and females has broad implications for studies of sexual dimorphism. Many of the reported findings of brain sexual dimorphism are influenced strongly by whether, or how, the size of subcomponents of the brain are adjusted for the ~10 % difference in total brain volume. Without adjustment, the absolute size of most structures is larger in males. If adjustments are made to subcomponents (via covariation or the use of ratios to total brain volume),

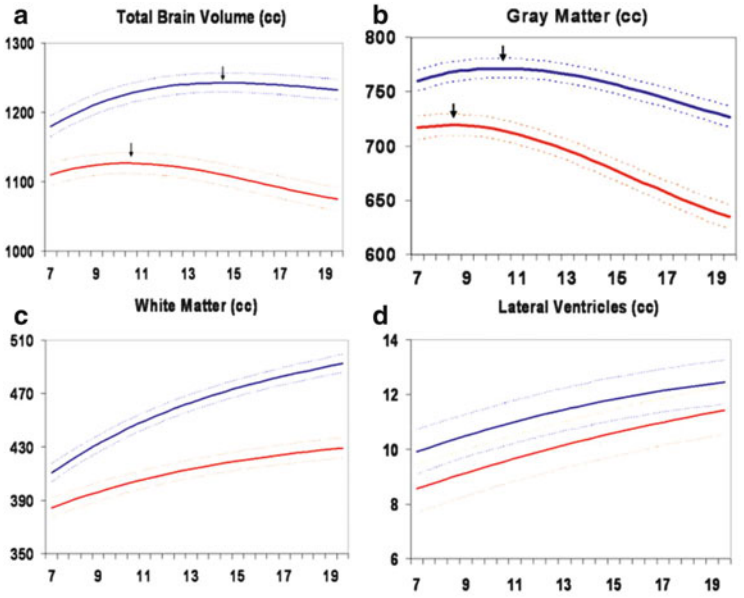

Fig. 1 Mean volume by age in years for males ($N = 475$ scans) and females ($N = 354$ scans). Middle lines in each set of three lines represent mean values, and *upper* and *lower* lines represent upper and lower 95 % confidence intervals. All curves differed significantly in height and shape with the exception of lateral ventricles, in which only height was different, and mid-sagittal area of the corpus callosum, in which neither height nor shape was different. (**a**) Total brain volume, (**b**) gray matter volume, (**c**) white matter volume, and (**d**) lateral ventricle volume (Adapted from Lenroot et al. 2007, figure in public domain)

an entirely different list of structures, varying by sample size and age distribution, is generated.

The challenge of how best to account for the male/female difference in sub-components of the brain in light of the total size difference is informed by allometry, the study of the relationship between size and shape. The size of neurons, vasculature, and other components of brain anatomy is constrained by metabolic and physical considerations, which creates the need for brains of different sizes to have variable enlargement of all parts (Finlay and Darlington 1995). For instance, in comparisons across and within species, white matter (WM) to gray matter (GM) ratios increase with enlargement of total brain volume following a 4/3 power law (Zhang and Sejnowski 2000). This phenomenon may account for why reported differences of greater GM/WM ratios in females (Allen et al. 2003; Gur et al. 2002) are not nearly as robust when comparing males and females with similar total brain volumes (Leonard et al. 2008).

Cerebellum

The cerebellum is relatively understudied in pediatric neuroimaging studies but has three features that make it of compelling interest. Of our large-scale measures, the cerebellum is (1) the most sexually dimorphic; (2) the latest to reach adult volume; and (3) the least heritable (i.e., most influenced by environment). Although only about 1/9 the volume of the cerebrum, the cerebellum contains more brain cells than the cerebrum. The cerebellum has traditionally been conceptualized as being related to motor control, but it is now commonly accepted that the cerebellum is also involved in emotional processing and other higher cognitive functions that mature throughout adolescence (Riva and Giorgi 2000; Schmahmann 2004).

Similar to the cerebrum, developmental curves of total cerebellum size follow an inverted, U-shaped developmental trajectory, with peak size occurring at 11.3 years in girls and 15.6 in boys (Tiemeier et al. 2010). The cerebellum is not a unitary structure but composed of functionally distinct subunits. In cross section, the anatomy of the cerebellum resembles a butterfly shape, with the central body part corresponding to the cerebellar vermis and the wings corresponding to the cerebellar hemispheric lobes. In contrast to the evolutionarily more recent cerebellar hemispheric lobes that followed the inverted, U-shaped developmental trajectory, cerebellar vermis size did not change across this age span.

Lateral Ventricles

The lateral ventricles are unlike the other structures reported here, as they are cerebrospinal fluid-filled compartments, not GM or WM. Increased lateral ventricle volume measures are usually interpreted as an indirect assessment of loss of the tissue from neighboring structures. Ventricular volume increases during typical child and adolescent development should be considered when interpreting the many reports of increased ventricular volumes in a broad range of neuropsychiatric conditions.

White Matter

Whether brain tissue is classified as GM or WM depends largely on the amount of myelinated axons. Myelination is the wrapping of oligodendrocytes around axons, which acts as an electrical insulator, increasing the speed of neuronal signal transmission. The insulating properties of myelin allow signals to travel at speeds up to 100× faster than in unmyelinated axons. Additionally, myelination allows ion pumps to reset the ion gradients only at the nodes between sections of myelin (called nodes of Ranvier), instead of along the entire expanse of the axons, resulting

in up to a 30-fold increase in the frequency with which a given neuron can transmit information. The combination of increased speed (100×) and quicker recovery time (30×) can yield a 3,000-fold increase in the amount of information transmitted per second. Myelination does not simply maximize speed of transmission but also modulates the timing and synchrony of neuronal firing patterns that convey meaning in the brain (Fields 2002). Signal processing plays a central role in developmental changes in the brain's ability to adapt in response to its environment by inhibiting axon sprouting and the creation of new synapses (Fields 2008). These non-subtle impacts of myelin on the brain's ability to process information may underlie many of the cognitive abilities associated with our species.

WM volumes increase steadily throughout childhood and adolescence (Fig. 1c), with similar rates across the major lobes (i.e., the frontal, temporal, and parietal lobes). However, for smaller regions, the growth rates can be quite dynamic, with as much as a 50 % change over a 2-year period (Thompson et al. 2000). The most prominent WM structure is the corpus callosum. It is comprised of approximately 200 million mostly myelinated axons connecting homologous areas of the left and right cerebral hemispheres. Its developmental trajectory reflects the general increases in total WM volume.

Increasing WM volumes on anatomic MRI and greater coherence on fMRI, EEG, and MEG converge to identify a pattern of increased connectivity among spatially disparate brain regions as a hallmark of adolescent development. Diffusion tensor imaging studies, which assess the directionality of WM, also demonstrate an increase in WM organization during adolescence. Changes in WM organization in specific regions correlate with improvements in language (Nagy et al. 2004), reading (Deutsch et al. 2005), response inhibition ability (Liston et al. 2006) and memory (Nagy et al. 2004). Characterizing developing neural circuitry and the changing relationships among disparate brain components is one of the most active areas of neuroimaging research, utilizing graph theory to quantify such things as the small world network properties of the brain (Hagmann et al. 2010).

Gray Matter

Cortical GM

GM is comprised predominantly of cell bodies and dendrites but may also include axons, glia, blood vessels, and extracellular space (Braitenberg 2001). Despite a lifelong reciprocal relationship and shared components of neural circuits, GM and WM have distinctly different developmental trajectories (Fig. 1b). In contrast to the roughly linear increase of WM, GM developmental trajectories follow an inverted, U-shaped curve with peak sizes occurring at different times and in different regions. For example, in the frontal lobes, peak cortical GM volume occurs at 9.5 years in

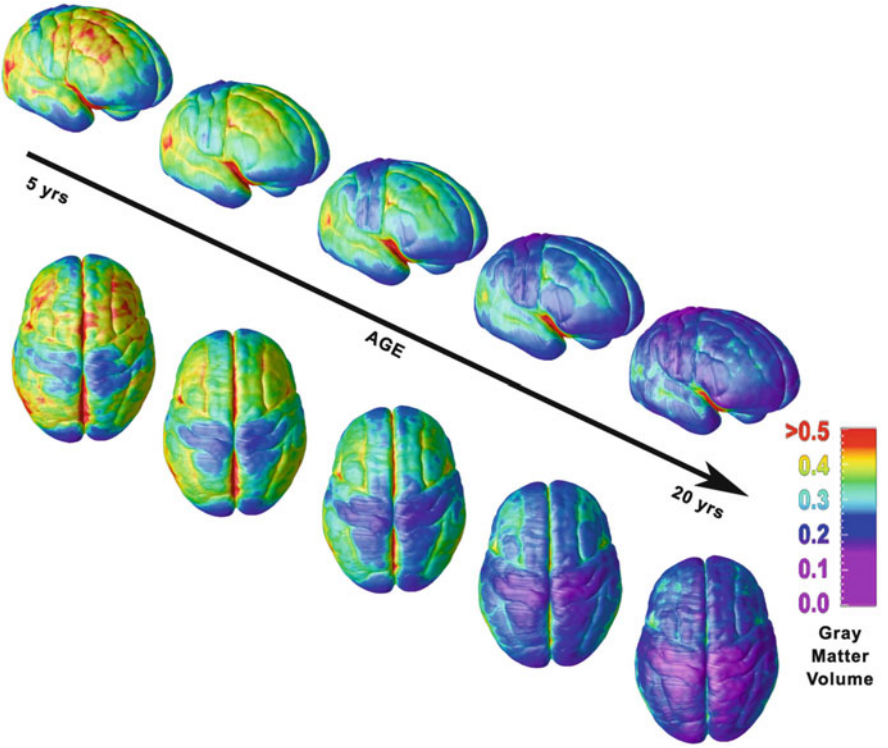

Fig. 2 Right lateral and top views of the dynamic sequence of GM maturation over the cortical surface. The *side bar* shows a color representation in units of GM volume. The initial frames depict regions of interest in the cortex (Adapted from Gogtay et al. 2004; copyright 2004 by the National Academy of Sciences)

girls and 10.5 in boys; at 10.0 in girls and 11.0 in boys in the temporal lobes; and at 7.5 in girls and 9 in boys in the parietal lobes.

Although lobar level GM volumes provide some functional relevance, the capacity to quantify GM thickness at each of approximately 40,000 voxels on the brain surface provides a better spatial resolution to discern functionally distinct regions. By analyzing scans acquired from the same individuals over the course of development, movies of cortical thickness change can be created. One such animation derived from scans of 13 subjects who had each undergone scanning four times at approximately 2-year intervals between the ages of 4 and 22 is available at http://www.nimh.nih.gov/videos/press/prbrainmaturing.mpeg. Still images of the movie at different ages are shown in Fig. 2 (Gogtay et al. 2004).

GM peaks earliest in primary sensorimotor areas and latest in higher order association areas that integrate those primary functions (i.e., dorsolateral prefrontal cortex, inferior parietal, and superior temporal gyrus). Postmortem studies suggest that part of the GM changes may be related to synaptic proliferation and pruning (Huttenlocher 1994). The connection between GM volume reductions, EEG

changes, and synaptic pruning was also supported by an MRI/quantified EEG study of 138 healthy subjects from ages 10 to 30 years. It was found that curvilinear reductions in frontal and parietal GM were matched by similar curvilinear reductions in the EEG power of the corresponding regions (Whitford et al. 2007). Because EEG power reflects synaptic activity, the temporally linked EEG power and GM changes suggest that the GM volume reductions are accompanied by reductions in the number of synapses. Another consideration is that myelination may change classification of voxels along the interior cortical border from GM to WM, resulting in ostensible cortical thinning as assessed by MRI volumetrics, but would not necessarily entail changes in the number of synapses (Sowell et al. 2001). Knowledge of the degree to which these and other phenomena may be driving the MRI changes has profound implications for interpreting the imaging results. Imaging of nonhuman primates with post-mortem validation may help discern the cellular phenomenon underlying the MRI changes.

Subcortical Gray Matter

Amygdala and Hippocampus

The temporal lobes, amygdala, and hippocampus are also involved in a myriad of cognitive functions particularly in the realms of emotion, language, and memory (Nolte 1993). These functions change markedly during adolescence (Diener et al. 1985; Jerslid 1963; Wechsler 1974), yet the relationship between the development of cognitive capacities and transformations in the size or shape of the temporal lobe structures subserving these functions is poorly understood.

Amygdala volume increases significantly during adolescence only in males, and hippocampal volume increases significantly only in females (Giedd et al. 1996). 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).

Basal Ganglia

The basal ganglia are a collection of nuclei (the striatum, pallidum, and thalamus) lying beneath the cortical surface. They are components of neural circuits involved in mediating movement but are also critical to diverse, developmentally emergent higher cognitive functions, attention allocation, and affective control. Basal ganglia anomalies have been reported for almost all the neuropsychiatric disorders that have been investigated by neuroimaging (Giedd et al. 2006).

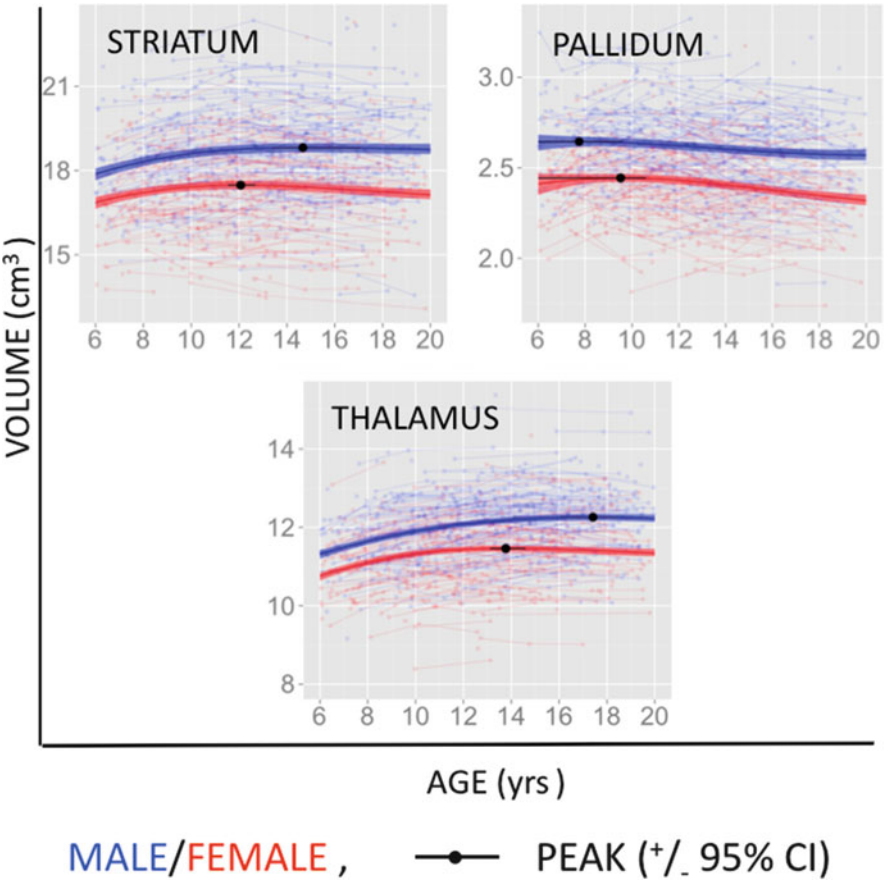

Fig. 3 Developmental trajectories for global volume. Plots showing individual-level anatomical data and best-fit group-level trajectories for bilateral striatal, pallidal, and thalamic volume. *Shaded ribbons* around each curve denote 95 % confidence intervals (Adapted from Raznahan et al. 2014; copyright 2014 by the National Academy of Sciences)

In a recent study of 1,171 longitudinally acquired MRI scans from 618 typically developing males and females aged 5–25 years, we showed that the striatum, pallidum, and thalamus each followed an inverted, U-shaped developmental trajectory (Raznahan et al. 2014).

The striatum and thalamus volumes peak later than cortical volumes and show a relative delay in males. Analyzing the changing shape of these subcortical structures over time reveals that striatal, pallidal, and thalamic domains linked to specific fronto-parietal association cortices contract with age whereas other subcortical territories expand. Furthermore, each structure has areas of sexual dimorphism that change dynamically during adolescence (Fig. 3). These differences may have relevance for sex-biased mental disorders emerging in youth.

Discussion

During adolescence the brain does not mature by becoming larger; it matures by becoming more inter-connected and more specialized. The increased connectivity is reflected in observed WM volume increases but also by electroencephalographic, functional MRI, postmortem, and neuropsychological studies. "Connectivity" characterizes several neuroscience concepts. In anatomic studies, connectivity can mean a physical link between areas of the brain that share common developmental trajectories. In studies of brain function, connectivity describes the relationship between different parts of the brain that activate together during a task. In genetics, it refers to different regions influenced by the same genetic or environmental factors. All of these types of connectivity increase during adolescence (Power et al. 2010). The greater communication among disparate brain regions underlies many of the cognitive advances that occur during the second decade of life. A tradeoff for the increased connectivity is that myelin releases molecules such as Nogo-A (Chen et al. 2000; GrandPr et al. 2000), MAG (GrandPr et al. 2000) and OMgp (McKerracher et al. 1994; Wang et al. 2002) that impede arborization of new connections (Huang et al. 2005; Schwab and Thoenen 1985) and thus decrease plasticity (Fields 2008).

The increasing specialization of the brain is reflected by the inverted, U-shaped GM developmental trajectories of childhood peaks followed by adolescent declines. This pattern is found not only for GM volumes but also for the number of synapses (Huttenlocher and Dabholkar 1997; Huttenlocher and de Courten 1987; Huttenlocher et al. 1982), glucose utilization (Chugani et al. 1987), EEG power (Thatcher 1991), and neurotransmitter receptor densities (Benes 2001). The powerful process of overproduction followed by selective/competitive elimination that shapes the developing nervous system in utero seems to continue to refine the brain throughout adolescent development.

The ability of the brain to change in response to the demands of the environment is often referred to as "plasticity," a highly adaptive feature of our species. Brain plasticity is a life-long process but tends to be most robust in early development. Compared to other species, humans have a very protracted period of life when they are dependent upon their parents or other adults for survival. A benefit of this protracted period of protection is that it allows our brains to stay flexible to changing demands, even more so than our close genetic kin, the Neanderthals, whose tool use changed remarkably little in over 1 million years. They were well suited to deal with the stable, albeit harsh, environment of the time but less facile at adapting to changing demands (Banks et al. 2008).

Plasticity enables humans to be remarkably adaptable to physical and social environments alike. In 10,000 years, we have gone from spending the majority of our time hunting for food and shelter to relying on words and symbols, skills that are approximately only 5,000-years-old. The adaptability of the adolescent brain is being put to the test in the modern world, where digital technologies have dramatically changed the way we learn, play, and interact (Giedd 2012).

The dynamic brain changes of adolescence do confer an increased risk of psychopathology (Paus et al. 2008), but they also provide an excellent basis for learning and resilience. We are faced with an important initiative to utilize our growing knowledge of developmental neurobiology to improve the lives of youth and their families.

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