

Published in final edited form as:

Curr Top Behav Neurosci. 2014 ; 16: 3–17. doi:10.1007/7854_2013_265.

The Neurobiology of Childhood Structural Brain Development: Conception Through Adulthood

Suzanne M. Houston,

Developmental Cognitive Neuroimaging Laboratory, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Division of Research on Children, Youth and Families, Department of Pediatrics, Children's Hospital Los Angeles, 4650 Sunset Blvd., Mailstop #130, Los Angeles, CA 90027, USA

Megan M. Herting, and

Developmental Cognitive Neuroimaging Laboratory, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Division of Research on Children, Youth and Families, Department of Pediatrics, Children's Hospital Los Angeles, 4650 Sunset Blvd., Mailstop #130, Los Angeles, CA 90027, USA

Elizabeth R. Sowell

Developmental Cognitive Neuroimaging Laboratory, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Division of Research on Children, Youth and Families, Department of Pediatrics, Children's Hospital Los Angeles, 4650 Sunset Blvd., Mailstop #130, Los Angeles, CA 90027, USA

Elizabeth R. Sowell: esowell@chla.usc.edu

Abstract

The study of the function and structure of the human brain dates back centuries, when philosophers and physicians theorized about the localization of specific cognitive functions and the structure and organization of underlying brain tissue. In more recent years, the advent of non-invasive techniques such as Magnetic Resonance Imaging (MRI) has allowed scientists unprecedented opportunities to further our understanding not only of structure and function, but of trajectories of brain development in typical and atypical child and adult populations. In this chapter, we hope to provide a system-level approach to introduce what we have learned about structural brain development from conception through adulthood. We discuss important findings from MRI studies, and the directions that future imaging studies can take in the concerted effort to enhance our understanding of brain development, and thus to enhance our ability to develop interventions for various neurodevelopmental disorders.

Keywords

Human brain; Maturation; Cortical thickness; Brain volume; Cortical area; Postnatal and subcortical; Development

1 Introduction

Interest in the organization and function of the human brain dates back to at least fifth century Greece, when cerebrocentric views of the mind emerged. Hippocrates, for instance, posited that the human brain was the central and most important organ for our sensory and cognitive experiences. Plato suggested that the brain was the seat of mental intelligence and, being capable of reason, was the organ that distinguished humans from other mammals. These top-down theories of the human brain, among others, led future philosophers and scientists alike to investigate both the organization and the localization of specific functions in the brain (Feinberg and Farah 2003; Werthheimer 2000).

In the late eighteenth and early nineteenth centuries, theories and interest regarding the neurobiological substrates for different cortical functions became more pronounced. In particular, Franz Josef Gall's theory of phrenology, which proposed that the morphology of the skull related to basic human mental faculties, prompted his contemporaries to evaluate his theory by assessing the postmortem brain tissue of normal and diseased brains. Using this method, Paul Broca, in 1861, was able to localize a region of the brain in the left frontal cortex responsible for speech production. Similarly, neurologist Carl Wernicke examined patients with acute brain injury, and determined that an area near the superior temporal gyrus may be responsible for speech and language comprehension (reviewed in Werthheimer 2000). Later, the German neurologist Korbinian Brodmann was able to publish a map of the mammalian cortex that detailed its cytoarchitectural organization. This map continues to serve as an aid to scientific endeavors exploring cortical maturation and localizing cognitive function (Werthheimer 2000).

The development of noninvasive techniques, such as Magnetic Resonance Imaging (MRI), allowed scientists to weave together past and present knowledge to provide a more comprehensive view of brain and cognitive development. In particular, advances in neuroimaging techniques over the past three decades have allowed scientists to map this knowledge onto more global templates of brain structure and has furthered our understanding of the underlying functional circuitry. In this chapter, we provide an overview of the development of the human cerebrum from conception through adulthood. Next, we review in greater detail what we have learned about postnatal brain development over the past decades since the advent of MRI. Lastly, we discuss future directions and the importance of the integration of multiple neuroimaging modalities in understanding the impact of biological and experiential factors on brain development.

2 Development of the Cortex

What do we know about the development and maturation of the human brain? Neural development begins shortly after conception and continues throughout the life span. Here,

we briefly summarize the landmark events during prenatal (conception to birth) and postnatal (birth to adulthood) neural development.

3 Prenatal Development

The cellular chain of in utero events that lay the foundation for the development of the human cerebral cortex begin soon after conception during what are known as the embryonic (conception-gestational week 8 (GW 8)), early fetal (GW 9-GW 20), and fetal periods (GW 9-birth). These complex events vary spatially and temporally, and are influenced by both positive and negative genetic and environmental influences (Stiles 2008; Stiles and Jernigan 2010). In this section, we will review the basic cellular process that take place in each of these periods and how they contribute to the eventual maturation of the human brain.

4 The Embryonic Period (Conception Through GW 8, First Trimester)

In the earliest post-conception stage, the mammalian embryo, or zygote, contains all of the genetic information from both parents that is necessary for development. This brief stage is characterized by rapid differentiation and enlargement of the zygote into multiple cells. By 2 weeks post-conception, the embryo has transformed into a blastula, or a two-layered cellular structure. Each layer of the blastocyst contains two different cell types: the epiblast cells of the upper layer, which will become the fetus, and the hypoblast cells of the lower layer, which will form extra-embryonic tissues. Following blastula development, a process called gastrulation occurs between days 13 and 20 of the embryonic period. It is during this time that the two-layered cell is reorganized into a three-layered structure via the migration and differentiation of the epi- and hypoblast cells into the ectoderm, mesoderm, and endoderm (Stiles 2008). Briefly, this process includes a split in the upper layer of the blastula, known as the primitive streak, as well as the formation of a molecular signaling structure called the primitive node. Once these structures are formed, a subset of the epiblast cells move from the midline of the embryo toward the primitive streak, and migrate to the under belly of the upper layer. As these cells pass the primitive node, they receive two molecular signals: (1) a signal that induces them to genetically produce a protein that binds to the receptors on the surface of the cells, and eventually induces their transformation into specific types of stem cells and (2) a signal that specifies their final destination. These events induce the differentiation of some of the epiblast cells into the neural progenitor cells. As the name suggests, the neural progenitor cells are capable of producing all of the cells necessary for development of the brain. They do this in two stages. First, the progenitor cells divide in a symmetric, or identical, fashion to produce more neural progenitor cells. Around gestational day 42, the cells begin to divide asymmetrically, whereby two different types of cells are produced: another neural progenitor cell, and a neuron. The new neural progenitor cells continue to divide within the ventricular zone. The neuron, however, leaves the ventricular zone and migrates to the neocortex (Stiles 2008).

The neural progenitor cells that remain in the ventricular zone begin the neural patterning that establishes the primary organization of the central nervous system. Specifically, the neural progenitor cells begin to fold into the tubular structure known as the neural tube. The caudal portion of the neural tube will become the spinal cord, and the rostral region will

evolve into the brain. In the rostral portion of the neural tube, the neural progenitor cells divide to form the forebrain (prosencephalon), the midbrain (mesencephalon), and the hindbrain (rhombencephalon). In order to accomplish this, the neurons produced by neural progenitor cells begin a process of migration that results in the anatomical development of the cortex, which primarily occurs during the fetal period.

5 Fetal Period (GW 9-Birth)

There are two successive types of neuronal migration that occur during the fetal period: (1) somal translocation migration and (2) radial glial migration (Nadarajah et al. 2001; Rakic 1972, 1995). These events allow for the “inside-out” formation of the neocortex into its 6-layered structure. Somal migration occurs at the earlier stages of development, when the cortex is small and neurons have less distance to travel. During somal migration, the neuron extends a long process that attaches to the most outer surface of the developing brain, termed the pial surface. This process then becomes the host for the cell body to migrate to the deepest cortical layer. As the brain becomes larger, somal migration is replaced by radial glial cell migration (Nadarajah et al. 2001). During this period, the neurons again extend a process that also attaches to the pial surface. But instead of the neural body traveling through this process to migrate to the neocortex, the process becomes a scaffolding, or highway of sorts on which other neurons can migrate to their appropriate place in the cortex.

These cellular changes contribute to the change in the appearance and anatomy of the cortex, which is marked by an orderly and sequential formation of the gyri and sulci of the brain (Stiles 2008; Stiles and Jernigan 2010). The primary sulci of the sylvian, cingulate, parieto-occipital, and calcarine regions develop during weeks 14 through 26. Next, the central and superior sulci form, and are followed by the formation of the superior frontal, precentral, inferior frontal, postcentral, and intraparietal sulci. During this time, the longitudinal fissure, which distinguishes the two cerebral hemispheres, begins to form from back to front, and is complete by GW 22 (Chi et al. 1977). It has been postulated that the folding of the neocortex into more complex patterns of sulci and gyri results from a tension of the axonal fibers that connect across brain regions, keeping the length of the fibers short, presumably reducing energy required to transduce between regions in the maturing brain (Van Essen and Drury 1997).

6 Postnatal Development

The majority of neuronal production and migration to regions of the developing cortex occur prenatally, but limited neurogenesis continues within the subventricular zone. These neurons eventually migrate to portions of the hippocampus and to the olfactory bulb. In contrast, the proliferation and migration of the neural progenitor glial cells continues throughout childhood and adulthood. These cells are thought to play an important role in the early organization of neural circuits in the postnatal brain. Specifically, after birth, the glial cells differentiate into either oligodendrocyte or astrocytes. Of these, the oligodendrocytes are thought to be important in increasing conduction speed in the developing brain. After being ensheathed by the fatty substance, myelin, these pathways of neuronal fibers becomes the brain's white matter. This process, known as myelination, typically begins during GW 20–

28 and continues into adulthood, allowing for enhanced efficiency in the transmission of information between these newly developed brain regions (Stiles and Jernigan 2010).

7 Studying Postnatal Brain Development with MRI

Postnatal brain maturation involves dynamic changes in both gray and white matter (Giedd 1999; Sowell et al. 1999a, b, 2004). These patterns are regionally and temporally specific, such that gray matter volume decreases and white matter volume increases between childhood and adolescence occur earlier in more primitive brain regions and later in phylogenetically newer ones (Gogtay et al. 2004; Sowell et al. 1999a, b). Changes in the MR signal and indices of brain structure over time are thought to reflect the postmortem findings that detail differences in the temporal and spatial patterns of synaptic pruning and myelination (Huttenlocher and Dabholkar 1997; Huttenlocher and de Courten 1987; Yakolev 1967). While we still do not know the precise cellular mechanisms that give rise to change over time in gray and white matter signals, it is likely that some combination of synaptic pruning, myelination, and glial cell proliferation result in the changes observed in vivo. Below, we present a review of how these morphological measures are seen to change across postnatal development.

8 Cortical Volume

Gray matter comprise neuronal cell bodies (high in water content), whereas myelinated axons (high in fat content) are the basis of white matter, and the water and fat in these tissues give rise to the different signals we observe with structural MRI. Over the years, MRI studies investigating brain volume development have typically explored proportional changes (relative to total brain volume) in gray and white matter, and have found dynamic changes in both. One of the earliest studies in typical children by Jernigan and Tallal (1990) reported differences in cortical gray matter as a function of age between children, adolescents, and adults, independent of total cortical volume. In this landmark study, it was found that, on average, children actually had more gray matter than young adults. Other cross-sectional studies of normal youth showed that gray matter volume development is curvilinear, generally peaking in late childhood and decreasing throughout adolescence. In contrast, white matter volumes demonstrate a consistent linear increase over time (Giedd 1999; Jernigan et al. 1991; Sowell et al. 2003). One growth curve study demonstrated that up to approximately age 20, there are nonlinear changes in gray matter volume, but linear changes in white matter (Giedd et al. 1999).

During the next decade, studies continued to observe patterns of volumetric change, with most reporting gray matter volume decrease throughout childhood and adolescence. These decreases not only varied in degree, but demonstrated proportional relationships with white matter development. For example, Giedd et al. (1999) studied 145 participants and found that gray/white matter exhibited nonlinear/linear relationships, respectively, for the frontal, occipital, and parietal regions. By contrast, both gray and white matter mature linearly in the occipital region.

9 Cortical Thickness

Toward the end of the 1990s, technological and methodological advances allowed for more precise measurement of cortical thickness (Fischl and Dale 2000; Kabani et al. 2001), which is considered to reflect the packing density of neurons, as well as other components of the neuropil. Similar to volume, cortical thickness shows regional and temporal specificity with development (Sowell et al. 2003, see Fig. 1). Figure 1 illustrates that, while in general there are nonlinear decreases in gray matter density across the life span (ages 7–87 years), some regions, such as the prefrontal (Fig. 1, e.g., plots A, G) and parietal regions (e.g., plots D, E) show steeper or prolonged rates of decline compared to occipital regions (e.g., plots N, T). Notably, temporal regions show a different trajectory altogether, with gray matter density increasing before starting to decline during adolescence (Fig. 1, e.g., plots Q, V, X). In one of the first longitudinal studies to measure cortical thickness in typical children, adolescents, and adults (ages 4–21), Gogtay et al. (2004) were able to confirm and provide visualization of the progression of thickness maturation throughout the cortex on a point by point basis. Using this technique, they confirmed early notions that phylogenetically older and newer regions have distinct maturational trajectories. Others were finding similar patterns of regional specificity in cortical thickness with development. For example, the left perisylvian language cortices were found to have a unique developmental pattern where cortical thickening occurs much later than that of the more dorsal cortices of the frontal and parietal lobes (O'Donnell et al. 2005; Sowell et al. 2003, 2004). Longitudinal studies of changes in cortical thickness over time were not only beginning to validate earlier findings of variable regional maturational trajectories observed cross-sectionally, but were beginning to relate these changes to the development of different cognitive skills. For example, in one of the largest longitudinal studies to date, Shaw et al. (2006) were able to explore the dynamic interplay between cortical morphology, age, and cognitive function. Here, researchers found that children of differing intelligence demonstrate different rates of maturation, particularly in frontal and temporal cortical regions, and that these trajectories interact with age (Shaw et al. 2006). In Fig. 2, we highlight another study by our lab that also found cortical thickness patterns to relate to cognitive function during development. Specifically, in a sample of 45 typical children aged 5–11, we found that an increase in thickness in the left inferior frontal gyrus was related to improved phonological skill but not motor skill, whereas thinning in the left motor cortex was associated with improved motor ability (Lu et al. 2007, see Fig. 2). In fact, these results show a double dissociation between cortical thickness and behavior, depending on the behavioral measure of interest (i.e., phonological processing or motor skill), thickness changes vary in a regionally specific manner. Taken together with previous findings, this research suggests that the development of cognitive skills has a direct relationship with the development of distinct cortical regions associated with those skills.

In the past few years, longitudinal and cross-sectional studies on larger samples have been able to further explore the relationship between cortical thickness changes as they relate to underlying neural architecture (Shaw et al. 2008; Tamnes et al. 2010, 2013). In a sample of 375 children, adolescents and adults ranging in age from 3.5 to 33 years, Shaw et al. (2008) reported that the growth trajectories in various regions of the cortex are simple or complex depending on the respective complexity of the underlying neural architecture (see Figs. 3

and 4). As seen in red in Fig. 3, a vast majority of cortex on the medial and lateral surface shows a cubic growth pattern, where increases in thickness are observed through late childhood/early adolescence, followed by a decline. Regions in the perisylvian and limbic cortices show a quadratic pattern, with thickness peaking much later in adolescence before a gradual decline (Fig. 3, green). Primary visual cortices, on the other hand, show linear declines in thickness across 3.5–33 years of age (Fig. 3, blue). Moreover, Fig. 4 depicts how some of these distinct linear and nonlinear cortical thickness changes parallel the underlying neural architecture. As shown in the orbitofrontal cortex, the frontal pole, and lateral regions, which are characterized by the homotypical six-layered isocortex, show a cubic trajectory of cortical development (Fig. 4, red). In contrast, the posterior orbital surface displays both quadratic and linear changes (Fig. 4, green and blue, respectively). Interestingly, the posterior orbital surface has a transitional pattern of neuronal organization with fewer and less well-demarcated layers, as well as lacks a clearly defined granular layer (layer 4). In summary, these findings suggest that developmental trajectories of cortical thickness are complex and are likely to vary based on the neuronal type and organization within a given brain region.

More recently, a cross-sectional study on 168 participants challenged previously held notions of the relationship between morphological measures derived from MRI. Here, in the first study to investigate the relationship between white matter, gray matter, and diffusivity, researchers reported that adolescent cortical thinning may not be explained by increases in white matter volume, and there was only a moderate relationship between cortical thickness and white matter volume and diffusivity (Tamnes et al. 2010).

10 Cortical Surface Area

To date, cortical volume and cortical thickness have been the most heavily studied morphometric measures, with cortical thickness being the most studied longitudinally (Shaw et al. 2008). However, recent studies have recognized that cortical volume measured in image analysis programs like FreeSurfer (Dale et al. 1999) is not an independent measure of cortical morphology, but a composite metric that is a *product of* cortical thickness and cortical surface area (Raznahan et al. 2011). Thus, it is important to explore how these cortical measures interact with each other, and how they are influenced by age and sex, in order to determine an overall trajectory of development. In this regard, one study confirmed that there are temporal and gender differences in these components, with cortical surface area peaking later in males and gyrification complexity peaking earlier than cortical surface area in both genders. In addition, the faster peak in surface area in males translated into an overall delay in cortical volume peak (Van Essen and Drury 1997). These findings suggest that surface area may be a more sensitive measure of cortical maturation.

11 Subcortical Brain Development

Similar to the cortex, subcortical regions undergo significant changes in morphology across childhood and adolescence (Giedd et al. 1996b; Koolschijn and Crone 2013; Sowell et al. 2002; Toga et al. 2006). These include areas important for sensorimotor processing, such as the thalamus and caudate, as well as limbic regions that are essential for emotion and

memory, such as the amygdala and hippocampus. Several studies have suggested that subcortical development may differ between boys and girls (Giedd et al. 1996b; Koolschijn and Crone 2013; Sowell et al. 2002; Toga et al. 2006). For example, both the caudate and the thalamus have been shown to peak in volume during the adolescent years, but demonstrate different peaks and trajectories between boys and girls (Brown et al. 2012; Lenroot et al. 2007). In a longitudinal study by Lenroot et al., caudate volumes were found to follow an inverted-U shaped trajectory, with an earlier peak in caudate volumes in girls (~10.5 years.) compared to boys (~14 years.) (Lenroot et al. 2007). In terms of limbic neurodevelopment, 8–15-year-old boys have been shown to have larger amygdala volumes than girls (Gogtay et al. 2006). However, analyses in a large cross-sectional sample of 4–18-year olds found this relationship to vary across development with larger amygdala volumes seen with age in boys only, whereas only girls showed larger hippocampal volumes with age (Giedd et al. 1996a). Given the sexually dimorphic developmental brain trajectories in adolescents, studies have begun to examine whether pubertal maturation may account for some of these patterns of subcortical brain development (Bramen et al. 2011; Peper et al. 2011, for more on hormones and the brain see “The Role of Corticolimbic Circuitry in the Development of Anxiety Disorders in Children and Adolescents”). Furthering our understanding of subcortical development is especially important, as maturation of these processing centers, and their connections to cortical areas, are likely to contribute to the dramatic changes seen in social and emotional processing that occurs during childhood and adolescence (Dahl 2004; Steinberg 2005).

12 Future Directions

While the past 15 years have provided a foundation for understanding changes in brain structure across childhood and adolescence, the field of neuroimaging is still relatively new. The development and utilization of additional techniques, such as cognitive tests and functional MRI (fMRI) to study brain activity, are helping us to elucidate how postnatal cortical maturation contribute to behavioral and cognitive changes that develop from childhood to adulthood (See Sections B and C of this book). Furthermore, novel analytic techniques for both diffusion tensor MRI (DTI), such as tractography, to estimate white matter pathways, and resting-state functional connectivity (rs-fcMRI), have allowed the field to assess how neural networks change with development. The research emerging from these studies suggests that cognitive and functional development occur in tandem, and is influenced by both genetic and environmental factors. However, it is still unclear what exact factors allow for the development of mature and efficient neural systems for societal, cognitive, and emotional functions. Understanding these patterns of change in typical development are especially important as they are likely to help us to elucidate what factors that may contribute to atypical development and neurodevelopmental disorders such as ADHD, Autism, and William’s Syndrome. Moving forward, it is clear that integrating our knowledge of structural neurodevelopment with additional neuroimaging techniques (i.e., fMRI, DTI, rs-fcMRI) may culminate in better understanding healthy trajectories of neurodevelopment.

Acknowledgments

This research was supported by the following organizations: National Institutes of Mental Health (NIMH); (5 R01MH087563-04), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) (7 R01HD053893-05).

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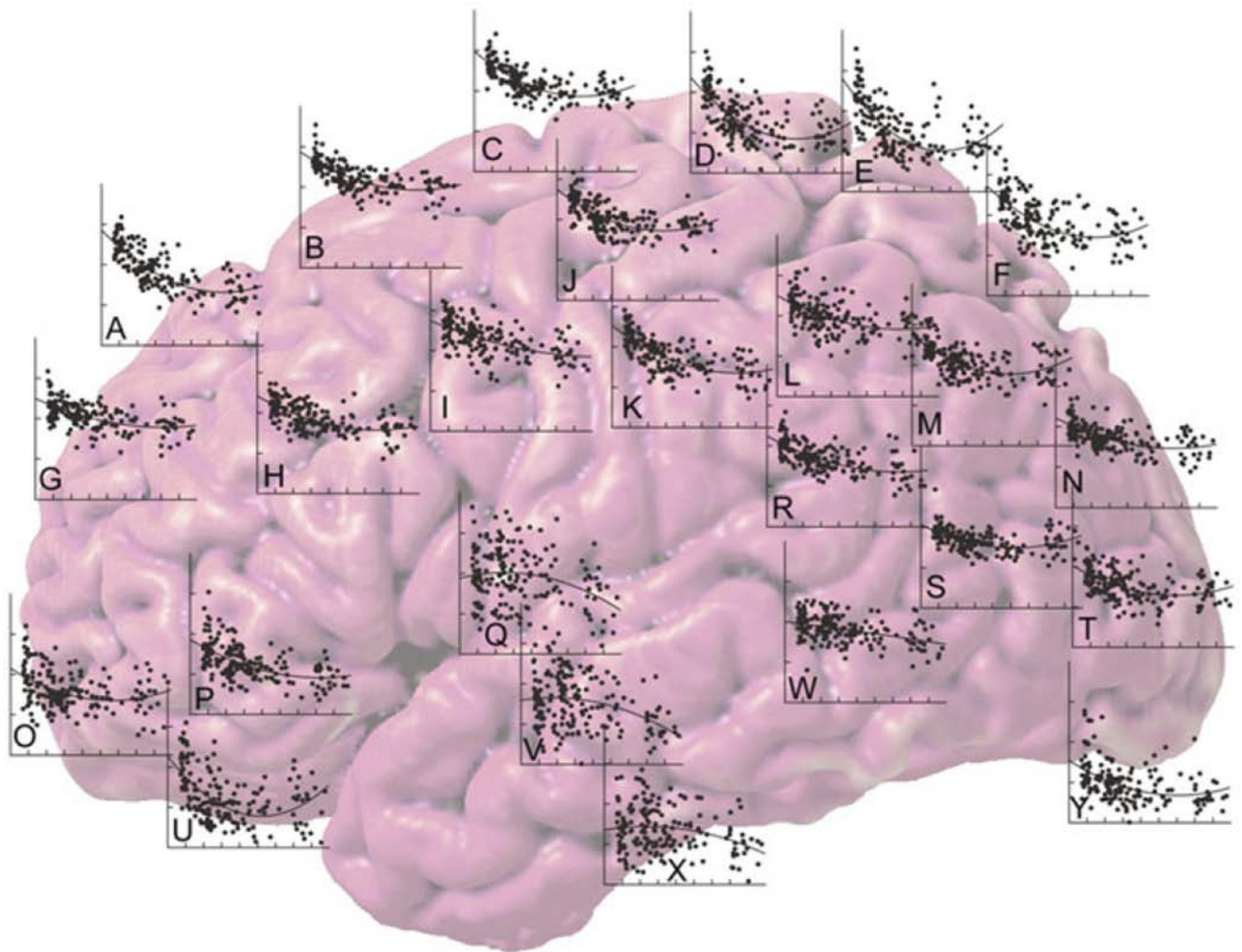


Fig. 1. Cortical thickness shows regional and temporal specificity with development (Sowell et al. 2003). Shown is a surface rendering of the left hemisphere of the brain (anterior to posterior is *left to right*), with scatterplots of nonlinear relationship between gray matter density and age in years. Graphs are placed over the corresponding brain regions. All axes are identical; gray matter density is plotted on the x-axis, and age in years (range: 7–87 years) is plotted on the y-axis. Prefrontal and parietal regions show steeper or prolonged rates of decline compared to phylogenetically older regions like the occipital lobe. In contrast, temporal regions show increases in gray matter density before starting to decline in adolescence

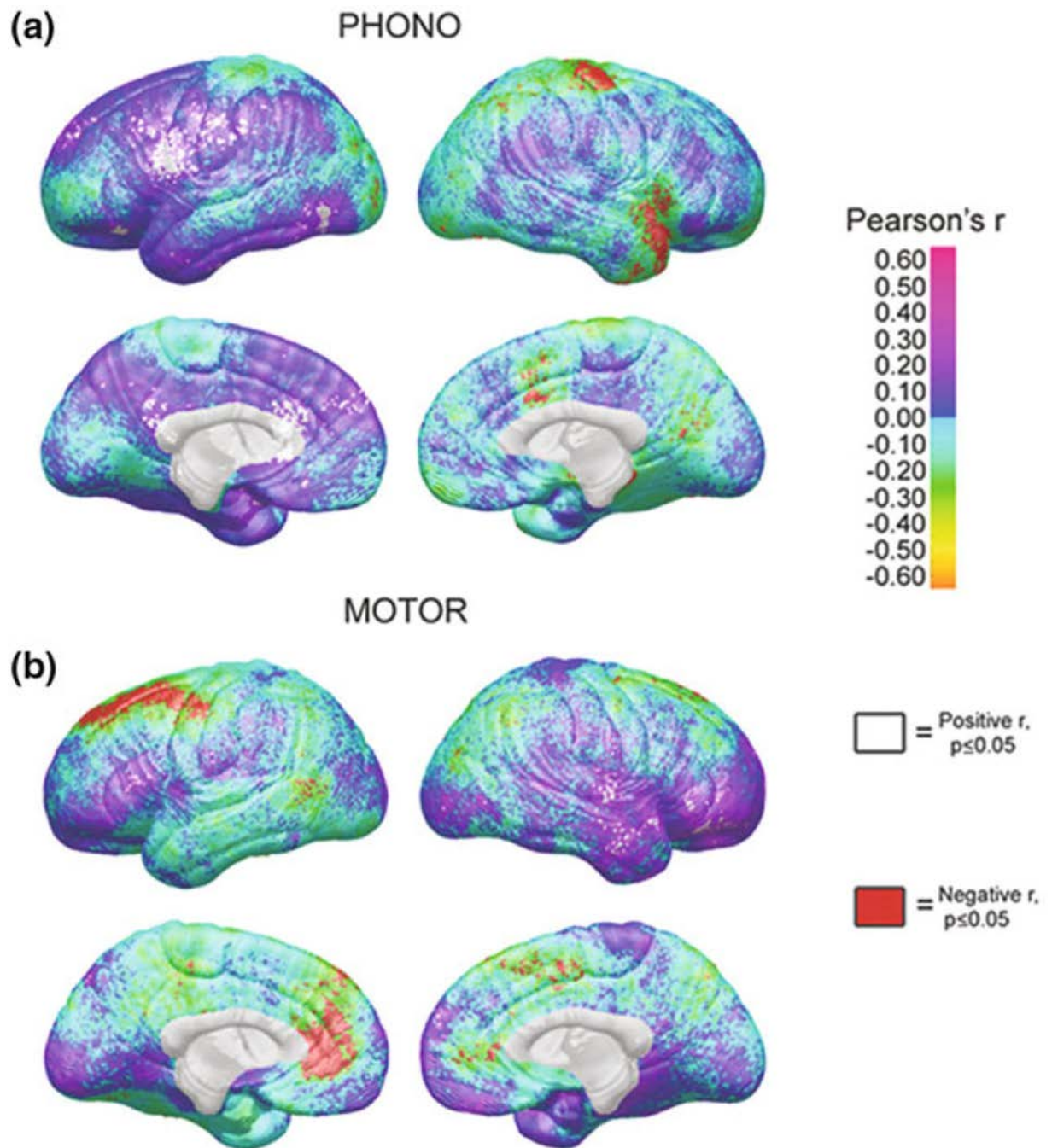


Fig. 2. Localized thickness maps of both cerebral hemispheres reveal Pearson's correlations ($p \leq 0.05$) between changes in gray matter thickness and behavioral scores on **a** phonological processing, and **b** fine motor skill in children (ages 5–11 years). A double dissociation is seen between thickness and behavior, as *white* areas represent positive relationships between behavior and thickness change; *red* areas represent negative correlations (used with permission; Lu et al. 2007)

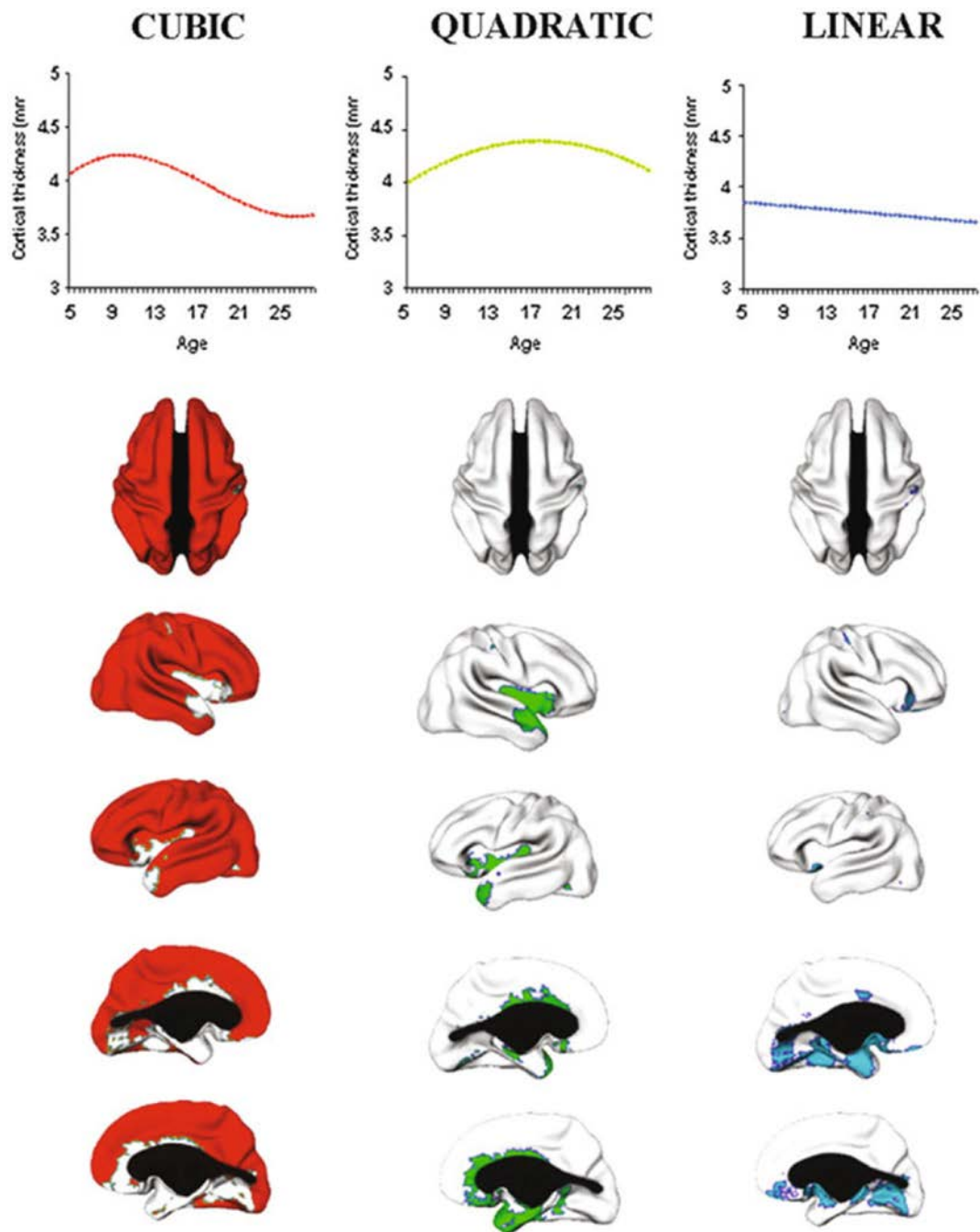


Fig. 3.

Graphs and cortical renderings depicting the complexity of cortical thickness development in a sample of 375 children, adolescents, and adults (aged 3.5–33 years) (used with permission; Shaw et al. 2008). Graphs depict the patterns of growth for their corresponding column. The brain maps show the vertices having a cubic (*red*), quadratic (*green*), or linear (*blue*) developmental trajectory. Vertical brain maps represent dorsal, right lateral, left lateral, left medial, and right medial views, respectively. The corpus callosum and subcortical regions are *blacked out*

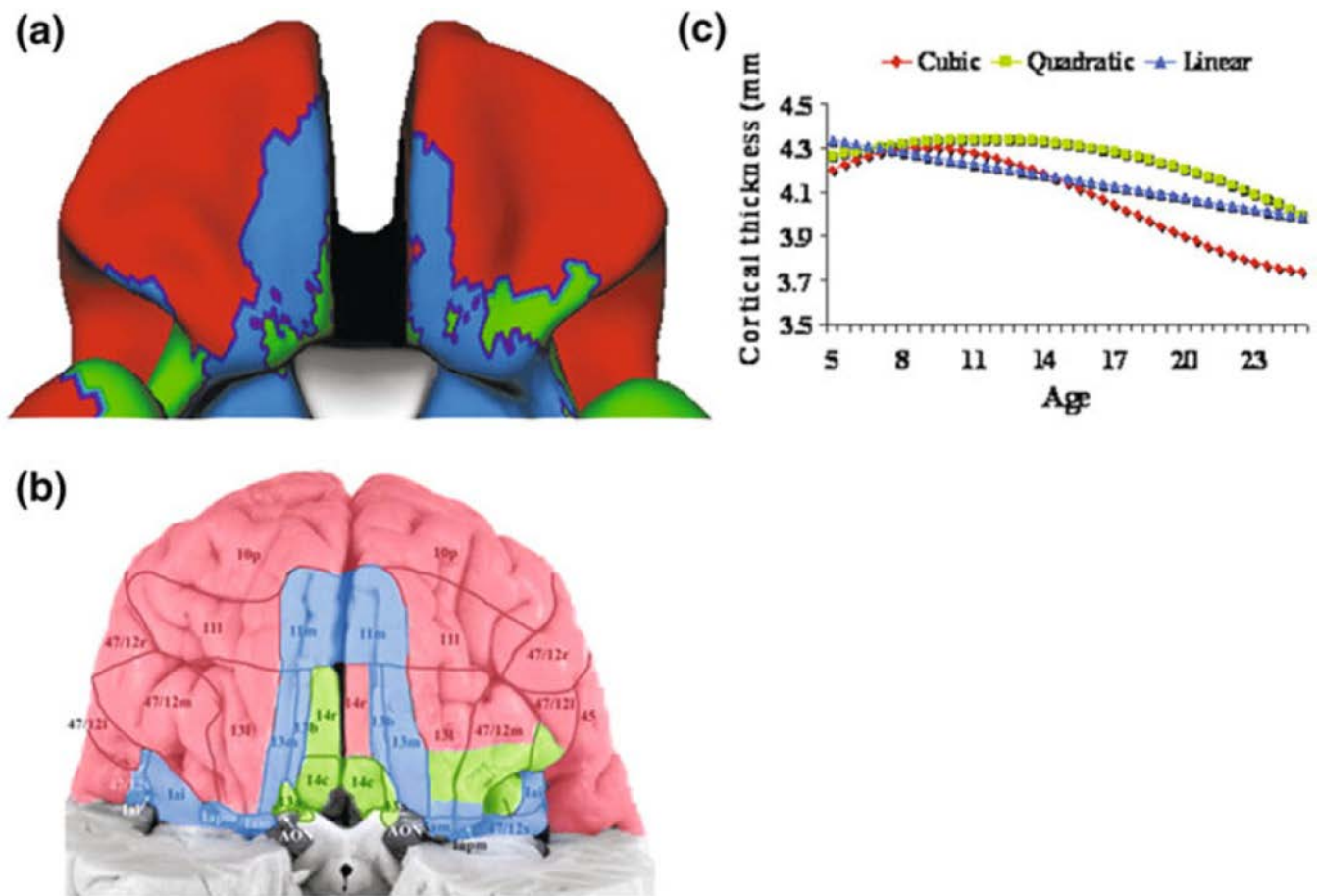


Fig. 4.

Linear and nonlinear development of orbitofrontal cortical thickness (used with permission; Shaw et al. 2008). **a** 3-Dimensional rendering of the anterior view of the brain with colors representing the different growth trajectories seen in the orbitofrontal cortex. Anterior and lateral orbitofrontal regions have a cubic fit (*red*); medial and posterior orbitofrontal regions demonstrate a quadratic fit (*green*) and linear (*blue*) trajectories. **b** Growth trajectories are superimposed on a cytoarchitectonic map, highlighting that the different growth trajectories correspond to underlying neural architecture. Cubic functions (*red*) are largely seen in regions where homotypical cortical layers (*six-layers*) are present, whereas regions of the orbitofrontal cortex with fewer and less organized layers tend to have quadratic or linear regions (*green and blue*). **c** Graphical depiction of the different type of growth trajectories seen in the orbitofrontal cortex