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CHAPTER 2

Brain and Cognitive Development

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INTRODUCTION

Research over the past several decades has greatly expanded our understanding of cognitive and brain development. The many chapters of this *Handbook* reflect the breadth and richness of the psychological studies (e.g., see Marshall, Chapter 7, Volume 1). From the elaboration of stochastic learning processes, joint attention, and phonological processing in young infants to the effects of cultural practices, peer interaction, and schooling on older children, our knowledge of how children come to know about and interact in the world has grown and changed significantly. We have made comparable progress in understanding the basic processes of brain development. Our models of brain development have changed considerably through discoveries about everything from the molecular mechanisms for neural stem cell differentiation and early patterning of the embryonic neural system to studies demonstrating the critical role of experience in pre- and postnatal brain development. Over this course of time, knowledge gained in these two critically important areas of developmental research progressed largely independently of one another. Studies linking behavioral development to change in underlying neural systems are comparatively limited. One consequence of this lack of interdisciplinary integration is a divergence in the theoretical models of development that each field offers to account for the observed changes. One important aspect of those theoretical differences concerns the issue of biological inheritance and the role it plays in development.

This chapter is the product of the collaborative efforts of experts representing different areas of neurocognitive development. As such, the substance of this chapter reflects the equal and independent contributions of the four authors. As senior author, Joan Stiles was responsible for the overall outline and organization of the chapter, minding of deadlines, and correspondence with editors. Beyond that, order of authorship is arbitrary and does not indicate the level of contribution.

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[1]Color versions of Figures 2.6, 2.8, 2.9, and 2.10 are available at http://onlinelibrary.wiley.com/book/10.1002/9780470147658.

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Models of Neurobehavioral Development

The central debate within developmental psychology for many decades focused on the question of whether and to what extent humans are innately prepared to interpret and act in the world, and to what extent they rely on learning and/or experience. Nativists propose the existence of a core set of innate concepts that form the necessary foundation for later learning (Gelman, 2000; Spelke & Kinzler, 2007). Proponents of traditional nurture-based views (represented, for example, by ecological, neoconstructivist, and information processing perspectives) argue that complex concepts emerge from more primitive, yet innate, sensory, motor, and learning abilities (Elman et al., 1996; S. P. Johnson, 2003; Sirois et al., 2008). Both sides in the psychological debate assume that innate factors originate within the organism and are presumably part of the biological endowment, while learned behaviors originate outside the organism and result from experience in the world. Thus, at issue in the traditional psychological nature-nurture debate is not whether there are innately specified behaviors, but rather whether there exists a privileged set of "core concepts" (Gelman, 2000) that should be included among the class of innately specified behaviors.

The dominant model of brain development 40 years ago was strongly deterministic. Brain development was the product of an intrinsic, innately determined maturational pathway (Gottlieb, 1976; Johnston, 2001). Contemporary models present a distinctly different view of inheritance and brain development. What is inherited at conception is quite specific: (a) the DNA, and (b) the first cell with the cellular machinery for translating the information in the nucleotide sequences of DNA into proteins (the active agents in all biological processes). Biological inheritance provides essential tools, but neither the genes nor environmental factors prescribe outcomes. Rather brain development proceeds via the complex interaction of molecular, cellular, and environmental systems and elements. The biological state of the organism at any moment is the product of developmental processes that involve an intricate interplay among complex cascades of gene expression interacting with influences from an ever-expanding range of environmental factors. Under this model, it would be a mistake to construe intrinsic factors as deterministic and extrinsic factors as modulatory. Rather, the complex interaction of many elements interacting dynamically over time brings about the progressive differentiation and specification of the nervous system.

The lack of alignment between the psychological and biological theories of inheritance and development presents a difficult and important problem. The theories from both disciplines intend to provide an account of human development. Yet, the differences in the assumptions about very basic processes lead to a divergence in focus and direction. Psychological theories include elements that are presumed to be innately specified and, thus, do not need to be explained. Biological theories underspecify the richness and range of input. In fact, humans are biological beings with brains that mediate their thoughts, feelings, and actions, *and* the development of stable, functioning neural networks depends critically on the experience of the individual and his or her actions in the world. Integrating theories of neural and cognitive development into a single model of neurocognitive development is essential for a full understanding of human development. Seeking such integration is the guiding principle for this chapter.

The Plan of the Chapter

The remainder of this chapter explores the current state of knowledge about the relationship between brain and cognitive development. The overarching goal is to forward an integrated account of how complex neurocognitive processes arise in humans. The study of the development of brain-behavior relationships is still in its infancy. Many areas of neurocognitive processing remain largely unexplored and more questions remain than have been resolved. Nonetheless, research in a number of different domains has progressed and the growing body of work in those areas can serve as a model for approaching these kinds of substantively and technically difficult interdisciplinary questions. We do not and cannot exhaustively review all extant knowledge about brain-behavior relationships across the range of cognitive domains. Rather, we focus on three cognitive domains for which a substantial body of neurocognitive data is available and more integrated models of neurocognitive development are emerging. These domains include studies of visuospatial processing of faces, cognitive control, and language.

One obstacle to interdisciplinary dialogue is that the methods of interrogation in the behavioral and neurosciences are very different. This makes evaluation of data from related fields difficult. Cognitive neuroscience relies on a range of clinical and neuroimaging methodologies that may be less familiar to behavioral scientists. This chapter begins with a Methods of Interrogation section to bridge this part of the interdisciplinary divide with a brief overview of the major investigative tools available for studying brain-behavior relations in developing children.

Any discussion of the nature of brain-behavior relationships assumes a substantial knowledge of the basics of development within both systems. Training in psychology has not historically included intensive instruction in the fundamentals of brain development. The section entitled Major Milestones in Anatomical Brain Development provides an overview of the basics of pre- and postnatal brain development. Brain development begins in the third week postconception and extends at least through late adolescence, and arguably throughout the lifespan. Contemporary models of brain development portray a dynamically developing system that relies absolutely on genetic, systemic, and experiential factors, all interacting in complex ways. An understanding of how brain systems emerge through the interaction of all of these factors is critical to the formulation of any model of neurocognitive development.

The sections that constitute the heart of this chapter, Brain and Cognitive Development in the Postnatal Period, follow the discussion of brain development. Three primary cognitive domains are considered. The discussion of visuospatial processing focuses on a well-studied aspect of visual processing, face processing (for a more extensive discussion of visuospatial processing, see Johnson & Hannon, Chapter 3, this *Handbook*, this volume). The review of cognitive control focuses on the development of attention, working memory, and inhibitory control. The section on language focuses on acquisition in late infancy and the early toddler period as well as later mastery of complex grammar and discourse skills.

All of the studies considered in this section rely on imaging or recording technologies of one type or the other. The age of the children under study and the particular empirical questions typically dictate the choices of imaging modality used. Discussions within each domain include as wide an age range as is possible, beginning as early in infancy as data are available and extending through late childhood or adolescence. Most studies are cross-sectional in design, thus providing snapshots of the state of the neurobehavioral system at specific points in time. Inclusion of multiple age groups within a single study allows for some extrapolation to developmental trajectories, but only with caution. The detailed study of developmental trajectories using longitudinal designs is rare but, as discussed in the closing sections of this chapter, will eventually need to become a critical part of the database.

A Neurocognitive Perspective on Human Development, the fourth section of the chapter, integrates the data reviewed in the earlier two sections, and offers a neurocognitive perspective on the nature of brain-behavior relationships. This section captures the dynamic nature of change in both brain and behavioral systems, and provides a means of aligning theory and data from developmental neurobiology and developmental neuropsychology. At the heart of this model is the idea that neurobehavioral development involves an ongoing and robust series of interactions among biological and environmental factors. It views development as a continuous process of adaptation shaped by genetic, environmental, and temporal constraints.

The chapter ends with a series of reflections on themes, trends, and future directions that emerge from the work reviewed in this chapter. This section attempts to synthesize common threads that emerge in the discussion of each domain separately. It begins with a discussion of trajectories of neurocognitive change, and considers commonalities and differences in the patterns of change in the neural networks that support particular functions as well as differences in the timing of those changes across domains. Next, the importance of multimodal and multidimensional approaches to the study of human development is considered. The models of neurocognitive development discussed in this chapter make clear the need for multidisciplinary approaches that integrate data from genetics to neural systems to behavior and the environment into a comprehensive and aligned system. That requires coordinated, multidimensional approaches to everything from data collection to model building. We emphasize the importance of the study of individual differences in development. It is likely that the "modal child" is a myth, an artifact of our statistical analyses. Our understanding of neurocognitive development will likely rely as much on our knowledge of the nature of the variability in trajectories of development as it does on our understanding of the common principles of development.

METHODS OF INTERROGATION

Historically, the major source of data for mapping brain-behavior relationships came from adult patient studies; yet, the application of these methodologies to developmental issues is complex and provides only limited information on typical trajectories of development. Advances in neuroimaging modalities now provide the tools necessary to precisely define developmental trajectories in structure, connectivity, and functional responsiveness over the entire brain in typical development. The following sections

provide a brief overview of the major methods for the study of brain-behavior relationships in developing children.

The Lesion Method

Historically, studies of adults with localized brain injury have been a major source of data about brain-behavior relations. This approach typically uses the logic of subtraction to define the function of a brain area. That is, the functional loss observed after injury to a particular brain area defines the original function or role supporting a function of that brain area. However, the adult lesion method does not work for developmental questions because the brain systems have not yet organized to mediate the targeted behavioral functions. Instead, the study of children with localized brain lesions provides a window on the processes of early brain plasticity and the capacity of the neural system to develop alternative patterns of organization as a means of adapting to injury (Stiles, Reilly, Levine, Trauner, & Nass, 2012). While important for informing our understanding of the dynamic nature of brain development, child lesion data provide limited information on typical trajectories of neurocognitive development.

Neuroimaging Methods

Understanding the associated development of behavior and brain requires multidimensional brain measures assessing changes across a substantial range of space and time. Spatial measures must span resolutions from the submillimeter to millimeter range to capture neurons, neuronal columns, and cortical layers, to the centimeter range to estimate regional maps, through to whole brain resolution to assess integrated brain systems. Temporal measures must span resolutions in the range of milliseconds to hours to capture dynamic brain activity through to days, months, and years to appreciate changes across the lifespan. Tools to measure typical human development must be noninvasive, or so minimally invasive that the cost of the information gained far exceeds the risk to the participant. The present day armamentarium of noninvasive techniques available to developmental researchers allows for the analysis of development across this vast breadth of spatial and temporal domains. The following provides a brief description of many of the most significant structural (anatomical) and functional (physiological) neuroimaging tools presently used in developmental cognitive neuroscience.

While modern neuroimaging has revolutionized our understanding of brain-behavior relationships across development, these techniques are not panaceas. Any single neuroimaging technique provides only a narrow window onto the complexity of developmental brain-behavior relationships; that is, each brain imaging technique has specific strengths and weaknesses in terms of spatial and temporal resolution. For example, structural MRI (sMRI) provides incredibly precise measures of brain anatomy from the near microscopic level to whole brain, yet a structural MRI scan provides only a single snapshot in time of brain status. Functional MRI (fMRI) can measure dynamic traces of neuronal activity from submillimeter resolution through to whole brain within seconds after stimulation and provide a highly dynamic description of brain function related to a cognitive task. Yet, the temporal resolution of fMRI that is measured in seconds necessarily suggests that we are observing an echo of brain activity that occurred within milliseconds to several hundred milliseconds after stimulation. Electroencephalography (EEG) and magnetoencephalography (MEG) can observe dynamic brain activity at millisecond resolution, but because these measures are acquired at the scalp, they lack unique or precise spatial resolution of the underlying brain generators of the response. Developmental cognitive neuroscientists are in complete agreement that comprehensive descriptions of brain-behavior relationships across development require multimodal imaging strategies of collecting data with multiple techniques to increase the observation power through converging methods with strengths across different spatial and temporal ranges.

Applying imaging methodologies to child populations is challenging. Many of the methodologies are sensitive to various kinds of movement that can render the data uninterpretable. Methods are emerging to address motion issues, yet even with these improvements, some neuroimaging techniques continue to present a challenge for testing infants and young children. Thus, the application of methodologies is not uniform across ages. In many cases, the absolute signal to noise of imaging techniques is low. This often necessitates the collection of many observations or stimulus repetitions to obtain reliable brain signals. Obtaining sufficient data requires time that may challenge the ability of children to sustain their attention and vigilance. Thus, researchers must frequently sacrifice multifactorial experimental designs to focus on essential variables to ensure sufficient data acquisition, particularly during tasks where performance may differ between younger and older participants.

Structural Magnetic Resonance Imaging (sMRI)

Structural MRI (sMRI) was the first application of MRI to developmental brain research and remains one of the most commonly used methods today. The tissue contrast of sMRI reflects tissue-specific variation in density and relaxation of magnetized protons in water molecules. Specifically, sMRI produces detailed images of sulcal and gyral patterns of the cerebral cortex and cerebellum because of strong signal contrast between the myelinated fibers of the brain's white matter and adjacent gray matter. The visual appearance of the brain on sMRI therefore changes appreciably over the first 2 to 3 years of life, and these changes mirror the orderly pattern of early myelination in white matter regions. Major advances have been made in quantitative sMRI morphometry techniques in the past two decades, and these have allowed investigators to detect subtler changes in brain structure that continue well past this age. A particular challenge for the interpretation of results from pediatric anatomical imaging is the dramatic change in gray-white contrast that occurs across the childhood age range. We discuss this issue briefly later in the chapter.

Diffusion Tensor Imaging (DTI)

Diffusion weighted imaging (DWI) is an MRI technique that measures the diffusion of protons in water molecules through brain tissue. This form of brain imaging yields several measures that exhibit strong age dependence during postnatal development, because myelination of brain fibers and other biological changes across development increasingly limit the diffusion of water molecules. The most common DWI index is a measure of the rate of diffusion called diffusivity. A common use of DWI involves fitting a tensor at each location that estimates the rate of diffusion along three orthogonal axes; that is, the tensor estimates diffusivity in different directions. Researchers refer to this method as diffusion tensor imaging (DTI) (see Figure 2.1). Tensors from locations in fluid-filled areas in the brain exhibit high, isotropic diffusivity; that is, diffusion occurs freely in all directions (Figure 2.1a). Diffusivity in gray matter is lower, because of restriction by cellular structures, but is also relatively isotropic (Figure 2.1b). In voxels that contain fiber bundles, the rate of diffusion is relatively higher along the long axis of the fibers. This phenomenon is measured as an index of *anisotropy*, usually as fractional anisotropy (FA). High FA is illustrated in the elongated structure shown in Figure 2.1c.

DTI and related methods provide information about the directionality of proton diffusion (Figure 2.1c) allowing researchers to trace the apparent courses of major fiber tracts within individual brains, an approach called tractography (Mukherjee, Berman, Chung, Hess, & Henry, 2008; Mukherjee, Chung, Berman, Hess, & Henry, 2008). Tractography can define tract regions of interest (ROIs) in order to estimate diffusion parameters specific to particular tracts, and it is sometimes used to try to determine the pattern of connectivity itself.

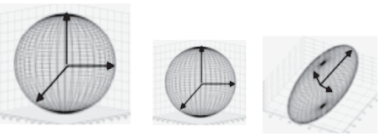

Figure 2.1 Diffusion Tensors: (a) Illustration of tensor from region with high isotropic diffusivity, as in cerebrospinal fluid. (b) Tensor exhibiting isotropic, but lower diffusivity, as in gray matter. (c) Elongated tensor exhibiting anisotropy, as in fiber tracts.

All sMRI methods are sensitive to participant motion. However, recent methodological advances allow investigators to reduce significantly the degradation of image quality associated with motion in children (Brown et al., 2010; Kuperman et al., 2011; White, Roddey, et al., 2010).

Functional Magnetic Resonance Imaging (fMRI)

Functional magnetic resonance imaging (fMRI) includes a range of methods using MRI measurements of physiological responses to neuronal activity. These typically target the dynamic moment-to-moment changes in brain signals related to mental activity and its associated blood flow response. In 1990, Ogawa and colleagues (1990) described a technique for *in vivo* measurement of a particular aspect of the hemodynamic response to neural activity: the intrinsic blood oxygen-level dependent or BOLD signal. While other fMRI measures are available (e.g., brain perfusion using arterial spin labeling; Buxton et al., 1998), BOLD signal studies are the most commonly used in basic and clinical research.

The BOLD signal arises from a complex relationship between biophysical properties of the local ratio of paramagnetic deoxygenated hemoglobin to nonparamagnetic oxygenated hemoglobin, and physiological properties of cerebral blood flow, cerebral blood volume, and cerebral oxygen metabolism changes related to neuronal activation. Researchers typically apportion the BOLD response into three phases: the initial transient decrease in BOLD signal, the main increased BOLD signal response, and the BOLD signal undershoot. The second phase BOLD

signal is the most frequent dependent variable in fMRI studies, beginning a few seconds after the initiation of neuronal activity and peaking many seconds later (e.g., 4–8 seconds). This phase begins with the increase of local blood flow that produces an increase in the volume of oxygenated hemoglobin thereby increasing the oxygenated to deoxygenated hemoglobin ratio (Fox & Raichle, 1986). It is now understood that all excitatory and inhibitory activity within local circuitry (neurons, glia, interneurons) contributes to the BOLD hemodynamic response function (Logothetis, 2002). While most developmental studies using BOLD focus on describing regional activation, there is growing interest in characterizing brain activation within networks, a style of analysis commonly called functional connectivity analysis.

The most significant challenge in pediatric fMRI is compliance, specifically the ability to remain motionless during a data acquisition period lasting several minutes and a session lasting up to an hour. Beyond compliance, physiological factors such as blood flow and neuronal metabolism, together with structural factors such as differences in capillary bed distribution, may influence developmental BOLD signal differences not tied to task or resting state factors (for review, see Harris, Reynell, & Attwell, 2011). Finally, important differences in resting state activation may influence the baseline BOLD signal from which task and other effects are measured (Haist, Adamo, Han, Lee, & Stiles, 2013).

Electroencephalography/Event-Related Potentials (EEG/ERP)

Electroencephalography (EEG) offers particularly sensitive measures of the timing aspects of brain activity. EEG records the electric potentials generated by neurons from electrodes placed on the scalp with millisecond resolution. Scalp-recorded EEG activity is believed to reflect the intermittent synchronization of extracellular current flows within small populations of neurons predominantly on the gyral surfaces of the cortex (Nunez, 1981). EEG cannot precisely localize activity to its cerebral sources because the electric potentials are smeared, distorted, and deflected as they conduct through different types of tissue (e.g., brain, dura, skull, scalp; Cuffin & Cohen, 1979). It is not possible definitively to identify the exact sources of the EEG signal (Pascual-Marqui & Biscay-Lirio, 1993), although modern source analysis tools can suggest the best source solution given certain assumptions. EEG data can be analyzed within both the frequency and event-related domains, extracting effects such as coherence or synchrony within particular frequency bands or averaged in relation to the repeated presentation of some time-locked stimulus of interest. Researchers refer to the latter averaged response as the evoked or event-related potentials (ERP). Different sensory, perceptual, and cognitive processes produce unique ERP components, which are traditionally labeled according to the polarity (positive or negative voltage deflection) and timing of the peak in relation to the stimulus (Polich, 1993). For example, the N170 is a negative-going deflection peaking at about 170 ms (in adults) following the presentation of a visual face stimulus. The P600 is a positive deflection peaking at about 600 ms that has been linked to cognitive operations in language and memory. ERP components are examined for changes in amplitude, latency, and scalp topography in relation to the manipulation of sensory, cognitive, or subject factors of interest such as clinical group or age.

The rapid development of EEG technology will allow it to be used freely outside the laboratory setting, a unique feature amongst brain imaging methods, and thus offers tremendous promise for use in developmental research. Systems coming to market allow for the easy user-friendly application of multiple electrodes that provide built-in analog-to-digital (A/D) converters paired with wireless transmitters (e.g., Bluetooth or Wi-Fi). Thus, researchers can acquire EEG and ERPs in diverse settings (i.e., schools) on easily portable machines such as laptops, tablets, and smartphones.

Magnetoencephalography (MEG)

Magnetoencephalography (MEG) is a technique similar to EEG. MEG measures fluctuations in the magnetic fields induced by voltage-gated and ligand-gated neuronal current flows with submillisecond resolution, limited only by the digitization rate (Cohen & Cuffin, 1983). MEG sensors, called SQuIDs (superconducting quantum interference devices), are contained within the helmet-shaped dewar that surrounds the participant's head. Unlike EEG, the spatial relationship between brain activity sources and the sensors is reasonably straightforward because magnetic fields pass through biological tissues with essentially no perturbation as they emanate from the brain (Cohen & Cuffin, 1991; Cohen et al., 1990; Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). Nevertheless, MEG source localization still requires inferences based on careful modeling because measurements are made at the scalp some distance from the brain. Many researchers now using MEG employ model constraints using information from an MRI from the subject. Noise-normalized,

anatomically constrained statistical parametric maps of MEG-derived brain activity show strong spatial correspondence with recordings from intracranial EEG for a variety of stimulus types and sensory and cognitive components (Dale & Halgren, 2001; Halgren, 2004). MEG has several practical advantages for use with children and infants. MEG does not require the placement of scalp electrodes, which can be time consuming and tiresome for young subjects. The MEG scanner is an entirely passive instrument and is quiet. And it allows either supine or upright data collection. Thus, it can be used when MRI is contraindicated.

Positron Emission Tomography (PET)

Positron emission tomography (PET) is an imaging technique used to measure chemical and physiological activity in a variety of body organs and has been used in developmental studies from neonatal ages and above (Phelps & Mazziotta, 1985). PET uses radiotracers that contain positron-emitting isotopes that are injected into the bloodstream. The emitted positrons immediately collide with negatively charged electrons leading to the destruction of both particles. This "annihilation event" releases energy in the form of two photons traveling in opposite directions. A PET scanner consists of a ring of scintillation sensors that detect and localize where these events occur. Using H_2O^{15} ("oxygen-15 water") as the isotope allows the researcher to quantify regional cerebral blood flow (rCBF), and by inference, localized changes in brain activity. PET can also track the synthesis of specific proteins or the uptake and binding of particular neurotransmitters. Since glucose and oxygen are fundamental to meeting the energy demands of the brain, many PET studies of early development have measured age changes in these substrates. Local cerebral metabolic rates for glucose undergo dramatic maturational changes in most parts of the brain, particularly in the cerebral cortex, and these changes continue over a protracted period (Chugani & Phelps, 1991; Chugani, Phelps, & Mazziotta, 1987).

The major limiting feature of PET for typical development studies is that it requires the injection of ionizing radiation, thereby making it one of the most invasive of the neuroimaging tools for studying development. Thus, developmental PET studies are most frequently reported from clinical populations with neurological diagnoses, such as pediatric cancer (see Jadvar, Connolly, Fahey, & Shulkin, 2007), seizure disorders (Kannan & Chugani, 2010), or neurodevelopmental disorders such as autism (see Chugani, 2012) and attention deficit hyperactivity disorder (see Mana, Paillere Martinot, & Martinot, 2010).

Near-Infrared Spectroscopy (NIRS)

Near-infrared spectroscopy (NIRS) is a noninvasive optical imaging method that measures the state of hemoglobin oxygenation in the brain that is modulated by regional levels of cerebral blood flow and cortical activity. NIRS uses light projected into the brain from scalp-based illuminators and sensors (optodes) located nearby to measure hemoglobin oxygenation changes in external gyri measured with a resolution ranging from tenths of seconds to seconds. NIRS recording systems are portable, allow subjects to move, operate silently, and require little setup and calibration time. These factors make NIRS appealing for research with infants and young children. A limitation of NIRS is difficulty in developing standard ways of mapping the locations of brain activity sources. Also, idiosyncratic factors such as skull and skin thickness and even skin color may affect recordings.

MAJOR MILESTONES OF ANATOMICAL BRAIN DEVELOPMENT

The anatomical development of the human brain begins in the first weeks of gestation and extends into adulthood. The processes that underlie brain development are dynamic, with each step laying the foundation for the emergence of new neural structures and systems. Development at the cellular level is most evident in the changing array of cell types that arise at critical points and contribute in varying ways to the gradually emerging neural structure. Some classes of cells form the permanent structures of the brain, while others contribute to transient systems that support a specific aspect of brain development and then disappear. At the macro level, the morphology of the brain undergoes a dramatic series of changes in the prenatal period as the major neural structures differentiate and the primary neural pathways extend and are refined and stabilized. Although the basic elements of mature neural organization can be discerned by the postnatal period, brain development is far from complete. The brain volume of a newborn is approximately 25% that of an adult and will reach 90% of adult size by 6 years (Iwasaki et al., 1997; Kennedy, Makris, Herbert, Takahashi, & Caviness, 2002; Paus et al., 2001). However, change in volume does not tell the story of brain development. Significant changes in the size of cortical regions and areas, thickness of the neocortex, and stabilization of pathways continue through childhood and do not reach adult levels until middle to late

adolescence. Genetic factors contribute to and constrain the trajectories of brain development in both the pre- and postnatal periods. Inputs from the environment strongly influence all of these changes. The sections that follow will provide a brief overview of the major milestones of pre- and postnatal brain development. They are intended to convey the dynamic and interactive nature of the processes that underlie the development of this most critical and complex biological structure.

Prenatal Brain Development

Developmental change in the prenatal period involves two fundamental processes: (1) the progressive differentiation of neural elements, and (2) the progressive stabilization of those emerging neural components into functional neural systems. Both of these processes involve complex molecular and functional interactions among different cell populations that affect the subsequent regional development of the prenatal brain. There are two main prenatal periods. The embryonic period includes the first 8 weeks after conception, and the fetal period from week 9 to birth. By convention, weeks after conception are referred to as Gestational Weeks (e.g., GW8 for the eighth week postconception) and days after conception as Embryonic Days (e.g., E13 for the 13th day postconception). The basic neural cell lines are established and the major spatial axes of the nervous system are defined during the embryonic period. Rapid change in neural structure and organization during the fetal period gives rise to the basic areal organization of the neocortex and the establishment of the major brain pathways including the corticospinal tract, the corpus callosum, the thalamocortical pathway, and many of the major association pathways.

Prenatal Changes in Brain Morphology

Gastrulation: Differentiation of Neural Tissue. Brain development begins during the third week after conception (GW3). The embryo is a flat, slipper-shaped structure that is composed of two cell layers at the beginning of GW3. The upper layer contains *epiblast* cells and the lower layer *hypoblast* cells. The embryo is transformed through a set of processes that are referred to collectively as *gastrulation* into a three-layered structure by the end of the third week (Sadler & Langman, 2010; Schoenwolf & Larsen, 2009). Although this seems a simple change, the transformations of cell lines that occur during gastrulation set the stage for all subsequent developments in the embryo. The epiblast cells of the upper cell layer will differentiate into the three primary *stem cell* lines that will eventually give rise to all of the structures in the developing embryo, while the hypoblast cells of the lower layer will form "extraembryonic" tissues such as the fetal component of the placenta and the connecting stalk. The neural stem cells are among the stem cell lines that emerge during gastrulation. The neural stem cells are capable of producing almost all of the different cells that make up the brain and central nervous system, and for this reason the neural stem cells are called the *neural progenitor cells*.

The appearance of a slit-like opening in the upper layer of the embryo called the *primitive streak* signals the first step in the gastrulation process. The primitive streak provides access to the lower regions of the embryo (see Figure 2.2a). Next, a subset of the epiblast cells detaches from the upper layer of the embryo and migrates toward the primitive streak. These cells change direction and pass through the primitive streak moving under the upper layer after reaching the opening (see Figure 2.2b). They change direction again and begin moving toward the rostral end of the embryo (see Figure 2.2c), which will develop into the baby's head. The earliest migrating cells move to the most rostral/head positions in the embryo, later migrating cells move to successively more caudal regions that will develop into the neck and trunk of the body. The migrating cells form two new embryonic layers. The deepest is the *endodermal* stem cell layer which gives rise to structures of the gut and respiratory tract, while the intermediate *mesodermal* stem cell layer gives rise to muscle, bone, cartilage and the vascular system. The remaining epiblast layer cells transform into one of two types of *ectodermal* stem cells. *Epidermal ectodermal* stem cells give rise to skin, nails, and sweat glands, while *neuroectodermal* stem cells give rise to the brain and central nervous system. The neuroectodermal stem cells are the neural progenitor cells. The differentiation of all three types of embryonic stem cell lines involves complex cascades of molecular signaling, but only the differentiation of the neural stem cells (neural progenitors) are considered here.

At the beginning of gastrulation, the epiblast layer cells that differentiate into neural progenitor cells are located along the rostral-caudal midline axis of the two-layered embryo (the central rectangle in Figure 2.2d). The differentiation of these cells into neural progenitor cells is the result of complex molecular signaling that involves multiple gene products (i.e., proteins) produced by several different populations of embryonic cells. Recall that at the beginning of gastrulation, epiblast cells begin to migrate toward and then down through the primitive streak to

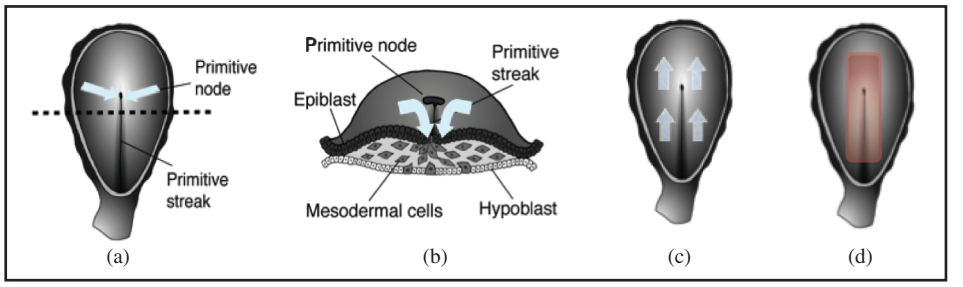

Figure 2.2 The major events of gastrulation occur between E13 and E20. (a) Gastrulation begins with the formation of the primitive streak and the primitive node. The primitive streak provides an opening to deeper embryonic layers. The primitive node is a critical molecular signaling center. On E13, cells from the epiblast layer begin to migrate toward the primitive node and streak (arrows). The dotted line indicates the cross-sectional view shown in panel B. (b) The migrating cells first move to the primitive streak and then move down and under the upper layer (arrows). As the cells pass the node they receive molecular signals that induce gene expression in the migrating cells. (c) Once under the upper layer, the cells change direction and begin migrating rostrally under the upper layer (arrows). The first cells to migrate form the most rostral regions of the newly forming endodermal and mesodermal layers. Later migrating cells form progressively more caudal regions of the layers. (d) Cells that migrate along the axial midline send molecular signals that induce cells in the overlying epiblast layer to differentiate into neuroectodermal cells (central rectangle) which are the neural progenitor cells. Migrating cells also receiving a second set of signals from the node that induce anterior or posterior fate in different subpopulations of the neurectodermal cells. Early migrating cells signal anterior fate in the progenitor cells, while late migrating cells signal posterior fate.

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form the lower embryonic layers. As the cells that migrate along the rostral-caudal midline of the embryo approach the opening, they pass another structure called the *primitive node*, which is a molecular signaling center (see Figure 2.2a). Primitive node cells send a molecular signal to the subset of cells that migrate along the rostral-caudal midline of the embryo and that signal, in turn, triggers gene expression in the migrating cells. Gene expression in the migrating cells produces a protein that is secreted into the space between the migrating cells and the cells remaining in the midline region of the upper epiblast layer. The secreted protein binds to receptors on the surface of cells in the upper layer of the embryo, sending a signal that leads to the differentiation of the epiblast cells into the neural progenitor cells.

In addition to providing the molecular signaling leading to the transformation of the overlying epidermal cells into neural progenitor cells, the primitive node generates a second set of signals that *change* over the course of gastrulation and serve to establish the basic rostral-caudal organization of the embryonic nervous system. Recall that the earliest migrating epidermal cells move to the most rostral/head end of the embryo and later migrating cells move to successively more caudal locations. In addition to the basic neuralizing signal, the primitive node provides each successive wave of migrating cells a second signal that specifies the regional identity for the neural progenitors. Thus, primitive node signals *early* migrating epidermal cells to produce molecular signals for the cells in the overlying epiblast layer to differentiate into neural progenitors capable of producing cells appropriate for forebrain structures, while later migrating cells signal differentiation of neural progenitors capable of producing cells appropriate for midbrain, hindbrain, or spinal cord structures.

In summary, by the end of gastrulation, cells located along the midline of the upper layer of the embryo have transformed into neural progenitor cells (central rectangle in Figure 2.2d). These cells are further specified to produce the kinds of neurons that are needed within the particular region of the developing neural system in which they are positioned. The differentiation of neural progenitor cells requires complex genetic signaling among at least three cell populations: the cells of the node, the migrating epiblast cells, and the cells that will become the neural progenitors. In the absence of this complex signaling, the prospective neural progenitor cells differentiate into *epidermal* ectodermal progenitor cells, leading to catastrophic failure of brain development.

Neurulation: The Formation of the Neural Tube. The formation of the neural tube, the first well-defined neural structure, is the next major step in brain development. The neural tube forms during the GW4, between E20-27. By the end of gastrulation, the neural progenitor cells have differentiated and are positioned along the rostral-caudal midline of the upper layer of the three-layered embryo in a region called the *neural plate*.

The first sign of neural tube development is the appearance of two ridges, or folds, that form along the two sides of the neural plate (Figure 2.3a). The neural progenitor cells lie between the two ridges. Over the course of several days, the ridges rise, fold inward, and fuse to form a hollow tube (Copp, Greene, & Murdoch, 2003). Fusion begins in the center of the developing neural tube and proceeds in rostral and caudal directions (Figure 2.3b and c). The *anterior neuropore* at the rostral end of the neural tube and the *posterior neuropore* at the caudal end, are the last segments to close, on E25 and E27, respectively (Figure 2.3d).

The neural progenitors form a single layer of cells that line the center of the neural tube immediately adjacent to the neural tube's hollow center when it is complete. The hollow center of the neural tube is cylindrical in the embryo, like the center of a straw. The shape of the hollow cavity changes to form the ventricular system of the brain and the central canal of the spinal cord as the brain becomes larger and more complex. Because the neural progenitors are located in the region that become the ventricles, the region is called the "ventricular zone" (VZ). The neural progenitor cells in the most rostral region of the neural tube give rise to the brain, while more caudally positioned cells give rise to the midbrain, hindbrain, and spinal column.

Differentiation of the Neural Tube. The embryo undergoes rapid growth over the next month. The embryo is 3 to 5 mm long at the end of neurulation (E28), and undergoes a tenfold increase in size to 27 to 31 mm by the end of the GW8. The shape of the primitive nervous system changes dramatically during this period. The anterior end of the tube expands to form the three primary *brain vesicles*, or pouches, just before neural tube closure (Figure 2.3e). The most anterior of these vesicles, called the "prosencephalon," is the precursor of the forebrain. The middle vesicle is the "mesencephalon," which is the precursor of midbrain structures. The posterior vesicle is the "rhombencephalon," which becomes the hindbrain. These three segments subdivide so that five secondary brain vesicles are present at the end of the embryonic period (Figure 2.3f). The prosencephalon divides into the "telencephalon" and the "diencephalon," and the rhombencephalon divides into the "metencephalon" and "myelencephalon." The mesencephalon does not further divide. These five subdivisions are complete by the end of GW6 and aligned along the rostral-caudal axis of the embryo to establish the primary organization of the central nervous system (Stiles, 2008).

Formation of Gyri and Sulci. The human brain begins as a smooth, "lissencephalic" structure that gradually develops the characteristic mature pattern of gyral and sulcal folding. The formation of gyri and sulci follows an orderly sequence. Primary sulci are first seen as grooves positioned in specifically targeted brain regions, secondary branches then begin to form off the primary sulci, followed by the tertiary branches. The longitudinal fissure that separates the two cerebral hemispheres is the first fissure to form. Its development begins in rostral regions as early as GW8 (Chi, Dooling, & Gilles, 1977) and proceeds caudally until it is complete at GW22. Other primary sulci form between GW14-26. These include: Sylvian, Cingulate, Parieto-Occipital, Calcarine in GW14-16, the Central and Superior Temporal in GW20-24, and Superior Frontal, Precentral, Inferior Frontal, and Postcentral, Intraparietal in GW25-26. Secondary sulci emerge between GW30-35; formation of tertiary sulci begins during GW36 and extends well into the postnatal period.

Cellular Elements

Neural Progenitor Cells. The human brain contains nearly a hundred billion neurons most of which are produced by mid-gestation as well as many more billions of support cells (Bayer, Altman, Russo, & Zhang, 1993; Rakic, 1995). The neural progenitor cells produce most of these cells. However, the pool of neural progenitor cells specified at the end of gastrulation is far too small to accommodate cell production on this scale. Thus, there must be a means of increasing their number. Unlike neurons, neural progenitors are mitotic cells; that is, they can divide to form new cells. The population of neural progenitor cells divides by a "symmetrical" mode of cell division from the end of gastrulation through E42 in humans. Symmetrical cell division produces two identical neural progenitor cells. Symmetrical cell division provides the means for augmenting the size of the neural progenitor pool over multiple rounds of cell division between E25 and E42.

Programmed cell death refers to a ubiquitous cell-intrinsic molecular program that leads to the destruction of the cell. All classes of neural cells exhibit programmed cell death as a means to regulate cell numbers, correct for cellular errors, and to eliminate cell populations that play a transient role in brain development. Most neuron production is complete by mid-gestation. Programmed cell death in progenitor populations begins to occur in small numbers early in the period of cortical neurogenesis (GW7), and increases across the fetal period,

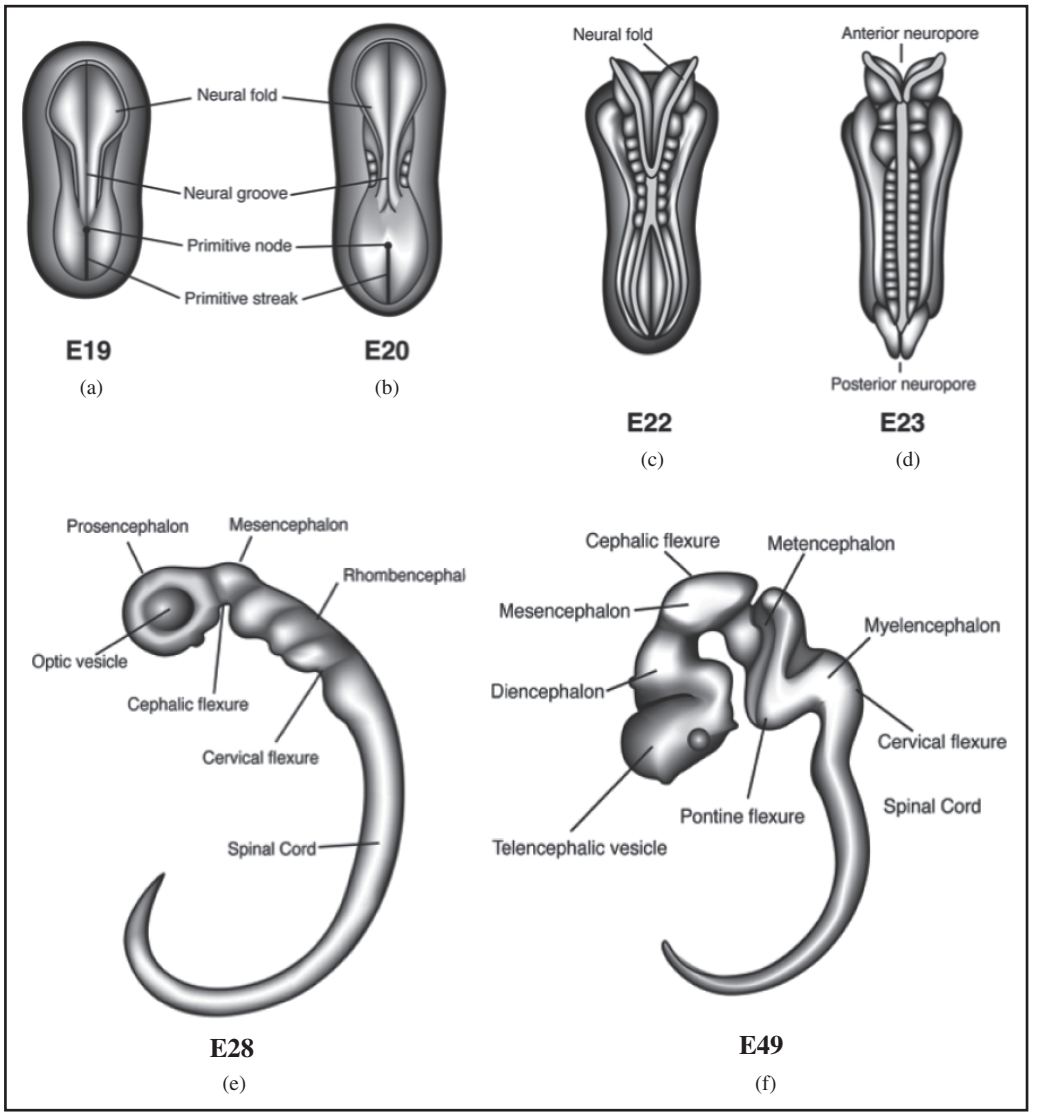

Figure 2.3 Changes in the morphology of the embryo in the embryonic period. (a) The emergence of the neural folds is observed on E19. (b) The ridges fold over to begin the process of neural tube formation. (c) Closure of the neural tube begins on E22 in central regions of the newly forming neural tube. (d) Closure continues in rostral and caudal direction. (e) Following the closure of the neural tube, the embryo begins to expand particularly in anterior regions. The primary vesicles are evident by E28. (f) By E49 the secondary vesicles emerge.

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resulting in cell death of 50%–70% of progenitors by the end of gestation (de la Rosa & de Pablo, 2000; Yeo & Gautier, 2004).

Neurons: Production, Migration, and Differentiation. In humans, neuron production begins on E42. It involves a shift in the mode of cell division from symmetrical to asymmetrical. Asymmetrical cell division in neural progenitors produces one neural progenitor and one neuron (Wodarz & Huttner, 2003). The new progenitor cell remains in the proliferative zone and continues to divide, while the neuron, which is postmitotic and no longer capable of dividing, leaves the proliferative zone to take its place in the developing neocortex. The shift to asymmetrical cell division in the progenitor population is gradual and initially includes only a small proportion of progenitors. Those numbers increase dramatically by the end of cortical neurogenesis. In humans the production of cortical neurons or "cortical neurogenesis" is mostly

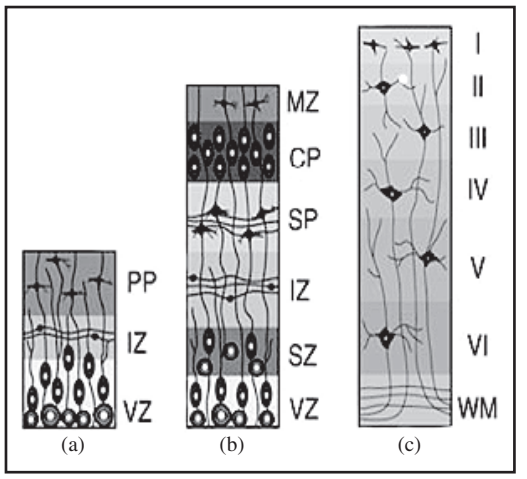

Figure 2.4 Development of the neocortex. (a) The earliest produced neurons migrate from the ventricular zone (VZ) to form the preplate (PP). (b) The next neurons split the PP into the marginal zone (MZ) and the subplate (SP), both transient brain structures. (c) The mature brain has six well-developed cortical layers (I–VI), but none of the embryonic structures (MZ, SP, VZ). The intermediate zone (IZ) becomes a mature white matter layer (WM).

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complete by approximately E108 (Clancy, Darlington, & Finlay, 2001).

Most neurons are produced in the VZ and an adjacent later developing region called the subventricular zone (SVZ). They migrate radially from the VZ/SVZ in the center of the brain out to the developing neocortex (see Figure 2.4). The great majority of neurons migrate from the VZ/SVZ to the cortex along a kind of cellular scaffold that was originally called the radial glial cell (Rakic, 1972). The cell bodies of RGCs are anchored in the VZ. These cells extend a kind of filament composed of the cell's wall called the cellular process that fastens to the far side of the developing cortical plate (CP). Newly produced neurons attach themselves to this cellular scaffold to migrate from the VZ/SVZ to the CP (Nadarajah & Parnavelas, 2002). Each glial scaffold can support the migration of many neurons.

A second proliferative zone is located in the region of the ventral telencephalon that will later develop into the basal ganglia (Anderson, Marin, Horn, Jennings, & Rubenstein, 2001; Nery, Fishell, & Corbin, 2002). These neurons migrate via "tangential migration," traversing the contour of the developing cortical mantle. Tangentially migrating neurons use a number of guidance molecules produced in local regions along their migratory route to direct their movement into the cortex (Marin & Rubenstein, 2001; Valiente & Marin, 2010).

The mature neocortex is a thin mantel of cells that covers the surface of the brain. The organization of the neocortex is well conserved across regions, indeed across mammalian species. Cortical thickness ranges between 2 and 5 mm, and all regions contain six layers of cells. The six-layered organization emerges with development, and is the product of the orderly migration of neurons from the VZ/SVZ in the developing neocortex (Cooper, 2008). Early migrating neurons form the deepest layers of cortex and later migrating neurons form successively more superficial layers (see Figure 2.4) such that the order of migration is "inside-out," with one exception. The very earliest set of migrating neurons is the exception to the inside-out rule. These first neurons to leave the proliferative zone initially form a primitive structure called the preplate (PP; see Figure 2.4a). Once the preplate is complete, the next wave of migrating neurons splits the preplate into two separate regions: the marginal zone (MZ) and the subplate (SP). These neurons begin to form a new region between the MZ and SP that is the emerging cortical plate (CP; see Figure 2.4b). The first neurons to arrive in the CP are the cells that will form cortical layer 6, the deepest layer of cortex, subsequently migrating cells will form progressively more superficial layers of cortex.

Both the MZ and the SP are transient cortical layers that play a critical role in the development of the cortex, but both largely disappear by the end of the fetal period (see Figure 2.4b and c). The MZ contains an important class of cells, the Cajal-Retzius cells (CR) that control the positioning of neurons into the correct layers of cortex. The CR cells produce Reelin, a molecular signal that is part of the pathway that signals neurons when to stop migrating and take up their positions in the cortex (Huang, 2009; Valiente & Marin, 2010). Each new wave of migrating neurons bypasses the previous wave. When they reach the most superficial position within the developing CP, they move into the zone of Reelin signaling and receive the cue to stop and take up their position in the neocortex. Neurons in the subplate layer do not participate in the formation of cortical layers, but as discussed later, they are essential for establishing the primary sensory pathways of the developing brain.

The young neurons become part of information processing networks once they reach the cortex. To do that, these neurons develop neuronal processes (axons and dendrites) that allow them to communicate with other neurons. Axons are the principle means of sending signals from the neuron,

whereas dendrites are major sites for receiving input from other neurons. Each cell has many dendrites that form dense "arbors" in the immediate vicinity of the cell, and a single axon that can extend for some distance away from the cell. The tip of each axon has a structure called a growth cone, which is the site of axon elongation and extension (Brown, Keynes, & Lumsden, 2001). The growth cone samples the local environment for guidance molecules that direct the axon toward its target as the axon extends. Some guidance cues are attractive and signal movement toward a source; others are repulsive and guide movement away. Connections called synapses form with the target cell once the axon has reached its target. Synapses allow for the transmission of electrochemical information that is the essential means of communication in the brain.

Production of the Brain's Glial Cells. Glial cells are much more numerous than neurons in the mature brain, yet make up only about half of the mature brain volume because they are smaller than neurons. The timing and duration of gliogenesis is quite different from neurogenesis. Neurons are produced before glia in most brain regions. Neurogenesis is largely complete by midgestation, while gliogenesis extends well into postnatal life. Astrocytes and oligodendrocytes are produced by the same neural progenitor cells that produce neurons in the early stages of glial development (Sun, Martinowich, & Ge, 2003), but spatially and temporally distinct subsets of neural progenitors appear to be responsible for production of different types of glial cells. Oligodendroctye precursor cells (OPCs) arise in multiple proliferative sites within the dorsal and ventral telencephalon (Kessaris et al., 2006). In humans, OPCs are first observed at about GW19-20 concentrated largely within the SVZ. A second population of OPCs is present in the subplate regions late in gestation. OPC production of oligodendroctyes appears to extend through the lifespan (Richardson, Young, Tripathi, & McKenzie, 2011). Astrocyte production follows a different course. Although astrocytes derived from radial glial cells and from the SVZ populate the cortex during the prenatal period, in the immediate postnatal period, there is a very large and rapid increase in numbers of astrocytes. In the cortex, this increase involves symmetrical cell division that produces new cells that become functionally integrated into local glial networks (Ge, Miyawaki, Gage, Jan, & Jan, 2012).

Neural Patterning in the Prenatal Period

Patterning of the nervous system begins early in the embryonic period. The patterning observed by the end of the embryonic period provides only a primitive map of eventual nervous system organization, yet it sets the stage for later developments (Sur & Rubenstein, 2005). Embryonic patterning affects all brain regions from the forebrain through the spinal column. By the end of the embryonic period major compartments within diencephalic and midbrain regions have differentiated (Kiecker & Lumsden, 2004; Nakamura, Katahira, Matsunaga, & Sato, 2005), dorsal-ventral structures have begun to segregate, and the segmental organization of the hindbrain and spinal column have been specified (Gavalas, Ruhrberg, Livet, Henderson, & Krumlauf, 2003).

Neocortical patterning also begins in the embryonic period. The mature neocortex is partitioned into well-defined structurally and functionally distinct "areas" differentiated by their cellular organization and patterns of neuronal connectivity. Areal patterning of the neocortex begins during the embryonic periodic with primitive specification of the major sensorimotor areas. Initial patterning of neocortex into cortical areas results from different molecular signals present in different regions of the neocortical proliferative zone. While a number of signaling molecules are now known to contribute to this early neocortical patterning (O'Leary & Sahara, 2008; Sansom & Livesey, 2009), the Emx2 and Pax6 molecules, which play an essential role in the early patterning of the presumptive neocortex, illustrate these important early processes (see Figure 2.5).

Emx2 and Pax6 are produced in opposite gradients along the anterior-posterior extent of the neocortical proliferative zone (see Figure 2.5a). The concentration of Emx2 is highest in posterior and medial regions, and lowest in anterior lateral regions; Pax6 has the opposite expression pattern. The interaction of these two gradients contributes to early patterning of the neocortex (Bishop, Rubenstein, & O'Leary, 2002; Hamasaki, Leingartner, Ringstedt, & O'Leary, 2004). High concentrations of Pax6 combined with low Emx2 induces progenitors to produce neurons appropriate for motor cortex (M1), while the inverse concentrations induce production of neurons for visual cortex (V1). Somatosensory cortices (S1) emerge at intermediate levels of both factors. Studies of mutant mice, for which expression of either Emx2 or Pax6 is reduced (thus altering the balance of signals across the cortical proliferative zone), show systematic shifts in the organization of cortical areas (Bishop, Goudreau, & O'Leary, 2000). These studies confirm that the interaction of the two signaling molecules induces change in the surrounding cell populations. When Emx2 expression is reduced, visual

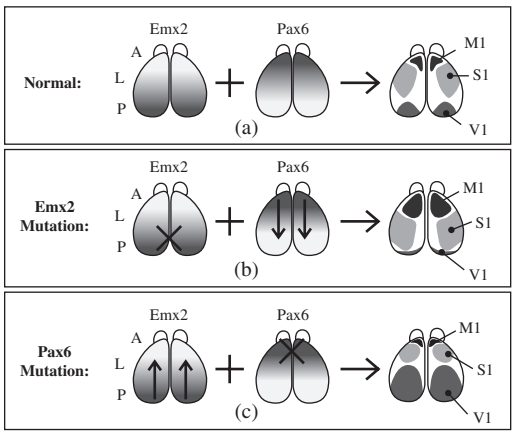


Figure 2.5 Emx2 and Pax6 are expressed in complementary concentration gradients within the neocortical proliferative zone. The combination of the two molecules at particular concentration levels determines the functional identity of the cortical region. Mutations affect the quantities of either molecule, alter cortical patterning. A = anterior, L = lateral, P = posterior, M1 = motor, S1 = somatosensory, V1 = visual.

Source: From "Regulation of Area Identity in the Mammalian Neocortex by Emx2 and Pax6," by K. M. Bishop, G. Goudreau, and D. D. O'Leary, 2000, *Science*, *288*(5464), pp. 344–349. Adapted with permission.

areas shrink and somatosensory and motor areas enlarge (Figure 2.5b); when Pax6 expression is reduced, visual areas enlarge while somatosensory and motor areas shrink (Figure 2.5c). Thus, the effect of the particular level of one molecular signal in combination with the level of another signal produces the classical pattern of sensorimotor organization in the developing cortex.

These graded patterns of molecular signaling occur in regions of the neocortical proliferative zone that were specified as "rostral" during gastrulation. This later patterning constitutes a regional elaboration or refinement of an earlier phase of neural patterning. Patterning within these regions is far from complete at the end of the embryonic period. Fundamental organizational features of the sensory and motor cortices do not arise until the late fetal period. The structural and functional identity of these basic brain areas remains malleable and subject to the effects of input and experience across the period of fetal and early postnatal development.

Formation of the Major Brain Pathways in the Prenatal Period

Studies of both monkeys and humans have documented widespread exuberant production of connections throughout all brain regions in the early postnatal period (Bourgeois, Goldman-Rakic, & Rakic, 1994; Huttenlocher & Dabholkar, 1997; Huttenlocher & de Courten, 1987; Zecevic, Bourgeois, & Rakic, 1989). Exuberant connectivity occurs in pathways as diverse as the corpus callosum, thalamocortical pathways, corticospinal tract, and pathways linking the temporal lobe and the limbic system (Innocenti & Price, 2005; Stanfield & O'Leary, 1985). A wide range of factors affects the retention or elimination of pathways. Competition for resources, such as neurotrophic factors, plays a significant role in selection of pathways. Importantly, afferent input plays a critical role in modulating the stabilization or elimination of pathways. This section considers the initial formation of several major pathways in the prenatal period.

Corticospinal Tract. The typical mature corticospinal tract (CST) originates in the frontoparietal cortices. The tract travels through the anterior half of the posterior limb of the internal capsule (the dense white matter system connecting cortex with the brainstem) forming the cerebral peduncles before reaching the brainstem. The CST crosses the midline to the contralateral side forming the medullary pyramid decussation in the lower medulla. The contralateral CST travels down the spinal cord synapsing on motor neurons (Armand, 1982). CST neurons initially exhibit an "exuberant distribution" during development (O'Leary & Kroll, 2009). The CST initially forms bilateral connections, in contrast to the mature pattern of contralateral organization (e.g., right motor cortex controls the left side of the body). The CST is discernable as early as GW13 (Eyre, 2007; Huang et al., 2009), and by GW24 projections originating in the motor cortex innervate *both* ipsilateral and contralateral spinal motor neurons creating dual pathways that are detectable through the first 3 months of postnatal life (Eyre, 2007). Thereafter, progressive withdrawal of the ipsilateral projections occurs resulting in clear contralateral dominance by 18 months. The CST forms a conduit between the motor cortex and the limbs of the body, such that activity in the motor cortex depends on the motor activity of the limbs and vice versa. This activity drives the maturation of the CST and modulates the balance between projection and withdrawal of contralaterally and ipsilaterally projecting CST axons (Eyre, 2007; Martin, 2005).

Corpus Callosum. The corpus callosum (CC) connects neurons in the two cerebral hemispheres and is the largest pathway in the brain. Its principal function is the coordination and transfer of information between the hemispheres. Critical events during the early embryologic period set the stage for CC development. During the differentiation of the telencephalon, the single vesicle of

the prosencephalon expands and divides into two compartments creating the characteristic two-vesicle structure of the telencephalon. The two cerebral hemispheres emerge from the vesicles of the embryonic telencephalon. The ventral portions of the two hemispheres are initially fused, but it is not until the end of the embryonic period that more dorsal regions also fuse, creating a substrate for the developing CC (Jovanov-Milosevic, Culjat, & Kostović, 2009; Richards, Plachez, & Ren, 2004).

Cortical layer 3 neurons are the principal source of the axons that make up the CC in primates. These neurons extend axons from the neocortex ventrally into the intermediate zone near the ventricles. The axons then change direction following the medial wall of the ventricle across the midline of the brain and from there they grow toward their cortical targets in the contralateral brain hemisphere. A large number of guidance molecules direct the axons' movement through these various brain compartments (Jovanov-Milosevic, Culjat, & Kostović, 2009; Richards et al., 2004). The first CC axons approach the midline by GW 11. All the major components of the CC (genu, body, splenium) are present by GW 18–20 (Huang et al., 2009; Jovanov-Milosevic et al., 2009). The CC structure is similar in shape and position to that of an adult by GW 19, although it is smaller in rostral-caudal extent and thinner. An areal cross section of the CC at GW19 is 5% the size of a 5-year-old, but by birth the cross section is 50% of a 5-year-old. Connectivity in the developing CC is extremely dynamic, exhibiting the kind of synaptic exuberance and pruning that is characteristic of many brain areas (Innocenti & Price, 2005; Paul, 2011). LaMantia and Rakic (1990) reported that the CC of a newborn Rhesus monkey contains 3.5 times the number of axons of a mature CC. Development of the CC is protracted, extending well into adolescence (Paul, 2011).

Thalamocortical Pathway. The thalamocortical pathway (TCP) relays visual, auditory, motor, and somatosensory information from the receptors in the retina, cochlea, muscle, or skin to the sensorimotor regions of the neocortex via the thalamus, the major subcortical sensorimotor relay center. The corticothalamic pathway (CTP) completes the feedback loop by transmitting information from cortex back to the thalamus. These essential pathways begin forming in the later part of the second trimester in humans, and are complete by GW26 (Kostović & Jovanov-Milosevic, 2006). The cells of the transient subplate layer of the developing brain play an essential role in establishing these pathways (see Figure 2.4b). TCP axons do not immediately make connections with neurons in the primary input layer of cortex (layer 4) when they arrive at the developing cortex during GW22. Rather, they make connections with the neurons of the subplate layer. The TCP-subplate connections last for approximately 4 weeks, during which time the subplate neurons make connections with neurons in cortical layer 4. The subplate neurons appear to provide instructive input to the TCP neurons during this period. In the absence of subplate neuron signaling, normal patterns of connectivity between TCP axons and layer 4 cortical neurons do not develop. The CTP pathway follows a similar pattern of instructive connectivity. Subplate neurons extend axons to the thalamus and establish connections with thalamic neurons before the normal CTP connections between cortical layers 5 and 6 neurons and the thalamus are formed. It is thought that subplate connections serve to guide the CTP axons to their positions in the thalamus. The subplate neurons retract their connections and the cells gradually die off once the TCP and CTP pathways are complete.

The primary visual pathway includes both the optic pathway and the visual component of the thalamocortical pathway. The pathway begins with the retinal ganglion cells (RGC) in the eye and projects along the optic pathway to the optic chiasm. There, 50% of the projections cross and project to midbrain targets in the contralateral hemisphere, specifically the superior colliculus (SC) and the dorsal lateral geniculate nucleus of the thalamus (dLGN), while the remaining projections synapse on comparable ipsilateral midbrain targets (Leamey, Van Wart, & Sur, 2009; Reese, 2011). Connections to the SC and dLGN are initially imprecise but are gradually refined. Exuberant projections are pruned to more restricted regions within the SC. Initially mixed and imprecise RGC connections segregate into eye specific domains within the dLGN (Haupt & Huber, 2008). Initial projections from the dLGN to occipital cortex along the optic component of TCP exhibit similar initial imprecision. Though controversial (Katz & Crowley, 2002), recent evidence suggests that waves of spontaneous retinal activity are necessary for this fine-tuning of the visual system connectivity (Huberman, Speer, & Chapman, 2006).

The auditory pathway includes both the brainstem auditory pathway and the auditory component of the TCP. The brainstem auditory pathway begins with the spiral ganglion cells (SGC) in the cochlea and projects to the cochlear nuclei in the brain stem (Appler & Goodrich, 2011; Moore & Linthicum, 2007). From there, the pathway extends to the olivary complex, to inferior colliculi (IC), and from the IC to the medial geniculate nucleus (MGN) of the thalamus.

The brainstem pathway is well established by the end of the second trimester. The auditory TCP is established during early third trimester, but undergoes considerable development postnatally. The auditory pathway exhibits tonotopic organization with cells responsive to different frequencies arranged in a linear fashion. Tonotopy is evident throughout much of the pathway including the cochlear nuclei, MGN, and primary auditory cortex. Although the mechanisms that underlie the functional development of the auditory pathway are not as well understood as those of the visual pathway, it is presumed to follow similar developmental principles. There is evidence, however, that the initial tonotopic mapping within the auditory system may be more precise than the retinotopic mapping of the visual system (Appler & Goodrich, 2011).

Association Pathways. Association pathways connect cortical areas within each cerebral hemisphere. Most of the major association pathways can be identified in the prenatal brain, although they emerge at different points in development. The external capsule can be traced as early as GW15, while the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and the uncinate cannot be clearly traced until GW19. The superior longitudinal fasciculus, an important pathway connecting frontal and parietal brain areas, is late developing, and is not evident at the end of the prenatal period (Huang et al., 2009).

Postnatal Brain Development

The human brain exhibits dramatic postnatal biological development. *In vivo* brain imaging of infants and children provides much of the information about the nature and timing of alterations during this exuberant brain growth and maturation period. Nevertheless, the specific biological processes giving rise to the effects observed via imaging remain obscure. Developmental neurobiology also adds critical information about postnatal brain development. Importantly, estimates of the extent and time course of human developmental processes generally must extrapolate from data acquired in other species, often rodents, and from limited human postmortem material. The result is uncertainty about the scale and temporal extent of cell proliferation, migration, differentiation, and regression, and about the relationship of these processes to each other, during the human postnatal period.

Progressive Processes in Postnatal Brain Development

The production and migration of neurons are largely prenatal events. Nonetheless, evidence shows that neurogenesis continues to a very limited degree postnatally in the subventricular zone, where new neurons continue to emerge and migrate to the olfactory bulb, and in the dentate gyrus of the hippocampus. These exceptional forms of neurogenesis produce only a small percentage of the neuronal population. By contrast, glial progenitors proliferate and migrate vigorously during the immediate postnatal years, and these processes continue for a protracted period. Indeed, progenitor cells (oligodendrocyte precursor cells, or OPCs), persist indefinitely in the adult brain in a wide anatomical distribution, and can differentiate in response to injury. Glial progenitors mostly proliferate in the forebrain subventricular zone and migrate radially and laterally into the overlying white matter and cortex, striatum, and hippocampus, where they differentiate into oligodendrocytes and astrocytes. Unlike neural progenitors, glial progenitors continue to proliferate as they migrate (Cayre, Canoll, & Goldman, 2009).

Initially, astrocytes in cerebral cortex arise from radial glial cells in the VZ and glial progenitors in the SVZ. However, evidence from rodent models suggests that, once established in cortex, these early differentiated astrocytes produce most cortical astrocytes through local symmetrical division. Astrocyte numbers increase rapidly during the immediate postnatal period in widely distributed brain areas (Ge et al., 2012).

Some OPCs begin to differentiate into oligodendrocytes by extending processes and upregulating myelin protein expression upon reaching their destinations. The new processes begin to form membrane wraps around nearby axons. The oligodendrocytes eventually form tightly wrapped multilayered sheaths from which most of the cytoplasm has been extruded. The best understood functional consequence of myelination is the effect on axonal conduction velocity; however, observations of functional interactions between oligodendrocytes and neurons suggest that they are complex and dynamic. Oligodendrocytes synthesize a number of trophic factors that contribute to the maintenance of axonal integrity and neuronal survival, and neuron-oligodendrocyte interactions influence neuronal size and axon diameter (McTigue & Tripathi, 2008).

An intriguing new line of evidence also suggests that a subset of the OPCs dispersed throughout the brain form excitatory and inhibitory connections with neurons, and thus may contribute actively and directly to neural signaling (Lin & Bergles, 2004). These cells, also sometimes referred to as nerve/glial antigen 2 or NG2 cells, account for most cell proliferation and differentiation in the postnatal and adult brain. They are dispersed roughly evenly

within white and gray matter regions and migrate over long distances postnatally (Mangin & Gallo, 2011). Many questions remain about these interesting brain cells. While they clearly contribute to the oligodendrocyte population that myelinates neuronal axons, there is growing evidence they may have other important functions as well in the nervous system (Mangin & Gallo, 2011).

Research has also focused on the so-called microglia, the bone marrow derived population of brain resident cells that colonize and persist in the central nervous system. Microglia, particularly in an immature amoeboid form, are present during fetal development. However, their numbers increase dramatically in early postnatal life and a protracted process of postnatal maturation occurs during which these cells disseminate throughout all regions of the brain and assume a highly ramified phenotype characterized by long, thin processes. The final distribution of cells suggests relatively nonoverlapping surveillance territories. Although maturation of this cell population is not well understood, there is evidence suggesting that microglia functions during development extend beyond their established role in immune activation to possible roles in regulation of neurogenesis, gliogenesis, synaptic remodeling, and myelination (for review, see Harry & Kraft, 2012).

In summary, proliferation and migration of glial precursors and maturation of astrocytes and oligodendrocytes, as well as ongoing maturation of microglia, are processes that extend long into the postnatal period. The full scope of their impact on neural dynamics remains unclear. Research continues to uncover additional molecular interactions between neurons, oligodendrocytes, astrocytes, and microglia. The existence of these interactions implies that the postnatal maturation of glial and microglial populations probably has widespread functional implications for developing neural systems.

Regressive Processes in Postnatal Brain Development

Brain development is characterized by early overproduction of neurons and glial cells, neural processes, and synapses. Although programmed loss of neurons has its peak during prenatal life, apoptosis in glial cell populations has a time course corresponding to the protracted postnatal time course of differentiation from glial precursors. Many excess oligodendrocytes undergo apoptosis within a few days after differentiating during the initial myelination period, and evidence suggests this process depends on signals from nearby axons, such that the number of surviving oligodendrocytes matches the local axonal surface area (for review, see McTigue & Tripathi, 2008).

Much of the regressive remodeling that occurs in the postnatal brain involves elimination or pruning of neuronal processes, i.e., axonal and dendritic processes, spines, and synapses. Studies of monkeys and humans reveal excess connections throughout distributed gray matter regions in the early postnatal period (Bourgeois, Goldman-Rakic, & Rakic, 1994; Bourgeois & Rakic, 1993; Huttenlocher & Dabholkar, 1997; Huttenlocher & de Courten, 1987; Zecevic et al., 1989). Several axonal pathways, especially in the corpus callosum, but also in thalamocortical pathways, corticospinal tract, and pathways linking the temporal lobe and the limbic system show exuberant connectivity (Innocenti & Price, 2005; Stanfield & O'Leary, 1985; Stanfield, O'Leary, & Fricks, 1982). The process of pruning excess connectivity is not fully understood. Influences such as competition for neurotrophic factors and the presence or absence of afferent input are implicated in this process. Studies using video microscopy reveal that neuronal processes continuously sample the surrounding space, forming and retracting synaptic connections dynamically, probably to varying degrees throughout the lifespan (Hua & Smith, 2004).

Imaging Studies of Brain Morphology

MRI studies reveal dramatic changes in the tissues of the developing brain during the postnatal brain growth spurt. These changes presumably reflect proliferation and maturation of oligodendrocytes, astrocytes, and microglia as well as the deposition of myelin. The changes provide information about the timing and anatomical distribution of these processes (Barkovich, 2000, 2005). Myelination changes first appear in sensorimotor pathways and commissural tracts and gradually spread throughout the white matter. The earliest MRI morphometry studies comparing children and adults revealed that gray matter volumes in the cerebral cortex and subcortical nuclei are considerably larger in school-aged children than in young adults (Jernigan & Tallal, 1990; Jernigan, Trauner, Hesselink, & Tallal, 1991; Pfefferbaum et al., 1994). This suggested more protracted tissue alterations related to brain maturation than was previously supposed. Although subsequent studies confirmed and extended these findings (for review, see Toga, Thompson, & Sowell, 2006), the underlying cellular changes remain a matter of speculation. MRI measurements indicate that cranial vault volume increases dramatically with age after birth but very little after the first decade. Evidence from MRI suggests that effects of waning progressive changes throughout childhood and adolescence, associated with continuing maturation of

glial populations and neurotrophic effects, are opposed by regressive changes, perhaps associated with "pruning" of neuronal processes. These observations are consistent with ample histological evidence for ongoing myelination across this period (Yakovlev & Lecours, 1967), and evidence for the reduction of synaptic density in cortex during childhood (Huttenlocher & Dabholkar, 1997). Nonetheless, it remains unclear to what extent these factors, or other tissue changes that occur concurrently, contribute to the changing morphology observed with MRI.

Employing mapping methods for visualizing the spatial pattern of age-related change across the late childhood range provides greater anatomical detail to MRI morphometry studies (Giedd, Snell, et al., 1996; Giedd, Vaituzis, 1996; Sowell et al., 1999; Sowell, Trauner, Gamst, & Jernigan, 2002). Such studies confirm the protracted course of postnatal white matter growth and the declining volume of tissue with the MR signal characteristics of "gray matter" in the cerebral cortex and some deep nuclei. These studies also seemed to indicate a modal pattern of childhood and adolescent change in the morphology of the cerebral cortex with growth, or thickening, of the cortex in the early years, followed by widespread cortical thinning (Gogtay et al., 2004; Sowell et al., 2004). One problem in interpreting these mapping studies is distinguishing the contribution of changes in cortical surface area from those in cortical thickness. The separation of these effects is a difficult computational problem, but is critical during the first decade of life when brain volume is increasing and the two effects could be strongly dissociated. The evidence from mapping studies suggests that apparent cortical thinning occurs first in primary sensory-motor cortex and then progresses into secondary, multimodal, and finally supramodal cortical areas throughout childhood and adolescence. Ostby et al. (2009) confirmed these observations in a large cross-sectional sample of participants aged 8 to 30 years with more advanced methods that provided concurrent estimates of cortical surface area and cortical thickness. Modest decreases in cortical surface area accompanied the more dramatic decreases in cortical thickness across this age range. Unfortunately, that study provided no information about the early postnatal period during which thickness and surface area are likely to exhibit distinct developmental trajectories.

The preschool years are still undercharacterized in brain imaging research; however, advances in MRI methods make it increasingly feasible to image younger children. Multimodal brain imaging was acquired in approximately 1,400 typically developing individuals between 3 and 20 years old in the Pediatric Imaging, Neurocognition, and Genetics (PING) study (Brown et al., 2012). This multisite study applied prospective head motion correction that significantly reduced lost data and artifacts from motion in the youngest children (Brown et al., 2010; Kuperman et al., 2011; White, Roddey, et al., 2010). Data from the PING study extend and clarify results of previous imaging studies of postnatal development beyond 3 years of age. Age-related change in cortical surface area and thickness are best presented in the maps of annualized rate of change shown in Figure 2.6a and b. Annualized rate of change is defined by a measure of the age-varying developmental slope across a 1-year age band, and is calculated at every point across the brain surface, displayed here as a map

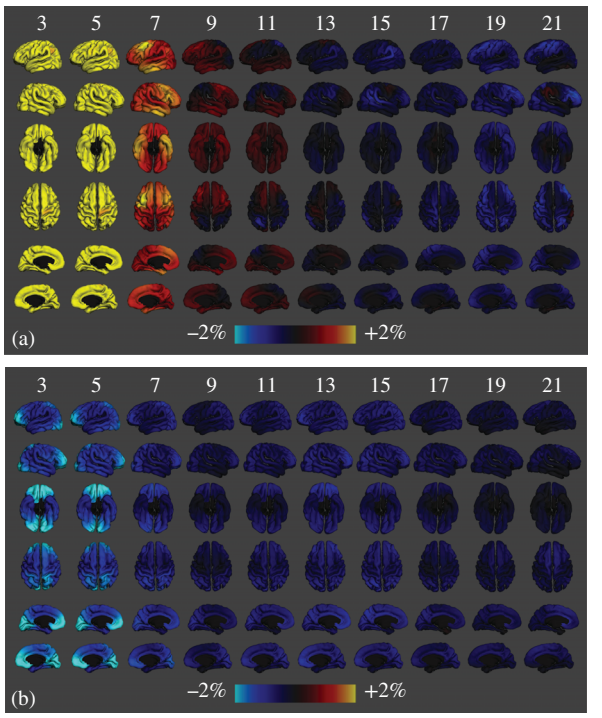


Figure 2.6 Annualized rates of developmental change in surface area (panel a) and thickness (panel b) across the human cerebral cortex. For each age conveyed, estimated instantaneous rate of change for a 1-year interval is shown at every cortical location, calculated as a percentage of the total measure at the lowest age within that interval. Both socioeconomic status and genetically derived ethnic ancestry are controlled for. Developmental changes in the average cortical surface geometry are also conveyed (note subtle lengthening with age). Yellow = 2% annualized increase; red = 1% increase; light blue = 2% decrease; dark blue = 1% decrease. Columns show results from ages 3 to 21 every 2 years (left to right). Rows show (from top to bottom) left lateral, right lateral, inferior, superior, left medial, and right medial views. Results were computed using 1109 subjects between the ages of 3.0 and 20.7 years. See footnote 1.

of changing characteristics of cortical surface area and thickness. As Figure 2.6a shows, there is significant expansion of cortical surface area during preschool ages and early school-age years. By 4 years, the greatest changes in area are occurring within higher order cortical regions such as prefrontal cortex and temporal association areas, still increasing but to a lesser extent are areas within primary sensory (visual, auditory) and sensorimotor cortex bilaterally. By the 10th year, some cortical regions begin to show decreases in area, especially within occipital and superior parietal lobes; however, continued cortical area expansion still occurs in some regions. From 10 to 16 years, the balance between contracting and late expanding areas shifts further until cortical area contraction is present throughout almost the entire cortex. These data show clearly that the peak of total cortical surface area at around 10 years represents the net effect of waning expansion in some regions and early contraction in others.

In stark contrast to cortical area, apparent cortical thickness shows no developmental increase at any point across this age range. In fact, thickness measures decrease throughout the cortex into young adulthood (Figure 2.6b). From 3 to 6 years, cortical thickness apparently decreases by about 2 percent each year within medial and polar occipital and prefrontal regions, as well as within parietal cortex. At these ages, the remainder of the cortical surface shows an annual decrease in thickness of about 1 percent that continues to age 20 years and likely beyond. Previous imaging studies have characterized developmental changes in the volume of cortical gray matter (Giedd, Snell, et al., 1996; Jernigan & Tallal, 1990; Jernigan et al., 1991). However, the PING study demonstrates why it is important to deconstruct volume into thickness and area, as they have different developmental trajectories overall and within different cortical regions (see also Sowell et al., 2004). Area and thickness may relate to cognitive and behavioral development differentially given their separate neurobiological origins, including evidence for distinct genetic factors influencing them (Panizzon et al., 2009). In summary, there is an early period of striking, widespread, but regionally varying surface area expansion that gives way gradually to contraction around puberty, while apparent cortical thickness decreases continuously across the childhood years.

The relationship of these effects to myelination is a germane issue. At the basic level, cortical "thinning" could simply reflect increased myelination in the white matter tracts coursing within and near the deepest layer of cortex. In other words, the "gray" signal of the unmyelinated fibers could simply be becoming more "white" as myelin is deposited. This is clearly part of the cortical thinning measured with morphometry, especially in preschool aged children. However, there is evidence that true regressive changes also occur in some structures—probably due to loss or simplification of neuronal processes (dendrites and/or axons). This is inferred from the fact that the progressive changes that are expected to result from continuing myelination do not seem to increase cranial volume in late childhood (as though they were opposed by regressive factors). Indeed, cortical surface area decreases slightly. Additionally, there are modest but significant CSF volume increases adjacent to the cortical surface and in the ventricular system over this age-range, as might be expected, *ex vacuo*, in the wake of the loss of neural elements in the adjacent tissues (Jernigan et al., 1991; Sowell et al., 2002).

The functional correlates of these changes in the neural architecture are unclear. It is possible that the functional changes resulting from myelination of fiber tracts stimulate cortical thinning, or conversely, that increasing activity due to intrinsic cortical maturation stimulates myelination of the axons in the maturing network. Neuron-glia signaling mechanisms mediate effects of action potentials on oligodendrocyte differentiation and myelination (for review, see Fields & Burnstock, 2006). Unfortunately, the interactions among these factors in developing brain tissues of children remain obscure. In any event, it is clear that ongoing maturation of fiber tracts plays a key role in the functional maturation of the brain.

Diffusion Imaging of Brain Development

Diffusion weighted imaging (DWI) has made it possible to examine the maturation of fiber tracts directly (Basser, Mattiello, & LeBihan, 1994; Mori & van Zijl, 1995). Diffusivity declines dramatically in the brain during postnatal development, in a widespread distribution that includes both gray and white matter structures (Cascio, Gerig, & Piven, 2007; Hermoye et al., 2006). Diffusivity in white matter of human newborns is high, and exhibits low FA (Hermoye et al., 2006). As the fiber tracts mature, and myelination proceeds, diffusivity declines, and FA increases. The denser packing of axons, their tightly wrapped myelin sheaths, and increasing axon diameters are factors likely to alter these parameters by reducing the extracellular space (Suzuki, Matsuzawa, Kwee, & Nakada, 2003); however, how these and possibly other factors, such as fiber morphology, contribute is still poorly understood.

Changes in diffusion parameters continue throughout childhood and adolescence in a regionally varying pattern

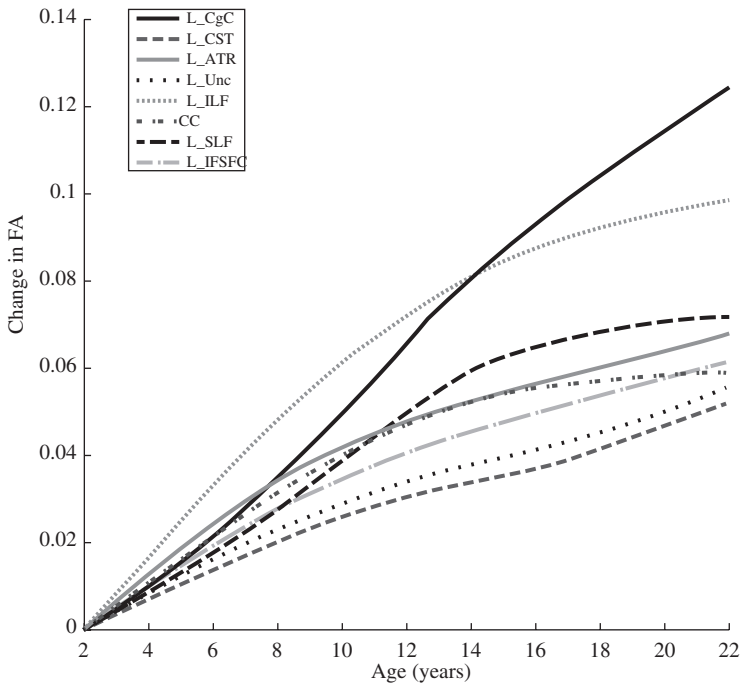


Figure 2.7 Relative age changes in fractional anisotropy (FA) by white matter tract. Spline-fit nonlinear curves are shown for the changes in FA with age for eight white matter fiber tracts, normalized to the earliest time point to reveal relative differences across time. Tracts are: corpus callosum (CC); left cingulum, main (L_CgC); cortico-spinal (L_CST); anterior thalamic radiations (ATR); uncinate (Unc); inferior longitudinal fasciculus (ILF); superior longitudinal fasciculus (SLF); and inferior frontal to superior frontal cortex (IFSFC). Trajectories were computed using 1,105 subjects between the ages of 3.0 and 20.7.

(Barnea-Goraly, Menon, et al., 2005; Schneider, Il'yasov, Hennig, & Martin, 2004; Snook, Paulson, Roy, Phillips, & Beaulieu, 2005). For example, FA reaches asymptote earlier in long projection and commissural than in association fibers, the latter continuing to exhibit age-related FA increases well into adulthood (for reviews, see Cascio et al., 2007; Huppi & Dubois, 2006; Mukherjee & McKinstry, 2006). Lebel et al. (2008) compared diffusion parameters in a large group of typically developing children to those in young adults. They observed robust increases in FA across the age-range from 5 to 12 years within multiple fiber tracts with varying time courses. This group also reported individual trajectories of tract FA obtained with repeated imaging of school-aged children (Lebel & Beaulieu, 2011). These data confirmed increases in FA over a period of 2 to 4 years within individual children, and highlighted wide individual differences in the pace of these changes across children.

The PING study (Brown et al., 2012) measured tract FA across a wider age range than previous studies and derived smooth age functions using generalized additive models (GAMs). GAMs allow for more data-driven, biologically plausible nonlinear estimates of developmental trajectories. The developmental changes observed in FA within eight major fiber tracts are shown in Figure 2.7. Here, normalized FA values at the youngest age convey the differences among the tracts in the degree and time course of FA change across the studied age range.

Although less often a focus of developmental studies than changes in fiber tracts, age-related decreases in diffusivity and increases in FA are also measurable in most deep gray matter structures, for example, in diencephalon and striatum (Barnea-Goraly, Eliez, Menon, Bammer, & Reiss, 2005; Hermoye et al., 2006; Lebel & Beaulieu, 2011; Lebel et al., 2008). The biological mechanisms that underlie these gray matter changes in diffusivity are not well understood, but investigators have speculated that changing cell density or neurite structure might play a role, for example, glial cell proliferation, increased neuronal or glial cell sizes, or increased dendritic density.

Developmental Changes on Positron Emission Tomography (PET)

Local cerebral metabolic rates for glucose (lCMRGlc) are about 30% lower at birth compared to adult rates across the entire brain but rapidly increase to adult levels by

about the second year of life (Chugani & Phelps, 1991; Chugani et al., 1987). These increases continue through the preschool ages, exceed adult levels by about three years old, and plateau from about the age of 4 to 9. At their peak, glucose metabolic rates are highest within the cerebral cortex, where they are twice the value of adult rates. In brainstem and cerebellum, lCMRGlc does not exceed adult values and appears to be relatively metabolically mature at birth. Other subcortical structures, such as the thalamus and basal ganglia, show intermediate glucose metabolic rate increases over adult values. At around the ages of 8 to 10 years, lCMRGlc begins to decline and comes to resemble adult levels by about 16 to 18 years of age.

Based on the developmental trajectories of synaptic proliferation and elimination, and on clinical observations of behavioral plasticity in children with brain damage, Chugani et al. (1991) proposed that early increasing lCMRGlc rates are directly related to the period of rapid overproduction of synapses and nerve terminals thought to occur within a similar timeframe. The cause of the plateau during which glucose metabolic rates far exceed adult levels may be a transient increased cerebral energy demand from this overly elaborated connectivity. Likewise, subsequent developmental decline in metabolic rates may correspond to the later period of selective elimination (i.e., activity-dependent "withering") of many of these connections, marking a time when plasticity seems to notably diminish. Chugani et al. (1991) have found support for these hypotheses in developmental studies with nonhuman animals.

Developmental Changes on Resting State Functional MR (rs-fcMRI)

Researchers using fMRI have developed techniques to look at brain network properties expressed as modulated interregional hemodynamic activity correlations measured at waking rest, in the absence of the presentation of any time-locked stimuli. Similar in concept to frequency domain analyses of EEG and MEG, resting state fMRI analyses look at correlated activity fluctuations on a much slower time scale, limited by the vascular BOLD response as a stand-in for neuronal activity. Resting state functional connectivity MRI (rs-fcMRI) has come to play a prominent role in neuroimaging research in both adults and children (Biswal et al., 2010; Snyder & Raichle, 2012). Resting functional connectivity studies of children have produced interesting developmental findings comparing school-age children to adolescents and young adults. From about 7 to 30 years of age, linked resting functional networks shift from a predominantly "local" organization in young children to a more "distributed" architecture in young adults (Fair et al., 2009). With development, greater overall connectivity is observed (Fair et al., 2010), characterized by significant weakening of short-range connections and strengthening of long-range functional connections with development (Power, Fair, Schlaggar, & Petersen, 2010). However, several large-scale studies have concluded that resting interregional activity correlations undergo a prominent developmental shift from "diffuse to focal activation patterns," seemingly contradicting findings that the functional organization develops from local to distributed (Supekar et al., 2010; Uddin, Supekar, Ryali, & Menon, 2011). This discrepancy may reflect an imprecision in the descriptive terminology, or it may relate more directly to the results themselves, but some reconciliation seems warranted (e.g., for discussion of the use of the term "diffuse," see Brown, Petersen, & Schlaggar, 2006).

It is important to note that head motion may cause particularly insidious artifacts in resting state connectivity studies (Van Dijk, Sabuncu, & Buckner, 2011). Thus, systematic differences in head motion from early childhood into young adulthood may underlie some of the major developmental effects (Power, Barnes, Snyder, Schlaggar, & Petersen, 2013). A rigorous characterization of the nature and scope of this problem is important because of the application of resting state functional connectivity to a wide range of child and adult clinical groups. These include studies of autism (Lee et al., 2009), attention disorders (Mennes et al., 2011), schizophrenia and psychosis (Alonso-Solis et al., 2012; White, Schmidt, Kim, & Calhoun, 2010), early deprivation (Behen et al., 2009), childhood epilepsy (Mankinen et al., 2012), fetal alcohol spectrum disorders (Wozniak et al., 2011), preterm and low birth weight children (Gozzo et al., 2009), pediatric Tourette syndrome (Church et al., 2009), and childhood mood disorders (Cullen et al., 2009). If children and adults with clinical issues systematically produce more motion in the scanner than people without these problems, these groups may spuriously appear to have more "immature" patterns of functional connectivity. This is a recurring theme in these studies. Reconciling these issues is an important area of research in rs-fMRI.

The Role of Experience in Brain Development

The events of the prenatal period serve to establish the core compartments of the developing nervous system from the spinal cord and hindbrain to the cortical structures of

the telencephalon. These early events also provide initial patterning within each of the major subdivisions of the brain, but this early patterning, particularly in the neocortex, is both underspecified and malleable. The mature organization of the neocortex emerges slowly during the postnatal period, and it requires diverse forms of input. Some of this input arises from within the organism in the form of molecular signaling and cross-regional activity. However, the specific experience of the individual organism also plays an essential role in establishing the mature organization of the neocortex. The development of normal brain organization requires input via all of the major sensorimotor systems. When specific aspects of input are lacking, alternative patterns of brain organization can and do emerge. These alternative patterns of organization reflect the effects of altered neural competition and capture a fundamental property of mammalian brain development, the capacity for plastic adaptation.

The Role of Input on Brain Development

Greenough, Black, and Wallace (1987) introduced the term "experience expectant" development to capture the idea that the early experience of the organism plays an essential role in normal brain development, particularly in the early postnatal period. Although cortical patterning begins in the embryonic period, it remains malleable for an extended period. Typical, expected, postnatal experience is necessary for the emergence of normal patterns of neocortical organization. When that input is lacking, brain areas develop differently, and the specific pattern of development reflects the kinds of input that the organism actually received. At later ages, the developing—and even the mature—nervous system continues to require input to acquire new knowledge and to develop functional neural systems. Greenough has termed this later phase of development "experience dependent" learning. These two important constructs suggest that experience plays an essential role in establishing and refining neural organization in ways that allow the organism to adapt to the contingencies of the world in which it lives throughout development. Studies that systematically manipulate the specific experience of the young organism provide insight into the dynamic and adaptive nature of brain development.

Two simple ways to alter input are enrichment and deprivation. Both have dramatic effects on the structural and functional organization of the developing brain. Greenough has shown that simply rearing animals in either impoverished (standard laboratory cage) or enriched environments (large enclosures with interesting and changing landmarks and multiple littermates) affects the development of a wide range of brain structures and functions (Black, Sirevaag, & Greenough, 1987; Greenough & Chang, 1988; Markham & Greenough, 2004). Animals reared in complex environments show enhancement in density of cortical synapses, increases in the number of brain support cells, and even augmentation of the complexity of the brain vascular system. Further, many of the effects of rearing in the complex environment persist even when the animal is returned to more impoverished conditions.

Sensory deprivation has more selective effects that target particular cortical sensory systems. The seminal studies of Hubel and Weisel (Hubel, 1982) showed that monocular visual deprivation in the early postnatal period could substantially alter basic patterns of organization within primary visual cortex (PVC). Within the typical primary visual pathway, inputs from the two eyes remain segregated from the retina to the thalamus to PVC. In PVC, the inputs from the two eyes form a distinctive banded pattern, called ocular dominance columns (ODC) that give the input layer of PVC a striped appearance. Suturing one eyelid closed produces striking effects on ODC organization. The bands representing the active eye widen and expand into the territory of the deprived eye; the bands representing the deprived eye shrink to thin stripes. The monocular reduction in activity introduced by the suturing procedure alters the competitive balance of input from the two eyes. The inputs from the active eye invade and subsume territory that would normally have received input from the deprived eye.

Neural Pathology and Input

The enrichment and deprivation studies provide powerful evidence of the role of experience on brain development. However, experimental studies can be more invasive, introducing procedures that directly affect or eliminate specific brain areas. These studies provide evidence that plasticity in developing neural systems can extend to the capacity to develop fundamentally different patterns of organization and function in the face of injury. For example, Sur and colleagues (Pallas, Roe, & Sur, 1990; Sur, Garraghty, & Roe, 1988) surgically eliminated the major input pathway to the primary auditory cortex (PAC) in 1-day-old ferrets to determine what would happen to this important sensory area in the absence of input. In the normal course of early development, the visual pathway from the retina extends what are typically transient connections to PAC, in addition to the normal connections to PVC. The retina-PAC connections are typically pruned

as part of the normal competitive processes. However, in the absence of competition, the inputs from the retina stabilize and form a functional visual pathway to PAC. PAC takes on patterns of internal organization that, while cruder, are characteristic of PVC (Sur & Leamey, 2001) and the "rewired" PAC functions as a visual area in behavioral testing (von Melchner, Pallas, & Sur, 2000). Thus, the altered early experience of the organism results in fundamental functional and structural reorganization of a primary sensory area, providing robust evidence for the role of neural plasticity in early brain development.

BRAIN AND COGNITIVE DEVELOPMENT IN THE POSTNATAL PERIOD

Over the past several decades, our understanding of how both cognitive and neural systems develop has made great progress. However, the advances in the two fields have been largely independent of one another. As a result, the role of change in biological systems is poorly specified in cognitive models, and the impact of emerging cognitive systems is underestimated in neurobiological models. Yet, these are interdependent systems. What develops over time is an integrated neurocognitive system that cannot be fully described in the absence of either behavioral or neurological data. This balkanization of scientific disciplines finds its origins in the complexity of the data within each area, and in the technical challenges of designing robust measures that can bridge and ultimately unify these complex data sets. The advances in neuroimaging technologies offer a means of approaching these very difficult and complex issues. The remainder of this section focuses on three cognitive domains for which a substantial body of neuroimaging data is available, and is beginning to be incorporated into more integrated models of neurocognitive development. These domains include studies of visual processing of faces, cognitive control, and language.

Development of the Brain Systems for Visual Processing of Faces

Faces are arguably the most important visual stimuli in our social environment. It is not surprising, therefore, that typically developed adults are expert face processors. Adult face expertise is characterized by the near universal ability to rapidly and accurately discriminate individuals from among thousands of highly similar faces encountered routinely and to extract extensive information about individuals from brief exposures to face stimuli.

Adult Face Processing Expertise

Advances in functional neuroimaging are largely responsible for the significant increase in our understanding of the mature brain architecture for human face processing in typical and atypical populations (Haxby, Hoffman, & Gobbini, 2002; Kanwisher & Yovel, 2006). Based chiefly on neuroimaging studies, two overarching systems have been proposed to capture the complexity of visual face processing. The "core" face system processes the invariant aspects of faces, such as facial features and identity (Haxby, Hoffman, & Gobbini, 2000). This system includes the functionally defined fusiform face area (FFA) in the fusiform gyrus (Kanwisher & Yovel, 2006), the occipital face area (OFA) in the lateral inferior occipital gyrus (Gauthier et al., 2000), and the posterior superior temporal sulcus (pSTS) (Haxby, Hoffman, & Gobbini, 2000). Recent evidence suggests that the fusiform gyrus may include multiple face processing regions occupying the posterior and anterior aspects of the fusiform gyrus (Pinsk et al., 2009). We use the acronym FFA to refer to all regions within the fusiform gyrus that show a functionally defined preference to faces. One critical feature of the mature core system, particularly the FFA and OFA, is that these regions are activated when viewing faces largely regardless of specific task demands. That is, activation is observed whether the task requires active face processing, such as remembering or matching specific faces (Gauthier, Curby, Skudlarski, & Epstein, 2005; Yovel & Kanwisher, 2005), passive viewing (Grill-Spector, Knouf, & Kanwisher, 2004; Haist, Lee, & Stiles, 2010), or implicit presentation when faces and other visual stimuli are presented in a fashion that precludes conscious perception (Morris, Pelphrey, & McCarthy, 2007). Activation of the pSTS is most closely associated with dynamic feature processing, such as monitoring eye gaze and mouth movements, and is thus observed in tasks in which these actions are factors (Ishai, Schmidt, & Boesiger, 2005; Rolls, 2007).

Recruitment of the "extended" face system regions tends to be task specific (Haxby, Hoffman, and Gobbini, 2000). For example, the amygdala, insula, and other limbic regions are recruited when tasks require the analysis of the emotional aspects of a face (Ishai, Pessoa, Bikle, & Ungerleider, 2004). The retrieval of semantic knowledge for faces may engage the inferior frontal gyrus, whereas episodic memory retrieval may recruit the precuneus, posterior cingulate cortex, and medial temporal lobe

(Gobbini & Haxby, 2007). Analysis of intentions can activate the region of the temporal-parietal junction, whereas processing attitudes and mental states recruits the anterior cingulate cortex (Redcay et al., 2010). The anterior temporal pole may be active in tasks requiring individuation of faces and biographical information retrieval (Nestor, Plaut, & Behrmann, 2011). In summary, the differential activation of extended face network brain regions stems from the fact that many face tasks require processing of a wide array of information beyond the general appearance of the face.

Development of Face Processing Expertise

The ability to process faces as distinctive visual stimuli begins in the first year of life. Newborns show a preference for and can discriminate faces from other classes of objects and abstract stimuli (Johnson & Morton, 1991). By 3 months, infants categorize faces by gender, race, and attractiveness (Quinn, Yahr, Kuhn, Slater, & Pascalis, 2002; Slater, Quinn, Hayes, & Brown, 2000), and by 5 to 7 months they begin to rely on both the specific features of faces (featural information) and the arrangement of those features on the face (configural information) for face identification (Cohen & Cashon, 2001). Despite this evidence of early face processing abilities, the preponderance of behavioral evidence clearly suggests that expertise in face processing develops slowly and over many years (see Lee, Quinn, Pascalis, & Slater, 2013). For example, children have difficulty processing featural and configural information relevant to face identification through the school-age period. The pattern of children's featural processing reaches adult levels at about 10 to 11 years, before which they first rely on outer face features for face identification and then gradually shift to rely on inner face features (Want, Pascalis, Coleman, & Blades, 2003). Extraneous features such as clothing and hairstyle easily distract children under 10 to 11 years when identifying individual faces (Mondloch, Le Grand, & Maurer, 2002).

The emerging consensus from neuroimaging studies indicates that mature face processing expertise is the result of a protracted developmental process. Cognitive electrophysiological studies using event-related potentials (ERP) have shown that the N170 waveform, a putative marker for face processing manifest as a negative voltage deflection recorded at posterior scalp electrodes occurring approximately 170 ms after the presentation of a face, emerges early in childhood (de Haan, Johnson, & Halit, 2003b). However, the N170 in children is significantly delayed and is smaller in amplitude than the adult N170. The N170 gradually shifts in time and increases in amplitude throughout development, reaching the adult form in the mid-teens (de Haan, Pascalis, & Johnson, 2002).

The overwhelming majority of developmental fMRI studies have focused exclusively or primarily on the core face network, specifically the FFA. The preponderance of evidence indicates that while the FFA can be observed in 5- to 7-year-old children (Cantlon, Pinel, Dehaene, & Pelphrey, 2011; Pelphrey, Lopez, & Morris, 2009), the FFA shows an extended developmental trajectory extending into mid-adolescence as measured by volume of the fusiform gyrus occupied (Golarai et al., 2007; Haist et al., 2013), the intensity of BOLD activation (Cohen Kadosh, Henson, Cohen Kadosh, Johnson, & Dick, 2010), and the spatial location of the FFA within the fusiform gyrus (Haist et al., 2013). A similarly prolonged developmental trajectory has been described for the other core face network areas of the OFA (Scherf, Behrmann, Humphreys, & Luna, 2007) and superior temporal gyrus/sulcus (Golarai, Liberman, Yoon, & Grill-Spector, 2010).

The prolonged developmental path to reach mature face processing expertise is supported additionally by the analysis of functional connectivity, or the interaction between face preferential brain regions. Cohen Kadosh et al. (2011) evaluated effective connectivity (i.e., directional functional connectivity) within the core face network. They scanned younger (7–8 years) and older (10–12 years) children and adults during face identity, emotion, and gaze detection tasks and found that all groups produced the same basic network pattern of the inferior occipital gyrus (i.e., occipital face area) that influenced activation in the fusiform gyrus (i.e., fusiform face area) and the superior temporal sulcus (STS). This suggested that an integrated core face network is observed in children as young as 7 years. However, the magnitude of effects among the child groups differed from adults. The old and young child groups exhibited weaker connectivity between inferior occipital gyrus (IOG) and fusiform gyrus (FG), and no significant connectivity between IOG and STS. Furthermore, the effects of task demand differentiated the adults and children. Different tasks selectively modulated network patterns in adults; specifically, the identity task increased IOG influence on FG, whereas the expression task increased IOG influence on STS. Children did not show such selective task effects. Thus, although the rudimentary structure of face-processing networks is observable in young school-age children, the interaction of the regions and their response to task effects is not mature.

The status of the developmental trajectories in the extended face network is currently very limited. Recently, Haist et al. (2013) reported findings from a developmental study of whole brain activity that used regression analysis across a continuous sample of age spanning 7-year-olds to adults. They found wide ranging hyperactivation of multiple regions of the extended face network in children that included the anterior temporal pole, amygdala, insula, inferior frontal gyrus, and lateral parietal cortex (see Figure 2.8). Moreover, these regions showed a reliable negative linear trend across age, indicating that younger participants produced the greatest activation in these regions and adults did not activate the extended network. They interpreted their findings as suggesting that development of face processing expertise is characterized by increasing modulation of the extended network so that regions are engaged in a task-appropriate fashion with increased expertise.

In summary, behavioral and functional neuroimaging data are in very good agreement that face processing abilities begin early in development and have an extended developmental trajectory. Mature levels of face expertise are not found until mid-adolescence. These effects cut across both the core and extended face networks.

Development of Brain Systems for Cognitive Control

Perhaps no other domain of functioning exhibits more dramatic and protracted development throughout childhood than do the processes that allow children to regulate and control their perceptual processes, thoughts, and actions in the context of goal-directed behavior. This review will focus on developmental research examining the neural bases of three forms of such control: working memory, spatial attention, and inhibitory functions. In each case, we describe relevant models of the neural circuitry of these functions drawn from animal and adult human studies, followed by the neurobehavioral observations obtained in studies of children.

Working Memory

Working memory has been conceptualized as a mental system used to transiently hold information in mind in order to attend to it, manipulate it, or act on it in relation to psychological and behavioral goals. Working memory is distinguished from so-called short-term memory by its active, goal-oriented, top-down nature, as opposed to a more passive, bottom-up trace maintenance. In a widely cited and elaborated theoretical model of working memory, Baddeley (1974) proposed a hierarchical, multicomponent system made up of a central executive that controls several slave systems, which include a phonological loop, a visuospatial scratchpad, and an episodic memory buffer (for review, see Baddeley, 2012). Across all models of working memory, there is agreement that it is a limited capacity system closely related to executive control, critical to a wide range of complex cognitive functions, and that ties together perception, attention, and memory (Cowan et al., 2005; Just & Carpenter, 1992; Postle, 2006; Roberts & Pennington, 1996).

Working memory relies on a distributed network of brain regions heavily involving lateral prefrontal and posterior parietal areas. Although task paradigms used in neuroimaging studies vary considerably, all require that the subject hold information in mind for a brief period, either to make a decision or response, to manipulate it, or to perform active transformations on it. For example, a simple spatial working memory task might require remembering a briefly cued location during a delay in order to retrieve a reward from that location after the delay. Often experimenters vary the duration of time the information is held "online," the type or number of bits of information, or the type or difficulty of manipulations that must be performed. Jacobsen (1936) first showed that lesions to the lateral prefrontal cortex impair working memory performance in monkeys. Fuster (1973) found that firing in individual prefrontal neurons during the delay period of a working memory task predicted the successful memory-based retrieval of food. Research with nonhuman primates has shown that similar delay-active neurons also exist in the posterior parietal cortex and in several subcortical structures including the thalamus and parts of the basal ganglia (i.e., globus pallidus, head of the caudate; Goldman-Rakic, 1995). This work also revealed the central role in working memory of recurrent excitatory glutamate pathways involving pyramidal cells within this network of brain regions.

Human adult functional neuroimaging studies of working memory show consistent involvement of lateral prefrontal and posterior parietal cortical regions, premotor and anterior cingulate cortex, the cerebellum, and the basal ganglia. Several PET and fMRI studies suggest a division of labor between ventrolateral and dorsolateral prefrontal cortex, with dorsolateral regions becoming increasingly involved when monitoring or manipulation of information is required, usually bilaterally, and ventrolateral regions supporting information maintenance (D'Esposito, Postle,

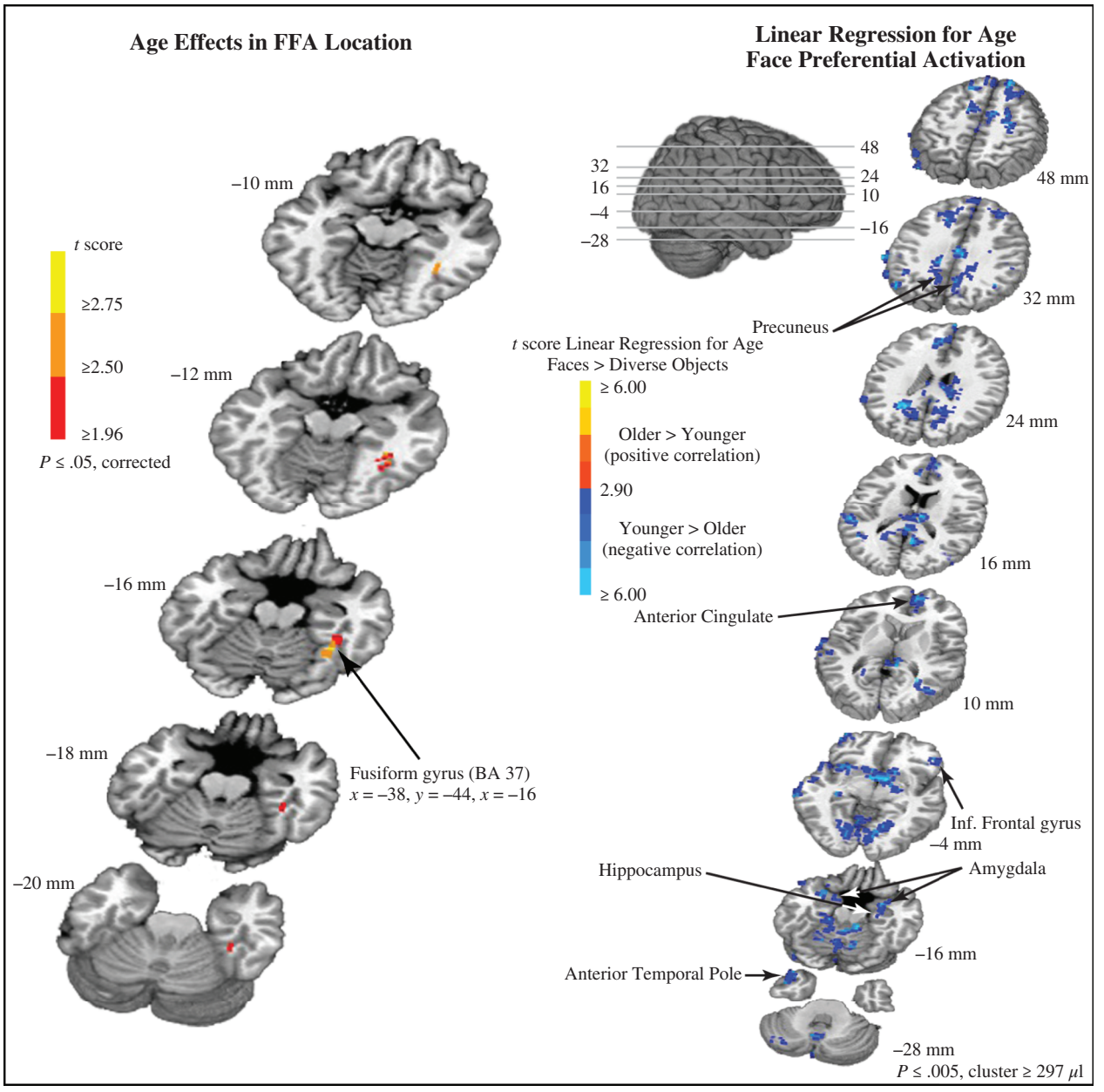


Figure 2.8 Example of fMRI findings for the development of face-processing expertise. These findings are drawn from a study of face processing that used a simple face and object viewing paradigm in a continuous age-sample of typical development from 6 years to adults ($N = 71$). The left panel shows the results from the first reported statistical analysis (logistic regression) of the developmental change in location of the fusiform face area (FFA). The region in the right middle fusiform gyrus (BA 37) produced a positive relationship with age (warm colors) indicating that this most commonly activated face preferential area across adult studies of face processing has a protracted developmental trajectory. That is, this region increasingly becomes specialized for face processing through development that extends into middle adolescence. The right panel shows the analysis of whole brain (voxelwise) activation using linear regression analysis for age. Cool blue colors indicate regions that showed a negative relationship with age, meaning that younger participants (i.e., children) activated these regions more than older participants (i.e., adults). Many of the regions indicated are part of the extended face processing network that adults typically use in a task-specific fashion. The passive nature of this task suggests that the "hyperactivation" of extended face network regions in younger participants results from immaturity in modulating brain activity for task specific purposes. See footnote 1.

Source: From "The Functional Architecture for Face-Processing Expertise: FMRI Evidence of the Developmental Trajectory of the Core and the Extended Face Systems," by F. Haist, M. Adamo, J. Han, K. Lee, and J. Stiles, 2013, *Neuropsychologia*, *51*, 2893–2908. doi:10.1016/j.brainres.2013.01.001. Reprinted with permission.

& Rypma, 2000; Jonides et al., 1998; Passingham & Sakai, 2004; Wager & Smith, 2003).

A common task used in working memory studies is the so-called "n-back" task. In the n-back task, participants are presented a sequence of individual symbols (e.g., numbers, letters) or spatial locations, and the subject must recall the identity or location of the item that was presented several items previously (e.g., 1-back, 3-back). This allows a parametric manipulation of processing load, providing sensitive within-subjects comparisons and task adaptation for different levels of functioning. In a meta-analysis of fMRI studies using the n-back task, Owen, McMillan, Laird, and Bullmore,(2005) found consistency across 24 studies in the involvement of dorsolateral and ventrolateral prefrontal, posterior parietal, anterior cingulate, premotor, and cerebellar regions. Comparing n-back tasks requiring subject attention to the location of objects versus their identity, they found that premotor activation was reported significantly more often during spatial working memory tasks (Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Haxby, Petit, Ungerleider, & Courtney, 2000; Postle, Stern, Rosen, & Corkin, 2000). For spatial working memory tasks, the activation foci in prefrontal regions have been observed in both right and left DLPFC, and whether spatial working memory is lateralized remains an issue of debate (Leung, Oh, Ferri, & Yi, 2007; Lycke, Specht, Ersland, & Hugdahl, 2008; Owen et al., 2005; Srimal & Curtis, 2008).

Working Memory in Infancy. In infancy, scientists have used simple hiding tasks to evaluate the development of working memory (Diamond, 1990; Jacobsen, 1935). EEG studies comparing baseline EEG levels to working memory task-related levels report generalized increases in EEG power and coherence during the first year of life as well as age-related changes in both indices between 5 and 10 months of age (Bell, 2012; Bell & Wolfe, 2007; Cuevas & Bell, 2011). Longitudinal investigation of the infants in Cuevas and Bell's study showed a shift in the location of EEG changes between 8 months and 4.5 years. Specifically, while 8-month-old infants showed task-related increases in both power and coherence for all electrode sites (16 right and 16 left sites), by 4.5 years these same children showed task-related changes in EEG power in the medial frontal region only, and task-related changes in coherence for medial frontal-posterior temporal, and medial frontal-medial occipital electrode pairs only. Thus, EEG measures suggest generalized task related increases in brain activity during the first year of life that localizes to fronto-parietal and fronto-occipital brain regions by the preschool period.

Later Working Memory Development. In typical development, working memory performance improves throughout childhood, showing changes in speed of processing, maintenance duration, capacity, and robustness to interference. From the ages of about 6 to 10, children show linear increases in performance on visual and auditory n-back tasks (Vuontela et al., 2003). In this study, working memory performance for visual stimuli was higher than for auditory tasks across age, and girls consistently outperformed boys. Comparing several verbal and spatial working memory and other putative "frontal lobe" tasks, Conklin, Luciana, Hooper, and Yarger likewise found consistent, monotonic performance increases across adolescence for tasks believed heavily dependent on prefrontal cortical areas (Conklin et al., 2007).

Developmental fMRI studies have found qualitatively similar patterns of brain activity in school-age children and college-age adults during performance of the same working memory tasks, with some regional location and activity amplitude differences (Casey et al., 1995; Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Klingberg, Forssberg, & Westerberg, 2002; Kwon, Reiss, & Menon, 2002). For example, during a spatial n-back task performed by children aged 8 to 10 years and young adults, both groups activated similar right dorsolateral prefrontal and parietal regions, but children additionally engaged left precuneus and bilateral inferior parietal lobule (Thomas et al., 1999). In several developmental fMRI studies, Klingberg and colleagues showed that the superior frontal sulcus and intraparietal cortex in particular are involved in visuospatial working memory in both school-age children and young adults (for review, see Klingberg, 2006). These studies have also demonstrated that the peak amplitudes of brain activity in the fronto-parietal network increase across these ages independent of performance, and that greater activity in these locations is related to higher working memory capacity (Klingberg et al., 2002). Structural brain development also relates to improving working memory skills from childhood into adolescence. For example, diffusivity parameters within white matter tracts (linked to biological maturation), particularly within fronto-parietal connections, show significant correlations with task performance (Bava & Tapert, 2010; Nagy, Westerberg, & Klingberg, 2004; Olesen, Nagy, Westerberg, & Klingberg, 2003; Vestergaard et al., 2011). In 7- to 13-year-old children, better spatial working memory performance was

specifically associated with increased fractional anisotropy in the superior longitudinal fasciculus, a tract connecting temporoparietal to prefrontal cortices (Vestergaard et al., 2011). Diffusion parameters in the left hemisphere tract exhibited stronger associations with spatial working memory than did the right hemisphere tract, and the associations were independent of age effects, or effects attributable to global white matter differences. Thus, the associations may have reflected individual differences in the pace of maturation in spatial working memory networks.

Spatial Attention

There exists a large scientific literature on the neural systems involved in spatial attention in adults, and research specifically on the endogenous (top-down) control of spatial attention has provided great insight into certain aspects of cognitive control. Most research has focused on aspects of visual attention rather than attention in other sensory modalities (e.g., auditory, tactile). Seminal behavioral studies conducted by Posner et al. (for reviews, see 2012; 1982; 1998; Raz & Buhle, 2006), using a simple but powerful spatial cuing paradigm, showed that directing a person's attention to a specific location in space facilitates subsequent processing of information at that location, resulting in faster response times. Related studies with stroke patients demonstrated a strong association between the functioning of parietal cortex and spatial attention operations, particularly the ability to actively disengage attention from an attended location (Posner, Walker, Friedrich, & Rafal, 1984). ERP studies subsequently helped to explain the temporal dynamics and neurophysiological bases for Posner's findings, demonstrating that the brain's sensory response to information at a particular spatial location is enhanced when attention is shifted to that location (Hillyard & Anllo-Vento, 1998; Mangun & Hillyard, 1991).

Landmark PET and fMRI studies have identified the principal neural systems involved in spatial attention in adults, which include right and bilateral posterior parietal cortex (especially intraparietal sulcus), the temporal-parietal junction, bilateral frontal eye fields within premotor cortex, anterior cingulate, and subcortical circuits (Corbetta, Miezin, Shulman, & Petersen, 1993; Coull & Frith, 1998; Nobre, Sebestyen, Gitelman, & Mesulam, 1997). Rapid event-related fMRI studies have identified several networks that contribute to different aspects of spatial attentional control. These include an anterior network involving the anterior cingulate, related to conflict resolution in attention; a dorsal fronto-parietal system involved in the allocation and maintenance of attention to a particular location; and a more ventrally lying, primarily right hemisphere, fronto-parietal network specific for disengaging attention (Corbetta, Kincade, & Shulman, 2002; Jack, Shulman, Snyder, McAvoy, & Corbetta, 2006; Thiel, Zilles, & Fink, 2004). The neural substrates for visual and auditory spatial attention may involve the same key networks, as several studies have found evidence that these systems are supramodal, maintaining representations of space that are independent of sensory modality and motor response (Downar, Crawley, Mikulis, & Davis, 2000; Driver & Spence, 1998; Farah, Wong, Monheit, & Morrow, 1989; Macaluso, Eimer, Frith, & Driver, 2003; Shomstein & Yantis, 2004).

A growing number of studies have investigated spatial attention and its functional neuroanatomy in infants and children. Infants 3 to 4 months old can shift visual-spatial attention (for review, see Johnson, 2001), and the speed and efficiency of attention functions increase significantly throughout childhood and adolescence (Enns & Brodeur, 1989; Ridderinkhof & van der Stelt, 2000; Schul, Townsend, & Stiles, 2003). The "zoom lens hypothesis" of attention posits that the field of attended space expands and contracts as a function of task demands, and that processing efficiency increases as the size of this field declines (Eriksen & St. James, 1986). Several researchers have suggested that the ability to control the contraction and expansion of the spatial attention field improves from the preschool into school-age years (Enns & Girgus, 1985; Pastò & Burack, 1997). As with working memory and other tasks requiring cognitive control, age-related differences and changes in cerebral functional organization have been shown for spatial attention processing (Johnson, 2001, 2003). Johnson suggests that the cortical mechanisms for spatial attentional control are different in infancy than they are in adulthood, relying relatively more on frontal cortex in their early form, and shifting to more posterior (i.e., parietal) control, and he posits that this might reflect a general learning mechanism by which frontal activity decreases as proficiency increases. An fMRI study compared school-age children and young adults during the reorienting of spatial attention and found very different patterns of activation despite similar levels of accuracy on the task. Although adults showed significant involvement of right inferior frontal gyrus, right temporal-parietal junction, and bilateral parietal lobes, children aged 8 to 12 years showed greatest activity in left superior frontal gyrus, right occipital-temporal gyrus, and left occipital gyrus (Konrad et al., 2005). Townsend, Haist, Adamo, and

Stiles also found developmental functional organization differences between school-age children and young adults for spatial attention processing (Townsend et al., 2003). During shifts of attention not accompanied by eye movements, adults showed bilateral intraparietal sulcus activity that was greater on the right, including activation in inferior temporal cortex. Children, in contrast, showed greatest activity in prefrontal and inferior temporal cortex, with weaker activation of parietal cortex, providing additional support for Johnson's front-to-back learning hypothesis.

One recent study examined associations between diffusion parameters and speed of responding in a simple spatial attention task in children between 7 and 13 years. Madsen et al. (2011) used a simple spatial choice reaction time task to measure response latencies to stimuli that appeared at one of five locations. Reaction time to the spatial stimuli decreased dramatically across this age range. Independent of age, however, faster five-choice reaction times were associated with lower diffusivity in the corticospinal tracts, putamen, and caudate. Although these effects were bilateral in the corticospinal tracts and putamen, right (relative to left) caudate diffusivity showed the stronger relationship to task performance. The results suggest a link between visuomotor performance variability in children and diffusivity in motor and attention systems perhaps related to individual differences in the phase of fiber tract and neostriatal maturation in children of similar age.

Response Inhibition

Models of Motor Response Inhibition. An important aspect of behavior regulation involves the ability to suppress execution of a planned action in response to a relevant cue from the environment. In recent years, motor response inhibition has been studied extensively in adults and clinical populations, using Go/No-Go, antisaccade, and stop-signal tasks (Chambers, Garavan, & Bellgrove, 2009). All of these tasks involve the suppression of a primed, or prepotent, motor response. The stop-signal task has been especially useful for examining individual differences in inhibitory functions because it is designed to provide a continuous measure estimating the amount of time a participant needs to suppress the response (Logan, Cowan, & Davis, 1984). Studies using this task in adults have implicated several brain structures in a neural network subserving response inhibition. Execution of volitional motor responses is linked to activity in a premotor-striatal-pallidal-motor cortical network (Chambers et al., 2009). A primarily right-lateralized network, involving the inferior frontal gyrus, presupplementary motor area, and subthalamic nucleus has been implicated in response inhibition (Aron et al., 2007; Aron & Poldrack, 2006); and fMRI studies have shown that inhibiting a prepotent response activates this network in adults (Aron et al., 2007; Aron & Poldrack, 2006; Aron, Robbins, & Poldrack, 2004; Chevrier, Noseworthy, & Schachar, 2007; Rubia, Smith, Brammer, & Taylor, 2003) as well as in children (Cohen et al., 2010).

Studies of Inhibitory Functions in Children. Studies in children reveal dramatic improvement in performance on motor inhibition tasks throughout childhood and adolescence (Liston et al., 2006; Luna, Garver, Urban, Lazar, & Sweeney, 2004; Madsen et al., 2010; Williams, Ponesse, Schachar, Logan, & Tannock, 1999). Individual differences in children's inhibitory function correlate with diffusion imaging indices of maturation within the neural circuitry outlined above. Liston et al. (2006) reported an association between faster reaction times in demanding conditions of a Go/No-Go task and higher FA in fronto-striatal white matter tracts of children and young adults. Madsen et al. (2010) employed the stop-signal task in a study of 7- to 12-year-old children and reported that better response inhibition was associated with higher FA and lower diffusivity in white matter of both inferior frontal and presupplementary motor regions of the right hemisphere (see Figure 2.9). Moreover, both of these effects remained significant after controlling for age and global white matter diffusivity parameters. Interestingly, the measures from the two regions contributed additively to the prediction of performance variability. Many questions complicate the interpretation of these kinds of associations. They could reflect links between individual differences in behavior and individual differences in the pace of fiber tract maturation. Alternatively, other effects on the neural architecture, unrelated to the pace of brain development, could map onto performance differences, such as experience-driven biological effects on the fiber tracts or genetically mediated differences in patterns of connectivity.

In contrast to the evidence from studies cited earlier, showing that motor response inhibition approaches adult proficiency during adolescence, there is considerable evidence for elevated risk-taking behavior during this age range. Epidemiological evidence confirms that high-risk behaviors such as unsafe driving, drug use, and sexual behavior are more prevalent during adolescence than at other times in the lifespan (Somerville & Casey, 2010; Steinberg, 2008). Such behavior would appear to suggest poor inhibitory function, since there is evidence that

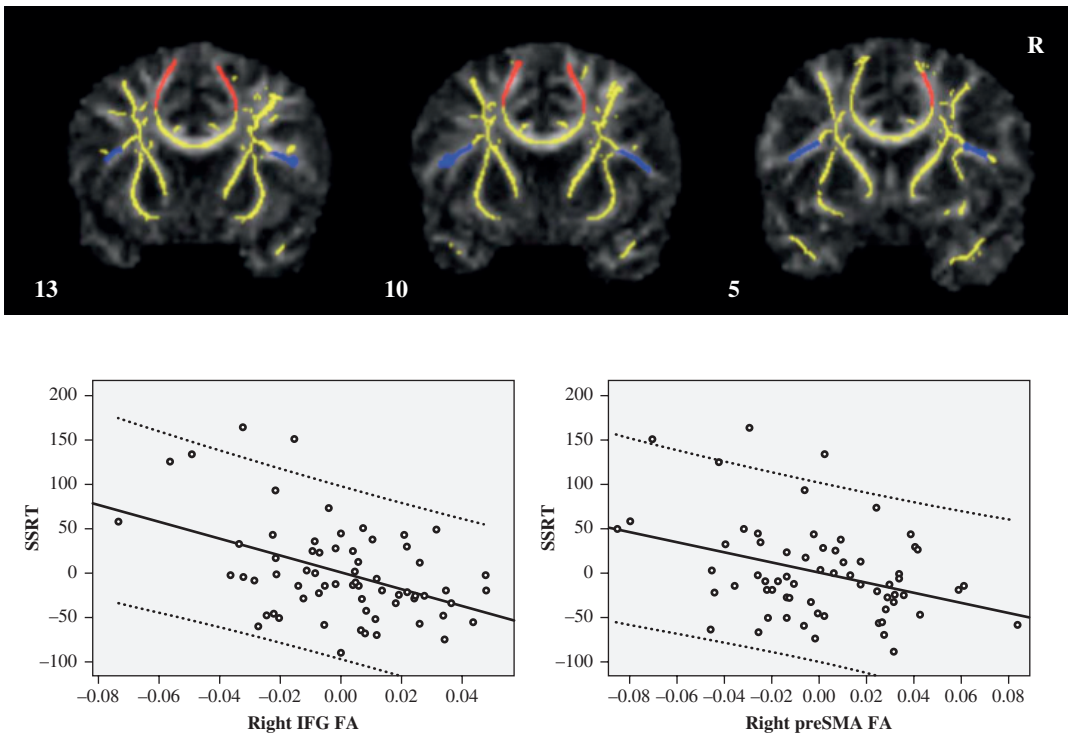


Figure 2.9 Fractional anisotropy in a region of interest (ROI) in the right inferior frontal gyrus (blue in right hemisphere) and in a right pre-SMA ROI (red) contributed additively in a regression model explaining individual differences in stop-signal performance in children (independent of age and other covariates). See footnote 1.

Source: From "Response Inhibition Is Associated with White Matter Microstructure in Children" by K. S. Madsen et al., 2010, *Neuropsychologia*, *48*(4), pp. 854–862. Reprinted with permission.

adolescents are well aware of the risks and capable of strong reasoning about such risks (Steinberg, 2008). However, as confirmed by Shenoy and Yu (2011) in their computational work with the stop-signal task, inhibitory behavior is influenced by reward sensitivity as well as by cognitive and perceptual processes. Indeed, studies employing experimental risk-taking tasks, while confirming that adolescents are less risk-averse than both younger children and adults, suggest that this effect may be more strongly related to reward sensitivity than to risk evaluation. Cauffman et al. (2010), using the Iowa Gambling Task, showed that adolescents exhibited a stronger "approach" response to positive feedback on the task than either younger children or adults, whereas "avoidance" engendered by negative feedback increased more linearly with age. Thus, the form of disinhibition manifest in adolescent behavior may arise because of selectively heightened sensitivity to the positive rewards associated with risk.

Several studies have investigated the neural bases of such age-specific behaviors of adolescence. Somerville and Casey (2010) reviewed results of work conducted by Casey and associates and proposed a model accounting for adolescent risk-taking as emerging from altered processing of appetitive and aversive cues. These alterations are further attributed to interactions between developing striato-limbic and prefrontal cortical brain systems. Specifically, using fMRI and a task requiring participants to process emotional faces, Hare et al. (2008) showed greater emotion-related amygdala activation in adolescents than in either younger children or adults. Similar findings of increased amygdala activation to negative cues in adolescents were reported by Ernst et al. (2005). Other studies have assessed the degree of ventral striatal response to appetitive cues in adolescents. Studies in adults have consistently shown activation in ventral striatum associated with anticipation of reward (Knutson, Momenan, Rawlings, Fong, & Hommer, 2001; O'Doherty, Deichmann, Critchley, & Dolan, 2002). Imaging studies in adolescents suggest heightened sensitivity to reward and more vigorous or prolonged reward-related activation of ventral striatum, relative to adults or children (Ernst et al., 2005; Galvan et al., 2006; May et al., 2004).

Functional imaging studies of emotion regulation suggest that successful regulation is associated with stronger prefrontal activation, and stronger functional connectivity between limbic and prefrontal regions (Pezawas et al., 2005; Phillips, Drevets, Rauch, & Lane, 2003). Somerville

and Casey (2010) note that, in contrast to the developmental effects observed in studies of reward sensitivity that suggest adolescents exhibit distinct differences from younger children in reward responses of ventral striatum, developmental change in both structure and function of prefrontal cortical regions appears to be more gradual and linear. Integrating these observations, the hypothesis that these authors advance is that the unique quality of inhibitory, or risk-taking, behavior in adolescents arises because of dynamic interactions between an accelerated course of development in brain systems subserving reward and punishment and a more gradual course of development in late-developing cortical functions involved in emotion and behavior regulation. The outwardly focused, and reward-seeking adolescent phenotype, which may have evolutionary advantages, gives way to a more cautious adult phenotype with a more measured approach to risk, presumably through the growing influence of learned associations better formed and retrieved with a more mature prefrontal cortex.

Development of the Brain Systems for Language

Language is a complex, multifaceted ability mastered over many years. Left-lateralized frontotemporal networks primarily mediate the major components of language for most adults. The majority of brain imaging studies of children have tried to determine whether these same core brain networks support language in children and whether there is systematic change in the patterns of activation with age.

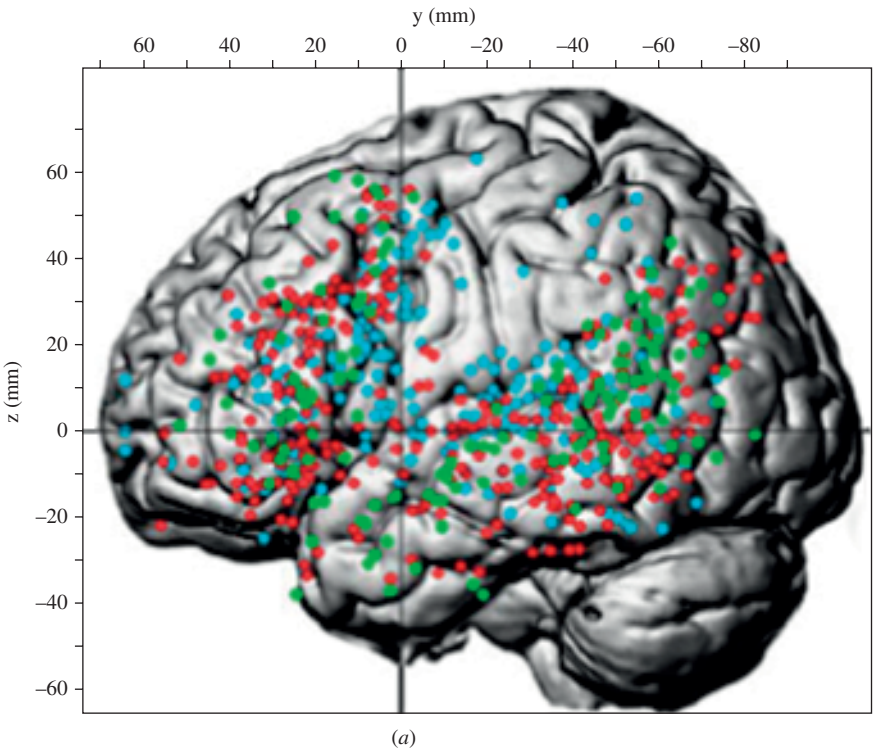
The Neural Architecture of Language Processing in Adults

Individual studies of language typically focus on a single aspect of linguistic processing, ranging from decoding the acoustic/phonological signal, to semantic processing of words or phrases, to syntax and sentence or text level processing. A full account of the brain networks that support the different aspects of language processing is beyond the scope of this section (for comprehensive reviews, see Price, 2012; Vigneau et al., 2006). However, a meta-analysis by Vigneau et al. (2006) provides a means of summarizing the major findings. They created a brain map illustrating the distribution of activation for three categories of language tasks: phonological (blue), semantic (red), and syntactic/sentence processing (green) based on 729 data points defined from peak activations taken from 129 published imaging papers (see Figure 2.10a). It is clear that while the activation points for the different kinds of tasks are overlapping, they tend to segregate into spatially distinct fields. Imaging studies also help define the neural pathways that connect the task-specific brain regions to form processing networks. Figure 2.10b provides a consensus view of the major language pathways. The arcuate fasciculus (AF) is among the important association pathways subserving language functioning, though its relationship to another major language pathway, segment III of the superior longitudinal fasciculus (SLFIII), remains unclear (Dick & Tremblay, 2012). Other language pathways include the uncinate fasciculus (UF), the extreme capsule fiber system (ECFS), the inferior longitudinal fasciculus (ILF), and the inferior frontal occipital fasciculus (IFOF). We discuss the functional significance of these pathways below.

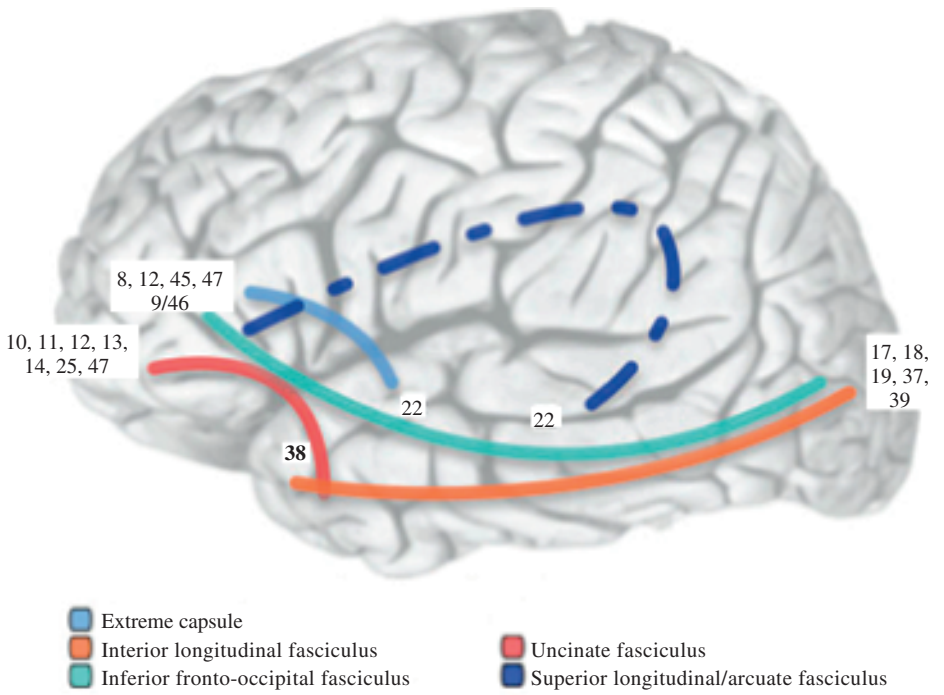
Phonological processing of speech sounds (blue) is concentrated along the superior temporal sulcus (STS, Brodmann's area [BA] 22) near Heschl's gyrus (BA 41, primary auditory cortex; DaCosta, 2011) and the planum temporale, both areas previously shown to be involved in phonological decoding (Friederici, 2011; Price, 2012). Further, the posterior STS (BA 22 posterior) has been shown to connect via the AF to premotor cortex, supporting auditory-motor ("sound to articulation") integration (Friederici, 2011).

Activation during semantic processing (red) involves frontal, temporal, and parietal regions. The inferior frontal gyrus (IFG) has long been associated with semantic processing. Different components of the IFG play somewhat different roles. Specifically, the pars opercularis (BA 44, see Figure 2.10b) has been associated with lexical decision (Heim et al., 2009), the pars orbitalis (BA 47) with semantic retrieval (Demb et al., 1995), the ventral region of the pars triangularis (BA 45) is associated with semantic processing, and the dorsal region supports phonological working memory (Hautzel et al., 2002). The angular gyrus (AG, BA 39) of the parietal lobe, regions of the anterior fusiform (BA 37 anterior), and anterior temporal pole (BA 38) within the temporal lobe are all involved in semantic processing (Vigneau et al., 2011). The network is connected by the ILF that links the posterior STS and angular gyrus to the temporal pole; the temporal pole is connected to the IFG via the UF (Catani, Howard, Pajevic, & Jones, 2002), thus creating a fronto-temporal-parietal network for constructing meaning. In addition, Friederici (2011) has proposed a second frontotemporal semantic pathway extending from the STG (BA 22 anterior) to the pars triangularis (BA 45) via the ECFS pathway. This subnetwork functions to transfer sound to meaning.

The neural systems for syntactic or sentence processing (green) show great overlap with other processing systems,



(*a*)



(*b*)

Figure 2.10 Overview of the neural networks for language in adults. (a) Summary of task specific patterns of activation during language processing. Each activation peak is color-coded according to its contrast category: phonology (blue), semantic (red), and syntax (green). (b) Summary of the major perisylvian pathways for language processing. The connectivity profile of the SLF/AF remains a focus of debate, and is thus represented as a single pathway (dashed line). Numbers indicate Brodmann areas. See footnote 1.

Source: (a) From "Meta-Analyzing Left Hemisphere Language Areas: Phonology, Semantics, and Sentence Processing," by M. Vigneau et al., 2006, *Neuroimage*, *30*(4), pp. 1414–1432. Reprinted with permission. (b) From "Beyond the Arcuate Fasciculus: Consensus and Controversy in the Connectional Anatomy of Language," by A. S. Dick and P. Tremblay, 2012, *Brain*, *135*(Pt 12), pp. 3529–3350. Adapted with permission.

in part due to the difficulty in separating sentence structure from meaning. Activations are observed widely within the frontoparietal networks, but few distinct networks have yet to be definitively identified. One possible candidate is a pathway between pars opercularis (BA 44) and posterior STS (BA 22) via the AF (Friederici, 2011). This pathway appears to support processing of nonadjacent elements in complex sentences, thus reflecting syntactic processing demands.

Most imaging studies examining the brain networks for language processing report stronger activity amplitudes within the LH than in the RH. Historically, two roles have been noted for the RH in language tasks, specifically prosody (Beaucousin et al., 2007) and the construction of meaning (Bookheimer, 2002; Lindell, 2006). In a recent metareview, Vigneau (2011) reanalyzed the data from his 2006 paper on LH activation, to look for explicit evidence of the RH engagement in the kinds of phonological, semantic, and syntactic processing tasks examined in the earlier review. He defined bilateral activation as activation of homologous regions of the two hemispheres, and unilateral activation as activity in only one hemisphere. Overall, RH activation in the language studies was low. Further, to the extent that there was RH activation, brainwide activity tended to be bilateral, unlike the pattern of predominantly unilateral activation in the LH. It is worth noting that defining brain activity as either activated or not according to an arbitrary threshold creates what might be a misleading dichotomy. To be clear, studies of language processing tasks frequently find significant engagement of right hemisphere regions as well, compared to baseline. However, the activity amplitudes within the left hemisphere are often relatively greater and so may be the only regions visible on thresholded activation maps.

Early Language Acquisition: Milestones and Brain Changes

Sublexical Level. The first steps toward the acquisition of language require the decoding of basic acoustic and phonological information during infancy (for reviews see Friederici, 2006; Kuhl, 2010). Among the many skills infants must master to build a foundation for receptive language are the abilities to differentiate speech from nonspeech sounds, to use the contours of speech intonations to parse structural units, and to identify and discriminate among the phonemes of their native tongue. Functional neuroimaging studies of brain responses during passive listening to speech sounds in young infants have found generally greater activity in the left hemisphere than in the right. Comparing forward speech to speech played backwards, sleeping newborns showed larger increases in oxygenated hemoglobin over left temporal brain regions than in right, as measured by optical imaging of cortical blood flow (Peña et al., 2003). At 3 months old, brain activity amplitudes measured with fMRI for forward speech were also greater in the left hemisphere and involved primary auditory cortex within Heschl's gyrus, the superior temporal sulcus, and extended to association areas in the left temporal pole (Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002). Interestingly, this study also found an active region within right prefrontal cortex, but only for infants who were awake, which the authors interpreted as related to attention.

The intonational contours of speech are also important cues for the infant, allowing the segmentation of auditory input into the structural units of language. During natural speech, breaks in prosody signal phrase boundaries, providing critical information about the syntax of the language that is to be learned. Using fMRI, investigation of the brain bases of prosodic processing in young infants revealed a similar functional neuroanatomy for normal and prosodically flattened speech, which included activity in bilateral temporo-parietal and frontal cortical regions for both conditions (Homae, Watanabe, Nakano, Asakawa, & Taga, 2006). However, a direct voxel-wise statistical comparison of brain activity during normal versus flattened speech showed significantly greater involvement of right temporo-parietal regions for normal speech, suggesting that the rightward hemispheric asymmetry for processing the pitch envelope that has been documented in adults is already evident at 3 months of age. ERP studies of infant prosodic processing demonstrate a qualitatively similar topographical brain organization between 8-month-old infants and adults, but reveal that the timing aspects of these cognitive operations undergo significant changes with development, showing delayed activity peaks in babies (Pannekamp, Weber, & Friederici, 2006).

Another class of acoustic information that must be parsed by the developing infant is the collection of phonemes for a given language. Each language uses a unique set of about 40 distinct sound elements that are combined to make whole words (Ladefoged & Maddieson, 1996). In order to begin acquiring words and their associated meanings within a given language, the infant must first make progress identifying and distinguishing among these foundational phonemic categories. During the first half of the first year of life, infants show a universal perceptual ability to distinguish all of the phonemes of all

languages. Between the ages of about 6 to 12 months, their ability to distinguish nonnative phonetic units declines. At the same time, perceptual abilities for native speech increase, demonstrating a learning mechanism that is tuned by the language experience of the individual (Best & McRoberts, 2003).

ERP studies of this transition from universal to native-specific phonemic abilities during infancy have commonly used the mismatch negativity (MMN) as a neural correlate of auditory discrimination skills. The principal generators of the MEG analog of the MMN in adults have been localized to bilateral primary auditory cortex (Alho et al., 1998). In ERP studies of adults, the mismatch response is always expressed as a negative-going deflection, but infants have been found to display either a negativity or a positivity, with somewhat varying scalp distributions and peak latencies (Cheour et al., 1998; Friederici, Friedrich, & Weber, 2002). In accordance with behavioral studies, brain indices of language-specific phonemic discrimination place the shift in these abilities between the ages of about 6 and 12 months (Cheour et al., 1998; Rivera-Gaxiola, Silva-Pereyra, & Kuhl, 2005). While infants younger than 6 months old show brain electrophysiological measures that discriminate among phonemic contrasts for both native and nonnative languages, older infants display discrimination brain response components only within their native language (Kuhl, 2004).

Early perceptual language abilities are intimately tied to the development of expressive language skills. Learning to produce the sounds characteristic of an individual's "mother tongue" is particularly challenging and requires a protracted period of accumulating expertise, typically not fully mastered until well into the school-age years (Ferguson, Menn, & Stoel-Gammon, 1992). As with receptive language, there is hierarchical regularity to the development of language production. Vocal imitation can be elicited from babies by about 20 weeks of age (Kuhl & Meltzoff, 1982), and by about 10 months of age infants raised in different countries can be distinguished from one another by their babbling sounds (de Boysson-Bardies, 1993). Kuhl and Meltzoff suggest that the close ties between infant language perception and production are linked by shared sensory and motor mechanisms within the brain. Sensory experience with a particular language lays down auditory traces stored in memory that are unique to that language, and these representations guide an infant's verbal motor attempts until a match is produced (Kuhl & Meltzoff, 1996). The ability to produce vocal imitations has also been suggested to depend on a specific brain system for social interaction, which, guided by joint attention, facilitates "mirroring" behaviors of various types and involves a complex network of brain regions bringing together visual, auditory, attention, and motor information (Hari & Kujala, 2009; Rizzolatti & Craighero, 2004).

Lexical and Semantic Level. Functional neuroimaging and recording studies of infants processing single words have shown, relative to adults, that young brain responses show generally longer latencies (i.e., slower timing to activity peaks after stimulus presentation) and often higher activity amplitudes, but age comparisons of the functional topography have varied widely by task paradigm, imaging modality, and analysis methods. ERP studies have demonstrated differential brain responses between known and unknown words in 11-month-olds (Thierry, Vihman, & Roberts, 2003) and 14- to 20-month-olds (Mills et al., 2004). Both of these studies found a negative component occurring between 200 and 400 ms after presentation of a word that was larger in amplitude for familiar than for unfamiliar words.

The N400 component has been used extensively in ERP research as an index of lexical semantic processing. Its amplitude and latency are modulated by several linguistic (and nonlinguistic) factors, such as word concreteness, frequency, class, repetition, and contextual integration difficulty (Kuhl & Meltzoff, 1996). N400 task paradigms typically involve presenting words auditorily within some context (e.g., at the end of a sentence or simultaneously with a picture), which allows for semantic congruity manipulation. In adults, the amplitude and latency of the N400 component are increased in relation to the degree to which the meaning of the word does not fit the context in which it is encountered. For example, a greater N400 modulation would result from the presentation of the word "mouse" simultaneously with an image of a car than with an image of a mouse. The primary neural generators of the N400 response in adults, measured with MEG, localize to bilateral anterior temporal cortex and left inferior frontal cortex (Halgren et al., 2002; Maess, Herrmann, Hahne, Nakamura, & Friederici, 2006). Similar task paradigms using fMRI have found significant activity within bilateral middle and superior temporal gyrus with greater activity in the left hemisphere, bilateral inferior frontal gyrus, as well as bilateral basal ganglia (Friederici, Ruschemeyer, Hahne, & Fiebach, 2003; Kotz, Cappa, von Cramon, & Friederici, 2002; Kuperberg et al., 2000; Mummery, Shallice, & Price, 1999). Overall, activity within frontal cortex appears to be heavily dependent on task demands, whereas temporal

cortical involvement seems tied directly to lexical semantic processes.

ERP studies of 1-year-olds demonstrate enhanced negativity over lateral, anterior electrodes from about 100 to 500 ms after word onset modulated by congruous versus incongruous pictures, suggesting an early form of the N400 (Friedrich & Friederici, 2004, 2005). The presence of this early N400 brain response at 19 months of age was shown longitudinally to discriminate children with age-adequate expressive language abilities from children with poor language skills at 30 months old (Friedrich & Friederici, 2006). Within ERP studies, the functional brain organization of lexical semantic processing appears to change from relatively bilateral at around 12 months old to somewhat more left lateralized by 20 months of age (Mills, Coffey-Corina, & Neville, 1997). A recent MEG study of the magnetic analog of the N400 found a qualitatively similar topographical organization in 12- to 18-month olds as has been previously reported in young adults, showing activity within frontotemporal cortex that was stronger in the left hemisphere (Travis et al., 2011). However, consistent with previous ERP research, the infant brain responses to processing words was delayed, commonly peaking around 550 ms (Holcomb, Coffey, & Neville, 1992).

Functional Neuroimaging Studies of Language Processing in School-Age Children and Adolescents

Imaging studies of the brain organization for language in adults have confirmed over a century of work from neuropsychological patients that a left lateralized frontotemporal and perisylvian network primarily mediates the major components of language (Rasmussen & Milner, 1977). Brain imaging studies of children primarily focus on whether these adult core brain regions support language in children and to what extent there is developmental change within these regions. The degree of left laterality in children is a central question.

Studies of Regional Brain Associations to Language Development. Most studies support a general pattern of increasing lateralization with development. Nevertheless, the findings reveal noteworthy task and age differences. Younger left lateralized activity patterns are typically found for passive lexical processing tasks (Balsamo, Xu, & Gaillard, 2006; Everts et al., 2009; Gaillard et al., 2003; Lidzba, Schwilling, Grodd, Krageloh-Mann, & Wilke, 2011) as compared to tasks assessing more complex aspects of language production, such as verb generation (Holland et al., 2001; Ressel, Wilke, Lidzba, Lutzenberger, & Krageloh-Mann, 2008; Szaflarski, Holland, Schmithorst, & Byars, 2006). On both passive and controlled types of lexical tasks, there are significant functional neuroanatomical changes in the spatial extent and/or amplitude of activity within traditional language areas, particularly in frontal regions (Brown et al., 2005; Gaillard et al., 2003). There is evidence for a developmental decline in task-related activity during language tasks for nonlanguage areas such as the ventral visual pathway (Balsamo et al., 2006; Schmithorst, Holland, & Plante, 2007) and right frontal regions (Brown et al., 2005).

On tasks requiring complex receptive and expressive language, the findings of robust increases in left lateralization are consistent. Verb generation tasks yield both developmental increases in activation within traditional left hemisphere language areas using fMRI (Ressel et al., 2008; Szaflarski et al., 2006) and MEG (Gummadavelli et al., 2013; Ressel et al., 2008), as well as developmental activation decreases in right hemisphere regions associated with attention and task performance (Szaflarski et al., 2006). Age-related increases in focal activity without age-related increases in laterality are reported within the superior temporal gyrus bilaterally using story comprehension tasks (Lidzba et al., 2011).

A NEUROCOGNITIVE PERSPECTIVE ON HUMAN DEVELOPMENT

The mature human brain is composed of approximately a hundred billion neurons that form trillions of connections, all in the service of orchestrating the equally complex processes that constitute human thought and behavior (Pakkenberg & Gundersen, 1997). The central question in the study of human development is how this remarkable neurobehavioral system comes into being. However, questions about how the brain and behavioral systems develop have been pursued largely independently, with neuroscientists focused on change in physical attributes of brain systems and behavioral scientists on addressing questions of change in specific aspects of behavior. The initial divergence of these paths of study was largely historical and attributable to the technical challenges of simultaneously studying the development of neural and behavioral systems in living human children. Nevertheless, the long-term consequence of this disciplinary divide is a lack of interdisciplinary integration of data and a divergence in the theoretical models of development that each field offers to account for the observed changes.

As illustrated by the studies reviewed in this chapter, recent advances particularly in brain imaging technologies have made it possible to begin to bridge this interdisciplinary divide. The findings that are beginning to emerge from this interdisciplinary work, coupled with existing data from studies of both brain and behavior, point to commonalities in basic principles of development that operate at very different levels of inquiry and analysis. The next two sections draw from the findings reported earlier in this chapter to provide a summary of the major developmental themes that arise, first, from current models of brain development and, then, studies of neurocognitive development. The final section examines commonalities in the themes that derive from these two bodies of data. It will argue that the principles that arise from the data on brain and behavioral development are consistent with a unified model of brain and behavioral development that is well characterized as dynamic and interactive; marked by progressive differentiation, elaboration, and gradual commitment of resources to neurocognitive structures that emerge slowly over the course of development.

The Dynamic Nature of Brain Development

The studies of brain development reviewed in this chapter support a strongly interactive model with genetic, physiological, behavioral, and environmental factors acting in concert as a complex and dynamic system that promotes the development of the brain (Stiles, 2008). Signals that support the processes of brain development arise from molecular sources in the form of gene expression, from interactions among individual cells, from electrical signaling between distant cell populations, and from signals arising in the external environment and transmitted to the developing organism. None of these factors acts in isolation to *determine* developmental outcome. Rather, each contributes to the many complex and multifaceted processes that underlie brain development. This is a view of neural development anchored in the *process* of development itself, with each step influenced by myriad cues arising from multiple levels of the emerging system. A few examples of the processes that are involved in cortical area formation illustrate this point.

Cortical area formation begins very early in the gastrulating embryo where multiple, sometimes migrating, cell populations engage in complex molecular signaling that alters the fate of the subset of cells that will become the neural progenitor cells for forebrain structures (Sadler & Langman, 2010; Schoenwolf & Larsen, 2009). The absence or alteration of any aspect of this signaling can have dire consequences, suppressing head growth and even compromising the viability of the embryo. At the end of the embryonic period, molecular signals originating from multiple signaling centers in the ventricular zone and expressed in concentration gradients across the cortical plate, act in concert to establish the rudimentary sensorimotor area organization of the emerging neocortex. Alterations in the level of any one of the signaling molecules can dramatically alter the size and location of cortical areas.

The establishment of the thalamocortical (TC) pathway is essential for maintaining and refining cortical sensory areas in the fetal period. Multiple cell populations in the ventral telencephalon provide guidance signals to the developing TC axons as they project to the input layers of the neocortex (Kahler et al., 2011; Kostović & Jovanov-Milosevic, 2006). Alteration of cells in these signaling centers can divert TC axon path finding and disrupt cortical organization. The TC axons synapse with cells of the transient subplate layer once they arrive at cortex. The subplate cells play an essential role in establishing functional connections between the TC axons and the layer IV cortical cells, and between layer IV cells and the thalamus (Eyler et al., 2011). Destruction of subplate cells disrupts TC pathway formation.

At birth, environmental input is essential for establishing and maintaining specific features of cortical area organization. For example, binocular patterned visual input is necessary for ocular dominance column organization (ODC) in primary visual cortex (PVC). Binocular elimination of input suppresses ODC patterning, while monocular input induces dramatic changes in the balance of inputs in PVC (LeVay, Wiesel, & Hubel, 1980). An even more dramatic example of the role of early input in cortical area organization is seen in the cortical rewiring studies (Leamey et al., 2009; Sur et al., 1988). These studies showed that elimination of auditory inputs to fetal primary auditory cortex induces the stabilization of normally transient visual inputs and redefines the function of the area as visual.

Postnatal imaging studies document the protracted nature of cortical area development. Throughout the preschool and school-age periods, both progressive and regressive region-specific changes in cortical area and thickness are evident. Indices of cortical thickness suggest gradual region-specific thinning of the neocortex that extends through adolescence (Gogtay et al., 2004; Ostby et al., 2009; Sowell et al., 2004). Region-specific changes in cortical area exhibit early expansion followed by contraction. A notable feature of these postnatal events is

that different cortical regions exhibit different trajectories of development for surface area and thickness (Ostby et al., 2009). Differential trajectories of development are observed in the major brain pathways that connect these cortical regions. Thus, the essential components of the major brain networks that support complex behavior exhibit not only protracted development, but also continuing change in the *relative* maturity of different components of the networks, thus creating different functional states throughout development. Neurogenomic imaging studies of adults are defining the relationships between specific patterns of gene expression and differences in cortical arealization and thickness. Nonetheless, the specific nature of the gene action that gives rise to these patterns and the mechanisms of gene activity during development are poorly understood (Chen et al., 2012; Eyler et al., 2012; Panizzon et al., 2009).

Associations Between Brain and Behavioral Development

Neuroimaging studies have begun to map associations between behavioral changes and change in the neural systems that mediate behavior. As represented by the discussions in earlier sections of this chapter, most neuroimaging studies focus on higher cognitive functions that begin to emerge in the first year of life and continue to develop gradually over many postnatal years. Although healthy neonates possess the basic sensorimotor abilities that are essential for the later development of higher functions, data on the emergence of these very early behaviors are extremely limited. Studies documenting patterns of neurocognitive change in older children are more extensive. Data from each of the domains considered in this chapter document the complex and protracted trajectories that are characteristic of the development of higher cognitive functions.

Neonates are capable of both simple volitional motor activity and rudimental sensory processing. By the time a human infant is born, the corticospinal tract (CST) system that supports central motor control (Armand, 1982; Eyre, 2007; Huang et al., 2009) and the thalamocortical tract (TC) system that supports the major sensory functions are largely established (e.g., Armand, 1982; Kostović & Judas, 2010). Indeed, there is some evidence that these systems begin to function in the prenatal period. Imaging studies of human fetuses have shown that soon after the establishment of the CST in GW 20, cortically based, bilateral movements are observed in the fetus, and between GW 26–32, independent movement of the extremities is common. In the late fetal period generalized mouth movements (open, close, swallow, tongue protrusion) and rhythmic "mouthing" movements similar to those observed in later motor speech are observed (Prayer et al., 2006). There is evidence that sensory information impacts later development. Within the auditory domain, prenatal exposure to maternal or community language is associated with later preferences for the prenatally available language (May, Byers-Heinlein, Gervain, & Werker, 2011). Similar effects are reported for music exposure. Very recent data from rats suggest the visual system may also be sensitive to prenatal input. Dark rearing of pregnant mice during the late gestational period (E16-17, for a 20-day gestation) results in a reduction in the number of retinal neurons measured in the rat pup postnatally. The mechanism for the change is linked to effects on the fetal vasculature and level of photopigment in the rat pups, which jointly regulate neuron number (Rao et al., 2013).

As these examples illustrate, the neonate brings a range of functional somatosensory systems to the task of acquiring higher cognitive functions. Additionally, there is substantial evidence that the neonate is capable of quite powerful statistical learning of environmental information. Statistical learning refers to the ability of the organism to extract statistical regularity from environmental input. A large number of studies have documented statistical learning during the first year of life for a wide range of domains including words (Saffran, Newport, & Aslin, 1996), musical tones (Saffran, Johnson, Aslin, & Newport, 1999) and spatial shapes (Kirkham, Slemmer, Richardson, & Johnson, 2007). Recently, this work has been extended to newborns who showed evidence of statistical learning for novel shapes (Bulf, Johnson, & Valenza, 2011).

Each of the higher cognitive domains considered in this chapter illustrate the protracted nature of development through childhood and adolescence. Face processing is an important basic skill that is essential for human social interaction. Preferences for faces over other classes of objects are documented in neonates, and by 3 months, infants can categorize faces by gender and race. Despite these early emerging abilities, face processing undergoes a protracted period of development extending well into adolescence (Lee et al., 2013). The brain networks for face processing are complex. They consist of both a core network for face identification that is located in ventral temporal regions and includes the fusiform gyrus, the inferior occipital gyrus, and the superior temporal gyrus (STG), as well as an extended network that includes additional regions in the medial temporal lobe, frontal lobe,

parietal lobe, and subcortical structures. Imaging studies have shown that patterns of activation in both core and extended networks for face processing undergo systematic change throughout the school-age period (e.g., Haist et al., 2013). In addition, electrophysiology studies also provide evidence for systematic change in the neural signatures of face processing (Shibata et al., 2002), with the classic N170 response undergoing protracted change from infancy through adolescence (de Haan, Johnson, & Halit, 2003a).

Studies of working memory abilities also document a protracted period of development. There is now an extensive body of behavioral evidence documenting the early emergence and rapid development of basic working memory abilities during the first year of life that correspond to systematic change in associated neural responses (e.g., Bell, 2012; Cuevas, Raj, & Bell, 2012). Throughout childhood (Vuontela et al., 2003) and adolescence (Conklin et al., 2007), a linear improvement in working memory performance is observed for a wide variety of tasks. FMRI studies suggest that the brain networks serving these important functions mirror the basic adult networks from very early in development, but are more distributed and less differentiated. Improvement in working memory performance accompanies changes in the specificity of the underlying neural systems (e.g., Klingberg, 2006; Thomas et al., 1999).

Finally, language is a complex cognitive ability that requires mastery and integration of a range of processes. Fluent language users seamlessly process many aspects of language including the acoustic, phonological, lexical-semantic, morphological, syntactic, and discourse levels when listening to or producing speech. Acquisition of each of these components of language develops on somewhat different temporal trajectories, with early acquired skills such as acoustic or phonological processing proceeding and serving as the foundation for later skills such as lexical or syntactic processing (e.g., Cheour, Leppanen, & Kraus, 2000; Peña et al., 2003; Werker & Tees, 1999). Considerable progress has been made in mapping the brain substrates of language in adults. Studies of children suggest that the functional brain systems employed for the various aspects of language emerge early but undergo protracted developmental change and in general reflect developmental increases in the leftward lateralization of functions and developmental decreases in activity within a language-learning "scaffolding" that includes areas outside the classic adult language organization, including right frontal, temporal, and occipital cortex (e.g., Balsamo et al., 2006; Everts et al., 2009; Friederici, Brauer, & Lohmann, 2011; Lidzba et al., 2011; Schlaggar et al., 2002; Szaflarski et al., 2006). These changes in the brain substrates for language presumably reflect the increasing specification and refinement of the neural systems for language that accompany the child's growing mastery of this complex set of cognitive processes.

Common Developmental Principles

A number of common themes arise in reflecting on the patterns of data observed in studies of brain and neurocognitive development. The first is the idea of progressive differentiation of system elements, where initially rudimentary structures are elaborated, refined, and integrated into increasingly effective systems. The second related theme is that of progressive commitment of elements and networks to particular processes, thus creating stable and effective neurocognitive systems. The third theme has two complementary aspects. On the one hand is the idea that the process of neurocognitive development is dynamic and interactive; on the other hand is the essential complement to dynamism, which is constraint. There are three primary sources of constraint on neurocognitive development: genetic, environmental, and temporal, and each plays an essential role in constraining developmental trajectories. These themes are considered in greater detail next.

Progressive Differentiation. Progressive differentiation refers to the ongoing increases in the complexity of the organism, which is one of the hallmarks of any developing system. Organisms and behaviors begin small and are gradually elaborated over time. The phenomenon is clearly illustrated in the events of embryonic brain development. The embryo goes from a two-layered to a three-layered structure as new cell lines differentiate and become organized and integrated. Migrating cells that will eventually form the mesodermal and endodermal germ layers of the embryo also establish signaling pathways that promote the differentiation of the neural progenitor cell population in the ectodermal layer. In addition, the progressive differentiation of neural progenitors has a spatial component that is critical for establishing the basic functional organization of the embryo. Concurrent with the signaling that promotes the differentiation of the neural progenitor cell lines, more specific signaling induces neurectodermal cells in rostral regions to become forebrain progenitors, and more caudally positioned cells to become spinal and hindbrain progenitors. A few weeks later, the graded expression of multiple transcription factor proteins in the rostral progenitor cell population will promote

further differentiation within cell populations destined to form the major sensorimotor areas of the emerging neocortex. Progressive differentiation, thus, brings increasing complexity at all levels of the neural system from cell lines to neural systems.

Progressive differentiation is also seen in neurocognitive systems. Language acquisition begins with the parsing of the acoustic stream and the differentiation of important speech sounds. The parsing of sounds sets the stage for identifying word boundaries. Combinations of words are linked in ways that serve simple specific meanings. Strings of meaningfully connected words and sentences combine to express complex ideas in discourse or text. Similarly with face processing, infants initially discriminate faces as an important class of stimuli, but it is several months before gender or race categories become salient. The basis for face discrimination remains fairly global for many years, as children rely more on external cues such as hairline or clothing rather than fine analysis of internal facial features. The neuroimaging studies of language and face processing suggest that the neural systems that support these developing behaviors undergo a concomitant shift from relatively imprecise engagement of system elements to increasingly specific, and presumably efficient, engagement. A critical aspect of progressive differentiation for both the brain and behavioral systems is that with each phase of development the processes of differentiation produce new structures that are essential for the next step in development.

Progressive Commitment. Progressive commitment refers to the stabilization of systems. Developing systems exhibit considerable plasticity and capacity to adapt to varying signals and contingencies. However, that plasticity declines with development as different neurocognitive elements become progressively committed to particular systems. We can see this phenomenon of progressive commitment in the course of brain development. Initially the cells of the embryo are totipotent, which means that they are capable of differentiating into any cell type in the body. Nevertheless, with development there is progressive restriction in that potential and therefore emerging constraints on plasticity. We also observe this kind of waning plasticity much later in development. Basic sensory areas in the neonatal brain retain the capacity to receive input that can fundamentally change their normally targeted function. Sur's (2001, 1990, 2005) neonatal rewiring studies demonstrated that when normal patterns of input are disrupted, primary auditory cortex retains the capacity to adapt to quite different modes of sensory input, in effect becoming a visual area. Early synaptic exuberance, found throughout the developing brain, underlies this capacity for plastic adaptation. However, widespread exuberance of the sort that can support cortical rewiring is a phenomenon of early development. While the mature brain retains some capacity for plastic reorganization, it is considerably attenuated.

Evidence for progressive commitment for higher cognitive functions is best seen in studies that directly or indirectly examine cognitive expertise. One example comes from studies of late second-language learners. These studies show late second-language learners are less proficient in overall level of mastery of the newer language. There is also evidence that they may process the second language differently from native speakers, applying rules appropriate to their native language when engaged in second-language processing. These processing differences suggest that early commitment of neurocognitive resources to the particular structural constraints of one language makes learning a language with different constraints more difficult (Hernandez & Li, 2007; Kotz, 2009). Age-of-acquisition effects that show that second-language proficiency varies as a function of duration between first- and second-language acquisition suggest that commitment of neurocognitive resources is gradual and extends over many years (Hernandez & Li, 2007). In addition, fMRI and MEG studies suggest differences in the neural systems for processing first and second languages. These relate to age of acquisition and mirror the developmental functional neuroanatomical changes observed during first language learning, where later acquired languages, even if highly proficient, utilize more right hemisphere resources (Brown et al., 2005; Hernandez & Li, 2007).

A second source of data on the effects of progressive commitment of neurocognitive resources comes from studies of face processing. Specifically, the demands of sociocultural exchange require that humans become expert face processors. An index of this expertise comes from behavioral studies showing that adults tend to use the individual level as the entry point of processing faces, making the discrimination of large numbers of similar stimuli more efficient. By contrast the entry point for processing common objects is the basic level (Tanaka, 2001). Evidence that face expertise may reflect a protracted process of progressive commitment comes from studies of cross-race face processing. These studies show that processing of own race faces is faster and more accurate than processing of other race faces, reflecting long-term exposure to certain classes of face stimuli and the acquisition of

greater own-race face expertise. Differences in own- and other-race face processing are also seen at the neural level. EEG studies show that processing differences of own- and other-race faces are detected within the first 250 ms after the onset of the face stimulus (Tanaka & Pierce, 2009; Vizioli, Rousselet, & Caldara, 2010). FMRI studies have documented subtle differences in both the intensity and location of responses to own- and other-race faces within ventral occipitotemporal cortices (Golby, Gabrieli, Chiao, & Eberhardt, 2001).

Constraints on Development

The studies on brain and neurocognitive development presented in this chapter highlight the dynamic and interactive nature of brain development. Indeed, one might legitimately ask whether such a model is too dynamic. There are many degrees of freedom in these complex, interactive signaling cascades, but, if it is assumed that there is no specific mechanism for *determining* a particular outcome, then how is it that development proceeds with such uniformity to produce species-typical individuals? The answer to this question lies in the fact that while development is dynamic it also occurs within the context of very powerful constraints that originate from three principal sources: genetics, environment, and time.

Genes are the first factor that imposes constraints on the developmental process. Each species, each individual, has a specific set of genes that has been acquired across the course of evolution. The availability of specific gene products at particular points in development is essential for normal outcomes. Further, the particular quantity of a particular gene product is an essential factor in developmental outcomes. As illustrated by the work of O'Leary and colleagues, modulation of the level of transcription factor expression can fundamentally alter the emerging organization of somatosensory and motor areas of cortex (Bishop, Garel, Nakagawa, Rubenstein, & O'Leary, 2003; O'Leary & Kroll, 2009). Thus, genes provide powerful constraints on developmental processes and play a large and essential role in brain development.

The second source of constraint comes from the environment. Like genes, the environment imposes rigorous constraints on how an organism can develop. From an evolutionary perspective, development is an adaptation to the contingencies of the environment. Early ontological development relies on what Greenough has called experience expectant change (Black & Greenough, 1986; Greenough et al., 1987). Normal development requires normal input from the world to modulate and shape the emerging functional organization of neural systems. Neural systems do not develop normally in the absence of typical environmental input. Studies of deprivation such as those illustrated in the work of Hubel and Wiesel provide powerful examples of the importance of normal, expected input on developing systems. The effects of environment play as powerful a role in the development of behavioral systems. Deprivation studies provide striking examples of the wide-ranging effects of impoverished conditions on all aspects of emotional and cognitive development (Nelson, Fox, & Zeanah, 2014; Pollak et al., 2010). Equally powerful are studies of the effects of behavioral interventions on the development of children in at-risk populations (Fletcher & Vaughn, 2009).

The third constraint is time. Development is a complex, multilevel process that unfolds over *time*. Biological and cognitive systems start out simple and become more complex over time. Across the entire period of brain development, the neural system depends on the availability of the right neural elements appearing at the appropriate moment in developmental time. Complex cognitive systems such as language develop in a similar temporal manifold (Elman, 2003). Often the emergence of a new element depends critically on the developmental events that immediately precede it. As such, the developing organism often creates as it goes the tools necessary for each successive step in development. Thus, time constrains what changes *can* occur and what factors *can* influence development. In that sense, development is a temporally constrained, self-organizing process.

Trajectories of Neurocognitive Development

One important aspect of the temporal constraint on development involves changing sensitivity of the organism to developmental signals. The level of development of the organism constrains the kinds of signals to which it can respond. At any point in time, the developing organism has both a state and a history that constrains its developmental potential. The history is the sum of all of the events that contributed to the current state of the organism. The state represents both the current structure and functional capacity of the organism, as well as its potential for further change. Sensitivity to a specific intrinsic or extrinsic influence depends on the current developmental state of the organism. For example, auditory input has no effect on the events of gastrulation, but is critical for the development of features such as tonotopy in primary auditory cortex. Similarly, language input is essential for normal acquisition of language skills but fluent language ability is robust to loss of input. Thus, the increasing variety

of structural elements (some permanent, some transient) creates diversity in the kinds of interactions that can be engaged in the complex signaling cascades that structure the developing neurocognitive system.

The state of the organism represents a "snapshot" at a single moment in developmental time. It is a temporally bound, two-dimensional cross section of a complex multidimensional developmental manifold. It is possible to specify the currently available elements of a system and their immediate relationships, but a critical factor missing from cross-sectional snapshots is the dimension of time. Even within the limited data considered in this chapter, it is clear, that each element within a given snapshot has its own developmental trajectory. Each individual brain area and neural pathway develops according to its own temporal trajectory (see Figures 2.7 and 2.11). That is also the case with sensory and motor systems, phonological and syntactic processing, and memory and inhibitory control. Further, each of these systems has its own subsystems that are also on individual temporal trajectories of development. This means that not only do the elements of the neurocognitive system differ at different time points; the relations among all of the elements also change with time. Thus, the trajectory of neurocognitive development is determined over time by ongoing interactions across the multiple levels of the neurobehavioral system. The processes of progressive differentiation and commitment continuously modify the existing state of the organism, such that the system is reorganized not once, but many times across the course of development. In that sense, development can be construed as a process of continuous, successive reorganization. The product of these developmental processes is a relatively stable (though still plastic) end-state organization that is characteristic of the mature individual.

FUTURE DIRECTIONS

The preceding sections outline remarkable progress in human developmental neuroscience. However, many lacunas in our understanding remain, especially about the relationships between observations made with different methods, in different age ranges, sometimes within different cohorts, cultures, or genetic groups. In this concluding section, we make the case for a more intensely interdisciplinary, more collaborative paradigm in developmental

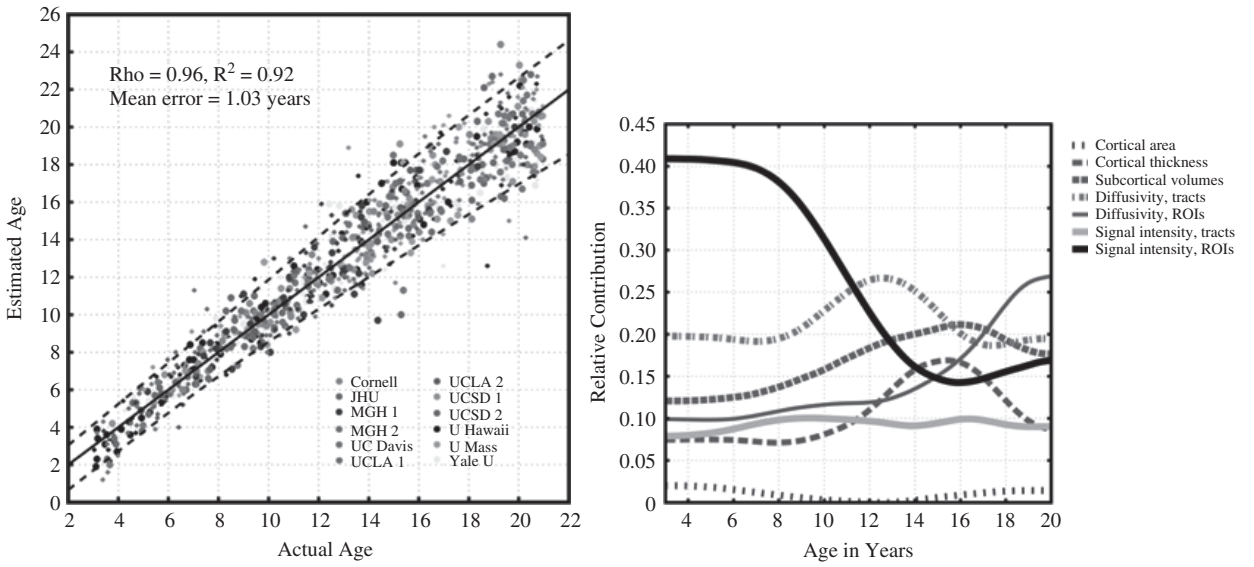


Figure 2.11 Multimodal imaging. (a) Multimodal quantitative anatomical prediction of age. For 885 individuals, estimated brain age is plotted as a function of actual chronological age. Symbol size represents subject sex (larger = female, smaller = male). A spline-fit curve (solid line) with 5% and 95% prediction intervals (dashed lines) is also shown. (b) Age-varying contributions of different imaging measures to the prediction of age. The relative contributions of separate morphological, diffusivity, and signal intensity measures within different brain structures are plotted as a function of age. Contributions are computed as units of the proportion of total explained variance.

science. This paradigm involves more studies employing multidimensional observations and multivariate modeling of developmental phenomena.

From Snapshots to Trajectories

Whether one focuses on the behavior, the neurobiology, or the structural and functional organization of the developing brain, the picture that emerges suggests multiple, parallel yet interacting processes that unfold over decades, and indeed are continuous across the entire lifespan. The confluence of these processes gives rise to an ever-changing, dynamic neurobehavioral system within each individual child. The typical assessment of a child produces a "snapshot" of this system, but this view cannot be understood absent an understanding of the history and continuing trajectory of these unfolding processes.

Emerging understanding of the meaning of the information coded in our genomes suggests that this information is less a recipe for our biology than a workshop for an always-adapting species, the hallmark of which is behavioral adaptivity itself. The code is therefore flexible, within the fitness limits set by our evolutionary history, and redundant, and is well tuned to the demands on members of our species to encode information available in the environment and to generate and update models of the world around them. In this context, if one is interested in the behavior, or the behavioral phenotype, of the child, it makes little sense to attempt to identify a level of representation of this dynamic system as "causal." The developing mind-brain is an extraordinarily complex phenomenon, and meaningful representations of important attributes and dynamics of the phenomenon are almost certainly present at all levels of analysis, across which many forms of isomorphism exist. An important question for the field is how best to advance the sophistication of what is now an exceedingly shadowy and fragmented model of the developing behavioral phenotype.

Given the challenges, the field would do well to organize its efforts around a data-driven and multivariate approach. For the first time ever, developmental scientists are poised to bring to their study of developing children a multitude of new, noninvasive techniques for monitoring the biological and functional attributes of the brain, as well as ever-advancing methods for characterizing genomic and epigenetic variation, neuroendocrine and hormonal factors, and immunological markers. The importance of a multidimensional approach is well illustrated by recent evidence suggesting that gonadal steroid hormones may substantially modify late brain maturation, giving rise to late emerging differences among youth in brain structure and connectivity (Perrin et al., 2008). Moreover, additional evidence suggests that these effects may interact with genotype (Peper, Hulshoff Pol, Crone, & van Honk, 2011; Perrin et al., 2008). Nonetheless, we need much more research to determine the behavioral implications of these effects, and of the well-known variability in pubertal trajectories among children.

Equally important are the increasingly sophisticated methods for complete assessments of the child in context and over time. New web-based, mobile, and wireless technologies are opening up opportunities for less obtrusive and higher dimensional assessments of the behavioral and physiological responses, experiences, activities, and environments of children. This new information promises to greatly augment data obtained from laboratory assessments. The developmental research community would do well to commit to collaborative efforts to aggregate information about developing children in large-scale, multidimensional databases. In the following section, we describe some examples of such multivariate approaches to aggregated data.

Multimodal and Multidimensional Approaches

There is an ever-growing and diverse collection of scientific tools available for noninvasively studying human brain development and relating it to behavioral and cognitive change. We have made significant progress using these technologies to characterize maturational differences and trajectories in structural and functional brain development. Despite these advances, however, across all types of imaging and recording methods, the vast majority of studies have investigated developmental changes within a single measurement modality; for instance, comparing brain features only *within* structural MRI, EEG, fMRI, DTI, or MEG. In order to begin to understand the complex interplay of anatomical and physiological growth and to better reveal the biological significance of our imaging measures, it will be necessary to study brain changes using integrated multimodal approaches that relate different kinds of measures to one another. Done rigorously, such studies will require more than just the addition of more variables to statistical models; the accurate spatial and temporal interrelation of multiple structural and functional brain measures demands the collaboration of researchers with expertise across difficult and diverse areas, including biophysics, signal processing, computational neuroscience, mathematical modeling and statistics, and the behavioral sciences. The technical demands and scientific promise

of multimodal imaging approaches are evident in the increasing publications using integrated brain measures. Successful examples of their application include integrating EEG and MEG data with structural MRI data (Dale & Sereno, 1993), MRI and MEG with fMRI data (Dale & Halgren, 2001; Dale et al., 2000), PET and fMRI (Gerstl et al., 2008), EEG and fMRI (De Martino et al., 2010; Oun, Numenmaa, Hämäläinen, & Golland, 2009), fMRI, MEG, and intracranial EEG (McDonald et al., 2010), resting state fMRI with DTI tractography (Uddin et al., 2010), and resting fMRI and DTI with voxel-based morphometry (Supekar et al., 2010). Besides just relating different kinds of measures, a major goal in integrating approaches is to capitalize on the relative strengths and bypass the relative weaknesses of each modality, for example, by combining the superior spatial resolution of fMRI with the millisecond-wise temporal resolution of MEG to study the detailed spatiotemporal dynamics of human memory and language processing (Dale & Halgren, 2001). Although usually developed first within studies of adults, integrated forms of multimodal structural and functional neuroimaging constitute an exciting prospect for future studies of child development.

A closely related but distinct issue involves the ability to model simultaneously the developmental change of a large number of biological or behavioral variables and relate them to each other in interpretable ways. Just as studies of brain development typically use measures from only one type of imaging, they also commonly characterize brain features and maturational trajectories only in isolation, as a list of separate, univariate dimensions along which developmental change occurs. For example, we know that there exist during school ages developmental increases in the volume of the thalamus, decreases in total diffusivity of the pyramidal white matter tracts, and decreases in cortical thickness. Nevertheless, how do these trajectories interrelate, and which types of changes are dominating at what ages? In developmental brain research, it remains a critical challenge to characterize the multidimensional nature of such features in a way that accurately conveys complex relations among them.

An example of such an attempt to characterize brain development integrating information from a set of multidimensional imaging phenotypes comes from the multisite PING Study. Using a regularized nonlinear modeling and cross-validation method, PING researchers developed an approach that quantifies the age-varying contributions of different biological change measures to the prediction of multidimensional developmental phase as defined by chronological age (Brown et al., 2012). Using this new technique, different components of brain development were quantified and compared directly, showing their relative roles in the dynamic cascade of changing brain characteristics. This study found that the composite developmental phase of an individual person can be captured with much greater precision than has been possible using other types of biological measures or approaches. Using a multimodal set of 231 brain biomarkers assessed in 885 subjects between the ages of 3 and 20 years, Brown and colleagues were able to predict the age of every individual within about one year on average (Figure 2.11a). This result indicates that a highly age-sensitive composite developmental phenotype is present within a set of biomarkers that includes measures of brain morphology, tissue diffusivity, and signal intensity. It reveals the presence of a developmental clock of sorts within the brain—a complex latent phenotype for which the timing of maturation is more tightly controlled and more closely linked to chronological age than previously understood. This multidimensional biological signal cuts through the high individual difference variability across children and adolescents and explains more than 92% of the variance in age.

The new method employed in the PING study also revealed how the neuroanatomical features that contributed most strongly to the prediction of age changed over the age range (Figure 2.11b). Interestingly, from the preschool years until about 11 years of age, the changes in normalized MR signal intensities within subcortical regions, including gray matter, explained the most variance in age. From the ages of about 11 to 15 years, changes in the diffusivity of white matter tracts (such as FA and ADC) were the strongest age predictor. Volumetric measures of subcortical structures explained the most variance in the age range from about 15 to 17 years. As many researchers are not measuring diffusion within these structures, it was surprising that diffusivity within subcortical regions, including gray matter, was the strongest contributor to the prediction of age between 17 and 20 years. This pattern suggests that continuously throughout development changes in tissue biology are cascading across the brain in a way that is systematic even among different individuals, and that these specific changes may be relatively insensitive to experiential variability typical among healthy children. While this is an interesting discovery, it does not provide by itself information about the role of these tissue changes in functional development. It is possible, even likely, that other composite phenotypes such as brain activity measures would associate more strongly with the individual

differences observable among developing children of the same age. Future applications of this flexible approach should examine whether cognitive, behavioral, and clinical variables are reliably predicted using multidimensional sets of brain measures.

Defining the Individual in Developmental Terms

The PING study has provided an unusual opportunity to apply advanced multivariate methods to extract new information from high-dimensional data in a large cohort of children across a wide age range. However, more information acquired over time from the same children is of critical importance for the success of future data-aggregation efforts in developmental science. Therefore, the designs of contributing studies must be longitudinal, or cohort-sequential. This is critical for several reasons.

Developmental trajectories are likely to explain behavioral phenomena that cannot be accounted for with concurrent measurements of relevant variables alone. One example of this emerged from imaging genomics. Individual differences in gross brain morphology are highly heritable, with estimates of the heritability of brain size, cortical surface area, and average cortical thickness that often exceed .80 (Baaré et al., 2001; Panizzon et al., 2009). However, a recent longitudinal study of developing twins confirmed that the rate of cortical thinning between the ages of 9 and 12 years was itself heritable (van Soelen et al., 2012). These effects were regionally variable, and cross-age genetic correlations suggested that different genetic factors influenced the rate of thinning at different points in the childhood age range. Such genetically mediated differences in trajectories of cortical development are likely to be relevant to adult behavioral phenotypes, in part because they will alter the nature of interaction between the still-developing neural systems. Without longitudinal study designs these effects of genetically mediated developmental differences will be difficult to detect and define because the structure of the mature brain may mask differences in the timing of its maturation.

We need large longitudinal studies to thoroughly investigate the influence of environmental and experiential factors, especially as they interact with other factors at the level of the individual. These interactions are likely to have important implications for prevention and intervention. For example, an intensive reading intervention administered to children receiving normal classroom instruction but experiencing reading difficulties not only improved their reading performance, but appeared to normalize, at least in part, pretreatment differences in the biology of specific fiber tracts (Keller & Just, 2009). These changes did not occur in a control group of poor readers or a control group of good readers who were assigned to normal classroom instruction. This study suggests that both the reading phenotypes of these children and the accompanying neural signature may reflect interactions between individual factors and the nature of the instruction they receive. Understanding these critical interactions is key to developing new interventions that prevent adverse outcomes in children.

The potential gains of better developmental models of behavioral phenotypes are immense. Because so much of previous research has focused on the modal course of development, and on the "net" effect of experiential variables on representative samples, very little is known about the interactions of experience with constitutional or genetic factors. Yet, virtually all "risk" phenotypes identified so far for adverse outcomes of development, such as academic failure, depression and anxiety disorders, substance-use disorders, social dysfunction, and other behavioral disorders, are heritable. This fact attests to the importance of detecting and explaining interactions of experience with genetic or other constitutional factors (such as early damage or toxic exposure of the brain). The languishing developmental phenotype of a child with a high risk for an adverse outcome may in many cases, and in many respects, be less a result of inherent limitations of the child's nervous system than the expression of an unusual brain responding to environments and cultures shaped to promote the development of the modal child. To the extent that this is true, it implies that, tragically, many children may not escape the negative outcomes for which they have increased risk only because the environment is unsupportive. It also implies, however, that intelligent interventions for children at increased risk, interventions that modify their environments and experiences adaptively, may both dramatically reduce the risk of adverse outcomes in these children and also promote previously underdeveloped capabilities that they possess, and that may even travel (e.g., genetically) with those risks. Exploring these possibilities is the often-repeated mandate for our field, but we have far to go in developing the basic science foundations that are most likely to yield powerful models and interventions.

In conclusion, we cannot overstate the urgency of a "big data" approach to investigation of the developing child. Large-scale, data-driven approaches have led to new discoveries, powerful predictive models, and intelligent and highly adaptive systems in physics, biology, engineering, and business. Yet, in spite of the enormous impact

such advances in human developmental research would have—for education, child welfare, and prevention and treatment of behavioral disorders—a large-scale, multidimensional study of the developing mind and brain has not yet been performed.

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