FUNDAMENTAL NEUROSCIENCE

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VII
BEHAVIORAL AND COGNITIVE NEUROSCIENCE

CHAPTER

51

Cognitive Development

Marilyn S. Albert, Adele D. Diamond, Roslyn Holly Fitch, Helen J. Neville, Peter R. Rapp, and Paula A. Tallal

The human brain has evolved over a very extensive period (Chapter 50), but an individual human brain develops swiftly over the first few years of life, allowing the nearly helpless human infant to gain control of locomotion, language, and thought. The story of the unfolding of brain development in the early years of infancy occupies the first part of this chapter. Later, we consider abnormalities that arise in this developmental process. In the final parts of the chapter, we consider brain changes that occur late in life and that can be accompanied by a reduction in mental ability.

POSTNATAL DEVELOPMENT OF BRAIN STRUCTURE AND PHYSIOLOGY

Many Processes Show Postnatal Development

Recent studies of the anatomy and physiology of the developing human cerebral cortex provide evidence of a postnatal development that is very protracted, highly dynamic, and variable from region to region. Figure 51.1 shows a gross overview of changes in the size and shape of the brain from conception through the first 9 months of life.

More detailed examination of brain growth shows that different components of the neuropil display different developmental time courses. Whereas most morphometric data have been obtained from studies of the primary visual cortex (area 17 or V1), the limited data from other brain regions, such as the frontal cortex, show considerable variability in the timing of maturation of different brain regions. Measures of cerebral metabolism and electrophysiological activity, like structural studies, indicate a long and variable time course of brain development.

The human brain displays many of the progressive and regressive structural events that have been described for nonhuman brains (see Section III). Distinctive features of the development of the human brain are its very prolonged postnatal time course, a lack of evidence for postnatal loss of neurons, a large number of redundant synapses, and the persistence of copious (*exuberant*) connectivity until the late teens.

The Cortex Thickens during Development

The classic studies of Conel and Rabinowicz documented the increasing cortical thickness during maturation of the human brain.[1,2] The primary visual cortex increases in thickness until around the 6th postnatal month, when it attains values observed in adults. Cell densities and overall structure are also mature by this time. In contrast, other cortical areas, including visual association areas, display a long and variable increase in cortical thickness that approaches maturity around 10 years after birth.

Formation of the gyri of the brain is basically complete by birth. Thus includes the superior temporal and middle temporal gyri, pre- and postcentral gyri, the superior and middle frontal gyri, and the superior and inferior occipital gyri. The primary gyri become well defined between 26 and 28 weeks of gestation. Development of secondary and tertiary gyri occurs later in gestation, and in the last trimester the sulci become deeply enfolded. Several left–right asymmetries have been observed in the fetal brain. The superior frontal and temporal gyri are present 1–2 weeks earlier on the right hemisphere than on the left. As in adults, more transverse gyri are present in the right hemisphere, and a larger temporal planum is present on

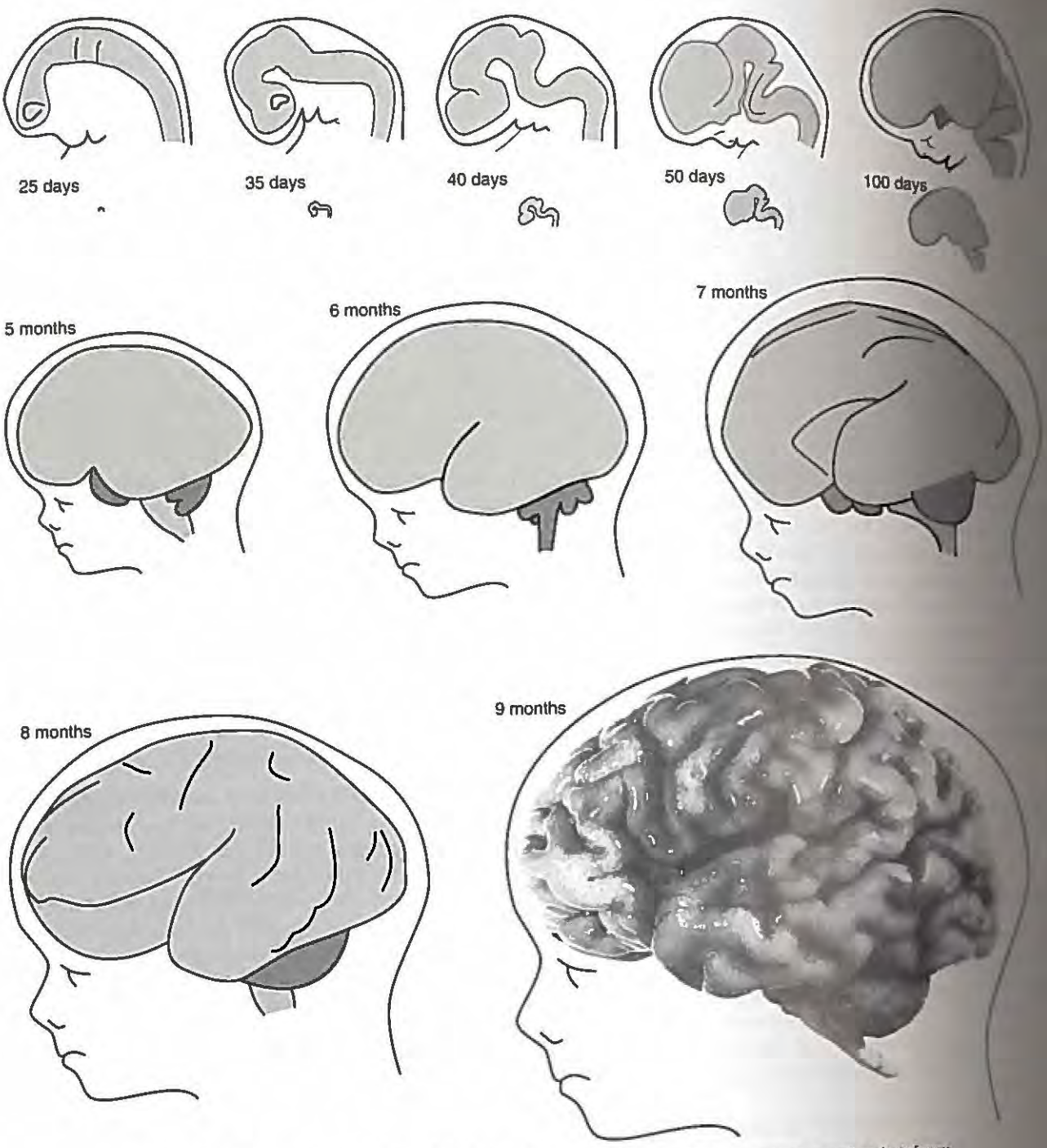

FIGURE 51.1 The size and form of the human brain as it develops through gestation and early infancy

the left temporal cortex than on the right.[3-5] (See also Chapter 52.)

Axons Myelinate during Development

The time course of myelination varies widely in different brain regions and systems.[6] Sensory and motor systems display mature myelination within the first 2 years of life. However, the nonspecific thalamic radiations do not reach mature levels until 5–7 years of age, and intracortical connections display increasing myelination well into the third decade of life.

The Volume of the Cortex Increases

The volume of the immature brain expands considerably. Quantification of the total volume of a given

area is necessary to estimate densities of neuronal structures; however, measurements of the volume of most cortical areas are not possible because of the difficulty in identifying clear structural changes between areas. The notable exception is V1, which is clearly bounded by the **stria of Gennari**, the large granular layer transected by a fiber bundle. Studies[7,8] show that there is rapid expansion of the volume of V1 throughout gestation and the first 4 months of postnatal life, by which time the adult volume is attained. This expansion is in marked contrast to remaining brain areas, which have attained only about 50% of the adult volume at that time.

The density of neurons in V1 decreases rapidly until birth, and then slowly decreases until it stabilizes around 4–5 months after birth; however, there is no evidence for neuronal loss during development, and the total neuronal number remains constant from 28 weeks of gestation until 70 years. This decrease in neuronal density in VI appears to be related to the expanding cortical volume due to the growth of axons, dendrites, and glia.

The Number of Dendritic Spines Increases

The formation of dendritic spines and the time course of development of the length and branching patterns of dendrites have been described for visual and frontal cortical areas in humans. Within the visual cortex the maximum density of spines is present around 5 months of age; this number then decreases until adult values are obtained around 21 months of age.[9] Progressive elongation of dendrites occurs up to 24 months, so that there may be a decrease in spine density during this period rather than a loss of spines[10] from 5 to 24 months. Dendritic development within the visual cortex reaches mature levels earlier in the lower than in the upper cortical layers and thus displays the "inside-out" pattern of cortical development that is characteristic of neurogenesis and migration.[11]

Development within the frontal cortex proceeds more slowly. Whereas neuronal density in the primary visual cortex reaches adult levels by 4–5 months, neuronal density in the frontal cortex has still not reached adult levels by 7 years of age.[12] Additionally, by 2 years of age, dendritic length (which is mature by 18–24 months in V1) is only half that found in adults, an observation suggesting a longer developmental time course in frontal cortex.[12] Left–right asymmetries exist in the dendritic branching patterns of pyramidal neurons within layer V of the inferior frontal and anterior precentral cortex.[13] Within the first year, growth is more advanced on the right side, but by 6–8 years of age the maturation of distal dendrites on the left exceeds that of the right.

Synapses First Increase and Then Decrease in Number

As in the brains of other animals (see Chapter 19), the immature human brain contains many more synapses than the mature brain. Within the primary visual cortex, synaptic density increases gradually during late gestation and early postnatal life; it then displays a steep increase from 2 to 4 months of age, during which period the density doubles. After 1 year of age, however, there is a decline in synaptic density until adult values (50–60% of the maximum) are attained at about 11 years of age (see Fig. 51.2).[14,15] The time course of the decrease in synaptic density varies within different cortical layers. The decrease does not display the "inside-out" pattern of development; rather, there is a considerable decrease, over time, in the number of synapses in every layer.[7]

The other cortical area for which data on synaptogenesis are available in humans is the middle frontal gyrus (layer III).[17] This area also shows a postnatal increase in synaptic density followed by a decrease, but these changes occur along a longer time course in the frontal cortex than in the primary visual cortex. The maximum density of synapses occurs around 1 year of age (compared to 4 months in the visual cortex). Adult values are not obtained until around 16 years of age (compared to 7–11 years for the visual cortex). Overall synaptic density in humans is greater in the frontal and motor cortex than in the visual cortex.[7,17,18]

In summary, these quantitative anatomical measures suggest that in humans there appears to be little role for programmed cell death. In animal studies this is not the case (see Chapter 20). On the other hand,

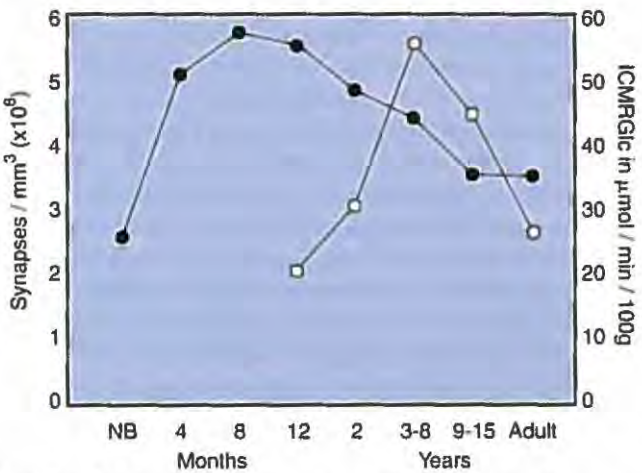

FIGURE 51.2 Variations in cortex with age: Density of synapses in human primary visual cortex (black circles)[11] and resting glucose uptake in occipital cortex (white circles).[15] Adapted with permission from M. Johnson.

synapse elimination in humans and other primates exceeds that in other animals, and perhaps this elimination is more important in the development of more complex systems. These results are consistent with a role for incoming afferent input in selectively stabilizing functional synapses and in eliminating or suppressing inactive contacts.[19-21] The redundancy of connections (synapses) may also make it possible to adjust cerebral organization following damage or altered input.

After Birth Cerebral Metabolic Rate First Increases and Then Decreases

Increases in neuronal activity have been linked to increases in cerebral metabolism, as measured by positron emission tomography (PET), and changes in cerebral metabolism in neurologically at-risk infants and children from 5 days to 15 years of age have been described. These data show substantial subcortical activation in newborns but little activation of cerebral cortex. However, over the first 3–4 years of life, the cortical metabolic rate increases until it reaches levels twice those observed in adults (see Fig. 51.3). After 4 years of age metabolic activity gradually decreases until adult levels are reached, around 15 years of age. The time course of the rise and decline of PET data parallels the rise and decline in the number of synapses in human frontal cortex, and suggests that the exuberant synapses there are metabolically active.

Electrophysiological Activity Also Undergoes Development

Averaged scalp recordings (ERPs or event-related potentials) largely reflect postsynaptic potentials of apical dendrites. These recordings show a highly variable and protracted course of brain development in their responses to sensory and cognitive information. Measures of brainstem and thalamic electrical activity (e.g., the auditory brainstem responses) reveal rapid decreases in *latency* from 30 weeks of gestation onward and then attainment of adult values by 2 years of age.[23] In contrast, the early cortical sensory responses (the N100-P200 vertex potential or N1-P2) do not appear mature in form until around 13–15 years of age[24-26] (Fig. 51.3). In addition, several later ERP events linked to cognitive functions that include attention and language do not display a mature pattern until even later, at 15–20 years of age.[25,27]

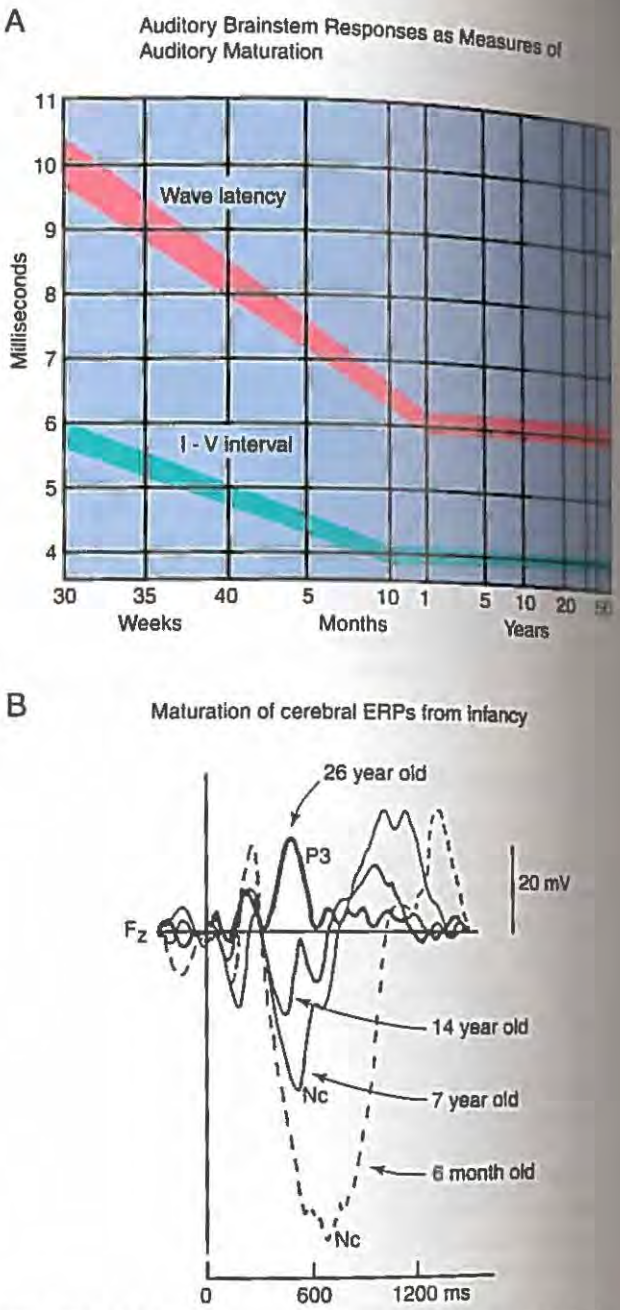

FIGURE 51.3 Changes in electrophysiological activity of the brain. (A) Declines over the first year of life in the latency of components of the auditory ERP that are generated by subcortical structures. (B) Changes in the ERP waveform at varying ages. The latency components generated by cortical structures change dramatically as development progresses (for a discussion of the ERP method see Chapter 54, Box 54.1).

Summary

Structural, metabolic, and physiological indices of human brain development all point to a long time course that displays considerable variability from region to region and from system to system.

THE FUNCTIONAL DEVELOPMENT OF NORMAL HUMAN BRAIN

Investigators are now attempting to link the types of evidence described in the preceding section to sensory and cognitive functions in infants and children. At present, such studies are limited in number. Central tasks are identifying factors that drive the dynamic and extensive changes observed in human brain development and assessing the relative contributions of intrinsic and extrinsic variables in the functional differentiation of different brain systems. Until recently, the predominant view was that postnatal development of the cortex is largely intrinsically determined. However, new studies of both animals and humans have revealed a central role for extrinsic factors in shaping the organization of neural systems and in permitting recovery from brain damage. Indeed, calculations showing that the information in the genome is not sufficient to specify the connectivity of the brain, together with evidence for the long-lasting existence of transient, redundant connections in primates, suggest that regressive phenomena under the influence of environmental input play a significant and persistent role in the development of the functional specificity of the human brain.

Anatomical Development of the Visual System in Infants Can Be Linked to Functional Development

Several parallels between anatomical changes and the emergence of function in human visual systems have been noted. Looking preferences are used to examine visual functions in infancy. To study acuity, infants are given a choice between two displays that differ in some way, for example, in spatial frequency, which is usually varied by the thickness of stripes.[28] Preferences for one of the two patterns indicates the limits in the infant's ability to discriminate between the two patterns.

The visual abilities of the newborn have been linked to subcortical structures that show mature anatomy and high metabolic rates during this period.[7,15,29,30] The limited visual abilities of the newborn are augmented by the appearance of smooth pursuit tracking around 6–8 weeks. This development may be accounted for by the maturation of cortical layers 4, 5, and 6 in V1. These layers connect magnocellular afferents from the lateral geniculate nucleus and the middle temporal (MT) region, a pathway important for visual attention.[31] Visual acuity and visual alertness increase dramatically around 4 months of age, when the volume of visual cortex reaches adult levels and the highest density of synapses is present. Around the same age of 4–5 months, binocular interactions that are clearly dependent on cortical function become apparent. These interactions, which include stereoacuity, binocular summation of the light reflex, and stereopsis, appear in the same time frame as maturation of the middle cortical layers and a rapid synaptogenesis in V1.[7,28,32,33] This period of rapid growth appears to be a time of increased vulnerability to altered afferent input. Strabismic amblyopia and amblyopia due to the absence of patterned input are reported to occur at this age unless corrected early.

The time period when visual impairments can be corrected is different for different visual functions. Correction for an absent lens (*aphakia*) due to cataracts may be completely effective only when performed prior to 2 months of age,[34] i.e., just prior to the onset of exuberant synaptogenesis in V1. On the other hand, very high synaptic density persists to at least the age of 4 years in V1. The presence of these unspecified synapses may account for the ability to recover from amblyopia (with forced use of the strabismic eye) during this time.

Recent studies suggest that the ability to see stereoscopically may not develop if the disruption of binocular convergence by strabismus is not corrected within the first year of life.[35] In contrast, these same children develop normal acuity and contrast sensitivity in the corrected strabismic eye even when the correction occurs after the first year of life. These results suggest there may be separate critical periods for the development of resolution acuity and stereopsis. Because the parvocellular system is thought to underlie acuity, whereas disparity detection is mediated by the magnocellular system, the magnocellular system may be more modifiable by environmental input than the parvocellular system, both in humans and in other animals.[26,33,36–38] This differential sensitivity may be due to the slower maturation of the magnocellular system[33,37–39] and/or to differences in the number of exuberant synapses within the systems.[26,40]

Studies of individuals born deaf and blind suggest that in humans, as in other animals,[41–44] there is a time period when cortical areas that normally process information from the deprived modality may become reorganized to process information from remaining modalities.[26,45–49] From the alteration of visual functions seen in individuals born deaf, it appears that areas of auditory cortex have been recruited for visual function (see Fig. 51.4). Deaf subjects show abnormally strong electrical responses to peripheral visual stimuli. These responses are not found in normally hearing individuals, even those exposed to sign language by deaf parents.

The prolonged persistence of exuberant cortico–

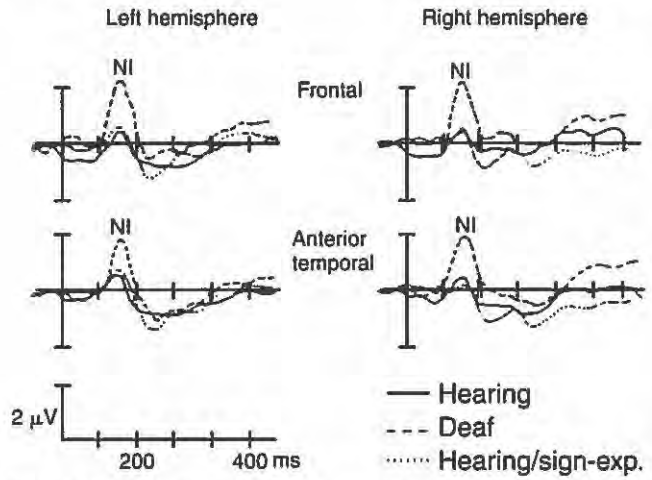

FIGURE 51.4 Visual evoked potentials to peripheral stimuli recorded from congenitally deaf subjects and from hearing subjects who had early exposure to sign language (hearing/sign-exposed) and those who did not. Only deaf subjects showed enhanced ERPs over temporal areas.

cortico connections may provide the substrate for such cortical reorganization.

Toward the End of the First Year of Life Infants Show Changes in Visual Search

Infants younger than 7 or 8 months of age will not uncover a hidden object. If a cloth is thrown over a toy while an infant of 5 or 6 months is reaching for it, the infant will withdraw his or her hand and stop reaching. By 7 or 8 months, most infants who watch an object being hidden can retrieve it. However, if the infant then watches as the object is hidden at a second location, most infants of 7–8 months search for the object at its first hiding location, which is now empty.

Jean Piaget called this the A-not-B error, because the infant is correct at the first hiding place (A) but not at the second (B). It is rare to see this error when there is no delay between when the object is hidden and when the infant is allowed to reach, but a delay as brief as 1, 2, or 3 s is sufficient to produce the error in infants 7–8 months of age. As infants grow older, the error is still seen if the delay between hiding and retrieval is increased. The delay at which the A-not-B error is produced increases by about 2 s per month from 7 to 12 months of age, although there is considerable individual variation among infants. The A-not-B error is a robust phenomenon that has been observed all over the world in children from diverse cultures, physical environments, socioeconomic backgrounds, and household and daycare arrangements and has been observed in dozens of laboratories using diverse procedures.

For Piaget, achieving the ability to retrieve a hidden object was a landmark accomplishment. A younger infant reaching for a visible toy might simply have been reacting almost reflexively to the sight of the object. However, reasoned Piaget, an older infant who reaches for something he cannot see and who must execute a sequence of actions (first removing the cloth and then reaching for the toy) to obtain it, must have had the goal of retrieving the toy in mind from the outset. For Piaget this marked the first clear appearance of intentionality, planning, and foresight. The A-not-B error reflected the fragility of these abilities and infants' poor understanding of the laws governing the location of objects in space. Either infants were not yet able to hold a representation of the object's location in mind for a few seconds or they did not yet quite understand the relationship of (a) their previous action of retrieving the object, (b) the subsequent hiding of the object in a different location (even though they observed the hiding), and (c) the object's present whereabouts.

The A-Not-B Task and the Delayed Response Test Depend on Frontal Lobe Function

The functions of dorsolateral prefrontal cortex in nonhuman primates have been studied extensively using "delayed response," a task that is virtually the same as the A-not-B task described above. Dorsolateral prefrontal cortex is one of the last regions of the brain to develop phylogenetically and ontogenetically. During primate evolution it has exploded in size, and is thought to be responsible for "executive" functions such as planning and foresight. Dorsolateral prefrontal cortex is defined in the macaque brain as that area of frontal cortex between the arcuate sulcus and the frontal pole on the dorsolateral surface. The most critical portion of this region for delayed response and A-not-B performance in macaques is the principal sulcus (roughly Walker's area 46). The entire region consists of Brodmann's area 9 and much of areas 8 and 10, as well as area 46. The homologous region in humans is thought to lie within the middle frontal gyrus.

When dorsolateral prefrontal cortex is ablated or inactivated, subjects fail the delayed response task. Subjects succeed on trials where cells within the principal sulcal region sustain their firing during the delay period, and fail on trials where this neuronal firing is not sustained. Judging by their firing patterns, some of these neurons encode the spatial location of the cue, while others encode the location where the animal should respond at the end of the delay.

Human infants improve on the delayed response task over the same age range and at the same rate as they do on the A-not-B task. Infants find both tasks easier, and succeed at a younger age, when the memory requirements of the task are reduced (by reducing the delay or by permitting subjects to orient toward the correct hiding place during the delay).

Primate Behavior Is the Result of Multiple Cortical Functions

Infant monkeys improve on the delayed response task over the same ages (1½ to 4 months) and at the same rate as they do on the A-not-B task. Ablation of dorsolateral prefrontal cortex impairs performance on both the delayed response and the A-not-B tasks. This is true in infant monkeys lesioned at 4½ months and retested at 5 months and in adult monkeys. Ablation of posterior parietal cortex (Brodmann's area 7) or of much of the medial temporal lobe (including the hippocampus, subiculum), and much of the entorhinal and parahippocampal cortices) does not affect performance on either task if the delays are the same as those used with human infants.

Prefrontal cortex may be important for the memory of temporal order information (before and after), although it is not yet clear which region(s) within prefrontal cortex are responsible for carrying out this function. Instead of conceiving of A-not-B and delayed response as presenting the problem of holding spatial information in mind ("Was the reward hidden on the right or the left?"), one might think of these tasks as requiring the memory of temporal order information ("Where was the reward hidden last?"). All subjects perform correctly on the initial trials at the first hiding place (where temporal order information is irrelevant); it is only when the second location comes into play that errors appear in infants (humans or macaques) or in macaques (infant or adult) in whom dorsolateral prefrontal cortex has been inactivated or removed. Perhaps dorsolateral prefrontal cortex is important for holding in mind the spatial–temporal context of stimuli; or for holding relational information in general in mind (nothing is "left" or "right," "before" or "after," except in relationship to something else; if this is true then dorsolateral prefrontal cortex might also be important for holding in mind "louder," "softer," "brighter," "dimmer," etc.); or when more than one piece of information must be held in mind at the same time (a relationship, after all, consists of at least two items). Further investigation is needed to determine which, if any, of these alternative interpretations is correct.

One hypothesis, however, is that the need to hold information in mind is not in itself sufficient for a task to require activity by dorsolateral prefrontal cortex. According to this hypothesis, the task must also require the subject to inhibit an action that he or she was predisposed to make; that is, tasks that require dorsolateral prefrontal cortex involvement must require the subject to keep information in mind and to act other than is the subject's first inclination. On A-not-B and delayed response tasks, rewarding subjects for reaching toward the first hiding place may strengthen the response to reach there, in essence conditioning subjects to repeat that response. If this is true, the conditioned response must be inhibited if subjects are to succeed when the reward is hidden in a different place, where a different response is required. Evidence indicates that even when subjects appear to know where the reward is, they have trouble resisting the tendency to reach back to the old location where they found the reward previously. If this hypothesis is correct, the more times a subject is rewarded for retrieving the object at the first hiding place, the more difficult it should become for the subject to change that response when the object is hidden at the other location. There is evidence that increasing the number of reinforced trials in the first location increases the errors that infants make when the second location is rewarded. Distractibility (being pulled by irrelevent stimuli during the delay) or sensitivity to "proactive interference" (being influenced by earlier trials when it is the present trial that is relevant) can also be looked at from two viewpoints: as problems on the A-not-B and delayed response tasks and as problems in the inhibitory control of behavior. Both prefrontal cortex and motor cortex are part of the frontal cortex. All areas of frontal cortex are probably concerned with action and with the control of our actions. It is possible that maturation of the prefrontal neural system is centrally involved with the development of self-control in children and with the development of children's ability to exercise choice and control over their actions.

Language Undergoes Rapid but Prolonged Development

In humans, the prolonged structural, metabolic, and neurophysiological maturation of "association" cortical areas, which continues well into the teens, provides the substrate for the panoply of higher cognitive functions that continue to develop during this time. Attempts have been made to link the very rapid development of speech and language skills over the first 3 years of life to these general changes. In general, this goal has remained elusive, probably because so many aspects of the brain and behavior are changing to-

gether. Moreover, key elements of language appear to be processed within systems organized at the cellular and synaptic levels, where functional observations by researchers are not possible at present.

There is wide agreement that language is strongly dependent on structures within the left perisylvian region (see Chapter 58). Very early on (by 28 weeks of gestation), structural asymmetries appear between the temporal lobes; these may provide the substrate for the functional asymmetries that appear later.[4] The rapid and early acquisition of phonological information and speech production and comprehension and the subsequent vocabulary burst may be linked to the rapid rise in the number of synapses and the marked increases in cortical metabolism that occur during the second year of life. Also, the persistence of large numbers of exuberant synapses through adolescence may provide the anatomical substrate for prolonged neural plasticity and recovery of language skills following cortical damage in the first decade of life. It is well established that language skills can display considerable recovery following large lesions to the left hemisphere during the first 7–10 years of life.[50–57] The impressive recovery of language skills in children in whom the left hemisphere has been removed is even more striking in light of the enduring language impairment of specifically language-impaired children in whom macroscopic aspects of brain structure are basically normal, as discussed later in this chapter. These findings underscore the importance of characterizing microscopic structural aspects of the brain and the functional organization of the brain in relation to processing.

The prolonged time course of development that may confer plasticity on the immature brain appears to be characterized by optimal or critical periods (see Chapter 22) for language acquisition. Several studies report that both first and second language acquisitions are impaired and cerebral organization is altered when language is acquired after the first decade of life.[58–61] Moreover, as has been observed for vision, different aspects of language appear to display different critical periods. Vocabulary items can be acquired long past the first decade of life, but the grammatical rules of a language appear to be most readily acquired before the age of 10.[26,58,59,62] Along with other evidence, this pattern suggests that different neural systems, with differing developmental time courses, mediate these various aspects of language.[25,26]

Studies of changes in cerebral organization during childhood suggest that both maturational factors and individual differences in levels of language skills predict the time course of the increasing specialization of the language systems of the brain.[26,63] Additionally, when language is acquired through visual–manual modalities, as in the case of deaf individuals acquiring American Sign Language (ASL), language-relevant brain systems display similarities to those that are active during the processing of oral–aural language, leading to the conclusion that there are intrinsic constraints on language-relevant aspects of brain organization.[61] In addition, however, when ASL is acquired, significant departures from the typical pattern of cerebral organization take place. These departures allow us to evaluate the role of external input in specifying the final pattern of cerebral organization for language.

Summary

Elements of normal brain development have been summarized within this section. These include the development of the sensory systems within the first year of life and development of frontal control systems and of language late in the first year and through the second year of life.

In the future, it will be possible to analyze the neural basis of cognition in more detail, by using the new high-resolution methods for imaging brain structure and function to study normally developing children and children with specific structural or functional deficits.

ABNORMALITIES IN THE DEVELOPMENTAL PROCESS

Developmental disabilities are typically defined by performance on specific psychological tests and are frequently classified as mental disorders, distinct from other physically characterized disorders of childhood such as cerebral palsy, muscular dystrophy, spina bifida, and congenital malformations. This classification suggests that developmental or childhood disorders can be neatly divided into categories of *physical* and *mental* disability. However, this is not necessarily the case. Developmental disabilities such as mental retardation can, for example, co-occur with physical disorders such as neural tube defect. Moreover, an increasing body of research demonstrates that there are physical (e.g., neural, genetic, and biochemical) anomalies associated with specific developmental (mental) disabilities.

Research in this field employs behavioral data to make the evaluation or clinical diagnosis. The neural features of behaviorally identified subjects are then studied for differences from normal controls. In other words, developmental problems, as expressed by behavior, bring a child to clinical attention, and then

researchers work to understand the underlying organic causes of the disorder. Some day, however, specific reading disorders like dyslexia may be confirmed or even diagnosed with a magnetic resonance imaging (MRI) scan. Quite possibly, neurological diagnosis of mental disorders may alter their very definitions, which are currently primarily behavioral. For example, it may be possible to diagnose neural anomalies associated with dyslexia prior to behavioral expression of the disorder (i.e., in a child who has not yet learned to read). With current technology, however, we continue to approach developmental disabilities from the perspective of mental disorders, in hopes that we will one day understand their physical basis.

The next section addresses how behavior and cognition are measured and how "disability" is defined.

Disabilities Are Defined in Relation to Normal Function

In studying human development, it is sometimes difficult to define what is normal. Most people would agree that human beings have two arms and legs, two eyes and ears, a nose, and a mouth. When it comes to human behavior and cognition, however, defining normal becomes increasingly complicated. One way in which human behavior and intellect can be assessed is via comparison with the **norm.** That is, researchers construct a test designed to measure a certain ability or characteristic. The test is then given to large, representative groups of people of both genders and a wide range of ages. Based on this sample population data, researchers derive an average score for certain age ranges, for boys and girls, for men and women. Measures of variation or **standard deviation** from the norm, which reflect the magnitude of individual differences, are also calculated. Typically, such normative data produce a bell **curve,** or a concentrated grouping of scores around the mean, and decreasing numbers of people with scores 1, 2, or more standard deviations above or below the mean (Fig. 51.5). Using such a standard curve, researchers can compare scores for individual subjects against "what is normal." Certain criteria, such as "a score of *X* or below," can then be set to define when an individual is significantly impaired for a specific function.

Because the process of standardized testing and evaluation is critical to the study of developmental disabilities, it is important to understand that commonly used psychological tests are only as valid and useful as the degree to which the populations used in standardization represent the real-world population for whom these tests are later used. For example,

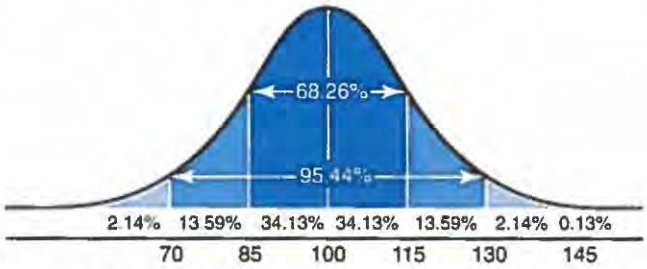

FIGURE 51.5 Intelligence tests are designed to have a mean of 100 and a normal distribution of scores around the mean with a standard deviation of 15. Each score can then be associated with a percentile, indicating the percentage of the population that would achieve that score or a score below it.

a language test standardized 25 to 50 years ago on a select sample of middle-class, Caucasian, native English-speaking children would not be representative of the current culturally diverse U.S. population. Hence, norms established for these tests could produce misleading evaluations of children from families with a low socioeconomic status or from families whose native language is not English. These issues are a source of political and educational controversy.

Efforts Are Being Made to Develop Biological Correlates of Disabilities

Recent advances in neuroimaging and gene linkage technology have vastly expanded research possibilities for noninvasive clinical studies. Even with a new arsenal of research technology, however, it has not been possible to isolate and define characteristics of each developmental disability. There are several reasons for these limitations:

1. Disagreement regarding criteria for subject selection. Because different researchers often use differing behavioral criteria, cross-study comparisons frequently show inconsistencies in results.

2. Heterogeneity of disorders. Even when consistent behavioral criteria are carefully applied, different underlying etiologies can result in the same behavioral profile.

3. Difficulties inherent to the study of children. Although modern MRI techniques are considered noninvasive, they are stressful and time-consuming, and parents will not always allow their affected children to participate in such studies. Although studies can be conducted using adults who have been affected since childhood, the data obtained from such studies may not accurately reflect anomalies that characterize early disruption of brain development, because brains change over time. Moreover, retrospective diagnoses

of childhood disorders frequently rely on memory (e.g., a patient is asked "Did you have difficulty reading as a young child?"), and hence can be unreliable.

Despite these difficulties, ongoing research has uncovered important neurological and genetic features that seem to be associated with specific developmental disorders. For instance, neurological studies have shown that developmentally disabled children do not simply exhibit focal lesions specifically in "reading" or "language" or "attention" areas of the brain, while all other systems and functions are intact. Although such localized damage can indeed occur in an older child (e.g., due to localized hemorrhage, trauma, or tumor), such neurological disorders are typically not classified as developmental disabilities. On the other hand, focal damage that occurs in the prenatal and early postnatal period, particularly during critical neural events such as neuromigration, does not remain focal. In this case, focal damage can result in developmental disability.

Although the neurophysiological basis of developmental disabilities cannot be characterized by discrete and localized lesions of specific functional areas, neural anomalies underlying specific disorders may be most evident in localized regions (e.g., atypical symmetry and cellular anomalies in left-hemisphere language regions) and may be expressed in relatively discrete cognitive deficits (e.g., reading impairment with normal oral language and nonverbal IQ). It may also be characterized by more pervasive anomalies (e.g., diffuse volumetric reductions and anomalies throughout the cerebral cortex and cerebellum) and be expressed as more pervasive behavioral deficits (e.g., autism with retardation).

In the following sections we will discuss what is known about how specific injuries or anomalies in development of the brain may result in specific patterns of cognitive and behavioral impairment. We begin by considering two specific contrasting forms of mental disability. The first is a specific language impairment that arises in development and produces a profound effect on this basic human skill. The second, Williams syndrome, spares the language system in many ways, but produces devastating losses in other forms of behavior.

Specific Language Impairment Is Defined Behaviorally

In the absence of peripheral disorders or general cognitive deficits, a child is classified as language-impaired (or dysphasic) if there is significant delay in acquiring language skills at the level predicted for his/her age.[66] Many children exhibit delays in language development, and there are many different reasons this can occur. The most common are hearing impairment or deafness, mental retardation, autism, and anomalies in development or use of the oral musculature (resulting from malformation of the vocal apparatus or paralysis of speech musculature). Severe environmental deprivation or abuse can also result in impaired language development. A diagnosis of specific language impairment (SLI) entails exclusion of all of these underlying causes for language delay and typically requires diagnosis by a team of professionals including a speech–language pathologist, psychologist, and pediatric neurologist. Only about one-third of children who exhibit language delays are ultimately diagnosed as having SLI. Some children exhibit specific difficulty in articulating the sounds of speech (e.g., lisp, stutter), but otherwise display normal language development. These children are diagnosed with speech articulation disorder, which is distinct from the cognitive disorder SLI. However, many children with SLI also exhibit concomitant speech-articulation disorders. Consequently, it is important that speech and/or language difficulties be carefully diagnosed by a speech–language pathologist.

In assessing this disorder, the diagnostician compares language scores against other cognitive measures such as nonverbal IQ, as well as motor skills and hearing levels. Specific language impairment is revealed by lowered language scores when intelligence and development otherwise fall in the normal range. By definition, SLI excludes other pervasive cognitive disorders such as mental retardation and autism that might be expected to cause depressed language scores. Children with SLI appear to be developing normally in all areas except for language.

Behavioral studies of children with SLI have demonstrated a broad range of linguistic disabilities. These children appear to exhibit difficulties with many components of language, from identifying and discriminating the building blocks that make up words (phonology), to syntactic (grammatical) and semantic (conceptual) aspects of language. Children with SLI can be divided into two groups based on a breakdown of deficits seen on standardized behavioral tests. The first group is characterized primarily by expressive (speech production) deficits with near-normal comprehension, and the second group is characterized by more pervasive language deficits affecting both expression and comprehension. Longitudinal studies have shown that outcomes are considerably better for children whose language disorders are primarily expressive than for children with both expressive and comprehension deficits.

There Are Symptomatic Biological Correlates of Specific Language Impairment

It is estimated that 7–8% of preschool children have SLI. Longitudinal studies show that a large majority of these children overcome the most noticeable aspects of preschool language delays and learn to talk. However, their disability does not disappear. Instead, it changes form, because children with SLI must use poorly established phonological systems to learn to read. Not surprisingly, children with SLI are highly likely to develop reading disabilities or dyslexia. For this reason, SLI and dyslexia are difficult to differentiate at a research level in studies of school age children, adolescents, and adults. This returns us to an issue raised earlier (see *Efforts Are Being Made to Develop Biological Correlates of Disabilities*). Specifically, neurophysiological studies of SLI reflect significant variance due to being from studies of adults screened on the basis of reading disability and unreliable retrospective reports of childhood language deficits. Variance also comes from studies that include older children with both SLI and dyslexia, as well as studies that include younger children with SLI but who *will develop* dyslexia. Finally, evidence strongly suggests the existence of persistent auditory rate processing deficits among adult dyslexics, but the difficulties inherent in retrospective clinical classification (i.e., trying to make a clinical diagnosis from childhood memories) limit the ability to determine whether adult dyslexics with auditory and phonological processing deficits also had SLI as children. For all these reasons, neuroscientists still do not know whether SLI and dyslexia are expressions of (1) different, (2) related and overlapping, or (3) identical underlying neurophysiological anomalies. At the behavioral level at least, evidence obtained from longitudinal studies strongly supports the existence of significant overlap between these two clinical populations.

There Is a Genetic Contribution to Language Impairment

One method of assessing the genetic contribution to developmental disabilities is to conduct family studies, in which evidence of the transgenerational incidence of disability is compared against known genetic models of inheritance. From such studies, SLI appears to be inherited by an autosomal dominant mechanism with full penetrance.[67,68] Other studies have examined the family history of specific individuals diagnosed with SLI, and again found an elevated incidence of SLI or related disorders among parents, siblings, and other biological relatives of the **proband**—the impaired individual bringing the family to clinical attention.[68,69] Studies of twins, for example, have demonstrated close to 100% concordance in language disability for monozygotic twins and, as expected, approximately half that for dizygotic twins.[70] Although these findings support genetic mechanisms of familial transmission of SLI, we should note that some SLI cases show no known family history of language-related disorders; thus, other factors may also be involved in the underlying etiology of SLI.

Brain Regions Can Be Abnormal in Specific Language Impairment

Studies of both receptive and expressive language impairment have focused heavily on regions of the brain known to be involved in language processing, particularly left-hemisphere regions of the temporal, parietal, and frontal cortex, such as **Wernicke's area**—a temporal cortical region involved in language comprehension—and **Broca's area**—a frontal region involved in speech perception and expressive language (see Chapter 57 for details). In most normal subjects studied, the planum temporale, which lies on the superior surface of the temporal lobe and encompasses a portion of Wernicke's area, is larger on the left side of the brain than on the right[3,4,71–73] (see also Chapter 59, Fig. 59.4). This structural difference is consistent with the left-hemisphere specialization for language processing found in behavioral studies, with neuroimaging studies, and with studies of the behavioral effects of lateralized lesions.

In one of the few studies of neuropathology underlying specific language impairment, researchers used MRI techniques to examine the cerebrum of 20 SLI and 12 matched control children. Results showed that the volume of the posterior perisylvian region (which includes the planum temporale) was reduced bilaterally in language-impaired children, most markedly in the left hemisphere. Although language-impaired children showed greater variability in the asymmetry of cortical volume for this region, the degree of asymmetry did not differ significantly between the impaired and control groups. However, asymmetries in the inferoanterior and superoposterior cerebral regions were significantly different in control and impaired children. In addition, bilateral reductions in the overall volume were found subcortically in the caudate, putamen, and diencephalic structures.

Associations between Neuropathology and Behavior Are Being Explored

The anomalies described in the preceding section provide a possible explanation for a paradox in the

field of developmental disabilities: Children with SLI appear to have relatively subtle neural anomalies, with the differences reported by Jernigan *et al.*[73a] evident only when groups of SLI and control children were compared. Examination of an individual MRI from a child with SLI generally shows nothing grossly atypical. Nevertheless, this same child can show remarkably severe behavioral deficits that are evident even to an untrained person. In contrast, another child may lose the entire left hemisphere through surgery to treat intractable epilepsy, and yet will still develop language skills in the normal range. How is it possible that subtle neurological anomalies can underlie massive behavioral deficits, when massive lesions produce relatively minor behavioral effects? One possible answer to this paradox may be found in the MRI data showing that cortical anomalies in children with SLI are bilateral; this may reduce chances for recovery via reorganization in homologous regions of the right hemisphere when left hemisphere language areas are damaged. Another explanation may involve the volumetric anomalies seen subcortically, because subcortical damage has particularly profound and lasting effects on language development. Finally, cellular evidence from postmortem analyses of dyslexic brains is discussed below. This evidence suggests that cellular anomalies not visible by MRI may exist in the brains of individuals with SLI and that such anomalies may result in subtle but dysfunctional organization of sensory neural systems critical to normal language development.

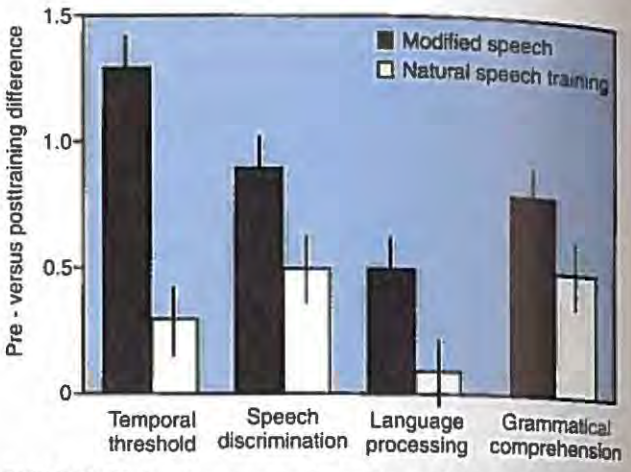

FIGURE 51.6 Human speech can be modified to lengthen or emphasize the rapid transients. Difference Z scores (posttraining minus pretraining) are shown for SLI subjects who received speech and language training with either acoustically modified or natural speech. Difference Z scores are presented for measures of temporal threshold (Tallal Repetition Test), speech discrimination (Goldman, Fristoe, Woodcock Diagnostic Auditory Discrimination Test), language processing (sentences of increasing length and grammatical complexity; Token Test for Children), and grammatical comprehension (Curtiss and Yamada Comprehensive Language Evaluation Receptive). Temporal threshold Z scores were converted to positive values for display purposes. Figure from Tallal *et al.*, 1996, *Science*, 271, p. 82. When children with specific language impairment are trained with these modified sounds (black bars), their speech discrimination and other language functions improve more than when they are trained with normal speech sounds (white bars).

Behavioral evidence supports the view that cognitive deficits in children with SLI arise from deficits in rate of neural processing for sensory information presented in rapid succession. In fact, children with SLI exhibit severe deficits in the ability to perform auditory discriminations of information that changes rapidly within a brief time window (350 ms or less). Although this deficit is profoundly evident when children with SLI are asked to discriminate speech stimuli characterized by brief and rapidly changing acoustic spectra (e.g., consonant–vowel syllables such as /ba/ and /da/), the presented material need not be linguistic for the deficit to be observed. While normal children are able to discriminate two 75-ms tones separated by as little as 8 ms, language-impaired children require an interval of at least 150 ms to perform this same discrimination.[74] Such auditory temporal processing deficits may significantly disrupt phonological processing, and consequently speech perception, leading to developmental impairment of language skills.[75]

In this regard, it is significant that training SLI children with computer-controlled acoustically modified speech leads to dramatic improvement in a number of acoustic processing and language skills. These studies were theoretically based on evidence that sensory maps in adult primate cortex are highly plastic and can be dramatically altered by intensive and adaptive sensory training, as well as on extensive research demonstrating fundamental auditory rate processing deficits in children with SLI.[75] In these training studies, Tallal and Merzenich developed a computer algorithm to alter the acoustics within speech syllables. Specifically, the rapidly successive acoustic cues that occur within speech syllables such as /ba/ and /da/, and which have been shown to be particularly difficult for children with SLI to discriminate, were artifically amplitude-enhanced and extended in time. A group of children with SLI then underwent extensive training using the modified speech. These novel computer exercises allowed children with SLI to speed up their rate of auditory processing and to improve their language abilities to more age-appropriate levels (Fig. 51.6). Ongoing results from this line of research have led to a wide availability of this therapy to children in clinics and classrooms.

Although the neurophysiological basis for deficits in processing auditory information at rapid rates has not been pinpointed, evidence strongly suggests a relationship to anomalies seen in postmortem analyses of the brains of dyslexics. Such analyses have shown cel-

lular anomalies in the cortex of dyslexics, in the form of atypical clusters of cells that have migrated improperly (specifically, ectopias and microgyric lesions). Interestingly, these anomalies are seen most often in left perisylvian (language) regions.

Anomalies have also been seen subcortically, in magnocellular regions of the lateral geniculate nucleus and medial geniculate nucleus (LGN and MGN). In the visual system, the magnocellular portion of the LGN is thought to specifically carry low-frequency, transient visual information (as opposed to high-frequency detail and color, which are transmitted in the parvocellular system). At the behavioral level, anomalies in magnocellular cells of the LGN of dyslexics are consistent with delayed neural response (as measured by evoked potential) to transient visual information.[76] More recent evidence has also shown anomalies in magnocellular cells of the MGN of dyslexics.[77] Although these latter anomalies have not been directly tied to behavior, it seems highly likely that they may relate to the deficits seen in processing transient (or rapidly changing) auditory information for individuals with SLI. Finally, these anomalies have been seen only in the postmortem brains of adults identified as dyslexic, and we do not know if they occur in individuals with SLI. Because the cortical anomalies (ectopias and microgyric lesions) are too small to be easily detected within the current limits of live neuroimaging, and because cellular anomalies in subcortical structures are also difficult to detect by MRI, we have not yet studied the brains of living children with SLI at this level. Nevertheless, data from postmortem analyses of brains from adults with dyslexia are suggestive because many children with SLI go on to develop dyslexia and because evidence shows that adults with dyslexia also exhibit the auditory rate processing deficits seen in children with SLI. Thus, it seems very likely that the neurological etiologies of dyslexia and SLI are related.

Tests with an Animal Model Suggest That Neuromigrational Anomalies and Auditory Processing Deficits Are Related

To further test the validity of a link between anomalous neurobiological development seen in dyslexics and aberrant auditory processing seen in SLI, auditory processing studies were performed on adult male rats with neuropathological anomalies like those seen in human dyslexics. Specifically, newborn rats received focal freezing lesions that resulted in microgyric cortical lesions. These rats were tested on an auditory discrimination task based on a two-tone sequence discrimination task used with control and SLI children. This task had revealed severe deficits in children with SLI for discriminating a two-tone sequence when that sequence occurred in a window of 350 ms or less.[74] In that study, control children were able to discriminate sequences that occurred in as little as 158 ms total (thus differing significantly from children with SLI). The experiment with rats showed that subjects with neocortical anomalies, like children with SLI, also exhibited significant impairments in discriminating auditory information presented at rapid rates (or conversely, within a brief time window of 350 ms or less[78]) (see Fig. 51.7). The parallel between the results of this experiment performed on rats with microgyric lesions and those of prior studies on

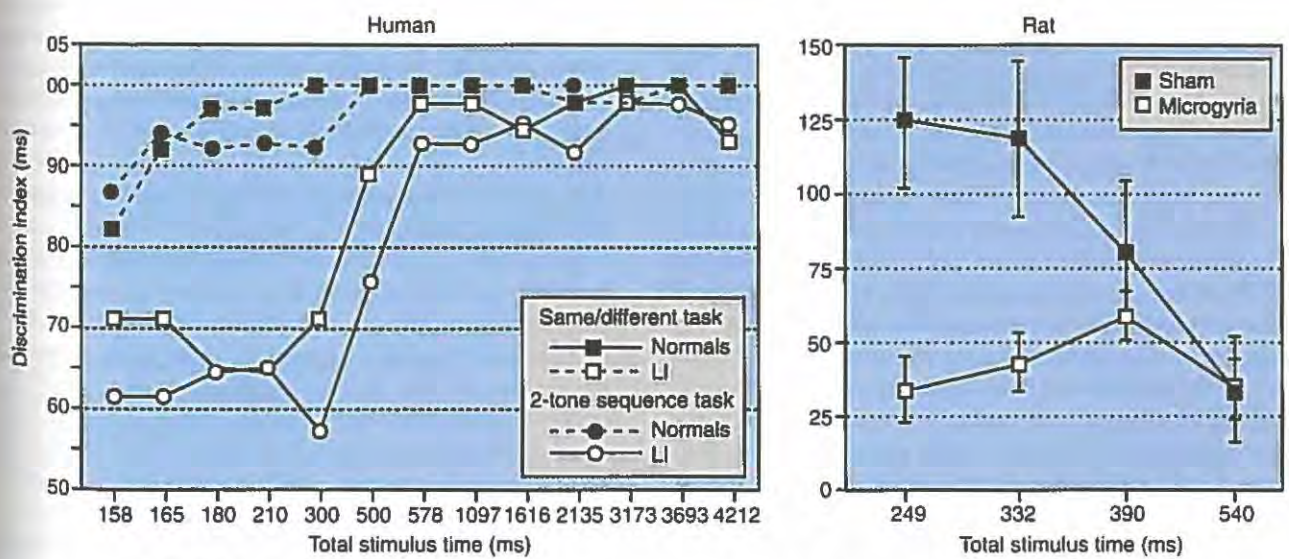

FIGURE 51.7 Left: Differences between normal and language-impaired (LI) children in their ability to report small tonal differences between tone pairs. Right: Similar differences in a rodent model.

children with SLI is compelling, and supports the view that the neuroanatomical anomalies seen in dyslexia are related to the auditory rate processing deficits seen in SLI.

These results suggested that neuropathological anomalies such as ectopias and microgyric lesions may be associated with subtle but pervasive reorganization of neural connectivity patterns. The notion of subtle but pervasive changes in the brains of language and reading impaired individuals is consistent with the fact that SLI and dyslexic individuals do not have large lesions or otherwise grossly atypical brains, but they do have profound behavioral deficits. The idea of pervasive reorganization caused by focal but cascading damage early in development (i.e., during periods of neuronal migration) is also consistent with evidence of subtle changes throughout the cortex and subcortex of these individuals, as well as the fact that sensory rate processing deficits are seen not only in the auditory but also in the visual, tactile, and motor modalities.[79-82]

In conclusion, individuals with SLI exhibit significant delays in language development and frequently display later reading disorders (or dyslexia) as well. Research has shown that both groups (SLI children and adult dyslexics) exhibit impaired or anomalous processing of rapidly changing auditory and visual information. Animal studies strongly suggest a link between the focal developmental anomalies seen in dyslexic brains and the auditory processing deficits seen in individuals with SLI. Thus, at least one theory that links behavioral and neural evidence from affected individuals is as follows. Focal cortical damage during early development (i.e., during periods of neural migration) may cause cellular anomalies in neocortex and may also adversely affect development of subcortical structures, including lateral and medial geniculate nuclei. These anomalies in critical sensory systems may be reflected in deficits in discriminating rapidly changing auditory and visual information, which in turn cause severe difficulties in understanding speech, in learning to speak, and in associating written letters with phonemic (sound) representations. Although this model is at present speculative, it provides a scenario linking high-level cognitive disorders such as language and reading impairment to pervasive deficits in neural organization and function in impaired individuals. Finally, it is worth noting the possibility that detrimental environmental factors in early development (e.g., sensory deprivation from chronic ear infections) may also produce pervasive neurophysiological changes in the brain. As with many other developmental disabilities, it appears that focal damage to the brain at the "wrong" time in early development may cause pervasive and dysfunctional reorganization of neural systems, with devastating consequences on behavioral outcome.

FIGURE 51.8 Left: Drawing of an elephant by an 18-year-old person with Williams syndrome (IQ = 49). Right: Verbal description by the same person. The figure illustrates the dramatic dissociation between spatial and language performance in this syndrome.

Williams Syndrome Is Inherited as an Autosomal Dominant and Is Associated with Characteristic Behavioral, Anatomical, and Physiological Anomalies

Williams syndrome (WS) is a relatively rare disorder, occurring in 1 in 50,000 children (an incidence of 0.002%). Behaviorally, it is characterized by severely depressed nonverbal IQ and visuospatial ability, along with paradoxical sparing of verbal fluency and grammar, an effect referred to as cognitive "fractionation." This disparity is illustrated in Fig. 51.8. Individuals with this syndrome are typically classified as mentally retarded on the basis of overall subnormal scores on intelligence tests.[84]

Physically, a child with WS is characterized by an "elfinlike" facial appearance, cardiac anomalies (including supravalvular aortic stenosis), hypercalcemia, and malformations in musculoskeletal, endocrine, and renal systems (see Bellugi *et al.*[84] or Bellugi *et al.*[85] for review). In all cases of WS examined, genetic analyses have shown a deletion on the long arm of chromosome 7, including the elastin gene.[86] WS appears to be inherited by an *autosomal dominant mode.*[87]

Morphometric analysis of the brains of individuals with WS has shown reduced cerebral volume, with

preservation in the size of the anterior cerebral and temperolimbic regions, as well as preservation of cerebellar volume.[88-90] These anomalies are consistent with the behavioral observation of spared verbal fluency, despite otherwise retarded cognitive functioning. The aberrant cerebrum–cerebellum ratio may distinguish this syndrome from other clinical disorders such as Down syndrome. Down syndrome represents another genetic disorder characterized by mental retardation, but in this case effects are pervasive (or nonspecific), with across-the-board reductions in intelligence scores. Bellugi and colleagues[84] postulate that the differing behavioral and neural profile of Down and Williams syndromes may provide a clue as to the developmental pathogenesis of these disorders. In individuals with WS, the cerebellum matures earlier than the cerebral cortex. In developmental terms, Down syndrome may be distinguished by factors that appear earlier in the developmental process and affect both cerebellum and cerebrum, while later processes selectively affecting cerebral cell populations may be characteristic of Williams syndrome. This view is supported by the results of postmortem cytoarchitectural analyses of an individual with WS. These analyses revealed evidence of aberrant neural migration, including ectopic neurons. Interestingly, such anomalies were previously described in dyslexic brains.

At the neurophysiological level, WS subjects appear to be hypersensitive to auditory stimulation and, following the presentation of tone sequences, show abnormally fast neural recovery as measured by event-related potentials. Spoken words were also found to elicit anomalous ERPs, although these differences were not seen for visually presented linguistic material. Individuals with SLI show basic auditory and visual processing deficits. Basic anomalies in sensory processing may thus affect systemic development of higher-order functions processing that sensory information. In the case of WS, hypersensitive auditory processing may actually facilitate sparing of language functions, whereas in SLI, the opposite auditory anomaly, a deficit in auditory processing, is associated with language impairment.

In Williams Syndrome Behavioral Abnormality Can Be Associated with Neuropathology

As with behavioral and neurological studies of individuals with SLI and dyslexia, we can find some association between neural and behavioral anomalies in WS. Recall that in dyslexics, cellular anomalies are seen in subcortical sensory areas critical to language development and also in cortical regions involved in language processing. MRI analyses of SLI individuals also showed volumetric reductions in cortical areas critical to language. In individuals with WS, we see a different pattern of behavioral deficits, with some verbal sparing but severely affected spatial processing. Accordingly, we see volumetric sparing of frontal and temporal cortical regions associated with language in WS, and preservation or even facilitation of auditory processing systems associated with language. Moreover, because individuals with SLI failed to show grossly atypical morphology in language-related areas of the brain, individuals with WS also fail to show grossly atypical morphology of right hemisphere regions associated with spatial processing. Instead, the mechanism underlying the expression of aberrant behavior in WS appears to be more subtle and pervasive. Indeed, postmortem analysis of the brain of a WS individual revealed cellular neuromigrational anomalies in the cortex (as seen in dyslexics), supporting the notion that early focal damage followed by pervasive and dysfunctional reorganization of neural systems is a hallmark of developmental disabilities. In the case of WS, it is not known which precise neural systems are affected, and the mechanism by which developmental changes in these system(s) are expressed in depressed spatial processing is not known. Nevertheless, this remains a fascinating area for future research, with enormous potential for understanding relationships between the development of complex neural systems and the expression of complex behavior including cognition.

Sex Hormones May Influence Neurodevelopmental Disorders

There are gender differences in the occurrence of neurodevelopmental disorders. The gender ratio of incidence is skewed toward boys for a variety of developmental disabilities, including severe mental retardation (1.3 boys/1 girl), speech and language disorders (2.6/1), learning difficulties (2.2/1), dyslexia (4.3/1), and autism (4/1). Why? Although the existence of sex differences in the area of language and learning disorders has been hotly contested on the basis that it is a result of teacher and clinician bias,[91] recent studies have supported the existence of a significant gender difference in the incidence of these disorders (e.g., see Liederman and Flannery[92]). Moreover, gender differences are also seen in clear-cut phenomena such as complications of pregnancy and birth,[93] where they cannot be

easily explained as a reflection of investigator or clinician bias.

One theory to account for this phenomenon is that male but not female fetuses invoke a form of "antigenic" response from the mother during pregnancy, being recognized by the immune system as "foreign." The hostile environment thus created for the male fetus *in utero* would explain not only a higher incidence of developmental disorder among boys but also the finding that later-born sons are increasingly likely to be adversely affected (consistent with increased immune responsiveness on repeated exposure).[93]

Another theory to account for uneven gender ratios in developmental disorders was put forth by Galaburda and co-workers.[94] These researchers reviewed a vast literature on the relations among hormonal exposure, gender, cerebral laterality, immune disorder, and developmental disorders. They concluded that exposure to some "male factor" (possibly androgen) during the last trimester of fetal development acts to slow cortical maturation in male fetuses, particularly in the left hemisphere, rendering them more susceptible to perturbation from the normal course of development. This exposure would explain the higher incidence of developmental disorders among boys. Conversely, faster CNS development in female fetuses would enable them to better withstand insult during late pregnancy and birth. This assertion is supported by evidence that female infants appear to show better cognitive recovery than male infants from intracranial hemorrhage resulting from prematurity. Such an assertion is also consistent with recently published data showing that induced microgyric lesions do not lead to anomalies in cell structure of the medial geniculate nucleus or to auditory rate processing deficits in female rats, although severe effects are seen in males.[95]

The Geschwind theory, as it came to be known, is generally consistent with evidence of sex differences in cerebral organization, particularly for language. For example, women exhibit significantly better verbal recovery after focal left hemisphere damage (via tumor, stroke, etc.) compared to men, and significantly less functional lateralization for processing verbal material (see Kimura and Harshman[96]). Studies have also revealed sex differences in the pattern of cerebral blood flow during the performance of verbal tasks, in asymmetry as measured by functional MRI during verbal tasks,[97] and in structural asymmetry, as measured by size of the right and left plenum temporale of men and women.[72] These results all point to sex differences in the pattern of cerebral organization of language (and language-related functions), particularly with regard to the degree of left-hemisphere specialization for language.

In summary, evidence supports the existence of sex differences in brain development and organization. These differences may in turn affect the response of the brain to injury as a function of sex, and hence be reflected in differing numbers of boys and girls affected by developmental disability.

Summary

In this section we have examined two forms of developmental abnormalities, SLI and WS. In both cases it has been possible to link the behavioral manifestations of the disorder to anomalies in neurobiological systems. In both cases, too, there appears to be a genetic component. In both SLI and WS, affected individuals do not show localized damage in circumscribed brain regions, but show evidence of cellular disturbance early in brain development (i.e., during neuromigration), which has given rise to pervasive and dysfunctional reorganization of critical neural systems underlying complex behaviors. Evidence suggests that this phenomenon may characterize other developmental disabilities, including autism, retardation, and attention deficit disorder.

In the case of specific language impairment, training based on neurological findings has shown some success in remediating the deficit. The success of this approach shows the subtle interplay of nature and nurture in fostering healthy development.

NORMAL AGING OF THE BRAIN

People born in the United States in 1900 could expect to live an average of only 50 years. Advances in health care and preventative medicine in the intervening years have led to dramatic increases in life expectancy, and current estimates suggest that mean life span in most industrialized countries will exceed 80 years early in the next century. A substantial segment of the population can expect to enjoy the benefits of increased longevity while remaining free of dementing illness and other debilitating disease. The process of normal aging is not always benign, however, and many otherwise healthy aged individuals experience declining cognitive function that substantially compromises the quality of later life. Because of these demographic trends, substantial efforts have been made to identify changes in the structure and function of the brain that might account for the cognitive deficits associated with

normal aging. Modern experimental approaches and analytic strategies, once a large descriptive enterprise, have opened new horizons for exploring the neurobiology of normal brain aging. In the process, many of our most entrenched assumptions about the effects of aging have been called into question.

Memory Serves as a Model Neuropsychological Framework for Exploring Normal Brain Aging

As discussed in Chapter 56, memory is not a unitary function, but encompasses a variety of dissociable processes mediated by distinct brain systems. Explicit or declarative memory refers to the conscious recollection of facts and events and is known to depend critically on a system of anatomically related structures in the medial temporal lobe, including the hippocampal formation and adjacent cortical regions. Although many important details about the cognitive structure and neurobiological organization of multiple memory systems remain to be clarified, information already available has guided research on the neural basis of age-related cognitive decline and provides a useful framework for reviewing current perspectives on normal brain aging.

Brain Structure Is Preserved in Normal Aging

Traditionally, moderate neuron death, distributed diffusely across multiple brain regions, was assumed to be an inevitable consequence of normal aging. Seminal studies conducted by Brody[98] provided support for this view, by indicating that neuron loss occurs throughout life, with more than 50% loss of cells in many neocortical areas by age 95[98] (see Brody[99] for historical review). While not all regions of the brain seemed to be affected to the same degree, significant age-related neuron loss was reported in every region examined, including both primary sensory and association areas of cortex. Thus, the concept emerged from early observations that diffusely distributed neuron death might account for many of the cognitive deficits associated with normal aging (reviewed in Coleman and Flood[100]).

Advances in Stereology Show That the Number of Cortical Neurons Is Largely Preserved during Normal Aging

Improved methods for quantifying cell number have led to a significant revision in traditional views on age-related neuron loss (see West[101] for a detailed discussion). Until recently, most investigators had focused their attention primarily on neuron density, defined as the number of neurons present in a fixed area or volume of tissue. Neuron density is measured experimentally by counting the number of neurons in a fixed volume of tissue within a brain region of interest. Typically, this is accomplished using standard histological staining procedures to visualize cells microscopically, and counting stained profiles of cell bodies, nuclei, or nucleoli, either manually or with automated image detection routines. A significant limitation of this approach, however, is that density can vary widely in the absence of any difference in cell number. For example, assume that the total numbers of neurons are identical in a region of interest in two brains, but that the sizes of the brains differ due to gliosis, white matter abnormalities, or other neuropil alterations. Under these conditions, average neuron density will necessarily be lower in a fixed volume of the larger brain. Therefore, volumetric differences between young and aged brains (either real or as an artifact of differential shrinkage during histological processing) could substantially influence measures of cell density in the absence of any actual loss of neurons. Other limitations of traditional cell counting methods have also been recognized (see West[101] for a recent discussion).

In contrast to measures of cell density, new methods in stereology are specifically designed to estimate total neuron number in a brain region of interest, providing an unequivocal measure for examining potential neuron loss during normal aging (see Box 51.1). Modern stereological tools have been widely used in recent years to reexamine neuron number in the aged hippocampus. In addition to the known importance of this structure for normal explicit memory, early studies based on cell density measurements suggested that the hippocampus is especially susceptible to age-related cell death and that this effect is most pronounced among aged subjects with documented deficits in hippocampal-dependent learning and memory.[102,103] The surprising outcome of investigations using newer stereological methods was that the total number of principal neurons (i.e., the granule cells of the dentate gyrus and pyramidal neurons in fields CA2, CA3, and CA1) is entirely preserved in the aged hippocampus. Similar results have been observed in all species examined, including rats, monkeys, and humans.[104–107] Data from animal models of cognitive aging have been particularly compelling, demonstrating that hippocampal neuron number remains normal even among aged individuals with pronounced learning and memory deficits indicative of hippocampal dysfunction[104–106]

BOX 51.1

THE OPTICAL FRACTIONATOR STEREOLOGICAL METHOD

Figure 51.9 shows the key features of a new stereological technique designed to provide accurate and efficient estimates of total neuron number in a brain region of interest. The hippocampal formation of the rhesus monkey brain is used as an example. The method consists of counting the number of neurons in a known and representative fraction of a neuroanatomically defined structure in such a way that each cell has an equal probability of being counted. The sum of the neurons counted, multiplied by the reciprocal of the fraction of the structure that was sampled, provides an estimate of total neuron number.

Serial histological sections are prepared through the entire rostrocaudal extent of the hippocampus and stained by routine methods for visualizing neurons microscopically. An evenly spaced series of the sections is then chosen for analysis (schematically represented by dotted lines at top left). This first level of sampling, the "section fraction," is therefore defined as the fraction of the total number of sections examined. For example, if every tenth section through the hippocampus is analyzed, the section fraction equals 1/10.

The appropriate sections are then surveyed according to a systematic sampling scheme, typically carried out

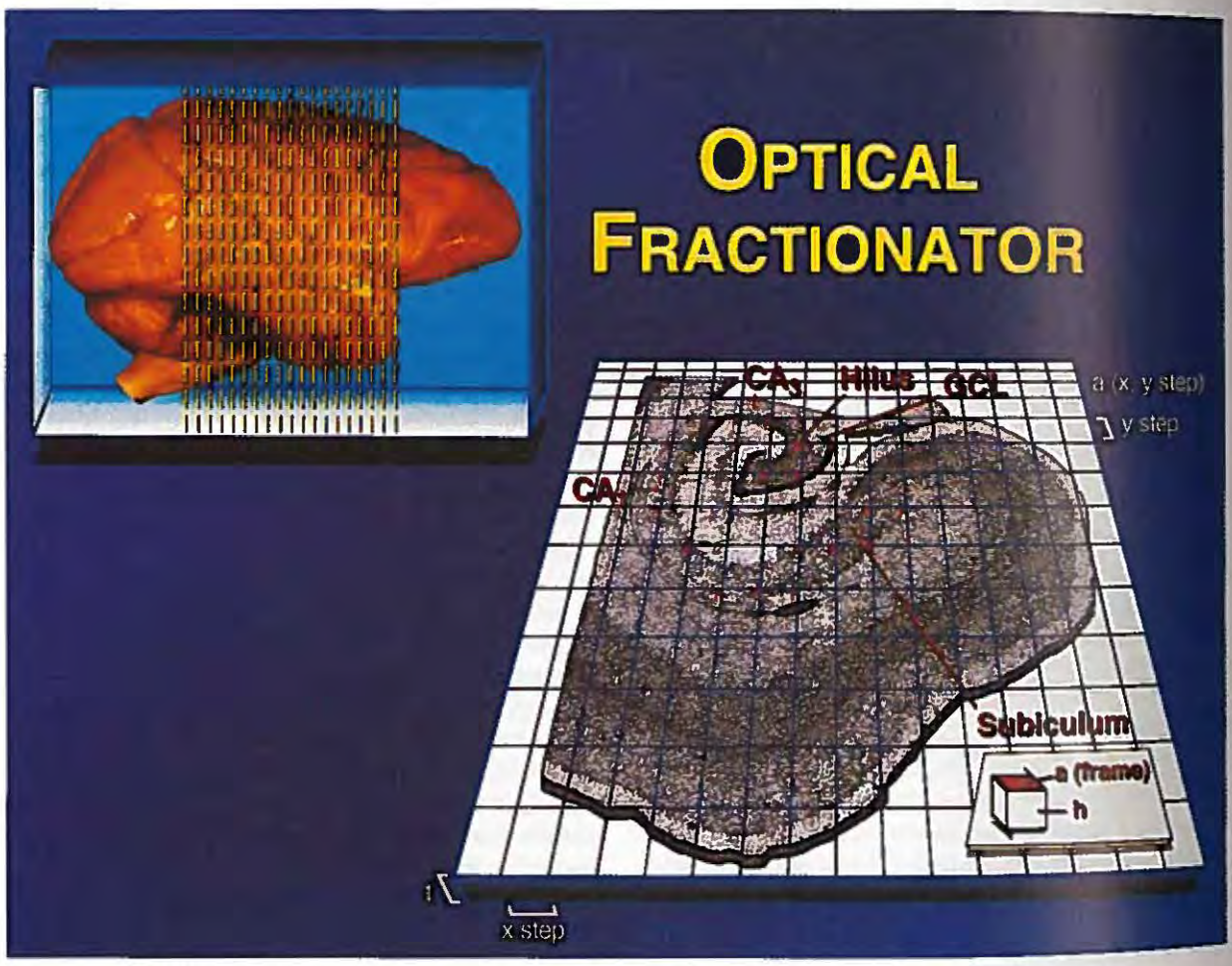

FIGURE 51.9 Illustration of optical fractionator. Original illustration design by P. R. Rapp and J. P. Stanisic.

on a microscope with a motorized, computer-controlled stage. The lower right panel illustrates this design in which the microscope stage is moved in even X and Y intervals, and neurons are counted within the areas defined by the small red squares. The second level of the fractionator sampling scheme is therefore the "area fraction," or the fraction of the XY step (XY_{area}) from which the cell counts are derived ("a" in the inset).

The last level of sampling is counting cells only within a known fraction of the total section thickness, avoiding a variety of known errors introduced by including the cut surfaces of the histological preparations in the analysis. This is accomplished using a high-magnification microscope objective (usually 100×) with a shallow focal depth. In the illustration provided, the "thickness fraction" is defined as h/t. Neurons are counted as they first come into focus, according to an unbiased counting rule, called the "optical disector," that eliminates the possibility of counting a given cell more than once.

Finally, the total neuron number in the region of interest (N) is estimated as the sum of the neurons counted (ΣQ^-), multiplied by the reciprocal of the three sampling fractions; the "section fraction," "area fraction," and the "thickness fraction." For the present example, total estimated neuron number is given by the formula

$$N = (\Sigma Q^-) \cdot (10/1) \cdot (XY_{area}/a) \cdot (t/h).$$

(Fig. 51.10). In a recent experiment, for example, young and aged rats were tested on a spatial learning task that is known to require the functional integrity of the hippocampus. As illustrated in Fig. 51.10, subsequent stereological analysis revealed that the numbers of principal hippocampal neurons were comparable in young subjects and in aged rats with or without spatial learning and memory deficits. These findings indicate that hippocampal neuron loss is not inevitable, as was traditionally assumed, and that neuron death in the hippocampus fails to account for age-related learning and memory impairment.

Age-Related Neuron Loss Preferentially Targets Subcortical Brain Systems

Quantitative data relating neuron number and aging are not yet available for all brain systems. Nevertheless, like the hippocampus, a variety of other cortical regions also appear to be relatively spared from significant age-related neuron loss. These regions include the dorsolateral aspects of the prefrontal cortex and unimodal visual areas. Aging does result in substantial *subcortical* cell loss, however, particularly among neurochemically specific classes of neurons that send ascending projections to widespread cortical regions. The loss of cholinergic neurons in the basal forebrain has been studied intensively because this system is the site of profound degeneration in pathological disorders of aging such as Alzheimer disease.[108] A smaller loss of these acetylcholine-containing neurons, affecting cell groups that project to the hippocampus, amygdala, and neocortex, is also observed during normal aging.[109–112] Cholinergic cell loss might disrupt the information-processing functions of these target regions, and significant correlations between the magnitude of loss and behavioral impairment have been documented in aged individuals.[111] Although cholinergic abnormalities alone are unlikely to account for the full profile of age-related cognitive decline,[113,114] combined with changes in other neurochemically specific projection systems,[115,116] subcortical contributions to normal cognitive aging may be substantial. These findings also highlight the concept that neuron loss during normal aging preferentially affects subcortical brain structures. Defining the cell biological mechanisms that confer this regionally selective vulnerability or protection remains a significant challenge.

Electrophysiological Markers Correlate with Functional Alteration in the Aged Hippocampus

To complement research on the structural integrity of the aged brain, physiological studies in rodent models have looked for changes in the functional and computational properties of neurons that might contribute to cognitive decline. These studies have focused prominently on the hippocampus, because of the known role of this structure in normal learning and memory and because forms of memory dependent on the hippocampus are frequently compromised during normal aging. In addition, cellular models of learning-related plasticity [e.g., long-term potentiation (LTP)] have been particularly well characterized in the hippocampus, so that there is a useful background against which to examine the effects of aging (see Chapter 55 for a discussion of LTP). A prominent theme emerging from this area of research is that age-related changes in hippocampal physiology are highly selective. Significant parameters generally unaffected by aging include the resting potential, input resistance, and the amplitude

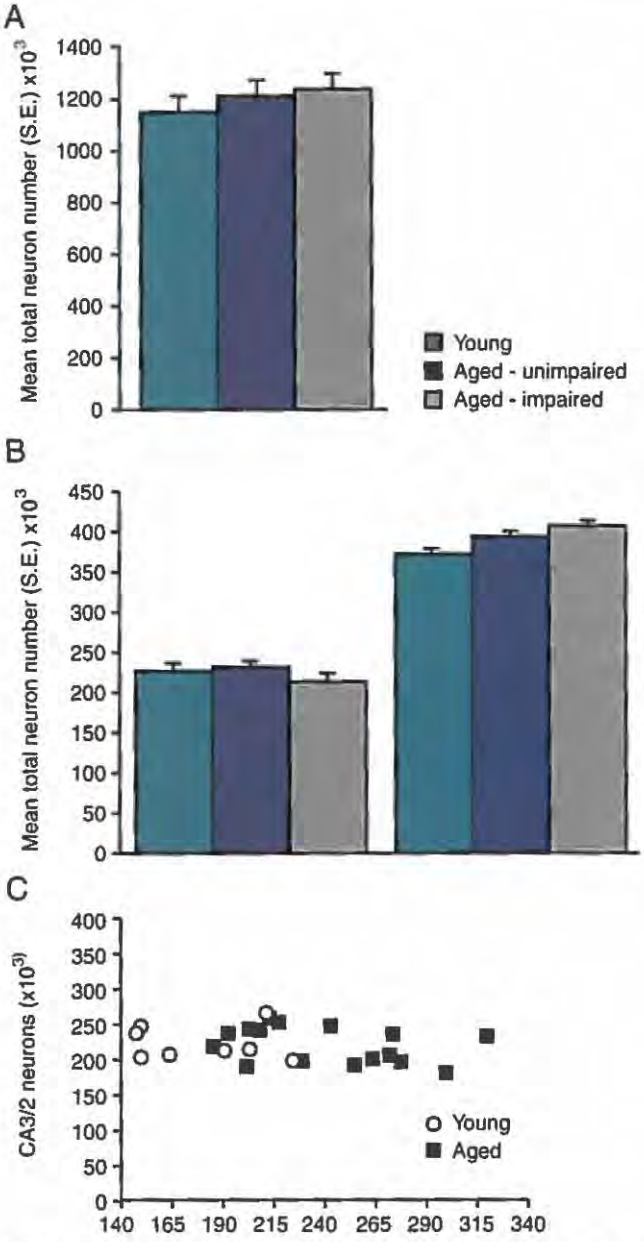

FIGURE 51.10 Estimated total neuron number in the principal cell layers of the hippocampus for behaviorally characterized young and aged rats. The total neuron number values illustrated are for one hippocampus from each brain. Prior to histological evaluation, subjects were tested on the spatial, hippocampal-dependent version of the Morris water maze. Half of the aged rats exhibited substantial learning deficits (aged-impaired); the other half performed within the range of learning scores for the young group (aged-unimpaired). (A) Mean estimated total neuron number (±standard error) in the granule cell layer for young, aged-unimpaired, and aged-impaired rats. Average granule cell number is comparable across the groups. (B) Mean estimated total neuron number (±SE) in the CA3/2 (left) and CA1 (right) pyramidal cell fields of the hippocampus for behaviorally characterized young and aged rats. Neuron number does not differ with age or cognitive status. (C) Scatter plot of total neuron number in the CA3/2 hippocampal field for individual rats plotted as a function of spatial learning scores (lower values indicate better learning). Neuron number is stable with age and across a broad range of learning capacities. Adapted from Rapp and Gallagher.[104]

and duration of evoked action potentials among principal hippocampal neurons (reviewed in Barnes,[117] Barnes *et al.*[118]).

Although many functions of the hippocampus are preserved, several aspects of its physiology and plasticity are compromised. For example, although the stimulus intensity necessary to induce maximal LTP is comparable in the young and aged hippocampus, and while the peak magnitude of the potentiated response remains normal, LTP decays to prepotentiated baseline levels more rapidly in aged subjects. This enhanced rate of decay is significantly correlated with the rapid forgetting that aged subjects exhibit on a test of spatial memory requiring the functional integrity of the hippocampus.[119] The aged hippocampus also shows alterations in location-specific firing[120,121] and abnormally inflexible coding of the relationships between task-relevant stimuli.[122]

Thus, although many aspects of hippocampal physiology are preserved, the functional organization of the hippocampus is substantially altered during normal aging. Future study is needed to determine whether these features of hippocampal aging originate intrinsically or occur as a result of disrupted information processing in other brain systems that project to the hippocampus. Research focusing on the connectional characteristics of the hippocampus provide a basis for addressing this issue.

Hippocampal Connectivity Is Prominently Affected during Normal Aging

The entorhinal cortex originates a major source of cortical input to the hippocampus, projecting via the perforant path to synapse on the distal dendrites of the dentate gyrus granule cells, in outer portions of the molecular layer. Proximal dendrites of the granule cells, in contrast, receive an intrinsic hippocampal input arising from neurons in the hilar region of the dentate gyrus. This strict laminar segregation, where there are two nonoverlapping inputs of known origin, provides a useful model for exploring potential age-related changes in hippocampal connectivity. Ultrastructural studies have demonstrated that the number of a morphologically distinct subset of synapses is depleted in both inner and outer portions of the molecular layer during aging in the rat.[123] Importantly, the magnitude of this loss in the termination zone of the entorhi-

nal cortex is greatest among aged subjects with documented deficits on tasks sensitive to hippocampal damage and in older animals that display impaired LTP and deficits in other physiological measures of hippocampal cellular plasticity.[124]

The same circuitry has been examined in the aged monkey using confocal laser microscopy to quantify the density of different glutamate receptor subtypes in the molecular layer.[125] Aged subjects display a substantial reduction in labeling for the NMDA receptor subtype, and this effect is anatomically restricted to outer portions of the molecular layer that receive entorhinal cortical input. The density of non-NMDA glutamate receptors is largely preserved. Although the relationship of this change to the status of hippocampal information processing has not been directly evaluated, these findings are potentially significant because NMDA receptor activity is known to play a critical role in mechanisms of plasticity that are thought to constitute the cellular basis of learning and memory. This background leads to the testable prediction that the magnitude of NMDA receptor alteration in aged individuals might correlate with the degree of age-related impairment in learning and memory supported by the hippocampus. Studies of this sort, combining behavioral and neurobiological assessment in the same subjects, are an increasingly prominent focus of research on normal aging.

Summary

The traditional view of normal brain aging is that cognitive decline is a consequence of mild and diffusely distributed neuron death. Recent evidence demonstrates that neuron loss is more anatomically selective and smaller in magnitude than previously assumed, and many cortical regions implicated in normal cognitive function display little or no significant neuron loss during aging. Prominent cell death occurs among a number of neurochemically specific subcortical systems, however, and information processing in cortical target regions could be substantially compromised as a consequence. Electrophysiological investigations confirm that neuronal coding and plasticity are altered in the aged hippocampus, and in some cases, these changes are tightly coupled to behavioral measures of hippocampal function. Although the neurobiological basis of these effects remains to be defined in detail, alterations in the normal connectivity of memory-related brain systems are likely to play a significant role.

We now have a solid foundation of descriptive information on the nature, severity, and distribution of neural alterations in the aged brain. The fundamental mechanisms responsible for the known behavioral and neurobiological signatures of normal aging, however, remain to be defined. Molecular biological techniques are revealing an increasingly broad profile of age-related changes with significant implications for cell structure and function.[126] Although it has sometimes proved challenging to incorporate these findings within a neural systems analysis, molecular, neurobiological, and behavioral approaches may soon converge on a more unified understanding of normal cognitive aging.

DEMENTIAS: PATHOLOGIES OF AGING

Dementia is a general term used to describe a chronic and substantial decline in two or more areas of cognitive function. This decline is in contrast to amnesia or aphasia, for example, where a patient shows a severe and striking deficit in only one area of function (memory and language, respectively). Approximately 50 disorders are known to cause dementia.[127] Most dementias are progressive, but some dementias are nonprogressive (e.g., alcoholic dementia).

The onset and progression of the patient's difficulties differ greatly among the major dementing disorders. Most of the dementias have an insidious onset and develop slowly and gradually; these include Alzheimer disease, Huntington disease, and frontotemporal dementia. The most virulent dementing disorder, Creutzfeldt–Jakob disease, develops insidiously, but is known for its rapid rate of progression from onset to death (often only 1 year). In vascular dementia, the initial symptoms develop acutely, but because multiple cerebral infarcts (large or small) are the cause of the cognitive decline, the ultimate clinical picture can take many years to develop, in a stepwise and stuttering fashion. The pattern of spared and impaired function in the early stages of each disorder is directly related to the neuropathological abnormalities that underlie it.

Alzheimer Disease Is the Most Widely Occurring and Widely Studied Form of Dementia

First described in 1907 by Alois Alzheimer, Alzheimer disease was originally thought to be a rare disorder affecting only people in the presenile age range (i.e., under the age of 65). It is now recognized as the most common cause of dementia, and alone is responsible for about 50% of all dementias; an additional 15–20% of dementias have combined Alzheimer and vascular pathology. The prevalence of the disease is directly

related to age. It can occur in the fourth decade of life but is extraordinarily rare at this age. The prevalence then increases logarithmically with each succeeding decade, and over the age of 85 at least 1 person in 4 is afflicted.[128] Because persons over 85 form the most rapidly growing portion of the population, Alzheimer disease represents a major health problem.

The pathological hallmarks of Alzheimer disease are the senile plaques and neurofibrillary tangles that Alzheimer first reported. Senile plaques are spherical and usually many times larger than a single neuron. They typically contain a central core of amyloid surrounded by degenerating neuronal processes. Neurofibrillary tangles are twisted abnormal filaments composed of the protein tau and other cytoskeletal proteins. The accumulation of plaques and tangles, and the progression of other pathological processes, leads to extensive neuronal loss, which is usually preceded by synapse loss.

In the early stages of disease, pathological changes are most evident in the perforant pathway of the hippocampal formation.[129] For example, in mildly impaired patients, layers 2 and 4 of the entorhinal cortex have a 60 and 40% loss of neurons, respectively.[130] These losses are entirely consistent with the fact that a memory problem, consisting of difficulty retaining new information over brief delays, is the most common symptom in mildly impaired patients. Problems with planning and set shifting (i.e., difficulties with "executive function" abilities) also occur early in the course of disease. This situation may be the result of the loss of neocortical synapses and long cortico–cortical projection systems[131] seen in Alzheimer disease; the partial degeneration of an intracortical projection system could produce difficulties in tasks that require the rapid and simultaneous integration of multiple types of information.

Following neuronal loss in specific cortical and subcortical regions, a number of neurochemical abnormalities become evident in Alzheimer disease. These abnormalities are related to the cholinergic system, the noradrenergic system, and the serotonergic system and arise from loss of cells in the basal forebrain, the locus coeruleus, and the dorsal raphe nucleus, respectively. As these abnormalities accumulate and spread throughout the brain, the patient shows increasing difficulty with cognitive function and ultimately a loss of all major cognitive abilities, including memory, language, spatial ability, and executive function.

Genetics Plays a Role in Alzheimer Disease

Genetics plays an important but complex role in the development of Alzheimer disease. To date, four genes have been associated with the development of the disease (Fig. 51.11). Three of these (on chromosomes 21, 14, and 1[132-134]) pertain to the development of early-onset AD (onset prior to age 60 or 65). Each of these three early-onset genes acts as a dominant, causative gene. Only one gene, the apolipoprotein E gene (*APOE*, on chromosome 19), has been associated primarily with the much more common late-onset form of Alzheimer disease (onset after age 60 to 65).[135,136] The apolipoprotein E gene has three alleles, designated 2, 3, and 4. Allele 4 has been shown in numerous studies to be associated with Alzheimer disease. The general consensus is that *APOE4* is acting as a risk factor for Alzheimer disease, rather than as an etiologic gene, and that several more genes related to the development of Alzheimer disease will be identified.

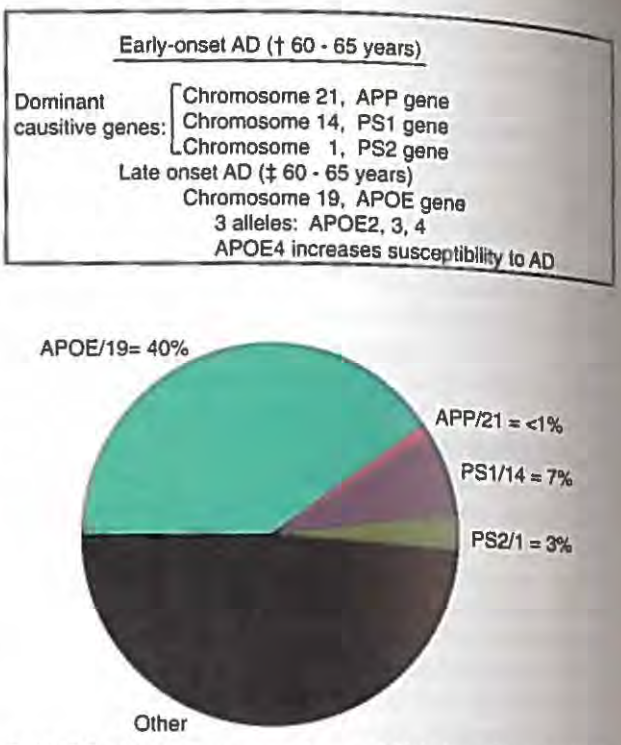

FIGURE 51.11 Percentage of cases of Alzheimer disease in which a specific genetic abnormality is implicated.

Important clues to the cellular and molecular basis of Alzheimer disease are being provided by genetic, pathological, and biochemical studies. Currently, various lines of evidence point to an important role for amyloid precursor protein (β-APP), the precursor of the β-amyloid in senile plaques. It is possible that the β-amyloid protein is directly responsible for the abnormal accumulation of the fibrillar material that kills neurons, or conversely that β-amyloid is important in protecting neurons from the accumulated effects of injury (as a result of aging, environmental insults, etc.).

Summary

This chapter has examined efforts to relate development over the life span to changes in the nervous system. In early development, profound changes in sensory systems, frontal areas, and language areas underlie many new achievements of the infant. These functions are clearly subject to developmental pathologies that may delay the emergence of complex functions such as language and organization rather than the number of neurons in many brain areas. Changes in the hippocampus may underlie difficulties in memory in normal aging. In pathologies such as Alzheimer disease, more profound changes in behavior emerge, probably first due to damage to the temporal lobe, but later throughout the cortex. These findings all indicate the relation between specific brain changes and differences found in development.

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