SECTION II.

FRONTAL LOBE DEVELOPMENT

Silvia A. Bunge Arthur W. Toga

INTRODUCTION TO SECTION II: FRONTAL LOBE DEVELOPMENT

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The structure and function of prefrontal cortex (PFC) change throughout life. Yet, most of what we know about the PFC comes from studies of human adults and mature animals. Researchers previously assumed that human PFC was silent during early childhood and that it was fully mature by adolescence. We now know, owing in large measure to technological advances in in vivo imaging, that PFC is already active in infancy and that it continues to mature in the second decade of life. These changes correlate with the emergence of the capacity for self-regulation, variably referred to as "executive function" or "cognitive control."

Just as advances in brain imaging techniques have made it possible to study PFC development at a macroscopic scale in humans, new technologies and methodologies in cellular and molecular neuroscience are advancing our understanding of the development of PFC microcircuitry, the distributed neural system of pathways and networks that comprise whole-brain connectivity and its complex dynamics during normal and abnormal brain functioning.

From both macro- and microscopic perspectives, we know that PFC is not a homogeneous region of the cortical mantle, but rather a collection of several distinct architectonic areas differing in major ways in terms of their cortical and subcortical connections. Undoubtedly, these differences in the local circuitry of the various prefrontal areas, which are manifest in the areas' specific cytoarchitectonic patterns and their distinct inputs and outputs, indicate specialized functional contributions. Determining the effects on cognitive functioning of age-related changes in each of these subregions is among the most daunting tasks confronting contemporary neuroscientific investigation—all the more so because the basic control processes mediated by these regions support a variety of high-level cognitive functions, from the ability to selectively attend to and organize goal-relevant information to the ability to regulate one's emotions and responses as needed to achieve a goal.

In this section, we survey diverse approaches that have helped to advance our understanding of the development of PFC in humans. We lead off with David Lewis and Darlene Melchitzky's contribution, "Postnatal Development of Neural Circuits in the Primate Prefrontal Cortex." These authors provide a comprehensive overview of neural refinements in local PFC

circuitry overdevelopment that support working memory function. Lewis and Melchitzky review the differential developmental trajectories of distinct classes of cells in PFC. Excitatory synapses in PFC undergo extensive and rapid proliferation between birth and adolescence, followed by a decline. By contrast, inhibitory synapses grow prenatally but reach stability at around the time of birth, maintaining a constant adult-like level of circuitry activity by 1 year of age. Finally, neuromodulatory inputs to the PFC from dopaminergic neurons in the midbrain increase gradually during postnatal maturation and reach a maximum in adolescence. These complex and developmentally protracted postnatal changes in macaque dorsolateral PFC physiology serve to elucidate the changes observed at the macroscopic level in human PFC structure and to model the improvements in working memory performance that characterize human development.

The sensitive period for development of PFC-dependent cognitive functions can be effectively probed and revealed in the study of children who have incurred damage to the frontal lobes, as Vicki Anderson and Megan Spencer-Smith document in "Children's Frontal Lobes: No Longer Silent?" Typically developing children exhibit incremental improvements in executive functions, or cognitive control, from infancy through adolescence. What happens when a brain structure that plays a critical role in cognitive control is damaged early during development? As Anderson and Spencer-Smith review, early frontal lobe injury is often associated with reduced attention, poor problem solving, and social difficulties. These deficits are typically revealed late in childhood, as specific cognitive skills fail to mature at critical developmental stages. Further, children with early damage to left or right PFC do not exhibit the predicted pattern of deficits based on neuropsychological research in adults, indicating that lateralization of PFC functions typically occurs late in childhood. Overall, the patterns of deficit become more adult-like by later childhood and adolescence when the brain is more mature, with commensurately diminishing vulnerability of the young brain through childhood, as neural networks develop and are firmly consolidated.

In "Adolescent Frontal Lobes: Under Construction," Jay Giedd, Armin Raznahan, and Rhoshel Lenroot review genetic, environmental, and hormonal influences on human frontal lobe development. Longitudinal magnetic resonance imaging (MRI) studies examining within-person changes in brain structure indicate that the frontal lobes continue to undergo robust anatomical changes during the second decade of life and thereafter. By comparing monozygotic twins, who share approximately 100% of the same genes, and dizygotic twins, who share approximately 50% of the same genes, Giedd and colleagues have estimated the relative contributions of genetic and environmental influences on trajectories of brain development. They have found that cortical thickness at several regions within the frontal lobes, such as the dorsolateral PFC,

is among the most genetically influenced. Seemingly counterintuitively, the heritability of these frontal regions *increases* during adolescence; Giedd and colleagues discuss several possible reasons for this finding. In revealing the fundamentally dynamic nature of brain development in general, and of the prolonged period of development of PFC in particular, this work holds promise for guiding new and more effective clinical interventions for childhood neurological disorders of genetic and nongenetic origin.

Key concepts and findings related to brain plasticity and environmental inputs affecting PFC structure and function are explored as well by Allyson Mackey, Rajeev Raizada, and Silvia Bunge in "Environmental Influences on Prefrontal Development." These authors provide an overview of studies in humans and other animals that reveal the negative and positive impacts of interacting genetic and environmental factors in PFC development as environmental stimuli influence the expression of genes that influence brain structure and function. Numerous physical and psychosocial factors can negatively impact PFC development. In the prenatal environment, these negative factors include exposure to substances that increase the risk of birth defects, such as alcohol and cocaine. In the postnatal environment, these factors include malnutrition, exposure to lead and other toxic substances, chronic stress, and prolonged social deprivation such as institutional or even home settings of limited resources and insufficient caregiving. Positive influences, by contrast, include environmental enrichment programs aimed at sensory, cognitive, and language stimulation, and interventions that can reverse the negative effects of extreme psychosocial deprivation during the sensitive period of PFC development. Much still remains unknown about the role of environmental influences in PFC structural and functional changes in the prenatal context and from infancy through adolescence. Basic questions include the period of maximal sensitivity for PFC development in humans and the role of factors such as physical exercise and nutrition on PFC plasticity.

Jessica Church, Steven Petersen, and Bradley Schlaggar elevate the vantage point on frontal lobe development to the level of distributed systems of neural connectivity in "Development of Cortical Networks for Top-Down Control." Through functional connectivity analyses of functional magnetic resonance imaging (fMRI) data, it is possible to identify sets of brain regions—functional networks—whose members exhibit a tight coupling of activation, even in the absence of specific task demands. These authors have previously identified two distinct brain networks that support cognitive control: a lateral frontoparietal network and a cingulo-opercular network. In adults, these two networks appear to operate in a largely parallel fashion, whereas in children the networks are more intertwined and possibly more multipurpose. The authors' research points to adolescence, by definition a period of broad-ranging physical, emotional, and physiological change for individuals, as the time frame in which the major transition occurs between

child and adult functional connectivity patterns. The authors note that long-range functional connections are strengthened during development, whereas short-range connections are weakened, resulting in the widely distributed functional networks observed in adults. As illustrated through a comparison of the control networks in children with and without Tourette syndrome, this research in typically developing individuals sets the stage for exploring disrupted networks in multiple neurodevelopmental disorders.

This emphasis on developmental changes in prefrontal networks also appears in the contribution of Kai Hwang and Beatriz Luna, "The Development of Brain Connectivity Supporting Prefrontal Cortical Functions." The maturation of PFC plays a critical role in the development of executive functions in part because of the unique ability of the frontal lobes to integrate information across cortical and subcortical regions supporting top-down control of behavior. Thus, the development of executive control is supported both by "functional specialization," the specificity and modularity of local brain regions that support specific processes, and "functional integration," the coordinated processing of a network of brain regions. To fully characterize the neurodevelopmental basis of executive function, we need to understand not only how activity within brain regions changes with development, but also how brain connectivity develops in supporting interaction across functional regions. Here, Hwang and Luna feature the main white matter tracts that link PFC with other brain regions and review age-related strengthening of these tracts. The authors then examine how these age-related structural changes make possible the increased functional connectivity observed as a function of age when individuals engage in cognitive control. As Hwang and Luna discuss, the investigatory challenge here encompasses anatomical and functional connectivity but also the complexity of synchronized brain rhythms (neural synchrony), which may be critical in shaping the emergence of functional circuitry but are themselves, in as yet unknown ways, enabled and affected by several critical brain maturation processes.

This section ends with a discussion of why the localization of function is vital to our understanding of cognitive development in "Mechanistic Accounts of Frontal Lobe Development" by Yuko Munakata, Christopher Chatham, and Hannah Snyder. These authors address the need for mechanistic investigation of how brain regions support cognitive functions. They make their point with two examples. First, they examine how computational trade-offs can help us to understand broad specializations across prefrontal cortical, posterior cortical, and hippocampal regions. Second, they examine how inhibitory processes can help us to understand one particular functional specialization within the left ventrolateral PFC. Through these examples, the authors illustrate the power of neural network models for providing insight into the emergence of high-level cognitive functions during childhood and adolescence.

The chapters in this section provide a good overview of the current state of knowledge about frontal lobe development. A mere 10 years ago, we would have been hard pressed to put together a large and varied book section on this topic. Today, our challenge is quite the opposite: it was simply not possible showcase all of the excellent research that is currently underway in this field. The work featured here highlights several current trends:

1. An emphasis on the development of brain *networks* rather than of individual brain regions—both at the local circuit level (Lewis and Melchitsky) and at the level of long-range connections between brain regions (Hwang and Luna; Church et al.)
2. The insight that it is not necessarily easier to recover from brain damage sustained during childhood than in adulthood, as is commonly assumed; in fact, early insults to the PFC can profoundly alter developmental trajectories (Anderson and Spencer-Smith)
3. The importance of longitudinal research for our understanding of individuals' brain development (Giedd et al.)
4. A growing appreciation of the role of the environment in human brain development, and of the need to better understand gene x environment and hormonal influences on brain development (Giedd et al.; Mackey et al.)
5. Increased efforts to provide converging evidence from multiple indices of structural and functional brain development, as well as from computational modeling (Munakata et al.)