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Publisher Psychology Press

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## Developmental Neuropsychology

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title-content=t775653638>

## Mechanisms of Postnatal Neurobiological Development: Implications for Human Development

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Online Publication Date: 01 April 2001

**To cite this Article** Webb, Sara J., Monk, Christopher S. and Nelson, Charles A. (2001) 'Mechanisms of Postnatal Neurobiological Development: Implications for Human Development', *Developmental Neuropsychology*, 19:2, 147 — 171

**To link to this Article:** DOI: 10.1207/S15326942DN1902\_2

**URL:** [http://dx.doi.org/10.1207/S15326942DN1902\\_2](http://dx.doi.org/10.1207/S15326942DN1902_2)

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# Mechanisms of Postnatal Neurobiological Development: Implications for Human Development

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This review focuses on the postnatal neuroanatomical changes that arise during the first years of human life. Development is characterized by 2 major organizational periods. The first period begins at conception and includes the major histogenetic events such as neurulation, proliferation, migration, and differentiation. It has been proposed that these events may be controlled by genetic and epigenetic events, which give rise to neural structures that are amenable to external influence. The second period is a time of reorganization in the human cortex. These events occur during gestation and continue postnatally, possibly through the 2nd decade of life. This stage is characterized by dendritic and axonal growth, synapse production, neuronal and synaptic pruning, and changes in neurotransmitter sensitivity. Although the initiation of these events is influenced by endogenous signals, further neural maturation is primarily influenced by exogenous signals. To illustrate both the progressive and regressive events during the postnatal period, we use examples from the development of the human cortex.

This review was undertaken to provide a summary of the current status of human developmental neuroscience and its intersection with behavioral development. As

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techniques in neuroscience have improved, allowing *in vivo* studies, our understanding of the construction of cortical circuits has also improved. However, despite the widespread accomplishments in the field, few articles have tried to synthesize the research on human neural development.

Many researchers have proposed that there is initially an overproduction and redundancy in synaptic connections (Changeux & Danchin, 1976; Goldman-Rakic, 1987; Huttenlocher, 1979b). As Katz and Shatz (1996) stated, "early in development, internally generated spontaneous activity sculpts circuits on the basis of the brain's best guesses at the initial configuration of connections necessary for function and survival" (p. 1133). Originally, this pattern of "sculpting" may rely on endogenous, spontaneous neural activity, but with maturation, increases in sensory input from the environment further influence neural patterning. It is possible that the circuits that stabilize and persist may be the circuits that benefit from the greatest amount of activity, but those that remain unspecified regress. This initial redundancy in synaptic connections, followed by their elimination, may be universal to all neuronal systems (Changeux & Danchin, 1976; Huttenlocher & Dabholkar, 1997; Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986; but see Purves, 1989) and may be the mechanism by which the brain is made ready to capture critical information from the environment (Black, Jones, Nelson, & Greenough, 1998).

Based on this model of development, we summarize the postnatal ontogeny of the cytoarchitecture in the human cortex following the major histogenetic events of neurulation, proliferation, differentiation, and migration. In particular, we discuss postnatal dendritic and axonal growth, synaptogenesis, pruning, neurotransmission, and myelination, as well as gross measures of brain development. Within each of these sections, we cover both the general mechanisms of development and their implications for behavior.

## AXONAL AND DENDRITIC DEVELOPMENT

Once neurons have migrated to their correct location, they begin the process of extending axons and dendrites. Axons are the primary mechanism by which neurons signal other neurons in the cortex and often must travel over several centimeters to reach their targets. The neuron sends out an axon, which migrates through the embryonic environment to its synaptic target. Most axons travel along simple linear "highways" that are marked by choice points along the way, providing decision-making cues that signal the axon to switch from one highway to another. The growth cone at the tip of the axon is responsive to different permissive and inhibitory ligands within the extracellular matrix. In the vertebrate central nervous system (CNS), guidance depends on the recognition of cell surface molecules and extracellular matrix cues derived from the cells along the pathway (Jessell, 1988)

and chemical signals from target and intermediate cells (Tessier-Lavigne, Placzek, Lumsden, Dodd, & Jessell, 1988). At least four different mechanisms serve to guide axon path finding: contact attraction, contact repulsion, chemoattraction, and chemorepulsion (Tessier-Lavigne & Goodman, 1996). These mechanisms work in combination to balance the attraction and repulsion cues at the choice points along a given pathway.

The complexity of growth cues is due to the fact that different populations of cortical axons react differently to membrane-associated molecules from a given cortical layer, and it is most likely that different cortical layers express different sets of receptors and have different signaling pathways (Bolz, Castellani, Mann, & Henke-Fahle, 1996). Moreover, recent findings demonstrated layer-specific differences in growth factors, neurotrophins, and the expression of their receptors, which regulate both axonal and dendritic growth (reviewed in Korsching, 1993; Thoenen, 1995).

In contrast to the complexity of cues driving axon outgrowth, there seems to be two mechanisms driving the early outgrowth of pyramidal neuron dendrites. First, due to genetically determined, activity-independent signals, neurons form early dendritic processes soon after they reach the cortical plate (e.g., McConnell, 1989). As cells develop receptor mechanism at their neuronal bodies, spontaneous electrical activity may signal the initial development of dendrites. Second, incoming axon processes can induce dendrites to form (Mrzljak, Uylings, Van Eden, & Judas, 1990). Further dendritic differentiation and elaboration may be dependent on the establishment of afferent input. Thus, receiving early connections is of critical importance for organization. Moreover, the same molecular mechanism that attracts invading axons also seems to be involved in signaling dendritic growth. The combination of these factors can be seen in the time course of dendritic sprouting, which begins to form as soon as neurons reach the cortical plate (at approximately 15 weeks), with spines typically appearing on both pyramidal and nonpyramidal neurons between the 25th to the 27th weeks of gestation and increasing through the 24th postnatal month in some cortical regions (Mrzljak et al., 1990).

Dendrites first appear as thick processes extending from the cell body with only a few spines. These first dendrites are both apical (extending from the peak of the neuron and crossing several layers toward the surface) and basilar (extending parallel to the surface within the same layer), but then oblique branches form off apical dendrites. As dendrites thicken and increase in number, they provide a greater area for synaptic contact, and it has been proposed that larger dendrites may reflect greater numbers of functional contacts. Researchers have proposed that the development of spines precedes synaptogenesis, but it is unknown if the number of spines on pyramidal neurons accurately reflects the number of synapses.

To produce a functional synapse, axons must make appropriate connections with dendrites. Thus, to have a final "overproduction" of synapses, there is also an overproduction of dendrites, dendritic spines, and axons. Axons are produced in

excess during perinatal life, and the final number may be achieved by the process of competitive elimination during the postnatal period. For example, in the corpus callosum of the infant rhesus monkey, the number of axonal fibers is at least 3.5 times that of the adult monkey (LaMantia & Rakic, 1990). LaMantia and Rakic suggested that early projection areas, in infragranular Layers IV and V, may exuberantly produce axons that are later eliminated, but later projection areas, in supergranular Layers II and III, survive. The phenomenon of overproduction of cortico-cortical axons is closely associated with the excessive synaptogenesis during the early postnatal period (Goldman-Rakic, 1987). This is best illustrated by examples from the visual cortex where the peak number of axon spines occurs at about 5 postnatal months, and the peak of synaptogenesis occurs around the 8th postnatal month (Michel & Garey, 1984).

During the first postnatal year, growth of dendritic trees and spine can be seen in all six layers, although these spines are still immature. Overall, a constant increase in spine number can be seen on all neurons; for example, the length of prefrontal dendrites increases 5 to 10 times in the first 6 months of postnatal life. Similar to axonal development, there are both regional and layer-specific differences in the time course of the development of dendrites. For example, the visual cortex shows rapid development between the 2nd and 4th postnatal month, with maximum dendritic arborization occurring at approximately 5 months and then regression to an adult level by 2 years (Michel & Garey, 1984). In general, pyramidal neuron branching increases rapidly at 28 weeks of gestation, with slower increases in branching continuing to 7 years of age (Becker, Armstrong, Chand, & Wood, 1984).

Dendritic arborization in the frontal cortex at birth is delayed compared with the visual cortex and the hippocampus where the full number is present by approximately 6 months postterm (Paldino & Purpura, 1979). The first apical dendrites of immature neurons are present at 13.5 weeks of gestation (Mrzljak, Uylings, Kostovik, & Van Eden, 1988, 1992). However, peak production of pyramidal neuron dendrites reaches its maximum number during the 2nd year of life (congruent with the peak of synaptogenesis between 2 to 3 years), but nonpyramidal neurons demonstrate a reduction in spine number during the same period (Mrzljak et al., 1990).

In two articles, Koenderink and colleagues (Koenderink & Uylings, 1995; Koenderink, Uylings, & Mrzljak, 1994) investigated pyramidal neuron dendritic development in Layers III and IV of the prefrontal cortex (PFC). In the PFC, Layer IIIc basilar dendrites of pyramidal neurons undergo a rapid dendritic growth phase postnatally to around 1 year of age, with increases in branching until early adulthood (Koenderink et al., 1994). By 7.5 months of age, the number of basal dendrites per neuron is at a constant level; however, the length of the basal dendritic field shows a marked increase between 7.5 months and 1 year. This increase is due to larger segments and additional branches. Similarly, in Layer V, the number of basal dendrites per pyramidal neuron of the PFC (ef-

ferent neurons that provide callosal, association, and subcortical projections) has stabilized by postnatal Year 1, although there is progressive elongation of the basal dendrite field through 5 years of age when they are morphologically mature. Neither of Koenderink's (Koenderink & Uylings, 1995; Koenderink et al., 1994) reports suggest that there is continued dendritic growth (in the PFC) past childhood, nor do they report transient exuberant growth, regressive events, or reorganization of the basal dendritic tree. However, as we discuss later, there are some limits to these interpretations, as analyses have only been performed on static samples of a dynamic process.

Unfortunately, the formation of appropriate axonal projections may be disrupted in a number of ways. First, early postnatal head trauma may block the pathway of axons due to tissue scarring. Second, anoxia, toxins, malnutrition, or genetic anomalies may alter path formation. For example, in a case study described by Lyon et al. (1990), three infants with congenital encephalopathy, profound weakness, and hypotonia presented marked deficiency in cerebral axons. Additionally, in children with X-linked aqueductal stenosis, postmortem examinations suggest a failure of neuronal innervation leading to axonal elimination in pyramidal tracts (Chow, Halliday, Anderson, Danks, & Fortune, 1985). Third, if the axon's target neuron has been damaged, either aberrant pathways may form to other cells or the axon will not receive the trophic support it needs, and thus both the axon and its cell body may die. However, it has been demonstrated that axons are also able to "surpass" pathological limitations. For example, if the spinal cord is hemisected, pyramidal tract axons cross over to the undamaged portion of the cord and complete their journey to the appropriate target area (e.g., in rats; Li, Yew, Chuah, Leung, & Tsang, 1994).

Abnormalities of dendritic development have been linked to inappropriate cell location, abnormal innervation, ingestion of neurotoxins, and undernutrition, as well as developmental pathologies such as angelman syndrome, fragile X syndrome, autism, and Duchenne muscular dystrophy (Volpe, 1995). For example, children with mental retardation have abnormalities of dendritic branching and spines (e.g., Huttenlocher, 1975, 1979a; Purpura, 1975, 1982) in which dendrites may be thinner, have smaller numbers of spines, or have shorter stalks. In autopsy studies, individuals with severe mental retardation of unknown etiology present defects in the number, length, and spatial arrangement of dendritic branching and dendritic spines. Purpura and colleagues (Purpura, Bodick, Suzuki, Rapin, & Wurzelmann, 1982) suggested that the decreased dendritic number results from a failure of cytoskeletal structure, where the microtubules do not align properly such that the cell shape is abnormal and cannot support the outgrowth of dendritic branches. In addition, premature infants who require a ventilator have decreased numbers of dendritic spines, abnormally thin dendrites, and long, thin dendritic spines in the medulla oblongata. These disturbances are not present in premature infants who did not require ventilator support (Tasashima & Mito, 1985).

## SYNAPTOGENESIS

Neurons transmit information to other neurons at their synaptic contacts. There are two types of synapses: electrical synapses (e.g., gap junctions) and chemical synapses. We primarily discuss the physiological role of the latter type of synapse, as little is known about the development of electrical synapses. At a chemical synapse, an electrical signal from the presynaptic cell is converted into a chemical signal that can be transferred through extracellular space to the postsynaptic cell. In synaptic transmission, an electrical signal is transferred from the soma (cell body) down the axon and signals the release of chemical messengers into extracellular space. The chemical messengers (typically neurotransmitters and neuropeptides), when combined with a receptor protein, can open or close ion channels on dendritic spines, changing the electrical current in the postsynaptic cell. This process allows for intercellular communication, with most synapses occurring between axons and dendrites (but also axon to soma, dendrite to dendrite, and axon to axon).

Similar to axon and dendritic growth, both spontaneous (Molliver, Kostovic, & Van der Loos, 1973) and environmentally induced neuronal activity leads to the formation and stabilization of synapses. It has been proposed that initially formed contacts are triggered by general, genetic stimulus formation mechanisms (Rakic et al., 1986). These synaptic components are synthesized through intrinsic programs prior to cell-cell interactions. However, retrograde and anterograde signaling, as well as neurotransmitter release, may also stimulate signaling patterns. These early synapses are labile, and most likely this mechanism is preparing the system for environment input. There are several examples of how synapses may be stabilized in the developing organism. In one example, stabilized synapses may represent coordinated activity at presynaptic and postsynaptic sites (Schlaggar, Fox, & O'Leary, 1993). Formation of adult patterns of connection involves the elimination of a limited number of immature labile connections with the elaboration and addition of appropriate connections. Those synapses that make functional connections receive a larger amount of coordinated activity and are stabilized, but those that do not may be eliminated or reabsorbed (Changeux & Danchin, 1976).

Synapse stabilization may occur through the local release of neurotrophins (nerve growth factor [NGF], neurotrophin-3 [NT-3], and brain derived neurotrophic factor [BDNF]). It has been posited that postsynaptic cells release neurotrophins and that axons whose parent cells have recently been activated are able to respond to these signals (e.g., Katz & Shatz, 1996; Thoenen, 1995). Glutamate receptors (the *N*-methyl-D-aspartate [NMDA] subtype) may also function in a similar manner by mediating postsynaptic activation of cortical cells (e.g., somatosensory barrel patterning in the rat; Schlaggar et al., 1993). For example,

stimulation by high frequency electrical activity leads to the coordination of presynaptic and postsynaptic activity through the NMDA glutamate receptors that detect and transmit this coordinated activity. The result is strengthening of the synapse for up to a few hours (long-term potentiation).

An important issue to consider when examining the development of synaptic connections is how synapses are defined. Most often, the criteria for documenting the presence of a synaptic connection are based on synaptic properties of the adult organism.<sup>1</sup> Thus, labeling of synapses in the developing organism is based on matching the physiological properties of developing synapses to mature synaptic properties. There are several problems that may then arise. First, is a synapse functional prior to it being structurally mature? If labeling of synapses is based on their structural similarity to the adult model, it is possible that developing synapses may possess some functional properties but not yet be structurally mature. For example, growth cones form functional synapses with muscle fibers within minutes of target innervation (Frank & Fischbach, 1979). Yet these early synapses lack the correlates of the mature synapse. Second, we may not be evaluating the ongoing growth and retraction of axonal branches during development, which may better reflect the construction and removal of synapses. Thus, we may be underestimating the number of synapses that are contributing to information transfer because they are highly dynamic in the developing system. Third, even in adulthood it is possible that developmental events are continuously occurring such that synapses may be formed and eliminated at the same rate (Zecevic & Rakic, 1991). This dynamic principle would account for the findings in the stability of synapse number in adulthood but would also allow for learning and plasticity in the adult animal.

Although we have cataloged some of the potential difficulties in interpreting synaptic development, researchers have demonstrated the presence of mature, functional synapses earlier in development than originally proposed. Molliver et al. (1973) identified the first synaptic junctions in the cortical plate at about 23 weeks gestation. However, peaks in the quantity of synapses typically occur during the first year of life. Although the timing of synaptogenesis is varied, adult values and peak levels of synaptic density in the auditory cortex, visual cortex, and medial frontal gyrus show similar aggregate values, suggesting that peak densities and synaptic elimination occur to a similar degree throughout the cortex (Huttenlocher & Dabholkar, 1997).

Huttenlocher and colleagues (Huttenlocher, 1979a, 1979b, 1984; Huttenlocher & Dabholkar, 1997; Huttenlocher & de Courten, 1987) documented the postnatal period of synaptogenesis in the visual cortex and prefrontal cortex. In the visual

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<sup>1</sup>Huttenlocher (1979b; Huttenlocher & de Courten, 1987) used the following criteria to define a *synapse*: presence of presynaptic dense projections, synaptic cleft, and postsynaptic band.

cortex (Huttenlocher & de Courten, 1987) the greatest increases in synaptogenesis occur between 2.5 to 8 postnatal months, with the most rapid increases between 2 and 4 months. Physically, the shape and structure of the eye and the retina are also undergoing massive transformations. However, it is the physical maturation in the eyes that has been attributed as the cause of improvements in vision (from 20/400 to 20/40), not the synaptic levels. What is unknown is whether further maturation of the visual cortex is correlated with improvements in depth perception and other associated visual abilities.

Similar to other cortical areas, the visual cortex matures at different rates. In a postmortem analysis of the visual cortex, Huttenlocher and de Courten (1987) found synaptic profiles in Brodmann area 17 of the human striate cortex as early as 28 weeks gestation. However, the synaptic density at this time is only 2% of adult value and by birth is only 17% of adult value. Maximum synaptic density is attained in the upper cortical Layers I to IVb by 4 months (projects to other cortex areas), by 8 months in Layer IVc (projects to Layer IVb), 11 months in Layer V (projects to the superior colliculus), and 19 months in Layer VI (projects to the lateral geniculate). Later developing synapses may reflect top-down modulation of the early visual areas (superior colliculus and lateral geniculate).

In the frontal cortex, synapse formation begins at 27 weeks gestation and does not reach its maximum density until after 15 postnatal months. In the middle frontal gyrus (MFG), which is implicated in abstract thinking and reasoning, synaptic density reaches its maximum number of synapses at 3.5 years (Huttenlocher & Dabholkar, 1997). At 3 months the MFG is at 50% of peak; however, the synapses are immature as compared to the adult morphology. It is not until 6 to 24 months that the synapses gradually became adult like (Huttenlocher, 1979b). Synaptic density also increases significantly between children (6 months to 7 years) and adults (16 to 72 years). Furthermore, neuronal density shows marked layer-related variations that also vary with age. Layer IV, which is the primary afferent layer, and Layers V and VI, which give rise to efferent fibers, develop more rapidly than Layers II and III, which are concerned with information processing (Huttenlocher & Dabholkar, 1997).

Data on the development of postnatal synaptogenesis in the hippocampus is relatively sparse in comparison to the visual and frontal cortex. In general, the onset of synaptogenesis appears long before interaction with the environment and the onset of cognitive function. In the hippocampus, synapses (asymmetric, axodendritic) are present in the marginal zone, cortical plate, and subplate zone as early as 15 weeks gestational age (GA; Kostovic, Seress, Mrzljak, & Judas, 1989). The strength of these early synapses are modulated by neurotrophins within minutes of innervation (e.g., Kang & Schuman, 1995). In rats, the formation of synapses between the perforant path (from the entorhinal cortex) and dendrites of the granule cells takes place concurrent with cell formation (Bayer & Altman, 1975; Crain, Cotman, Taylor, & Lynch, 1973). In the dentate gyrus in the rhesus monkey

(Eckenhoff & Rakic, 1991), the highest synaptic density was observed in the 4th and 5th postnatal months, with adult levels reached by 10 months of age.<sup>2</sup> These changes occur in absence of volumetric changes in the dentate, which reaches maximum volume at approximately 5 months.

There is an important caveat to this section. Synaptogenesis in the human neocortex seems to be different from that seen in the nonhuman primate neocortex. In particular, in rhesus monkeys concurrent synaptogenesis is found in all neocortical areas (Rakic et al., 1986), unlike the topographic differences seen in the human. Moreover, development is compressed in the monkey as compared to the human. For example, the period of synaptogenesis is much shorter in the primate, with synapses beginning during the last 2 months of pregnancy and being completed by approximately the 2nd postnatal month (except archicortex–hippocampal formation). However, similarities do exist in the early formation of synapses in the cortical plate after early neuronal migration. Nonhuman primates also demonstrate the rapid overproduction of synapses during early development, with plateaus during childhood and decreases in the mature adult (Zecevic & Rakic, 1991). Despite these seeming differences between the monkey and the human, these conclusions may be premature. The human data are represented by a limited number of samples at each age, with more observations at some ages than others. Thus, the potential for variability in the human data may be enormous.

Why the possible overproduction of synapses? It has been proposed that the initial overproduction in the cortex may be related to the functional property of the immature brain to allow recovery and adaptation after focal injury or malformation (Huttenlocher, 1984) and may represent a critical or vulnerable period. This overproduction may also be the mechanism by which the brain is made ready to receive specific input from the environment. Studies of synaptogenesis demonstrate important developmental increases in the postnatal period and Goldman-Rakic (1987) proposed that the period of early overgrowth is important for the onset of cognitive function. For example, in the monkey synaptic density in the principal sulcus peaks between 2 and 4 months postnatally (Rakic et al., 1986). This period of excess coincides with the emergence and improvement of delayed response on the AnotB task. Similarly, in the human infant, the frontal cortex begins to dramatically increase its synaptic density at 8 months and peaks at 2 years (Huttenlocher, 1979b), which coincides with increases in the length of delay infants can tolerate on the AnotB task. Goldman-Rakic (1987) suggested that the “signatory functions” of cortical areas might express themselves concurrently with peaks in synapse number, with mature function occurring as a result of synapse elimination.

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<sup>2</sup>If there is a 1:4 correspondence between nonhuman primate and human development, this would suggest that synaptic density in the human hippocampus peaks at approximately 16 to 20 months and reaches adult levels by 4 to 5 years.

It is difficult to determine the functional significance of synaptogenesis, as axonal and dendritic development, myelination, and synaptogenesis are co-occurring processes. Hypotheses as to the functional significance of synapses arise from correlations between multiple neural events and behavioral measures. However, work with rhesus monkey suggests that there is something important about this period of overproduction in that visual, somatosensory, motor, limbic, and associative functions seem to emerge during the period when the density of cortical synapses, their neurotransmitter, and their receptor levels are at their highest (Goldman-Rakic, 1987). For example, between 2 and 3 postnatal months, the peak number of synapses is reached in the somatosensory cortex of the monkey. Concurrently, infant monkeys also begin to be able to distinguish basic textures, regardless of early sensory input (Carlson, 1984). In addition, by 6 months infant monkeys can discriminate object size, and at puberty, when synapses have reached adult levels, the monkey has full somatosensory functions. In contrast to the idea that synapse production is driven by experience, Zecevic and Rakic (1991) suggested that this early postnatal synaptic production might be a continuation of the autonomous synaptogenesis seen in the prenatal period, as synaptic density often correlates with conceptual age rather than experience.

## PRUNING

It has been proposed that the elimination of synapses may be universal to all neuronal systems and that the patterned connections within the brain are based solely on large-scale regressive events (Changeux & Danchin, 1976; Huttenlocher & Dabholkar, 1997; Rakic et al., 1986; but see Purves, 1989). Pruning, or loss of synapses in the absence of cell death, refers to environmentally regulated changes in the density of synapse per unit of dendritic length, not the loss of the whole neuron. The developmental time course of pruning in humans follows a period of rapid synaptogenesis during infancy and a plateau in childhood in which values are still above adult levels. Synapse elimination occurs late in childhood and in adolescence in both the human and the rhesus monkey (Huttenlocher & Dabholkar, 1997). Although there are topographical differences in the time course of synapse formation and elimination, quantitative measures have found a common pattern: The number of synapses seen at peak during childhood is reduced by approximately 40% to reach the adult value (Huttenlocher, 1979a; Huttenlocher & de Courten, 1987). In general, both the presynaptic and postsynaptic neuron plays a crucial role in organizing and supporting synaptic contact through the distribution of transmitter receptors on the presynaptic cell and the availability of neurotrophins from the postsynaptic cell.

First, presynaptic neurotransmitters play a role in the stabilization of synapses and modulation of cortical neuron activity (Kostovic, 1990). In particular, changes in the distribution of excitation and inhibitory inputs may lead to pruning. For ex-

ample, Diebler and colleagues (Diebler, Farkas-Bargeton, & Wehrle, 1979) proposed that the amount of inhibitory neurotransmitter (-aminobutyric acid [GABA]) at cortical synapses might drive elimination. Glutamate decarboxylase, a marker for GABA, reaches its maximum at 1 year of age and declines to 50% at the time of synapses elimination. Thus, GABA may support activity during the creation of synapses. When the level of GABA decreases, the lack of this support substance may lead to synaptic decreases.

Second, pruning is thought to be caused by limited availability of neurotrophic factors derived from the target neuron and by trophic interactions with afferents. This may occur by way of specific neurotransmitters—NGF, NT-3, BDNF—or thyrotrophin releasing hormone (Patterson & Nawa, 1993). Thus, only collaterals that are electrically active can respond to synaptogenic factors, and synaptic contacts that are not incorporated into neuronal circuits may be gradually eliminated (Changeux & Danchin, 1976). Furthermore, it is most likely that only inappropriate synapses and their branches disappear, whereas arborization in appropriate layers may increase in size and complexity.

The competition for limited neurotrophins may occur by two mechanisms. First, cells may make quantitative adjustments, that is, number matching presynaptic to postsynaptic connections. For example, Purkinje cells in the cerebellum initially receive inputs from a number of climbing fibers (from the inferior olive); yet, in the adult cerebellum each Purkinje neuron is innervated by a single climbing fiber. Even if cells are not number matching, the postsynaptic cell may have a finite amount of neurotrophins, which would limit the number of inputs that could be supported. Second, neurons may refine their input such that projections that are aberrant or incorrect may be eliminated (but see Armand, Olivier, Edgley, & Lemon, 1997; Purves, White, & Riddle, 1996).

Measures of cerebral energy metabolism (as measured by positron emission tomography) show an interesting parallel to the data on synaptogenesis and pruning. In general, the cerebral metabolic rate for glucose rises rapidly during infancy, remains high throughout childhood, and decreases during adolescence. The decrease in energy metabolism seen during adolescence occurs concurrently with the fall in synaptic density (Chugani, Phelps, & Mazziotta, 1987). In particular, the PFC lags by about 5 to 8 months in amount of cerebral energy metabolism (Chugani et al., 1987) as compared to the rest of the cortex, similar to the lag in synaptic density values seen in the PFC by Huttenlocher (1979b).

## NEUROTRANSMISSION

Neurotransmitters function as the chemical messengers in which information from the presynaptic terminal is communicated to the postsynaptic neuron. Neurotransmitters are synthesized by neurons, are stored in synaptic vesicles, and are released

at the terminals as a result of electrical activity at the presynaptic neuron. Once released into the synaptic cleft, neurotransmitters stimulate specific receptors on the postsynaptic cell, leading to the depolarization of the neuron and the transfer of the action potential to the postsynaptic cell. In the presence of its neurotransmitter (directly gated transmission) or a neurotransmitter and a second messenger (indirectly gated transmission), a gated channel receptor on the postsynaptic cell opens its ion selective channel. While the channel is open, ions enter (sodium) and leave (potassium) the postsynaptic cell, generating local currents that stimulate an action potential at the postsynaptic cell. Broadly speaking, there are two types of synaptic activity: Excitatory postsynaptic potentials depolarize the cell (involving sodium and potassium ion channels) and inhibitory postsynaptic potentials neutralize positive charges in the cell, making it more difficult to depolarize or excite it (involving chloride and potassium ion channels).<sup>3</sup>

There are approximately a dozen classical neurotransmitters and dozens of neuropeptides that function as transmitters, and small concentrations of almost all of these neurotransmitters are present from the first weeks of gestation as messengers or as trophic factors. There seems to be episodic involvement of neurotransmitters, which is not synchronized throughout the human brain. In addition, neurotransmitter production often occurs independently of the development of postsynaptic receptors (Lidow & Rakic, 1992).

Neurotransmitters can be divided into several classes. Most neurons in the nervous system secrete one of the small molecule transmitters (acetylcholine [Ach], glutamate, and GABA or the biogenic amines (dopamine, epinephrine, norepinephrine, and serotonin). Although this review could not possibly do justice to the complexity of neurotransmitter effects on the developing brain, several pathways are worth mentioning.

First, both glutamate and Ach have a role in the development and maintenance of neuronal architecture, being capable of controlling neuronal, axonal, and dendritic architecture and activity dependent synapse modification (Court et al., 1993; Hattori & Wasterlain, 1990). In the forebrain, cholinergic and glutamatergic systems are generally believed to be the central features of cognitive and memory processes (Court et al., 1993). Both glutamate and Ach are also likely to be involved in developmental neuronal plasticity.

Furthermore, the cholinergic transmitter Ach may participate in the stabilization and plasticity of synapses in different cortical regions (e.g., Goldman-Rakic, 1987). According to one hypothesis (Kostovic & Goldman-Rakic, 1983), Ach may signal the end of active growth and differentiation in the afferent system. Staining for Ach in the frontal cortex changes dramatically during the first year, showing peak intensities in adolescence. Kostovic and colleagues (Kostovic, Skavic, &

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<sup>3</sup>The postsynaptic receptor determines whether a neurotransmitter is excitatory or inhibitory; thus, neurotransmitters may have contrasting effects at different receptor sites.

Strinovic, 1988) suggested that Ach initiates the innervation of cortical associative neurons and the formation of layers during cognitive development.

Second, the NMDA and  $\alpha$ -amino-3-hydroxy-5-methylisoxazolepropionic acid (AMPA; to a lesser degree) subtypes of the glutamate receptor are essential for neuronal differentiation, the establishment and elimination of synapses, and activity-dependent plasticity in the developing brain (Komuro & Rakic, 1993). Glutamate NMDA receptor binding in the fetus is equal to that of the adult in the hippocampus and entorhinal cortex, but binding in the frontal cortex is low in the fetus and reaches its highest levels at birth (Court et al., 1993). Conversely, levels of AMPA receptors rise early in life, peak perinatally in the frontal cortex, and in the first or second decade in the hippocampus and entorhinal cortex.

Third, as mentioned earlier, Diebler et al. (1979) proposed that GABA might support synapses during their overproduction. GABA neurons are also among the first to differentiate in the hippocampus, have distinct properties from those seen in the adult, and may support the maturation of receptors for other neurotransmitters (Davies et al., 1998). In the human, binding sites for GABA are low at birth but increase to 50% of adult levels by 3 weeks postnatal. By 1 year, markers for GABA have reached peak levels and then decrease concurrently with synaptic pruning. The role of GABA in synaptic support may also be mediated by the synthesis of the neurotrophins NGF and BDNF, which are up regulated by glutamate and down regulated by the GABA system (Thoenen, 1991).

As a caveat, we have chosen to highlight only two of many levels of interaction between neuromodulators and development. In addition to the developmental trajectory of different transmitters and their receptors, the densities of ion channels as well as the relative proportion of various ion channel types, such as the voltage-gated calcium channels and calcium-dependent potassium channels, are modulated during ontogeny (rat cortex; Foehring & Lorenzon, 1999). Another mechanism of developmental change may be through neurotransmitter transporters, which remove neurotransmitters from the synaptic cleft. The four glutamate transporters that are present during human brain development each have their own unique distribution and temporal expression in the cortex (Bar-Peled et al., 1997).

A more concrete example of how neurotransmitter systems may alter brain development is found in the role of excitatory amino acids (EAAs, e.g., glutamate) in developmental neurological disorders. McDonald and Johnston (1990) suggested that EAAs contribute to the pathophysiology of neuronal injury, in particular hypoxic-ischemic episodes. Hypoxia-ischemia produces sustained neuronal depolarization and large increases in synaptic glutamate release, inhibition of glutamate uptake, or both. This cascade of events may cause excitotoxicity. In experimental animals, hypoxia-ischemia induced neuronal injury is reduced when animals are pretreated or posttreated with EAA antagonists (primarily through the NMDA receptor). Hippocampal areas CA1 and CA3 are especially susceptible to hypoxia-ischemia, as they have a high distribution of NMDA receptors. This ef-

fect is augmented in early development, as only CA1, in the adult, is as sensitive to hypoxia-ischemia (see McDonald & Johnston, 1990, for review).

## MYELINATION

Myelin is a fatty sheath that insulates nerve fibers (axons) both in the peripheral and CNS. This insulation provides for more rapid impulse conduction and energy efficiency. Myelin is composed of lipid proteins and glycolipids, including myelin basic proteins, proteolipid protein, glycoprotein, and enzymes (Braun & Brostoff, 1977). In the periphery, myelin is comprised of Schwann cells, whereas in the CNS, myelin is formed by oligodendrocytes.

Myelination occurs in several stages. First, after the extension of an axon, glial cell hyperplasia occurs in the vicinity of the axon. The glial cells accumulate myelin lipid components cytoplasmically before the actual appearance of myelin. Second, myelin becomes visible to the microscope (Stage 1), then to the naked eye (Stage 2), and in Stage 3 reaches adult density levels. These stages do not occur linearly; the shift from Stage 1 to 2 may occur rapidly, but the shift from Stage 2 to 3 may take many months or years.

There are some limited assumptions that can be made about myelin development. First, myelination occurs in a caudal to rostral direction. Second, the behavioral systems that function early in development also show the earliest pattern of myelination. In the cortex, Gibson (1981) found that primary sensory and motor projection areas of the cortex develop in advance of the association areas; layers subserving communication with the brain stem and spinal cord (Layers I, IV, V, VI) myelinate prior to layers subserving communication with the cortex (Layers II, III). For example, the rhombencephalic portion of the medial longitudinal fasciculus<sup>4</sup> is one of the earliest CNS tracts to myelinate, followed by the fasciculus cuneatus, caudal medial lemniscus,<sup>5</sup> trapezoid body, and lateral lemniscus<sup>6</sup> (Benes, Turtle, Khan, & Farol, 1994). These pathways myelinate prenatally and carry information from systems concerned with movement, posture, and auditory signals. Third, myelination progresses along the "flow of information" (e.g., Benes et al., 1994); thus the fasciculus gracilis (originating from the dorsal horn of the spinal cord and ascending to the nucleus gracilis in the medulla)

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<sup>4</sup>The medial longitudinal fasciculus is a bundle of axons situated near the midline of the brain stem and descends mainly from the upper medulla, superior colliculus, the accessory oculomotor nuclei, the pontine reticular formation, and the vestibular nuclei. The axons in this pathway carry information about the visual tracking of moving objects and coordinate movements of the eyes, head, neck, and trunk.

<sup>5</sup>The caudal medial lemniscus carries information about localized touch, movement, and position.

<sup>6</sup>The lateral lemniscus carries auditory information from the cochlear nuclei.

myelinates prior to the medial lemniscus (originating from arcuate fibers that arise from the nucleus gracilis in the medulla and ascend to the brain stem).

Prenatally, postural, orientation, and vestibular stimulation tracts are fully myelinated. Major tracts of the visual system (superior colliculus, optic tract, and optic nerve) begin to myelinate prior to birth and are mature by 9 months of age (Brody, Kinney, Kloman, & Gilles, 1987). In Years 1 and 2, myelination of the corticospinal tract (motor system) correlates with gains in neuromuscular functioning (Brody et al., 1987), reaching mature levels in the brain stem by about 1 year and mature levels at the spinal cord by approximately 28 months. In contrast, the superior medullary lamina (subicular region) shows a progressive increase in myelin between birth and 40 years of age through lateral locations of the presubiculum and parasubiculum (Benes et al., 1994).

Is myelin related to behavior? Disorders of myelination suggest some relation between anatomical state and behavior, but some neurological functioning begins prior to the appearance of myelin, and some systems such as the autonomic nervous system do not myelinate. Disruptions in myelination are likely to contribute to decreased conduction velocity, increased refractory periods after synaptic firing, more frequent conduction failures, temporal dispersion of impulses, and increased susceptibility to extraneous influences (Konner, 1991). Possible origins of myelin deficiencies may occur from amino acid or organic acid disturbances, congenital hypothyroidism, undernutrition, and periventricular leukomalacia (Volpe, 1995). As a general link between structure and function, Harbord et al. (1990) examined a heterogeneous group of children with developmental delay (in addition to associated neurological abnormalities). Using MRI, the authors found that nearly two thirds had delayed or absent myelination as the only visible abnormality.

## WHOLE BRAIN GROWTH

Dramatic changes in the volume of the human brain occur after birth with brain weight increasing fourfold from birth to 10 years. The volume of brain structures is determined by the number, size, and density of neurons and glia as well as dendritic and axonal number and density. Although there are few data to suggest that proliferation continues postnatally, glia cells do undergo a constant cycle of proliferation and cell death and may contribute to volume measures. Changes in total brain volume (TBV) reflect changes in the ratio of cerebral gray matter, white matter, and cerebrospinal fluid volumes. Although these may seem like somewhat coarse measures, gross structural differences have been implicated in a variety of child onset psychiatric disorders, including volumetric differences in the basal ganglia in attention deficit hyperactivity disorder (ADHD), Sydenham's chorea, and Tourette's syndrome, as well as the midsagittal corpus callosum in dyslexia and ADHD and ce-

rebral volume, planum temporale, and asymmetry differences in dyslexia and other learning disorders (see Giedd et al., 1996, for review). Total brain volume also differs in the normal population; Between 5 to 17 years of age, Reiss and colleagues (Reiss, Abrams, Singer, Ross, & Denckla, 1996) found that TBV predicted 20% of the variance in IQ in a bell-shaped function. In general, cerebral volume outside of the normal range has been associated with suboptimal functioning in children.

There are some general findings of intracranial volume that seem to apply to development. First, boys have slightly greater total cerebral size than girls, even in the prenatal period (e.g., Giedd et al., 1996). Second, head size rises from birth and peaks at about 5 to 10 years of age (Giedd et al., 1996; Reiss et al., 1996); however, infants from multiple births differ from singletons in TBV during the prenatal period beginning at the 34th week of gestation (Huppi et al., 1998). Third, when whole brain size is controlled, differences in regional size disappear in the normal population. Fourth, gray matter decreases with age, whereas white matter increases with age (Reiss et al., 1996).

Gray matter changes are likely to reflect cell growth, arborization, synaptogenesis, and cell proliferation. Decreases in gray matter are thought to reflect pruning and normal neuronal elimination during childhood. At 30 weeks of gestation, 35% of the TBV is from gray matter, increasing to 50% at birth (Huppi et al., 1998). These changes are primarily due to increase in cortical gray matter, not subcortical structures. In an older sample (13–17 years of age), cortical gray matter volume decreases are found in the frontal cortex (2.6%) and the parietal cortex (4.1%), with small, nonsignificant changes in the occipital and temporal regions (Rapoport et al., 1999). Adolescents with schizophrenia (child onset) show similar, yet exaggerated, patterns of gray matter volume decreases across the frontal, parietal, and temporal lobes.

In contrast, white matter seems to be increasing during development. From 29 to 41 weeks of gestation, white matter increases fivefold (Huppi et al., 1998). White matter continues to increase through childhood (Reiss et al., 1996), with increase in the dorsal, frontal, and parietal regions continuing through adolescence (Sowell et al., 1999). Concurrently, few changes are occurring in the temporal and occipital lobes during the same period (Sowell et al., 1999).

As an example of volumetric measurements in a single structure, Pfluger et al. (1999) documented changes in the hippocampus using MRI. In a group of normal children ages 1 month to 15 years, the authors found asymmetries in the hippocampus, with the right being larger than the left in the absence of significant differences in the right and left hemispheres. Maximal growth velocity for the hippocampus occurred at around 1.5 months and was slightly earlier in the right versus left hippocampus. This side bias becomes even more prominent after 25 months of age and continues through the 3rd decade of life (Sowell et al., 1998). In addition, females had steeper growth curve rates than males for the hippocampus, but males showed steeper growth curves for total brain growth than females.

## CORTICAL CIRCUITS

Although Katz and Shatz (1996) proposed that sensory experience is actually a special case of a more general role of neuronal activity, much of which can be generated spontaneously, postnatal experience historically has been viewed as the strongest force guiding mature circuit formation. However, major structural changes in axonal and dendritic development are occurring prior to birth and often just subsequent to neurogenesis. These anatomical and chemical changes, including prenatal synaptogenesis, may be preparing the infant brain for sensory input by establishing circuits that may then be further strengthened or eliminated based on the postnatal environment.

Greenough, Black, and Wallace (1987) proposed that neural circuits function along two basic principals: experience-expectant systems and experience-dependent systems. In an experience-expectant system (such as language or visual development), development is based on the expectation that appropriate environments (and thus, experiences) will provide the information that the brain needs to select the appropriate subset of synaptic connections. Contrastingly, in an experience-dependent system, development is unique to each person and most likely involves the active formation of new synaptic connections throughout the life span (vocabulary).

It has been proposed that infancy is a critical period of development, in which rapidly growing structures are more sensitive to damage (e.g., Huttenlocher, 1984). For example, disturbances such as disease, metabolic disturbances, malnutrition, sensory impairment, and trauma produce both structural and functional impairments in the development of the cerebral cortex if they occur during periods of synaptogenesis (Taylor & Alden, 1997). These same global conditions, when occurring in the older child or adult, do not seem to produce the same degree of impairment in both structure and function. In addition, many children with early brain insults, including those who sustain traumatic brain injury, are susceptible to both immediate and long-term neurobehavioral impairments (e.g., Vargha-Khadem et al., 1997). In some cases, there is little evidence that sequelae resolve with age.

In contrast, the infant brain also demonstrates greater ability to recover from some types of injury than seen later in development. The best examples of neural system reorganization to environmental input come from studies of adult animals in enriched environments (reviewed by Renner & Rosenzweig, 1987) and infants deprived of sensory input (e.g., Bowering, Maurer, Lewis, & Brent, 1997). When adult rats are exposed to enriched environments, the most profound changes are found in those areas relating to synapse density (e.g., Black, Isaacs, Anderson, Alacantara, & Greenough, 1990; Juraska, Greenough, Elliott, Mack, & Berkowitz, 1980), vasculature (increased capillary volume; Sirevaag, Black, Shafron, & Greenough, 1988), glia volume to neuron ratios (e.g., Anderson et al., 1994), and

synaptic vesicle contents (Nakamura, Kobayashi, Ohashi, & Ando, 1999). Middle-age rats trained on motor-learning tasks showed extensive dendritic growth in the cortex involved in forelimb function (Greenough, Larson, & Withers, 1985) compared to a voluntary exercise condition. In addition, Anderson et al. (1994) found a high correlation across the treatment groups between the number of synapses per Purkinje cell and the volume of astrocytes per cell, suggesting that increases in astrocyte processes follow synapse formation. Moreover, “acrobatic” rats, those trained on complex motor coordination tasks, show increased numbers of synapses per neuron in the cerebellum (Black et al., 1990). In addition, the greatest changes in neuronal dendritic fields (visual cortex of rats) are seen when the laboratory animals are reared in enriched environments, from weaning to adolescence (Juraska et al., 1980).

In a human model, evidence of functional brain reorganization can be demonstrated in models of early sensory deprivation in people who are blind or deaf, patients with chronic unilateral brain injury, and patients who have undergone cortical resections for the alleviation of intractable epilepsy (reviewed in Chugani, Muller, & Chugani, 1996). However, as Chugani and colleagues (Chugani et al., 1996) have emphasized, the neurobiological rules that govern reorganization of function in the brain are, at present, poorly understood. For example, children who are profoundly deaf, deprived of speech stimulation, and then provided with cochlear implants (giving them access to speech frequencies) show improved performance on speech perception and production tasks relative to those children who receive implants subsequent to 5 years of age (Robinson, 1998). Even though a number of studies seem to confirm these results—earlier intervention leading to greater functional recovery—there are still large individual differences in performance among children that cannot be accounted for by age or intervention. In addition, Bates (1999) reviewed two studies of recovery of function after developmental lesion and found that worse cognitive outcomes were associated with children who suffered their injuries between 1 and 5 years as compared to those with congenital injuries or those who sustained injuries between 5 and 12 years of age. These results suggest that we are not likely to find a general linear relation between age and recovery of function.

However, to say that infancy and young childhood is the only period in which new neural circuitry is established would grossly understate the complexity of the human neural system. In particular, several new lines of research (in the animal model) have documented ongoing neurogenesis and synaptogenesis in the adult animal. Recent results suggests that neurogenesis continues in the dentate in marmosets (Gould, Tanapat, McEwen, Flugge, & Fuchs, 1998), macaques (Gould et al., 1999), and humans (Eriksson et al., 1998). Kempermann and colleagues (Kempermann, Brandon, & Gage, 1998) documented continual neurogenesis in the dentate gyrus of the adult mouse that is influenced by both genetic and environmental factors. In animals living in enriched environments, more cells differenti-

ated into functional neurons than in animals in standard cages. The increases in the number of dentate neurons also correlate with observed behavior changes in these mice.

More recent results suggest that hippocampal learning is important to the survival of these newly formed dentate neurons. In particular, Gould et al. (1999) suggested that new neurons, even in adult animals (rats), might be more sensitive than mature neurons to the effects of activity (see also Van Praag, Christie, Sejnowski, & Gage, 1999). If we extend this model to the human, not only must we look at the development of synapses during the prenatal and postnatal period when we discuss neural plasticity but also the possibility of ongoing neurogenesis and synaptogenesis in some areas of the cortex. The mechanisms that we have specified earlier may be active throughout life and may involve some of the same mechanisms as seen in the developing organism.

## CONCLUSIONS AND FUTURE DIRECTIONS

Huttenlocher (1979b) suggested that postnatal cortical development could be divided into two phases. Phase 1, from birth to Year 1, is characterized by a decline in neuronal density, increases in synaptic density, number of synapses per neuron, dendritic growth, and total cerebral volume. The second phase extends from Year 1 to adolescence and is characterized by a slow decline in both synaptic and neuronal density, increases in dendritic growth, and the decrease of synaptic density along dendrites. The mature cortical organization may depend on the relocation, retraction, or both, of cortico-cortical axons, on the elimination of excessive synapses, and eventually on naturally occurring cell death (Kostovic, 1990).

Although this general pattern of development is well established, the mechanisms of human neural development are still far from being fully understood. Researchers have made significant headway into the understanding of the endogenous mechanisms that drive axonal and dendritic formation and the timeline of neurotransmitter development, synaptogenesis, and pruning. However, our understanding of how experience alters synaptic circuits postnatally is far from complete, especially as these events are occurring *in vivo* (for discussion, see Nelson & Bloom, 1997). As a cautionary note, it is important to remember that many of the human-based results discussed previously have been developed from postmortem studies. Thus, there are few experimental data to suggest how normal experience sculpts these early circuits, as most of the data on dendritic, axonal, and synaptic values are correlated to age and are rarely correlated to an individual's behavior.

In general, Diamond (1995) proposed that there are two guidelines for the study of brain-behavior relations. First, researchers must study the progress or performance on a particular behavior task; second, links between performance and spe-

cific neural systems should be investigated. As the tools in neuroscience become better able to examine neural development in functioning healthy people, our understanding of the brain–behavior relation will also improve. Currently, the use of event-related potentials and functional MRI provides insights into the neural correlates of behavior in infants and children by allowing neural imaging to occur as behavioral performance is being measured. To further elaborate our understanding of the developing human, we will need to not only continue work on the molecular basis of neural development (both in animal and human models) but also look to methods across neurological and psychological domains.

### ACKNOWLEDGMENTS

The writing of this article was made possible by Grant NS32976 from the John D. and Catherine T. MacArthur Foundation and the National Institutes of Health (to Charles A. Nelson), by National Research Service Award MH12132 from the National Institutes of Health (in support of Sara J. Webb), and by training Grant HD01751 from the National Institutes of Health to the Minnesota Center for Cognitive Sciences (in support of Christopher S. Monk).

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