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Susan L. Andersen
Daniel S. Pine *Editors*

The Neurobiology of Childhood

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Preface

During the past years there has been rapid progress in the understanding of how environmental factors, including stress exposure, and genetic factors impact psychopathology in children. The first two parts of this book present the basic principles of brain development describing anatomical, functional, and molecular changes and the effects of hormones and genes. Next, the development of the most important neuronal systems is discussed. This includes systems involved in emotion processing, cognitive control, and social processes. These first two general sections are followed by an overview of recent research on various neuronal and psychiatric disorders, where environmental exposures and altered brain development play an important role: sleep, autism, ADHD, and other developmental forms of psychopathology.

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Part I
General Principles of Brain

The Neurobiology of Childhood Structural Brain Development: Conception Through Adulthood

Suzanne M. Houston, Megan M. Herting and Elizabeth R. Sowell

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 a-typical 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

Contents

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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 gryus 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 blastocyte 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 patters 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

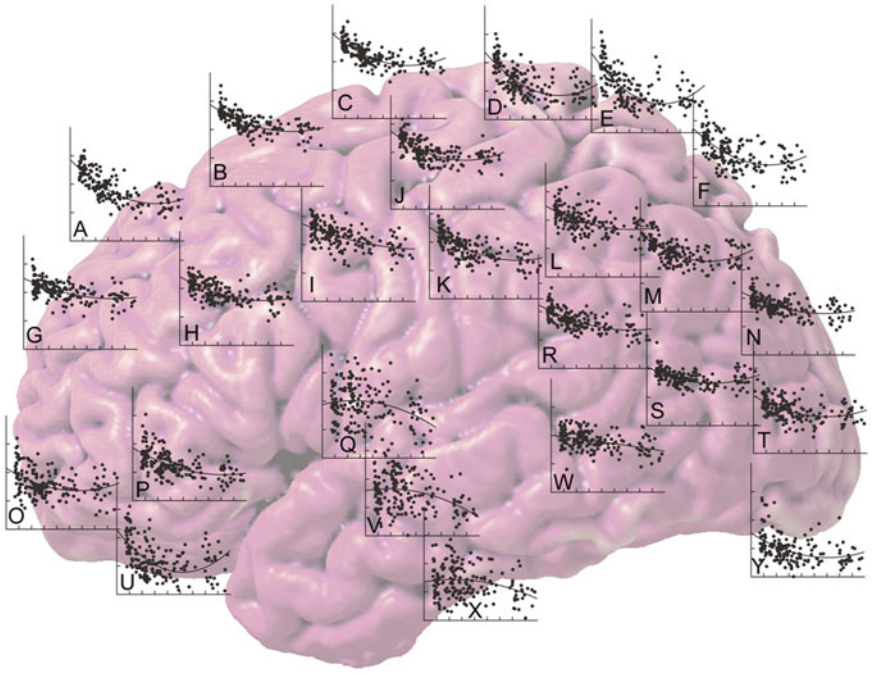

Fig. 1 Cortical thickness shows regional and temporal specificity with development (Sowell et al. 2003). Shown is a surface rendering of the left hemisphere of the brain (anterior to posterior is *left* to *right*), with scatterplots of nonlinear relationship between gray matter density and age in years. 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

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

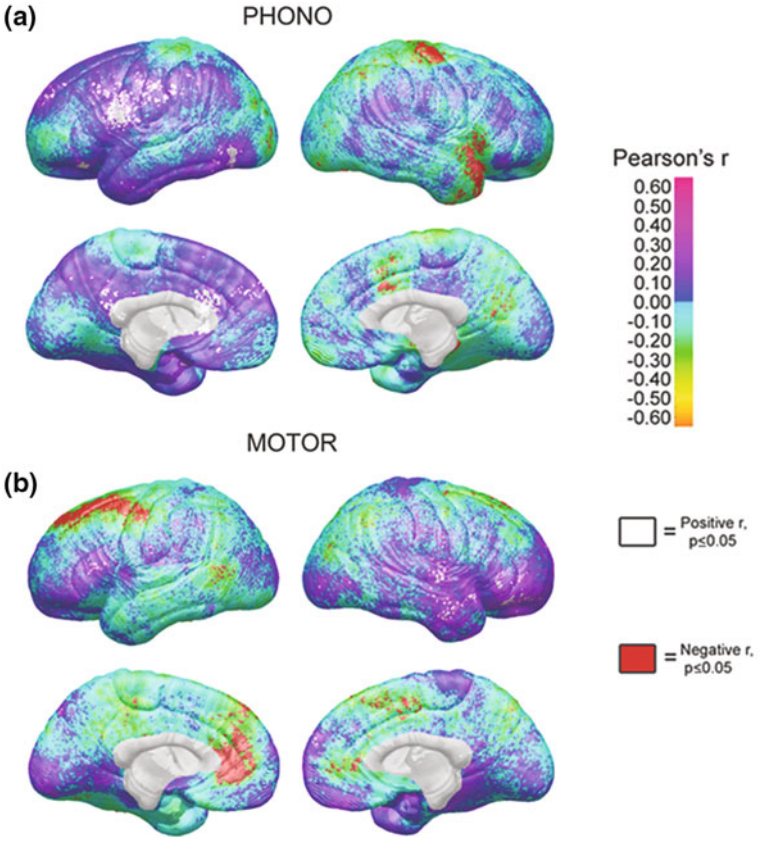

Fig. 2 Localized thickness maps of both cerebral hemispheres reveal Pearson's correlations ($p \leq 0.05$) between changes in gray matter thickness and behavioral scores on **a** phonological processing, and **b** fine motor skill in children (ages 5–11 years). A double dissociation is seen between thickness 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)

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).

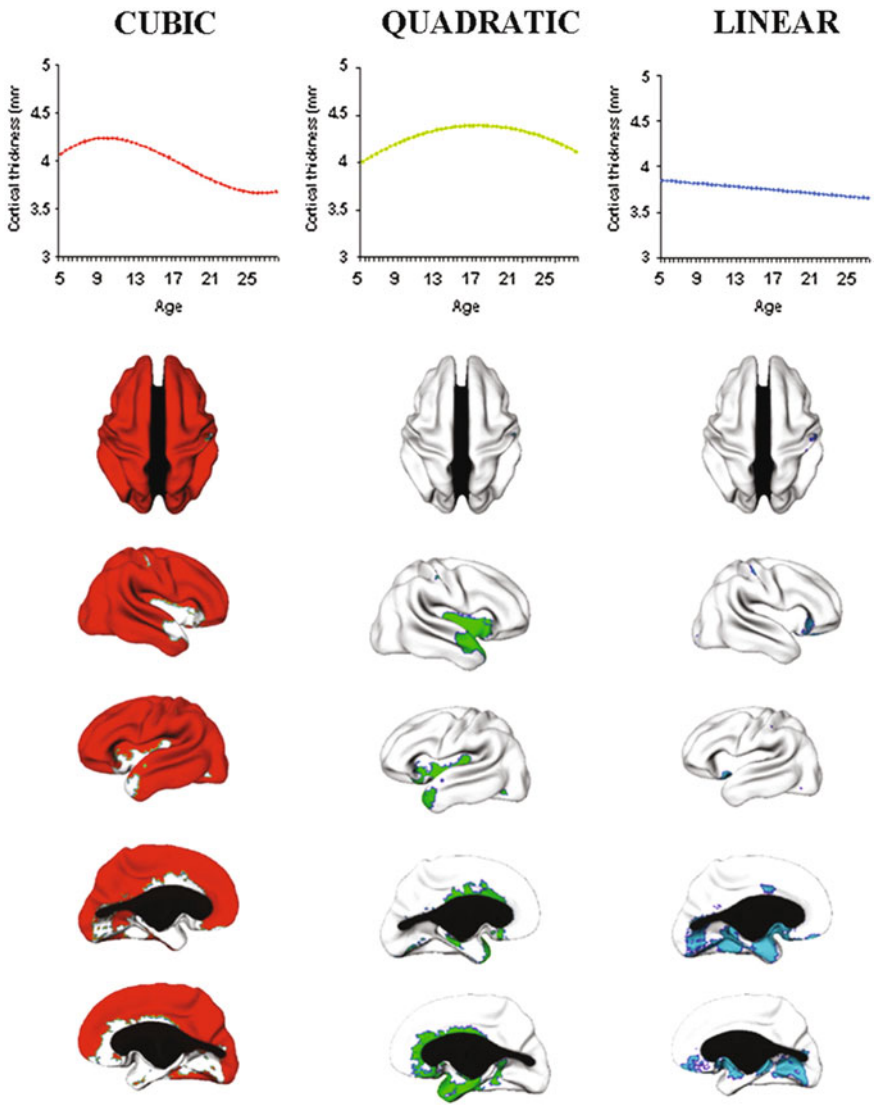

Fig. 3 Graphs and cortical renderings depicting the complexity of cortical thickness development in a sample of 375 children, adolescents, and adults (aged 3.5–33 years) (used with permission; Shaw et al. 2008). Graphs depict the patterns of growth for their corresponding column. The brain maps show 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

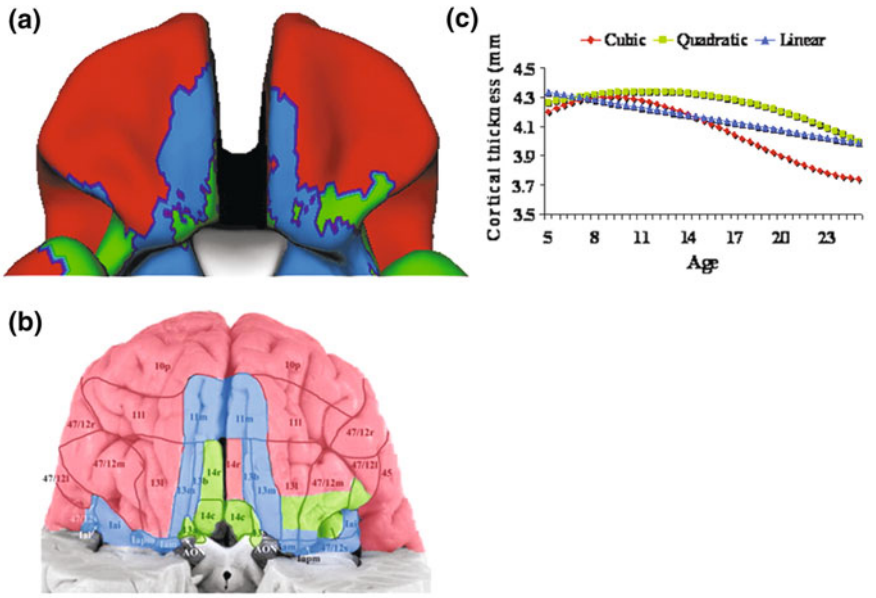

Fig. 4 Linear and nonlinear development of orbitofrontal cortical thickness (used with permission; Shaw et al. 2008). **a** 3-Dimensional rendering of the anterior view of the brain with colors representing the different growth trajectories seen in the orbitofrontal cortex. Anterior and lateral orbitofrontal 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** A graphical depiction of the different type of growth trajectories seen in the orbitofrontal cortex

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 ($\sim$10.5 years.) compared to boys ($\sim$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.

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References

Bramen JE, Hranilovich JA, Dahl RE, Forbes EE, Chen J, Toga AW, Sowell ER et al (2011) Puberty influences medial temporal lobe and cortical gray matter maturation differently in boys than girls matched for sexual maturity. Cereb Cortex 21(3):636–646

Brown TT, Kuperman JM, Chung Y, Erhart M, McCabe C, Hagler DJ Jr, Dale AM et al (2012) Neuroanatomical assessment of biological maturity. Curr Biol 22(18):1693–1698. doi:10.1016/j.cub.2012.07.002 S0960-9822(12)00793-2 [pii]

Chi JG, Dooling EC, Gilles FH (1977) Gyral development of the human brain. Ann Neurol 1(1):86–93. doi:10.1002/ana.410010109

Dahl RE (2004) Adolescent brain development: a period of vulnerabilities and opportunities. Keynote address. Ann N Y Acad Sci 1021:1–22

Dale AM, Fischl B, Sereno MI (1999) Cortical surface-based analysis I: segmentation and surface reconstruction. Neuroimage 9(2):179–194

Feinberg TE, Farah MJ (2003) Behavioral neurology and neuropsychology, 2nd edn. McGraw-Hill, New York

Fischl B, Dale AM (2000) Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A 97(20):11050–11055. doi:10.1073/pnas.200033797 200033797 [pii]

Giedd J (1999) Brain development, IX: human brain growth. Am J Psychiatry 156(1):4

Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Rapoport JL et al (1999) Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci 2(10):861–863

Giedd JN, Snell JW, Lange N, Rajapakse JC, Casey BJ, Kozuch PL, Rapoport JL et al (1996a) Quantitative magnetic resonance imaging of human brain development: ages 4-18. Cereb Cortex 6(4):551–560

Giedd JN, Vaituzis AC, Hamburger SD, Lange N, Rajapakse JC, Kaysen D, Rapoport JL et al (1996b) Quantitative MRI of the temporal lobe, amygdala, and hippocampus in normal human development: ages 4-18 years. J Comp Neurol 366(2):223–230

Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Thompson PM et al (2004) Dynamic mapping of human cortical development during childhood through early adulthood. Proc Natl Acad Sci U S A 101(21):8174–8179

Gogtay N, Nugent TF 3rd, Herman DH, Ordonez A, Greenstein D, Hayashi KM, Thompson PM et al (2006) Dynamic mapping of normal human hippocampal development. Hippocampus 16(8):664–672

Huttenlocher PR, de Courten C (1987) The development of synapses in striate cortex of man. Human Neurobiol 6(1):1–9

Huttenlocher PR, Dabholkar AS (1997) Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol 387(2):167–178

Jernigan TL, Tallal P (1990) Late childhood changes in brain morphology observable with MRI. Dev Med Child Neurol 32(5):379–385

Jernigan TL, Trauner DA, Hesselink JR, Tallal PA (1991) Maturation of human cerebrum observed in vivo during adolescence. Brain 114(Pt 5):2037–2049

Kabani N, Le Goualher G, MacDonald D, Evans AC (2001) Measurement of cortical thickness using an automated 3-D algorithm: a validation study. Neuroimage 13(2):375–380

Koolschijn PC, Crone EA (2013) Sex differences and structural brain maturation from childhood to early adulthood. Dev Cogn Neurosci 5:106–118. doi:10.1016/j.dcn.2013.02.003

Lenroot RK, Gogtay N, Greenstein DK, Wells EM, Wallace GL, Clasen LS, Giedd JN et al (2007) Sexual dimorphism of brain developmental trajectories during childhood and adolescence. Neuroimage 36(4):1065–1073. doi:S1053-8119(07)00234-0 [pii] 10.1016/j.neuroimage.2007.03.053

Lu L, Leonard C, Thompson P, Kan E, Jolley J, Welcome S, Sowell E et al (2007). Normal developmental changes in inferior frontal gray matter are associated with improvement in phonological processing: a longitudinal MRI analysis. Cereb Cortex 17(5):1092–1099. doi:bhl019 [pii]10.1093/cercor/bhl019

Nadarajah B, Brunstrom JE, Grutzendler J, Wong RO, Pearlman AL (2001) Two modes of radial migration in early development of the cerebral cortex. Nat Neurosci 4(2):143–150. doi:10.1038/83967

O'Donnell S, Noseworthy MD, Levine B, Dennis M (2005) Cortical thickness of the frontopolar area in typically developing children and adolescents. Neuroimage 24(4):948–954. doi:S1053-8119(04)00610-X [pii]10.1016/j.neuroimage.2004.10.014

Peper JS, Hulshoff Pol HE, Crone EA, van Honk J (2011) Sex steroids and brain structure in pubertal boys and girls: a mini-review of neuroimaging studies. Neurosci 191:28–37

Rakic P (1972) Mode of cell migration to the superficial layers of fetal monkey neocortex. J Comp Neurol 145(1):61–83. doi:10.1002/cne.901450105

Rakic P (1995) Radial versus tangential migration of neuronal clones in the developing cerebral cortex. Proc Natl Acad Sci U S A 92(25):11323–11327

Raznahan A, Shaw P, Lalonde F, Stockman M, Wallace GL, Greenstein D, Giedd JN et al (2011) How does your cortex grow? J Neurosci 31(19):7174–7177. doi:10.1523/JNEUROSCI.0054-11.201131/19/7174 [pii]

Shaw P, Greenstein D, Lerch J, Clasen L, Lenroot R, Gogtay N, Giedd J et al (2006) Intellectual ability and cortical development in children and adolescents. Nature 440(7084):676–679. doi:nature04513 [pii] 10.1038/nature04513

Shaw P, Kabani NJ, Lerch JP, Eckstrand K, Lenroot R, Gogtay N, Wise SP et al (2008). Neurodevelopmental trajectories of the human cerebral cortex. J Neurosci 28(14):3586–3594. doi:10.1523/JNEUROSCI.5309-07.200828/14/3586[pii]

Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, Toga AW (1999a) In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. Nat Neurosci 2(10):859–861

Sowell ER, Thompson PM, Holmes CJ, Batth R, Jernigan TL, Toga AW (1999b) Localizing age-related changes in the brain structure between childhood and adolescence using statistical parametric mapping. Neuroimage 9(6 Pt. 1):587–97

Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW (2003) Mapping cortical change across the human life span. Nat Neurosci 6(3):309–315. doi:10.1038/nn1008

Sowell ER, Thompson PM, Toga AW (2004) Mapping changes in the human cortex throughout the span of life. Neuroscientist 10(4):372–392. doi:10.1177/1073858404263960

Sowell ER, Trauner DA, Gamst A, Jernigan TL (2002) Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. Dev Med Child Neurol 44(1):4–16

Steinberg L (2005) Cognitive and affective development in adolescence. Trends Cogn Sci 9(2):69–74

Stiles J (2008) The fundamentals of brain development: integrating nature and nurture. Harvard University Press, Cambridge

Stiles J, Jernigan TL (2010) The basics of brain development. Neuropsychol Rev 20(4):327–348. doi:10.1007/s11065-010-9148-4

Tamnes CK, Ostby Y, Fjell AM, Westlye LT, Due-Tonnessen P, Walhovd KB (2010) Brain maturation in adolescence and young adulthood: regional age-related changes in cortical thickness and white matter volume and microstructure. Cereb Cortex 20(3):534–548. doi:10.1093/cercor/bhp118bhp118 [pii]

Tamnes CK, Walhovd KB, Dale AM, Ostby Y, Grydeland H, Richardson G, Fjell AM et al (2013) Brain development and aging: overlapping and unique patterns of change. Neuroimage 68:63–74. doi:10.1016/j.neuroimage.2012.11.039S1053-8119(12)01151-2[pii]

Toga AW, Thompson PM, Sowell ER (2006) Mapping brain maturation. Trends Neurosci 29(3):148–159

Van Essen DC, Drury HA (1997) Structural and functional analyses of human cerebral cortex using a surface-based atlas. J Neurosci 17(18):7079–7102

Werthheimer M (2000) A brief history of psychology, 4th revised edn. Hartcourt College Publishers, Fortworth

Yakovlev P (1967) Regional development of the brain in early life. Blackwell Scientific, Oxford

Signaling Mechanisms of Axon Guidance and Early Synaptogenesis

Michael A. Robichaux and Christopher W. Cowan

Abstract The development of the vertebrate nervous system, including the brain and spinal cord, progresses in a step-wise fashion that involves the function of thousands of genes. The birth of new neurons (also known as neurogenesis) and their subsequent migration to appropriate locations within the developing brain mark the earliest stages of CNS development. Subsequently, these newborn neurons extend axons and dendrites to make stereotyped synaptic connections within the developing brain, which is a complex process involving cell intrinsic mechanisms that respond to specific extracellular signals. The extension and navigation of the axon to its appropriate target region in the brain and body is dependent upon many cell surface proteins that detect extracellular cues and transduce signals to the inside of the cell. In turn, intracellular signaling mechanisms orchestrate axon structural reorganization and appropriate turning toward or away from a guidance cue. Once the target region is reached, chemical synapses are formed between the axon and target cell, and again, this appears to involve cell surface proteins signaling to the inside of the neuron to stabilize and mature a synapse. Here, we describe some of the key convergent and, in some cases, divergent molecular pathways that regulate axon guidance and synaptogenesis in early brain development. Mutations in genes involved in early brain wiring and synapse formation and pruning increase the risk for developing autism, further highlighting the relevance of brain development factors in the pathophysiology of neurodevelopmental disorders.

Keywords Axon guidance · Synaptogenesis · Growth cone · Filopodia · Spine · Cytoskeleton · Rho-GTPase

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Abbreviations

4EBP	eIF-4E Binding Protein
ABL	Abelson
BDNF	Brain-Derived Neurotrophic Factor
CAM	Cell Adhesion Molecule
CAMKII	Calcium/Calmodulin Kinase II
CAN	Calcineurin
cAMP	Cyclic Adenosine Monophosphate
cGMP	Cyclic Guanosine Monophosphate
CH	Calponin Homology
CNS	Central Nervous System
DCC	Deleted in Colorectal Cancer
DRG	Dorsal Root Ganglia
EVH1	Ena/VASP Homology 1
FAK	Focal Adhesion Kinase
GAP	GTPase Activating Protein
GEF	Guanine Nucleotide Exchange Factor
GDP	Guanosine Diphosphate
GIT	G-Protein Coupled Receptor Kinase Interacting Protein
GSK-3β	Glycogen Synthase Kinase 3Beta
GTP	Guanosine Triphosphate
Hh	Hedgehog
MTOR	Mammalian Target of Rapamycin
NRP	Neuropilin
OTK	Off-Track
PAK	P21-Associated Kinase
PKA	Protein Kinase A
PP1	Protein Phosphatase 1
PSD	Postsynaptic Density
RER	Rough Endoplasmic Reticulum
RGC	Retinal Ganglion Cell
ROCK	Rho-Kinase
SEMA	Semaphorin
SFK	Src Family Kinase
Shh	Sonic Hedgehog
SMO	Smoothened
SPAR	Spine-Associated Rap GAP
TRP	Transient Receptor Potential
VDCC	Voltage-Dependent Calcium Channel
WNT	Wingless Integration
ZBP	Zipcode-Binding Protein

Contents

1 Introduction: Circuit Formation in the Developing Brain

The mammalian brain first emerges from the neural tube as a morphologically distinct structure at around gestational day 26 in humans (embryonic day 10 in mice). At this early stage, the future forebrain, midbrain, and hindbrain are patterned as the prosencephalon, mesencephalon, and rhombencephalon, respectively (for review, see Keynes and Lumsden 1990). Within this rudimentary brain structure, numerous sequential and simultaneous developmental processes occur that enable expansion, stereotyped organization, connectivity that characterizes a mature, functional brain. Developmental processes, such as cell division, neurogenesis, gliogenesis, and cell migration, are required for the growth and basic cellular organization of the brain; however, brain morphology is also defined by the white matter axon fibers that interconnect neurons and hardwire brain circuitry. Indeed, one the most fascinating and complex aspects of brain development is the process by which neurons interconnect in a highly stereotyped fashion. The proper establishment of brain circuitry requires the precise navigation of growing axons to their appropriate target region(s) within the brain and periphery. Once axons arrive at their terminal destination, they will form chemical synapses with target neurons or effector cells (e.g., muscles). These two developmental processes are often referred to as axon guidance and synaptogenesis, respectively. The importance and complexity of these processes becomes clear when one considers that billions of neurons will form trillions of targeted, stereotyped synaptic connections within the developing brain.

Decades of neurobiological research have contributed to our understanding of the "decisions" made by neurons in the developing brain that drive circuit formation. In most cases, the navigation of axons to appropriate target regions, and eventual formation and remodeling of synapses, is determined by complex cell signaling events initiated when cell surface receptors encounter, and are activated

by, extracellular ligands (guidance cues or synaptogenic ligands). In some cases, the same cell surface receptors that mediate axon guidance are known to play dual roles in synapse formation (reviewed, Shen and Cowan 2010). For axon guidance, the binding of an extracellular guidance cue to a cell surface guidance receptor initiates local, intracellular signaling cascades that change the axonal morphology, substrate adhesion properties, and motility of the axon. Activated axon guidance receptors can signal long distances back to the soma and nucleus to facilitate axon outgrowth and guidance, but local signaling events within the axon's distal tip—a structure known as the growth cone—are thought to be most critical for proper axon navigation. Once an axon reaches its appropriate target region, chemical synapses are established between the axon and a target cell (e.g., on a neuronal dendrite or on a target cell's plasma membrane), and again, it is the binding and/or activation of cell surface receptors that initiate the formation of functional, chemical synapses. In this chapter, we will describe current knowledge about some of the key local signaling processes that are critical for axon guidance and synaptogenesis, and discuss how these events function to orchestrate proper neuronal connectivity in the brain (Table 1).

2 Axon Guidance

2.1 Overview

A newly born neuron establishes a cell polarity and extends a morphologically distinct axon that is supported by microtubules within its axon shaft and a morphologically complex structure, called the growth cone, at its distal tip. Subsequent guidance of the axon to its local or distant target region is coordinated by numerous extracellular cues that push or pull the distal growth cone. The growth cone is a complex, dynamic, and motile structure that is supported by cytoskeletal proteins, such as filamentous actin (F-actin) and microtubules. F-actin is a linear polymer of actin proteins that generates microfilaments, whereas microtubules are tubular polymers of tubulin proteins. Together with these cytoskeletal components, numerous axon guidance receptors and cell adhesion molecules (e.g., integrins) are expressed at its surface and interact with the underlying cytoskeleton to control growth cone shape and extension/retraction. Growth cones are tasked with interpreting extrinsic environmental signals, known as axon guidance cues, and responding properly through rapid cytoskeletal remodeling that can effectively steer the extending axon toward its stereotyped destination. Guidance cues are broadly classified as "attractive" or "repulsive" based on the growth cone response when presented with the guidance cue. However, many guidance factors, including ephrins and semaphorins, can promote either growth cone attraction or repulsion based on axon guidance receptor composition and other factors, many of which are still poorly understood. In normal development, navigating axon growth

Table 1 Summary of receptor proteins and functions described in this chapter

Surface receptor	Ligand	Function	References
DCC	Netrin-1	Axonal extension	Briancon-Marjollet et al. (2008), Corset et al. (2000), Gitai et al. (2003), Kennedy et al. (1994), Leung et al. (2006), Li et al. (2004), Liu et al. (2004), Meriane et al. (2004), Ren et al. (2004), Serafini et al. (1996), Shekarabi and Kennedy (2002), Tcherkezian et al. (2010), Wu et al. (2006), Yao et al. (2006)
Eph (A4, B2)	Ephrin	Axonal extension Axonal repulsion Dendritic filopodial activity Spine stabilization	Cowan et al. (2005), Dalva et al. (2000), Egea and Klein (2007), Harbott and Nobes (2005), Henkemeyer et al. (2003), Kayser et al. (2006, 2008), Malartre et al. (2010), Pasquale (2005), Petros et al. (2010), Sahin et al. (2005), Shamah et al. (2001), Shi et al. (2007), Tolias et al. (2007), Wahl et al. (2000), Yu et al. (2001), Castellani et al. (1998), Dodelet et al. (1999), Hansen et al. (2004), Iwasato et al. (2007), Kao et al. (2009), Knoll and Drescher (2004), Mohamed et al. (2012), Richter et al. (2007), Srivastava et al. (2013), Yates et al. (2001)
Nr-CAM	Semaphorin (3B, 3F), Neuropilin (2)	Axonal extension	Castellani et al. (2002), Falk et al. (2005)
Frizzled	Wnt (5A, 7A)	Axonal extension Axonal repulsion Spine stabilization	Ciani et al. (2011), Farias et al. (2009), Li et al. (2009), Wolf et al. (2008)
Ryk	Wnt (4, 5A)	Axonal extension Axonal repulsion	Hutchins et al. (2011), Li et al. (2009), Wouda et al. (2008)
Patched	Hedgehog	Axonal extension Axonal repulsion	Charron and Tessier-Lavigne (2007), Tenzen et al. (2006), Trousse et al. (2001)

(continued)

Table 1 (continued)

Surface receptor	Ligand	Function	References
Trk (A, B)	BDNF	Axonal extension Dendritic filopodial motility Spine stabilization	Hale et al. (2011), Luikart et al. (2008), Miyamoto et al. (2006), Yao et al. (2006)
Plexin (A1, B1)	Semaphorin (1A, 3A, 4D), Neuropilin (1 & 2), Off-track	Axonal repulsion Spine stabilization	Hu et al. (2001), Hung et al. (2011), Ito et al. 2006), Lin et al. (2007), Oinuma et al. (2004a, b), Swiercz et al. (2002), Turner et al. (2004), Yang and Terman (2012)
Robo	Slit (2)	Axonal repulsion	Bashaw et al. (2000), Dickson and Gilestro (2006), Yu et al. (2002), Piper et al. (2006), Wu et al. (2005)
L1-CAM	Semaphorin (3A), Neuropilin (1)	Axonal repulsion	Castellani et al. (2000, 2002), Maness and Schachner (2007), Raper (2000)
Ephrin-B (B1, B3)	EphB	Spine stabilization	Aoto et al. (2007), Lai and Ip (2009), Segura et al. (2007), Zhang et al. (2005)
Cadherin (N-cadherin)	Cadherin	Spine stabilization	Abe et al. (2004), Paradis et al. (2007), Togashi et al. (2008), Xie et al. (2007)