EIGHTEEN

Neural Correlates of Early Language Learning

Barbara Clancy and Barbara Finlay

The course of language development is exceedingly complex, characterized by massive variability across children and by multiple bursts and plateaus within individual children. This complexity is well illustrated in other chapters in this reader and in an extensive review from which this chapter is excerpted (Bates et al., in press). Learning plays an extremely important role throughout the development of language, beginning even in utero when children start to pick up language-specific preferences. Across development, language can be "tuned" in various directions depending on the nature of the input. This is not the original view of language development. Language milestones were previously believed to timed by a "biological clock" that also governed motor milestones like crawling and walking (Lenneberg, 1967). However, this notion of lockstep development (based on average onset times across different samples of children) implies a set of correlations that should hold up within individual children as well.

Doubts about such a lockstep process were raised when Bates et al. (1979) looked for such correlations in their longitudinal study of language and communication in a sample of healthy, normal children aged 9–13 months. They found no significant links between motor and language milestones, and, if anything, the non-significant correlation between walking and talking seemed to run in the wrong direction, as if there were a slight tendency for children to make some kind of choice about where to invest their energies among the various skills that are starting to emerge around this time. And yet we know that the nervous system continues to develop after birth in our species. Surely it ought to be possible to find neural correlates (and perhaps neural causes?) for the dramatic changes that characterize language development in the first few years of human life.

During a previous search for such correlates (Bates et al., 1992), two candidates appeared promising. First, the period between 8 and 10 months is a behavioral watershed, characterized by marked changes and reorganizations in many different domains including speech perception and production, memory and categorization, imitation, joint reference and intentional communication, and of course word comprehension. It seemed plausible that this set of changes (which *are* correlated within individual children) might be related to patterns of connectivity and brain metabolism. Second, the

period between 16 and 30 months encases a series of sharp nonlinear increases in expressive language, including exponential increases in both vocabulary and grammar. A link seemed possible between this series of behavioral bursts and a marked increase in synaptic density and brain metabolism that was estimated to take place around the same time.

However, the search for neural correlates of language learning has turned out to be vastly more complex than previously thought. Although brain maturation undoubtedly plays a role in language learning, we now are somewhat wary of summaries or tables that imply any simple form of cause and effect. There are three main reasons for this new skepticism.

First, it has become increasingly clear that learning itself plays a massive role in language development. Of course this has to be true in some trivial sense, because we know that English children learn English and Chinese children learn Chinese. However, there has been a long tradition of suspicion about learning in the child language literature, because language development is characterized by so many funny-looking events, including long plateaus interrupted by exponential shifts, with occasional steps backward. These nonlinearities led many investigators to underplay the role of "garden-variety" learning in favor of a maturational view in which discontinuities at the behavioral level were caused by discontinuities in the nervous system (Pinker, 1994; Wexler, 1996). As it turns out, that simply isn't true. Artificial neural networks (Elman et al., 1996) have shown us that simple structures can be very good at learning, even simulating in considerable detail many of the discontinuities that characterize language development. Moreover, in "real life," we now have compelling evidence that even very young infants are capable of rapid and powerful forms of statistical learning (e.g., Bates & Elman, 1996; Elman & Bates, 1997; Saffran et al., 1996).

Second, we know much more than we used to know about human brain development, before and after birth. Some years ago, it seemed plausible that prenatal development was characterized primarily by *additive* events (e.g., neural tube formation, cell proliferation, the first wave of connectivity). Postnatal development seemed to be characterized primarily by *regressive* events (e.g., cell death, axon pruning) perhaps occurring under the guidance of experience. We now know it's not that easy – certainly it does not happen in any simple two-stage form. In fact, the picture of human brain development that we present here is one that is quite compatible with the burgeoning literature on early (even prenatal) learning, because so many of the events required to create a learning machine take place within the first two trimesters of prenatal human life. Everything that happens after that is really a matter of degree – maturational changes at every level of the system, in multiple overlapping gradients. There is little evidence for the old-fashioned notion of modular brain systems that "turn on" at a particular time, like successive levels in a computer game.

Third, it has become increasingly clear that the relationship between brain development and behavior is bi-directional. Although that was understood some years ago (Bates et al., 1992 underscored the role of experience in subtractive events, yielding the metaphor of experience as a sculptor working away in the studio of life), recent advances in developmental neurobiology have shown that the bi-directional dance between brain development and experience occurs at many more levels of the system, including additive events throughout the lifetime of the organism (Kempermann et al., 1998; Kornack & Rakic, 1999). Even in adulthood, learning induces striking new morphological changes in brain regions related to a new task (Kleim et al., 1996; Kleim et al., 1997). As a result of all this new information, we can no longer assume that correlated changes in brain and behavior reflect a causal flow in one direction. It could just as easily be the other way around.

With these lessons in mind, we will attempt to replace the conventional notion of a lock-step version of language milestones and neural development, replacing it with a more dynamic, challenging, and ultimately more hopeful story. We are now able to offer support for a complex neural/language relationship that is actually quite forgiving in its very complexity. Dynamics of neural interactions, gradients, and overlapping events impart flexibility and plasticity, underscoring the value of remedial strategies and intervention training.

Here we will provide an overview of basic events in human brain development that precede, prepare, parallel, and (perhaps) participate in the language-learning process (for a comprehensive review of the literature on the language learning process and more detail on neural development, see the chapter from which this section is excerpted, Bates et al., in press). We will review neural events globally rather than concentrating on those areas conventionally viewed as "language areas" in the adult. In fact, it is more accurate to think of language acquisition and production as an interactive process involving auditory, visual, somatosensory, motor, memory, emotional, and associative functions.

First we will briefly review some basic neural terminology. Our discussion focuses primarily, but not exclusively on the brain region called the *isocortex* (a synonym for *neocortex* that neuroanatomists prefer because it does not make false assumptions about how "new" in phylogeny the cortex is). This is the convoluted sheet of layered neurons that appears on surface views of the brain (gray matter). Visual, somatic, language, all sensory/motor processing is accomplished here, associated with input relayed via the *thalamus*. The thalamus is a subcortical "relay-station" that transmits virtually all sensory input from the body surface and special sense organs (except olfaction) to the isocortex. Even during development, the thalamus maintains the "packaging" that separates one kind of input from another (e.g., visual, auditory, somatosensory). We will also briefly discuss the *limbic* system, a circuit of widely distributed neural structures that includes the hippocampal formation (associated with memory and spatial learning) as well as neural regions associated with olfaction and emotion.

On a basic level, these and all neural regions are made up of two types of cells, *neurons* (or nerve cells) and *glial* cells. A typical neuron has three divisions: a cell body (*soma*), an *axon*, which transmits chemoelectrical signals, and several branch-like *dendrites* that contain *receptors*, the receiving units of the neuron. Small currents of positively or negatively charged chemical ions cause a signal (or action potential) to travel down an axon. Glial cells are supporting cells for neurons. Some form white fatty sheaths, *myelin* (white matter), which insulate axons and so increase the speed and efficiency with which the signals can be transmitted. Chemical data (neurotransmitters or neuromodulators) are passed between cells at a gap where an axon from one cell almost, but not quite, meets a dendrite or cell body of another neuron. This point is called a *synapse*. Information transfer, or *synaptic transmission*, occurs when chemicals stored in a signaling neuron are released across the synapse onto receptors of another

neuron. On some neurons, especially during development, the gap is even smaller than normal and the transmitting and receiving cells are almost contiguous. These points are called *gap junctions* or *electrical* synapses. Neural cells are formed in a process called *neurogenesis*, while the formation of the connections between neurons is called *synaptogenesis*. These types of formative events are considered additive events. The elimination of cells, axons, or synapses are considered regressive events.

With these definitions in hand, we will now address our attention to three main topics.

1. *Prenatal neural events: fundamental brain scaffolding*: What is the state of the brain at or before birth when language learning begins?
2. *Postnatal neural events*: What types of neurodevelopmental events take place after birth and across the period in which languages are learned?
3. *Interactions of neural patterns and events with language learning*: Do any neurodevelopmental events seem placed or ordered in such a way as to constrain when events in language learning might occur? Alternately, does language learning itself alter the course of brain development?

Prenatal Events: Fundamental Brain Scaffolding

Fixing the timing of events

There are no experimental studies directly relating language and cognitive development to brain maturation, and there are only a handful of studies that have tried to relate disorders of brain and behavioral development to fundamental cellular processes. As a result, our estimates of maturational timing in the human brain must be based on correlational and comparative approaches. We are aided by recent investigations showing that the schedule of human brain development can be mapped with some precision onto the maturational schedules of other animals (Clancy et al., 2000; Darlington et al., 1999; Finlay & Darlington, 1995). In fact, the order and relative spacing of brain development is remarkably stable across all mammalian species, permitting use of a regression equation to generate predictions of dates for events that are not able to be empirically measured in humans. This analysis has shown that primates (including humans) differ systematically from other mammals in the timing of neurogenesis in two key neural regions, the limbic system and the isocortex. Neurogenesis of the limbic regions is abbreviated in primates, resulting in uniformly smaller limbic structures when compared to similar areas in nonprimates. In contrast, the isocortex in primates has a relatively protracted neurogenesis, and a consequently increased relative size (Clancy et al., 2000; Finlay & Darlington, 1995). A very simple principle underlies this difference in the relative size and shape of brain systems: if a species gains extra cycles of neurogenesis across the course of evolution, the greatest relative enlargement occurs in the parts of the brain that develop relatively late.

With this fact about primate variability factored into the statistical model we are able to produce reliable predictions for the dates of several aspects of neurogenesis, pathway formation, and various regressive events across brain systems which would typically require invasive procedures for accurate determination (discussed in more detail in Clancy, et al., 2000). Unless indicated, all statements in the following text about the time of occurrence of maturational events in human neural development are drawn from data produced using this comparative mammalian model.

First trimester

It is startling to realize how much of fundamental brain morphology and organization is already laid down by the end of the first three months of life (before many mothers even know that they are pregnant). A region of the embryo called the neural tube generates stem cells which give rise to almost the entire brain in the first trimester (the last layers of the isocortex and the external granular layer of the cerebellum are born during the second trimester). Two exceptions are the hippocampal dentate gyrus and the olfactory bulb, which are (as far as we now know) the only regions in which neurons are generated throughout life (Bayer, 1982, 1983; Kornack & Rakic, 1999; Kuhn et al., 1996; Luskin, 1998). One of the first activities of the early-generated neurons is to lay down the basic axonal pathways of the brainstem (Easter et al., 1993). There is no simple lockstep plan for all neurons like "Migrate; become electrically excitable; produce axon; produce dendrites; make neurotransmitter, fire away." To take the case of axons alone, axons can be produced while neurons are migrating; not produced until the terminal site is reached; may show growth of multiple stages and types (branching or not, for example); may be produced and then retracted; or may show prolonged periods of no apparent growth (waiting periods).

Two more critical processes are virtually complete by the end of the first trimester: the differentiation of cells into different subtypes (also called cell specification) and the migration of cells from their birthplace to their ultimate destinations in the isocortex. Neurons begin to express various complements of neurotransmitters and neuromodulators even before migration (Lidow & Rakic, 1995) and continue to develop in the following months. Although there are many different kinds of neurochemicals within and across cell types, there seems to be a general developmental principle at work: during development, neurons will often co-express multiple transmitters and modulators whereas single cells in the mature brain exhibit much less diversity.

Second trimester

This is the period in which the basic wiring of the brain takes place, i.e., large patterns of connectivity develop between neural regions, including the isocortex (Honig et al., 1996). From a developmental point of view, one of the most important events is the establishment of connections from the thalamus to all regions of the isocortex. These connections are set up in the second trimester in a pattern that very much resembles the adult pattern from the start, with animal studies showing that visual, somatosensory, auditory, and limbic areas of cortex all receive projections fairly exclusively from those thalamic nuclei that will project to them in adulthood (Miller et al., 1993; Molnar et al., 1998; O'Leary et al., 1994). This is particularly important for theories of development, because it means that the brain is "colonized" by the body long before birth and well before the outside world has a chance to instruct the brain. Intracortical pathways (i.e., connections from one cortical region to another) also begin to establish their mature connectivity patterns in the second trimester. The

connections start to communicate (produce synapses) in their target structures in short order, although the bulk of synaptogenesis will occur later (Antonini & Shatz, 1990; Bourgeois & Rakic, 1993).

A particular kind of regressive event called apoptotic neuronal death begins in the second trimester (*apoptosis*, a type of cell death associated with an orchestrated program, not a disorganized dissolution of the cell). Overall, this early neuronal death seems to serve to grossly fix cell numbers in interconnecting populations and to fine-tune topographic projections between structures (Finlay, 1992), but does not contribute to the kind of fine-tuning of connectional anatomy associated with learning from the extra-uterine environment in the isocortex.

The second trimester is also the period in which something akin to learning or self-instruction begins, a process of activity-dependent self-organization of the nervous system. While the physiological and cellular consequences of this phenomenon have been best studied in the visual system, it seems like such a useful developmental mechanism for organizing spatially distributed systems that it is likely to be utilized elsewhere. For example, the first motor activity of the fetus begins at 2–3 months post conception and continues through intrauterine life, and although the neuroanatomical consequences of this activity are not known, the pattern of activity that it generates in the nervous system is structured and phasic (Robertson et al., 1982). At a time corresponding to the second trimester in humans, "waves" of activity begin to be propagated across the surface of the retina of cats and ferrets, beginning after basic connectivity is established and stopping before eye opening (reviewed in Wong, 1999). This organized activity can be the basis for a kind of primitive categorization, a process in which similar (correlated) inputs hang together while dissimilar (uncorrelated) inputs dissociate. This self-organizing process has some very interesting theoretical implications for developmental psychologists because it seems to occupy a middle ground in the nature–nurture debate. Similar organizing mechanisms will be used later for learning from the outside world, but they begin in utero to help set up the basic functional architecture of the brain.

Third trimester

By the beginning of the seventh month of gestation, a remarkably large number of neural events are complete. The human fetus has matured to the point where the eyes move and remain open for measurable periods of time. Reciprocal connectivity from higher-order cortical areas to primary areas has also begun (Burkhalter, 1993). Pathways exhibit the initial process of myelination (Yakovlev & Lecours, 1967). Large descending pathways from the cortex are also in the process of development. Aside from the more obvious role of descending pathways in motor control, the appearance of descending pathways also means that the brain has started to "talk back" to the body, a form of interaction found in all sensory and motor systems.

In the eighth and ninth months, a massive and coordinated birth of connections (synaptogenesis) begins in the neurons of the isocortex and related structures. (This mass production will extend postnatally and is discussed in more detail below.) It is fair to say that the infant arrives in the world with a nervous system whose working components are in place and organized. All cells are generated, major incoming sensory pathways are in place and have already gone through a period of refinement of their total number of cells, connections, and topographic organization. Intracortical and connectional pathways are well developed, though output pathways lag behind. This brain is up and running by birth, ready to learn (or rather, ready to keep on learning).

Postnatal neural events. Now we turn to a consideration of events that extend past birth, with special emphasis on the neural events that surround language learning.

Myelination

In the central nervous system, increases in the fatty sheaths around axons tend to occur earlier in sensory areas than in motor areas. This sequence of myelination has previously been offered as a possible contributor to a word comprehension/production disparity observed in some children. And since myelination of some neural regions continues well into maturity (Yakovlev & Lecours, 1967), there have also been speculations about its involvement in behavioral development (Parmelee & Sigman, 1983; Volpe, 1987). However, there are no clear-cut transitions in myelination and "undermyelinated" connections in the young human brain are quite capable of transmitting information. Interest in the role of myelination has waned in favor of other events in early brain development that are influenced by interactions of maturation and experience, such as synaptogenesis.

Synaptogenesis

An event that occurs within the critical time window for early language development is synaptogenesis. Synapse formation seems optimally placed for the rapid statistical learning infants show in both the visual and auditory realms during this time (Saffran et al., 1996). There are some interesting features to the formation of synapses and their restructuring and elimination within the perinatal period that seem quite closely related to early language acquisition.

Synapses are actually made up of several regions which we will briefly describe because some are altered during the same time period when language develops. On the transmitting side of the synapse, the axon contains the metabolic machinery to produce neurotransmitters and package them in vesicles. It also includes a *pre-synaptic specialization*, a thickening of the cellular membrane that helps transfer the contents of vesicles to the receiving neuron. The receiving *post-synaptic* cell also has a visible thickening of the membrane and includes the machinery to take up, and perhaps degrade the neurotransmitter, and to cause a reaction in the post-synaptic cell. Most, but not all, excitatory synapses have *asymmetric* synapses, in which the pre-synaptic specialization is thicker and denser than the post-synaptic one; most inhibitory synapses are *symmetric*, with pre- and post-synaptic thickenings of equal density. The location of the synapse is significant to its function – a synapse can be located on the cell body of the neuron itself, on the shafts of dendrites, or on small spikes appropriately called dendritic spines. This placement has consequences for how effectively the pre-synaptic input can induce changes in the post-synaptic cell.

A primary mode of learning in the nervous system (though not the only mode) takes place when the synaptic juncture is formed or modified as a function of experience, a

"strengthening" or "weakening" referred to as *Hebbian* learning. If we ask ourselves where the nervous system stores its "knowledge" (assuming that this term is useful at all), most neuroscientists would agree that synaptic connectivity is a primary means by which knowledge is represented in the brain (Elman et al., 1996). This is why there is so much interest in the role of synaptogenesis and synaptic connectivity in behavioral development.

In cognitive science, the number of synapses is often thought of as an index for the amount and complexity of information transfer in a structure. Even though synaptic number might be used as such a metric in some comparisons (for example, after certain kinds of experience (Greenough, 1984), it is misleading to understand synaptic numbers in development in only this way. More in development does not necessarily mean better, more complex, or more mature. To take an extreme case, sudden infant death syndrome (SIDS) is associated with an excess number of persisting synapses in the medulla (O'Kusky & Norman, 1994, 1995). This point is important for understanding a high-profile controversy about synaptogenesis and the peak of synaptic numbers in the isocortex of primates and humans. Briefly, in work with rhesus macaques, Rakic and colleagues described a rapid increase in the number of synapses that seemed to take place almost simultaneously across a number of cortical areas, reaching a peak at around the same time in frontal, cingulate, somatosensory, and visual cortical areas (Bourgeois et al., 1994; Granger et al., 1995; Rakic et al., 1986; Zecevic et al., 1989; Zecevic & Rakic, 1991). In contrast, Huttenlocher, working with human material, showed that the peak of synaptic density varies between visual, auditory, and somatosensory regions, with the frontal regions not reaching their peak until 3–4 years after birth, while the visual and auditory regions peak more closely to birth (Huttenlocher & Dabholkar, 1997).

A closer examination proves that the story these two investigators tell is not very different after all. Rakic and Huttenlocher have both shown that the number of synapses accelerates wildly beginning just before birth, in both the macaque and the human, and across a wide variety of cortical areas. In macaques, the peak of synaptic density across cortical areas is reached two to four months after birth (Figure 18.1a – replotted from Bourgeois et al., 1994; Granger et al., 1995; Rakic et al., 1986; Zecevic et al., 1989; Zecevic & Rakic, 1991). In humans, the curves are very similar, with a marked perinatal increase in synaptic density that begins around birth and flattens postnatally across all cortical areas (Figure 18.1b – from Huttenlocher & Dabholkar, 1997).

The synapse counts may, or may not, vary across different cortical regions. In the graph, for example, synapse counts in human auditory cortex appear to outnumber those in other human and macaque cortical regions. However, for many methodological and technical reasons (reviewed in Bates et al., in press), absolute values of synapse counts should be considered somewhat conditional, especially in human tissue. Moreover, in the graph, we have attempted to normalize the data by plotting synapse numbers as a percent of the total at puberty, which we arbitrarily defined as 12 years in human and 3 years in macaque. The take home message from the graph lies not in the absolute numbers, but rather in the pattern of *relative* changes. The most interesting feature in both the macaque and the human data lies in the strikingly similar timing of acceleration and deceleration.

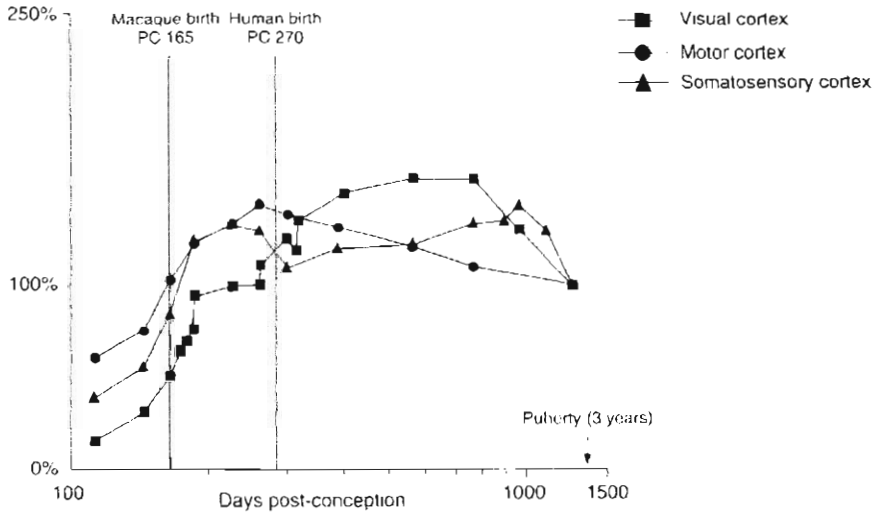

Figure 18.1A Macaque synaptogenesis. PC 112d – puberty.

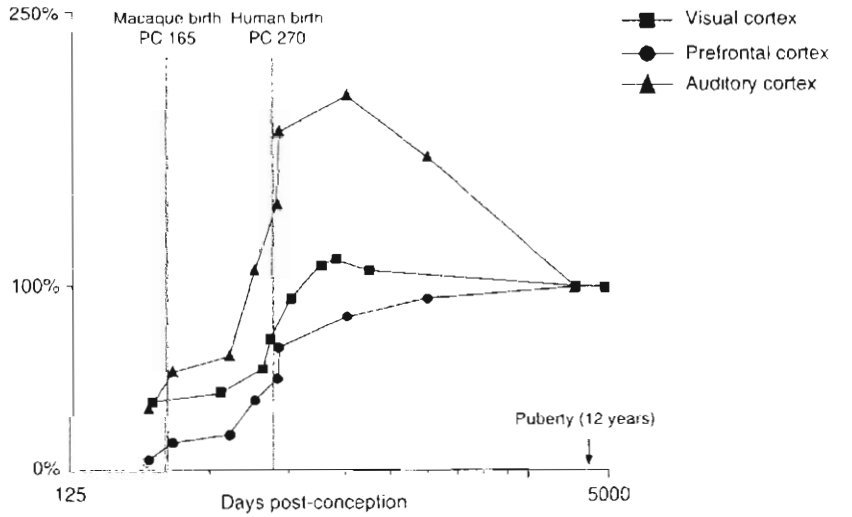

Figure 18.1B Human synaptogenesis. PC 192d – 12 years (converted to macaque days PC 146d – puberty).

We can safely conclude that the generation of synapses in the entire isocortex of humans accelerates around birth, overshoots by a substantial proportion in the first six months or so, and then declines to its adult value. Where the exact peak lies is probably not too important, as it will be influenced by any number of co-occurring additive

and subtractive events. The important point is that the brain suddenly starts to generate massive numbers of synapses just before environmental experience, in all of its regions associated with sensory, motor, motivational, and linguistic ability.

What causes the dramatic perinatal acceleration of synaptogenesis? In this case, it does not seem to be experience. When monkeys and cats were deprived of visual input, the timing of the initial acceleration and peak of synaptogenesis did not change, though later events of changing proportions, cortical layering and so forth, did change markedly (Bourgeois & Rakic, 1996; O'Kusky, 1985). Moreover, when monkeys were delivered three weeks prematurely, so that a barrage of experience would begin much sooner than it would normally occur (Bourgeois et al., 1989), there was no effect on the timing of synapse acceleration and peak – it occurred precisely when it should occur, based on the monkey's anticipated gestational birthdate, not the prematurely induced one. Secondary effects on types and distributions of synapses were also seen in this study, so experience does matter. However, experience doesn't seem to be responsible for the perinatal burst in synaptogenesis.

Humans present an evolutionary experiment that is the opposite of the premature delivery manipulation, because we are born rather late with respect to neural milestones such as neurogenesis. Although we think of human infants as being behaviorally immature at birth (compared to monkeys for example), there are many aspects in which the human brain is unusually mature at birth. When we look at the relationship between synaptogenesis and birth in humans, we find a rare and rather exciting exception to the general laws of neural development that create such orderly similarities between humans and other mammals: synaptogenesis seems to occur much later in humans than it occurs in other primates. If humans were born at the neural maturational stage corresponding to the stage when macaques show rapid synaptogenesis, human birth would occur at about 7 months post-conception (Figure 18.1b).

Recent work has shown that it is a signal from the fetus that initiates labor, coordinating maturation in the fetus with physiology in the mother. It would be interesting if this same signal might also initiate wholesale neuroanatomical changes in the fetus itself (Nathanielsz, 1998). In any case, the bottom line for present purposes is this: experience does not cause the initial burst in synaptogenesis instead evolution has coordinated synapse production with birth.

Why does nature bother to produce so many elements just to throw them away? The massive overproduction and subsequent pruning of synapses is a expensive neural tactic in terms of neural components and energy cost. Between ages 2 and 5, it has been estimated that 5,000 synapses are disappearing each second in the visual cortex alone (Bourgeois, 1997), and similar recessions are most likely occurring in all cortical areas that participate in language. What purpose could this steady decline serve, especially occurring as it does in a period when details of language (including complex grammar) are mastered? The strategy of excess production followed by pruning has been documented in other neural areas, notably in callosal axonal connectivity, where it has been proposed to permit the neural adjustments that favor evolutionary changes (Innocenti, 1995). Certainly flexibility is a primary outcome of such a system, but refinement, defined in terms of accuracy and speed despite complexity, may be another important consequence of these regressive stages.

Empirical studies are limited to observed descriptions of gross synapse counts, but computer simulations have been run that yield interesting information about the computational consequences of this peculiar strategy of overproduction and pruning (Elman et al., 1996). For one thing, in adaptively constructed neural networks that employ overproduction and removal of synapses, input information is more reliably preserved than it is in simple feed-forward networks (Adelsberger-Mangan & Levy, 1993, 1994). Networks constructed using adaptive synaptogenesis also manage to "sculpt" connections that permit quicker transformations of complex data when compared to networks constructed with conventional non-adjustable connective mechanisms. Moving away from machines back to humans, it is true that the net numbers of synapses are decreasing during adolescence; however, new ones are still sprouting, resulting in constant and co-occurring processes of production and trimming that could also serve to adjust and improve on initial connections.

So now let's take a closer look at the various kinds of synaptogenesis that occur before and after birth, and also consider some of the local and global events that affect the learning potential (and perhaps the learning style) within and across brain regions. A summary of the timetable of synaptic stages can be found in Figure 18.2, in which milestones of language acquisition and production are mapped alongside sequences of some of the human neural events that are discussed in this section.

Developmental differences in synapse morphology and distribution

The sequence of synaptogenesis can be classified into five stages (reviewed in Bourgeois, 1997). In the initial stage, synapses are present in a region of cortex called the "preplate" which comprises the earliest-generated cortical neurons. This is followed by a secondary stage in which synapses are generated in the cortical plate itself, initially following a gradient corresponding to that of the developing cortical neurons. Phase III of synaptogenesis is the synchronized global perinatal burst phase described above; at its peak in the infant macaque, it is estimated that 40,000 synapses are formed each second in the visual cortex alone (Bourgeois, 1997). Phase IV is a stabilized high level that lasts from late infancy until puberty, while in the last phase, which extends from puberty to adulthood, synapses steadily decline in density and absolute number.

Variations in morphological characteristics of the third stage of proliferating synapses make it clear that the complexities of the synaptogenic peak extend beyond sheer numbers. There are also interesting development changes in the kinds of synaptic connections that are being made. This includes a change in the ratio of asymmetric to symmetric synapses during the perinatal period – recall that asymmetric synapses are more likely to be excitatory and symmetric inhibitory. During Phase III of synaptogenesis, the asymmetric (putative excitatory) connections decline in number while the numbers of symmetric (putative inhibitory) synapses remain about the same (Bourgeois & Rakic, 1993; Zecevic & Rakic, 1991). Functionally, this means that there may be a developmental shift from a high proportion of excitatory activation toward a more tempered balance between excitation and inhibition, which seems a plausible account of the increasingly better coordination of perception and action.

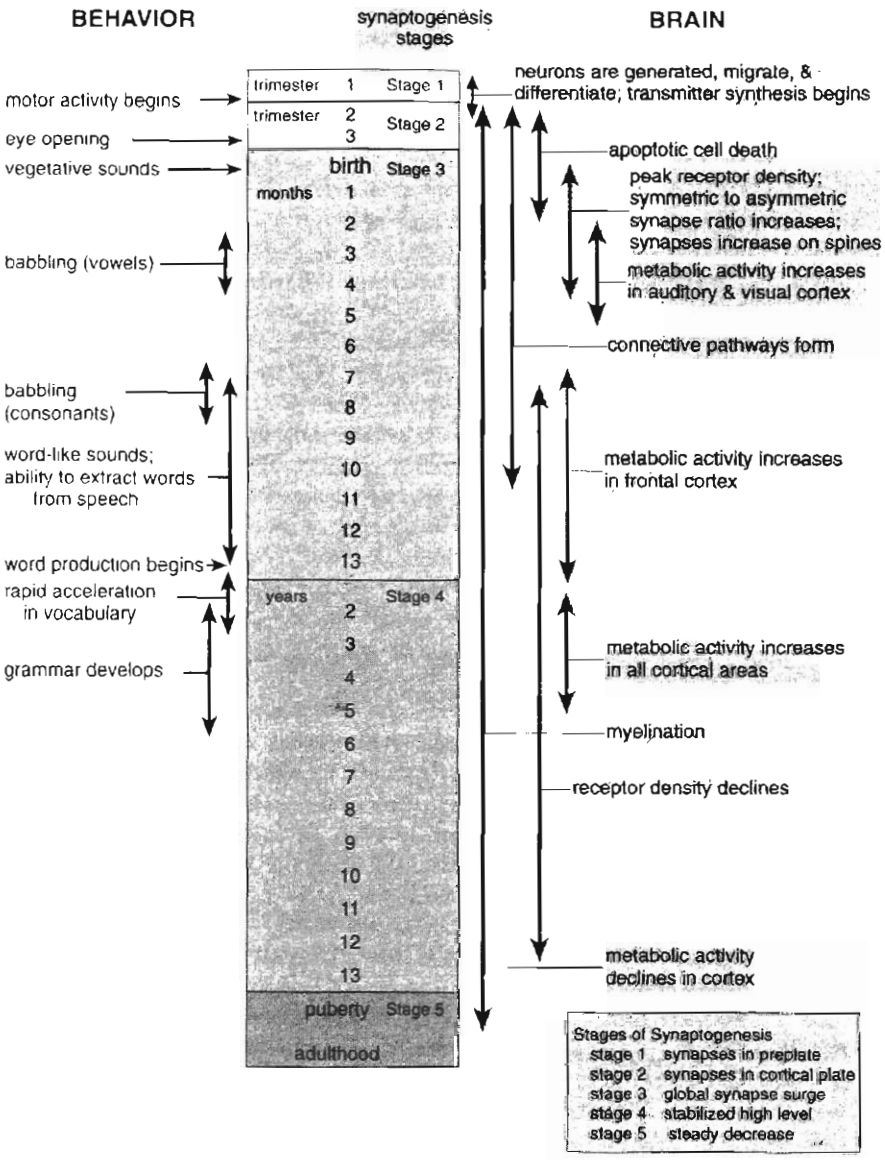

Figure 18.2 Neural events and language development.

The sites of synaptic innervation are also altered over development (Zecevic & Rakic, 1991). Early in development (in the more exuberant phase), large numbers of connections are made (or attempted) on the shafts (the trunks and branches) of dendrites. Later there is a shift in contact site, with more connections on dendritic spines. Because

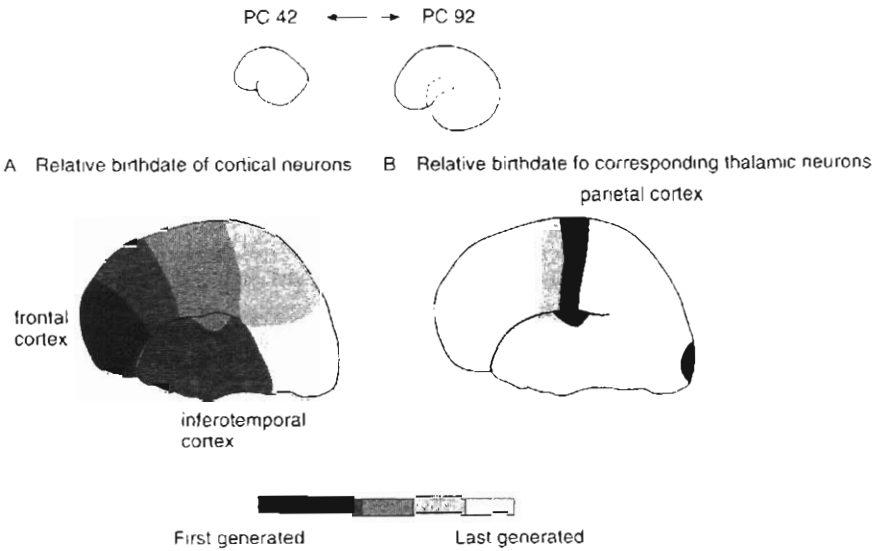

Figure 18.3 Gradients of neurogenesis.

spine contact may allow neurotransmitter release to be localized with more specificity than shaft contact (Harris & Stevens, 1989), this shift in site might reflect an increase in connectional efficiency during the early learning process. Theoretical models, as well as imaging experiments which can track ion flow in single cells, also support the role of spine contact in the induction of the plasticity associated with learning (reviewed in Koch & Zador, 1993). Overall, the significance of these changes in the constellations of the types and forms of synaptic interaction is just beginning to be understood.

We will now turn to other, larger-scale changes in brain structure and function that start prenatally but extend well into the postnatal period.

Maturational gradients of the isocortex in the early postnatal period

There is not a single dimension called maturational state that any area of the isocortex can be retarded or advanced on (which makes it less likely there could be a moment when a region turns on). Rather, each isocortical area is best viewed as an assembly of different features, including neurogenesis, process and axon extension, neurotransmitter inclusion, type and rate of synaptogenesis. (The simultaneous perinatal peaking of synaptogenesis across all cortical areas, supporting the notion of a global signaling process, is an exception to this general rule.) Figure 18.3 contrasts the gradients that are observed in two critically different aspects of cortical development: the timing of neurogenesis in different cortical areas compared to similar timing in their corresponding thalamic nuclei, superimposed on the cortex of a schematized human brain. Because different areas of the brain follow maturational gradients

that don't match in order, interesting temporal asynchronies are produced – for example, in some areas, intracortical connections will be relatively more mature than thalamic connections (the frontal cortex), and in others, the reverse will hold (primary visual cortex).

Intrinsic cortical gradients

The isocortex has its own gradient of maturation that is quite conserved across all mammals. Bayer, Altman and colleagues have produced detailed studies of the timing of neurogenesis in rodents (Altman & Bayer, 1979a,b, 1988; Bayer et al., 1993) and we are able to apply the comparative mammalian model of Finlay and Darlington (1995) to predict a similar time sequence for humans. Neurogenesis begins at the front edge of the cortex where frontal cortex abuts inferotemporal cortex and proceeds back to primary visual cortex, framing a period of genesis that can last over 50 days during the first trimester of human gestation. However, there is little direct association between the time of a neuron's genesis and when it makes its connections as this also depends heavily on the maturational/trophic status of the regions it must connect to. Paradoxically, the frontal cortex, viewed in conventional hierarchical models as the last maturing cortical area, is in fact one of the first to be produced and thus quite "mature" in some features.

Imposed thalamic gradients

Each area of cortex receives a thalamic input by maturity, but as depicted in Figure 18.3, the order of thalamic development in no way resembles the intrinsic cortical gradient. If intrinsic cortical gradients and imposed thalamic gradients occur in different orders, then we have a dissociation with potentially very interesting consequences. It is the thalamic order of neurogenesis that gives rise to the hierarchical notion of cortical development (e.g., visual matures early; frontal matures late), although this gradient is really not a general rule. This difference in developmental gradients might mean that frontal cortex, the area that bears so much weight in speculation about human evolution (e.g., Deacon, 1997) is primed for higher-order associative function from the start.

General modulatory cortical input

In addition to the thalamus, there are other subcortical structures that project to the cortex that are deeply implicated in systems of arousal, attention, and emotion in adulthood, and in modulation of plasticity and growth in development. In general, *cholinergic* fibers arise from the basal forebrain, *norpinepherine* fibers from the locus coeruleus, *serotonin* fibers from the raphe nuclei, and *dopamine* fibers originate in the cells of the substantia nigra. During development, these long-range systems are focused throughout the entire isocortex with the exception of the less diffuse dopamine system which focuses more specifically on limbic and prefrontal cortical regions. Unlike the precocious thalamic afferents, cholinergic and aminergic innervation begins relatively late in development, with much elaboration after birth, and even extending into adulthood (Dori & Parnavelas, 1989; Kalsbeek et al., 1988; Lidov & Molliver, 1982). We really don't know what these systems are for developmentally, except that disturbance of them disturbs normal development. Because we can reasonably conclude that the

timing of this innervation, like other neural events, is conserved across species, we can extrapolate these innervation dates to begin in the second or third trimesters of human gestation, likely extending well into the first postnatal year and, for some, even into the adolescent years.

What might the protracted and largely postnatal innervation of these neural fibers mean to a human infant or toddler in the process of learning so many behaviors, including language? We know that that these connections transmit substances that are highly implicated in mechanisms of arousal and reward, but they also have multiple functions in many distributed systems. It would seem that the progressive innervation of these substances into the developing brain is timed so that they can optimally influence learning behaviors, but much additional research will be needed to tease out a distinct role for each.

Neurochemicals and receptors

The transmitters used in the systems described above are just a small number of the chemicals that can be set in motion from the presynaptic (transmitting) side of the synapse. About 20 neurotransmitters (which have rather strict classification criteria) have already been identified (glutamate and GABA are high-profile examples) and many more are under investigation. Upon maturity, the neural areas subserving functions associated with language will contain unique combinations of neural transmitters and modulators in distribution patterns distinctive to each area, a form of neural fingerprint. The synthesis and distributions of these neural substances change over the course of maturity (Goldman-Rakic & Brown, 1982; Hayashi et al., 1989; Hornung & Fritschy, 1996) making them strong candidates for roles in development. Although much research remains to be done, it is certainly likely – given the timing of the fluctuations and combinations – that these variations in neural substances may play a functional role in maturing behaviors such as language learning.

Neural receptors are the receiving side of the synapse – the part of the postsynaptic complex where neurotransmitters and modulators can exert influence on the cells they contact. One developmental alteration has been consistently documented regardless of the species, the cortical area under investigation, or the related neurosubstance: there is a dramatic overproduction of virtually every type of receptor which occurs around the time of birth (Gremo et al., 1987; Herrmann, 1996; Hornung & Fritschy, 1996; Lidow et al., 1991), similar to – and simultaneous with – the perinatal surge of synaptogenesis. The receptor surge greatly supports the notion that the synapses are functional since the necessary transmitter docking mechanisms appear to be produced concurrently. Similar to the many other events we have described in the developing brain, interactions between receptor formation, neurosubstance synthesis, and synaptogenesis are likely to be more complicated than any simple cause-and-effect mechanism.

Interactions of Neural Events and Language Learning

The picture of human brain development that we have provided here leaves little room for a lockstep table of correlates between language milestones and neural events, but

it does provide some useful constraints on how we should conceive of this complex bidirectional relationship, with implications for both normal and abnormal development. We close with four conclusions, or better yet, four working hypotheses to guide future research in this area: (1) readiness for learning, (2) experience-driven change, (3) rethinking two specific postnatal correlates of language, and (4) sensitive periods.

Readiness for learning

There was a period in developmental psychology when the capacities of the newborn infant for perception and learning were vastly underestimated. Much-needed correctives to this misunderstanding have come in two waves: research demonstrating rich perceptual skills in the first few weeks of life (e.g., Bertenthal & Clifton, 1998; Johnson, 1998; Kellman & Banks, 1998), and research demonstrating at least some learning in utero, as well as a capacity for rapid learning of arbitrary statistical patterns (including language-specific phonetic details) in the first months of life. With the first wave, there was extensive speculation in the literature on infant development regarding the stock of innate knowledge that infants must possess in order to perform so well in (for example) tasks that require response to complex transformation of objects, including their disappearance and reappearance (Spelke, 1994; Spelke et al., 1992; Spelke & Newport, 1998). With the second wave, it has become increasingly evident that we have underestimated the power and speed of learning even in very young infants, forcing a revaluation of the extent to which infant performance is influenced by learning vs. innate perceptual, motor, and perhaps even conceptual biases about the nature of the physical and social world (Elman & Bates, 1997; Seidenberg, 1997; Thelen & Smith, 1994, 1998). The material that we have reviewed in this chapter provides support for the idea that the infant brain is up and running at or before birth. We see no evidence for the hypothesis that whole bounded regions of the brain are prefunctional, quiescent, inactive, or waiting for some key maturational event before they can "turn on" in the postnatal period.

However, even though the relevant neural systems may be in place and ready to work from the beginning, that does not mean that they are being used in an adult manner, nor that they are being used in all the tasks for which they will eventually be relevant. Recent neural imaging studies of human adults have shown that the configuration of highly active areas changes markedly across a 20-minute period as the subject attains expertise in a new task (Petersen et al., 1998). If that is true for mature and sophisticated adults, over a very short period of time, it will undoubtedly prove true for children who are in the process of acquiring language.

Experience-driven changes

It is now clear that learning itself contributes to the structure of the developing brain, in infants and in adults. Particular clear examples of an experience-dependent increase can be found in a series of experiments by Greenough and colleagues examining the effects of enriched housing and/or skill learning on morphological changes in rodent brain. These studies have consistently documented significant increases in dendritic fields and in the ratio of synapses per neurons in rats exposed to complex environments

or involved in learning tasks when measured against handled controls (Black et al., 1990; Greenough et al., 1985; Turner & Greenough, 1985). Experience-based synaptogenesis is also accompanied by increases in populations of glial cells (Sirevaag & Greenough, 1987), as well as by increases in metabolic activity (Sirevaag et al., 1988; Sirevaag & Greenough, 1987). We may reasonably conclude that similar reactive neural changes accompany learning in the developing human brain.

Hence, if we do eventually find evidence for neuroanatomical and neurophysiological events that correlate with milestones in language development, we must be open to the possibility that these correlations are the product rather than the cause of language learning. In the same vein, if we find evidence of neuroanatomical and/or neurophysiological differences between children who are developing normally and children who are substantially delayed in language learning, we should not assume that this neural indicator has caused a language delay. The brain may still be in a relatively immature state because the relevant experience-driven events have not yet taken place. This insight certainly applies to the burgeoning literature on neural correlates of Specific Language Impairment and/or congenital dyslexia, and it may apply to other disorders as well.

Rethinking two postnatal correlates of language

We noted earlier two previously proposed postnatal correlates of major language milestones: changes in frontal lobe activity that seemed to coincide with the 8–10-month watershed in comprehension, communication, imitation, and reasoning, and changes in synpatic density that seemed to coincide with bursts in vocabulary and grammar between 16 and 30 months.

However, the idea that behavioral events late in the first year of life are correlated with changes in frontal lobe function rested primarily on two sources of evidence. The first was a positron emission study (PET) of human infants suggesting that there is a marked increase in frontal lobe metabolism starting between 9 and 12 months postnatal age (Chugani et al., 1987) that did not occur in response to any particular stimulus or task. It was suggested that this sharp increase in glucose metabolism might be caused by a burst in synaptogenesis. The second source of evidence came from lesion studies showing that infant monkeys with bilateral frontal lobe lesions behave very much like age-matched normal controls but only until a critical point in development (roughly equivalent to 8–12 months in postnatal human life) when normal animals learn to solve short-term memory tasks that are failed by the lesioned animals and by adults with frontal lobe pathology (Diamond & Goldman-Rakic, 1989; Goldman-Rakic, 1987; Pennington, 1994). Findings like these led to a previous hypothesis that the frontal lobes "come on line" around 9 months of age, coinciding in humans with dramatic changes in many aspect of language, cognition, and social interaction. However, it now seems very clear that the frontal lobes are functional (though still immature) by the end of the second trimester, and may actually be *more* mature than other areas in terms of their intracortical connectivity.

How can we reconcile these apparently contradictory claims? The resolution may lie in the difference between *absolute functionality* (i.e., whether or not an area is working at all) and *task-specific functionality* (i.e., whether the organism has reached a state in

which that area is recruited and activated for a given task). Evidence for the latter view comes from a study by Jacobs, Chugani and colleagues (Jacobs et al., 1995), a PET study of infant monkeys that shows high levels of frontal lobe metabolism at birth, well before the point at which monkeys solve the short-term memory tasks that have been associated with frontal lobe function. These authors do find a further increase in metabolism later on, in many regions of the brain including the frontal lobes, compatible with the idea that metabolism and synaptogenesis increase together after birth. However, the amount of activity seen in the frontal lobes of newborn monkeys is not compatible with the standard view that frontal lobes develop especially late. If Goldman-Rakic's classic findings are not "caused" by the sudden appearance of mature frontal cortex, how can we explain the sudden relevance of frontal lesions for memory tasks around the human equivalent of 8–10 months of age? We suggest that these results can be reinterpreted within the bi-directional framework that we have recommended here, in which areas are *recruited* into complex tasks across the course of learning. On this argument, normal infants (humans and monkeys) cannot succeed in so-called frontal lobe tasks until they have made enough progress (perceptual, motor, mnemonic) to realize that a new set of strategies is required – strategies that are, in turn, only possible with the involvement of the frontal lobes. We tentatively suggest that the 8–10-month behavioral watershed in human infants may involve a learning-dependent change in social and cognitive systems that have developed in parallel because they began in parallel (at or before birth), are roughly similar in complexity, and are likely in communication with each other. As a result, all of these systems reach a certain critical level of organization around the same time (approximately 8–10 months).

The hypothesized parallel between synaptogenesis and the correlated burst in vocabulary and grammar that are observed from 16–30 months requires more recharacterization still. It is now reasonably clear that the initial burst in synaptogenesis itself is independent of experience, arranged to coincide with the barrage of experience that will arrive at birth. It is certainly intriguing that the peak and plateau of synaptogenesis in humans brackets the primary events in early language development (from word comprehension to the mastery of fundamental aspects of grammar), but we still need to learn much more about these events.

Is there any possibility that we should rule out? In our view, it would be wise to rule out the idea that the "vocabulary burst" and the "grammar burst" depend entirely on synaptogenesis for their shape and size, because such bursts are also observed when learning occurs in a non-linear dynamical system with a stable architecture (Elman et al., 1996). Such exponential bursts are characteristic of learning, and are observed whether or not they are superimposed on a burgeoning brain. Hence the compelling parallel between the language burst and the synapse burst may represent a mutually beneficial relationship, but not a crucial and direct relationship of cause and effect.

Sensitive periods

The term sensitive period is preferred by neurobiologists over the widely used and widely misunderstood term critical period, because the former term implies a softer and more plastic set of developmental constraints and transitions. The term critical period is still used in the literature on language development, and it is often used to imply hard

boundaries and a crisp dissociation in the mechanisms that are responsible for language learning in children vs. adults (for discussions, see Bates, 1999; Bialystok & Hakuta, 1994; Elman et al., 1996; Johnson & Newport, 1989; Oyama, 1992; Weber-Fox & Neville, 1996). The notion of a critical period for language has been invoked to explain differences between first- and second-language learning, and to account for age-related changes in recovery of language abilities following left-hemisphere injury. It has been shown that adults and children perform at similar levels in the early stages of second-language learning when learning conditions are controlled (Snow & Hoefnagel-Hohle, 1978). The one compelling exception to this general rule is the ability to learn a second language without an accent, which seems to elude all but a very rare subgroup of talented adults. However, studies that focus on the later stages of language learning have shown that adults tend to "fossilize" at a level below native speakers, while children generally go on to acquire full competence (Johnson & Newport, 1989). Results like these provide support for the idea that there is an age-related decrease in plasticity for language learning, but there is no consensus about the shape of this function or its cause. Some investigators (e.g., Johnson & Newport, 1989) conclude that there is no single moment when the window of linguistic opportunity slams shut, but rather, a series of gradients that vary with task difficulty and other poorly understood parameters.

The literature on brain development may also shed light on this issue. In the well-studied primate visual system, multiple overlapping sensitive periods have been identified (Harwerth et al., 1986) and it is likely that human language acquisition is affected by similar complex receptive intervals. Although these learning periods were once thought to be fixed in time, it is now clear that the temporal windows when adequate experiences is necessary for proper development are more flexible than previously assumed, and may be retarded or advanced by natural or empirical means (e.g., Stryker & Harris, 1986; Kroodsma & Pickert, 1980).

We are by now quite prepared to accept that learning itself affects the subsequent ability of the brain to learn something new. Brain maturation affects experience, but experience returns the favor, altering the very structure of the brain. Hence the putative critical period for language (which really comprises many overlapping sensitive periods) may be one more example of the bi-directional events that have been a focus of this chapter.

The search for a neuroanatomical basis for language learning has, at this time, no unequivocal conclusion. We have noted here some neural developmental alterations that accompany language milestones. These neural events may drive, or alternatively, reflect, developmental behaviors such as language learning – although the complexity of the interactions remains to be researched. What is clear is that timetables for human neural developmental events cannot be simply mapped onto sequences of language acquisition and production. As depicted schematically in Figure 18.3, the human brain develops as an overlapping and interconnected series of multimodal additive and regressive neural events, many of which are completed prior to birth. Although certain cortical events, especially developmental modifications in the numbers, components, and locations of synapses, may contribute somewhat more directly, all pre- and postnatal events should perhaps be considered essential to the language-learning process.

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